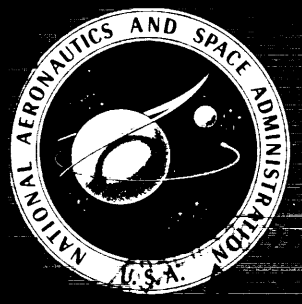
NASA SP-152

THIRD SYMPOSIUM ON THE ROLE OF THE VESTIBULAR ORGANS IN SPACE EXPLORATION



NASA SP-152

THIRD SYMPOSIUM ON

THE ROLE OF THE VESTIBULAR ORGANS IN SPACE EXPLORATION

Held under the auspices of the National Academy of Sciences — National Research Council Committee on Hearing, Bioacoustics, and Biomechanics

Naval Aerospace Medical Institute
Naval Aerospace Medical Center

Pensacola, Florida

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General Chairman: ASHTON GRAYBIEL
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Foreword

This volume reports the proceedings of the third symposium featuring problems in space exploration which implicate the vestibular organs. A glance at the table of contents indicates the areas of concentration. The choice was somewhat arbitrary inasmuch as the symposium series is designed to provide material for later incorporation into a handbook. This purpose necessarily precludes the function of providing a forum for all of the relevant research which deserve presentation in a given year.

The viewpoint of NASA as the "user" was well expressed by Walton L. Jones who, in his welcoming address, suggested that we consider the systems analysis approach to the solution of problems, not only because NASA engineers are familiar with this approach but also because of the high degree to which vestibular problems lend themselves to this type of analysis. Surely it would be difficult to point to another area that requires closer collaboration among physicists, engineers, and biomedical scientists than the receptor systems which sense the gravitoinertial force environment. The field force receptor systems in the vestibular organs slavishly respond to changes in our force environment within the range of their response characteristics. It must never be forgotten that these sensory organs have evolved through natural selection in the struggle for survival. This "struggle" occurred in natural not artificial force environments. In exposing man to the unique gravitoinertial forces which are or will be encountered in the exploration of space, it will be necessary to cope not only with sensory information which may differ quantitatively and qualitatively from that in any previous experience, but also to cope with transitions so abrupt as to exceed the rate at which adjustments can be made. A common understanding of basic concepts underlying the roles of receptor systems which sense the force environments encountered in space exploration is almost essential to productive interrelationships among the many different disciplines involved in a successful space mission.

The opening address by Maxime Faget,[1] a deputy director at the NASA Manned Spacecraft Center, was concerned with habitability in orbital space stations, with particular reference to generating artificial gravity by causing the spacecraft to rotate. Based on "preliminary" findings in parabolic flight, it was tentatively concluded that habitability requirements might be met at relatively low subgravity levels, i.e., 0.2 g. Faget emphasized that complicating side effects incidental to rotational velocity may be aggravated by perturbations.

Review topics dealing with basic background information focused on (1) the circulation of the endolymph, (2) the efferent nerve fibers to the labyrinth, and (3) the blood supply to the inner ear. The presentations were made by meticulous scientific observers who probed deeply and comprehensively into the problems encountered in their areas. Their contributions are foundation stones in providing a solid base of background information.

[1] In collaboration with Edward H. Olling.

The two practical topics chosen for review dealt with functional tests of the semicircular canals and otolith organs. Despite progress in these areas and the excellence of the presentations, the fact remains that better, simpler tests than we now have are required and that studies relating behavior to test scores are urgently needed.

Two additional highlights deserve mention. One was the special section by Tristan D. M. Roberts from the University of Glasgow who, in effect, gave an excellent preview of his new book, *Labyrinthine Control of the Postural Muscles.* The other was in the nature of a gift; permission was given by Barry J. Anson to reproduce in this volume his splendid collection of illustrations depicting the anatomical features of the inner ear.

In summary, despite spectacular advances, the long neglect of the vestibular organs continues to show through. The difficulties encountered in dealing with the effects of "natural" stimulation of these organs are several magnitudes of effort greater than those concerned with hearing and vision. Unless progress is to be measured by years rather than decades, a high level of effort is required; fortunately, it is rising rapidly.

This symposium was held under the auspices of the National Academy of Sciences, National Research Council, and the best expressions of appreciation were manifested in the discussions by the participants. Much work inevitably falls on many persons in connection with holding a symposium, and the assistance of all is gratefully acknowledged.

ASHTON GRAYBIEL
Naval Aerospace Medical Institute
Naval Aerospace Medical Center

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Welcome

WALTON L. JONES

Office of Advanced Research and Technology, NASA

These symposiums on the role of the vestibular organs in space exploration have now been held at regular, 1-year intervals since 1965. During initial preparations we questioned the advisability of scheduling them each year. It was felt that a 2- or 3-year interval might be more appropriate in terms of allowing more research to be completed between meetings and thus allowing more information to be exchanged at meeting time. The experience with the second meeting did not bear out these misgivings, and the more than 30 papers presented herein for the third symposium suggest that there is even more information to exchange. It may be that holding these symposiums is serving to accelerate research concerning vestibular mechanisms. If so, the National Aeronautics and Space Administration is indeed pleased to be at least partly responsible. The human-balance mechanisms are of obvious importance in the normal gravity of an Earth environment, in reduced gravity fields, and under conditions of complete weightlessness.

The reports of the first and second symposiums (NASA SP–77 and SP–115, respectively) have been well received in professional circles. The bringing together of this fund of information concerning one of the primary systems of the body represents a contribution both to the medical sciences and to the long-range interests of NASA.

In the opening remarks of the first vestibular symposium, I stated that NASA is especially interested in the solution of two vestibular problems posed by manned space flights. These are the prevention of vestibular disturbances in weightlessness and the possible need to generate artificial gravity.

For many of the development problems which confront NASA, it has been found that a systems-engineering approach is appropriate. It might be useful to examine the kinds of research which have been reported previously to see if these efforts are consistent to any degree with the systems-engineering paradigm.

In a systems-engineering approach, there are a number of discrete categories of effort. Let us consider the extent to which research activities in vestibular physiology fall within these categories. It may be that certain useful implications then can be drawn.

A major category in a systems-engineering analysis deals with the "Definition of System Components." Studies dealing with the ultrastructure of the labyrinth and those concerned with the form and innervation of vestibular components are representative of efforts which would fall within this category. These studies are those which attempt to define, at an appropriate microscopic level, the precise morphology of the vestibular system.

A second important category is that concerned with "Delineation of Subsystem Function." While it is rather obvious, by this time, that the primary role of the vestibular system is to provide information to man concerning the orientation of his body in space, it seems there is still a great deal to be learned concerning the specific nature of vestibular components. Studies dealing with the effect of otolith stimulation on semicircular canal functions appear to be representative of a rather sophisticated attempt to deal not only with individual functions but with collective functions as well. Also in this category of function delineation might fall studies showing the manner in which the vestibular system contributes to retinal image stabilization.

In the third category I would place those studies which describe the "Scaling of System Operations." By this I refer to those studies which measure, with as great precision as possible, the response of a physiological system to a wide range of stimuli along a particular physical dimension. The response, either of the complete system or of individual nerve fibers, to a specific type of acceleration force is the basic issue of concern with studies in this category. However, I also would include studies which point out the manner in which a given sensory input can produce a perception which is in conflict with reality. All studies of illusions due to vestibular stimulation are of this type. Finally, research concerned with development of new test methodology, such as the use of ocular counterrolling as an index of the magnitude of vestibular stimulation, falls within this class.

The fourth category from systems engineering includes attempts to develop an "Analytic Model of System Functions." Here we find programs such as those underway at the Langley Research Center, the Franklin Institute, and MIT in which a mathematical model is developed which describes the response of the vestibular system to any combination of stimulus forces. The ultimate objective is to be able to describe total system output to a realistic combination of physical forces and, having established the appropriate set of descriptive equations, to be able to predict system output to stimulus forces for which laboratory testing is not feasible.

The final category includes studies of the "Effect of Atypical External Forces on System Function." Studies of habituation and adaptation to extended periods of rotation might be placed in this category. Also included are studies of the effects of weightlessness. Finally, I would add those which examine the effects of change in the internal environment, that is, drug-induced biochemical changes, on the operation of the vestibular system.

This exercise in systems-engineering description offers an avenue for describing the manner in which NASA views the potential contribution of these symposiums.

To begin with, we are very much interested in any problems of disorientation or impaired balance which might influence the success of long-range space missions. The tremendous expense of these ventures and the human lives which are involved make it imperative that we do everything possible to insure successful mission completion. In terms of the systems classification of research efforts, the principal interest of NASA is in the fifth category, that concerned with unusual environmental forces. This being the case, what is the best way to acquire the necessary information concerning the effects of such forces?

In studying problems of disorientation under space conditions, which certainly constitute unusual environmental forces, there are two approaches which NASA might take. The first would be based entirely on inductive procedures and would involve collecting pieces of information from a large number of sources which show how the human reacts to some feature, actual or potential, of the space environment. For example, by simply taking the data from orbital flights to date, from rotating-room studies, from sensory-deprivation studies, and from centrifuge tests, we can make a rather well-educated guess as to the likelihood of disorientation during a long-range mission. An inductive approach of this type certainly represents a very direct method of seeking an answer to a specific question.

An alternative approach would be based more on deductive procedures and would involve developing a rather complete descriptive model dealing with the operation of the vestibular system. In terms of our classification scheme, this means focusing on category four, the "Development of Analytic Models." However, as all model builders appreciate, the success of a model is very much dependent on the adequacy of the available information concerning specific characteristics of the system under study. We must know a great deal about the microstructure of the system. We must have insights into the function of specific system components. We must know the physiological response of system elements as the magnitude of a specific stimulus force is varied. In other words, a worthwhile analytic model cannot be constructed unless research efforts within the first three categories are continuously providing information for inclusion within the model.

By its support of rather diverse research activities falling within all the categories I have described, it is apparent that NASA is interested in a deductive approach yielding a detailed analytic model of vestibular system operations. There are three reasons why this approach appears best. First, when the model is complete, a framework will be available within which important evaluation tests can be conducted. In other words, a generalized curve of system output can be drawn and then tested empirically at critical points. The testing program thus can be made maximally efficient. Second, meaningful extrapolations can be made to situations for which laboratory testing is not feasible at all. For example, if we understand how the total vestibular system responds to a combination of stimulus forces and how specific system elements adapt to different force fields, we should be able to predict the likelihood of disorientation as the first astronaut guides a spacecraft to a landing on the surface of Mars. For purposes of designing a Martian landing system, it is critical that we know the extent to which we can rely on normal operation of the vestibular system.

There is yet a third reason for favoring the deductive approach which, although not as directly related to the immediate needs of NASA as the first, is nonetheless considered quite important. When the analytic model is complete, we will have greatly improved insight into the normal functioning of the vestibular system. This, in turn, will make it easier for the medical sciences to deal with problems of abnormal functioning. Thus, basic research into vestibular mechanisms, conducted within the framework of our national space effort, will bear results which can be used for the betterment of all mankind. This is the kind of additional payoff which adds justification for space expenditures and which eases our task of acquiring the necessary funding.

It is my belief that current research concerning the vestibular system will provide information having a very practical value for NASA and will, at the same time, serve a humanitarian purpose as it expands our knowledge of the operation of the human body.

Session I-A: MAN IN SPACE

Chairman: HENNING E. VON GIERKE
Aerospace Medical Research Laboratories
Wright-Patterson Air Force Base

Orbital Space Stations With Artificial Gravity

MAXIME A. FAGET
AND
EDWARD H. OLLING
Manned Spacecraft Center, NASA

INTRODUCTION

It is quite probable that orbital space will someday be permanently occupied by men and women accomplishing a variety of useful tasks. These persons will most likely live and work in large orbiting stations, perhaps as large as the one shown in figure 1. In this case 100 or more

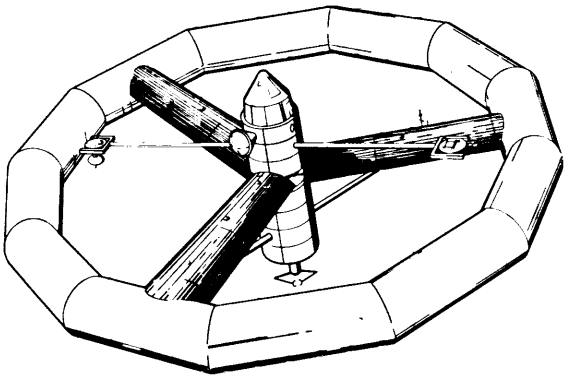

FIGURE 1.—*Orbital assembled toroidal space station.*

persons could be accommodated in a structure that would be assembled in orbit from components carried there by a number of individual rockets. The structure would weigh perhaps 1 million pounds and have a diameter of 400 feet.

PURPOSE

The initial uses for a space station would evolve around the fact that, outside the Earth's atmosphere, an observation platform would provide unique opportunities that are not obtainable anywhere else. Such a platform would be above the Earth and moving over great portions of the Earth's surface. From that vantage point, the Earth can be observed in a manner that cannot be duplicated in any other way. Another factor is that, beyond the Earth's atmosphere, objects other than the Earth can likewise be observed in a unique manner. When the 200-inch telescope was built about 30 years ago, the ultimate performance for optical observation of things beyond the Earth was essentially achieved. Even at present, it would be of very little value to try to improve on the 200-inch telescope as an earthbound means of optically observing celestial bodies.

Many of the limitations associated with making observations from the Earth's surface are eliminated in space; and, initially, this factor may be the primary justification for the space station. But, eventually, the everyday familiarity with the orbital environment that will be created will generate other productive activity.

LIVING-VOLUME REQUIREMENTS

One of the basic considerations concerning the size of a space station is the amount of living volume that must be provided for each individual. Living-volume requirements have always been a matter of individual opinion. However, an attempt to arrive at a rational volume requirement has been made (fig. 2). In this case, total living volume in cubic feet per man for a number of comparable situations has been plotted against the total amount of time that the volume is occupied. It can be seen that, as a general rule, the longer the period of occupancy, the greater the amount of volume provided. Actual experi-

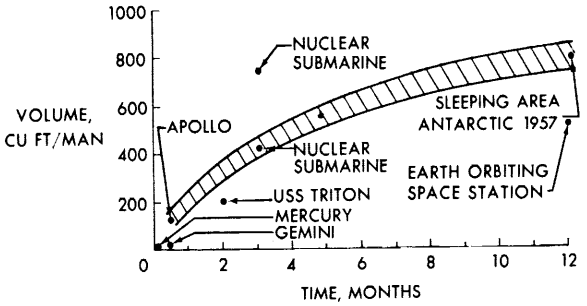

FIGURE 2.—*Total living volume.*

ence in space flight has been limited up until this time to the 14-day Gemini flights. For longer durations, the volumes of submarines and Antarctic shelters are known. These examples have been used because they represent situations where the living volume has been a design constraint. A design point for an orbiting space station indicates less sleeping volume than that provided in the Antarctic in 1957. This smaller volume is based on the assumption that a great deal more attention to design detail will be provided and the efficiency of volume utilization will be greater. In other words, by placing emphasis on specialized comfort features, it is expected that a smaller amount of volume will provide an equivalent amount of comfort.

Research into the amount of volume provided for Antarctic expeditions reveals an interesting trend in the accommodations provided in the successive expeditions. This trend is illustrated in figure 3 in which is shown that, in successive expeditions, not only was the number of men used during the expeditions greater but also the

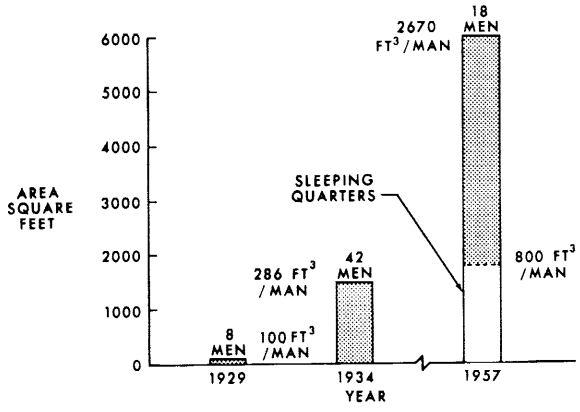

FIGURE 3.—*Antarctic expeditions, habitable area.*

amount of volume provided for each man was considerably greater. Perhaps this trend will also be found to be the case in space-station design in which, in later flights where the performance margins are not so narrow, more attention to comfort can be provided. Typical sleeping quarters that may be provided in a space station for various mission durations are shown in figure 4. For a mission duration of 60 days,

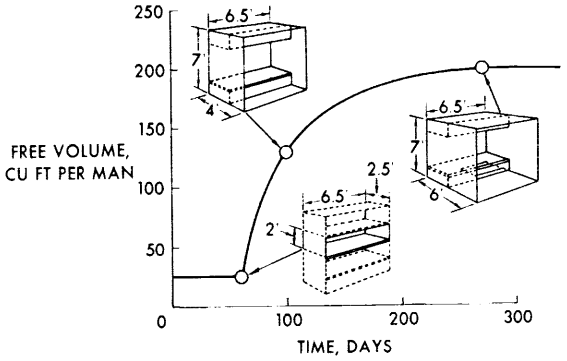

FIGURE 4.—*Privacy/sleeping quarters.*

there may be two men in one cabin; for longer duration missions, the desire for privacy suggests that individual cabins should be provided, and there may be a need for more volume in each cabin. An example of the total habitable-floor-area requirements for 9, 12, and 24 men in a space station of 1-year duration is shown in table 1.

The habitable area not only includes the sleeping quarters but also room for preparing and eating food, recreation and exercise, hygienic needs, and control operations.

TABLE 1.—*Habitability Area Requirements*

	Floor area, ft²		
	9-man crew	12-man crew	24-man crew
Sleeping quarters	315	420	840
Wardroom	125	165	330
Food preparation	16	16	36
Hygiene	28	28	56
Sickbay	108	108	135
Gymnasium	60	60	90
Command station	32	32	48
Total	684	829	1535

ARTIFICIAL GRAVITY REQUIREMENTS

Undoubtedly, one of the most important and yet unsettled design considerations for a space station is the provision of artificial gravitation. The amount of artificial gravitation required, a suitable radius, and the speed of rotation are all facets in this consideration. In order to gain a better understanding of what might be a suitable level of artificial gravitation, a series of subgravity-level flight tests were performed in an Air Force C–135 aircraft. This airplane has been extensively used for simulating both weightlessness and the 1/6-g level that will be experienced on the Moon. Such tests are made in support of the ongoing manned space-flight program. In a test made to define artificial gravity requirements for a space station, parabolas were flown at 0.1, 0.2, 0.3, and 0.5 g. During test parabolas which lasted about one-half minute each, a test subject carried out certain predefined tasks. Data were obtained by motion-picture records and from comments made by the test subject. The test subject was an experienced technician who had previously flown more than 300 parabolas at a 1/6-g level and may, therefore, be considered to be partially acclimated to a subnormal gravity level. Because of the preliminary nature of the program and to assure completion of the task during the subgravity period, only simple tasks were evaluated. These tasks were as follows: Two containers, a small one weighing 60 pounds and a large one weighing 136 pounds, were carried at a walk including a 180° turn; a bolt was tightened; an electrical connector was connected and disconnected; and water was poured back and forth between two containers. These tests, although preliminary in nature, indicated that 0.2 g provided a much better environment for such tasks than did 0.1 g. At gravity levels greater than 0.2 g, very little gain in performance was indicated. Furthermore, the test subject reported that at 0.5 g he felt every bit as sure of himself and as comfortable as he did at 1.0 g. A human-factor design envelope for utilization of artificial gravity is shown in figure 5. The shaded area in this figure is indicated as the region of useful operation. This region is bounded by a lower limit of 0.2 g and an upper limit of 1.0 g, a maximum

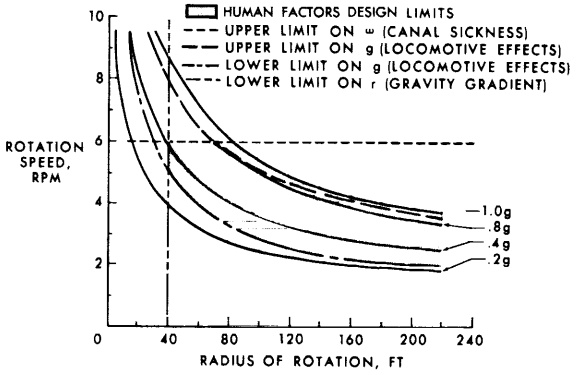

FIGURE 5.—*Human-factors design envelope.*

rotation speed of 6 rpm, and a minimum radius of 40 feet. Speeds of rotation are limited to those in which test experience indicates that acclimatization can reasonably be expected. Although these limits have been formulated on the basis of numerous tests, such tests have been made with the deficiencies associated with an earthbound environment. A final assessment of artificial gravity by rotation can be carried out only in space.

THREE BASIC CONFIGURATIONS

There are three basic configurations that have been suggested for the artificial-gravity space station, as shown in figure 6. These configurations are the I, the Y, and the "toroidal" configurations. The names, of course, refer to the basic shapes of the configurations. Not only the geometry of the space station as it would appear in orbit but also the manner in which the space station would be folded for launch is shown in figure 6. It is evident that each of these configurations can be suitably supported and is in an arrangement that is practical for launching with a Saturn V launch vehicle. In each case, a reasonably simple scheme for deployment into the orbital configuration has been worked out. Both the Y and toroidal configurations have a great deal of rotational stability in that the greatest moment of inertia is about the axis of rotation. The I-configuration, however, has a large moment of inertia in two axes. Therefore, its stability must be augmented by a stabilizing device such as a momentum wheel. Of the three configurations, the I- and the Y-configurations have an advantage in that the various crew sta-

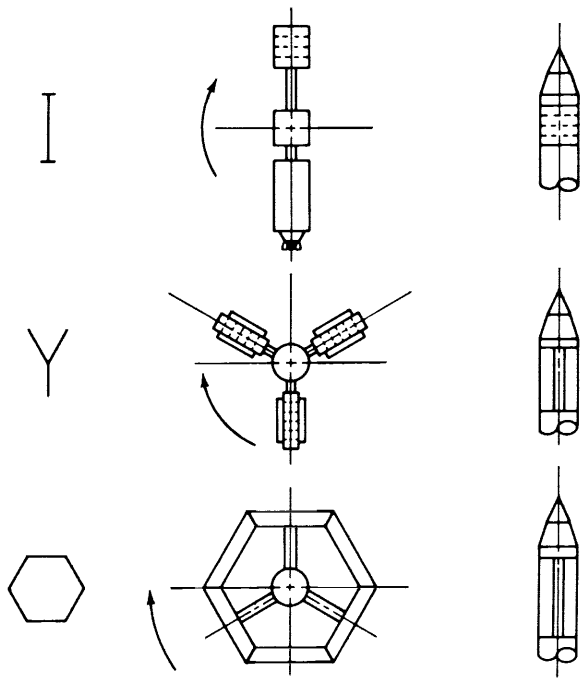

FIGURE 6.—*Basic rotating space station configuration candidate concepts.*

tions are properly oriented with the gravity vector when they are in the launch position. These configurations may also be slightly less complicated to deploy. These two configurations are shown in more detail in figures 7 and 8.

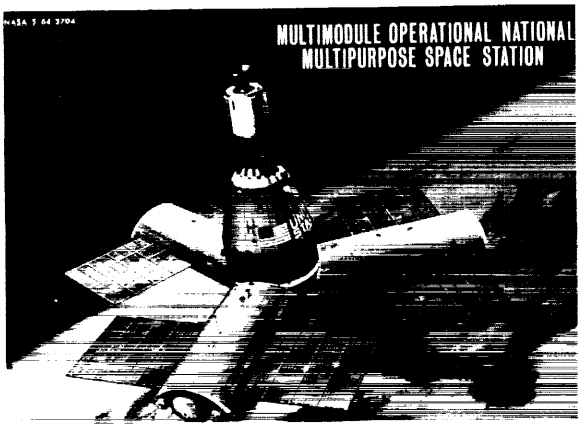

FIGURE 7.—*Space station, Y-configuration.*

Since the I-configuration has recently been studied in depth, additional discussion of possible features of this type of space station may be of interest. It can be seen in figure 9 that the space station utilizes the spent S–II stage of

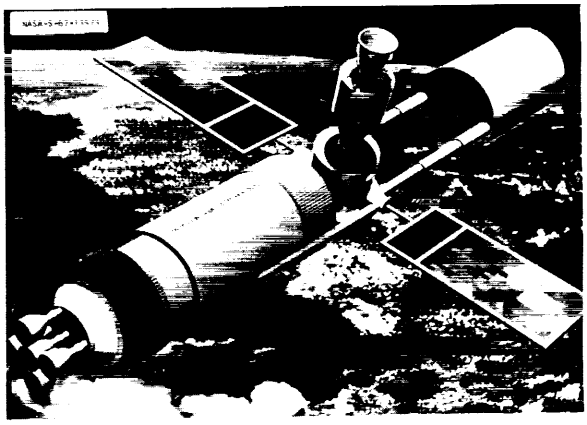

FIGURE 8.—*Space station, I-configuration.*

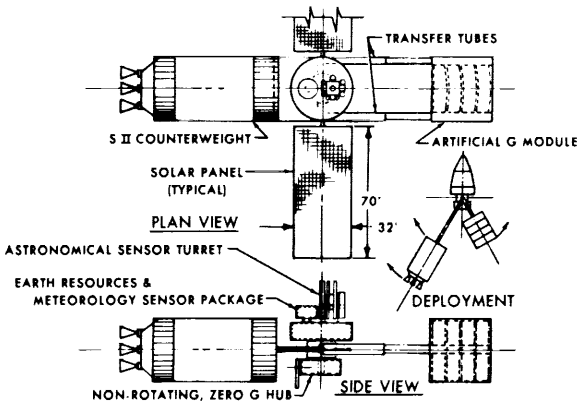

FIGURE 9.—*Space station concept I, artificial g, 24-man, 396 inches in diameter.*

the Saturn V as a counterweight for rotation. With this arrangement, all of the living space provided with artificial gravity is located in one module. This accommodates easy communication between the various activities that are carried out in artificial gravity. This artificial-gravity module is connected by two transfer tubes or passageways to the hub where the nonrotating zero-g modules are located. The details of this hub and nonrotating modules are shown in figure 10. It can be seen that various sensors are mounted on stabilized platforms attached to the nonrotating modules. These sensors would be used for astronomical observations and for Earth-oriented programs such as the survey of natural resources and meteorology research. The rotating elements are attached to the nonrotating elements of the space station through gimbals and a flexible tunnel, as shown in

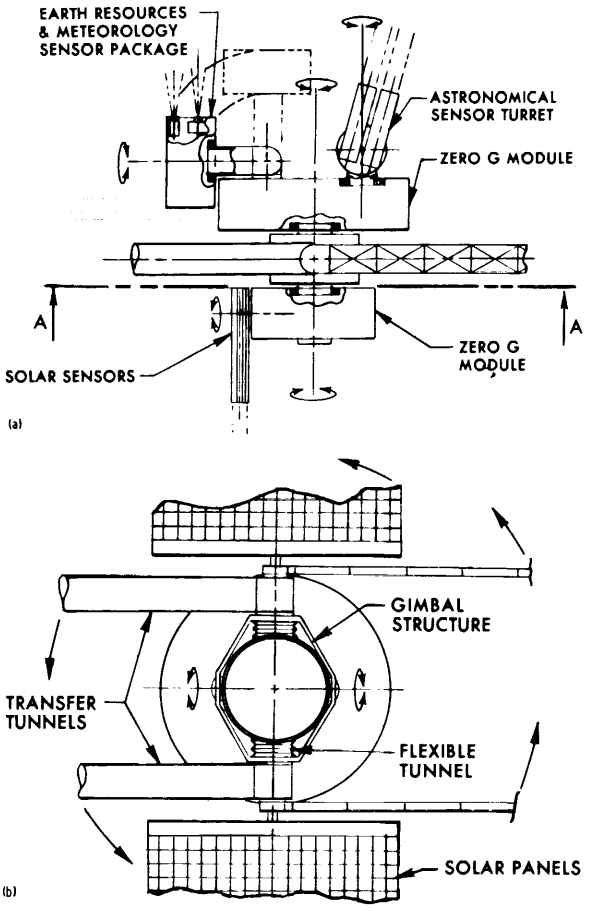

FIGURE 10.—*Detail, artificial-g space station hub (396 inches maximum diameter).* (a) *First view; and* (b) *second view (sec. A–A of first view).*

figure 10(*b*), to provide mechanical isolation of the rotating mass from the nonrotating mass and, thus, greatly enhance the rotational stability by decoupling the asymmetrical nonrotating element from possible wobble of the rotating element. The isolation of the nonrotating element also facilitates maintaining the zero-g laboratories in a steady, inertially fixed attitude, although the rotating elements may be wobbling. This steady attitude is important because of the need for accommodating delicate, zero-g experiments and because the nonrotating module is the mounting platform for various optical and other stabilized sensors which require fine pointing.

The manner in which the space station would wobble because of the movement of the crew in the artificial-gravity area is illustrated in figure 11.

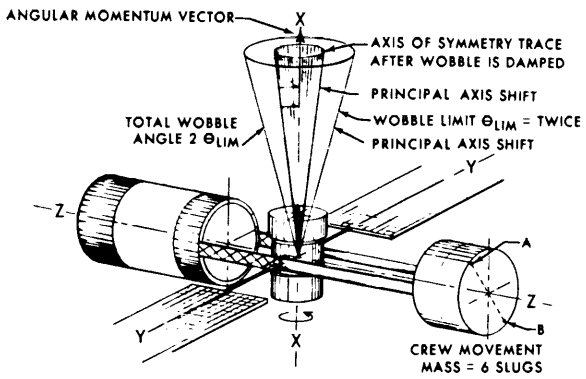

FIGURE 11.—*Response to internal mass movement in artificial-gravity space station.*

In the example illustrated, a man assumed to have a mass of 6 slugs moves from point A to point B across the floor of the artificial-gravity module. As he does this, he displaces the inertial axis from the geometrical axis. If the space station were to rotate about its new inertial axis, the geometrical axis would trace the inner cone (shown greatly exaggerated). Since, however, a man's movement represents a disturbance, the space station would not immediately rotate about the inertial axis but would wobble. This wobble would persist until damped, at which time the geometric axis would remain at a constant displacement θ from the axis of rotation. During the wobble, the geometric axis would wander from a displacement of 0 to 2 θ. In the actual case, the displacement of rotational axis should be small. The displacement angle for the case of crew movement cited would be less than 0.1°. Thus, it can be seen that the motion of the crew about the artificial-gravity laboratory will have very little effect on the apparent attitude of the room occupied by the crew. Obviously, the necessity to move large masses about the laboratories will require mass compensation. Shifting the position of the counterweight or possibly the use of ballast tanks is a suitable means for compensation.

A rotating space station that uses solar cells for power is almost forced to rotate with its spin axis oriented parallel to the rays of the Sun, as illustrated in figure 12. With such a spin-axis orientation, the accommodation of astronomical and Earth sensors must be consistent with the attitude of the space station. Solar sensors would obviously be mounted on the sunny side.

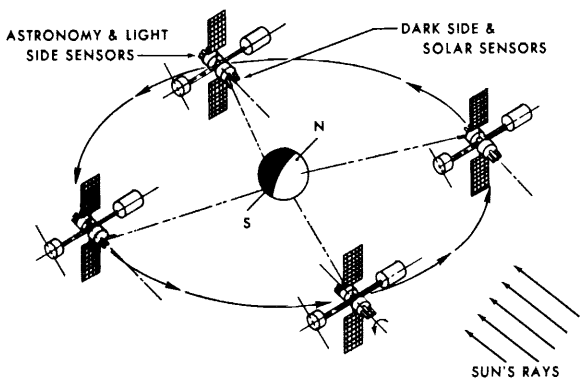

FIGURE 12.—*Spin axis orientation parallel to Sun's rays.*

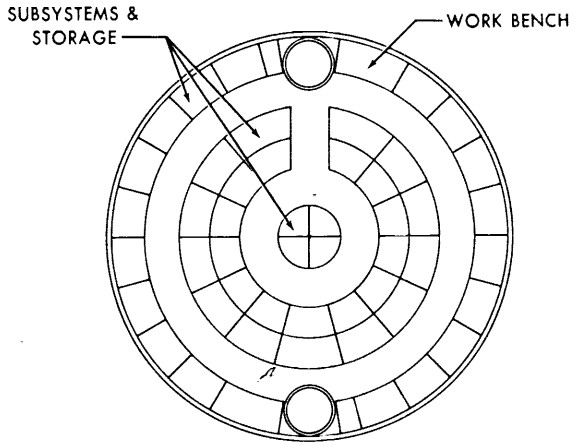

FIGURE 13.—*Subsystems module annular arrangement.*

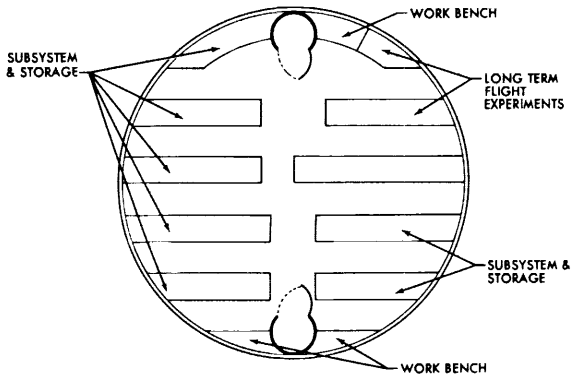

FIGURE 14.—*Subsystems module parallel arrangement.*

Since astronomical sensors would normally face away from the Sun, they would only be able to observe approximately one-half of the sky. However, as the space-station spin axis is precessed in accordance with the desire to maintain solar orientation, the sky that may be viewed is continually changing. During a period of one-half year, most of the sky would be available for observation. Sensors that are used to view the Earth present a different problem. In this case, separate sensors must be provided to view the dark and light sides of the Earth. However, only a few duplicate sensors will be needed, since it is likely that the sensors used for viewing the light side would be different from those used on the dark side. Thus, it can be seen that, although the rotating space station has some constraints as a platform for observation, these constraints constitute only a nominal penalty.

The space station under discussion provides rooms which may be as large in diameter as the Saturn V, which is approximately 33 feet in diameter. The efficient use of this size of room leads to an interesting layout consideration. The most efficient layout appears to be one wherein the various compartments, workbenches, and storage areas are laid out in an annular arrangement, such as that shown in figure 13. An alternate arrangement, however, would be one in which the various pieces of equipment would be laid out in a parallel arrangement, as shown in figure 14. The advantage of the parallel arrangement is that it provides the crew with a continual orientation as to the direction of rotation. This is expected to be important because the kinesthetic effects of moving along the axis of rotation, as opposed to moving perpendicular to the axis of rotation, will be different and may prove to be confusing and annoying if such effects are unexpected. The layouts of three other decks with space for control of the spacecraft, for laboratory work, for crew quarters, and for other activities are shown in figures 15 and 16.

Although extensive research has been carried out to assess man's ability to adapt to a rotating environment, little or no data exist where a wobble, a bounce, or other minor perturbing motions have been imposed onto the motion of rotation. It is obvious from the dynamics of a rotating space station that there may be a certain amount of such motion. The magnitude of wobble will depend on many things, such as the mass of space station and the degree of sophistication of the stabilization system used. The bounce or the springiness of the floor will

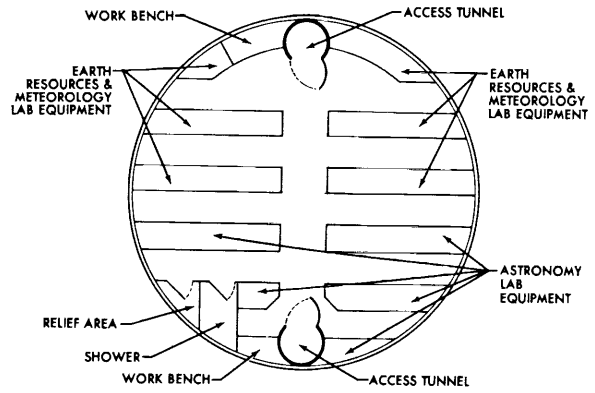

FIGURE 15.—*Laboratory module.*

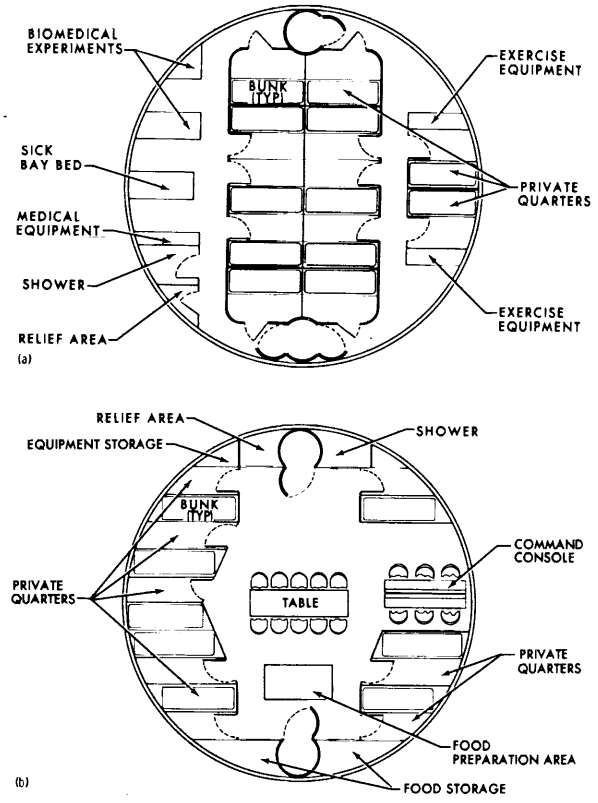

FIGURE 16.—*Crew quarters module.* (a) *Deck with biomedical facilities; and* (b) *deck with food facilities.*

depend to a great degree on the structural design. Normally lightweight, highly efficient structures tend to be elastic. Therefore, it is quite likely that the floor of the space station will be somewhat springy. The apparent pitching and heaving effects on the space station as one crewmember walks across the floor will depend to a great degree on the amount of attention the designer will give to such considerations. At this time there are no definitive standards to which a designer can refer. It would, therefore, seem appropriate that those who do research on motion sickness give some attention to the combined effect of such perturbing motions and of rotation.

Since all work on slow rotation has been carried out in the 1-g environment of Earth, the evaluation of the effects of a rotating environment has been limited. It is obvious that, prior to initiating serious design work on a large artificial-gravity space station, some realistic evaluations with artificial-gravity environment must be made in space. Such an evaluation can only be carried out by providing adequate and realistic living accommodations for the crew for a period of 1 or more weeks. It, therefore, seems appropriate to consider an artificial-gravity habitability experiment in Earth orbit. A possible

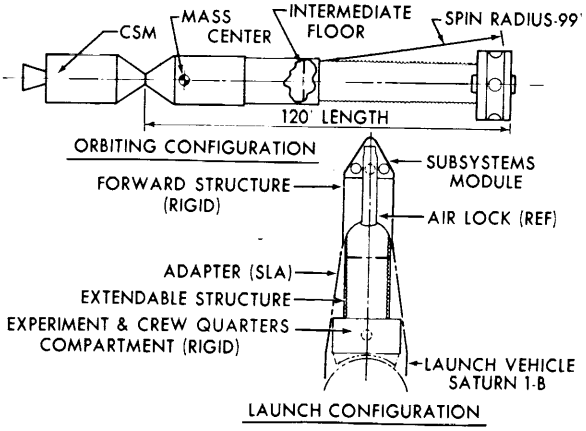

FIGURE 17.—*Artificial-gravity configuration.*

configuration for such an experiment is shown in figure 17. In this case, a separately launched artificial-gravity laboratory would rendezvous in Earth orbit with an Apollo command and service module. The main feature of this configuration is that it would accommodate various radii of rotation and various spin rates. A possible arrangement of the living quarters, which would be located at the maximum spin radius, is illustrated in figure 18. The drawing is of a 15-foot-diameter structure and indicates that such a size is adequate for evaluation of habitability in the artificial-gravity environment.

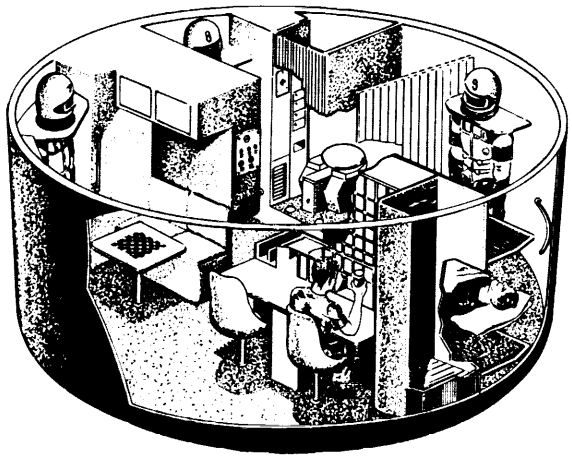

FIGURE 18.—*Living quarters compartment.*

DISCUSSION

KELLOGG: What did you have in mind in the selection of 0.01 g for the lower limit in a rotating space station?

FAGET: I did not have anything in mind; I was just quoting the manual. The same question has occurred to me. Why was such a low limit as 0.01 g chosen? However, it is in the NASA manual.

VON GIERKE: Would not these secondary effects you talk about, these dynamic effects, be of very low frequency? I mean, roughly with the rotation frequency?

FAGET: The wobble would be at the rotation frequency. The bounce unfortunately would not. The bounce would be a function of the design. Extra weight can be put into the structure to make all the major load-bearing members stiff and minimize the bounce. If the load-bearing members are designed just to take these loads, they get very slender. And if they are long, you can get a fairly annoying frequency. I would imagine the frequency could be somewhere between 3 and 4 cps to maybe ½ cps. I consider that an annoying frequency.

VON GIERKE: Did you make estimates as to what these frequencies would be for the designs you have?

FAGET: I am sure we have. The number I gave you is just my recollection of about where they fell; but I have no specific number I can give you right now.

BERGSTEDT: You did not mention what the circulation physiologists require. Are they satisfied with 0.2 g or do they ask for 1.0 g to keep up the strength of the heart for adaptation of the blood circulatory system?

FAGET: Who are the "they" whom you are referring to now?

BERGSTEDT: I refer to those who are studying the cardiovascular system. Are they satisfied with 0.2 g or do they ask for 1.0 g?

FAGET: What we have found up to this date is, of course, that after the missions, there was some effect in the circulatory system due to the fact that the man had been at zero g for a period of time. There was a deconditioning. Our experience has been that the time for recovery of conditioning is about the same for the men who experienced 3 and 4 days of flight as for those who have had, maybe, about 14 days of flight. To project a curve that appears to be leveling off at 14 days up to a year or two, I think we will all agree is a little bit tenuous. I would be out of my field to try to say we can identify anything. I am not sure, but my impression is that to fly at zero g for missions as long as 1 or 2 years is reasonable. We are right now studying some Mars missions where it is acceptable at this time to go with no g for this period of time. That does not mean no g and nothing else. There will be exercise machines and other things. There may be some attempt made to artificially induce the same effect of a g-field on the circulatory system by pressure changes and things of that nature, or perhaps we will carry a small centrifuge. These are the things that are current in the thinking that come to my mind.

GRAYBIEL: Are we to infer from what you said this morning that a fairly definite decision has been made to send aloft an orbiting rotating spacecraft?

FAGET: I wish I could say yes; I really do. I have a lot of enthusiasm for orbiting rotating spacecraft. And, of course, a number of people inside and outside NASA do, but there has been no such decision. Furthermore, there have not been any decisions to fly the experiment depicted in my last slide. These are things being studied and proposed, and I am hopeful.

PARKER: I would like to know the amplitude of the bounce; do you have any estimates of this amplitude?

FAGET: I am almost beginning to regret I brought it up. No, I do not. Again, these things are a function of the design. If we build a rather large space station, and it employs a really efficient structure (and these are the kind engineers like to build, light and efficient), then you get a lot of elasticity in the thing. It is hard to say how bad it will be until we have gone through an actual design, but if it is undamped and the frequency is the same at which you walk, then the amplitude

could build up. Apparently, you are asking me what we may run into, and I am asking you what is acceptable. We are at a starting point. That is all I would like to say.

VON GIERKE: I think once we know the amplitude, the frequency spectrum, the direction, and the approximate duration of these vibrations, we can make pretty good estimates with respect to their acceptability and their interference with various tasks.

WAITE: In response to Captain Kellogg's question about the 0.01 g mentioned in the NASA manual, this was computed as the minimum acceleration required to orient fluids against capillary action and for the removal of suspended solids from the atmosphere. It has nothing to do with the vestibular system.

DAVEY: In continuation of the problem of bounce, if I may be permitted a speculation, by analogy with some clinical problems we can give you a partial answer. Patients who have cervical spondylolysis very frequently have disturbances of gait and of ability to judge the position of their feet on the floor. It has been described as a feeling of being on a trampoline, an annoying experience. I am not quite sure just which of the long tracts are involved, it may be vestibulospinal, but nevertheless patients who have this disability find it a very disturbing and annoying thing. So if your bounce had a certain constancy to it, I think it would be very disturbing.

MELVILL JONES: It seems to me that of prime importance in connection with any kind of movement in a habitable platform is the predictability of that movement. I imagine the frequency range within which that predictability occurs is also important; but the predictability is the really important thing. In the parallel example of the rotating-room experiments on the ground, one can habituate, presumably because any given angular head movement relative to the body always generates the same response, whatever one's orientation in the room. Predictability allows auto adaptation or habituation. But in a rotating space station we know that one can only predict the response if the plane of movement is known relative to the plane of space-station rotation, and this makes prediction of response much more difficult. Now in connection with the secondary modes of vehicle movement which you mention, it can be shown that in natural life many body movements, such as stepping off a platform to the ground, are brought about entirely by preprogramed muscle activity. In this case, one must predict the entire neuromuscular activity associated with stepping to the ground. So it seems to me that if the vehicle movements are within the range of predictability in the biological system, the condition will be acceptable. But if there are coupled modes of action which introduce a sufficient number of, let us say, sinusoidal waveforms to make it appear to be unpredictable to the human, then serious difficulty will arise. Would you care to comment on this point?

FAGET: I think what you say is probably right. Of course, this is not an uncommon experience. There is nothing more disturbing than taking a step in the dark which you did not expect to take, and that is because of what you say. Also, I guess everybody gets his sea legs for the same reason. I think what you say is probably right, and probably it will be predictable, at any one part in the space station.

MONEY: In view of the risk of vestibular problems rotating at 3 rpm, if there is not in fact a cardiovascular problem which you are trying to overcome, why would you want to rotate a spacecraft at all?

FAGET: We have debated this. And to make it quite clear, there are very strong proponents of a zero-g space station. From an engineering standpoint, you can provide the same volume and the same amount of electric power and everything else in the zero-g station for less cost than you could in a rotating one. So it has that value. It is simpler. And for a special-purpose situation, it might be the thing to do. What we are talking about is a space station that is multipurpose and is flexible in concept, flexible in predicted operation. And what we wish to avoid is the situation wherein every time we wish to carry something new to do in that space station, we would have to go through the 2- or 3-year design period of making that a useful thing to do in a zero-g environment. We would rather just do it the same way we did on Earth, where we know that particular operation will work. There are a great number of secondary and tertiary procedures which are involved around the mainstream of that which you may wish to accomplish. These are all done by habit in 1.0 g. If you wish to carry out a rather complex series of tasks in zero g, you have to think about all the things that may be involved from the start to the end and make sure that you can indeed accommodate them in zero g. This is all right if you know exactly what you are to do ahead of time and you have the time to plan. So if we have a special-purpose space-station project that may have a planning period of probably 4 or 5 years before flight, during that time we can also accommodate all the planning that will be necessary to make sure that all the operations are feasible at zero g. But if we attempt something that is less well planned as far as the operational mode and is intended to be flexible, we think that the rotating environment with artificial g would be much preferred. There are other considerations such as just plain physical accommodations, comfort, things like that, which are brought in as arguments in favor of artificial g.

MONEY: Is there good reason to think that the 3 rpm will be less troublesome than zero g for what you have in mind, or for things, in fact, you do not have in mind but you might want to plan later on?

FAGET: Yes. We are, of course, dealing again in opinion. We have not had anybody at 0.2 g or 0.3 g at 3 rpm in any extended period of time. We have had people at zero g for periods of 2 weeks. These people have not had any trouble doing things as long as they were inside the spacecraft. But think of the kinds of things they were doing. They were not dealing with loose objects. They were dealing with everything that was in their immediate reach. They were firmly anchored to their seat. And in just about every respect we tried to anticipate their needs in zero g and provide for them; and we were successful. I guess what I am trying to say is that for multipurpose flexible utility, we would like to go to a more offhand mode. There is great controversy on EVA, as you know. How much of the difficulty was due to lack of preparation for an unfamiliar environment? I do not know. I think an analogy has been made by somebody else. It is perhaps like swimming. You may take an experienced

swimmer, and perhaps he has not been in the water for 5 or 10 years and is out of physical condition. You can throw him into a swimming pool, and he can stay afloat with very little effort. On the other hand, you may take someone that has not been in a swimming pool before ever in his life, but is in perfect physical condition. You throw him into a pool, and he wears himself out in 2 or 3 minutes because he just does not know what to do. We would like to end up with a situation where we do not have to train the people, where we would be able to accommodate a greater variety of experimenters and not have to end up accommodating for every particular task prior to flight. These are the arguments for an artificial space station. I think that is about all I can say for them.

MONEY: Even in the point of not having to train people, though, rotation at 3 rpm is quite a problem. You might require as much training for 3 rpm as you would for zero g.

FAGET: Here, again, we are dealing with opinion. Three rpm is three times as fast as the second hand moves around your wristwatch. I do not think very many people would have trouble accommodating to that. That is just opinion.

VON GIERKE: In any practical design, how much could you vary the rpm, once you are in orbit or in flight?

FAGET: From a design standpoint, the maximum rpm must be known ahead of time in order that the structure will withstand centrifugal loads. I will say quite frankly that at this time the loads associated with the centrifugal forces are not important loads. The loads associated with pressurization of the structure, the loads associated with launching and perhaps others are much more significant loads than those particularly associated with accommodating the centrifugal force once in orbit. So it is not very difficult during the design to accommodate the need for a higher-g field. I think we probably will do that. Beyond that, the other cost is in expendables to maintain a higher rpm, and these might be significant. It costs you something in propellants to initially spin it. All of our analyses indicate that while the thing stays in orbit, we would like to keep orientation toward the Sun. This means we have to pay for the cost of precessing its axis 1° a day, which mounts up, of course, to 360° during the year. This turned out to be a significant amount of propellant. Of course, the faster you are spinning, the higher the cost of precession will be.

VON GIERKE: But from your maximum rpm, you could regulate downward any time you want to?

FAGET: Yes; I would think so. Again, a word of caution here. I think once an rpm is decided upon, depending on how firmly we decide on it, we will probably design the dampers and stabilization system and the sensors and all to go with that rpm. To accommodate some range in rpm in a design would not be difficult. To be able to accommodate a wide variation in rpm and still provide suitable stability, suitable damping, I do not know the answer, but I anticipate it might be troublesome.

Transfer of Habituation on Change in Body Position Between Vertical and Horizontal in a Rotating Environment

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SUMMARY

The changing symptomatology manifested by four normal young subjects throughout the course of an experiment involving exposure in a slowly rotating room (SRR) was used in studying two derived phenomena: susceptibility to SRR sickness and transfer effects. The unique feature in the experimental design required the subjects to shift from either a start-horizontal or a start-vertical mode to the other mode at the middle of a 4-day perrotation period. To insure an adequate degree of comfort and a fairly comparable level of activity in the horizontal as compared with the vertical mode, the subjects were encased in articulated fiber-glass molds and supported on air bearings.

The findings indicated that susceptibility to overt symptoms of SRR sickness was similar in the two orientation modes. At the end of 2 days' rotation when habituation was complete, a sudden change in mode evoked trivial temporary sy nptoms of SRR sickness in two subjects but no symptoms in the other two. The fluid balance and excretory rates for the catecholamines and corticoids were not easily interpreted as a result of the added variable of dealing with both the vertical and horizontal body positions. With regard to postural equilibrium, rough estimates of habituation were made perrotation when subjects were in the vertical mode, and quantitative measurements prerotation and postrotation. In experiments where the subjects initially were in the start-vertical mode, initial difficulties (ataxia) in maintaining equilibrium largely disappeared by the end of the second day before the change in mode occurred. In experiments with subjects in the start-horizontal mode, difficulty in maintaining equilibrium was evident on change to the upright; i.e., transfer was poor.

An incidental finding of theoretical interest was the postrotatory perseveration of postural habituation to the rotating environment as long as 36 hours after the cessation of rotation during which time the subjects were restricted in their activity.

With the limitations of this experiment taken into consideration, the findings regarding SRR sickness indicate that habituation acquired in the Slow Rotation Room with a subject parallel to the axis of rotation transfers to the orientation with subject at right angles to the axis of rotation, the situation in a rotating spacecraft. Our findings with respect to postural disequilibrium indicate that simulation of spacecraft conditions in the laboratory will, at best, be poor, but that elucidation of the underlying mechanisms is possible.

INTRODUCTION

Previous reports from this laboratory have described the symptomatology and associated phenomena manifested by persons exposed in a slowly rotating room (SRR) which simulated in some important respects conditions in a rotating spacecraft (refs. 1 to 5). Nearly all of these manifestations were the result of Coriolis accelerations generated by bodily movements in the rotating environment. The symptoms characteristic of motion sickness had their genesis in the vestibular organs stimulated in a bizarre manner when the head was moved out of plane of the room's rotation. Difficulty in walking had its genesis both in the vestibular organs and in nonvestibular proprioceptor systems. Through the mechanisms of habituation and adaptation, the manifestations of motion sickness soon disappeared, and ataxia was greatly reduced unless the stressful stimuli were severe.

In two important respects, conditions in the SRR mentioned above did not simulate those in a rotating spacecraft. First, no attempt was made to simulate subgravity conditions, although the subjects were required in some experiments to remain near the center of rotation to minimize the level of centripetal force. This was a significant limitation, inasmuch as the influence of g loading on vestibular responses has been demonstrated beyond doubt (refs. 6 to 11), and evidence is accumulating that susceptibility to motion sickness is altered as a function of the gravitoinertial load.

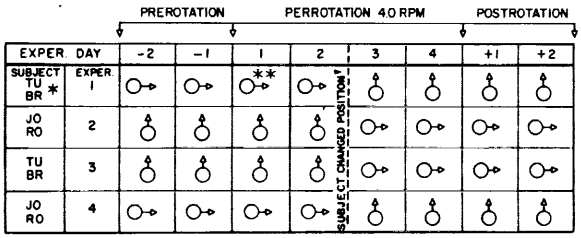
A second aspect not simulated is related to the difference in body orientation in the SRR where man is parallel to the axis of rotation when upright and that in the rotating spacecraft where he would be at right angles to this axis. This factor is important for two practical implications; namely, whether this difference affects susceptibility to side effects and whether there is transfer of habituation from one orientation mode to the other, e.g., between SRR and spacecraft.

In the experiment now to be described, a comparison was made between the effects of exposure in the SRR with man parallel and those when he was at right angles to the axis of rotation. Although exposure in the horizontal mode simulated to a small degree subgravity conditions, the present experiment did not feature this aspect. Rather, attention was focused on motion sickness, ataxia, and the phenomenon of transfer of habituation. An incidental finding involving homeostatic mechanisms is of scientific interest.

PROCEDURE

General Plan

Four subjects were divided into two pairs, and each pair participated in two experiments carried out over a period of 3 months. Experiments involving the same pair were separated by 35 days or more to minimize order effects. Except for the initial 5-day rotational trial, the period of rotation was 4 days in each of the experiments and was preceded and followed by control periods of 2 days. The level of stress chosen was sudden exposure to an angular velocity of 4 rpm which past experience indicated would evoke mild symptoms. One pair of subjects was first habituated to rotation in the start-horizontal mode, then changed to the vertical mode in the middle portion of the perrotation period; in their next experiment they were first habituated in the start-vertical mode. The order was reversed



* TU and BR spent 3 days in horizontal mode during perrotation phase in first experiment.

** When in the horizontal mode, during a 24-hour period subjects spent between 5 ½ and 6 ½ hours in the air-bearing device, between 6 and 10 minutes upright, and the remaining time on a bunk.

† Occurred around 0930 hours.

FIGURE 1.—*Design for exposure to stress in the Slow Rotation Room.*

for the second pair. The design dealing with these features is shown in figure 1 where the four experiments are listed in chronological order.

Exposure in the horizontal mode posed a difficult operational requirement because of the need to insure a degree of comfort and level of activity comparable to that provided the subjects when they were in the vertical mode. This was

accomplished by encasing the subject in an articulated fiber-glass mold and supporting him on air bearings at right angles to the axis of rotation; this would accord with his orientation in a rotating orbiting spacecraft.

The daily schedule of events and tests was as follows:

0730	Awakened. Urine collection, clinical evaluation, motion-sickness questionnaire
0830	Breakfast
0900	Clinical and behavioral tests
	Blood samples
	ECG and tilt-table test if subjects in vertical mode
	In middle of perrotation period, change in mode
	Forced head movements
	"Ball toss"
	"Reaction time"
	Hand steadiness
	Time estimation
	Hand dynamometer
1200–1400	Luncheon. Recreation
1400–1730	Behavioral tests; exercise if in horizontal mode
	Math test
	Logit
	"Panel test"
	"Cap screw test"
	Exercise
1730–1830	Free time
1830–2200	Dinner. Recreation
2200	Retire

Departure from this routine mainly involved free-time activities. Baseline measurements were made on prerotation day −2 (daytime only) and on day −1, and rotation began around 0930 on day 1. There was no interruption of rotation except momentarily in the third experiment when the emergency switch was pressed accidentally. Following cessation of rotation, tests and measurements were continued during postrotation day +1 and the daytime portion of day +2. A tight scheduling of events for the entire day was planned, partly to avoid boredom. Some of the "tests" were in effect tasks designed to keep the subjects occupied and moving their heads. Such tasks are indicated in the daily schedule by quotation marks.

Subjects

Four Navy enlisted men participated as subjects. A comprehensive medical evaluation revealed no significant abnormalities, and the pertinent findings are summarized in table 1. All had previously participated in experiments in the SRR and were practiced in the methods used, but none was aware of the goals of the experiment. The experimenters were DE, a physician 30 years of age, and RI, an assistant 45

TABLE 1.—*Clinical Findings in 4 Subjects*

Subject	Age, sex, health	Auricular findings					
		History of disease or injury	Auditory test (V. Békésy)		S–Canal Threshold Caloric [a]		Otolith C–R Index [b]
			R	L	R	L	Min of arc
BR.....	20 M Good	None	Normal	Medium notch at 6 kHz	36.4	36.4	337
JO.....	22 M Very good	None	Normal	Normal	36.0	36.2	289
RO.....	19 M Good	None	Slight notch at 4–6 kHz	Slight notch at 4–6 kHz	36.4	36.6	382
TU.....	20 M Very good	None	Normal	Normal	36.0	36.2	521

[a] In °C. Minimum reduction of exit temperature of water (irrigation for 40 sec) causing nystagmus.

[b] One-half the sum of the maximum counterroll on left and right tilt (up to 64° except BR 50°). Typical values, 240–480.

years of age. Both were above average in susceptibility to SRR sickness.

Rotation Device

The experiment was conducted in a circular windowless room 20 feet in diameter, 10 feet high, and without any central supporting members. It had a direct motor drive capability of controlled angular accelerations between 0.1 and 15.0 deg/sec^2, with maintenance of angular velocities between 2 and 200 deg/sec with an accuracy of ± 1.0 percent. Rotation was counterclockwise and continuous at 4.0 rpm, and the accelerations at onset and cessation of rotation were approximately 4.0 deg/sec^2. The 10 000-pound payload was more than sufficient to provide for operation in the "housekeeping mode" and for the air-bearing devices described below. The communications systems and bioinstrumentation facilities were not taxed in this experiment. A sample-ejector device permitted offloading of small objects during rotation.

Air-Bearing Device

The requirement was to provide decent living and working conditions with the subjects horizontal with respect to the axis of rotation. The main features were: (1) air-bearing supports for two subjects within articulated fiber-glass body molds insuring comfort and freedom of movement (fig. 2); (2) a level polished surface over three-fifths of the floorspace; and (3) a walkway on the wall (fig. 3) with exercise steps. That the requirement was, eventually, met was demonstrated by the absence of complaints of the subjects who spent approximately 6 hours a day in the air-bearing device (ABD) carrying out the required tests. During the remainder of each 24-hour period, they were vertical for 6 to 10 minutes and recumbent the rest of the time.

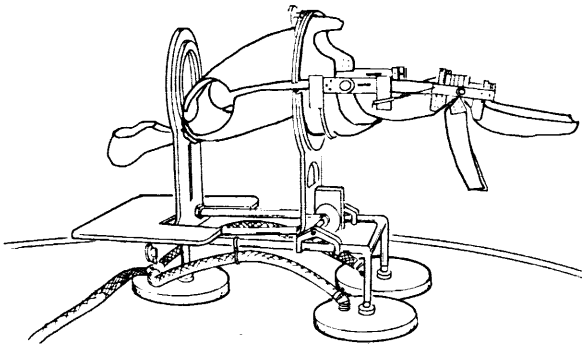


FIGURE 2.—*Air-bearing device supporting subject when horizontal to axis of rotation and allowing subject freedom to rotate about long axis, move head and limbs, and carry out required activities.*

Force Environment

A subject living in a rotating environment, such as that generated by the SRR, is subjected to a complex array of accelerations consisting of the acceleration of gravity, the centripetal acceleration generated by rotation, and the Coriolis accelerations generated by simultaneous motions of room and occupants. Except for the acceleration of gravity, all these accelerations would be upon an astronaut in a rotating space-

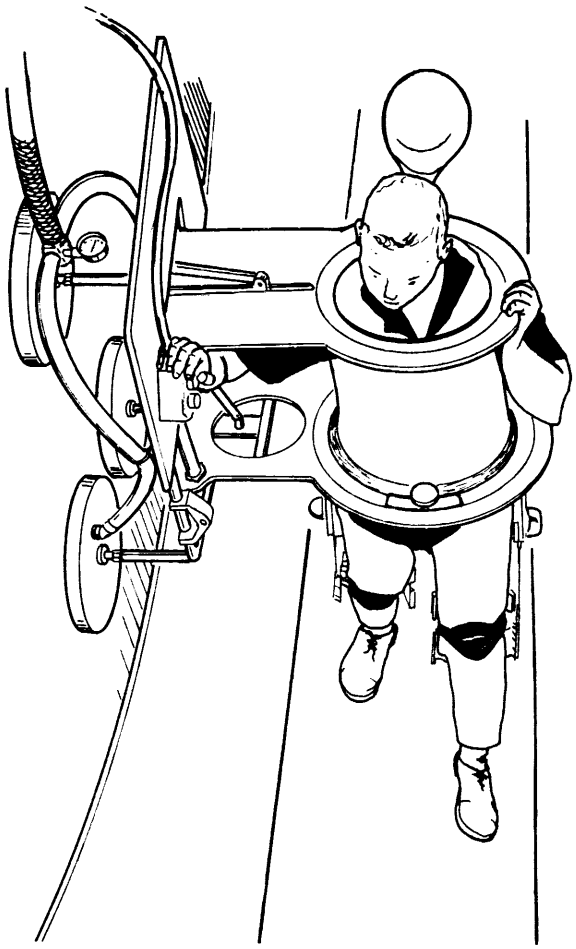


FIGURE 3.—*Subject walking in air-bearing device. Orientation accords with direction of "up-down" in long axis of body.*

craft. These accelerations will be discussed with emphasis on differences between man static and dynamic and between the horizontal and vertical modes.

Gravitational Force

The force acting on the subject opposing the acceleration of gravity of the Earth is an undesirable factor from the standpoint of this experiment; however, the use of the air-bearing device minimized the effects of this force along the long axis of the body for the horizontal orientation or fractional G.[1]

Centrifugal Force

This is the force opposing the centripetal acceleration of the subject's mass when he is constrained to a rotating environment. Centrifugal force derives from $r\omega^2$, where r = radius and ω = angular velocity; or, when expressed in G units $F_{CA_n} = 0.000341\ N^2 r$, where N = angular velocity of the room in revolutions per minute, r = radius of rotation to center of mass in feet. At 4 rpm the centrifugal force ranged from 0 at the center to 0.054 G at the periphery (fig. 4), where the gravitoinertial vertical deviated from the Earth vertical by approximately 3°. When the vertically oriented subjects were in a fixed position, they were scarcely aware of this inertial force, and it had negligible effects in terms of circulatory dynamics. In the horizontal mode with the subject supporting his mass through his feet touching the walkway and his Earth weight supported by the ABD, his center of mass was approximately 6 feet from the center of rotation, resulting in a centrifugal force at 4 rpm of 0.035 G. His static-position apparent weight was increased by the "weight" of the ABD, or about 5 pounds, and its center of mass was approximately 2 inches from his center of mass along the long body axis and approximately 12 inches from his center of mass across the short axes. For a 200-pound subject his centrifugal force weight under these conditions would be 7 pounds,

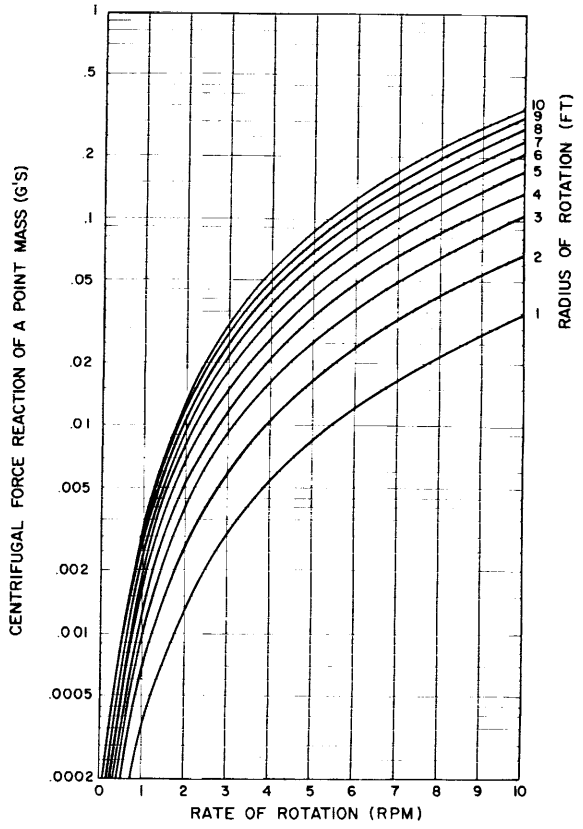


FIGURE 4.—*Centrifugal force reaction of a mass in a rotating environment. Force in pounds = Earth gravity weight* × G units.

plus the 5-pound ABD "weight," or a total apparent weight of 12 pounds.

Coriolis Force

In 1835, Gaspard G. de Coriolis, a French civil engineer, described the complete significance of the accelerations which apparently acted upon bodies as a result of the rotation of the Earth, and thereafter these "compound centrifugal" forces were known as Coriolis forces. The fundamental law relating the time rate of change of a vector, as measured by an observer in a space rotating with respect to the reference space, may be expressed mathematically by the vector equation:

$$\left(\frac{d\mathbf{V}}{dt}\right)_r = \left(\frac{d\mathbf{V}}{dt}\right)_m + (\omega_{rm} \times \mathbf{V})$$

where

$(d\mathbf{V}/dt)_r$ = change in velocity vector with respect to the reference space

[1] The capital letter, G, is used as a unit to express inertial resultant to whole body acceleration in multiples of the magnitude of the acceleration of gravity, g_0, which is 980.665 cm/sec² or 32.1739 ft/sec². Hence, Earth weight multiplied by the G units of any of the other forces acting on a subject gives the magnitude of the force.

$(d\mathbf{V}/dt)_m$ = change of velocity vector with respect to moving space

$(\omega_{rm} \times \mathbf{V})$ = change of velocity vector due to rotation of moving space

To a subject in the rotating environment, this acceleration or force vector may manifest itself in two ways. First, it adds to the apparent weight of a body moving with, or in, the direction of rotation and subtracts from the apparent weight when moving against the direction of rotation. Second, when a body moves toward the center of rotation, the Coriolis force is exerted in the direction of rotation at right angles to the body's motion; when moving away from the center of rotation, the force is opposite to the direction of rotation. A motion parallel to the axis of rotation will generate no Coriolis acceleration. The value of Coriolis acceleration in G-units for a body moving perpendicularly to the axis of rotation in a spinning system may be determined by

$$F_{(\text{Coriolis})} = 0.00651\ VN$$

where

V = velocity of body relative to rotating vehicle in ft/sec

N = vehicle rate of rotation in revolutions per minute

For any motion not exactly perpendicular to the axis of rotation, the component of the velocity that is perpendicular is used to determine the Coriolis force; hence, the value must be multiplied by the sine of the angle between the angular rotation rate vector and the velocity vector.

Figure 5 illustrates the Coriolis force in G-units for various rates of movement perpendicular to the axis of rotation at various rates of the room's rotation. The Coriolis force plus the centrifugal force influence the ataxia exhibited by subjects. From figures 4 and 5 it is apparent that at 4 rpm a person in the horizontal mode walking in the direction of spin at about 2 ft/sec reaches zero apparent weight and no traction results. When walking with the direction of rotation, a much higher walking velocity is possible. Also, moving toward the center facing against the direction of spin produces a tendency to pitch backward, and moving toward the periphery produces a tendency to pitch forward. These, of course,

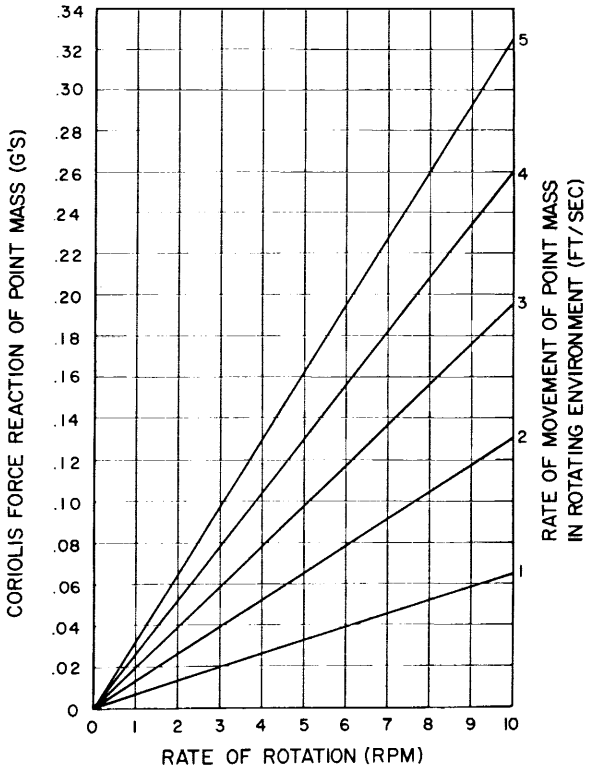


FIGURE 5.—*Coriolis force reaction of a mass moving in a rotating environment. Force in pounds = Earth gravity weight* × G *units.*

would be reversed when facing with the spin direction.

The semicircular canals are structured to respond to Coriolis accelerations with movement of the head out of the plane of rotation of the room (ref. 11). The changing patterns of Coriolis forces affecting the cupula endolymph system for the several canals associated with different head movements have never been calculated. Limited treatments involving different concepts have been presented (refs. 12 to 14). It is sufficient here to deal in terms of angular velocity of the SRR and "head movements." In this experiment the Coriolis forces were complicated by direct and indirect effect related to the subject's orientation.

Vestibular Stimulation in the Vertical and Horizontal Modes

It is necessary to make a distinction between fine and gross bodily activities. Fine movements include rotations of the head which gen-

erate stressful Coriolis accelerations stimulating the vestibular organs, but are otherwise relatively unimportant. Gross movements affect not only the vestibular organs but also nonvestibular proprioceptor systems which influence postural equilibrium and taxis.

With regard to the semicircular canals, the angular or Coriolis accelerations generated by rotary motions of the head would be the same whether a person was in the vertical or horizontal mode. Nevertheless, several factors may account for differences in response in the two modes. One factor is the so-called "free movement," i.e., rotation of the head in the same plane as the room's rotation, which does not generate stressful levels of Coriolis accelerations. The free movement when a person is upright is a right or left rotation; while in the horizontal mode, it is flexing motion in the plane of rotation. A second factor is concerned with the possibility that for comparable levels of Coriolis accelerations generated by head movements, the more stressful in terms of response would occur with the subject in the horizontal mode. A third factor deals with the possibility that the canals are directly influenced by the magnitude and direction of the gravitoinertial load. As indicated above, there is ample evidence of an influence, but it is not completely clear whether this is a direct effect, or a modulating effect via otolithic stimulation, or both.

With regard to the otolith organs, there is much evidence that their effects on behavioral responses are greatly influenced not only by their orientation with respect to the resultant force vector but also by its magnitude. In terms of their influence on egocentric visual localization of the horizontal, they contribute much when the subject is upright and less when he is horizontal (ref. 15).

Effectiveness of Simulation in the Present Experiment

SRR Sickness

Until validating observations have been made aloft, the degree of effectiveness will not be known. One aspect simulated quite accurately was the orientation of the canals with respect to the axis of rotation. The free movement might be a little more difficult to determine in a rotating spacecraft than in the SRR, inasmuch as the "floor" of the spacecraft does not provide the necessary orientation cue. The otolith influences would be different in the two conditions, and the role of each deserves investigation. It should be mentioned that in the SRR, the subject in the horizontal mode was restricted in types of movements to a greater degree than he would be in a rotating spacecraft, but to some extent this was controlled by exposing him in both horizontal and vertical modes in the SRR.

Ataxia

In the experiment with man vertical, the simulation was poor with reference to the subgravity conditions in the spacecraft. In the horizontal mode the subject was supported by the air-bearing device; postural equilibrium was never a problem when he was static. While he was walking, postural equilibrium was aided by the ABD; hence, simulation of spacecraft conditions was only fair.

TESTS AND RESULTS

General Health

This experiment involved four subjects and many experimental devices over a period of 3 months, and neither illness of subject nor breakdown of equipment faulted the experimental findings. The subjects were under the constant surveillance of the onboard physician, and, in addition to a brief medical evaluation each morning, certain routine determinations and special tests reflected the general fitness of the subjects. Routine daily determinations included body temperature, pulse and respiratory rates, blood pressure, urinalysis, and examination of blood films. These tests did not reveal any unexpected findings.

The results of tilt-table tests are of twofold significance, first as an indication of "deconditioning," and second, as a factor influencing performance in the ataxia test battery. Tilt-table tests were conducted daily when the subjects were in the vertical mode. Nine pulse-rate and blood-pressure readings were obtained during a 15-minute backward tilt 20° from the vertical with the subject's weight on his feet. The measurements were reduced to standard scores, and any change of two standard deviations from

the control values was considered significant. Two subjects manifested slight changes. On the first day of rotation RO had a slight rise in systolic blood pressure on tiltup, not accompanied by changes in diastolic pressure or pulse rate; this rise was noted on one measurement and its consequences were insignificant. On change in mode from horizontal to vertical during rotation, BR had a slight temporary fall in systolic and diastolic pressure the first day on tiltup and a slight fall limited to the systolic pressure on the second day; the consequences of these changes were insignificant. Slight changes in baseline levels in pulse rate were noted.

SRR Sickness

This term is used to indicate motion sickness occurring in a rotating room or similar device. Unlike turbulent conditions at sea or in the air, the stressful stimuli cease on fixation of the head with reference to the room, and a subject can, by this means, become symptom free, while remaining "susceptible." This makes it difficult to follow the precise course of habituation and adaptation. Consequently, in the present experiment, both the symptoms manifested in the course of daily activities ("incidental symptoms") and symptoms manifested in response to experimenter-paced head movements ("forced symptoms") were recorded with the aid of a motion-sickness questionnaire.

The response to experimenter-paced head movements was determined using a modification of the dial test (ref. 1). A "movement" consisted of a rotation or flexion of the head away from its usual position, with reference to the thorax, and return. Five different standardized head movements, not in the plane of the room's rotation, constituted a "sequence." The subject was required to complete either 50 or 100 sequences. A motion-sickness rating method (ref. 16, and A. Graybiel, C. D. Wood, E. F. Miller II, and D. B. Cramer, "Diagnostic Criteria for Grading the Severity of Acute Motion Sickness," Aerospace Med., in press) was used to indicate the level of severity of symptoms.

Clinical Signs and Symptoms

The findings are summarized in figure 6. Points on the curves indicate the severity of

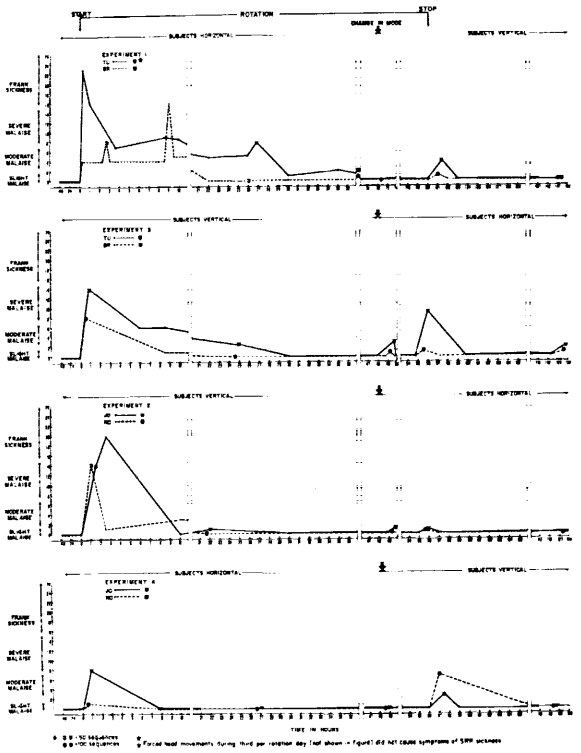


FIGURE 6.—*Changes in severity of clinical manifestations of SRR sickness as functions of length of exposure to 4 rpm, perrotation change in* mode, *and cessation of rotation. Points on the curve refer to "incidental" and squares or circles to "forced" symptoms. (See text.)*

incidental symptoms; if solid, circles or squares on the curves indicate the severity of forced symptoms resulting from 100 sequences of head movements; if half solid, they indicate 50 sequences.

Severe symptoms were experienced only during the first day of rotation. In the first experiment, BR's symptoms were aggravated by having him change from the horizontal to the vertical mode to perform an ataxia test, a test subsequently not repeated under this circumstance. Forced head movements, until the subjects were habituated to rotation, were an important factor in raising the level of severity of symptoms. At the beginning of the second day, perrotation symptoms were absent or inconsequential even during forced head movements, except in the case of TU.

All the subjects in all experiments were free of subjective symptoms and manifested no signs

of SRR sickness prior to change in mode during rotation. After the change in mode, even forced head movements did not evoke symptoms in experiments 1 and 4, and in 2 and 3 the symptoms were trivial.

On cessation of rotation, forced symptoms were insignificant except for TU in the third and JO in the fourth experiment, which were mild. Individual variations were demonstrated, TU and JO being the more susceptible members of the two pairs and TU more susceptible than JO.

A comparison between susceptibility to SRR sickness in the two modes is complicated by an order effect and, probably, by greater incidental activity in the vertical than in the horizontal modes. With these factors taken into account, the differences in susceptibility demonstrated were small. Transfer of habituation from one mode to the other during rotation was good.

Clinical and Biochemical Tests

Blood samples were drawn each day, and hemoglobins, hematocrits, and leucocyte counts were made. Total urine outputs were collected not only for routine testing but also for the determination of hourly excretion rates of 17-hydroxycorticosteroids (ref. 17) and the catecholamines, epinephrine and norepinephrine (ref. 18). Aliquots of the urines were stabilized at pH 1–2 and frozen for the analyses of these compounds at a later time. A record of the volumes of all fluids consumed was kept for each subject.

Fluid Balance

In figures 7 and 8 are shown the mean values for fluid intakes, urine outputs, hemoglobins, and hematocrits for all subjects with the same change in mode. It is seen that fluid inputs and outputs decreased and hemoglobin and hematocrit values increased significantly only when subjects were in the horizontal mode during rotation. Since a change in position was not involved, in the start-horizontal mode the alterations were probably attributable to vestibular influences as demonstrated in previous experiments (ref. 19). In the start-vertical mode, significant alterations appeared only after shift to the horizontal mode. If poor transfer of vestibular habituation was a

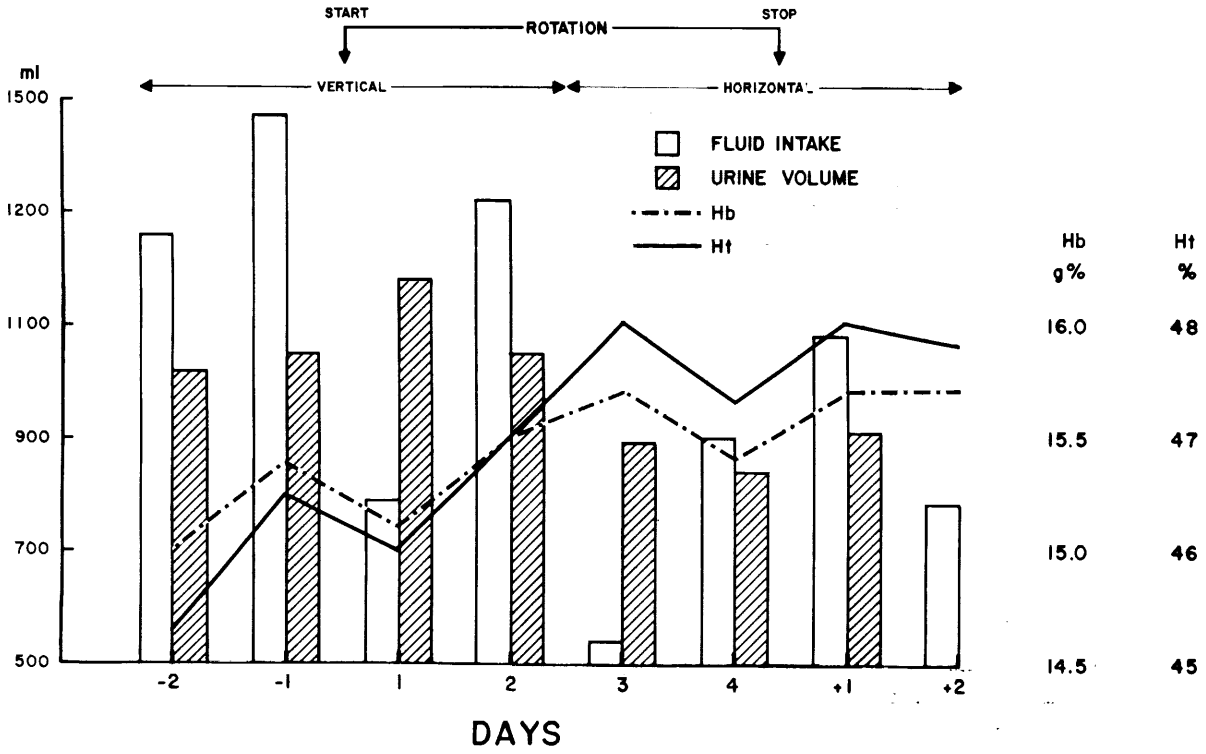


FIGURE 7.—*Comparisons between mean values for four subjects' fluid intake-output and changes in hemoconcentration during the entire experimental period in two start-vertical experiments.*

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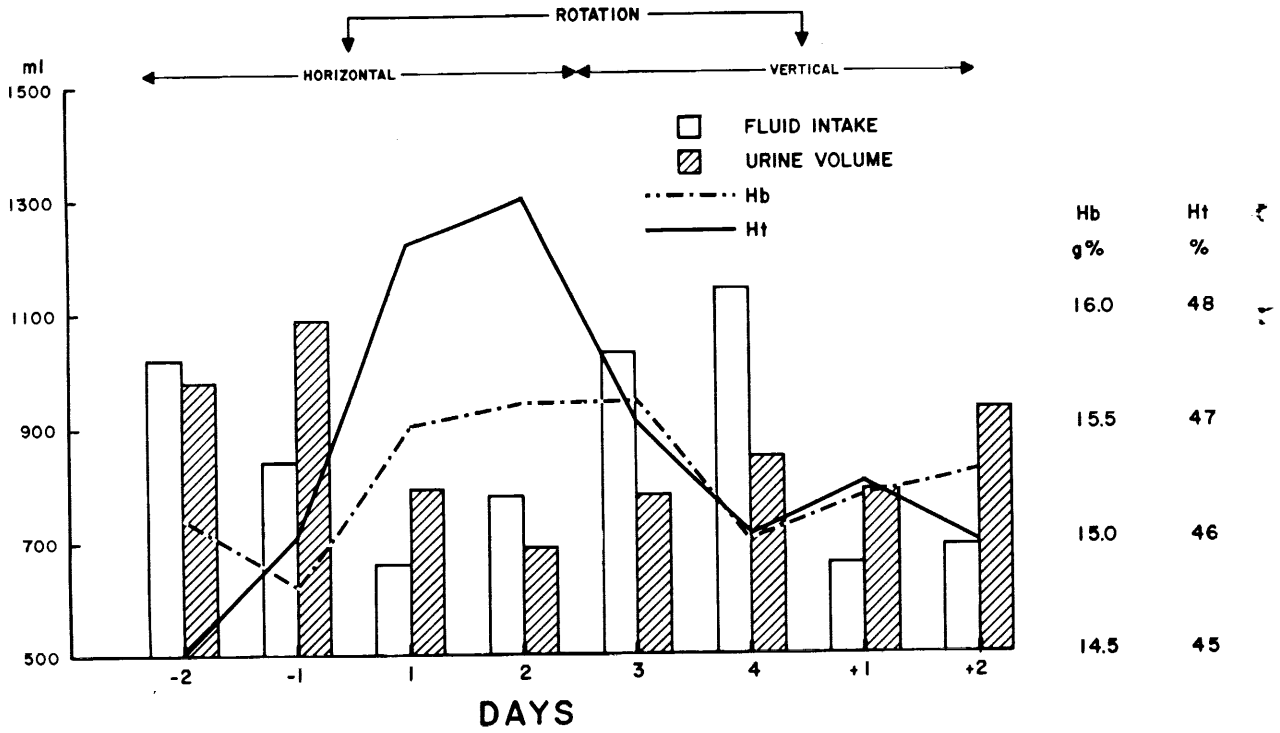

FIGURE 8. — *Comparisons between mean values for four subjects' fluid intake-output and changes in hemoconcentration during the entire experimental period in two start-horizontal experiments.*

contributing factor in these alterations, this would have interesting implications; e.g., the clinical signs and symptoms would have limitations as predictors of complete vestibular habituation. Although past experience (ref. 5) suggests that such a limitation is indeed demonstrable, the low level of stressful Coriolis accelerations in the present experiment renders vestibular influences an unlikely significant factor.

Catecholamines and Corticoids

Figures 9 and 10, respectively, show mean changes in the excretion rates of epinephrine and norepinephrine for all subjects in the start-vertical and start-horizontal positions. Change in body position from vertical to horizontal during rotation produced the most significant changes in excretion rates of the catecholamines. When body position changed from horizontal to vertical, there was no significant change in trend of catecholamine release; however, on the last day of the experiment a slightly elevated rate of catecholamine excretion was noted in the finish-vertical mode.

Corticoid excretion rates showed two well-defined peaks during the experiments when subjects initially were in the horizontal mode, one on the day of the start of rotation and one on the day before rotation ceased (fig. 11). Again, as with the catecholamines, the steroid response in the second set of conditions was less well related to a change in experimental conditions.

The vestibular influences which may have slightly affected the excretion rates are almost impossible to separate from other influences, partly because the vestibular influences were mild.

Psychophysiological Tests

Hand Dynamometer

A subject's daily score was the single best of three trials employing a standard model Stoelting hand dynamometer.

Performances became slightly worse during the first 2 days of rotation, improved slightly after body mode was changed each time during rotation, but did not change systematically after rotation ceased (fig. 12).

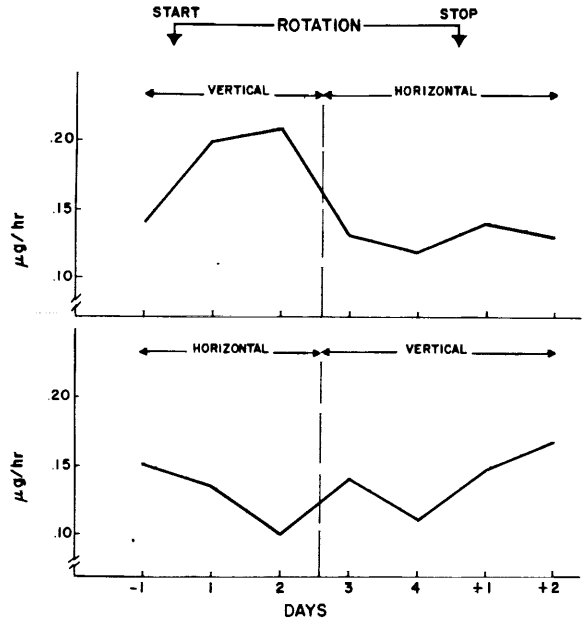

FIGURE 9.—*Mean changes in the excretion rates of epinephrine for four subjects throughout the entire experimental period.*

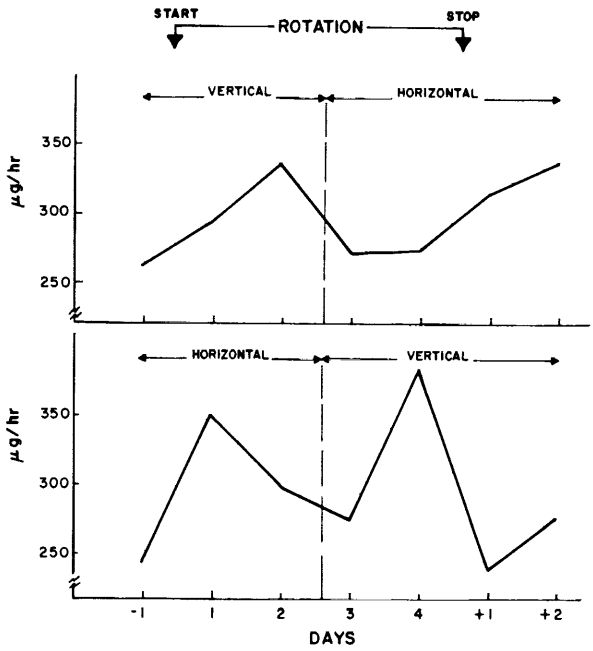

FIGURE 11.—*Mean changes in the excretion rates of 17-hydroxycorticosteroids for all subjects in the start-vertical and start-horizontal modes.*

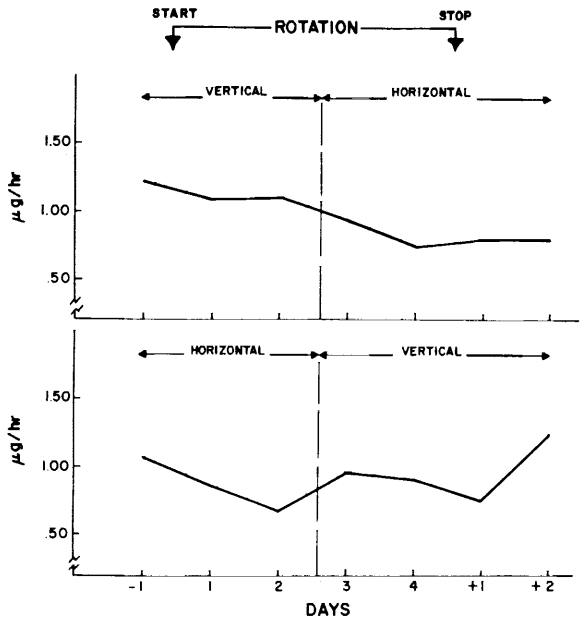

FIGURE 10.—*Mean changes in the excretion rates of norepinephrine for four subjects throughout the entire experimental period.*

Hand Steadiness

Drilled in a vertical aluminum plate 10 by 14 inches were three holes (0.250, 0.199, and 0.188 inch in diameter) into which subjects inserted a stylus 0.042 inch in diameter. The number of times the stylus contacted the sides of the holes was registered on a counter. Three 60-second trials were administered for each hole, and the mean of means constituted the score.

Some improvement was observed during the first 2 days of rotation in both the horizontal and vertical modes, but mean performances did not change systematically during the remainder of the experimental period (fig. 12).

Time Estimation (60 seconds and 10 seconds)

Subjects were required to depress a switch to activate a Standard Timer Model S–1. Five judgments were scored for each time period.

Sixty-second performances (time estimation, long) improved slightly during the first 2 days of rotation; they became worse after body mode was changed on each run during rotation, and performance again improved when rotation stopped (fig. 12).

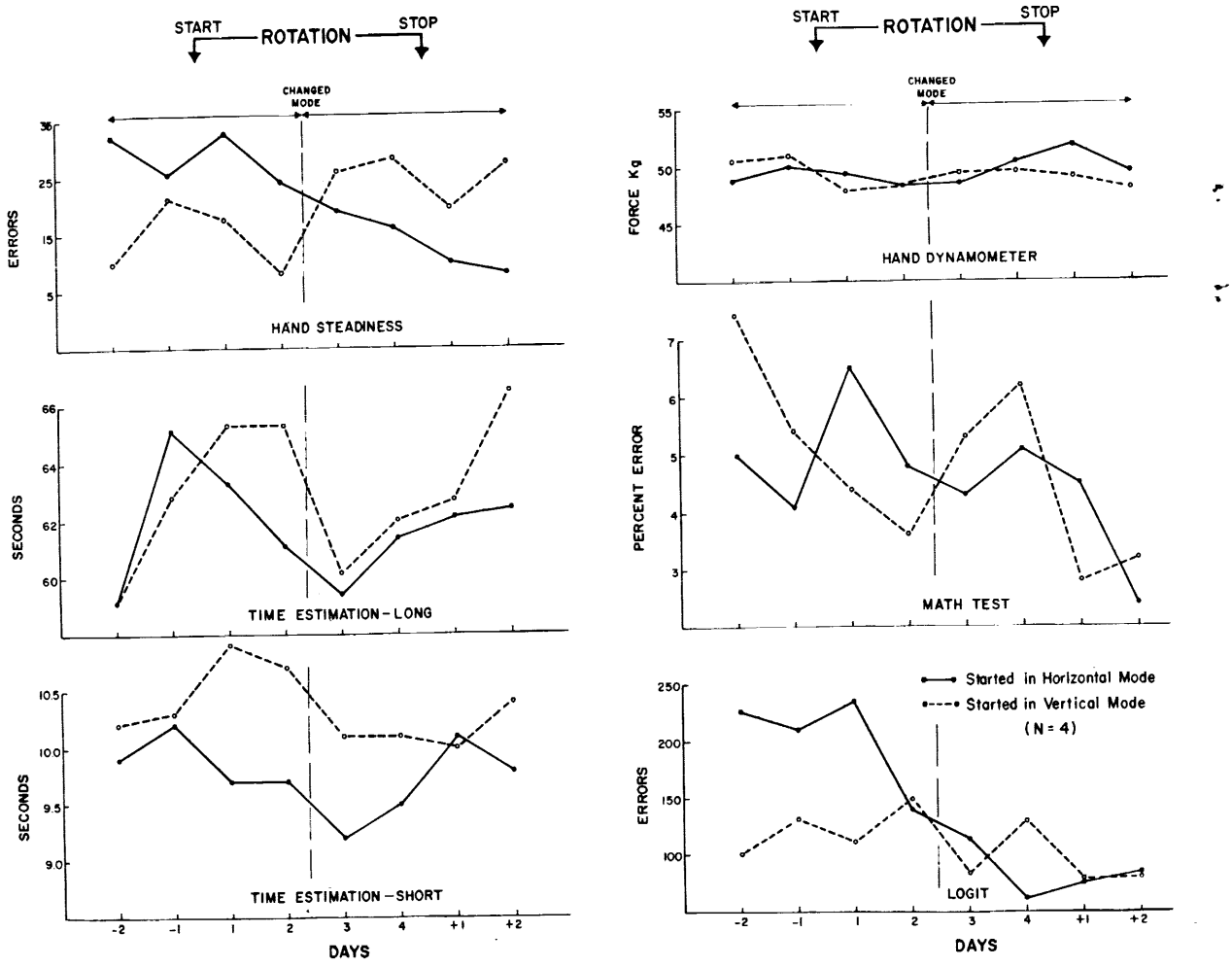

FIGURE 12.—*Changes in mean scores for all subjects in psychophysiological tests in the start-horizontal and start-vertical modes.*

Ten-second performances (time estimation, short) decreased slightly during the first 2 days of rotation but did not change systematically during the remainder of the experimental period (fig. 12).

Math Test

Four Nixie tubes displayed in a rectangular configuration were energized in pairs by a step relay. The subject placed his answers to variously difficult and randomly presented addition, subtraction, and multiplication problems by means of an electric adder. The 336 problems presented were scored in terms of errors.

Performances did not change systematically during rotation but improved considerably when rotation stopped (fig. 12).

Logit

The logical inference test (Logit) designed by French (ref. 20) was used to measure performance involving higher mental processes. The subject faces a console with 20 buttons arranged in 4 rows, which are illuminated when pressed. His task is to learn the order in which the button should be pressed to solve a particular "problem." The experimenter can program an almost unlimited number of problems and monitor the time required and extra buttons (errors) pressed.

Performances did not change systematically during the first 2 days of rotation, but improved slightly to considerably during the remaining experimental period as seen in figure 12.

Discussion

With practice effects and the expected day-to-day variation under controlled conditions taken into account, there appeared to be a slight decrease in strength of grip during the first 2 days of rotation. A slightly lower performance perrotation compared with postrotation was demonstrated in the Logit and math-test scores. There were no order effects; i.e., differences in scores between the start-horizontal and the start-vertical modes in any of the tests. These minimal differences in performances were not unexpected in the light of previous findings (ref. 5).

Postural Equilibrium and Locomotion

The original intention was to administer a quantitative test battery (ref. 21) throughout the entire experimental period, but the first attempt in the first experiment demonstrated that it was neither feasible nor desirable during the perrotation period when subjects were in the horizontal mode. Rough estimates, however, were made perrotation (vertical mode) whereas quantitative measurements were made prerotation and postrotation.

The ataxia test battery was administered in the following sequence: (1) Sharpened Romberg (SR), (2) Walk Eyes Open (Walk E/O) on a 3/4-inch-wide rail, (3) Stand Eyes Open (Stand E/O) on the 3/4-inch-wide rail, (4) Stand Eyes Closed (Stand E/C) on a 2 1/4-inch-wide rail, (5) Stand One Leg Eyes Closed (SOLEC–R and SOLEC–L), (6) Walk a Line Eyes Closed (WALEC), and (7) Walk on Floor Eyes Closed (administered simultaneously with the WALEC but scored differently).

Several days before onset of rotation, the subjects were tested on several occasions to establish plateau baseline performance levels. After cessation of rotation in the vertical mode, the subjects were tested 5.5 hours and again 29.5 hours later; after cessation of rotation in the horizontal mode, they were tested 36 hours later.

Results

All of the subjects were noted to experience difficulty in walking with the onset of rotation when in the vertical mode. This difficulty greatly diminished during the first day and was minimal on the second. At the time for change in mode there was no doubt that habituation and adaptation had occurred, although it was not demonstrated quantitatively.

The ataxia test findings on each of the four subjects (table 2) were highly representative of findings from the group as a whole as summarized[2] in figure 13. In making comparisons between postrotation scores when subjects were either "finish-horizontal" or "finish-vertical," differences between physical activities in these modes should be kept in mind.

Walking-test performances were less affected by rotation than standing-test performances. This differential result may reflect the fact that (1) the walking tests had less "top," i.e., were less difficult than the standing tests in terms of the ease with which maximum scores were obtainable; and (2) the process of walking afforded greater opportunity for rehabituation to the static environment. For example, on the first trial of the *Walk a Line Eyes Closed* and *Walk on Floor Eyes Closed* tests the feet swung and landed opposite to the intended direction on each step and almost caused the subject to sidestep, but only a few seconds later, or on the second or third trial, the subjects had quickly learned appropriate corrective maneuvers, permitting nearly total return of their locomotor coordination. On the standing tests return to normal via sensory-motor feedback mechanisms was more critically "hard won" by virtue of the more limited head and body motions required.

Characteristically, the subjects felt that their body balance had returned to normal long before the objective, stringent ataxia test procedures registered its return to normal.

There were no systematic order effects; i.e., results of initial exposure to rotation in the vertical mode did not differ essentially from results of initial exposure to rotation in the horizontal mode.

GENERAL DISCUSSION

The changing symptomatology manifested by the subjects throughout the course of this experiment was used in studying two associated or "derived" phenomena, namely, "transfer effects" and "susceptibility," which will be dis-

[2] Except *Walk on Floor Eyes Closed*, which did not change quantitatively.

TABLE 2.—*Individual and Mean Effects on Postrotation Ataxia After Habituation in Each of 2 (Vertical and Horizontal) Modes During Exposure to an Angular Velocity of 4 rpm on 4 Normal Subjects*

Ataxia test battery	Baseline scores					Rotation mode														
						Horizontal					Vertical									
						36 hr—postrotation					5.5 hr—postrotation					29.5 hr—postrotation				
Subjects	JO	RO	BR	TU	$\bar{\sigma}$	JO	RO	BR	TU	$\bar{\sigma}$	JO	RO	BR	TU	$\bar{\sigma}$	JO	RO	BR	TU	$\bar{\sigma}$
Sharpened Romberg[a]	207	240	240	237	231.0	80	179	187	240	171.5	122	204	[b] N.T.	N.T.	163.0	240	240	240	240	240.0
Walk Eyes Open on ¾-in.-wide rail	15	15	15	15	15.0	14	15	15	15	14.8	15	15	14	15	14.8	15	15	14	15	14.8
Stand Eyes Open on ¾-in.-wide rail	86	103	73	101	91.0	16	56	23	34	32.3	40	103	45	36	56.0	44	154	37	39	68.5
Stand Eyes Closed on 2¼-in.-wide rail	159	180	180	173	173.0	31	158	180	86	113.8	134	180	180	79	145.8	136	180	180	180	169.0
Stand One Leg Eyes Closed—R	146	148	135	149	144.5	62	150	150	113	118.8	150	150	N.T.	N.T.	150.0	150	150	150	150	150.0
Stand One Leg Eyes Closed—L	145	138	141	145	142.3	85	145	106	82	104.5	91	150	N.T.	N.T.	120.5	150	150	133	150	145.8
Walk a Line Eyes Closed[c]	12	11	9	10	10.5	6	4	8	16	8.5	18	9	34	9	17.5	10	2	6	7	6.3

[a] Standing, heel-to-toe on floor, eyes closed.

[b] Not tested.

[c] 12-foot length, on floor, heel-to-toe.

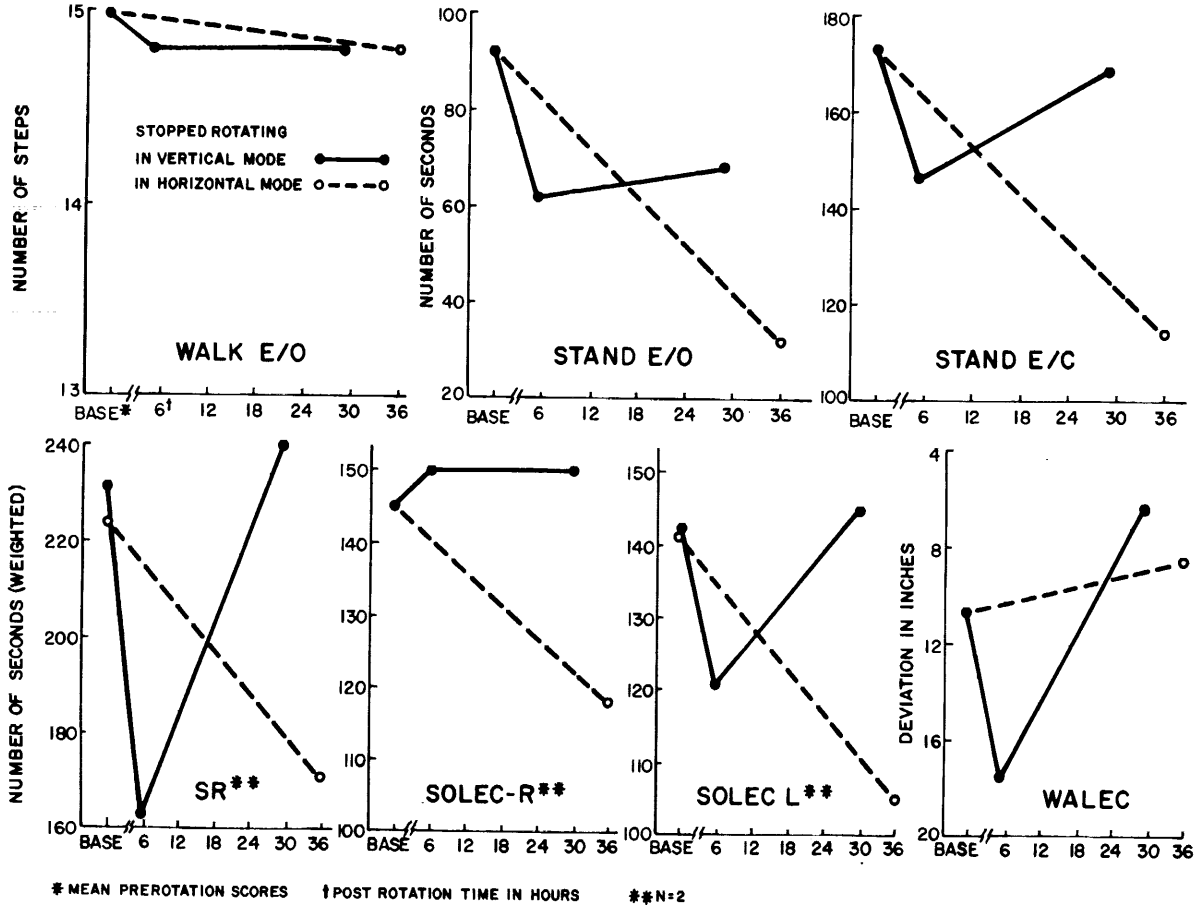

FIGURE 13.—*Mean effects on postrotation ataxia after habituation in each of two (vertical and horizontal) modes during exposure to an angular velocity of 4 rpm on four normal subjects. (See text for explanation of tests.)*

cussed in this order. In addition, the long postrotatory perseveration of postural habituation acquired during rotation deserves additional comment.

Transfer Effects

In designing and conducting this experiment, chief attention was given to the overt signs and symptoms of SRR sickness, and change in mode was not effected until the subjects were completely habituated and adapted, as evidenced by a disappearance of these symptoms and signs. The findings were clear cut in this regard; habituation in one mode transferred to the other. It is particularly noteworthy in the case of change from the horizontal to the vertical, the reason being that subjects in the horizontal mode actually remained horizontal for all but a few minutes of each 24 hours.

Inasmuch as the symptoms under consideration do not appear in persons who have lost vestibular functions, transfer effects have implications for the semicircular canals and otolith apparatus individually as well as collectively. In terms of the intralabyrinthine "conflict" theory as an important etiological factor in the causation of motion sickness, our findings would imply that the resolution of such conflicts not only is accomplished in the horizontal mode but also transfers to the vertical mode. Insofar as our orientation to the gravitoinertial vertical is concerned, the otolith organs function more accurately when man is upright compared with when he is in the horizontal position. Moreover, the influences and interactions involving cues from the visual and force environments concerning perception of extrapersonal space

demonstrate greater concordance when man is upright than when he is tilted rightward or leftward away from the upright (ref. 22).

It is also noteworthy that in experiments conducted in a rotating room with subjects upright, habituation acquired as a result of movements of the head in the frontal plane leftward 45° from the upright and return did not transfer very well to the same movement to the right (refs. 23 and 24). Insofar as we are aware, data points between the poor transfer just described and the findings in the present experiment where transfer was good have not been determined.

Our findings have practical significance in terms of habituating astronauts under terrestrial conditions for exposure aloft in rotating spacecraft insofar as the overt signs and symptoms of SRR sickness are concerned. Also, within the experimental limits mentioned above, it justifies the extrapolation of findings obtained in earlier SRR experiments to conditions in rotating spacecraft.

The complication introduced by changing man's orientation from one mode to the other introduces a variable that makes it difficult to determine, in this experiment, transfer effects with regard to excretion of catecholamines and corticoids and possibly release of vasopressin which might have affected fluid balance.

Just as our findings were clear cut regarding transfer effects in connection with overt symptoms, they were almost equally clear cut with regard to postural disequilibrium, but in the opposite sense. Clearly, the "disturbing variables," to use Mittelstaedt's terminology (ref. 25), were not the same. Walking and standing involve nonvestibular proprioceptor mechanisms as well as vestibular ones, and whatever habituation was acquired walking and "standing" in the horizontal mode either was incomplete or, if complete, transfer was poor. Although taxis is not so important an operational problem as SRR sickness, nonetheless elucidation of the underlying mechanisms is of practical importance in the preparation of astronauts for exposure to rotation environments aloft and is also of theoretical interest.

Homeostasis

The finding of greatest scientific interest was the perseveration of postural habituation to the rotating environment long after cessation of rotation. The general phenomenon had been noted previously (refs. 1, 5, and 24), and the desirability of designing an experiment with this objective in mind was recognized. Although the chief objectives of the present experiment did not include a study of this phenomenon, the design afforded a good opportunity for a pilot study. Although only few data points plotting postural habituation were obtained, this does not lessen the significance of the phenomenon observed from a qualitative standpoint. In short, it was demonstrated that for at least as long as 36 hours after rotation ceased, the "rearrangement" involving posture and locomotion established during rotation was preserved. The shorter perseveration in the finish-vertical compared with the finish-horizontal mode, seen here as well as in past experiments, proves the importance of standing and walking in habituating again to the stationary environment. Stated differently, habituation in this case was not lost "spontaneously" on cessation of rotation, at least in the period of observation. It was not an example of the disturbance of a system in equilibrium simultaneously generating a reaction tending to restore the original state and carrying with it the implication of impaired reserve. Rather, it is an example of adaptation to rearrangement of sensory input establishing a new state conceivably as satisfactory as the one it replaced. This would apply equally well to habituation involving SRR sickness, but the difference may be explained by the muscular activity required in standing or walking. Held and Rekosh (ref. 26) have demonstrated that when the visual field is displaced by means of prisms (disturbing variable), habituation does not occur if only passive corrective movements are observed. The important omission in effecting homeostasis involves the initiation and execution of active movements. Stated briefly, a comparison between the message sent to the muscles and the observance of its effects constitutes the essential mechanism in adaptation. The Slow Rotation Room is an excellent device to explore some of the elements in a theoretical model, inasmuch as critical variables can be systematically manipulated.

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DISCUSSION

HENRIKSSON: Dr. Graybiel's presentation very clearly points out the fact that vestibular habituation is different on different levels and on different parts of the vestibular reflex arc. From previous experiments also we know that the habituation of nystagmus is direction specific and, further, that the pattern of habituation of nystagmus differs from that

of sensation. By 10 caloric irrigations we can wipe out all vestibular sensation, while nystagmus, although diminished, will still be present. This is in contrast to a peripheral vestibular nerve preparation of a frog in which you will have no habituation at all even with long-lasting stimulations. Dr. Graybiel's study is very important in pointing out also from a more practical point of view the different kinds of habituation.

GRAYBIEL: Dr. Guedry carried out an experiment some time ago in the Slow Rotation Room in which subjects were required to move the head toward one shoulder and back to the upright until there was a decline or disappearance of the initial Coriolis nystagmus. There was little transfer of habituation to the unpracticed side; i.e., on moving the head toward the other shoulder. On cessation of rotation, flexing the head toward the shoulder on the practiced side evoked nystagmus of opposite sign in some subjects. This was termed a "conditioned compensatory response." Nystagmography was not done in this experiment; a rotation speed of 4 rpm is rather low to evoke a Coriolis nystagmus on moving the head. Past experience suggests that ordinary activities involving a sufficient number of head movements in different planes relative to the room's rotation will result in habituation in all planes. How many discrete planes of rotation might be required has not been studied insofar as I am aware.

BENSON: The question I want to ask Dr. Graybiel is about the conditioned inhibitory response which was revealed when the subjects came out of the rotating environment. Did the group who started off in the horizontal position have a higher incidence of motion-sickness symptoms than the group who started off in the vertical position, and, also, when they came out of the room have mild symptoms of motion sickness?

GRAYBIEL: Yes. I am glad you brought that up. When you take into consideration all of the differences between experiments in the start-horizontal and start-vertical modes, I am not sure that we could say too much about the differences between the two modes in susceptibility to motion sickness. The subjects themselves felt that they would a little rather be horizontal than upright. About all we can say is that the differences in susceptibility between the two modes were not great. I am glad you brought up the matter of symptoms after cessation of rotation, which I slighted in the presentation. Subjects in the finish-vertical mode probably moved about more than in the finish-horizontal mode, thereby increasing their predisposition to symptoms when systematic head movements were made. Only the two more susceptible subjects experienced symptoms to any significant degree.

MELVILL JONES: I have three points to make. First, one would expect there to be difficulty in generating correct vestibulo-ocular reflexes for image stabilization during quick head movements. Is there any evidence that this is the case? Second, both in the case of standing erect in the Slow Rotation Room and in the real case of a rotating satellite, one is constantly making *active* effort to balance. But this presumably is not the case with your subjects having body constraint and "horizontal" support. Do you think this absence of active postural control in the new situation would be a significant factor? Perhaps, for example, one might attribute their subsequent difficulty in balance to this factor.

Third, there are, of course, two essentially conflicting requirements here; namely, alinement of the long axis of the body, on the one hand, with a horizontal radius and, on the other hand, with the resultant force vector, i.e., apparent gravity. In these experiments radial alinement was chosen, necessarily implying, I presume, at least 60° misalinement with the apparent direction of gravitational field. I imagine this would seriously prejudice the ability of a subject to feel he was "right way up." Perhaps it would be worth trying to split the difference between the two conflicting requirements and tilt the subject at, say, 30° to the horizontal so that he lies midway between the two required alinements. This could be arranged by making the floor appropriately conical. Presumably the sensed errors in alinement would both be "cosine errors," so that possibly a fairly realistic impression could be created by such a trick. Do you think this would be a sensible suggestion?

GRAYBIEL: Those are certainly all good points. We did not attempt to do visual acuity studies; this is something that might well be done. At 4 rpm, however, I am not sure they would have very much trouble. We have rotated subjects at much higher angular velocities, and they did not complain in terms of their ability to read and carry out tasks requiring vision while moving their head.

With regard to your second question, undoubtedly "walking" in the horizontal mode was aided by the supporting frame, but skill required practice; they had to learn to walk along the wall. I had anticipated that they would do a little better than they did on change from the horizontal to the vertical mode during rotation. The transfer of vestibular habituation involving motion sickness was not a good indicator involving taxis. I think you are right in believing that active postural control is a factor.

In regard to your last question, we thought of using cloth screening to see if we could aid their sense of feeling that they might be upright while they were walking. Your suggestion of "splitting the difference" might be a very good one but difficult to carry out. Increasing the apparent weight might do it.

YOUNG: I have a brief practical question relating to the possible application to a rotating spacecraft. The habituation times that you showed on most of the functions were of the order of 1 to 2 days, it would appear. Is it too early to speculate whether these would be the habituation times you might find following launch of a space vehicle until the men felt comfortable walking about in a rotating spacecraft? As a corollary to that, to what extent do you feel that pretraining, with a 1-g bias such as in the rotating room, might speed up this habituation process when it was performed in space?

GRAYBIEL: In all likelihood, prelaunch preparations would insure that astronauts exposed to 4 rpm in a rotating orbiting spacecraft would not experience symptoms of motion sickness. This might be accomplished by a gradual increase in velocity of rotation or by such other means as selection, training, habituation, and even drugs. In the

present experiment, conditions were not loaded in favor of the subjects, rather the reverse, in order to determine whether habituation in slow rotation rooms would transfer to conditions aloft. At this point it might be safe to conclude that ground-based experience will prove to be valuable before going aloft.

Display Monitoring in a Rotating Environment[1]

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General Dynamics, San Diego

INTRODUCTION

When the first of these symposia was held 2 years ago, many of us who were conducting experiments to determine man's tolerance to rotating environments left the meeting stimulated to find out more about the importance of subject positioning. The factor of concern was that studies then being performed (ref. 1) had the subjects with their spines almost perpendicular to the plane of spin which would result in side-to-side head turns being in the plane of spin rather than perpendicular to it. Nodding motions, on the other hand, were primarily perpendicular to the plane of rotation which theoretically produces maximum vestibular stimulation from cross-coupled accelerations. In a rotating space platform, head turns from side to side would be perpendicular to the plane of spin and, consequently, could be anticipated to provide considerably greater cross-coupled acceleration than that observed under the simulated conditions being studied on Earth. In space the nodding motion could vary from being in, to being 90° out of, the plane of rotation.

To our study group, the questions were:

(1) How serious is the experimental artifact due to subject positioning?

(2) Is it possible that this artifact can be quantified in terms of decreased crew performance and in terms of the physiology involved?

[1] This study was sponsored by the Manned Spacecraft Center under NASA Contract NAS 9-5232.

[2] For complete details of experimental procedures, the reader is referred to the final report for NAS 9-5232, NASA, Manned Spacecraft Center, Houston, Tex., entitled "Study of Performance in a Revolving Space Station Simulator as a Function of Head Rotation About Y and Z Axes," Nov. 21, 1966.

METHOD[2]

A previous study, performed in our laboratory as a pilot investigation, suggested a possible approach that could be used to assess this artifact (ref. 2). The simulator which we use revolves about a remote axis; it is an 8- by 4-foot floor area suspended at an 18-foot radius and is trunnioned so that the floor can be positioned normal to the resultant force. Figure 1

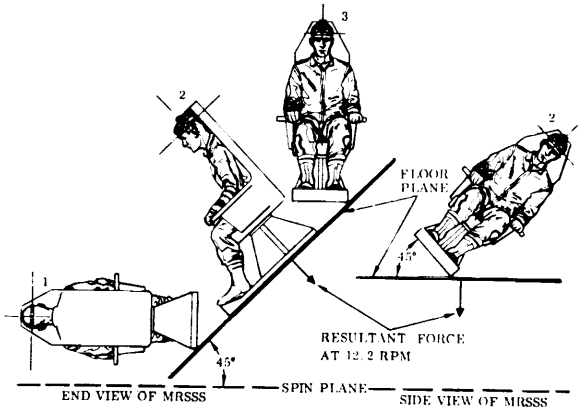

FIGURE 1.—*Orientation of subjects in the Manned Revolving Space Station Simulator (MRSSS). (From ref. 7.)*

depicts the subject orientation within the simulator inclined at a 45° angle. When the simulator is spun at a 12.2-rpm rate and the floor is inclined at 45°, the resultant of the centripetal and gravitational vectors is perpendicular to the floor; the effective radius is then 20 feet. When a subject is placed in a chair inclined 45° to his left, it is possible, by simply rotating the chair about its central axis, to orient the man so his spine lies in the plane of spin or perpendicular to it. All intermediate positions

give planes of alinement between the perpendicular and the "in-plane" position. When the man is alined radially with his head toward the center of rotation, as seen in position 1 (fig. 1), nodding head turns are then made in the plane of spin, and side-to-side motions will be perpendicular to the plane of spin. This is a position similar to the orientation of a man in space when he is facing either the forward or trailing bulkhead of a revolving station. In position 2 the man is facing the center of rotation; his spine is then 45° from the plane of spin, and both his nodding, which we will call Y-axis head turns, and his side-to-side head turns, which we will refer to as Z-axis head turns, are at an angle of 45° to the plane of spin. The third position depicted in figure 1 shows the man with his spine perpendicular to the plane of spin, similar to the position within on-the-Earth-based simulators used at Pensacola and General Dynamics when he is rotated at low angular velocities. Here, the Z-axis head turns are parallel to the plane of spin, and the Y-axis head turns are perpendicular to the plane of spin. Figure 2 summarizes the

SUBJECT ORIENTATION TO MOTION	POSITION	BETWEEN SPINE AND RESULTANT	BETWEEN HEAD TURN PLANE AND SPIN PLANE	
			Z AXIS	Y AXIS
Forward	1	45°	90°	0°
Backward	3	45°	0°	90°
Toward Center of Rotation	2	45°	45°	45°

FIGURE 2.—*Orientation angles as functions of subject position. (From ref. 7.)*

subject orientation of these various positions, and it should be pointed out that the angle between the spine and the resultant acceleration is constant; that is, it is 45° off the apparent vertical at all times. We feel that this is an important control factor; in all positions the relation between the otolith and semicircular canal is consistent, and the variable of concern is the resultant cross-coupled accelerations produced by the man's head turn and centrifuge rotation in each orientation. The 12.2-rpm speed is necessary to provide the correct vector alinement of resultant forces. We do not believe it would ever be necessary to provide such a high rate of rotation for the purpose of producing artificial gravity in space. It should also be pointed out that the positioning of the man was selected to provide uniformity in the cross-coupled acceleration being produced. In all positions the cross-coupling resulting from head turns results in an apparent roll sensation. The $Z_{90°}$ and the $Y_{90°}$ orientations produce a pure roll, and these can be compared directly. The 0°-interplanar angle between head turn and the plane of vehicle spin produces no cross-coupled acceleration for either Z or Y, as both head and vehicle motions are in the same plane. The Z and Y head turns at 45° have roll plus a pitch and a yaw cross-coupled component, respectively.

The experiments which we have been performing during the past 2 years to assess this artifact of positioning and to determine its significance upon vehicle design criteria can be generally grouped into three basic experiments. The inclined chair and the subject-simulator alinement just described was used in all of the three experiments. Figure 3 depicts the restraint

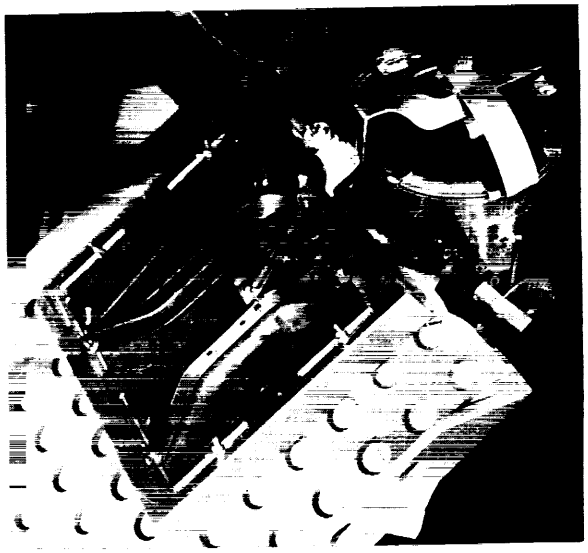

FIGURE 3.—*Head-restraint system. (From ref. 7.)*

system used to insure proper head alinement in the plane being studied. It consists of a supporting truss attached through a circular ball-bearing race, to a rubber headpiece to restrain the Z-axis head turns; these head turns were limited to magnitudes of 70°. Y-axis head turns required an adjustable tilt point to allow the subject to make comfortable nodding motions. All head turns were restricted to 70° of arc.

The degree of freedom not being used was locked at midpoint. Considerable adjustment in this restraint is required because of the anthropometric differences between subjects and the way in which they turn their heads. This restraint system was common to all of the three experiments to be described.

PROCEDURES

Experiment 1

Figure 4 shows the interior of the simulator

FIGURE 4.—*Inclined chair with the LOGIT. (From ref. 7.)*

and the chair. The purpose of experiment 1 was to determine the effect of rapid head turns in each of the planes of concern upon the man's performance capability immediately following such a rapid head turn. The LOGIT (Logical Inference Tester) (ref. 3) was used as a performance test, and head-turn rates were measured by the use of potentiometers mounted at each of the turn axes. The LOGIT test consists of 20 buttons which must be pushed in the proper order for each button to remain illuminated. All erroneous buttons turn off whenever a button is depressed that is earlier in the sequence than those pressed in error. Both total responses and correct responses are recorded automatically. The subject memorized the order in which the 20 buttons should be pushed and was able to identify and correct whenever errors were made. Each subject was trained until he achieved a constant performance level. Ten head turns were made in each position; each turn was followed by a test period of 15 seconds, after which the subject returned his head to the resting position for 20 seconds. A signal light indicated when he should turn his head and start the test. This arrangement was done with the signal on the subject's left and the console on his right for side-to-side or Z-axis head turns, and for Y-axis head turns the console was placed in his lap and the signal light placed above his head.

Experiment 2

In experiment 2 the purpose was to determine what the physiological mechanisms were that caused the performance degradation observed in experiment 1. Subjects complained of difficulty in seeing the task and a fuzziness in vision following the head turns. The task then appeared to be one of correlating amount of nystagmus produced by the various interplanar head-turn angles with the associated performance degradation. The LOGIT console, however, requires eye movements to scan over an area of approximately 1 square foot. This in itself gives a sufficient amount of eye movement to obviate interpretable nystagmographic recordings. A second performance test called the RATER (Response Analysis Tester) (ref. 3) was used because the presentation to the subject could be modified to provide a single point display upon which he could fixate. The RATER, shown in figure 5 as it is usually used, was

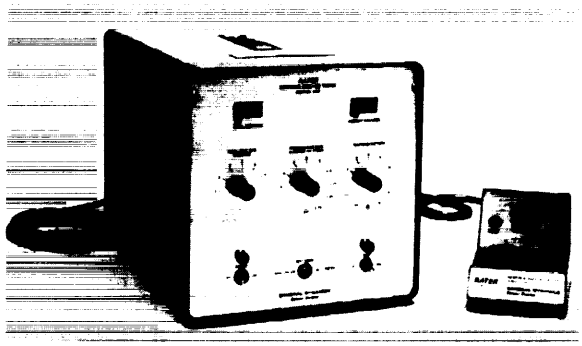

FIGURE 5.—*Response analysis tester (RATER).*

altered so a collimated display was presented to the subject with a visual angle of 1°, and the four response buttons were altered so they could

be operated remotely and placed in the subject's lap (fig. 6). The RATER presents four different

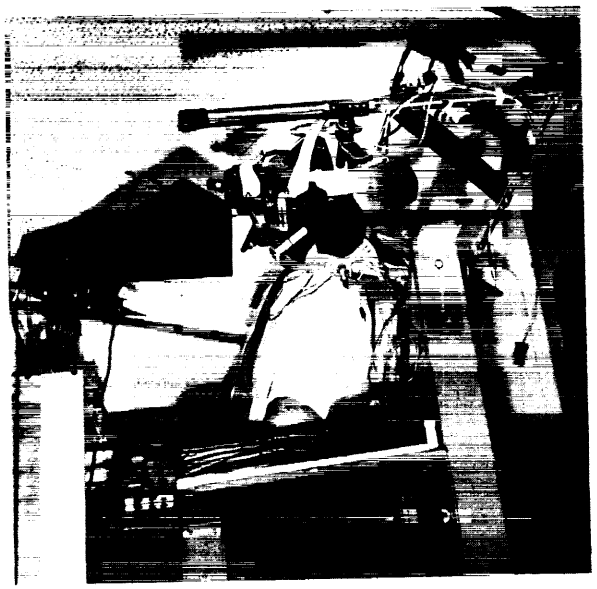

FIGURE 6.—*Collimated RATER display.*

colored lights in random sequence; each color is represented by one of four response buttons. When the correct button for the color being presented is pressed, a new colored light appears to the subject. The object of the test is to make as many correct responses in the time period allowed as possible without errors—as the score is the number of correct responses minus errors. Again, subjects were practiced until the score was consistent. Beckman electrodes were used to obtain both horizontal and vertical oculomotor recordings with a paper speed of 5 millimeters per second and a sensitivity setting of 100 microvolts per centimeter. These recordings were AC and made with eyes open in the subdued light of the cabin.

The nystagmograms indicated that the problem of visual fixation was not due to nystagmus alone, but also to a leading eye movement or anticompensatory response which has been previously described in the literature (refs. 4 to 6). The task then became one of determining whether a correlation existed between such eye movement at the various planes of head turns and performance degradation. This was accomplished by modification of a Westgate eye motion camera so that it could be mounted upon the head-restraint system and precisely fixed to the subject's head by means of a bite bar (fig. 7). The principle of the Westgate camera

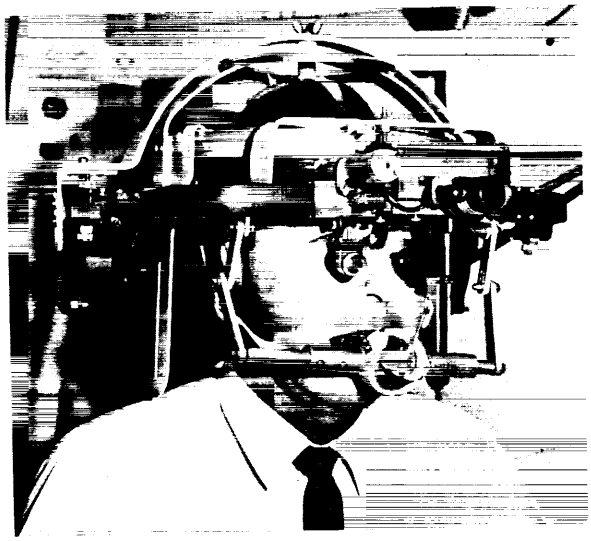

FIGURE 7.—*Eye camera modification.*

is to photograph the field of regard at which the subject is looking and simultaneously expose the film to a point of light reflected from the surface of the subject's eye. A bright spot of light is focused upon the subject's left eye, and the reflection (the first Purkinje image) is conducted by means of a prism onto the backside of the film photographing the area of regard. It is then possible to calibrate the system and determine where the subject is directing his gaze at any instant. Eight subjects performed all the tests with the RATER in both the Y- and Z-axes for each of the positions described in experiment 1.

Experiment 3

Experiment 1 indicated that the least performance decrement occurred following Y-axis head turns and in that position where the subject was facing tangentially in the direction of spin; it was necessary then to determine how such a position would affect the "reach" response of the subject. The RATER test was again used for experiment 3. However, now the head was fixed in a constant position and the RATER display was as seen in figure 8. The response buttons were placed along a bar which could

FIGURE 8.—*Experimental arrangement for the reach experiment.*

be rotated through 90°. Reaching motions made in a pure radial fashion, which appears to be the optimum display positioning from the results of experiments 1 and 2, should theoretically cause the greatest arm deflection problem from Coriolis forces. The purpose of experiment 3 was to compare accuracy of reach motions when button arrangements were spread 12 inches, 24 inches, and 36 inches parallel to the axis of vehicle rotation (apparent horizontal position) with the radial (apparent vertical) arrangement. The experiment was performed twice, once with the subject striking 1-inch buttons with his index finger and the second time, for a more sensitive test, with the subject inserting a ¼-inch-diameter probe through a ⅜-inch hole to depress the button.

RESULTS

The detailed results of experiment 1 have been recently published (ref. 7) and are only briefly mentioned in order to define the objectives of experiments 2 and 3. Figure 9 depicts the performance degradation following head turns of various interplanar angles, and it can be seen that performance falls off as had been anticipated from earlier theoretical considera-

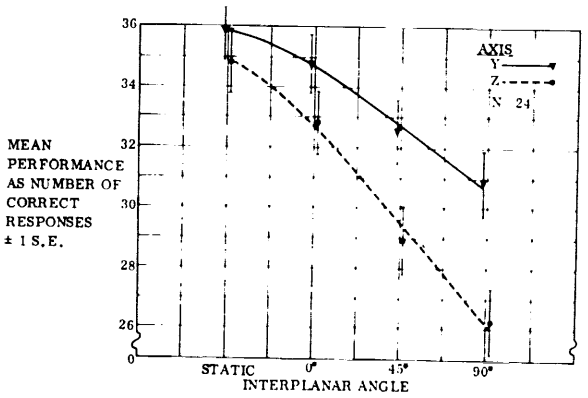

FIGURE 9.—*Performance as a function of interplanar angle. (From ref. 7.)*

tions (ref. 8). At the $Y_{0°}$ position (0° interplanar angle) the man is oriented as he would be in the space station facing the leading bulkhead, while the $Y_{90°}$ position corresponds to that wherein the subject's spine is parallel to the rotation axis as in the simulator, and the latter orientation is seen to be more detrimental to performance than the space station situation. There is a continual degradation in performance as the head turn angle is increased out of the plane of spin. Z-axis head turns in the 0° interplanar angle represent the situation as it would be on an Earth-based simulator. Again, performance degradation continues at almost linear fashion as the interplanar angle is increased to 90°, producing a very significant decrement in performance. At this position, the man is oriented as in an artificial-g space station. The difficulty encountered in the $Z_{90°}$ orientation is also reflected in the mean time that the subjects took to make head turns. In figure 9 it is seen that as the interplanar angle is increased, so is the time required to make the head turn. A quite significant difference exists between the Y and the Z head turns times the 90° interplanar angle.

In the orientations used for this experiment, the Y-axis head turns appear to be less detrimental to subsequent performance than do the corresponding Z-axis head turns. Though this appears to be in disagreement with what was previously reported by Stone and Letko (ref. 9), the results are not actually comparable. As was pointed out earlier, both the Y- and the Z-axis head turns at 90° in this experiment were made with an apparent roll resulting from cross-

coupled accelerations. In the Stone and Letko experiments the subjects in the $Y_{90°}$ position were facing perpendicular to the tangential orientation of this experiment which produces an apparent yaw from a nodding motion, Y-axis turn, and an apparent pitch from the Z, side-to-side, head turn. This emphasizes the importance of considering the resulting cross-coupled accelerations produced in a rotating environment rather than just the position of the subject.

When the data are plotted by individual performance scores for each of the 15-second trials (fig. 10), it is seen that adaptation of some

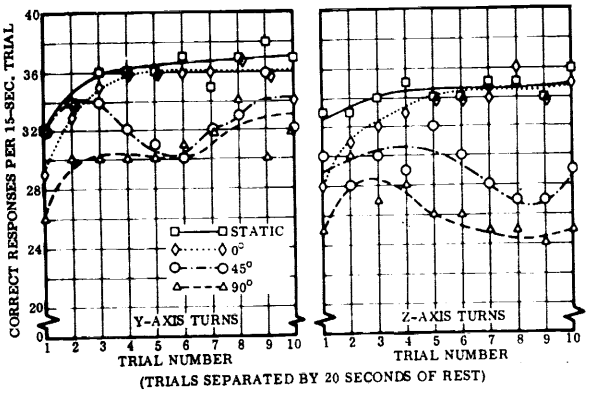

FIGURE 10.—*Performance change upon repeated head turns.*

sort is taking place during each test. In the Y-axis head turns, effective adaptation appears to be possible for all of the planes considered. However, in the Z-axis turns, considerable performance degradation was taking place at 45° and 90° interplanar angles even during the latter trials of the test. It is in these positions that the subjects express feelings of the greatest disorientation and impending stomach disturbance.

From the subjects' complaints of difficulty in fixating on the performance test console, it was hypothesized, as previously mentioned, that considerable nystagmus was taking place. The experiments were repeated with 12 subjects using the RATER as a performance test device with the results shown in figure 11. The results for Y-axis head turns compared with the Z-axis head turns are essentially the same for the RATER as for the LOGIT test device used in experiment 1. This is the third performance study we have made

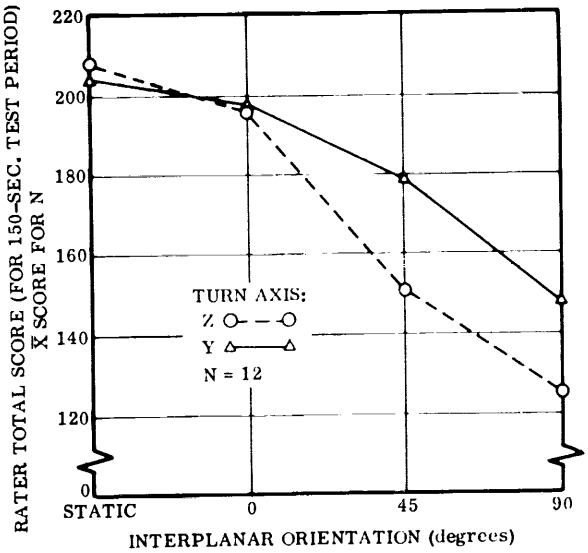

FIGURE 11.—*RATER performance as a function of subject turn axis and orientation.*

with the Z-axis orientations of 0°, 45°, and 90° out of the plane of spin (ref. 2), using essentially three different test formats. The ratio of performance decrement observed in all three from $Z_{0°}$ to $Z_{90°}$ compared to $Z_{0°}$ to $Z_{45°}$ is 1.6. This may indicate the magnitude of the artifact involved when extrapolation is made from the simulator testing results to the actual space conditions for degradation due to Z-axis head turns.

The nystagmograms, however, were not as had been expected. Figure 12 shows the vertical and horizontal eye movements of one subject during the period of testing. The deflection in the top horizontal line indicates the test period, and during this period visual fixation appeared to limit the amount of nystagmus. Following the testing with the head turned back to the resting position, however, considerable nystagmus was observed. It therefore appeared that nystagmus was not the principal factor for limiting performance. There was, however, consistent large amplitude eye movement during the beginning of each test period. When the total number of degrees of eye movements were measured and plotted as shown in figure 13, it was seen that the Z-axis test performance was accompanied by more oculomotor activity than the Y-axis test performance and that the

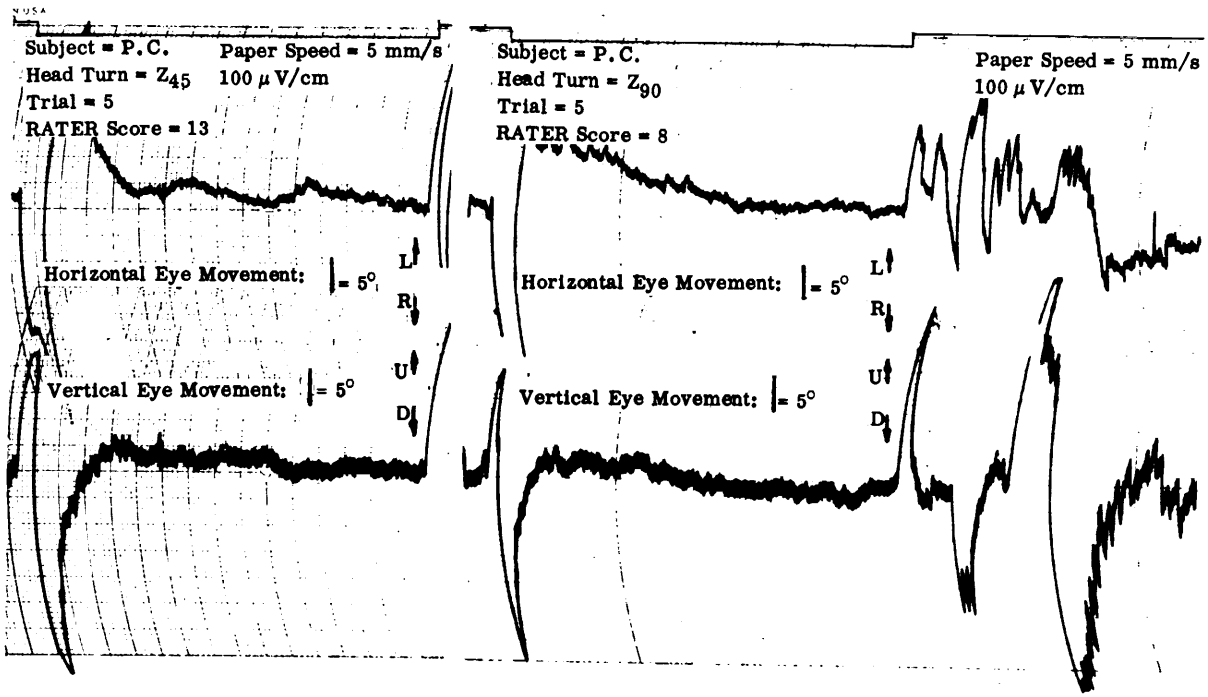

FIGURE 12.—*Horizontal and vertical eye movements of one subject during period of testing.*

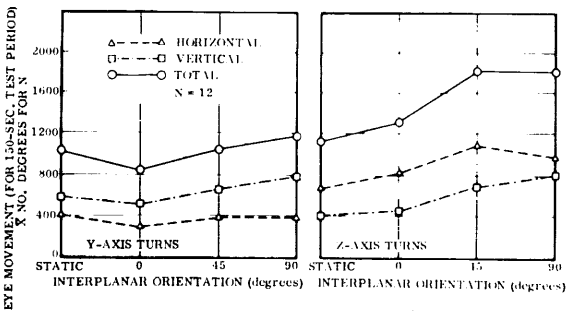

FIGURE 13.—*Eye movement as a function of subject turn axis and orientation.*

activity was predominantly horizontal eye movement. The RATER provides a response latency signal that records a downward sweep for each correct response that is made. The representative electro-oculograms shown in figure 14 indicate that the subjects did not begin responding correctly to the test until these large, horizontal eye motions had ceased.

The past-pointing test of Bárány is dependent upon the judgment error from the faulty interpretation of vestibular signals. This is common for a rotating environment, and it would seem logical that past looking might be a corollary of this phenomenon. The hypothesis then was that a head turn would cause the subject to look past the point at which he wished to fixate (refs. 5–7), and if this were under the control of the vestibular and visual kinetic drive, it would be reasonable that it would be affected proportionately to the vestibular signal or stimulation resulting from the cross-coupled effects.

Photographs of the eye spot and area of regard were made on each of eight subjects making the head turns and performing the RATER task as was done previously. Eye position relative to the target was plotted, and it was found that the leading eye movement occurred to some extent in all positions. Its amplitude and time duration correlated directly with the extent of performance degradation as it was related to the turn orientation. It appears from figures 15(*a*) to 15(*c*) that the exaggerated leading eye movement becomes progressively more disorganized as the stress of the head turn is increased and that recovery time for the subject increases directly as the performance is degraded. Figure 16 is a plot of the fixation time in seconds for the eight subjects observed. *Z*-axis head turns were more susceptible to this past looking following the rapid head turns than the *Y*-axis head turns, and this appears to be a reasonable explanation for the

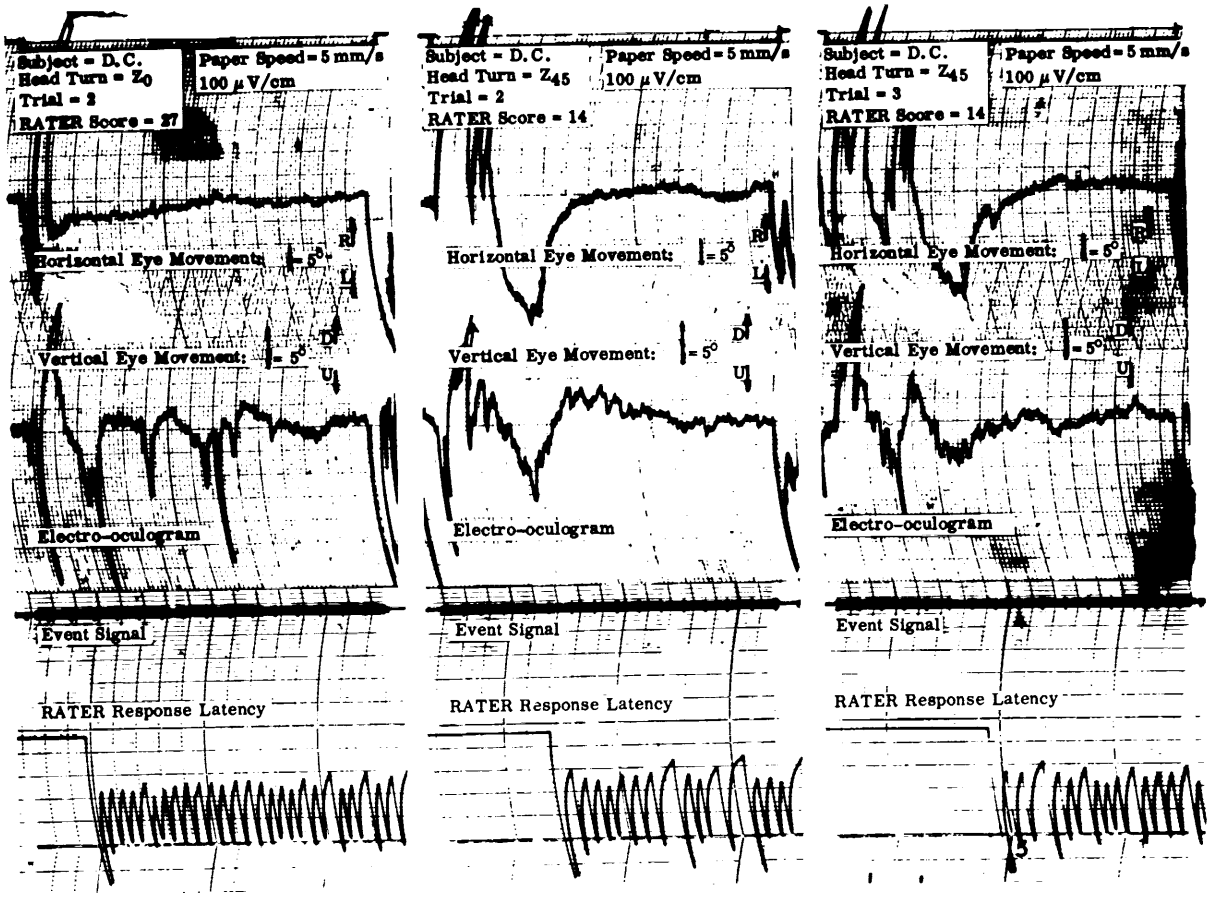

FIGURE 14.—*RATER response latencies and electro-oculographic recordings indicating difficulty in visual fixation.*

performance degradation following the more stressful head-turn positions.

The previous experiments had demonstrated that the *Y*-axis, or head-nodding, motions would be the optimal arrangement for display orientation. To avoid confusion in control, however, it is usually desirable to have a control placed close to the associated signal display indicator. If the display in a revolving spacecraft is to be oriented along the apparent vertical, this will require hand motions in a radial direction. It is this direction of arm movement which has been anticipated to cause the greatest displacement problem from Coriolis accelerations. Contrary to this, control movements requiring hand motions which are parallel to the floor or along the apparent horizontal, being parallel to the rotational axis of the spacecraft, should cause the least Coriolis displacement. To assess the magnitude of this possible complication, four subjects again performed the RATER task; this time, however, pressing the response buttons required their reaching horizontally or vertically as was previously described. Figure 17 depicts the results of that experiment. The buttons were arranged over a 12-, 24-, or 36-inch range for each of the positions under consideration. There were differences in scores among the various ranges of arm movement; it took longer to tap buttons spread over a 36-inch span than it did over a 12-inch span. However, at none of these ranges was there any significant difference between the scores achieved in the horizontal and vertical reach. It was felt at the end of the first test that perhaps the buttons being used were too large and that the task was too easy.

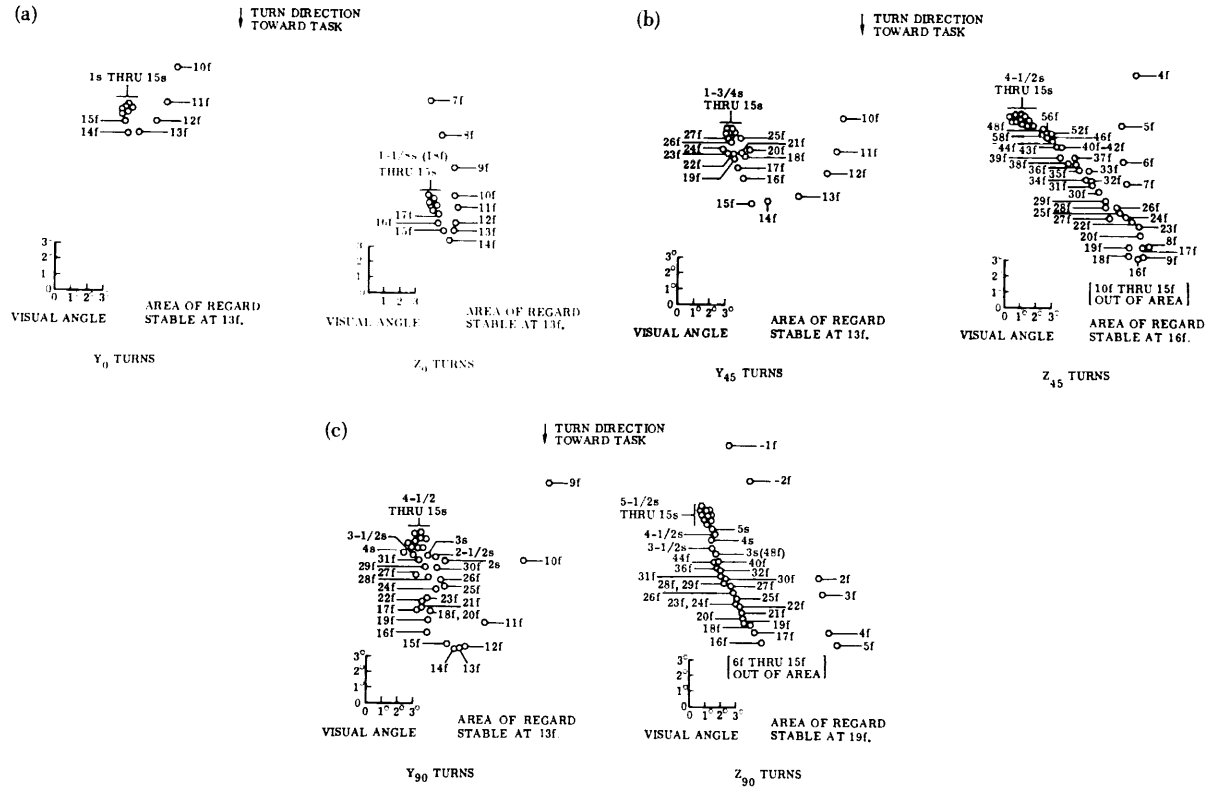

FIGURE 15.—*"Past-looking" resulting from the cross-coupled accelerations induced by head turns at 12.2 rpm.* (a) $Y_{0°}$ *and* $Z_{0°}$ *turns;* (b) $Y_{45°}$ *and* $Z_{45°}$ *turns; and* (c) $Y_{90°}$ *and* $Z_{90°}$ *turns.*

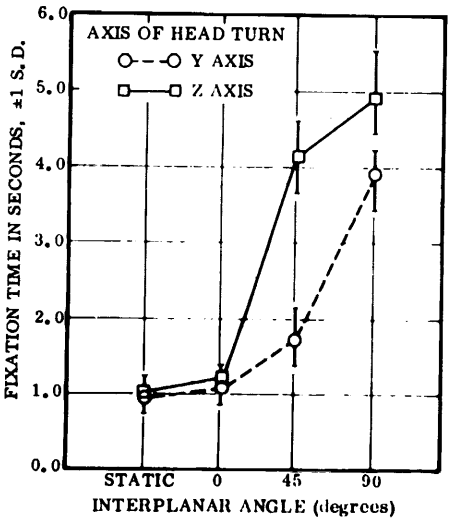

FIGURE 16.—*Eye-fixation time as a function of head-turn plane. Time measured from beginning of subject's head turn to fixation of eye movement within ±0.5° of visual angle. Values are mean times for all trials for the eight subjects observed.*

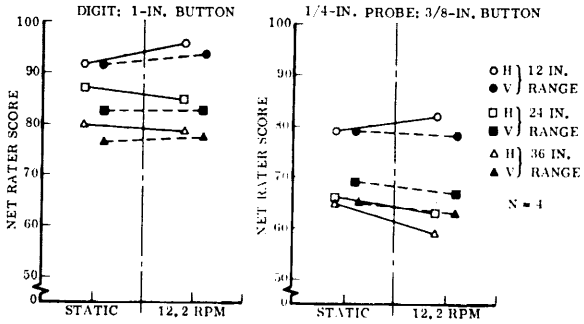

FIGURE 17.—*Horizontal versus vertical reach effectiveness during rotation.*

The test was repeated, and to increase the sensitivity, subjects were made to press the buttons with a stylus of 1/4-inch diameter through a 3/8-inch hole placed in a template fastened to the front of each button. Again the 12-, 24-, and 36-inch range was tested. The results were essentially the same and though the lower scores

reflect the increased task difficulty, there is no significant difference between horizontal and vertical arrangements in either the static or rotating environment.

CONCLUSIONS

The results of these experiments have indicated that head motions out of the plane of spin become quantitatively more disorienting as the interplanar angle approaches 90°; that Y-axis head turns are significantly less affected than comparable Z-axis head turns in an environment rotating at a highly stressful rate and under the orientations studied in this experiment. The space orientation which will tend to increase the requirements for $Z_{90°}$ interplanar-angle head turns may, therefore, be anticipated as being more disorienting than the simulator orientation. Adaptation appears to take place rapidly for those head turns performed near the plane of spin, but becomes increasingly more difficult as the interplanar angle increases.

The experimental results also suggest that a console operator in a rotating space station can perform without perceptual motor decrement even prior to adaptation if he is positioned in the spin plane facing tangentially to the direction of spin and his head turns are restricted to nodding motions with a ±45° range from the plane of spin. There do not appear to be any serious constraints upon hand or arm motions. Prior to adaptation to the space-vehicle spin, some performance decrement may be entailed in deviations from the above constraints. However, our previous experiments have shown that rapid operator adjustment, even to the highly stressful Z-axis head turns, may often prevent performance decrement in precision, perceptual-motor tasks prior to physiological adaptation (refs. 10 and 11).

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DISCUSSION

BERGSTEDT: Did you record nystagmus in darkness or with eyes closed?

NEWSOM: It was in light and during performance testing.

BERGSTEDT: With eyes open?

NEWSOM: Yes.

BERGSTEDT: When they began to suspect this low intensity?

NEWSOM: Yes.

WENDT: I would like to make a comment about eye movements which are normally associated with the voluntary initiation of a head movement. In a voluntary movement while maintaining fixation, there is no latency in the eye movement. That is, the head movement and eye movements start at the same time. If your voluntary task is to look at something laterally, then your eyes jump ahead as the head

turn starts. As the head completes its turn, the eyes make a coordinate compensatory movement which is the same as the eye movement when you merely move the head from side to side and maintain visual fixation. The coordinate compensatory movement was first described by, I think, Raymond Dodge, and the other was first done by, I think, Hobart Mowrer.

NEWSOM: Right. If we had had a little more time, I was going into anticompensatory response and LEM-leading eye movement in more detail. However, I thought most people here know more about that than I do.

The Effects of the Plane of Vestibular Stimulation on Task Performance and Involuntary Eye Motion

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Langley Research Center, NASA

INTRODUCTION

An analytical examination (ref. 1) indicates that the orientation of the astronaut within a rotating space vehicle has considerable influence on the stimulation of his vestibular system. This postulation of different stimulations for different orientations was also experimentally indicated in reference 2. The analysis of reference 1 further indicates that while a subject is erect with his long body axis parallel to the axis of rotation, as in the slow rotating room at Pensacola (ref. 3), the direction in which he faces has no effect on the stimulation of the vestibular system. In contrast, however, with the subject's long axis perpendicular to the axis of rotation as it would be in a rotating space vehicle, the stimulation of the vestibular system is affected by the direction in which the subject faces while standing. Facing tangentially causes stimulation different from that caused by facing axially. All experimental studies at the Langley Research Center have been performed with the subject facing axially; that is, with his neutral or face-forward position being axial (refs. 1, 4, and 5). When performing head motions in those referenced studies, the subjects moved their heads about $\pm 45°$ from the axial position. Because of the previously mentioned effect of orientation, experiments are now being performed with subject facing tangentially. This paper presents the results obtained thus far with this subject orientation.

SYMBOLS

α_{G_θ} cross-coupled nodding acceleration

α_{G_ψ} cross-coupled turning acceleration

α_{G_ϕ} cross-coupled rolling acceleration

$\omega_{G_\theta} = \int \alpha_{G_\theta}\, dt$

$\omega_{G_\psi} = \int \alpha_{G_\psi}\, dt$

$\omega_{G_\phi} = \int \alpha_{G_\phi}\, dt$

ω_{h_θ} nodding velocity—a fore and aft motion of the head at the neck or from the whole body

ω_{h_ψ} turning velocity—a motion about the neck or long-body axis

ω_{h_ϕ} rolling velocity—a sideways motion of the head or from the body

(ω_{h_θ}, ω_{h_ψ}, and ω_{h_ϕ} are angular head motions and may be from motions at the neck and shoulders or from body bending, etc.)

ω_V vehicle rotational velocity

ω_{h_x} total angular velocity of head about rolling axis

ω_{h_y} total angular velocity of head about nodding axis

ω_{h_z} total angular velocity of head about turning axis

t time

$\theta_G = \int\int \alpha_{G_\theta}\, dt^2$

$\psi_G = \int\int \alpha_{G_\psi}\, dt^2$

$\phi_G = \int\int \alpha_{G_\phi}\, dt^2$

θ_n nodding displacement

ψ_n turning displacement

ϕ_n rolling displacement

θ_e, ψ_e, ϕ_e Euler angular displacement using the order of rotation shown in figure 2 of reference 1

θ_{sc} backward tilt of semicircular canals from X_bY_b plane

ψ_{sc} rotation of semicircular canals from X_bY_b plane

X, Y, Z inertial space axes

X_b, Y_b, Z_b body axes

Subscripts:

lr, ll right lateral and left lateral canals, respectively

pr, pl right posterior and left posterior canals, respectively

ar, al right anterior and left anterior canals, respectively

A dot over a symbol indicates its first derivative with respect to time.

ANALYSIS

An analytical development of the angular accelerations which stimulate the semicircular canals is presented in reference 1. The results of this development are the three angular accelerations of the head as functions of head position and vehicle angular velocity. These are:

$$\left.\begin{aligned}\dot{\omega}_{h_x} &= \dot{\omega}_{h_\phi} - \omega_l(\omega_{h_\theta} \sin\theta_e + \omega_{h_\psi} \cos\theta_e \sin\psi_e)\\ \dot{\omega}_{h_y} &= \dot{\omega}_{h_\theta} - \omega_l(\omega_{h_\psi} \cos\theta_e \cos\psi_e - \omega_{h_\phi} \sin\theta_e)\\ \dot{\omega}_{h_z} &= \dot{\omega}_{h_\psi} + \omega_l(\omega_{h_\theta} \cos\theta_e \cos\psi_e + \omega_{h_\phi} \cos\theta_e \sin\psi_e)\end{aligned}\right\} \quad (1)$$

The two extremes of orientation possible for an upright subject standing on the floor of a rotating space vehicle, as has been noted previously, are facing axially as on the right of figure 1, and facing tangentially as on the left of figure 1. When facing axially ψ_e is zero or 180°; while facing tangentially ψ_e is 90° or 270°. Generally, θ_e, a measure of the nodding position of the head, is near zero except when nodding the head, or when bent over, or when lying on the floor or parallel to the floor. The experiments considered in this paper are with $\theta_e = 0°$ and with $\psi_e = 0°$ or 270°, with the head being turned about these values of ψ_e, as neutral positions. The equations for these two specific situations by appropriate substitution in equations (1) above are:

$$\left.\begin{aligned}\dot{\omega}_{h_x} &= -\omega_l\omega_{h_\psi} \sin\psi_e = \alpha_{G_\phi}\\ \dot{\omega}_{h_y} &= -\omega_l\omega_{h_\psi} \cos\psi_e = \alpha_{G_\theta}\\ \dot{\omega}_{h_z} &= \dot{\omega}_{h_\psi}\end{aligned}\right\} \quad (2)$$

The significance of the difference between facing axially or tangentially lies in the value of ψ_e as noted previously. Table 1 lists the physical stimulation that occurs because of these different orientations. The accelerations listed are for each of the three canals of the right ear. Also shown is the effect of canal orientation within the head, indicating the effects of the range of variations of canal orientation for the ranges noted in reference 6. Essentially what is indicated by equations (2) and table 1 is that when turning the head while facing axially, the cross-coupled angular acceleration is in the nodding sense, whereas when turning the head while facing tangentially, the cross-coupled angular acceleration is in the rolling sense. These cross-coupled angular accelerations are, of course, the unnatural accelerations encountered in a rotating environment and those which cause visual illusions, nausea, and nystagmus.

Actually, the value of ψ_e is variable when the head is being turned. Figure 2 is a graphic indication of the cross-coupled angular acceleration that would occur while turning the head about 45° from the left to 45° to the right of the neutral positions of $\psi_e = 0°$ and 270°. The head motion shown in figure 2 is an actual motion from which the head position was measured. The apparent motions were computed for the axially and tangentially facing conditions based on equations (2). There is, as implied previously, a considerable difference in the stimulation. Generally, one would expect an illusion of the spacecraft pitching relative to the subject when

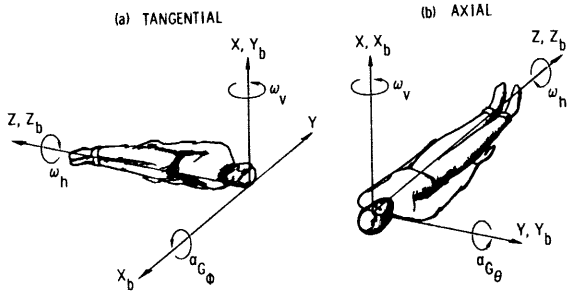

FIGURE 1.—*Sketch showing axial and tangential orientation of subjects.*

TABLE 1.—*Canal Stimulation for Various Orientations on the Canals in the Head (Head Turning)*

[Assume that the head moves steadily through the noted values of ψ_e, ϕ_e, and θ_e for consideration of this table]

Canal acceleration	$\theta_{sc}=15°$		$\theta_{sc}=30°$	
	ψ_{sc}		ψ_{sc}	
	35°	65°	35°	65°
Axial orientation, $\psi_e=\phi_e=\theta_e=0$				
$\dot{\omega}_{sc_{lr}}$	0	0	0	0
$\dot{\omega}_{sc_{ar}}$	$-0.8192\omega_l\omega_{h_\psi}$	$-0.4226\omega_l\omega_{h_\psi}$	$-0.8192\omega_l\omega_{h_\psi}$	$-0.4226\omega_l\omega_{h_\psi}$
$\dot{\omega}_{sc_{pr}}$	$-0.5736\omega_l\omega_{h_\psi}$	$-0.9063\omega_l\omega_{h_\psi}$	$-0.5736\omega_l\omega_{h_\psi}$	$-0.9063\omega_l\omega_{h_\psi}$
Tangential orientation, $\psi_e=270$, $\phi_e=\theta_e=0$				
$\dot{\omega}_{sc_{lr}}$	$0.2588\omega_l\omega_{h_\psi}$	$0.2588\omega_l\omega_{h_\psi}$	$0.5000\omega_l\omega_{h_\psi}$	$0.5000\omega_l\omega_{h_\psi}$
$\dot{\omega}_{sc_{ar}}$	$-0.5540\omega_l\omega_{h_\psi}$	$-0.8754\omega_l\omega_{h_\psi}$	$-0.4967\omega_l\omega_{h_\psi}$	$-0.7894\omega_l\omega_{h_\psi}$
$\dot{\omega}_{sc_{pr}}$	$0.7193\omega_l\omega_{h_\psi}$	$0.4082\omega_l\omega_{h_\psi}$	$0.7094\omega_l\omega_{h_\psi}$	$0.3660\omega_l\omega_{h_\psi}$

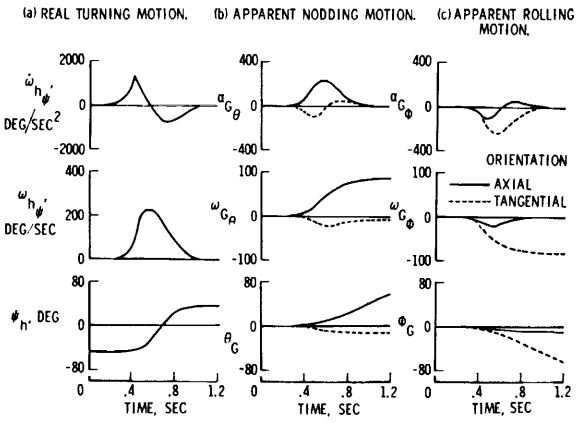

FIGURE 2.—*Typical head motion and resulting apparent motions while turning the head in a vehicle rotating at 10 rpm. Subjects are oriented facing axially and tangentially.*

facing axially, and an illusion of the spacecraft rolling relative to the subject when facing tangentially. When facing axially, one also expects that a vertical nystagmus will occur because of the real pitching or nodding stimulation; this is experimentally verified in reference 2. When facing tangentially where the cross-coupled angular stimulation is in the rolling sense, one may expect that some eye counterrolling will be incurred.

TEST EQUIPMENT AND TECHNIQUE

The experiments performed to evaluate the influence of the differences in stimulation discussed previously were performed on the Lang-

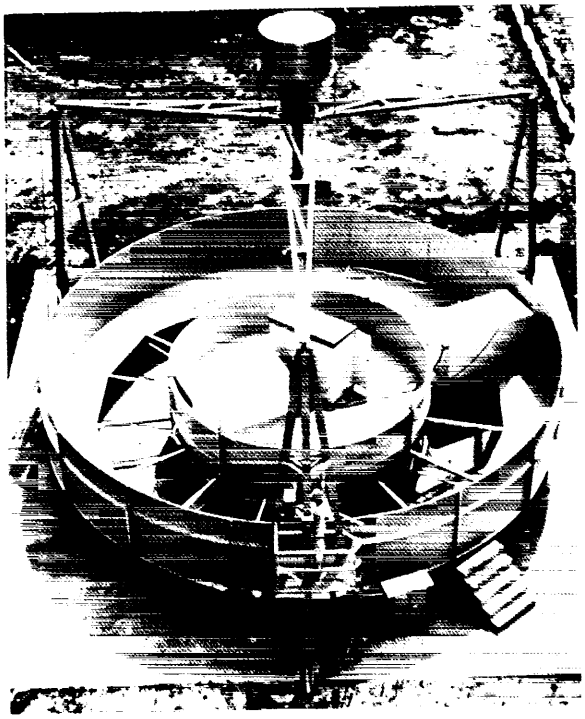

FIGURE 3.—*The Langley rotating-vehicle simulator.*

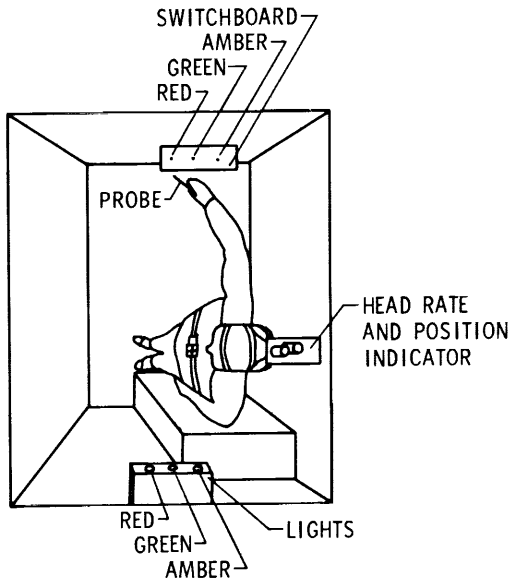

FIGURE 4.—*Internal features of simulator.*

ley Research Center's rotating space vehicle simulator shown in figure 3. This device consists basically of two concentric rotating cylindrical walls, one with a 20-foot diameter and the other with a 40-foot diameter. These cylindrical walls simulate the floor of a rotating vehicle upon which subjects, as described in reference 1, can walk and otherwise perform as they would in a rotating space vehicle. The tests performed for the purposes of this report, however, did not use the simulator in the sense just described. For the current study a small cabin was installed on the short-diameter cylinder similar to that described in reference 1. Thus the radius for these experiments was 10 feet. For the purposes of the current study, the subjects lay in this cabin on their sides facing tangentially with their long-body axis oriented radially (perpendicular to the axis of rotation) with their feet outward. On previous experiments, using another simulator, the subjects were lying on their back facing axially and with their feet 15 feet from the center of rotation. The system, measuring devices, and testing techniques were the same as used in previous experiments at Langley and are described in reference 1. A sketch showing the internal features of this simulator is shown in figure 4. Briefly, the subjects were required to turn their heads to the left and observe three lights of different colors. When a specific light was lit, the subject was required to turn his head to his right and turn off the light by placing a probe in an appropriate hole to extinguish the light. The head position and rate of head motion and the time required to extinguish the light were measured. Results presented herein were obtained from 12 subjects, all facing in the tangential direction. Each head-turning experiment lasted 1 hour and rates of rotation of 0, 9, 12, 14, and 16 rpm were used. The lights were activated in a random fashion with time periods between tasks of from 20 to 35 seconds. This is as essentially described in reference 1. Some motion pictures of the eyes were made to determine the motion of the eyes under the conditions of the experiment.

RESULTS AND DISCUSSION

To determine the effect of the subject orientation and the resulting differences in cross-coupled angular accelerations on task performance, the results of reference 4 are compared with the present results in figures 5, 6, and 7.

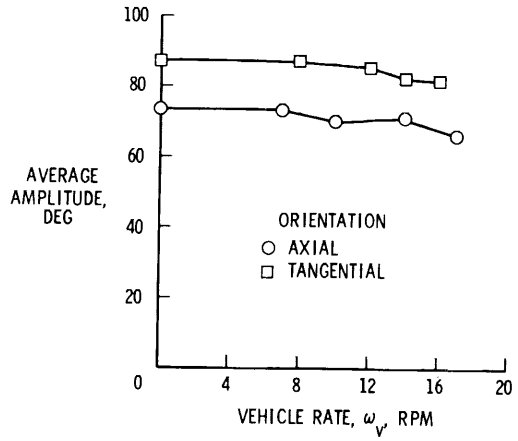

FIGURE 5.—*Amplitude of head-turning motion at various rates of simulator rotation for subject facing axially and tangentially.*

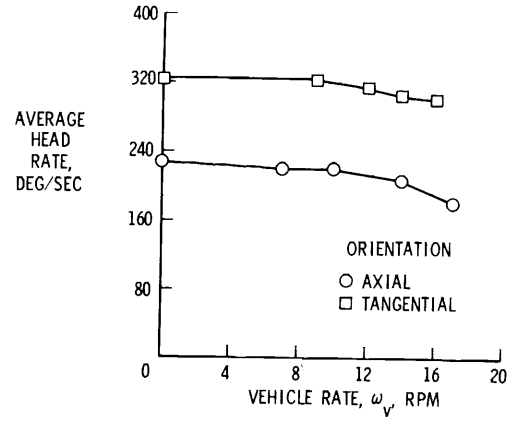

FIGURE 6.—*Rates of head turning at various rates of simulator rotation for subjects facing axially and tangentially.*

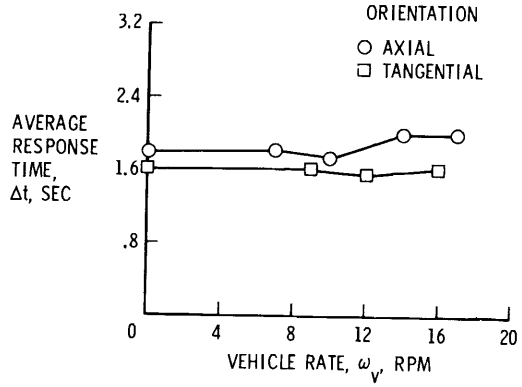

FIGURE 7.—*Response time while turning head at various rates of simulator rotation for subjects facing axially and tangentially.*

It should be pointed out that the present results were obtained on the rotating simulator shown in figure 3 with the subject's feet 10 feet from the center of rotation, while those of reference 4 were obtained on another simulator with the subject's feet located 15 feet from the center of rotation. However, it can be assumed that, based on the data of reference 1, the radius of rotation would have an insignificant effect on the results. The results of reference 1 indicated that there was little or no effect of radius on the performance and tolerance for nodding head motions when the results obtained at the 3 radii, 10, 15, and 20 feet, were compared. It is felt that the effects of a 10-foot or 15-foot radius for the comparisons presented here will not be significant. The data presented on figures 5, 6, and 7 are the numerical averages from all the subjects participating. There were 29 subjects oriented facing axially in the tests of reference 4, and 12 subjects oriented facing tangentially for the present tests.

The average amplitude of head motion plotted against vehicle rpm is shown in figure 5, with the axial and tangential orientation of the subjects represented by the circles and squares, respectively. The amplitude of head motion used by the subjects oriented axially was generally about 12° less than that used by the subjects when oriented tangentially. This may be due to small differences in the location of the lights and switches and in the way the subjects used their eyes. For both orientations there was a small decrease in head-motion amplitude with increase in vehicle rpm. This was also true for the head-turning rate variation with rpm shown in figure 6. This was probably caused by the subjects attempting to limit the magnitude of the stimulus and the resulting disquieting effects. The subjects of reference 4 first found motion intolerable at a head rate of about 220°/sec at a vehicle rate of 10 rpm. Although one of the subjects of the present test turned his head at rates considerably lower than this, even at 9 rpm, in order to avoid malaise, he completed the entire experiment. As can be seen from figure 6 the subjects of the present tests averaged rates of head turning which were 100°/sec higher than those of reference 4. This indicates that, in general, the subjects could tolerate greater cross-coupled

accelerations while oriented facing tangentially than when oriented facing axially. It should be pointed out that only two subjects participated in both sets of tests.

The variation of response time with vehicle rpm is shown in figure 7 for both subject orientations. There was essentially only a small effect of vehicle rate or orientation on the response time (time from light activation to time light was extinguished). The response time for the tangential orientation was about 0.2 to 0.4 second less than that for the axial orientation. However, this decrease was not so great as would be expected on the basis of the greatly increased head rate used in the tangential orientation. One of the factors which may have affected this result is that different arm movements were used in the different orientations. For the tangential orientation the subject's arm had to be raised vertically to extinguish the light, and this evidently is not so easy as moving the arm laterally as was required in the axial orientation.

Since it is felt that the level of distress experienced by the subjects during rotation depends on the magnitude of cross-coupled accelerations, tolerance to rotation can be assumed to be determined by tolerance to cross-coupled accelerations. Thus constant values of this acceleration, which is the product of head rate and vehicle rate, form boundaries above which motion can become intolerable.

Figure 8 presents a comparison of the tolerance boundaries for the axial and tangential orientations together with some test points from both experiments. The figure is a plot of head rate versus vehicle rate of rotation. The curves shown are hyperbolas and are loci of constant cross-coupled accelerations. The tolerance boundary from reference 4, shown by the solid curve, was prepared on the basis of 10 rpm where the subjects of reference 4 first found motion intolerable. This curve represents a cross-coupled acceleration of 4.0 rad/sec^2. The circles at 14 and 17 rpm represent, respectively, the conditions tolerated by 80 percent and 50 percent of the subjects of reference 4. For comparison purposes the boundary for the tangential orientation of the present tests was also prepared based on the results obtained at 10 rpm and is shown by the dashed curve in figure 8. This curve represents a constant cross-coupled acceleration of 5.85 rad/sec^2. However, as shown by the data points for the tangential orientation, the subjects generally tolerated cross-coupled accelerations considerably higher than this value. In contrast to the previous experiment where only about 50 percent of the subjects completed the entire experiment, all of the subjects completed the present tests. These results tend to indicate that tangentially oriented subjects apparently can tolerate cross-coupled accelerations of considerably greater magnitude than those tolerated by subjects oriented axially. As mentioned earlier, the cross-coupled acceleration for the tangentially facing subjects is in the rolling sense, while that for the axially facing subjects is in the nodding sense.

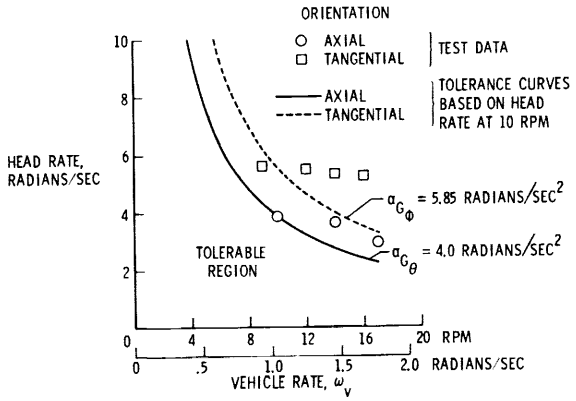

FIGURE 8.—*Tolerance to cross-coupled angular accelerations while head turning for subjects facing axially and tangentially.*

CONCLUDING REMARKS

Consideration of the results of this paper indicates that, for a turning head motion, the stimulation experienced by the tangentially oriented subjects is considerably different from that experienced by the axially oriented subjects, the stimulation being a cross-coupled acceleration in the rolling sense when tangentially oriented and in the nodding sense when axially oriented. The data of both experiments generally indicate a tolerance to 10 rpm for most subjects. The data also indicate that the subjects could tolerate greater cross-coupled accelerations when facing tangentially than they could

while facing axially. The results presented are for a limited number of subjects performing a relatively simple task for short periods and should be confirmed by other subjects and experiments.

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DISCUSSION

MAYNE: Did I detect a certain amount of rolling in the eyes in your moving picture?

LETKO: In which situation?

MAYNE: During the head movement.

LETKO: You mean eye movements?

MAYNE: Yes; a rolling of the eyes, not a linear nystagmus.

LETKO: There was in the tangentially oriented subjects.

MAYNE: I am pleased to hear this because it seems to confirm an idea of ours that the Coriolis illusion involves the linear as well as the angular vestibular system. But a more detailed analysis of your data would be required to confirm this idea.

LETKO: We are not exactly sure of all the inferences here, but it is possible.

MAYNE: Will your published paper give enough of a sequence of pictures to make possible a detailed study of this rolling motion of the eyes?

LETKO: I believe the film can be borrowed for short periods of time. (Note: Film number is L-947.)

JONGKEES: I have been listening to a number of very interesting papers about very intricate experiments this morning. From the first speaker we learned that we are not quite sure how man in space will be placed in relation to his instruments under zero g, 0.1 g, etc. We also do not know whether the spacecraft will be rotating or not. In addition, we have extremely little knowledge about the labyrinth and what the reactions from the canals and otoliths are. If you want to really know what will happen to someone placed in circumstances different from those on Earth, I am not quite sure of the advantage of fine instrumentation and complicated instruments. Would it not be better to go really into the matter, to go back to the first real experiment, and try to see what we do know about the function of the vestibular organ in respect to one single stimulus? When we know exactly what one specific stimulus does, then we can add another. But what we are doing is combining a lot of stimuli, then being disappointed at what we find. I would suggest that we avoid disappointments by keeping things simple. Perhaps we could keep vestibular physiology, as far as we can influence it, as simple as possible.

NEWSOM: I should like to attempt a reply to Dr. Jongkees: One of the nice things about these symposia is that they are becoming more and more mixed. They are mixed with people who know a great deal about vestibular organs and with other people who have to make decisions about how to build something that will be affected by those organs. Our engineers are at the point of technology where they can do the things that Dr. Faget told us about today; somebody has to make a decision to tell them how to design those parts affecting the crew. Engineers are not satisfied with abstract postulates, and if you do not tell them, they will build it the way they think it should be built; and this might have nothing to do whatsoever with even the very little that we do know about vestibular physiology. So I think the objective of these symposia should be the very thing that you bring out, getting your ideas, apprehensions about the basic aspects, so we who have to define parameters on paper can do the required research to tell the engineers how to limit their designs. It is this cross-stimulation that I think is the very thing that is so fine about these meetings we have had.

Session I–B: *MAN IN SPACE*

Chairman: **MAXIME A. FAGET**
Manned Spacecraft Center, NASA

289-013 O 68—5

Response Differentiation in Slow Rotation

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Ames Research Center, NASA

SUMMARY

Rats were trained to respond on a nose response key in a rotating chamber with food as the reinforcement. For each subject a selected speed of rotation (0 to 25 rpm) was paired with reinforcement, and in some cases one or two speeds were paired with nonreinforcement. Extinction testing for stimulus generalization to the training speeds, plus four other speeds, produced orderly differential rates of responding. Those speeds similar to the speed reinforced during training yielded high rates, and those speeds similar to the nonreinforced training speeds yielded low response rates. These results indicate that rats are capable of discriminating different speeds of rotation. It is suggested that the mechanism involved is the sensitivity to centripetal acceleration of the otolith organ.

INTRODUCTION

This experiment used the classical behavioral technique of stimulus generalization of an operant conditioned response (refs. 1 and 2). Stimulus generalization is a behavioral phenomenon in which organisms tend to respond similarly to those stimuli which are most alike along a physical dimension. The closer the stimuli are on the physical dimension, the more likely they are to produce similar responses. For example, a bird trained to make a response in the presence of a red light would be more likely to make a similar response to an orange light than to a blue light.

The present experiment used this procedure with speed of rotation (0 to 25 rpm) of rat subjects as the stimulus dimension which was varied.

APPARATUS

The apparatus is schematized in figure 1. It consists of a drum with an inside radius of 6 inches which is rotated about its vertical axis. The rat pushed with its nose on the response key mounted at the perimeter, and food pellets (45 mg, Noyes) were dispensed in a hopper adjacent to the key. This response produced small accelerations in the plane of rotation and minimized vertical Coriolis accelerations. A small light behind the key provided illumination during the session. The watering device was not used in the study reported here. Programing of the schedule of reinforcement and the selection of the speed of rotation were remotely controlled by standard relay equipment. Rotation speed was held within 1 percent by a remotely located servosystem which controlled voltage to the variable speed motor and received input from the pre-

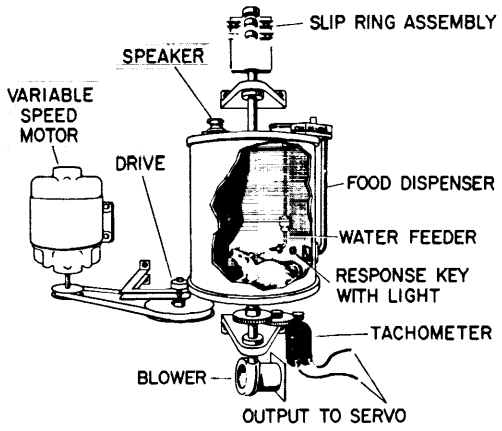

FIGURE 1.—*Schematic drawing of Ames rotating drum.*

cision tachometer. White masking noise was fed continually into the speaker mounted on top of the drum.

Data were recorded by an on-line digital computer which monitored the responses of the rat and the speed of the drum.

PROCEDURE

Training

Twenty-nine male, Long-Evans rats served as subjects and were maintained at 80 percent normal body weight. Water was available only in the home cage. Each daily session lasted approximately 1 hour. During the first two sessions the rats were conditioned to press the key, and for each response up to a total of 50 responses they received one pellet. This is called a CRF level of reinforcement. During the next three sessions they were rotated at a preselected speed, and reinforcement was maintained at CRF; that is, one pellet was dispensed for each response. This speed served as the discriminative stimulus (S^D), signifying that reinforcement was available.

In the sixth session the variable-interval (VI) schedule of reinforcement was introduced and remained in effect until extinction testing. In this schedule, reinforcement was presented for the first response occurring on the average 1 minute from the last reinforcement, with a range of intervals varying from 4 seconds to 4 minutes. The subject received 50 reinforcements during the session. The variable-interval schedule has the effect of maintaining a very consistent rate of response (fig. 2) and, therefore, a relatively consistent orientation to the plane of rotation with nose toward the perimeter and tail toward the center of the drum.

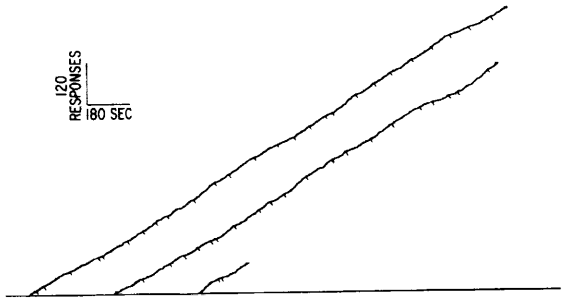

FIGURE 2.—*Cumulative record showing steady response rate during 1-hour session of rotation at 8.2 rpm. Hatch marks represent food reinforcement.*

With some of the subjects another speed of rotation was introduced during the sixth session and continued in use throughout training. In the presence of this speed (S^Δ), responses were never reinforced. Rats under S^Δ training received 30-second exposures to S^D alternated with 10-second exposures to S^Δ. The schedule of reinforcement remained at VI-1 minute during S^D. When two S^Δ conditions were used, the schedule was alternated between 30 seconds S^D, 10 seconds of one S^Δ and 30 seconds S^D, 10 seconds of the other S^Δ.

Extinction

When the criteria for stable performance were maintained for three consecutive sessions, S^Δ responding less than 10 percent of S^D responding and total responding varying less than 20 percent among the sessions, extinction was introduced in the next session. During extinction no reinforcement was given. In place of each 30-second S^D period, the subjects were presented with one of five speeds randomly programed; each was presented a total of 20 times. The five speeds included the previously reinforced S^D, but reinforcement was no longer presented. Sequencing of the test stimuli and S^Δ remained the same as in training.

RESULTS

$S^\Delta = 0$ rpm

Figure 3 shows a direct relationship between speed of rotation and percentage of responding. Animals trained to respond only during rotation respond differentially more to higher speeds of rotation. In generalization gradients with both S^D and S^Δ training, the peak of the gradient is shifted from the S^D point away from the S^Δ (refs. 2 and 3). All of the data in this figure are generally comparable to generalization data obtained using other stimuli and are suggestive of discriminable differences among the stimuli in the ranges tested. A flat gradient would have indicated no discrimination.

S^{Δ} = 25 rpm

The data in figure 4 show that rats trained to not respond with S^{Δ} higher than S^{D}, as would be expected tend to respond less to the higher test stimuli. However, rather than a peak shift, each of the graphs shows peaks at the S^{D}. This indicates, possibly, that there is an undefined procedural S^{Δ} occurring at 0 rpm. For example, because the subjects have been raised at 0 rpm, the results may be somewhat biased.

S^{D} Only

In figure 5 the generalization data from animals trained without a defined S^{Δ} look similar, for the most part, to the data from animals with an S^{Δ} at 0 rpm (fig. 3). Because there was no S^{Δ} present, these data would be expected to peak at the S^{D} and slope off equally at both lower and higher rpm. This result again supports the notion of a 0-rpm bias.

Two S^{Δ}'s

When animals are trained with a single S^{D} between two S^{Δ}'s, the generalization gradients tend to the shape of those in figure 6. The data peak at the S^{D} and slope downward to both S^{Δ}'s.

The data presented from these experiments indicate that methods for evaluating the sensitivity of animals to auditory and visual stimuli are also applicable to rotational stimuli. Manipulations of these stimuli produce similar effects during generalization testing.

The range of centripetal accelerations at the perimeter was calculated at 0.015 g for 3 rpm to 0.106 g at 25 rpm. These values are above threshold for otolith response (ref. 4) and are

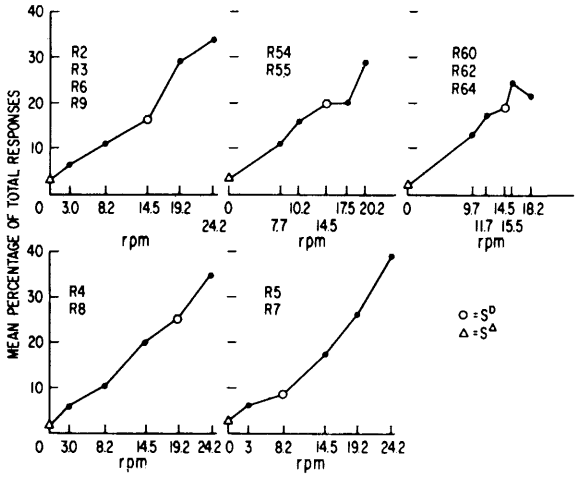

FIGURE 3.—*Mean extinction response data for rats that received training at* $S^{\Delta} = 0$ *rpm. Top three graphs show different ranges of extinction test stimuli for animals trained at* $S^{D} = 14.5$ *rpm. Bottom two graphs are from animals trained at* $S^{D} = 19.2$ *rpm and* $S^{D} = 8.2$ *rpm, respectively.*

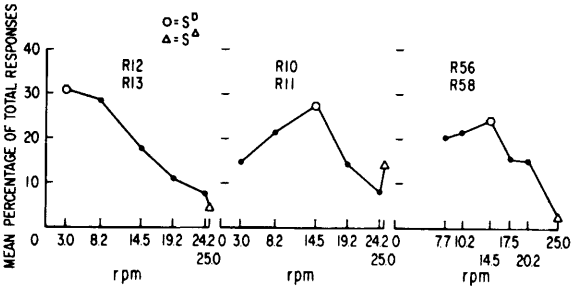

FIGURE 4.—*Mean extinction response data from animals receiving* $S^{\Delta} = 25$ *rpm training. Graph on the left is from animals with* $S^{D} = 3$ *rpm training. Remaining two graphs are from animals with* $S^{D} = 14.5$ *rpm and different ranges of extinction test stimuli.*

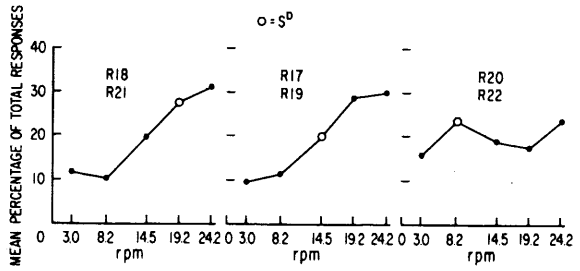

FIGURE 5.—*Mean extinction response data for animals trained with* S^{D} *only. Each of the three graphs represents a different* S^{D}.

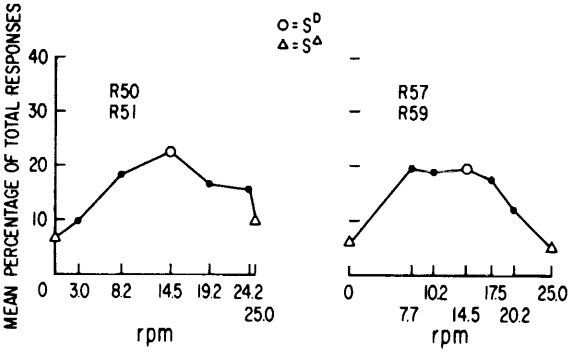

FIGURE 6.—*Mean extinction response data from animals trained with* $S^{\Delta} = 0$, $S^{D} = 14.5$, *and* $S^{\Delta} = 25$ *rpm. The two graphs show different ranges of extinction test stimuli.*

probably the effective stimuli in this experiment. Vertical Coriolis accelerations were minimal in this study because most of the movements of the rats were along the radius of centripetal acceleration.

With further experimentation we hope to be able to build toward psychophysical threshold measurements for rotational stimuli as well as a more explicit definition of the stimulus aspects of our rotational stimulus.

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DISCUSSION

KILLEBREW: Can you tell us in more detail what role the sound, the white noise, played in this series of experiments? Did the intensity change with the velocities of rotation?

WEISSMAN: We tried to keep the device as quiet as possible, but, in addition, we presented the white noise as a masking noise.

THACH: Would you care to elaborate on what it was the animals were discriminating? It seems to me that, in this situation, otoliths are implicated, but there are rather a large number of other sensory inputs (you just added another one), perhaps vibration related to the gears and even particularly the role that head movements might play. In some experiments with rats we found that with a very minute change in the response topography we required, such as having a vertically moving small lever rather than one in the same position moving over the same amplitude, but which could be moved in any direction to count as a response, we could get about a 20-percent change in sensitivity to rotation. I was wondering if you wanted to comment along this line.

Another question. Apparently you are using this as a demonstration that rats can discriminate speeds of rotation. Could you not just have had a certain discriminative stimulus and done it in a much simpler fashion?

WEISSMAN: In terms of the stimulus, I would prefer to leave that until we can do some more experimentation. As I did suggest, it is possibly within the range of otolith sensitivity to centripetal acceleration. And this is as good a candidate as any, I believe. In terms of your question about using some other procedure, I really do not think there is a more simple procedure. There is an aspect of stimulus generalization which is discrimination; that is, when I trained the animals to first respond at 14.5 rpm for food and 25 rpm where they did not get food. Discrimination procedures seem a little bit complicated in looking to narrow the range of the stimulus. I do not really know what range is a reasonable range to ask these animals to respond differentially. Should I work with differences of ½ rpm or 5 rpm? I think we can get to this question more quickly with stimulus generalization procedure.

Vestibular End-Organ Damage in Squirrel Monkeys After Exposure to Intensive Linear Acceleration[1]

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AND
MASAO NAGABA
Naval Aerospace Medical Institute

SUMMARY

Fifty-four squirrel monkeys were exposed to different levels of high-intensity linear acceleration stimuli which were directed so as to produce a backward ($-G_x$) reaction force.

Otoconia dislocation from the maculae was observed by light microscopy after an exposure of 1 minute at the 60-g level and above, but was more constant and extensive after 1 minute at the 150-g level and above. No architectural change was detected either in the semicircular canal cristae or organ of Corti. In the monkeys which were exposed to 200 g for 1 minute and to a peak of 450 g, the ultrastructural changes noticed were increased lysosomes and transformation of mitochondria in the nerve chalice.

Macroscopic examination immediately after exposure showed the severity of gross ataxia in the monkeys to be relatively parallel to the intensity of g-levels. The ataxia rail test of dynamic equilibrium under a behavior-conditioning program carried out 2 to 35 days after exposure demonstrated the same results. No significant change from preexposure values was observed in the caloric threshold tests. Motion-sickness tests in the slow rotation room exhibited almost similar results, although the data were more fluctuating.

INTRODUCTION

Exposure to extreme intense linear forces might be expected only on very rare occasions such as an unusual circumstance during space flight, or an accidental injury in the spacecraft. However, it is still worthwhile to investigate the possible morphological changes which might take place in the inner ear end organs after the exposure to high-g forces.

In the original work of Spoendlin et al. (ref. 1), the ultrastructure of the maculae, as investigated by electron microscopy, was not altered in any of the squirrel monkeys exposed to 10.92 g for periods up to 10 minutes. In the present study an attempt was made to investigate the different morphological vulnerability among the different inner ear end organs after exposure to linear acceleration at several much higher levels. Squirrel monkeys were chosen as they are subhuman primates and have, as far as the inner ear end organs are concerned, structures identical to those of the human inner ear (refs. 2–5).

PROCEDURE

Fifty-four squirrel monkeys were exposed to different levels of linear acceleration by using the Space Flight Acceleration Profile Simulator at Space/Defense Corp., Birmingham, Mich. (ref. 6). Each monkey was restrained and placed in a chair prior to the exposure (fig. 1). Acceleration was applied in the frontward direction,

[1] The experiments reported herein were conducted according to the principles enunciated in "Guide for Laboratory Animal Facilities and Care" prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

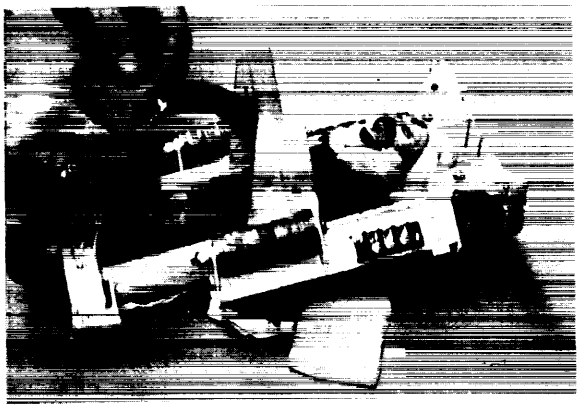

FIGURE 1.—*The squirrel monkey being restrained and placed in the chair before the exposure to high-g linear acceleration.*

resulting in a backward ($-G_x$) reaction force. Twenty-eight monkeys which belong to the first group were exposed to mainly between 60 and 200 g. After the level of otolithic membrane dislocation was detected in those monkeys, the exposure levels for 26 monkeys of the second group were decided upon. They were exposed mostly to 20- to 60-g, and 200- to 500-g levels.

Gross ataxia tests on the floor and on a bar (about 2 inches in diameter), and the observation of nystagmic eyeball movement (in head-erect, supine, and head-hanging positions) were carried out on all monkeys immediately after centrifugation. Selected representatives were used for motion-sickness tests in the slow rotation room (ref. 7), threshold caloric tests (ref. 8), and monkey ataxia rail test under the behavioral-conditioning program (ref. 9 and M. Igarashi, J. S. Thach, Jr., and A. Graybiel, "Dynamic Equilibrium After Selective Ablation of Labyrinthine Organs in Squirrel Monkeys," in preparation). For the latter test, squirrel monkeys that have been screened initially as suitable for the avoidance-behavior-conditioning study each have a performance threshold determined after the necessary basic training of going across a rail which may be rotated at different revolutions per minute when desired. The speed of the rotating rail is increased gradually. More than three consecutive falls from the rail rotating at a given rpm determines the threshold for the ability to carry out this task (criterion). All of these tests were performed before and after the exposure.

One ear from each of 11 representative squirrel monkeys from the second group exposed to different g-levels (8 animals for 20 to 60 g, 1 animal each to 200 g, 400 g, and 450 g) was used for electron-microscopic investigation, while the other ear from these animals was studied by light microscopy. Fixation for electron microscopy was done by immersing the inner ear in Millonig's 1 percent osmium tetroxide solution after routine stapedectomy procedure. Then, each specimen was postosmicated for 1 hour, dehydrated in ethanol, embedded in Epon 812 or Durcupan. The thin sections were made by LKB ultratome and stained with uranyl acetate. Electron micrographs were made with a Phillips EM 200 electron microscope operated at 60 kV. In addition to the other ear from these animals, all other animals' ears were used for light microscopic study. All of these ears were fixed by means of the intravital cardiac perfusion with Heidenhain-Susa solution, and thereafter processed following the standard temporal bone procedure.

RESULTS AND DISCUSSION

Morphological Findings

The pronounced difference of morphological vulnerability among different inner ear end organs was the most important finding in the present investigation. The otoconia dislocation from the macula was observed after exposure to 60 g and above for 1 minute. At 150 g and above for 1 minute, the otoconia dislocation was more constant and more extensive.

In the peak-g exposure group, very definite otoconia dislocation was also observed at a peak exposure level of 200 g and above.

No architectural change was detected either in the semicircular canal cristae or in the organ of Corti, even after the most intensive g-exposure. No definite hair-cell lesion was observed with the light microscope in the maculae where the otoconia dislodgment was investigated.

The pattern of otoconia dislocation from the saccular macula was identical in almost every case. The anterior part of the otolith membrane was more easily dislodged toward the posterior (figs. 2 and 3). The loose otoconia from the saccular macula was found posteriorly, in the saccular duct (fig. 4), inferiorly, in the ductus reuniens (fig. 5), but not in the cochlea duct of the vestibular cecum.

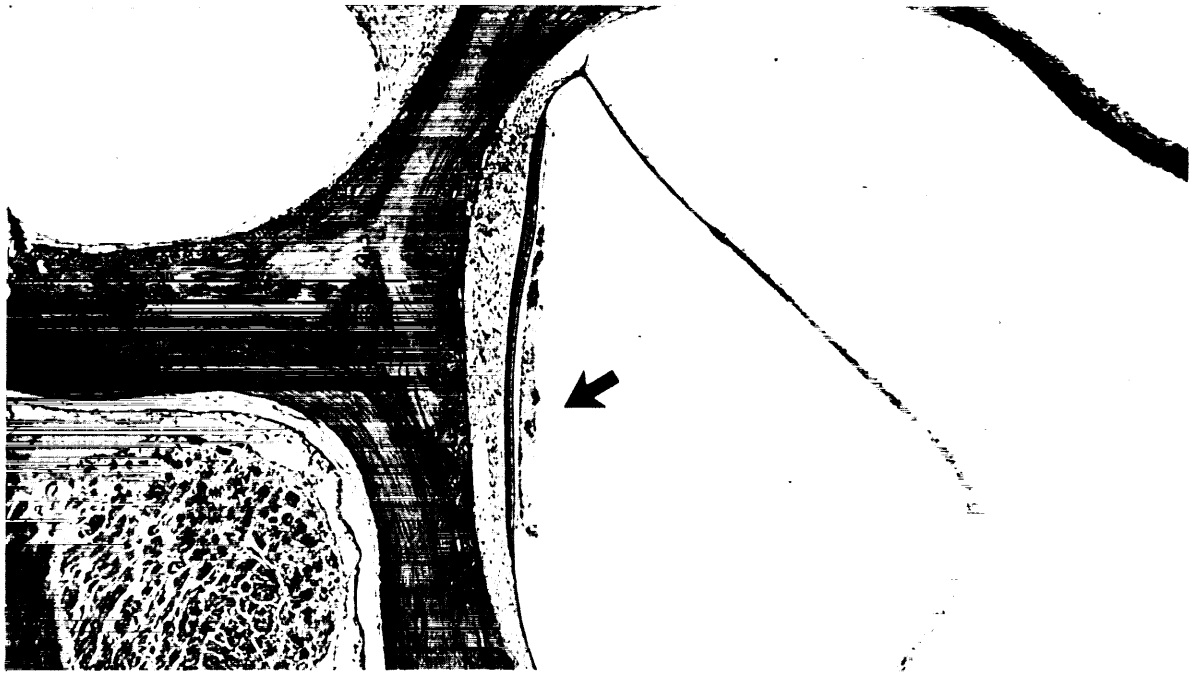

FIGURE 2.—*The pattern of otoconia dislocation* (arrow) *from the saccular macula immediately after 1-minute exposure to 75 g.* 63×

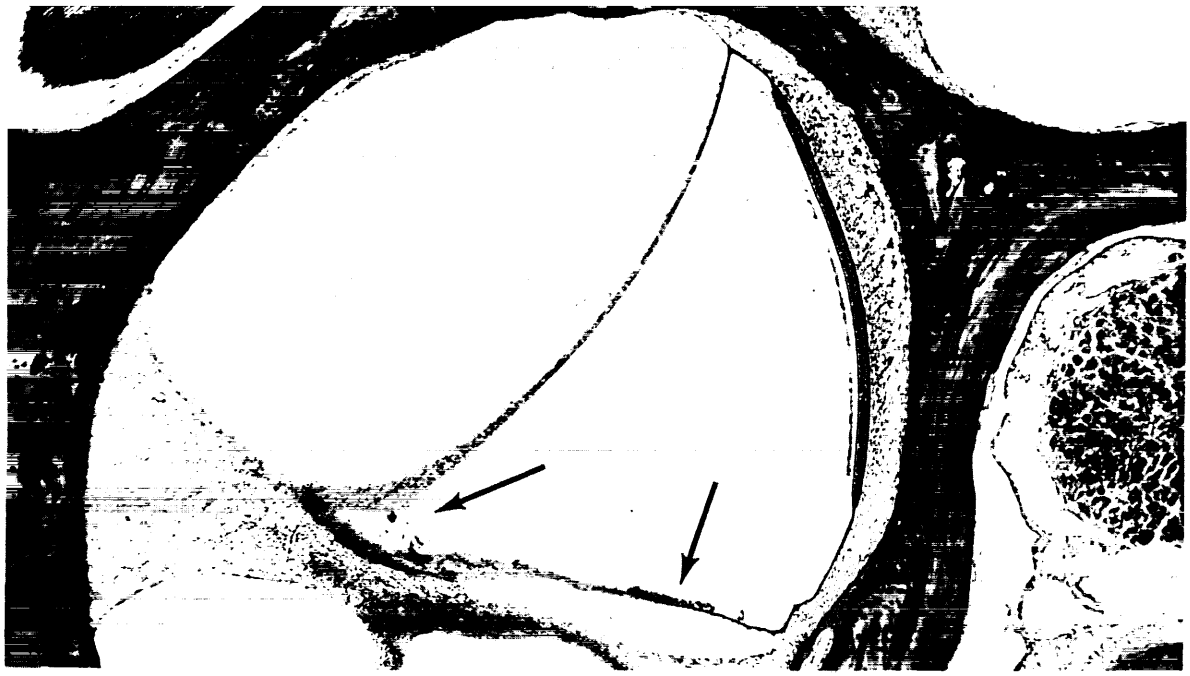

FIGURE 3.—*Photomicrograph showing otoconia dislocation from the saccular macula immediately after 1-minute exposure to 100 g. The otoconia is located along the lateroposterior saccular wall* (arrow). 52×

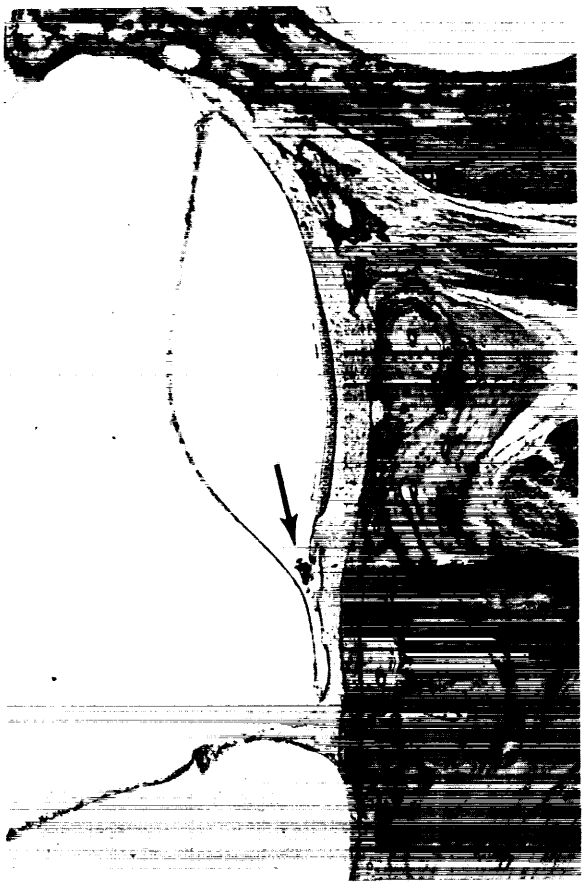

FIGURE 4.—*View of the otoconia dislocation from the saccular macula immediately after 1-minute exposure to 200 g. The otoconia* (arrow) *is situated posteriorly, in the saccular duct.* 52×

The dislocation of otoconia from the utricular macula exhibited a slightly different pattern between strong peak-g exposure and 1-minute-g exposure; however, these were essentially the same. In the animals exposed to a peak of 300 g or above, the otoconia were dislodged from the medial portion of the macula (figs. 6 and 7). In those cases exposed to less than 200 g for 1 minute, the otoconia were released commencing at the central portion of the macula and extending toward the medial portion, and were usually dislocated posterointeriorly (figs. 8 and 9). The lateral part of the macula utriculi seemed to be less affected by this type of exposure.

Dislocated otoconia from the utricular macula were found at many different locations in the vestibular endolymphatic space. In quite a few instances, it was found somewhere in the posterior semicircular canal area, either in the ampulla (figs. 10 to 13) or in the crus (fig. 14). In a very few instances, the loose otoconia were found in the superior semicircular canal ampulla area (fig. 15), or in the horizontal semicircular canal ampulla area (fig. 16).

Schuknecht (ref. 10) has proposed an interesting theory regarding the peripheral origin of the benign paroxysmal-type positional nystagmus. He stated that this type of nystagmus was due to the action of loose utricular otoconia on the cupula of the posterior semicircular canal. Only one of his four cats subjected to unilateral section of the superior vestibular nerve and of the anterior vestibular artery demonstrated positional nystagmus of a rotatory nature 3 months after the operation. In the present study the percentage of positional nystagmus with otoconia in the posterior semicircular canal area seen 2 weeks after the exposure was the same (25 percent). However, loose otoconia were also found somewhere around the posterior semicircular canal area 2 weeks after the exposure in all the other animals that did not demonstrate positional nystagmus. Therefore, the existence of the dislodged otoconia in the posterior semicircular canal ampulla does not necessarily explain the peripheral origin of the positional nystagmus. In addition, most of the positional nystagmus observed in chronically examined animals of the present series was of a rather straight-upward nature all the time. The effect of the loose otoconia appeared only through the remaining posterior semicircular canal crista in Schuknecht's animals, while in the present series it might appear throughout any vestibular end organ. Also, the methods of vestibular destruction in the two studies were completely different; Schuknecht used a surgical procedure, and in this study mechanical stimulation was used.

Ultrastructural findings of the utricular macula and the horizontal semicircular canal crista were compared among the animals which had been exposed to the different g-levels. The emphasis was placed on investigating the apical part and the basal part of the hair cells, and especially on investigating the organellae, such as lysosomes, mitochondria, nerve endings, synaptic structures, and inclusion bodies. In the animals that were exposed to 60 g or below

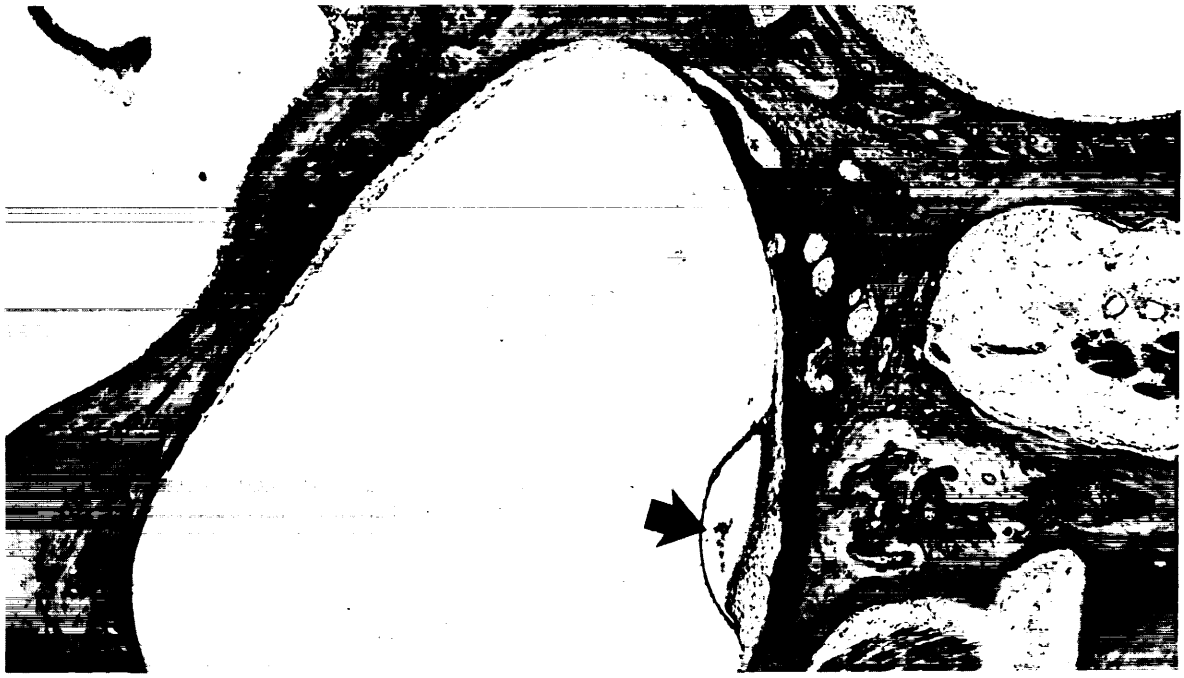

FIGURE 5.—*Photomicrograph demonstrating the dislocated saccular otoconia* (ARROW) *in the ductus reuniens after 1-minute exposure to 100 g. 56×*

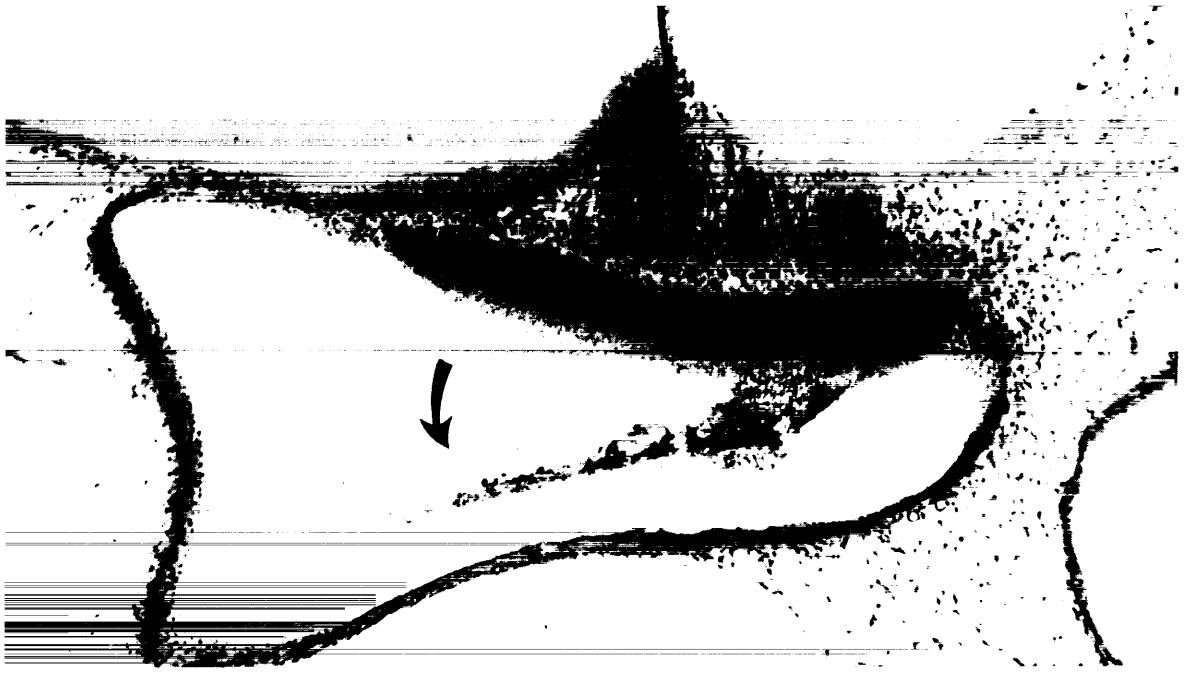

FIGURE 6.—*Photomicrograph exhibiting the otoconia dislodgment from the utricular macula immediately after exposure to peak of 400 g. The medial part of otoconia* (ARROW) *is hurled away from the macula. 98×*

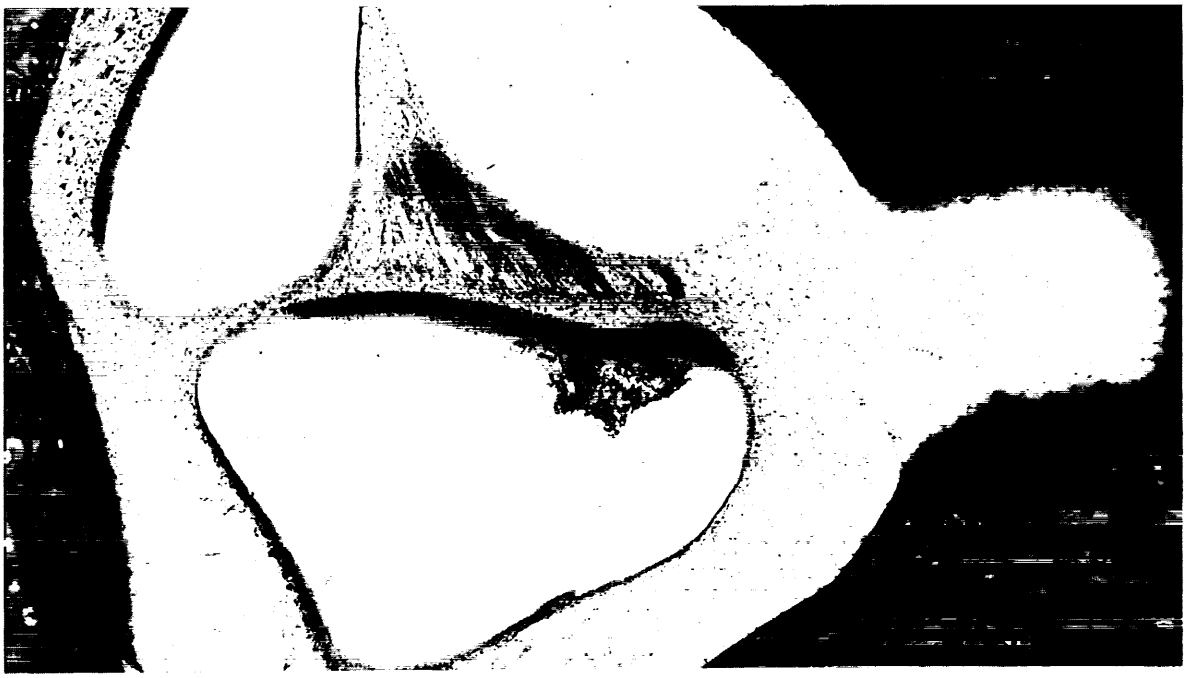

FIGURE 7.—*View of otoconia displacement from utricular macula after exposure to peak of 450 g. The medial part of otolith is pushed away toward the lateral. The animal survived for 3 weeks after the exposure.* 63×

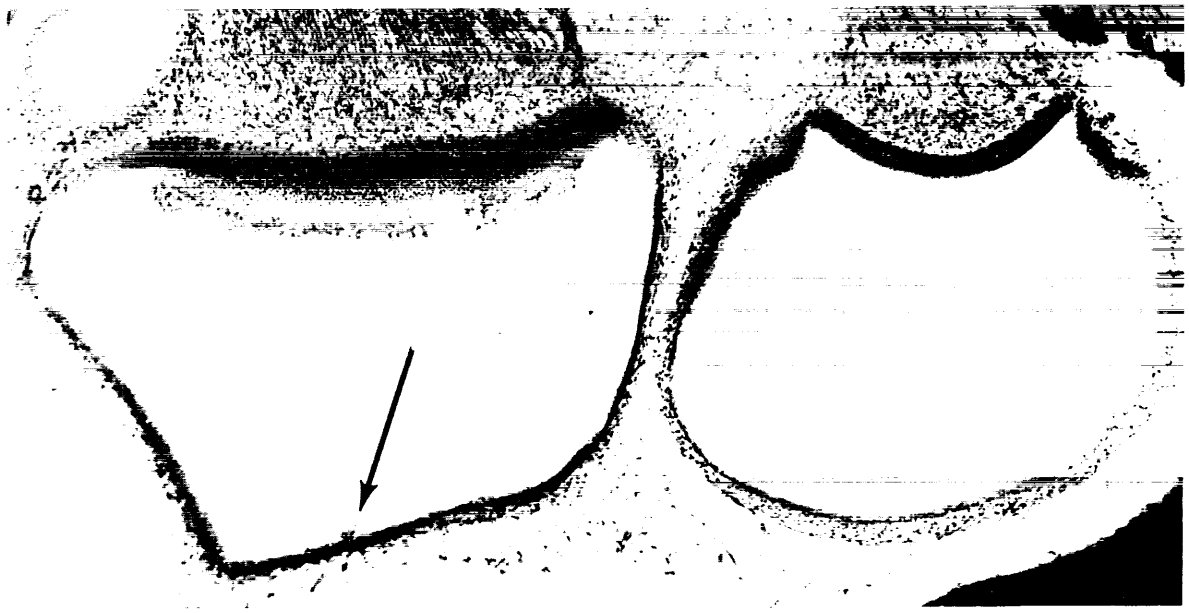

FIGURE 8.—*Photomicrograph demonstrating very little otoconia dislodgment from the utricular macula immediately after 1-minute exposure to 60 g. The otoconia* (arrow) *is placed along the posterior utricular wall.* 70×

FIGURE 9.—*View of otoconia dislocation from the utricular macula immediately after 1-minute exposure to 200 g. The otoconia* (ARROW) *is located along the utricular wall. Both horizontal semicircular canal crista and organ of Corti in basal turn are morphologically intact.* 45×

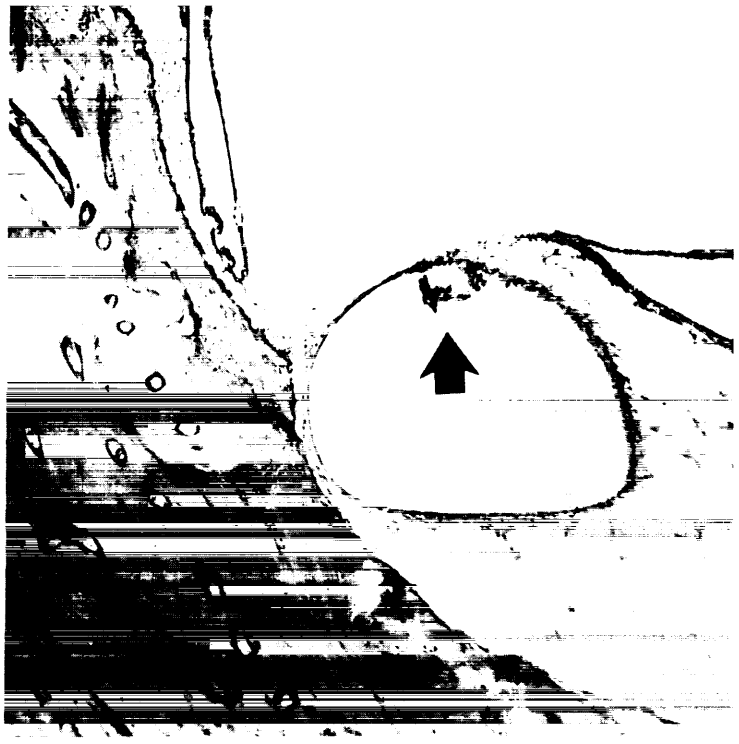

FIGURE 10.—*View of a dislocated utricular otoconia* (ARROW) *located at inferior utricular sinus-posterior semicircular canal ampulla junction, after exposure to a peak of 350 g. The animal survived for 3 weeks after the exposure.* 98×

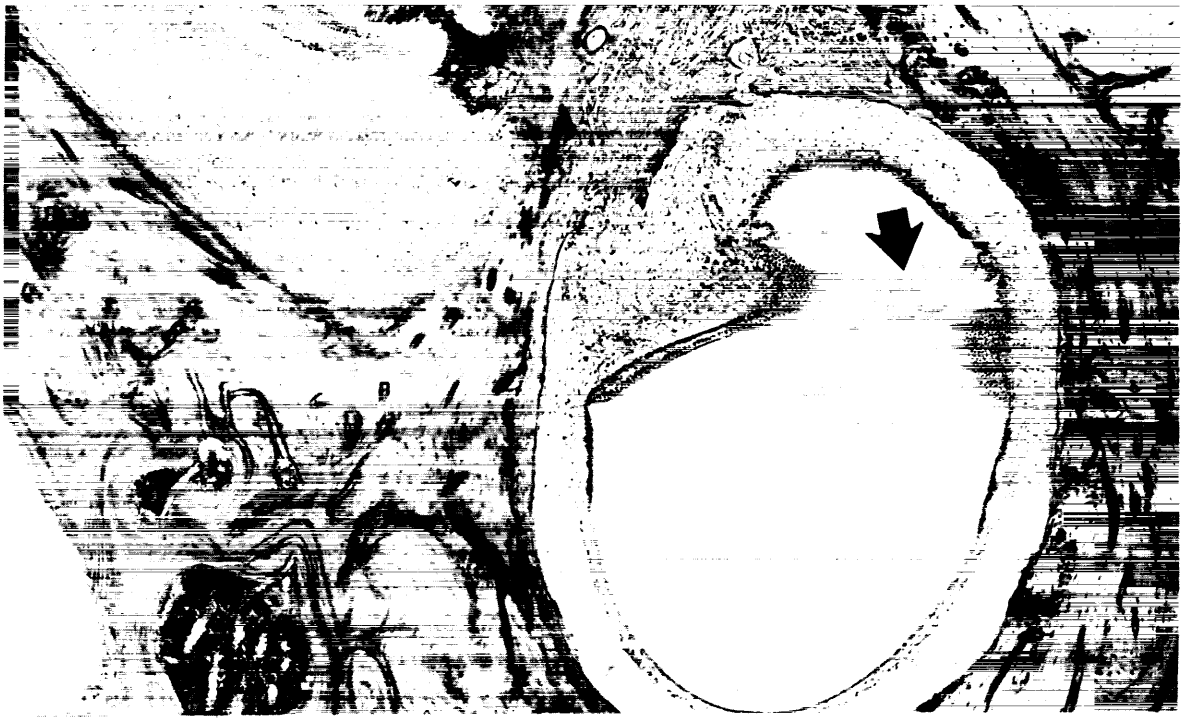

FIGURE 11.—*Photomicrograph exhibits dislocated utricular otoconia in the posterior semicircular canal ampulla* (arrow) *after 1-minute exposure to 80 g.* 66×

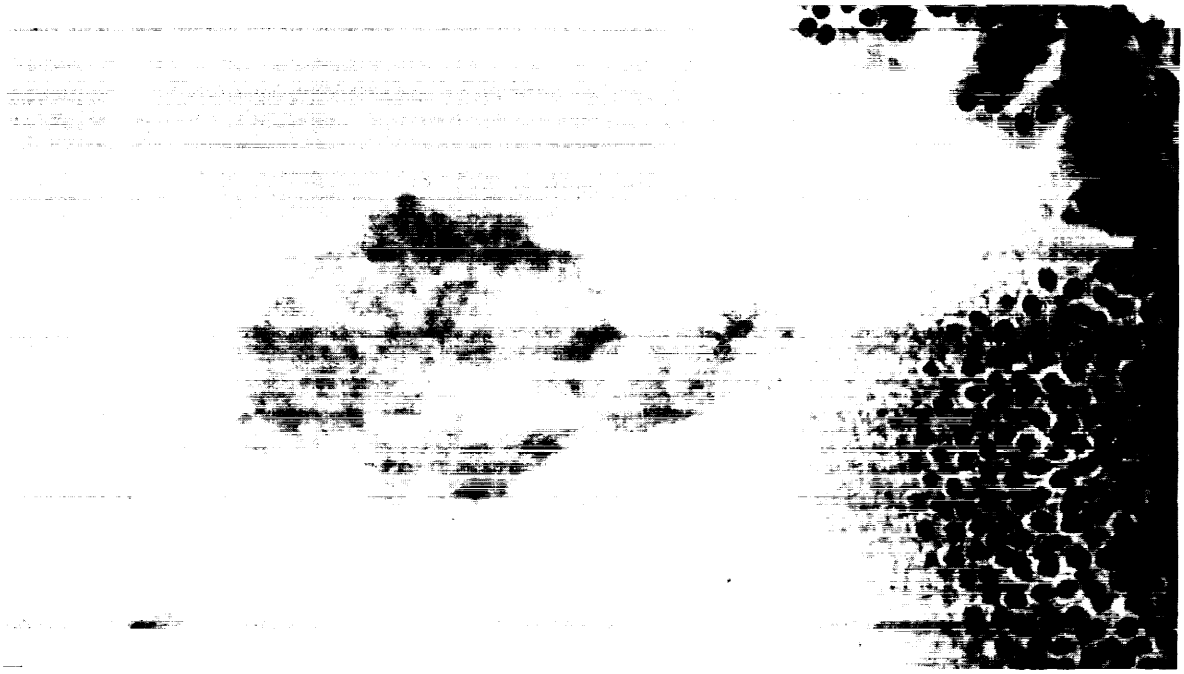

FIGURE 12.—*High magnification view of figure 11 demonstrating otoconia situated next to the crista.* 480×

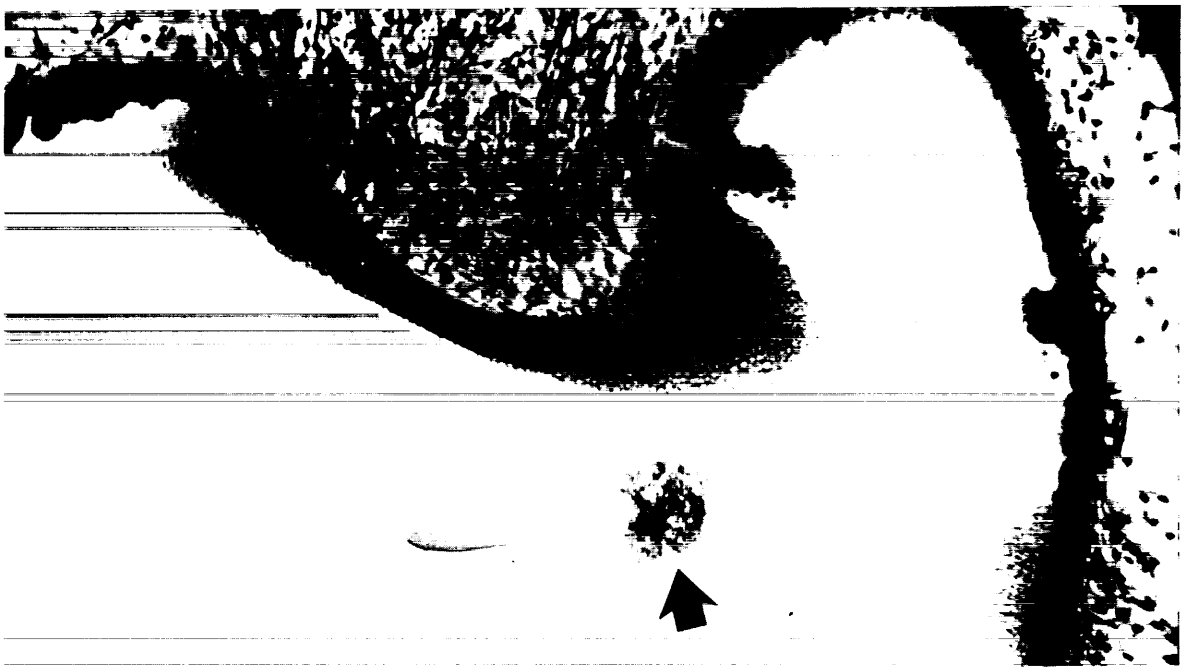

FIGURE 13.—*Photomicrograph demonstrating dislocated utricular otoconia* (arrow) *on the cupula of the posterior semicircular canal crista after exposure to a peak of 400 g.* 185×

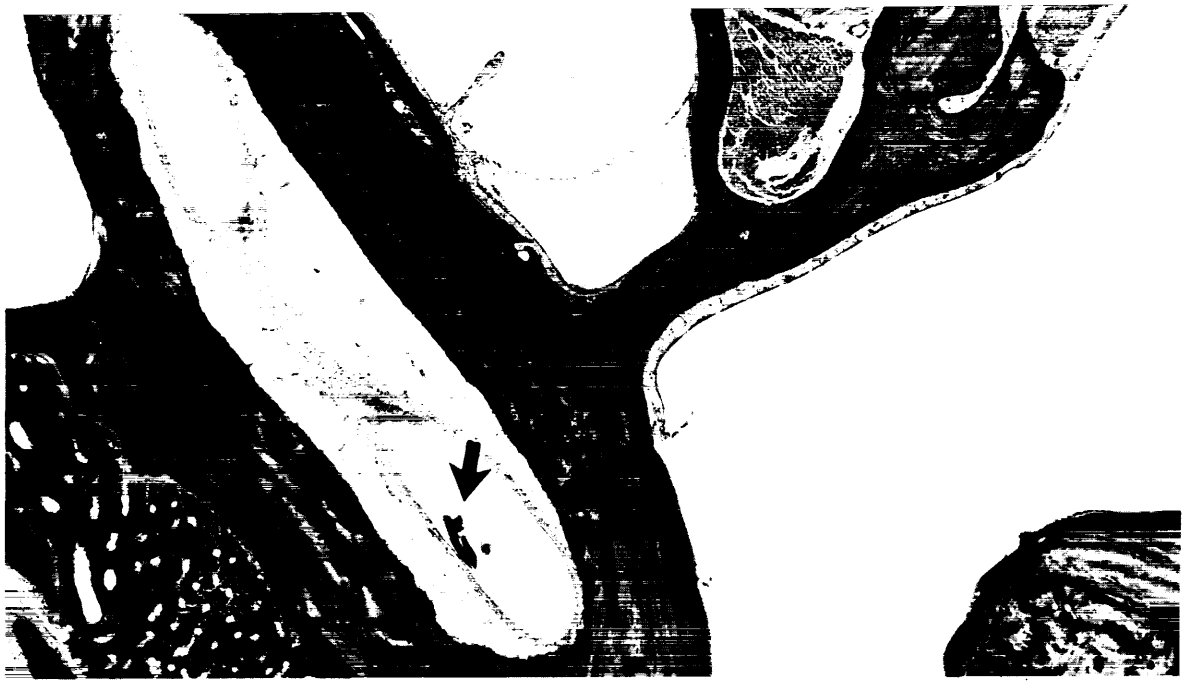

FIGURE 14.—*Photomicrograph showing dislocated otoconia in the posterior semicircular canal crus* (arrow). *The animal was exposed to 150 g for 1 minute.* 42×

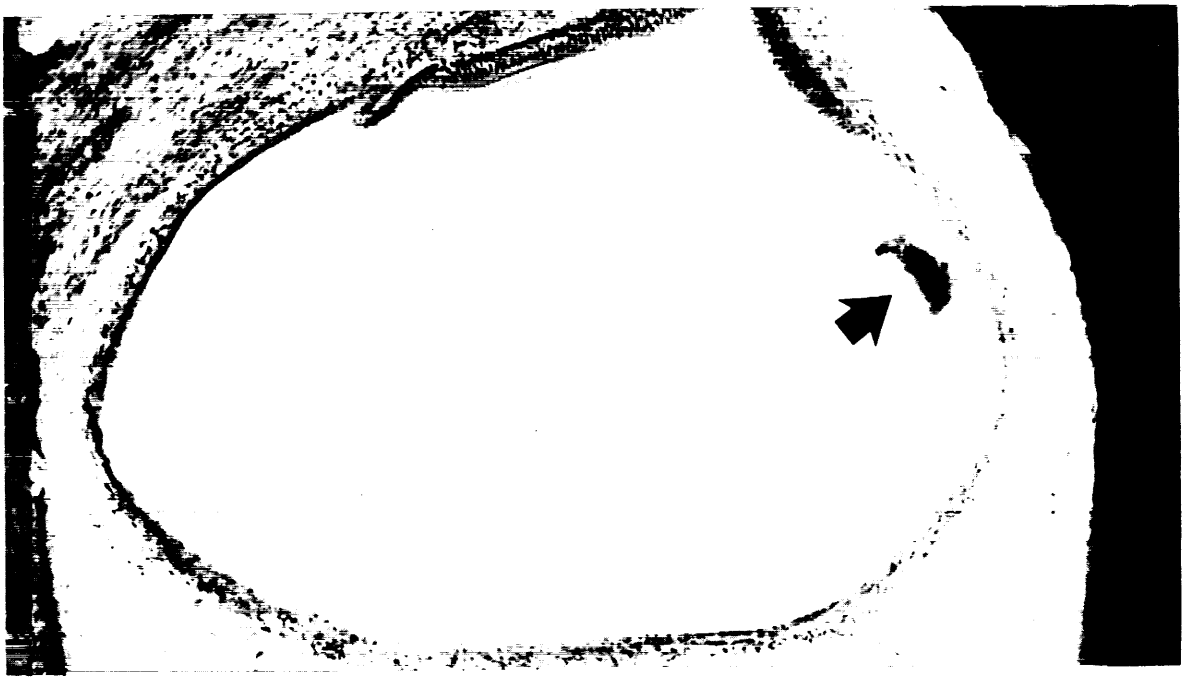

FIGURE 15.—*View of dislocated utricular otoconia* (ARROW) *in the superior semicircular canal ampulla after 3-minute exposure to 200 g. The animal died during the exposure.* 120×

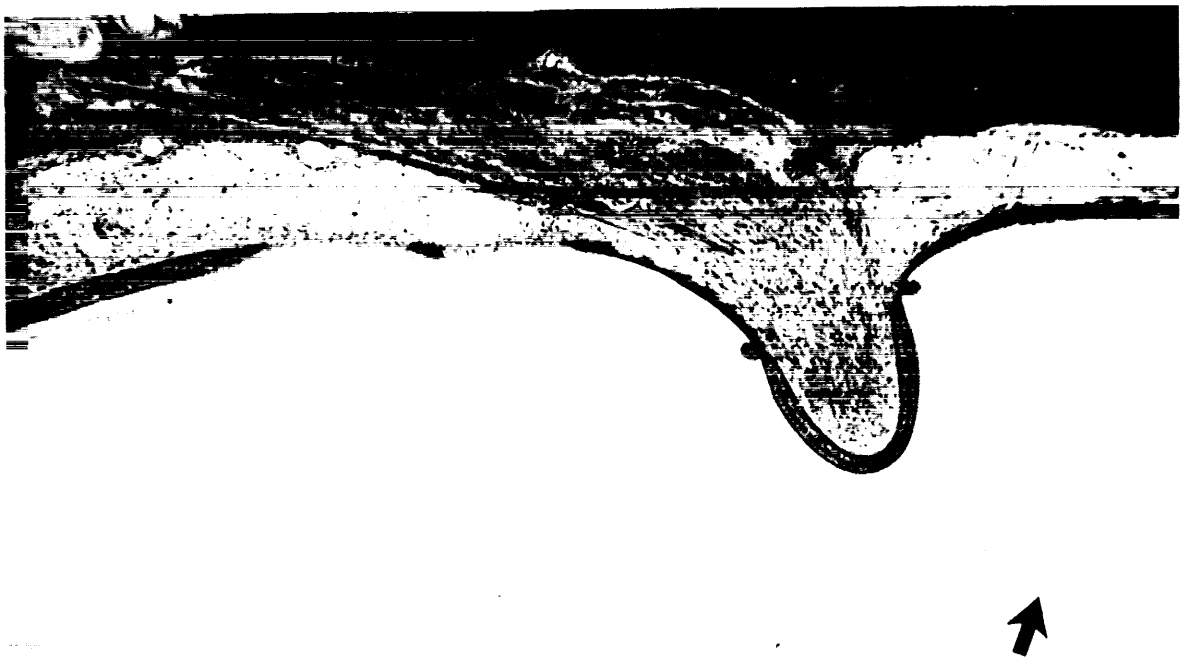

FIGURE 16.—*Photomicrograph demonstrating dislocated otoconia* (ARROW) *situated next to the cupula of horizontal semicircular canal crista, after 1-minute exposure to 75 g. Both utricular macula and horizontal semicircular canal crista are structurally normal.* 98×

for 1 minute, no definite ultrastructural alterations were observed. All findings were exactly the same as those in normal morphological controls (figs. 17 and 18). In the animals which were exposed to 200 g for 1 minute and to a peak of 450 g (fig. 19), the following ultrastructural changes were observed: (1) increased lysosomes (fig. 20), and (2) transformation of mitochondria in the nerve chalice (fig. 21).

Lysosomes could be seen also in control animals; however, in monkeys exposed to extremely high g, the lysosomes increased in size and complexity, appearing as a gross lysosome, especially in hair-cell cytoplasm. Novikoff (ref. 11) has observed gross lysosome formation in experimental anoxia, or at the start of cell necrosis. These gross lysosomes were considered to be a prodromal sign of cell death.

The nerve chalice of Type 1 hair cells of squirrel monkeys which were exposed to a peak of 450 g exhibited transformed mitochondria which appeared to have a ring-shaped or layered structure. In general, the number of mitochondria and the complexity of their internal structure vary with the energy requirements for the specific functions carried out by the cell itself. Ring-shaped or layer-appearing mitochondria exhibited simplification of their internal structure, and the findings might suggest relative inactivity of the nerve chalice. Van Nimwegen and Sheldon (ref. 12) reported in their study on early postmortem changes in neurons that the transformation of mitochondria has been felt to be the most sensitive indicator of abnormal cellular condition. If this transformation of mitochondria in the nerve chalice is the result of anoxia, even though temporary, the nerve chalice might be the weakest structure. Or, this might be the result of overstimulation to the impulse transmission system.

The enormous variety and large number of synaptic structures in the vestibular sensory epithelia of squirrel monkeys have been reported by Spoendlin et al. (ref. 1), who suggested that uninterrupted synaptic transmission might be provided in order to guarantee a steady function. A large number of various kinds of accessory synaptic structures in the hair cells of normal monkeys and of those exposed to different high-g fields were observed in the present investigation (fig. 22).

Based on these ultrastructural findings, it is supposed that extremely intensive linear forces could probably influence the mechanism of impulse transmission, either directly or indirectly, through the regional circulatory disturbances.

Functional Tests

The severity of the ataxic posture and gait, both on the floor and on a rod, and spontaneous eye movements immediately after the exposure, were roughly parallel to the intensity of the g-levels of exposure (table 1). Some squirrel monkeys exposed below 60 g did, and others did not, exhibit very slight signs of ataxia, which is a slight waddling on the floor or on a rod, and none showed spontaneous eye movement. In animals exposed to 100 g or above, all ataxic signs were more steadily positive, and spontaneous nystagmus was more frequently observed. Severe symptoms were usually observed

TABLE 1.—*Gross Ataxia and Spontaneous Eye Movement Immediately After Exposure to High-Intensity Acceleration Stimuli*

[*p*, peak-g exposure; +++, severe; ++, moderate; +, slight; ±, questionable; −, negative]

g-level	Number of animals	Ataxia		Spontaneous eye movement
		Floor	Bar	
20	2	−	−	−
30	3	±	±	−
40	2	+	−	−
50	3	+	+	−
60	4	++	++	−
75	2	+	+	−
80	1	±	−	±
100	3	++	++	±
125	3	++	++	±
150	6	+++	+++	+
175	4	+++	++	+
200	6	+++	++	+
200 *p*	1	−	−	−
250 *p*	1	+	++	+
300 *p*	1	−	+	+
350 *p*	3	++	+++	+
400 *p*	3	++	+++	++
450 *p*	4	++	+++	±
500 *p*	1	+++	+++	++

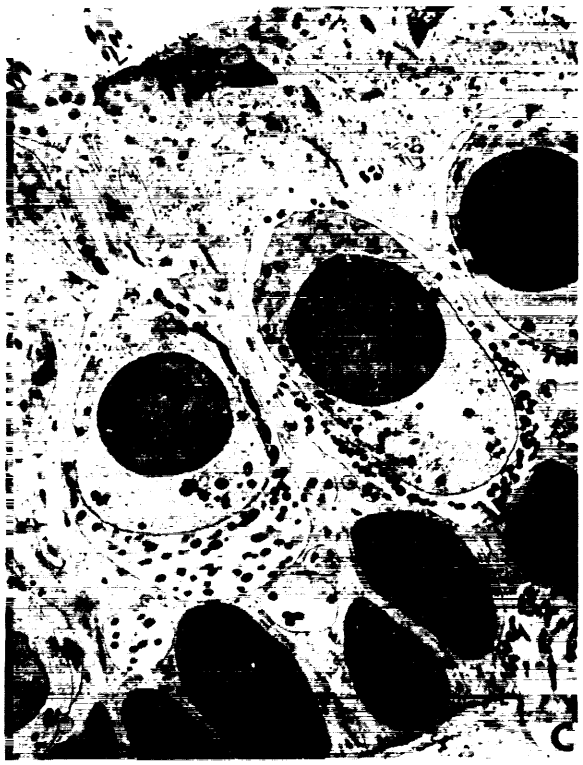

FIGURE 17.—*Electron micrographs demonstrating the apical part of sensory epithelium in the utricular macula from the animal exposed to 30 g for 1 minute. Slightly oblique section through hair-cell type 1* (HI) *is seen in* A, *and type 2* (H) *in* B. (C): *Nerve chalice. No significant changes could be found.* C *shows general view of the sensory epithelium. 2600* ×. *Scale 1 micron.*

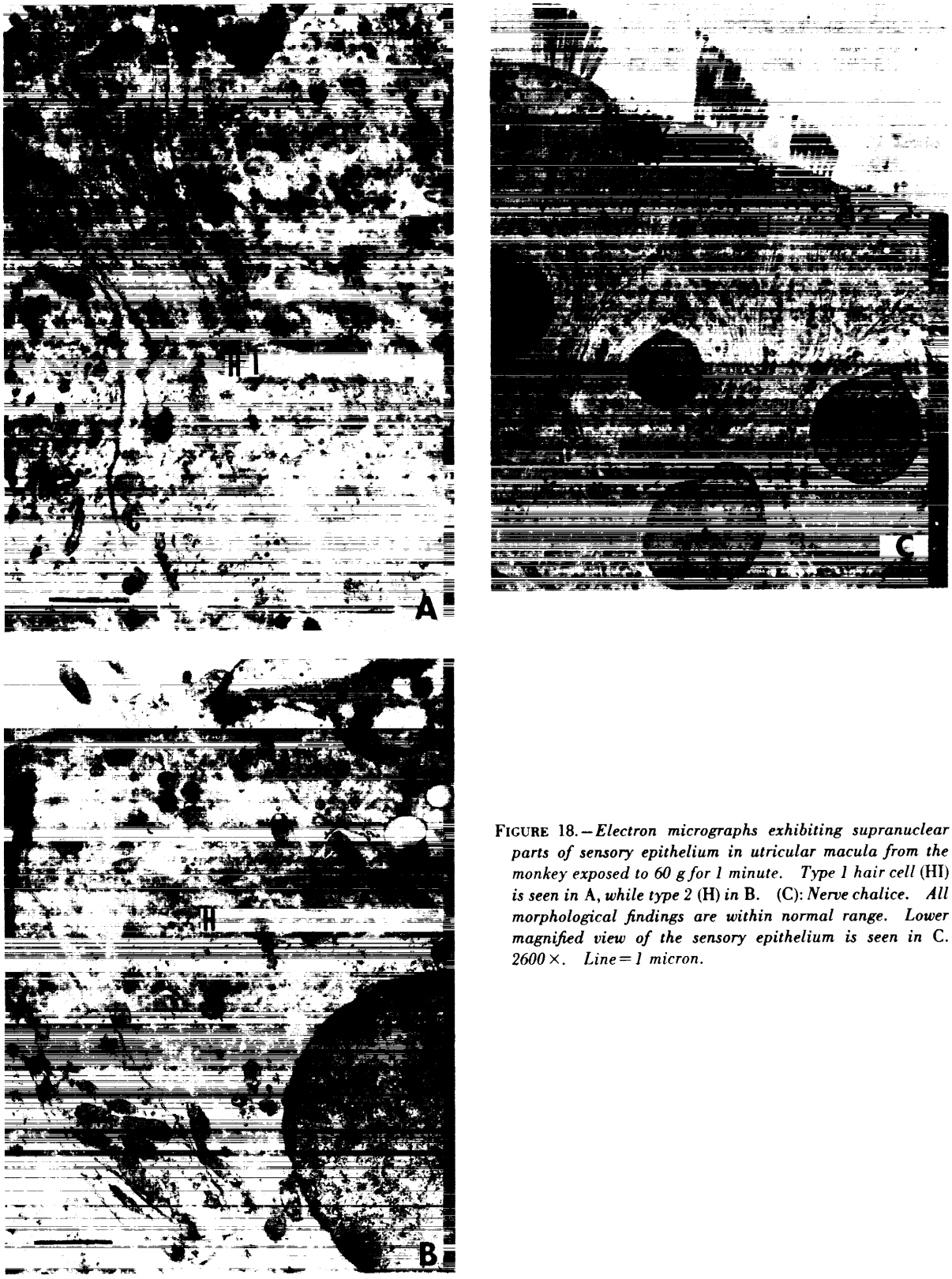

FIGURE 18.—*Electron micrographs exhibiting supranuclear parts of sensory epithelium in utricular macula from the monkey exposed to 60 g for 1 minute. Type 1 hair cell* (HI) *is seen in* A, *while type 2* (H) *in* B. (C): *Nerve chalice. All morphological findings are within normal range. Lower magnified view of the sensory epithelium is seen in* C. *2600×. Line = 1 micron.*

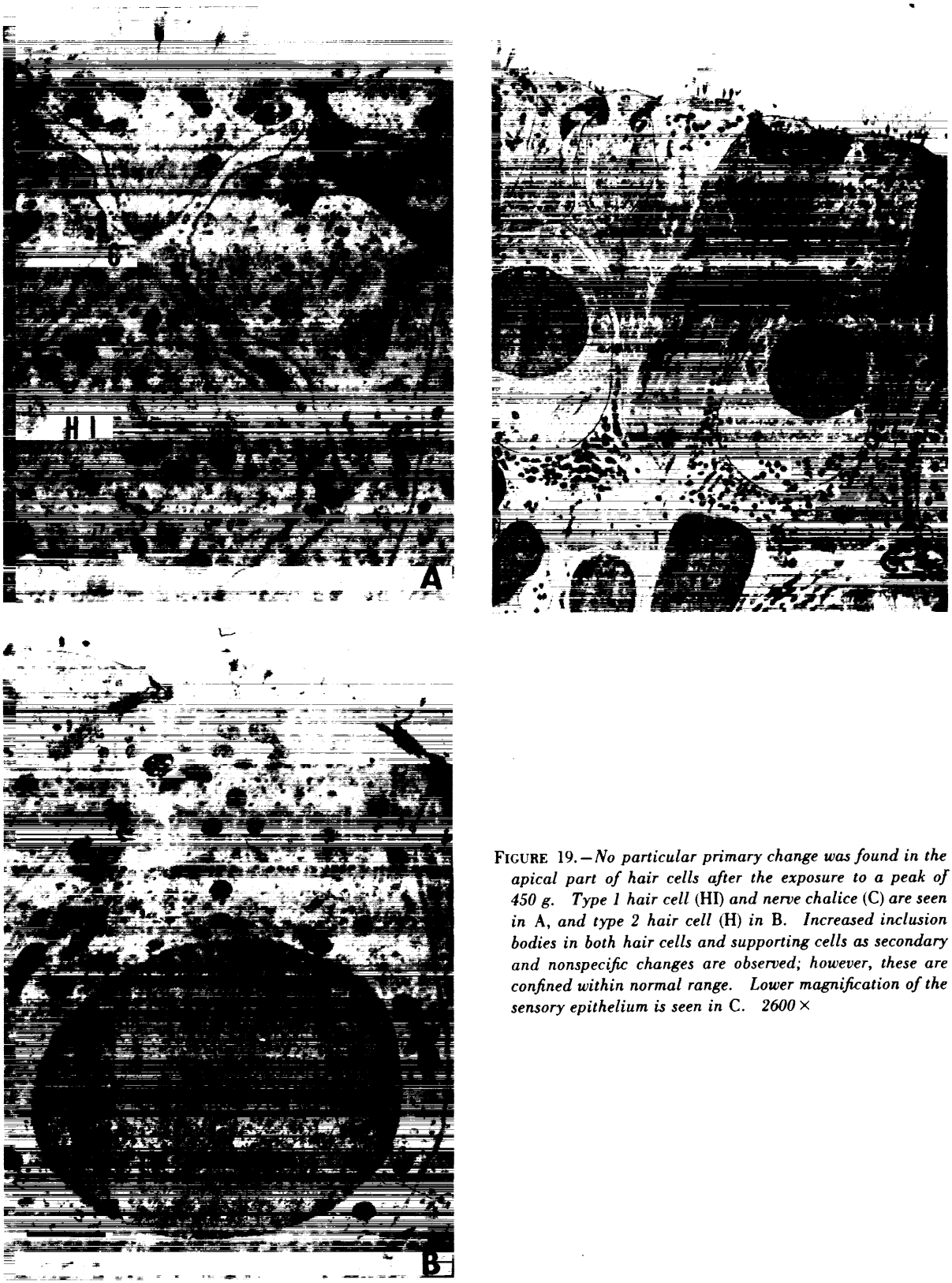

FIGURE 19.—*No particular primary change was found in the apical part of hair cells after the exposure to a peak of 450 g. Type 1 hair cell* (HI) *and nerve chalice* (C) *are seen in* A, *and type 2 hair cell* (H) *in* B. *Increased inclusion bodies in both hair cells and supporting cells as secondary and nonspecific changes are observed; however, these are confined within normal range. Lower magnification of the sensory epithelium is seen in* C. *2600 ×*

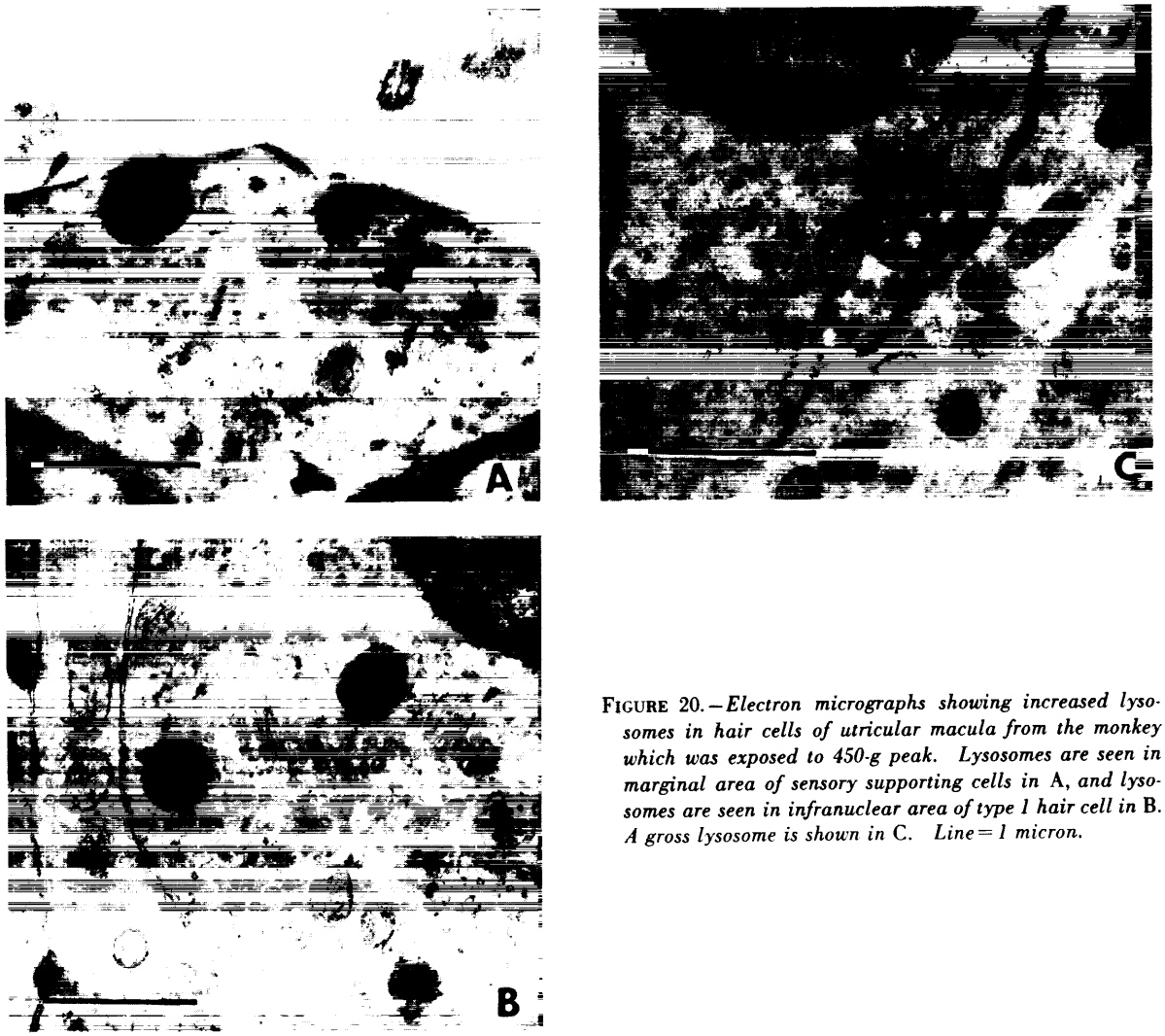

FIGURE 20.—*Electron micrographs showing increased lysosomes in hair cells of utricular macula from the monkey which was exposed to 450-g peak. Lysosomes are seen in marginal area of sensory supporting cells in* A, *and lysosomes are seen in infranuclear area of type 1 hair cell in* B. *A gross lysosome is shown in* C. *Line = 1 micron.*

above the 150-g level of exposure (figs. 23 and 24). These gross ataxic symptoms were found to diminish fairly rapidly in consecutive examinations carried out 4, 8, 24, 48, and 72 hours after exposure. These symptoms could not be considered only as a result of the otolith end-organ disorders, but more probably as a combination of the peripheral end-organ disorder and the temporary and rather direct effects to the regional circulatory system or the higher nervous system. However, regardless of the level of the g-force, no pathological lesions were observed by light microscopy in the vestibular nuclei area of six representative animals.

The results of monkey rail tests under the behavior-conditioning procedure were almost identical with the gross ataxic symptoms, except in the case of one animal exposed to 30 g (table 2). The animal which was exposed to a peak of 450 g required about 1 month to regain its pre-exposure threshold value. This result was also identical to that found after surgical utriculosaccular ablation.

Figure 25 demonstrates the difference in caloric thresholds obtained prior and subsequent to the different g-level exposures in 19 squirrel monkeys. Each dot represents the difference between caloric threshold values (average of both ears) before and after the exposure. The differences were neither significant nor exactly related to the exposed g-levels, and were almost within the normal range, except for a few cases.

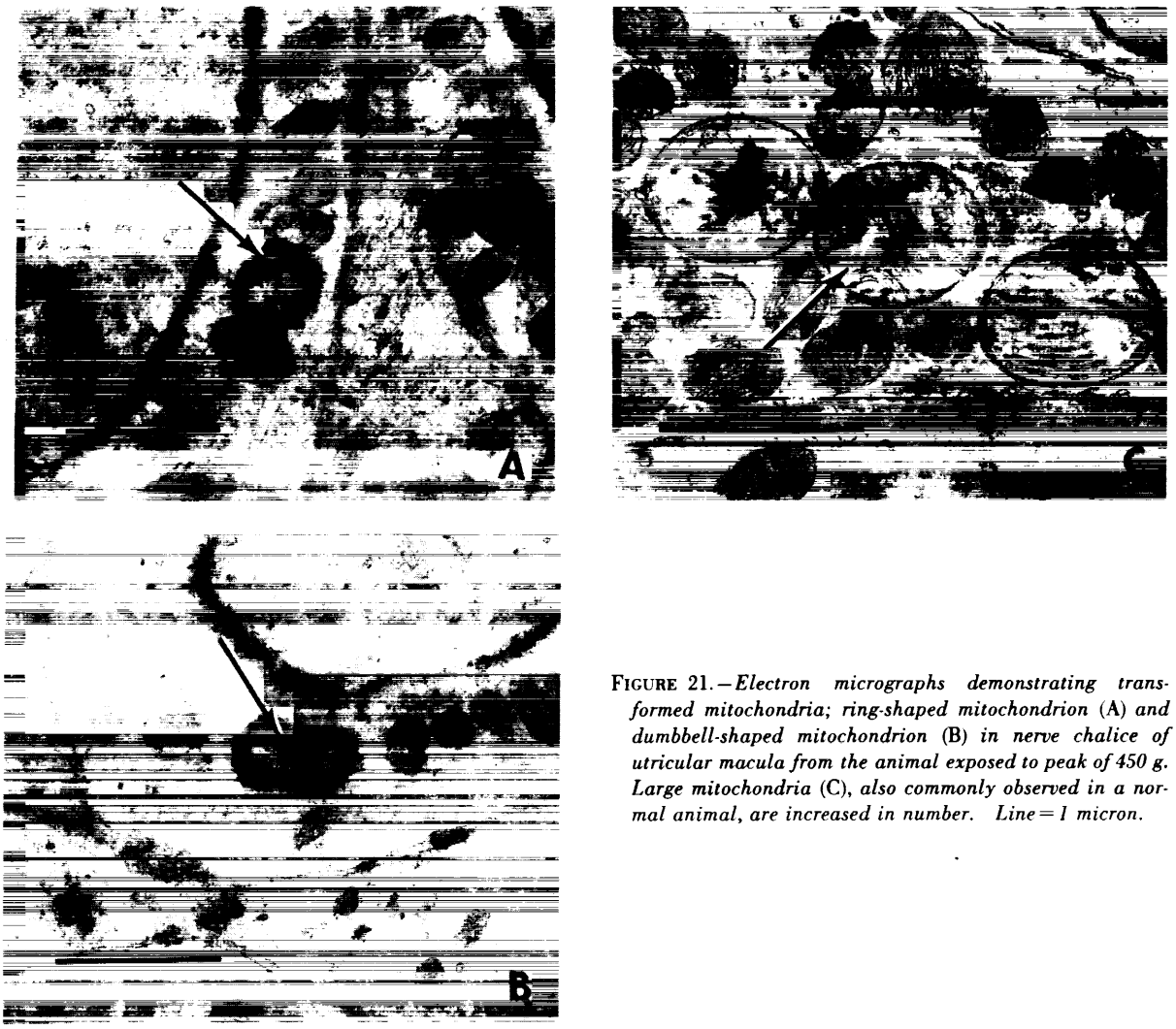

FIGURE 21.—*Electron micrographs demonstrating transformed mitochondria; ring-shaped mitochondrion* (A) *and dumbbell-shaped mitochondrion* (B) *in nerve chalice of utricular macula from the animal exposed to peak of 450 g. Large mitochondria* (C), *also commonly observed in a normal animal, are increased in number. Line = 1 micron.*

TABLE 2.—*Results of Ataxia Rail Tests Under the Behavior-Conditioning Program After Exposure to High-Intensity Linear Acceleration*

[Smaller number in rpm indicates the severity of disequilibrium. *p*, peak-g exposure; N.D., no data obtained. (Successive numbers in postexposure threshold column indicate the number of days after exposure)]

Animal	g-level	Pre-exposure threshold, rpm	Postexposure threshold, rpm																		
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	22	30	35
A	20	450	.....	450	300	350	.....	.....	450	450	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
B	30	950	.....	950	950	950	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
C	30	750	.....	450	.....	450	.....	.....	650	700	650	.....	550	.....	.....	.....	.....	.....	550	700	750	800
D	40	750	.....	950	950	950	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
E	50	950	.....	950	950	950	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
F	50	800	.....	800	950	950	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
G	60	950	.....	950	950	950	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
H	60	800	.....	800	800	800	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
I	200	N.D.	.....	N.D.	.....	500	.....	.....	950	950	950	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
J	450 *p*	700	.....	50	.....	.....	.....	.....	250	300	400	.....	.....	.....	.....	.....	.....	.....	500	450	700	550

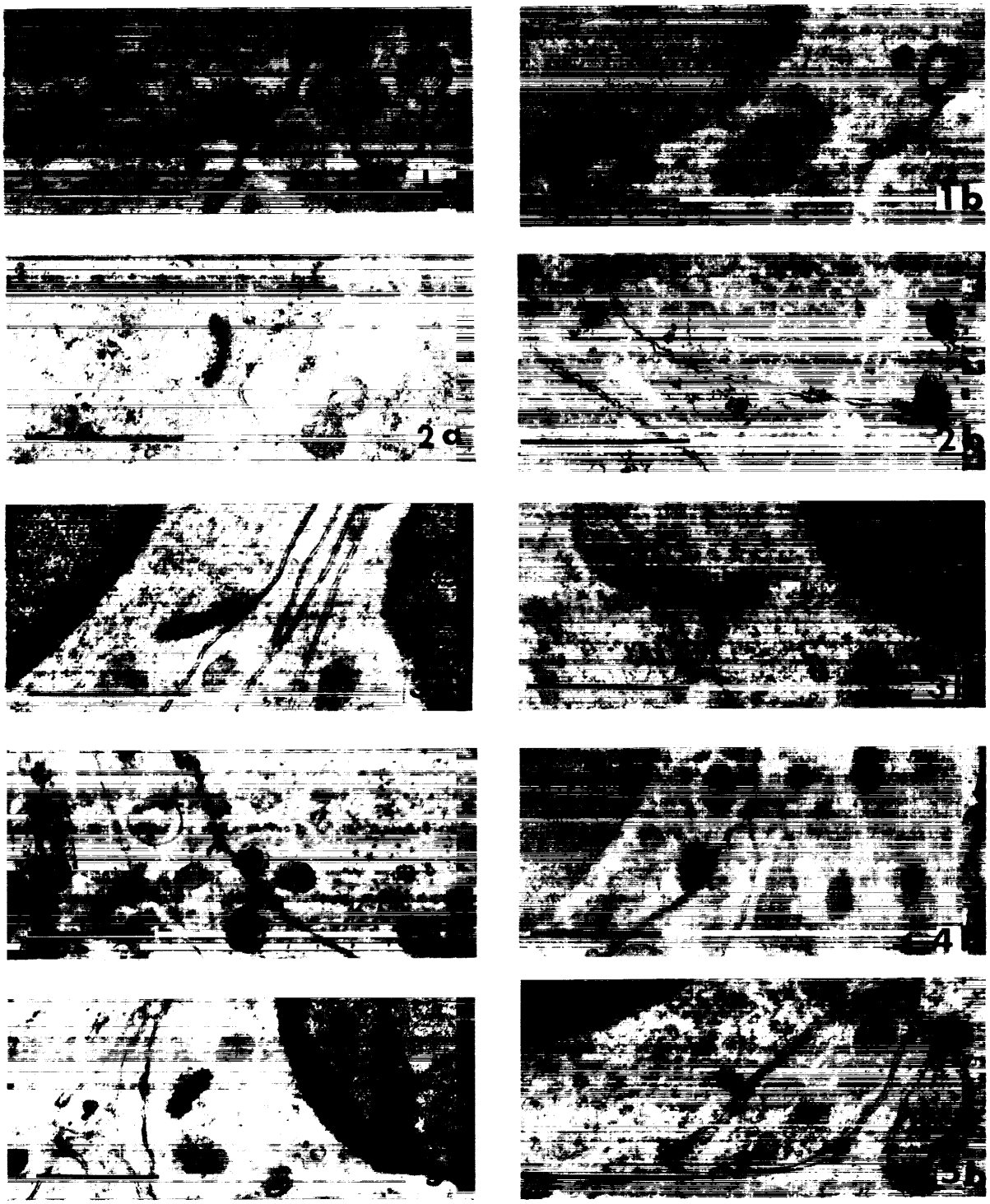

FIGURE 22.—*Electron micrographs demonstrating different accessory synaptic structures from monkeys exposed to different g-levels.* (1) *normal;* (2) *30 g, 1 minute;* (3) *60 g, 1 minute;* (4) *60 g, 1 minute; and* (5) *450 peak-g.* a *series: type 1 hair cell, and* b *series: type 2 hair cell.*

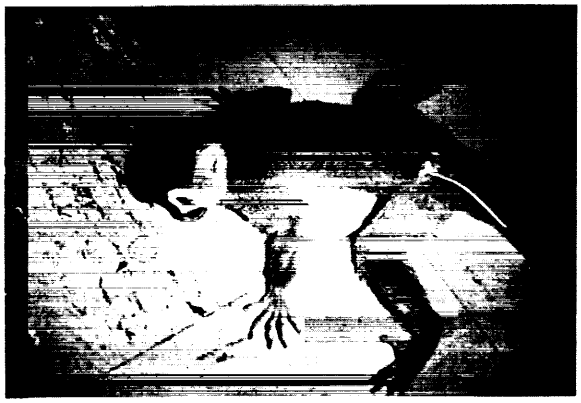

FIGURE 23.—*Severe ataxic posture of the squirrel monkey on the floor after the exposure to 200 g for 1 minute. Note stretched fingers indicating attempt to maintain balance.*

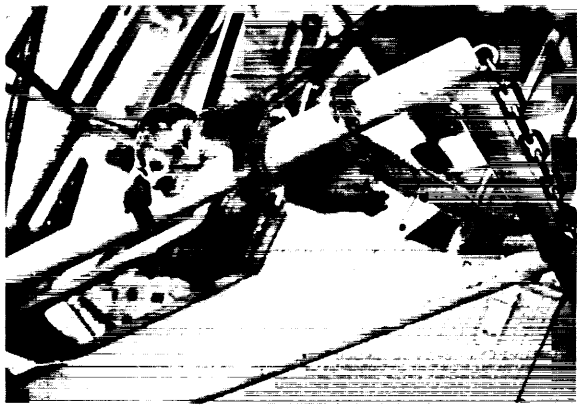

FIGURE 24.—*Squirrel monkey demonstrating difficulty in staying on rod after exposure to 175 g for 1 minute. They ordinarily stay on rod (tree branch) in their daily lives.*

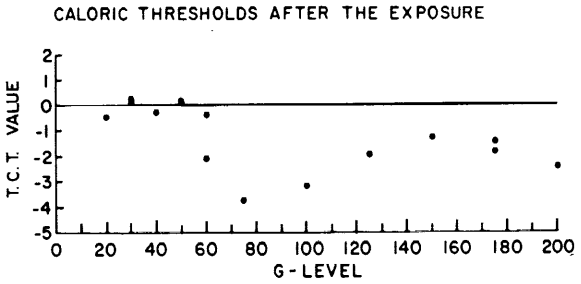

FIGURE 25.—*Each dot represents the difference between caloric threshold values (average of both ears), before and after the exposure, in each animal. (T.C.T., threshold caloric value.)*

Results of motion-sickness tests in 10 squirrel monkeys rotated at 10 rpm for 15 minutes in the Pensacola slow rotation room after their exposure to the acceleration stimuli are presented in table 3. During preexposure testing in the room, motion sickness had occurred three times out of the three trials given in all but two of the animals; in those two, the frequency of occurrence was two out of the three trials. After exposure to a level of 60 g and below, seven squirrel monkeys fairly consistently demonstrated emesis, even on the eighth postexposure day. No emesis was seen in two monkeys exposed to 60 g or 200 g for 1 minute nor in the one exposed to a peak of 450 g until 3 weeks' postexposure at which time it was evident in two of the animals (one at 200-g and one at 450-g peak).

This delayed recovery of some part of inner ear function presents several interesting points. First of all, as has been demonstrated by Johnson et al. (ref. 13), the inner ear end-organ apparatus is essential to cause emesis in the slow rotation room. Absence of emesis cannot be the result of suppression of nervous-system function because almost all data reported from other threshold caloric tests, gross ataxia tests, and monkey rail tests demonstrated good recoveries and functions. Therefore, the results of the present study in the slow rotation room trials are more likely to be indicative of some effect at the end-organ level. If emesis is the indication only of semicircular canal function, then either canal function is directly suppressed by the high-g exposure itself, or canal function is temporarily altered because of the otolith end-organ ablation. The results of the present threshold caloric tests, however, demonstrated good semicircular canal function. If emesis is the reflection of both otolith and semicircular canal functions, or of otolith function only, the otolith end organ might have had some initial importance in causing emesis, and it was replaced by semicircular canal function, as the destroyed otolith end organ will not regain its function. Or, most probably, otolith end-organ destruction was incomplete in the present series. The essentiality of the inner ear end organs for emesis has been confirmed by another investigation (ref. 9); however, there are many other factors involved in the cause of emesis. For example, some squirrel monkeys show somewhat unsteady data in successive tests; and on certain days, squirrel monkeys demonstrate a tendency not to vomit easily.

TABLE 3.—*Results of Motion-Sickness Test in the Slow Rotation Room at 10 rpm for 15 Minutes*

[*p*, peak-g exposure; +, positive emesis within 10 minutes; +., positive emesis between 10 to 15 minutes; ±, prodromal sign of emesis only and no real emesis; −, no emesis]

Animal	g-level	Days, postexposure										
		1	2	3	4	5	6	7	8	9	10	21
A	20		+	−	±				+			
B	30		+	±	±				+			
C	30		−	+.	−				−			
D	40		+	+	+				+.			
E	50		+	+.	+.				+.			
F	50		+	+	+.				+			
G	60		+	+	−				+			
H	60		−	−	−				−			−
I	200		−	−	−				−			+
J	450 *p*		−	−	−				−			+

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DISCUSSION

SMITH: In regard to the otoconia which were displaced from the macula and found at various places in the vestibule, could any of this displacement have occurred, or been changed, in the preparation process? Could the otoconia have been shifted to other parts of the vestibule from that to which they were displaced by the experimental exposure? Did you look at any of the maculae in the intact animal?

IGARASHI: Yes. We examined quite a few control animals by a similar procedure, but we could not see any dislocation or disappearance of otoconia. Another point I would like to emphasize is this pattern of dislocation. The amount of dislodgment is fairly parallel to the level of exposed g-force. In other words, if the monkey was exposed to very high g, the otoconia were completely washed out. If it was exposed to 60 g, very few otoconia were dislodged from the macula utriculi.

SMITH: In acoustic trauma, which might be a somewhat similar exposure in that there is an excessive pull on the hairs of the cochlear hair cells, one finds that the hair cells are first of all greatly distorted, then they are swollen and displaced. Of course, the maculae are more compact tissue, and the cells may not so readily swell there. But perhaps the excessive pull would displace some of the hairs or pull the cuticular plate out of the macula. Did you see anything of that sort?

IGARASHI: Not clearly. It seems to me that the cuticular plate is a fairly strong structure, and below the cuticular plate level, I do not believe I could detect any striking difference in the macula.

HUERTAS: Did I understand you correctly that you studied also the brain stem and did not find any changes in its structure?

IGARASHI: Yes. I have only six representative cases. In these cases, we could not detect any neuropathological change in the vestibular nuclei area.

BERGSTEDT: For your purpose, 1-minute exposure is naturally reasonable, but have you ever tried to shorten the exposure time to fractions of a second and increase the g? I am thinking about all the traffic accidents after which positional vertigo appears. This would be of some interest. Another point is in regard to the old discussion as to whether the cupula has a specific weight different from that of the surrounding fluid. After studies like this one, I believe this problem can almost be excluded.

BENSON: What is the effect of smaller g-forces applied for a longer time? A number of subjects who have run on the centrifuge and were exposed to transverse accelerations of 4 g for some 15 to 20 minutes, found in the 24 hours following this exposure that they have had quite severe positional vertigo, which took 3 days to pass off. Is there evidence of physical damage with much smaller but longer applied linear accelerations?

IGARASHI: What I have done is on the basis of only fixed time periods; so, I really cannot answer.

THOMPSON: I think my question was already asked in another form. However, as impact levels of 500 to 800 g are survivable by the head in many cases and the time is in microseconds, do you think that you could extrapolate your data to those short periods?

IGARASHI: I do not know.

Behavioral Loss and Otoconia Displacement in Guinea Pigs Following Linear Acceleration[1,2]

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SUMMARY

Guinea pigs were examined with behavioral tests, gross dissection, and celloidin serial sections of the temporal bone following exposure to either linear acceleration, vibration, or loud sound. The major results of these investigations are as follows: (1) Minimum acceleration intensity for loss of the righting reflex and swimming ability is approximately 50 g applied for 60 seconds. Loss of otoconia from the maculae may be produced by acceleration as low as 12 to 25 g for 195 to 330 seconds. Acceleration at 100 g for 30 seconds results in severe loss of otoconia from all maculae. Although the stimulus intensity required to produce evidence of behavioral loss is greater than the stimulus intensity which results in structural damage, ability to perform the righting reflex and otoconia loss ratings are highly correlated ($r = -0.69$). (2) Recovery of swimming ability and the righting reflex may take place from 1 to 64 days following exposure to accelerations of up to 300 g for 15 seconds. Exposure to 400 g for 15 to 20 seconds results in irreversible loss of the righting reflex and severe disturbance of swimming ability. No histological evidence for otoconia reformation during the postexposure period was obtained, but the possibility of replenishment of the gelatinous layer is suggested.

INTRODUCTION

This paper is concerned with the effects of intense linear acceleration on the vestibular system. Exploration of stimulus parameters which produce damage to the vestibular apparatus has been our major interest. Assessment of vestibular damage following exposure to acceleration stimuli has been accomplished with (1) behavioral techniques, (2) gross dissection, and (3) histological examination of celloidin serial sections of the temporal bone.

Studies of vestibular damage are of theoretical as well as practical interest. From a theoretical view, determination of thresholds for structural damage with a variety of stimuli should lead to a more complete understanding of the dynamics of vestibular stimulation, particularly with regard to functional characteristics of the various components and sections of the vestibular apparatus. From a practical view, exposure of human beings to unusual acceleration environments during aerospace missions and as a result of accidents indicates

[1] Support for this work came from U.S. Air Force under Contract Nos. AF 33(615)-2276 and AF 33(615)-1252 with the Washington University School of Medicine and with the Space Defense Corp.

[2] The Rules for Animal Care established by the National Society for Medical Research were followed throughout the course of these experiments.

the necessity for obtaining information regarding the response of the vestibular apparatus to intense stimulation.

EXPERIMENT I. LINEAR ACCELERATION: RELATIONSHIP BETWEEN EXPOSURE DURATION AND PEAK ACCELERATION

Purpose

This experiment was designed to investigate the relationship between exposure duration and peak acceleration, for triangular or trapezoidal g-time exposure histories, in the production of vestibular damage. If the otoconia and supporting cells are assumed to be a simple mass-spring system, two types of damage threshold effects would be expected: (1) minimum peak acceleration for long exposure times, and (2) minimum velocity change or area under g-profile for short-exposure durations. The purpose of this investigation was determination of a duration-peak acceleration damage threshold curve.

Method

Subjects

Data from 32 guinea pigs which were run on five separate occasions were compiled to provide a picture of the relationship between exposure duration and peak g in the production of vestibular damage.

Apparatus

The apparatus employed to accelerate the subjects, the Space Flight Acceleration Profile Simulator (SFAPS), has been described in previous articles (refs. 1 and 2).

Essentially the SFAPS is a centrifuge which consists of a 92-centimeter primary arm, rotational center, mass balance, payload capsule, motive power source, support structure, and instrumentation to detect the acceleration profile. Special design features allow onset and decay rates up to 40 g/sec.

Exposure and Behavioral Assessment Procedures

Prior to and following exposure, the experimental animals were subjected to tests of the righting reflex and, in most cases, of swimming ability in order to obtain an estimate of vestibular capability. With this procedure each animal served as his own control.

The phrase "righting reflex" refers to the complex series of movements whereby a blindfolded animal which is dropped in an inverted position achieves a "four-point landing." Prior to exposure the animals were able to right themselves consistently when dropped from heights of 25 to 30 centimeters. Swimming ability was determined by placing the guinea pigs in a 45- by 100-centimeter tank which was filled with water to a depth of 25 centimeters. Normal guinea pigs are excellent swimmers; they will move in straight lines unless presented with a barrier and will surface readily when submerged.

For each run on the SFAPS the subject was placed in a coffinlike box which provided dorsal support. The subject's nose was taped to a molded headpiece which assured proper alinement of the temporal bones during acceleration. All animals were subjected to acceleration in the $+G_x$ orientation, as illustrated in figure 1.

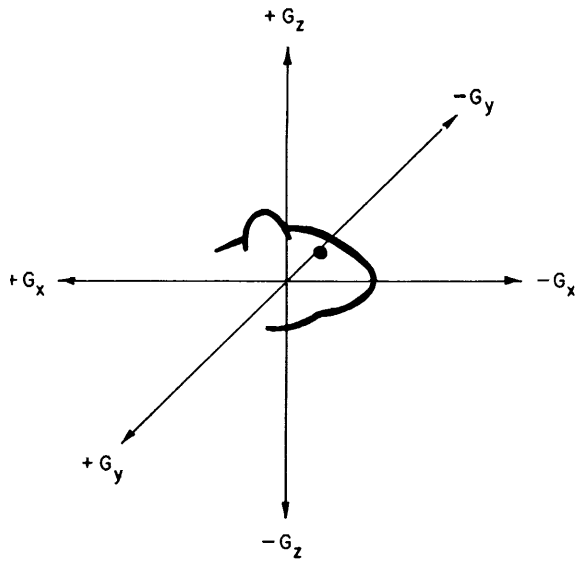

FIGURE 1.—*Orientation of the subject with respect to the forces generated by the Space Flight Acceleration Profile Simulator. The arrows represent the inertial resultant of the head acceleration, and otoconia displacement for the various directions would be as follows:*

$+G_x$ *nose to neck*	$-G_z$ *eye to jaw*
$-G_x$ *neck to nose*	$+G_y$ *left to right*
$+G_z$ *jaw to eye*	$-G_y$ *right to left*

For runs which were designed specifically to attack the problem of long-exposure duration, a trapezoidal acceleration profile was employed. After the initial rise, acceleration was maintained at a specified peak g for varying periods before return to zero. Desired dwell periods were determined after consideration of the area under the acceleration profile, which may be presented in g-seconds. An attempt was made to determine threshold for behavioral loss in terms of the number of g-seconds as well as peak g.

Behavioral observations were performed prior to exposure. Behavioral damage determinations were not made until 24 hours after exposure in order to eliminate transient effects.

Anatomical Procedures

Gross dissection.—Examination of the temporal bone with the techniques of gross dissection was employed following suggestions by Engström and Spoendlin (personal communications). Careful removal of the stapes footplate and surrounding bone affords the experimenter an excellent view of the membranous labyrinth, and it is a simple matter to determine major otoconia displacement under low magnification.

Histology.—All guinea pigs were anesthetized with veterinary Nembutal and the thorax opened. A cannula was inserted into the aorta through the left ventricle, and blood was washed out with physiological saline. This was followed by fixative (Heidenhain-Susa). The temporal bones were then removed and put in more fixative for 16 hours. This was followed by 95 percent alcohol for 16 to 24 hours after which each bone was placed in 3 percent HCl and changed daily for 3 to 5 days or until decalcification had been completed. The specimens were then washed for 24 hours in running water, dehydrated in different grades of alcohol (50, 70, 80, and 95 percent, and absolute) for 12 hours each, then immersed in absolute alcohol and ether (equal parts) for 6 hours, after which they were put into 2, 4, 8, and 12 percent celloidin for 3 days each, and finally embedded in 12 percent celloidin. Sections were cut serially at 15 microns, and every fifth section was stained with Harris' hematoxylin and eosin and mounted in Canada Balsam. Occasionally, it was necessary to stain and mount intervening sections when additional information was needed.

Degree of otoconia loss was judged on a basis of 1+ to 5+. A rating of 5+ was employed to indicate complete removal of otoconia from the macular surface. The rating levels of 1+ to 4+ were used to indicate milder degrees of otoconia loss or, as in the case of 1+, otoconia dispersion and rearrangement.

Results

Behavioral Observations

The results of experiments on the relationship between duration of acceleration exposure and peak g are presented in figure 2.

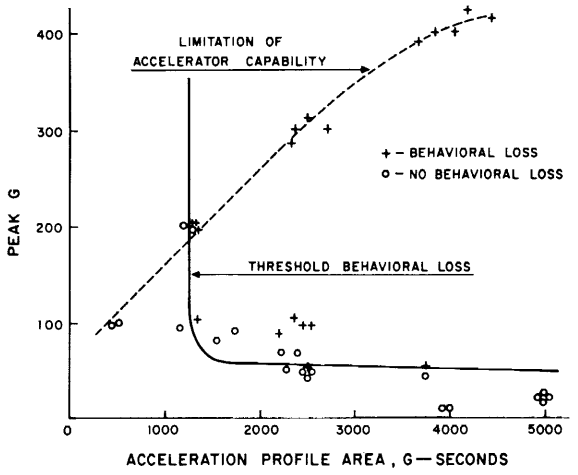

FIGURE 2.—*Behavioral loss as a function of exposure duration and peak g. The ordinate indicates peak acceleration for the particular profile. The abscissa indicates the area under the acceleration profile in terms of g-seconds. The + marks indicate the exposure coordinates for animals which exhibited loss of the righting reflex 24 hours after acceleration exposure, and the O-marks indicate the coordinates for the animals which exhibited no behavioral loss. The solid line represents the approximate threshold for behavioral loss. The dashed line indicates the rise and decay time limitation for the SFAPS at particular peak-g levels.*

Examination of figure 2 indicates that damage is produced at the 300- and 400-g levels by the shortest acceleration profiles within the capability of the apparatus, which are 16 to 20 seconds. Animals which were able to successfully perform the righting reflex fewer than six times in 10 drops 24 hours after exposure were

classified as demonstrating behavioral loss. The integrals over the acceleration profiles which have peaks between 295 g and 425 g range between 2250 and 4410 g-seconds.

Three of six animals exposed to accelerations in the 200-g range manifested behavioral loss. Area measures associated with the 200-g peaks varied between 1200 and 1325 g-seconds.

Three of the ten animals exposed to approximately 100-g peaks demonstrated behavioral loss. The animals which exhibited loss were exposed to acceleration profiles of 2000 to 2500 g-seconds.

Two of ten animals which were exposed to accelerations of 45 to 65 g manifested behavioral damage. Acceleration profiles for the damaged animals were 2500 to 3750 g-seconds.

None of the animals which were exposed to less than 45 g demonstrated behavioral evidence of vestibular damage 24 hours after exposure. Included in this no-loss group are animals which were exposed to 12 g for periods of 5.5 minutes and 25 g for over 3.5 minutes. Profile area measures for the 12-g and 25-g animals were 4020 and 5000 g-seconds, respectively.

Anatomical Observations

Gross dissection.—During the development of gross dissection procedures, several normal animals were examined. A group of guinea pigs which had been exposed to 300 g on the SFAPS were also examined. For the SFAPS animals, otoconia were observed throughout the membranous labyrinth, including the ampullae. An example of otoconia displacement into an ampulla is presented in figure 3.

Histological observations.—Selected photomicrographs from the animals in experiment I are presented in figure 4(*A*) to 4(*F*). Figure 4(*A*) is a photomicrograph of the left utricular macula from animal V–1. This animal had been exposed to a 100-g peak over a trapezoidal acceleration profile of 30 seconds. The otoconia from the anterior one-half appear to have been displaced to the posterior part of the macula. Only a few otoconia are present on the macula of the saccule from the same labyrinth (fig. 4(*B*)).

The appearance of the left maculae from animal V–3, which was exposed to 50-g peak acceleration over a profile of 55 seconds, is

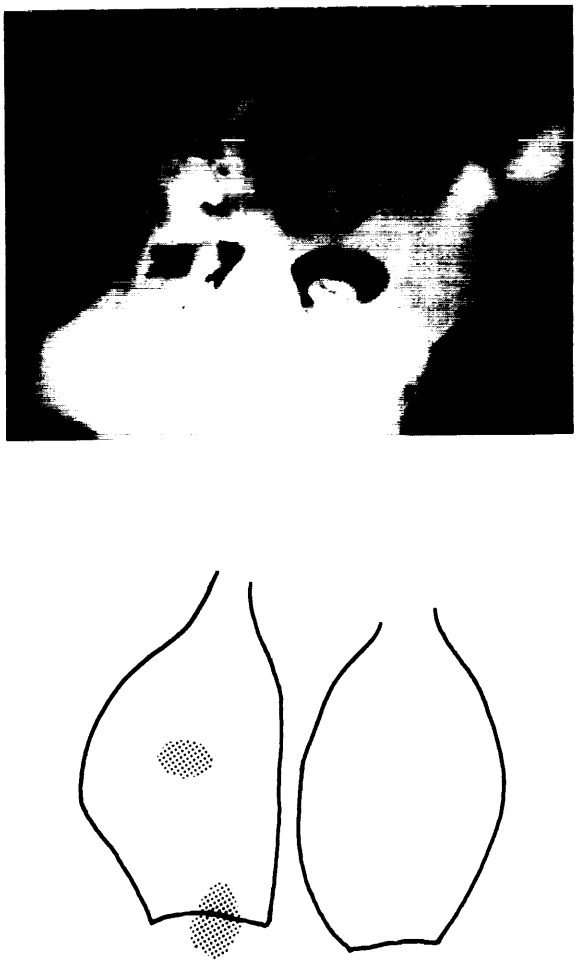

FIGURE 3.—*Damage to ampulla following high linear acceleration. The ampullae of the superior and lateral semicircular canals are depicted in the photograph. Displaced otoconia can be seen in the ampulla of the superior canal which is to the left. The stippled areas in the schematic drawing indicate the location of the displaced otoconia. Otoconia in this location would account for an infrequently observed positional nystagmus. These ampullae were taken from a gross-dissection practice animal which had been exposed to linear acceleration of 300 g over a time period of 17 seconds in the* $+G_x$ *orientation.*

shown in figure 4(*C*) and 4(*D*). There is an accumulation of otoconia over the posterior end of the left utricular macula and fewer otoconia present over the remaining portions (fig. 4(*C*)). The macula of the left saccule shows a few otoconia evenly distributed, except for the posterior margin where none is present (fig. 4(*D*)). Changes in the right labyrinth were practically identical for the utricular macula,

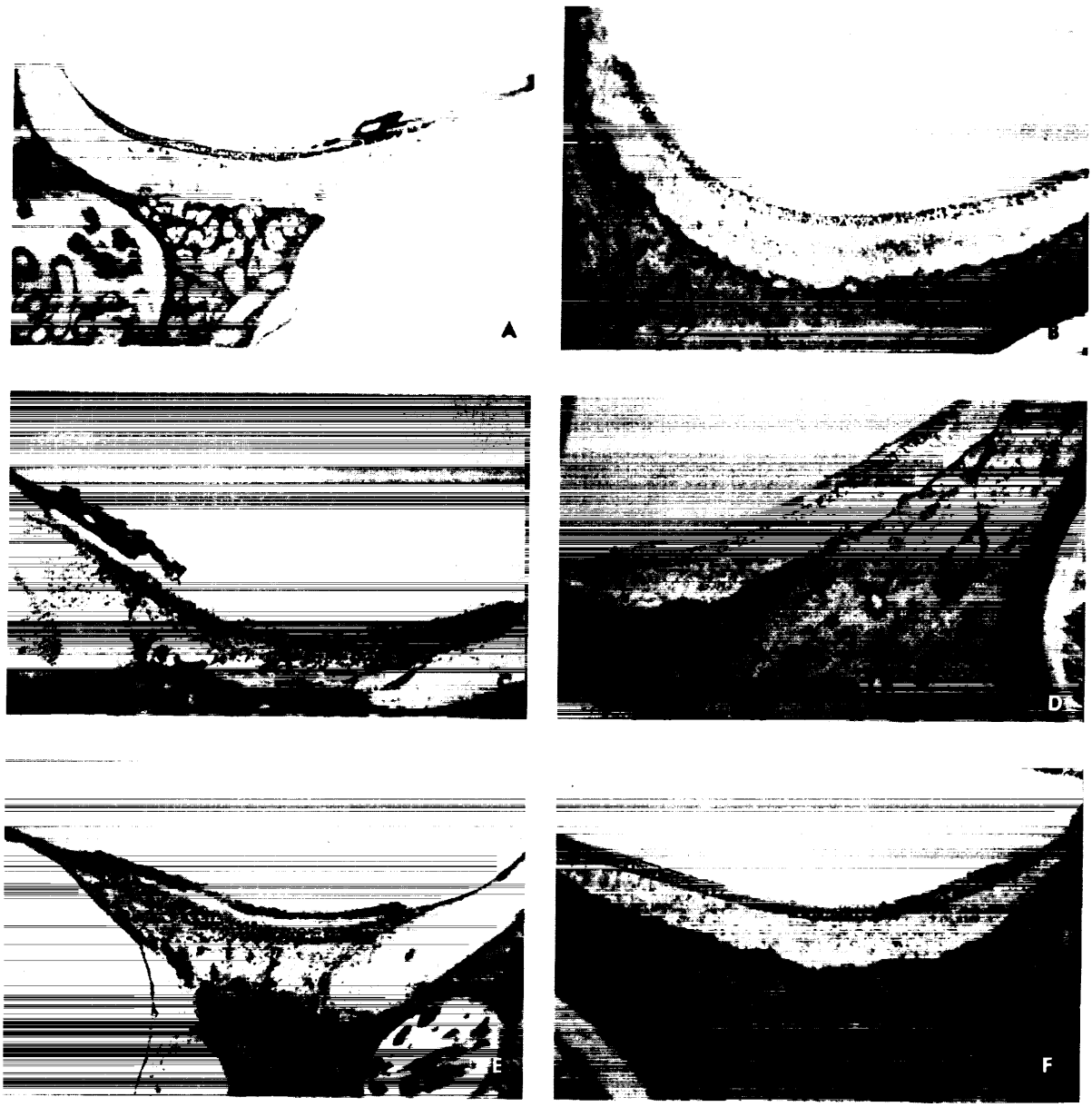

FIGURE 4.—*Histological observations for stimulus duration-peak G animals:* A: *Macula of utricle of left labyrinth of animal V–1 showing loss of otoconia from anterior one-half with an accumulation over posterior part. 100-g peak over a trapezoidal acceleration profile of 30 seconds.* B: *Macula of saccule of same labyrinth as shown in* 4(A). *There are only a few otoconia present.* C: *Macula of utricle of left labyrinth of animal V–3. Otoconia are accumulated over posterior end with only a few prisms remaining elsewhere. 50-g peak acceleration over a profile of 55 seconds.* D: *Macula of left saccule of animal V–3 showing a few remaining otoconia prisms evenly distributed except for posterior margin where none is present.* E: *Macula of utricle of left ear of animal V–6 showing slight loss but some redistribution of the otoconia. 25-g peak over a profile of 105 seconds.* F: *Macula of saccule of same ear as shown in* 4(E). *Central and posterior portions show only a few otoconia while more are present over anterior portion.*

but the macula of the saccule revealed a complete loss of otoconia.

Animals IX–2 and X–5 were exposed to the same acceleration profile as animal V–3, but in each instance the animal's head slipped caudally and to the left during the exposure. The otoconia were practically all removed from the maculae of the left labyrinth of animal X–5, but only slight to moderate otoconia loss was noted for the maculae of the right labyrinth. The findings for IX–2 were not consistent with those from the other animals which had received the same acceleration exposure, as only a moderate loss of otoconia appeared along the inferior border of the macula of the right saccule.

For animal IX–4, the duration of the acceleration profile for 50 g was increased to 80 seconds. In this animal, the posterior one-half of the right utricular macula exhibited complete loss of otoconia, and there was a moderate loss from the anterior one-half as well as from the macula of the right saccule. On the left side, the otoconia were missing over the posterior border of the utricular macula, and changes in the macula of the left saccule were similar to those observed on the right side. In this experiment the head of the animal slipped to the right and caudally.

Following exposure to 25 g over a profile of 105 seconds, the histological observations for animals V–5 and V–6 were similar to those noted previously. There was evidence for a redistribution of otoconia without much loss for the utricular maculae, as demonstrated for the macula of the left utricle of animal V–6 (fig. 4(*E*)). The macula of each saccule revealed loss of otoconia from the central and posterior areas as shown for the macula of the left saccule of animal V–6 (fig. 4(*F*)).

Increase of exposure duration to 205 seconds for the 25-g animals (IX–5, IX–6) elicited no major additional changes. As previously, the maculae of the saccules showed a greater loss of otoconia than did those of the utricles.

Animals IX–7 and IX–8 received exposure to 12 g over an acceleration profile of 340 seconds. Following this exposure, animal IX–8 revealed a complete loss of otoconia from the anterior one-half of the right utricular macula and a 2+ change in the macula of the right saccule. The left maculae were without much change.

In summary, stimulus durations of 20 seconds at 100 g and 45 seconds at 50 g are sufficient to remove most of the otoconia from the maculae of the saccules and utricles. After exposure to 25 g for 95 seconds, the maculae of the saccules usually show incomplete removal of otoconia while the maculae of the utricles reveal only slight changes in the distribution of the otoconia. Histological observations for these animals are summarized in table 1.

EXPERIMENT II. LINEAR ACCELERATION: LONG-TERM RECOVERY

Purpose

The possibility of functional or structural recovery following vestibular damage has been discussed previously (refs. 3 and 4). The present experiment was designed to explore the possibility of recovery of vestibular capability following exposure to intense linear acceleration. In the course of this study, guinea pigs were observed for periods up to 66 days following exposure to various acceleration-time histories.

Method

Subjects

Thirteen guinea pigs were employed in this study of long-term recovery following exposure to high acceleration. The animals were divided into two groups according to date of exposure. Nine animals were run in group A and four animals were run in group B.

Apparatus

The apparatus employed in this experiment was the Space Flight Acceleration Profile Simulator which is described in experiment I.

Procedure

The procedure in this series of experiments was similar to the procedure described in the previous section. All animals were exposed in the $+G_x$ orientation as illustrated in figure 1.

The 13 animals were subjected to peak accelerations of approximately 200, 300, and 400 g. Distribution of the animals among these profiles was as follows: four animals at 200 g, five animals at 300 g, and three animals at 400 g. One animal

TABLE 1.—*Otoconia Loss Ratings for Selected Animals From Experiment I*

Animal No.	Peak g	Rise (dwell), fall	Post-exposure days	Percent rightings		Ear	Macula of utricle	Group	Macula of saccule	Group	Remarks
				Pre-exposure	Post-exposure						
V-1	100	5(20)5	15	90	30	Rt.	O=5+	I	O=5+	I	
						L	O=4+	II	O=4+	II	
V-2	100	5(20)5	15	90	0	Rt.	O=5+	I	O=5+	I	Otitis media.
						L	O=5+	I	O=5+	I	Otitis media.
V-3	50	5(45)5	15	80	0	Rt.	O=5+	I	O=5+	I	
						L	O=5+	I	O=4+	II	
V-5	25	5(95)5	15	100	100	Rt.	O=1+	III	O=4+	II	
						L	O=1+	III	O=2+P, 5+R	II	
V-6	25	5(95)5	15	100	100	Rt.	O=1+	III	O=4+A, 1+P	II	Otitis media.
						L	O=1+	III	O=2+, 4+c	II	Otitis media.
X-5	50	5(45)5	7	90	100	Rt.	O=2+	III	O=2+	III	Head slipped up (caudal) to left.
						L	O=5+	I	O=4+	II	
IX-2	50	5(45)5	7	90	100	Rt.	O=1+	III	O=2+Inferior	III	Head slipped up and to left.
						L	O=1+	III	O=1+	III	
IX-4	50	5(70)5	7	90	50	Rt.	O=5+P, 2+R	II	O=2+	III	Head slipped to right and down. Hemorrhage into macula of utricle.
						L	O=5+P, 1+R	II	O=2+	III	
IX-8	12	5(330)5	7	90	100	Rt.	O=5+A, 1+R	II	O=2+	III	
						L	O=1+	III	O=1+	III	
IX-6	25	5(195)5	7	90	100	Rt.	O=1+	III	O=2+	III	
						L	O=1+	III	O=2+	III	

Abbreviations

A Anterior
P Posterior
R Remainder
O Otoconia
c Central

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was retained as a control. The acceleration profiles, which were nearly triangular in shape, covered temporal durations of about 14 seconds for the 200-g peak, 17 seconds for the 300-g peak, and 21 seconds for the 400-g peak. Immediately after each exposure the subject was examined for nystagmus and general orientation. Subsequent behavioral testing continued for periods up to 66 days. After completion of behavioral testing, all of the animals in this group were transported to the Washington University Medical School where the temporal bones were prepared for histological examination.

Results

Behavioral Observations

Immediately following exposure to short-duration, high acceleration, the animals exhibited a variety of behaviors indicative of disorientation. These behaviors included nystagmus, tremor, and a position reflex. Nystagmic eye movements were manifested for periods of 2 to 3 minutes following exposure. Interestingly, the plane of the nystagmus did not remain constant, but shifted from horizontal to vertical in a seemingly random fashion. The animals also exhibited a shaking or tremor which diminished in amplitude and frequency over a period of 5 to 10 minutes following acceleration. This movement resembles that seen in shaker mice. Finally, the animals in the 300- and 400-g groups rolled or fell over the front of the shoulder when they attempted to stand. The animals rolled as readily to the left as to the right.

Tests of swimming ability were performed at periods of 2, 30, and 60 days for the animals in group A. Two days after acceleration the animals which were exposed to 300 and 400 g manifested difficulty in swimming. These difficulties included listing, circling in the horizontal plane on the surface, and a rather maladaptive circling in the vertical plane. Only two animals, II–3 and II–7, continued to demonstrate swimming difficulties 30 days after exposure. Animal II–7 was still unable to swim in a normal fashion after 60 days of recovery. Tests of swimming

TABLE 2. — *Recovery of Righting Reflex Following High Acceleration: Percentage of Successful Rightings*

Group A		Postexposure day									
Animal	Peak g	1	7	15	22	30	34	44	51	60	64
II–1	200	100	100	100	100	80	80				
II–2	210	100	100	100	100	100	100				
II–3	310	0	40	20	40	60	80				
II–4	295	0	0	40	20	60		40	0	60	80
II–5	(1)	100	100	100	100	100		100	100	100	100
II–6	205	0	0	0	20	10		80	20	60	60
II–7	410	0	0	0	0	0		0	0	0	0
II–8	300	0	0	20	0	0	0				
II–9	425	0	40								

Group B		Postexposure day							
Animal	Peak g	2	4	8	15	26	33	40	46
IV–2	200	0	0	0	70	70	90	60	70
IV–3	315	0	0	0	0	0	0	20	0
IV–4	320	0	0	0	100	90	90	100	100
IV–6	420	0	0	0	0	0	0	0	0

(1) Control.

ability were not performed on group B because these data are difficult to quantify and seem to yield the same information as the tests of the righting reflex.

A summary of the results of testing with the righting reflex is presented in table 2. The data presented in table 2 may be classified into four general patterns: (1) no loss, (2) early recovery, (3) late recovery, and (4) no recovery. Recovery patterns typical of these four classes are presented in figure 5. Two of the 200-g animals demonstrated no loss of the righting reflex, as typified by animal II–1 in figure 5.

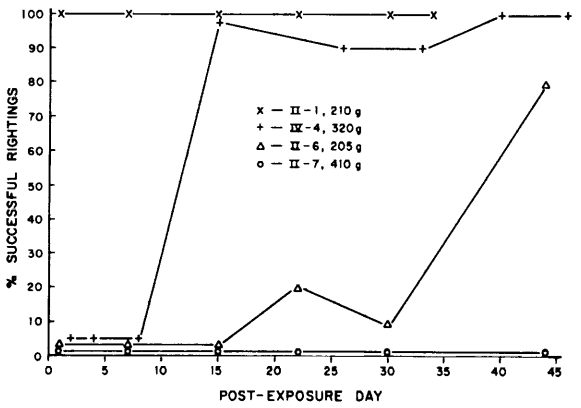

FIGURE 5.—*Long-term recovery patterns. Four types of recovery patterns are presented in this figure. The "no loss" classification is represented by animal II–1; "early recovery" is illustrated by animal IV–4; "late recovery" is represented by animal II–6; and "no recovery" is represented by animal II–7. Peak acceleration exposure is noted adjacent to each animal number. The ordinate represents percentage of successful rightings in 10 drops, and the abscissa indicates number of days after acceleration exposure.*

Four of the eight animals which were exposed to accelerations of 300 and 400 g failed to demonstrate evidence of recovery to above the 40 percent level of successful righting. This "no recovery" classification is represented by animal II–7 in figure 5. The remaining animals exhibited initial loss with either early or late recovery. Two of the animals which had been exposed to 200- and 300-g peaks demonstrated early recovery; that is, recovery to the 70-percent level of successful response by the 15th postexposure day. This early-recovery classification is represented in figure 5 by animal IV–4. Finally, three animals which had been exposed to 200 or 300 g exhibited late recovery, more than 30 days to the 70-percent level. This late recovery classification is represented by animal II–6 in figure 5.

Post-mortem examination revealed that animals II–4, II–5, and II–7 had contracted otitis media. Table 2 reveals that the data for these animals are rather erratic after postexposure day 44. The infection may have developed during the recovery period and contributed to the erratic behavior of the recovery functions. Although these data are retained in table 2, they are viewed with suspicion and were not employed in plotting figure 5.

Histological Observations

Figure 6(*A*) illustrates the appearance of the macula of the utricle in a control or nonexposed animal. The otoconia are in a compact layer and evenly distributed. Figure 6(*B*) shows the macula of the saccule, from the same ear as shown in figure 6(*A*), at a slightly higher magnification. The epithelium of each macula is well preserved.

The utricular macula illustrated in figure 6(*C*) shows well-preserved epithelium but a complete loss of otoconia. This animal (II–3) had been exposed to a peak acceleration of 300 g and allowed to survive for 34 days. No righting reflexes could be elicited after the exposure. The opposite utricular macula revealed a similar complete loss of otoconia. The maculae of the saccules showed remaining otoconia near the anterior ends. The gelatinous layer remained over the whole surface, although most of the otoconia were missing.

Figure 6(*D*) is a higher power view of the epithelium of the macula of the left saccule from animal II–3. The otoconia density is somewhat reduced, particularly to one side of the raised otoconial layer, and the epithelium shows some destruction of supporting and sensory cells. Similar epithelial changes are not unusual in other specimens.

There is no adequate evidence from this series of 12 animals that any particular reparative process occurs to explain the return of the righting reflexes after exposure. However, there is a

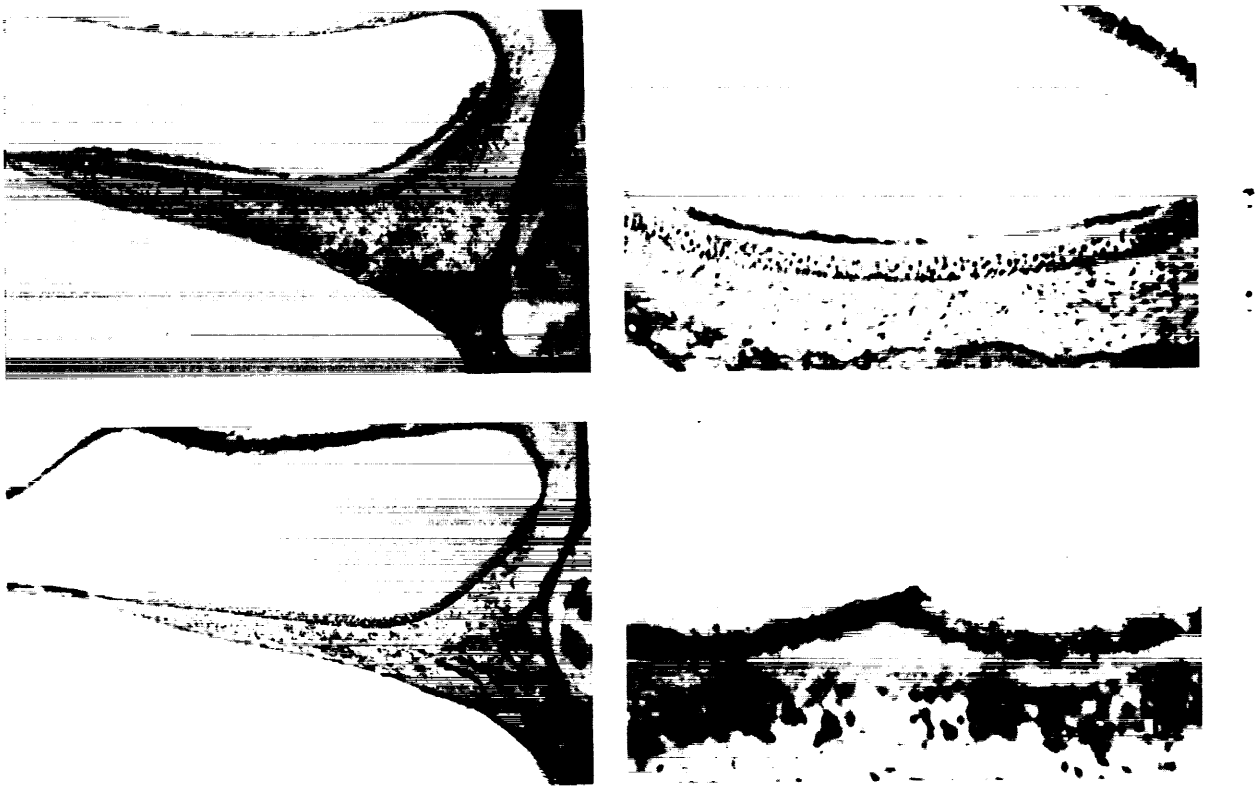

FIGURE 6.—*Histological observations with long-term-recovery animals.* A: *Macula of the utricle of a nonexposed animal showing usual density and distribution of otoconia.* B: *Macula of the saccule of the same ear as shown in figure 6*(A). *The layer of otoconia is compact and epithelium is without alterations.* C: *Complete loss of otoconia from macula of utricle of animal II–3 exposed to 300-g peak and allowed to survive for 34 days.* D: *Incomplete loss of otoconia from anterior one-half of macula of left saccule of animal II–3. The loss is abrupt and epithelial damage is evident. The gelatinous layer is intact.*

possibility that the gelatinous layer of a macula can be replenished, if epithelial damage has not been too severe. If this layer, in the absence of otoconia, can maintain some function of a macula, it is important to study it further. In the present series of exposures a peak acceleration of about 400 g revealed a complete loss of otoconia and gelatinous layer, but the animals that were exposed to a peak acceleration of from 200 to 300 g usually revealed an incomplete loss of otoconia and the presence of an intact gelatinous layer. How much, if any, of the latter can be related to return of righting reflexes during the postexposure period is unknown. Results of the histological observations with the long-term recovery animals are presented in table 3.

DISCUSSION

Relationship Between Behavioral and Anatomical Observations

The results of these investigations provide support for the statement that performance of the righting reflex and swimming ability are dependent on intact vestibular maculae. Figure 7 is a scatter diagram which relates (1) the percentage of successful rightings at the final observation, and (2) the histological rating of otoconia loss (0 to 5+). The product-moment coefficient of correlation has been plotted for the data represented in figure 7, with the result that $r=-0.69$. With a correlation coefficient of this magnitude we are able to reject the null

TABLE 3.—*Otoconia Loss Ratings for Long-Term Recovery Animals*

Animal No.	Peak g	Rise (dwell), fall	Post-exposure days	Percent rightings		Ear	Macula of utricle	Group	Macula of saccule	Group	Remarks
				Pre-exposure	Post-exposure						
II–1	200	7(0)5	34	80	80	Rt.	O=5+	I	O=4+I, 2+R	III	Otitis media.
						L	O=5+	I	O=5+	I	Otitis media.
II–2	210	6.8(0)5	34	100	100	Rt.	O=5+A, 3+R	II	O=5+I, 2+R	III	
						L	O=5+A, 3+R	II	O=5+I, 2+R	III	
II–3	310	9(0)6.8	34	100	80	Rt.	O=3+	II	O=4+I, 3+R	II	
						L	O=5+P, 3+R	II	O=2+	III	
II–4	295	9(0)7	64	100	80	Rt.	O=5+A, 3+R	II	O=5+	I	Otitis media.
						L	O=5+	I	O=5+	I	Otitis media.
II–6	205	7.2(0)5.5	64	80	60	Rt.	O=5+A, 1+R	II	O=5+	I	Otitis media.
						L	O=5+	I	O=5+	I	Otitis media.
II–7	410	11(0)8	64	70	0	Rt.	O=5+	I	O=5+	I	Otitis media.
						L	O=5+	I	O=5+	I	Otitis media.
II–8	300	9(0)6.5	34	70	0	Rt.	O=5+	I	O=3+	II	
						L	O=5+	I	O=4+	II	
II–9	425	12(0)8	5	100	40	Rt.	O=5+	I	O=5+	I	
						L	O=5+	I	O=5+	I	
IV–2	200	7(0)5	50	100	70	Rt.	O=3+A, 5+R	II	O=1+	III	Nose about 20° to left during run.
						L	O=3+A, 5+R	II	O=3+	II	
IV–3	315	9.5(0)8	50	100	0	Rt.	O=4+	II	O=5+	I	
						L	O=5+	I	O=4+	II	
IV–4	320	10(0)7	50	90	100	Rt.	O=3+	II	O=4+	II	
						L	O=2+	III	O=3+	II	
IV–5	430	11(0.1)8	8	90	0	Rt.	.....	.....	.....	.....	Labyrinthitis, otitis media.
						L					
IV–6	420	11(0.1)8	50	90	0	Rt.	O=5+	I	O=5+	I	
						L	O=5+	I	O=5+	I	

Abbreviations

A Anterior
I Inferior
O Otoconia
P Posterior
R Remainder

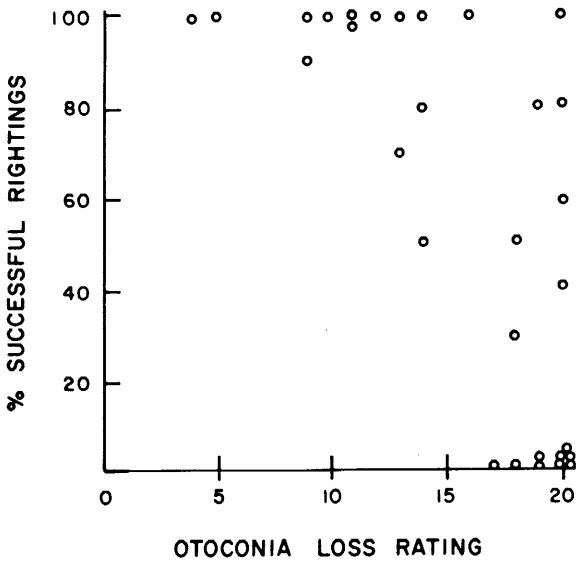

FIGURE 7.—*Scatter diagram relating righting reflex capability to otoconia loss rating. The ordinate indicates percentage of successful rightings at the final observation, and the abscissa represents the sum of the histological ratings for otoconia loss from all maculae. The product-moment correlation coefficient calculated from these data is −0.69.*

hypothesis that there is no relationship between the behavioral and histological observations with confidence beyond the 0.001 probability level. Of course, it is impossible to state with certainty that the observed behavioral deficiency is not also strongly correlated with damage to some other part of the equilibrium apparatus. However, examination of the vestibule and the vestibular nuclei failed to reveal extensive disturbance at sites other than the maculae.

Positional Nystagmus

Nystagmus was exhibited by animals which were placed in particular positions following exposure to high acceleration on the SFAPS. Anatomical observations (fig. 3) support the hypothesis that this positional nystagmus is dependent on stimulation of the crista by displaced otoconia which have been thrown into the ampulla.

CONCLUSIONS

The major conclusions which may be derived from this work are as follows:

(1) Behavioral loss, in terms of the righting reflex and swimming ability, may be produced by exposure of guinea pigs to accelerations of 50 g for periods of approximately 60 seconds. Accelerations below 50 g do not produce behavioral loss. Accelerations of 100 g for 30 seconds result in consistent evidence of behavioral disturbance. Exposure to 200 g over a triangular g-time history of 10 to 15 seconds may result in behavioral loss. Acceleration exposures of more than 200 g for periods of 15 to 20 seconds elicit consistent evidence of behavioral damage.

(2) Light-to-moderate loss of otoconia from the maculae may be observed following exposure to 12 to 25 g for 195 to 330 seconds. Moderate to severe otoconia displacement results from acceleration exposures of approximately 50 g for 1 minute. Accelerations of 100 g for 30 seconds and of over 100 g for 15 to 20 seconds produce severe otoconia loss from all maculae.

(3) In those cases where righting reflex loss is produced by accelerations of less than 300 g, functional recovery usually occurs from 1 to 64 days after the exposure. Exposure to 400 g for 15 to 20 seconds generally produces irreversible loss of the righting reflex.

(4) No histological evidence for reformation of the otoconia was observed up to 70 days after exposure. The hypothesis is suggested that the maculae may be functionally operative if the gelatinous layer remains intact or is replenished during the postexposure period.

(5) Observations from this work support the hypothesis that positional nystagmus results from displacement of otoconia into the canal ampullae.

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DISCUSSION

MONEY: How thick were your histological sections? And when you did your righting tests, did you blindfold the animals?

PARKER: To answer the second question first, the animals were blindfolded during tests of the righting reflex. Contrary to statements in the literature, ability to perform the righting reflex may be dependent on visual cues in some cases. Second, the histological sections were 20 microns thick.

WEISSMAN: When were these tests made? Were they immediately after acceleration?

PARKER: Behavioral tests were performed up to 60 days after exposure. Also, examinations were performed immediately after exposure. However, the data presented in figure 2 of the text were obtained 24 hours after exposure. We chose to use the data from 24 hours in order to avoid measuring the transient disorientation effects of centrifugation.

HAWKINS: This is by way of discussion of both of the preceding papers. Dr. Lars Johnsson in our laboratory at the Kresge Hearing Research Institute has been doing some very beautiful dissections of the human cochlea. Recently he has turned his attention to the vestibular organs. A few days ago when he showed me a strange fibrillar structure that he had lifted from the surface of the macula of the saccule, I realized from a certain similarity to the tectorial membrane that it could only be the otolithic membrane. I also realized that I had never actually seen an otolithic membrane before. Since I suspect that this may also be true of almost everyone else here, I wonder if Dr. Johnsson might have a minute or two to show you some slides illustrating the otolithic membranes of the human saccule and utricle.

JOHNSSON: As Dr. Hawkins has said, our conception of the otolithic membrane has been somewhat nebulous, mainly because up to now we have all seen it almost exclusively in cross sections. Figure D1 shows the entire saccular membrane from a human ear, as it appears when it has been lifted off the macular epithelium and examined as a surface specimen under the stereomicroscope. Note the well-defined structure specimen under the stereomicroscope. Note the well-defined structure and the feathery pattern of the fibrils. This is no homogeneous jelly as it is usually described in the literature. Figure D2 shows the utricular membrane, which is of quite a different pattern and a much finer texture. In both specimens almost all of the otoconia have been removed, so that what we are looking at is the bare otolithic membrane. A few calcite crystals still cling to it, but they are *not* embedded in it as the books say. The arrows indicate the thickest part of the membrane, which Werner has christened the "striola," and which corresponds to the heaping up of otoconia that Engström appropriately calls "the snowdrift." It also matches the dividing line of the hair-cell pattern of the neuroepithelium that Spoendlin has described.

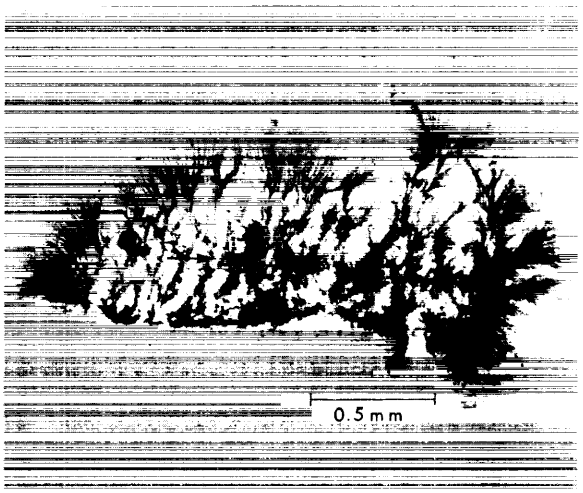

FIGURE D1.—*Intact otolithic membrane of the right macula sacculi in man. Most of the otolithic mass has been removed, and the remaining otoconia appear black by transillumination. Note the pronounced fibrillar pattern. The arrow indicates the thickened portion of the membrane which Werner has named the "striola," and which underlies Engström's "snowdrift" of otoconia.* (OsO_4 *fixation.*)

The otolithic membrane of the utricle is thin and delicate and easily torn, but the saccular membrane is thicker and more resistant. A part of its striking pattern is clearly seen in higher magnification in figure D3. This is a phase-contrast picture along the inferior margin, below the striola, which is marked by an arrow. There are still some small heaps of otoconia, but they do not obscure the complicated design. Under the thin, irregular border can be seen some tiny, round disks, which we have found both in fresh and in fixed specimens. Unfortunately, we have no idea yet what they do, but we are not able to dismiss them as artifacts.

PARKER: Regarding the macula of the utricle, Dr. Johnsson. You also see the C-shaped formation: Is this a "snowdrift" or an area in which the otoconia are more sparse than in the surrounding area? It appears that the utricle does not exhibit a clear snowdrift which you can see in the saccule.

JOHNSSON: It may be true that the snowdrift of the saccule is more impressive in some animals than that of the utricle, but I am not at all sure that this is the case in man. The saccular snowdrift is slightly curving; the utricular one has a definite horseshoe shape, as Odenius pointed out 100 years ago. Of course the snowdrifts are caused both by a greater accumulation of otoconia and by the thickening of the otolithic membrane to which Werner gave the name "striola."

FIGURE D2.—*Otolithic membrane of the right macula utriculi in man, slightly torn on the medial edge (at left). The texture is more delicate and the fibrillar pattern less emphatic than in the saccular membrane. Dark spots are remaining otoconia. The arrow indicates the "striola."* (OsO_4 *fixation.*)

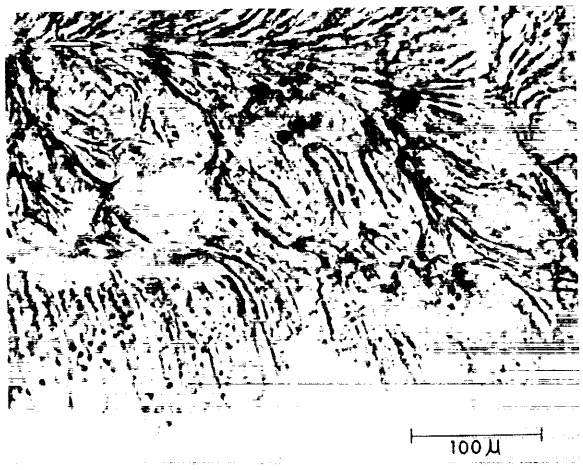

FIGURE D3.—*A portion of the inferior margin of the saccular otolithic membrane in man. Note the feathery fibrillar pattern, and the irregular edge. Small heaps of otoconia remain on the membrane, and small disks (ca. 10 μ in diameter) are seen below the margin. The arrow marks the "striola."* (OsO_4 *fixation; phase contrast.*)

PARKER: The line is fairly clear in the saccule. However, with regard to the utricle, I have had the impression that, although the membrane may be thicker, there are fewer otoconia over this area, whereas in the saccule there is a greater density of otoconia in the central region.

JOHNSSON: I think the snowdrifts of the utricle and saccule are essentially similar in makeup. They must provide for a maximum of stimulation to the neuroepithelium just under the striola, which consists of hair cells of Wersäll's type I.

ROBERTS: My question is in relation to the preparations I have seen, which are skate (or ray). In the unfixed state, which is presumably the state in which you do your dissection, is it possible to decide something about general shape of the bag of either the utricle or the saccule? In many histological sections, the macula appears to be straight, flat. This does not fit with my understanding of how the organ should work. When the skate is dissected in the fresh condition, both of these organs are rounded bags, and this makes an important difference so far as interpretation of function is concerned. Are these membranous labyrinths rounded in the unfixed preparation?

PARKER: The main part of the utricular macula in the guinea pig is a shallow dish. Also, you find the dorsal lap, which is relatively flat. I believe that you can treat the utricular macula as lying in approximately two planes. Is that your experience, Dr. Johnsson?

JOHNSSON: I am not sure that I have entirely understood the question, but we must of course distinguish between the form of the utricle and saccule—the endolymph-containing "bags," if you will, that have membranous walls and are surrounded by perilymph—and the shapes of their respective maculae. So far as I can tell, the forms of the bags are about the same in fresh as in fixed specimens, but of course they tend to be more or less collapsed in the usual celloidin section, which is apparently what was referred to. The maculae have approximately the same outlines as the membranes that I have just shown, and they are slightly concave. The otolithic membrane conforms in each case to the underlying neuroepithelium, but it is very elastic in fresh specimens and its shape may change somewhat with strong g-forces.

ROBERTS: I would agree to that. From my experience, when you try to look for it, by the time you are near enough to see what shape it is, it is gone.

SMITH: I think the shape and the form of the otolithic membrane vary in different animals. For example, in some amphibians, it appears as a ball-like structure, almost filling the utricle, but in mammals it is more flat.

VON GIERKE: I would like to direct a question to Dr. Graybiel or anyone else in the audience. When we discussed the preliminary experiments of this type 2 years ago, we were informed, I guess by Dr. Pollard, that there was a NASA–DOD project going on to study previous centrifuge subjects and deceleration test subjects for possible vestibular damage or other aftereffects. I have tried many times to get any information on this project and have not been able to get any. I wonder what the status of this project is and where these data are at the present time.

GRAYBIEL: To answer your last question first; the results of most of the tests conducted on some 30 subjects in Pensacola are in my file. At the time of exposure to high-level g-forces, only a few complained of symptoms referable to the sensory organs of the inner ear which persisted for more than a matter of minutes. At the time I saw them, none complained of symptoms which might be attributed to the vestibular organs. A few had slightly raised thresholds to stimulation of canals with cool water, and a few made rather poor scores on the ataxia test battery. Two or three had low counterrolling values. In brief, there were few departures from typical normal responses.

MONEY: Dr. Johnsson, were the nice dark-red fibers in your preparations groups of nerve fibers or what were they?

JOHNSSON: No; those are the fibrils of the otolithic membrane radiating in its supposedly gelatinous substance. They are not nerve fibers. You can see an analogous but less dense arrangement of fibrils in the tectorial membrane, which looks just the way Retzius pictured it.

SESSION II: CIRCULATION OF THE ENDOLYMPH

Chairman: GRANT L. RASMUSSEN
National Institutes of Health

N 68-29136

Secretion and Absorption of the Endolymph[1]

G. F. DOHLMAN

Defence Research Medical Laboratories

SUMMARY

The conclusions from this critical review of the literature on secretion and absorption of endolymph might be summarized as follows.

The mechanism of secretion, its products and their importance for the function of the sensory cells and the ways and mechanisms for absorption have been the subjects for this discussion.

Microscopic and electron-microscopic studies have over the years accumulated morphological evidence for a secretion from *stria vascularis* in the cochlea and *plana semilunata* in the ampullae. Physiological evidence for a mucopolysaccharide secretion from *planum semilunatum* and equivalent areas in the cochlea in birds was produced with the use of labeled isotopes. The unique constitution of the endolymph, high potassium and low sodium concentration, has been firmly established. In the last few years it has been shown that this electrolyte pattern is produced and maintained by an active energy consuming secretion and a selective and likewise active excretion of sodium around the sensory areas. Extensive investigation on the process of absorption in the endolymphatic sac of waste products and of potassium has strongly supported and extended the information on the circulation of endolymph. The hypothesis of nutrition of the hair cells from the endolymph has been reviewed, since recent studies of the oxygen and nutrient content of endolymph seem to indicate that the hair cell areas cannot be dependent on the endolymph for their survival. Revised knowledge of the vascular supply to the cochlear hair cells has shown the supply routes of the blood vessels to be the most important source of nutrition. If its primary function is not that of a carrier of nutrients, it remains to consider what purpose the elaborate apparatus for secretion and absorption might serve beyond providing a suitable vehicle for transmission of mechanical movements to the hair cell areas.

Sufficient facts are lacking, however, for the final or conclusive evaluation of the role of the mucopolysaccharides in the endolymph. The secretion of these compounds together with potassium ions gives the high d.c. potential. The functional significance of this potential as well as that of the high potassium and low sodium concentration in the endolymph is still an unsolved problem.

INTRODUCTION

Since ancient times, the study of the inner ear has been regarded by a few dedicated research workers as an important and intriguing field for investigation. The immensely rapid development of methods and refinement of experimental techniques during the last decade have made it possible to outline the morphology of cells and their structures with greater exactness than earlier, to analyze the chemical composition of fluids like those in the inner ear, and to establish the function of cells and tissues. These advances have in recent years been of great advantage for the study of the mechanism of endolymph circulation. It is the purpose of this paper to review the work done in this field in an attempt to proceed toward a meaningful conception of the significance of this fluid system for the function of the sensory cell areas of the ear.

EARLY RESEARCH

It might be of interest to mention that Cotugno in 1775 (ref. 1) by injection of mercury into "a sac in the dura" found that he could fill the cavities of the inner ear and that he showed that fluid and not air filled the inner ear. It is also worth mentioning that Corti in 1851 (ref. 2)

[1] DRML Review Paper No. 661.

during his morphological dissections did visualize the significance of the stria vascularis and "felt tempted to assume a certain connection between this vascular area and a secretion of endolymph." However, what Corti meant by "endolymph" was all of the "fluid" in the inner ear. That same year a thesis was written by Reissner (ref. 3) describing the membrane that later carried his name. This discovery showed for the first time that the ear contained two fluid systems, but 10 years elapsed before this was realized by the anatomists when the two fluid systems were described by Von Kolliker (ref. 4).

From this time on, the improvements in microscopic techniques and the interest in hearing physiology gave an impetus to further morphological study of the inner ear. Thus, Boettcher (ref. 5) made the first histological description of the structures which later were given the names of ductus and saccus endolymphaticus by Hasse (ref. 6). Boettcher assumed from his morphological findings that the endolymphatic sac secreted fluid which then was believed to flow through the ductus to fill the inner ear. Hasse, on the other hand, and later Rudinger and Iwata, believed that openings in the walls of the saccus could allow endolymph to flow from the saccus to the "epicerebral" spaces or to surrounding lymphatic spaces. This suggested a possibility of drainage of endolymph from the labyrinth. Sterzi (ref. 7) and Siebenmann (ref. 8) were unable to find such openings, and therefore denied the possibility of flow of endolymph toward the endolymphatic sac, which led to the assumption by Siebenmann and by Kolmer (ref. 9) that the saccus represented only a rudimentary organ which presumably had no connection with the production or absorption of endolymph.

Using trypan blue and isamin blue, Fleischmann (ref. 10) tried to locate a possible source of production of endolymph and perilymph. These experiments gave only negative results which led him to conclude that no secretion occurred in the inner ear and that therefore endolymph and perilymph were not independent fluids and for this reason must be derived from the cerebrospinal fluid.

The meticulous dissections and microscopic examinations of the labyrinths of a great many animal species, including man, made by Retzius (ref. 11) resulted in a large atlas, "Das Gehororgan d. Wirbeltiere." This is the most precise and clarifying description of this organ and is still modern in many respects.

The discovery by Flourens (ref. 12) that the semicircular canals were not a hearing organ, but had a function related to the maintenance of equilibrium, had been unnoticed until Mach, Breuer, and Crum-Brown produced their experimentally supported theory of the functions of the semicircular canals in 1861. The ensuing studies of vestibular physiology by Ewald (ref. 13), Breuer (ref. 14), and others did not arouse any general interest beyond a small circle of physiologists.

Labyrinthine Fluids

After this period of basic morphological and physiological observations, it was not until the introduction of clinical functional tests of the labyrinth by Bárány (ref. 15) that a new era began. Bárány's work caused immense and widespread interest in the study of the function of the vestibular apparatus and its clinical application which has continued to the present. In this research the endolymph occupied a central place in the explanation of the mechanism of labyrinthine stimulation. It was recognized as a fluid in which movement relative to the sensory epithelium occurred due to inertia, stimulating the hair cells by bending the hairs of these cells. To execute this function, the endolymph could be any kind of fluid of suitable density and viscosity.

Absorption

From this point of view a new aspect was introduced by the classical investigations of Guild in 1927 (refs. 16 and 17) which changed the concept of an exclusively mechanical function of the endolymph. Guild injected solutions containing iron salts, which could be traced in the tissues as Prussian blue, into the scala media of the cochlea and could in this way show a fluid movement from the cochlea through the duct to the endolymphatic sac where evidence for an absorption and excretion of these elements was presented. This indicated that the endolymph was a "living" fluid and subject to an exchange which might serve other functions than merely that of a vehicle for purely physical movements. Similar experiments were made by

Doi (ref. 18), but in this case the iron-salt solution was injected into the canals of the vestibular apparatus. The result was again a transport of the test substance into the endolymphatic sac where it appeared to be absorbed.

These experiments were criticized as being unphysiological and therefore unable to demonstrate an endolymph flow under normal physiological conditions. For this reason, Anderson (ref. 19) used trypan blue applied intravenously and interpreted the results as indicating that the dye could pass into the endolymph in small amounts and was gradually accumulated in the endolymphatic sac, where it was absorbed by intrasaccular cells.

Altmann and Waltner (ref. 20) used another approach to the problem by injecting iron salts into the subarachnoid space. In rabbits, they found that these substances could pass into the perilymphatic spaces through the cochlear aqueduct which is known to constitute an open communication between these two fluid systems in this and some other mammals, but not in man. At the same time some of the iron salts seemed to penetrate through Reissner's membrane and appeared to be absorbed into the tissue spaces of the spiral ligament and crista spiralis. In 1956, however, Van Egmond and Brinkman (ref. 21) made some experiments injecting trypan blue systemically after having removed the whole labyrinth, leaving the endolymphatic sac intact. The examination of the sac showed that trypan blue was accumulated in the walls of this structure even without the labyrinth.

In spite of these contradictory results, Guild's experiments, as well as those of Altmann and Waltner and of Anderson, had presented enough persuasive evidence for an endolymph flow toward the endolymphatic sac that it seemed tempting to assume that the distention of the endolymphatic system found by Hallpike and Cairns (ref. 22) in patients with Ménière's disease could be caused by a dysfunction of the endolymphatic sac. Destruction of the endolymphatic sac failed, however, to create cochlear dysfunction or histological changes in the membranous labyrinth in monkeys and cats (refs. 23–26). Incidentally, in recent experiments on guinea pigs, Kimura and Schuknecht (ref. 27) were able to produce an endolymphatic distention by operative destruction of the endolymphatic sac. These results together therefore seemed to indicate that in some animal species other absorbing elements are able to take over the function of the endolymphatic sac while in other species this does not occur.

Even though the difficulties of investigating the absorption of endolymph had been great and at this time seemed to have caused several controversial problems and indecisive results, the question of where and how the endolymph is created has posed even greater difficulties.

Formation and Secretion

Ever since the vaguely expressed assumption made by Corti (ref. 2) that endolymph might be secreted by the stria vascularis, many morphological findings have been added in support of this hypothesis. Retzius (ref. 11), Held (ref. 28), Shambaugh (ref. 29), and Kolmer (ref. 30) have all pointed to the morphological possibility of a secretion in the stria vascularis, in the tegmentum vasculosum in birds and reptiles, the planum semilunatum in the ampulla of the semicircular canals, and some epithelial areas around the macula of the utricle and saccule.

Iwata (ref. 31) made an extensive study of the cell areas of the labyrinth of bats and described as "regiones secretoriae" areas on both sides of the crista, separated from the hair cell areas by a narrow band of "indifferent" epithelial cells. These areas were described as surrounding the sensory areas of the cristae and the maculae as a continuous layer proceeding into the crus commune of the vertical canals. Further, in an extensive study of the secretory elements in the labyrinth, Hazama (ref. 32) examined 150 species, confirming the findings of Iwata in most of his specimens.

In 1936–37, Von Fieandt and Saxen (refs. 33 and 34) made a meticulous study of the cells in the labyrinthine walls, which they on their morphological evidence also regarded as secretory. Beside the cells of the stria vascularis they described the cells of the "plana semilunata" as secretory areas. From their description and microscopic pictures, it is evident, however, that what they have regarded as planum semilunatum is not the area in the side walls of the ampulla, as it earlier had been described by Retzius (ref.

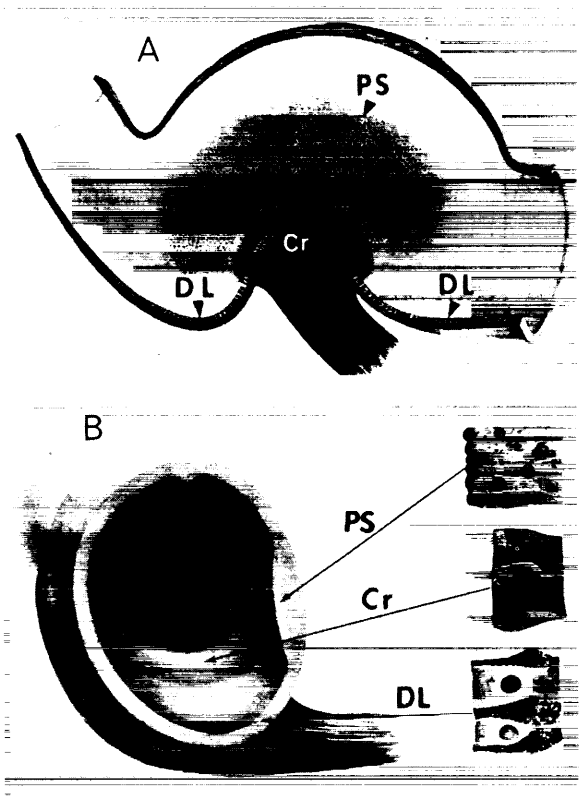

FIGURE 1.—*Drawings of the interior view of a horizontal ampulla.* (A) *Longitudinal section of the ampulla;* (B) *cross section of the ampulla seen from the utricle.* (PS) *planum semilunatum* (Cr) *crista with hair-cell area covering part of the lateral wall.* (DL) *"dark and light" cell areas corresponding to "regiones secretoriae" by Iwata and "planum semilunatum" by Von Fieandt and Saxen.*

11) and others (fig. 1), but the cell areas on the slopes of the crista corresponding to Iwata's "regiones secretoriae." They found that these cells are not uniformly the same in the whole area. The location of the nuclei and the Golgi apparatus, as well as the form of the cells, varies widely. They explained this as being due to different stages in the process of secretion. No accumulation of experimentally injected dyes or foreign substances in the cells of the stria, planum semilunatum, or "regiones secretoriae," which would be direct evidence of a secretory or absorptive function, had been found by earlier investigators. Nevertheless, the abundant blood supply and the morphological structure of the epithelial lining, at least in the stria vascularis, seemed to convince these authors that a secretory function must be assigned to this region.

In electron-microscopic investigations of the stria vascularis, the spiral prominence, and the epithelia of the utricle, Smith (ref. 35) came to the conclusion that the evidence for the stria vascularis being the site of endolymph formation "is mostly of indirect nature"; the presence of a rich capillary network surrounded by deeply staining cells, however, is suggestive of a secretory function. Moreover, she was convinced that the stria vascularis and the spiral prominence do participate in the production of endolymph. Further, an important statement read that "endolymph also must be formed and absorbed in the vestibule as well as in the cochlea." It was also emphasized that the cells which cover the spiral prominence are like those which she had found in the utricle and were not equivalent to those in stria vascularis. This seems even to hint at the possibility of absorption by some of these cellular elements.

Chemical and Physical Properties

Several attempts had meanwhile been made to determine the chemical and physical properties of the labyrinthine fluids. The viscosity was studied by Rossi (ref. 36). The refractive index had been determined by Szasz (ref. 37) and Ledoux (ref. 38). The osmotic pressure was studied by Aldred, Hallpike, and Ledoux (ref. 39), who found that the endolymph and perilymph were virtually iso-osmotic. The protein and electrolyte content was investigated by Kaieda (ref. 40) and Ledoux (ref. 41); the proteins by Ledoux (ref. 42) and by Waltner and Raymond (ref. 43). The results were often inconclusive but seemed to support the assumption that both labyrinthine fluids had the characteristics of extracellular fluids within smaller variations. When Smith, Lowry, and Wu (ref. 44) analyzed the electrolyte concentrations of the labyrinthine fluids using methods revised to increase precision, they were able to show that the endolymph had a high potassium concentration, 144 meq/l, comparable to that of an intracellular fluid, and a very low sodium content, 15.8 meq/l, whereas the perilymph had the low potassium and high sodium content of an extracellular fluid. This surprising result revealed that the endolymph must be a fluid unique in its composition among extracellular fluids. When Von Békésy (ref. 45) discovered the high

positive endocochlear potential of up to 90 to 100 mV, this did not seem to be compatible with the electrolytic composition found by Smith et al. (refs. 44 and 46) from an electrochemical point of view. These analyses of the endolymph have therefore been repeated over and over again (refs. 47–57), always with the same result, a potassium concentration of 120 to 150 meq/l and a sodium content of only about 15 to 25 meq/l in mammals and man. In fishes the potassium concentration is higher than in the perilymph, but the sodium concentration is equal to perilymph.

Further histochemical investigations of the cochlea by Wislocki and Ladman (ref. 58) and by Belanger (refs. 59 and 60) showed that the endolymph contained mucopolysaccharides. Jensen (ref. 48) and Vilstrup and coworkers (refs. 47, 61, and 62) also produced evidence for a rather high concentration of mucopolysaccharides, presumably mostly as hyaluronic acid, in the labyrinth of sharks and in teleost fishes. In guinea pigs, mucopolysaccharides were shown by Citron et al. (ref. 49). An interesting point in this connection is the absence of an endolymphatic sac in the elasmobranch fishes. Thus the endolymphatic duct ends on the surface of the head and the selachian labyrinth communicates with the surrounding sea water. From the analysis of the endolymph by Murray and Potts (ref. 50), it is learned that even in these special conditions of communication with the sea water, the potassium concentration is 19 times higher in the endolymph than in perilymph. In Anura as in the frog, the saccus endolymphaticus is a very large calcium containing sac in the intracranial space continuing from the base of the brain all along the spinal cord. In birds the endolymphatic sac is situated inside the dura, whereas in mammals the sac is confined inside a duplicate of the dura. It is interesting to notice that the lamprey has both types of endolymphatic sacs, one inside and one in the dura, and still both types of the sac seen to have the same function.

The conflicting findings and explanations regarding the production, function, and removal of the endolymph, as well as the surprising and electrochemically incompatible results of the endolymph pattern, seemed to call for two lines of investigation: first, to obtain physiological evidence for a secretion from cell elements which seem to have the structures for a secretory function; and second, to obtain evidence for an excretion and to establish the cell elements engaged in this process and also to establish the category of substances being excreted under physiological conditions. A possible significance of the circulation of the endolymph for the function of the hair cells might then be found.

RECENT RESEARCH

Radioisotope Studies

One area in the vestibular labyrinth which is well defined with regard to the character of its cells, as well as its boundaries, is the planum semilunatum in the lateral walls of the ampulla of the semicircular canals. It contains long slender cells, which have been assumed to be secretory, arranged in a half-moon-shaped area.

Radioactive isotopes have been used for the study of many metabolic functions. Considering the fact that the endolymph has been shown to contain mucopolysaccharides (refs. 47, 58, 61, and 62), it seemed feasible to use an isotope, which could be assumed to be incorporated into the secretory constituents of the endolymph, in order to study the process of secretion of endolymph without interfering with the normal processes of the living cells. On the assumption that sulfur would be incorporated into the acid mucopolysaccharide molecules in the endolymph, radioactively labeled sulfur (S^{35}) was injected systemically in pigeons and traced by autoradiography in the membranous labyrinth.

This study (ref. 63) showed that an accumulation of the labeled isotope took place in the high cylindrical epithelium of the plana semilunata on the sidewalls of the ampulla (fig. 2). This accumulation was apparent ½ hour after the injection of the isotope, and reached a maximum level about 4 hours after the injection, and decreased until it appeared to have passed the epithelium 20 to 24 hours after the injection. The endolymph was found to contain the isotope in increasing amounts very early after the start of the experiment until, after a few hours, it was considerably more radioactive than the planum semilunatum cells. At the same time the mesh-

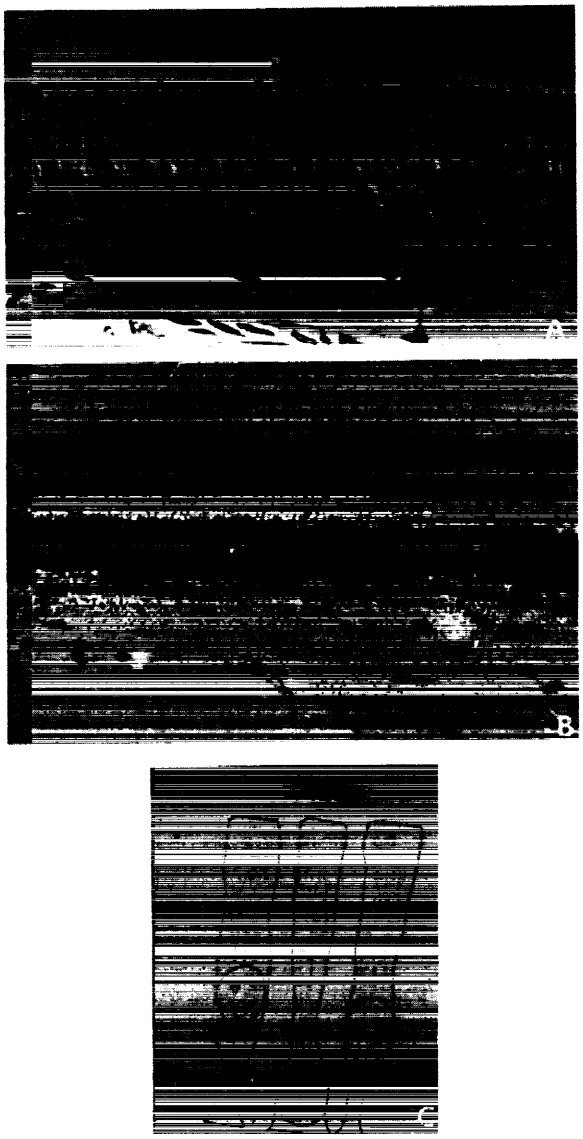

FIGURE 2.—*Planum semilunatum cells.* (A) *in phase contrast microscopy; and* (B) *with heavy accumulation of exposed silvergrains showing concentration of labeled sulfur in these secreting cells 4 hours after systemic injection of* S^{35}; (C) *as drawn by Retzius (ref. 11).*

work of the cupula also was increasingly invaded by the radioactive sulfur. These findings have been confirmed in the chicken by Belanger (ref. 60) and by Esteban-Lasala and Esteban-Velasco (ref. 64).

The concentration of labeled sulfur in the endolymph then slowly decreases. Three to four days after the injection considerable radioactivity is found in the distal part of the endolymphatic duct (fig. 3(*A*)), indicating a concentration in this region of the organic compounds from the endolymph at a time when most of the labeled sulfur has been removed from the endolymph. From these results it can be concluded that a secretion of mucopolysaccharides occurs from the planum semilunatum, that this is a relatively slow process, and also that their removal through the walls of the endolymphatic sac is a matter of days.

In the endolymphatic sac, labeled substances were found, together with the usual finding of free cells, within the walls of the sac wrinkled by richly vasculated septa and lined by large cuboid cells (fig. 3(*B*)). From their appearance in the light microscope, these cells could have the function of either secreting or absorbing.

When studying other cell areas in the inner ear by the same method, it became apparent that the cells on the slopes of the crista corresponding to the "regiones secretoriae" de-

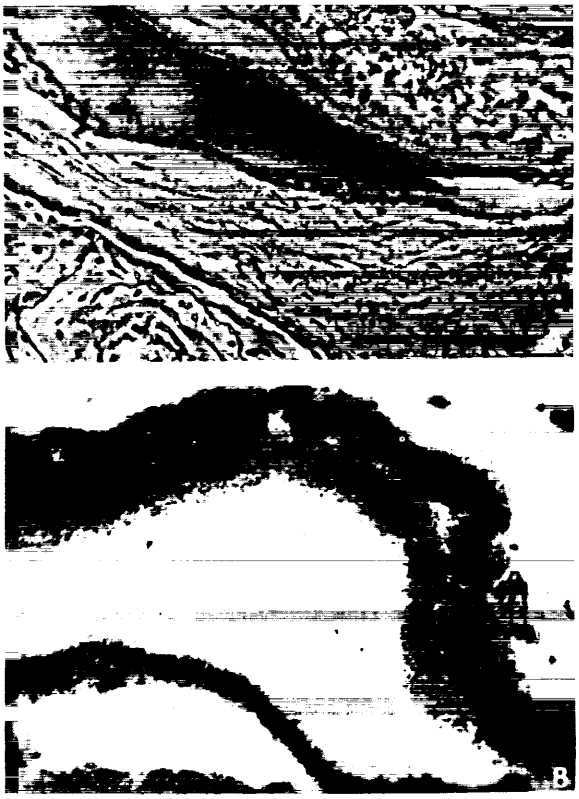

FIGURE 3.—(A) *Distal part of endolymphatic duct (autoradiography); and* (B) *Part of the endolymphatic sac 3 days after injection of* S^{35}. *Radioactivity evidenced by the silvergrains over the organic contents in the sac.*

scribed by Iwata (ref. 31), Von Fieandt and Saxen (refs. 33 and 34), and Smith (ref. 35) do not secrete sulfur-containing compounds. They might, however, produce substances which differ from those secreted by the planum semilunatum. When examining the tegmentum vasculosum, which in birds and reptiles is regarded as the equivalent to a combined stria vascularis and Reissner's membrane, it was evident that these cells used the labeled sulfur in a manner similar to that in which the plana semilunata do but to a lesser degree. This proves that they are secretory cells. Other possible functions of these cells, however, are not established by this method.

The cells on the slopes of the crista and the bottom of the ampullae and utricle, the "regiones secretoriae" of Iwata or "planum semilunatum" of Von Fieandt and Saxen, must therefore have some function other than that of secreting sulfur-bonded mucopolysaccharides.

Dark and Light Cells

When the cells of the "regiones secretoriae" are fixed with osmium tetroxide, it becomes apparent even in light microscopy (fig. 4) that they do not represent merely different stages in one secretory process. There are two kinds of cells: one type of "dark" cell which has a greater affinity for osmium and another type which appears considerably lighter. In phase-contrast microscopy these two types are found in this animal species in a very regular sequence of alternating "dark" and "lighter" cells. These cells were actually described by Retzius in 1884 (ref. 11) (fig. 5) and have occasionally been seen also by other investigators but have always been labeled as secretory cells.

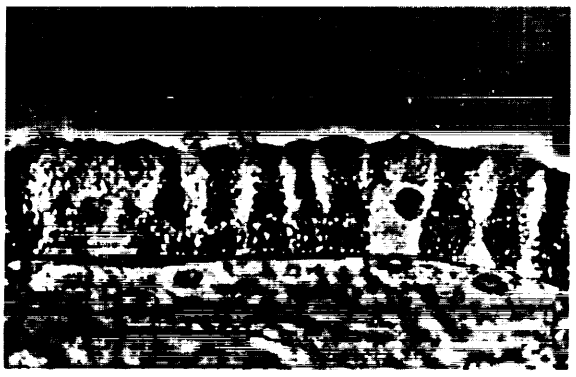

FIGURE 4.—*Cells from the slopes of the crista. "Dark and light" cells.*

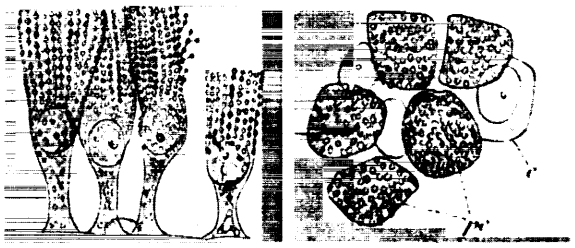

FIGURE 5.—*"Dark and light" cells from drawing by Retzius (ref. 11).*

Normally these cells have a very electron-dense cytoplasm which makes it difficult to reveal the details in their organelles in electron microscopy (fig. 6). It is clear, however, that the cytoplasm is nearly filled with mitochondria. The endolymphatic surface of the cell carries a thick brim of microvilli. The nucleus is irregular in its shape and shows frequently indentations caused by vacuoles, most of them with a clear content. The base of the cell membrane is

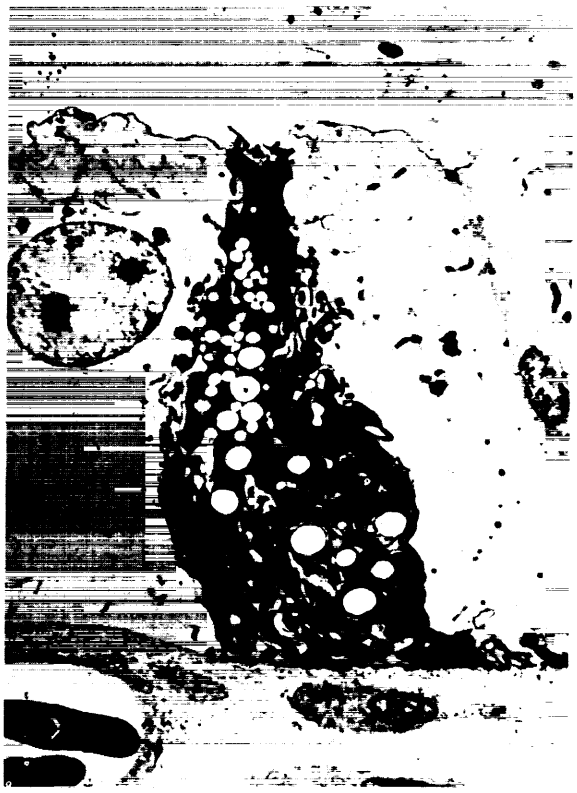

FIGURE 6.—*One "dark" and two "light" cells as seen in low power electron microscopy.*

deeply indented, which gives a peculiar pattern of duplications of the cell membrane containing only little cytoplasm but rows of long and slender mitochondria (fig. 7). A section parallel to the cell surface (fig. 8) at or close to the nucleus shows spokelike extensions of these infolded membranes, toward the surface of the surrounding light cells, which probably corresponds to the "intercellular bridges" referred to by Iwata (ref. 31) or as "Reiserbesenzellen" by Held (ref. 65). A section closer to the base of the cell can show all variations of whirllike membrane duplicates containing long and flat mitochondria (fig. 7). Between these extensions of the cell membrane the spaces are in fact extracellular spaces varying in width. This configuration of the cell membrane evidently increases the surface area of the cell enormously, thereby facilitating the fluid exchange through the basal membrane.

If the membranous canal is opened, however, thereby allowing the sodium-rich perilymph to enter into the endolymph, the "dark" cells appear to change. This becomes even more apparent when they are examined in the electron microscope. Under normal conditions the "dark" cells show a relatively small number of vacuoles or vesicles, but if the endolymphatic spaces are opened or if some sodium chloride solution is injected into the ampulla, the cells appear to be filled with both large and small vacuoles. If some methylene blue is added to the injected fluid, it can be seen even in light microscopy that this dye is taken up by the dark cells within 10 minutes after the injection, not in the cytoplasm of the cell but only in what appears to be droplets corresponding to the vacuoles seen in electron microscopy (fig. 9). In the pigeon, killed 30 minutes to an hour after the application of the dye, methylene blue can be found in the subepithelial connective tissue and around the capillary walls. This shows that the work done by these cells consists of

FIGURE 7.—*Detail of the basal part of a "dark" cell. Whirls of duplicates of the cell membranes enclosing mitochondria. The spaces between these indentations are extracellular spaces.*

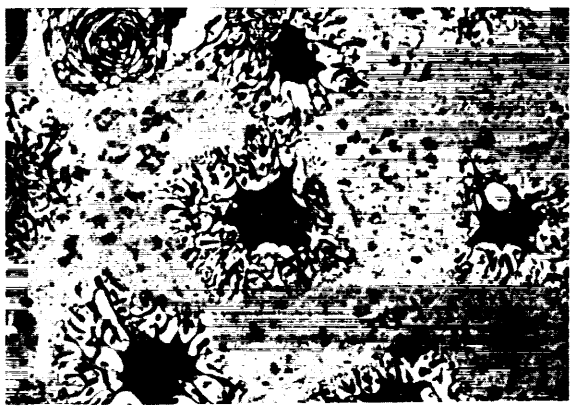

FIGURE 8.—*Cross section of "dark and light" cell area.*

FIGURE 9.—*Methylene blue absorbed by the "dark cells" accumulate in the large vacuoles only.*

pinocytotic movement of solutes and solvents from the endolymph toward the bloodstream.

These "dark" cells are not unique in regard to their morphology, as seen in the electron microscope. They are similar to several cell types engaged in pinocytosis but seem to be in nearly perfect conformity with the cells in the so-called "salt glands" in birds, like seagulls, which must dispose of their surplus of sodium chloride from their food intake (refs. 66–68). These glands can secrete a salt solution of 4 to 5 percent concentration. The only difference with regard to their microscopic appearance is the absence of the microvilli which are seen on the surface of the "dark" cell of the ear.

Komnick and Komnick (ref. 68) developed a method of precipitating the sodium ions with antimony compounds in order to show their location in these cells in electron microscopy. Using this method, they could show that the "dark" cells in the salt glands contained sodium, and therefore must be assumed to be engaged in moving these ions. By using the same method in the ear it was possible to show that these precipitates were overwhelmingly confined to the "dark" cells, with only occasionally single grains in the light cells. Further, precipitation of the chloride in the tissues with silver lactate showed that the chloride ions moved in the intercellular spaces, probably dragged by the intracellularly actively transported sodium ions by means of their electric charges, demonstrating the activity of the "sodium pump" of these cells.

The area which has been referred to here as consisting of "dark" and "light" cells is located on the slopes of the crista down on the bottom of each ampulla to the macula of the utricle (fig. 1). This region is situated between the "plana semilunata" of the ampulla but, as mentioned earlier, the cells of these regions are morphologically as well as functionally totally different from those of the "planum semilunatum." Thus, the cells of planum semilunatum secrete mucopolysaccharides, whereas the dark cells are absorbing cells, actively moving sodium ions and other compounds, such as methylene blue.

Between the "dark" cells as shown in figures 4, 7, and 8 there are "light" cells in a regular pattern. In electron microscopy it can be seen that the dark and light cells in these species have a very intimate connection with each other. The light cells have a lightly stained cytoplasm, few mitochondria, several lysosome-like organelles, and many vesicles. Some of these can be seen to open up at the endolymphatic surface of the cell. The cytoplasm contains a Golgi apparatus and some endoplasmic reticula with ribosomes. These findings have been confirmed by Hamilton (ref. 69) in reptiles and by Lundquist et al. (ref. 70) in guinea pigs. Even if the distribution of these cells is different in mammals, as can be inferred from earlier histological studies (refs. 11, 31, and 71), their morphology and probably their function might be the same as in birds.

In the pigeon, sacrificed 1 to 1½ hours after the injection of methylene blue into the endolymph, it was possible to see a faint-blue stain in some larger vesicles in the basal parts of the light cells. At this time the stain had passed through the dark cells into the subepithelial tissue spaces and the capillary walls. This suggests that the "light" cells are secreting cells. Their intimate relation with the "dark" cells might indicate that they return to the endolymph fluid and possibly also substances which were removed from the endolymph together with the sodium ions by the dark cells.

The following conclusions can be made from the above studies:

Fact 1: The autoradiographic experiments with labeled sulfur indicated the production in the planum semilunatum of mucopolysaccharide compounds under conditions which can be regarded as physiologically normal. They also showed an accumulation of these compounds in the ductus and saccus endolymphaticus, indicating that they are excreted in this region.

Fact 2: The investigations of the areas corresponding to Iwata's "regiones secretoriae" (ref. 31) showed that they contain two distinct different kinds of cells which do not represent different phases in a secreting process, as assumed by Von Fieandt and Saxen (ref. 33). The "dark" cells were shown to be absorbing cells, moving fluid and solutes by pinocytosis and removing sodium by active transport into the cell cytoplasm from the endolymph. The

morphology of the light cells seems to indicate a secretory function which is different from that of the planum semilunatum.

Fact 3: The presence of "dark" cells in the labyrinth in several animal species has been described by many investigators (refs. 11, 28, 30, 32, 69, 70, and 72), but such cells have usually been assumed to be secretory. Only Smith (refs. 35 and 72) mentions the possibility of absorption by the cells in the utricular walls. This seemed to support the hypotheses expressed by Von Fieandt and Saxen, who regarded the cells in the external spiral sulcus of the scala media to be the place of excretion for the cochlear endolymph but believed that the endolymphatic sac absorbed the endolymph from the utricle and the canals, since no absorptive cells had been found in this area.

The results of the investigations reviewed above have laid emphasis upon other problems, especially with regard to the significance of endolymph circulation for the hair-cell stimulation.

Circulation of Endolymph and Nutrition of the Tissues

The trend in recent investigations has centered on histochemical studies of enzymes of the cells lining the labyrinthine walls, as a manifestation of their requirements and function as well as the constituents of endolymph and perilymph, with the view that these fluids might be carriers of nutritive substances necessary for cell function.

These investigations evidenced that the hair cells as well as the cells in stria vascularis and the "regiones secretoriae" show a high enzymatic activity like most cells in the body with a high functional performance (refs. 55, 56, and 73–87). Further, Falbe-Hansen (ref. 80) and Falbe-Hansen and Thomsen (ref. 81) showed that glycogen was constantly present in the organ of Corti, decreasing in amount from the apical to the basal turns. They also showed that the glycogen did not seem to be diminished as a result of prolonged acoustic stimulation.

On the other hand, Kawamoto and Kakizaki (ref. 77), Gottesberge et al. (ref. 88), and Rauch (ref. 89) showed that the oxygen consumption in the stria vascularis was greater in the lower turns and decreased toward the apical part. Misrahy and his colleagues (refs. 90–92) made the endolymph oxygen deficient using an oxygen-consuming enzyme system, and came to the conclusion that oxygen and glucose in endolymph are needed for normal cochlear function and that the hair cells must obtain their oxygen solely or predominantly from the endolymph. From the point of view of cell nutrition, especially of the hair cells, it might be pertinent to correlate these studies with some recent investigations by Silverstein (refs. 55 and 56) and Lawrence (ref. 93).

Silverstein found that the enzymes malic and lactic dehydrogenases which are found in high concentration in the cytoplasm and mitochondria of cells and are present also in extracellular fluids, but in greatly reduced quantities, could be demonstrated in the endolymph as well. Even though these enzymes showed a higher value in the endolymph than in perilymph and blood serum, this was interpreted to reflect only the high enzymic activity of the cells lining the membranous walls. Silverstein also analyzed the glucose content of the labyrinthine fluids. If endolymph is a carrier of nutrients to the sensory areas, it would be expected to contain cell nutrients in considerable quantities. This applies especially to glucose which is regarded as the most important substance in cell metabolism. This investigation showed, however, that the glucose concentration in endolymph amounted only to an average of 15.2 mg/100 g (0–25 mg/100 g), whereas perilymph contained 70 and serum 145 mg/100 g.

In this connection it seems pertinent to correlate these findings with some illuminating experiments by Lawrence (ref. 94). He was able to show that obliteration of the arterial supply to the stria vascularis produced a degeneration of this structure but did not influence the function or structure of the organ of Corti. If, however, the blood supply to the network of the spiral vessels in the scala tympani side of the basilar membrane was obliterated, the organ of Corti degenerated, leaving the stria vascularis intact, indicating the evident dependence of the hair cells on the vascular supply routes rather than an indirect way through the endolymph.

To this can be added the observation made by Nachlas and Lurie (ref. 95) that in specimens

with hereditary changes, abnormalities in the organ of Corti were found to be accompanied by changes in the stria, whereas changes in the stria were not necessarily accompanied by abnormalities in the organ of Corti.

The findings and conclusions presented by Davis (ref. 96) that the reticular lamina is a chemically and electrically impermeable barrier, therefore indicating that the nutrition of the organ of Corti including the hair cells cannot come from the endolymph, must also be taken into consideration. It therefore seems most unlikely that the very low glucose content and equally low concentration of other organic compounds in the endolymph should be able to serve the nutrition of the hair cells, when the capillary supply of 10 times higher serum glucose concentration close to the "Corti-lymph" (refs. 97 and 98) apparently seems to be indispensable for the survival of the hair cells.

It is well known that the sensory areas of the vestibular crista and macula obtain a very good blood supply by means of the subepithelial capillary network and are totally dependent on this vascular supply for their survival. It therefore seems rather unlikely that the hair cells in these regions should get any physiologically important part of their requirements via a detour through the endolymph. It seems also equally unlikely that a basically different mechanism should exist for the nutritional supply of sensory cells in different parts of the ear, as the cochlea and the vestibular system.

In his extensive investigation into the biochemistry of the inner ear fluids which was mentioned earlier, Silverstein (refs. 55 and 56) has also investigated the fluid in the endolymphatic sac. The comparison with the endolymph is very significant. The enzymes LDH and MDH have a concentration in cochlear endolymph of 218 and 615 International micromoles/ml, respectively, whereas the values for the endolymphatic sac are 3800 and 7100, respectively. The protein in the cochlear endolymph was 126 mg percent, but 5200 mg percent in the sac. These values evidently indicate a considerable condensation of the protein fraction and increase in enzymatic activity involving the processes in the sac. On the other hand, the analyses of potassium showed the usually expected endolymphatic value of 150 meq/l but only eight in the endolymphatic sac fluid, whereas the values for sodium were the reverse, 25 meq/l and 153 in the sac. This seems to indicate an active removal by excretion of potassium in the endolymphatic sac.

Ischi, Silverstein, and Balogh (ref. 87) had also injected foreign protein into the cochlear duct, which then was found phagocytized in the free cells of the sac after 2 days, while labeled proteins injected into the sac were found in the perisaccular tissue within 85 minutes. This illustrates the slow movement of the endolymph toward the endolymphatic sac, but the active process of excretion in the sac.

The mechanism of the sac was further clarified by electron-microscopic studies by Lundquist and colleagues (refs. 70 and 99). They came to the conclusion that, morphologically, pinocytosis appeared to be the main function of the intermediate most active part of the sac. Using injection of colloidal silver particles or bacteria into scala media, Lundquist et al. (ref. 70) obtained evidence that these substances were conveyed to the endolymphatic sac where they were phagocytized by free cells in the lumen of the sac and by cells in the epithelial lining.

The histochemical studies of the enzyme activity in the cells of the endolymphatic sac are therefore consistent with the phagocytotic function which was shown to exist in these cells, and also demonstrate a potential for proteolytic processes with the possibility for digestion of debris and corpuscular elements which have been transported to the sac by the endolymph flow from the different parts of the inner ear endolymphatic system.

From what has been presented concerning the flow of endolymph, noting regional absorption, on one hand, and longitudinal endolymph flow, on the other, together with absorption and excretion in the endolymphatic sac, it might seem clear that a "radial" or, more adequately expressed, regional excretion of certain compounds exists; that is, the sodium chloride excretion in the "dark" cells at the bottom of ampulla and vestibular sacs and probably similar processes in the external spiral sulcus of the cochlea. On the other hand, it seems equally clear that, under normal conditions, a slow but conspicuous

longitudinal flow can carry debris and cell products from the cells lining the walls of the whole endolymphatic system through the endolymphatic duct to the sac, to be digested and removed in this area.

Another aspect of this problem has been studied in the investigations by Honrubia et al. (ref. 100) on the cochlear potentials during asphyxia. The perilymphatic space of scala vestibuli was perfused with a variety of solutions with different contents of oxygen, carbon dioxide, and potassium. The perfusion maintained the cochlear potentials CM, EP, and SP at a relatively high level when the animal then was made anoxic, irrespective of O_2, CO_2, or K^+ concentration of the perfusing fluid. It appeared that only perfusion rate was a critical variable. This was interpreted to mean that the maintenance of the potentials in this experiment, and thus the function of sensory cells, was dependent on the flow rate of removal of accumulated toxic metabolites during anaerobic metabolism and to a much lesser extent dependent on the oxygen supply or electrolyte concentration.

Thus, there seems to be very little, if any, factual support for the hypothesis that the endolymph should be the carrier of nutrient to the cells in the labyrinthine walls.

Role of Mucopolysaccharides and Electrolytes in Endolymph

There remains for discussion the fact that the endolymph contains mucopolysaccharides and an electrolyte composition which is unique among extracellular fluids in the body.

All extracellular fluids seem to contain mucopolysaccharides (ref. 101). The question then is whether the endolymph contains more of these compounds than other fluids or whether these mucopolysaccharides have a special composition which could be assumed to serve a special purpose in the functional mechanism of the inner ear.

The mucopolysaccharides have been analyzed in elasmobranch fish (refs. 47, 48, and 61), in the guinea pig (refs. 49, 58, and 62), and in the pigeon (ref. 63). They were found in fish in the endolymph, mostly as hyaluronic acid, but also in perilymph. In the pigeon they could be shown bound to labeled sulfur, but not in mammals. The mucopolysaccharides therefore seem to have a different constitution in different animals which makes it difficult to assign to them a special role, chemical in nature, of importance to the function of the sensory epithelium. Only some common physical properties of these polysaccharides can therefore be considered. The molecules of these compounds are very large. Each molecule is equal in molecular weight to three collagen molecules, but in solution they occupy a space which is 25 000 times greater. These special physical factors and their special property of changes in charge due to movements and bending of their molecular chains have led to the assumption that they could constitute a first link in the process of producing the electrical changes at the hairs of the sensory cells (refs. 61, 63, and 102). The factual basis for this assumption is still incomplete which prevents a definite evaluation of this hypothesis, but it must be kept open for discussion.

The process of secretion of polysaccharides into the endolymph might, however, be discussed from another point of view. Polysaccharides secreted by the salivary glands for instance have a high potassium content (19.7 meq/l) (ref. 103) presumably bound to the polysaccharide molecules. It has also been shown that the secretion at the surface of the glandular epithelium has a high positive charge.

The experiments by Tasaki and Spyropoulos (ref. 104) showed equally that the source of the normal endolymphatic positive d.c. potential of up to 100 mV found by Von Békésy (ref. 105) is in the stria vascularis, where the secretion contains 144 meq/l. This implies that the secretion of the mucopolysaccharides and potassium ions is a function of these particular secretory areas in the cochlea and in the vestibular labyrinth, and that the positive potential is produced in this process of secretion. The polysaccharides which apparently are a part of all extracellular fluids, therefore, may or may not be indispensable for the mechanism of hair cell stimulation. As mentioned earlier, the role of the mucopolysaccharides in the ear has not been sufficiently investigated to warrant a judgment on this problem.

The importance of the potassium ions in the endolymph has been subjected to several investigations. Experimentally it was shown by

Tasaki et al. (ref. 106) that an isotonic potassium chloride solution is well tolerated in the endolymphatic space while a sodium chloride solution is not. When an isotonic potassium solution was introduced into scala tympani, however, the action potentials of the nerve and the cochlear microphonics disappeared due to depolarization, but the high d.c. potential remained unchanged. This indicates that while the endolymphatic surface of the hair cells tolerates and probably needs the potassium environment, but not sodium, potassium ions applied to the rest of the cell surface depolarize the cell and block its activity as shown from the cochlear microphonics. This indicates also that the sodium ions have an injurious effect on the functioning sensory mechanism, which underlines the importance of the particular electrolyte composition and, specifically, the particularly low sodium content.

The extensive distribution of sodium excreting "dark" cells around every area of sensory cells in the vestibular labyrinth seems also to indicate that the low sodium concentration is essential for the function of these cells. This has been supported by several experimental results by Lawrence (ref. 107) showing degeneration of hair cells in regions close to an experimentally made communication between perilymph and endolymph but not further in the direction of an assumed longitudinal flow. Lawrence therefore interpreted the results of his experiments as indicating a radial flow and regional absorption of endolymph instead of a longitudinal flow to the endolymphatic sac. Konishi et al. (ref. 108) perfused the scala media with isotonic KCl solution, Ringer solution, and perilymph. Using the cochlear microphonics as an indicator of hair-cell function, they showed that perilymph and Ringer's solution produced a marked and consistent depression of the hair-cell function.

In other experiments made in an attempt to demonstrate the paths for secretion and absorption by using ferritin particles, no traces of ferritin could be found to indicate a path of secretion through the stria vascularis after intravenous injections (ref. 109). However, if the ferritin was applied in the endolymph of scala media, it was found in the cells of the spiral prominence and external spiral sulcus. This is in accordance with some findings by Saxen (ref. 110) which he regarded as indicative of an absorptive and phagocytotic function of the epithelium in the external spiral sulcus, and also with the statement made by Smith (ref. 72) that the cells covering the spiral prominence are like those in the utricle; that is, where the "dark" sodium absorbing cells are found.

In a new approach to these problems, Naftalin and Harrison (ref. 111) suggested that fluid and electrolytes proceeded from the perilymph through Reissner's membrane to form the endolymph. Stria vascularis, or more probably the spiral prominence and external sulcus cells, should then act as a selectively absorbing site, extracting sodium and exchanging this ion for potassium. The purpose of Reissner's membrane would be to prevent the flow of potassium out of the scala media.

Using labeled potassium, Rauch and his colleagues (refs. 52 and 112) were able to show that this isotope was rapidly moved from the perilymph of scala vestibuli to the endolymph through Reissner's membrane but not in the opposite direction. This showed that Reissner's membrane has the property of an energy-consuming active transport of potassium ions against a high osmotic as well as electric gradient between these two fluid systems. Further, using different compounds radioactively labeled, Schreiner (ref. 57) was able to show that Reissner's membrane is permeable to ions and to molecules the size of amino acids but not to albumins. Experiments on tissue respiration (ref. 113) have also shown that Reissner's membrane has a high metabolic rate which explains its capacities in this regard.

Later, Rauch (ref. 114) also showed that the labeled potassium could pass into the area of the stria vascularis and spiral ligament, thereby indicating an absorbing function somewhere in this region, supporting the view that a certain "radial flow" of endolymph exists. Choo and Tabowitz (ref. 115) have also studied the electrolyte movements forming the cochlear fluids. Using K^{42}, they showed that when a steady state was achieved after 48 hours, the K^{42} concentration in endolymph was 30 times that in the plasma. In perilymph it was only twice the plasma concentration. From this they concluded

that the selective movements of potassium into the endolymph are the result of a secretory process.

All these investigations seem to be in accordance with the assumptions that potassium is secreted into the endolymph together with or combined with mucopolysaccharides and that the cells of Reissner's membrane can selectively keep these ions from escaping into the perilymph.

The potassium concentration in endolymph being equal to the intracellular potassium content would imply a chemical concentration potential similar to the negative intracellular potential. However, it is well known that the endolymph in the cochlea has a high d.c. potential (refs. 45 and 105). This discrepancy has been investigated by Johnstone (ref. 116) who was able to show that the positive endolymphatic potential becomes negative, to as much as − 50 mV, in about 2 minutes when the cochlea is made anoxic. This is what would be expected if the electrolyte potential should be dependent entirely on the electrolyte concentration or the high potassium and low sodium if no other factors were involved. It is further known that, after death of the animal, the sodium and potassium ions are completely equilibrated between the perilymph and endolymph within a few hours (ref. 117). In parallel with this decrease in potassium concentration and replacement with sodium, Johnstone showed that the negative endolymph potential declined to zero, thereby indicating that the negative endolymph potential is a concentration potential and that the normal positive d.c. endolymph potential is an expression for oxidative metabolic reactions leading to the known secretional processes in the stria vascularis and equivalent regions in the vestibular labyrinth. What then remains of the image of the endolymph in its functional capacity is a fluid conveying mechanical movements to the sensory areas of the hair cells, without means for being a carrier of nutrient or even oxygen to the sensory cells but with a unique electrolyte composition necessary for the hair-cell function.

Regulation of Production and Absorption of Endolymph

Much conflicting evidence has been presented with regard to the effect of interference with the sympathetic innervation to the inner ear in patients with Ménière's disease. The same applies to the experimental approach to the stimulation or resection of the sympathetic branches to the ear (refs. 118–131).

Recent investigations have shown that a rich network of adrenergic nerves follows the vascular ramifications into the inner ear (refs. 132–134). A critical appraisal, however, of the neural influence on the labyrinthine blood supply seems to indicate that sympathetic stimulation can give only an insignificant change, if any at all. The same applies to the effect of sympathetic stimulation on the response of the ear to sound.

Experiments interfering directly with arterial or venous blood supply to the cochlea seem to show that changes in blood flow are related to the changes in carotid blood pressure. Changes produced by pressor agents do not change the cochlear microphonics. The circulation in stria vascularis, which was shown to be remarkably stable, might depend on the regulating effect of the arteriovenous arcades in the stria (refs. 135–139). There is no indication that the absorbing areas are supplied with nerves.

An interesting observation was made recently by Stupp and his colleagues (ref. 140). They were able to show that ototoxic antibiotics are removed very slowly, in comparison with other similar compounds, from the inner ear fluids, which underlines the specificity of the excreting mechanism and explains the injurious effect of prolonged exposure of the sensory cells to certain substances.

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DISCUSSION

HAWKINS: Do the root cells of the outer sulcus have any function? You mentioned the possible absorptive function of the cells over the spiral prominence; I wonder about the activity of the root cells which have a peculiar structure and position.

DOHLMAN: Yamamoto and Nakai have injected ferritin into the endolymphatic space and found it only in the outer sulcus cells and the spiral prominence, not in the stria vascularis. If injected systemically, nothing was found in the stria vascularis or in any other cells in the walls of scala media. If I have correctly read Dr. Smith's pictures, I have the impression that the cells of the spiral prominence show microvilli at their surface which would be more in line with absorption than with a secretional function. Dr. Smith has also emphasized that these cells are much more like the cells in the utricle which are the dark and light cell areas than with the cells in the stria.

SMITH: I think Dr. Hawkins was referring to the cells that extend back from the external spiral sulcus. The cells I described were those over the spiral prominence, and in the vestibule also.

DOHLMAN: Yes. As far as I remember, Yamamoto and Nakai found that all the cells in this area had ferritin inclusions, but I am not sure.

SMITH: I would like to ask about the absorptive function of the dark cells as related to the vacuoles in the cells. You showed that the cell membrane made many infoldings around the sides and base of the cells. If one makes a cross-section of these, then some of the infoldings might appear as rounded structures. I wondered if possibly some of the structures which appeared to be vacuoles inside the cell may actually be extracellular spaces between two cells. The material could be taken in at the surface of the cell, passed out along the side between two cells, and then down into the connective tissue space.

DOHLMAN: That is quite correct; but one can find both situations. Smaller and larger vacuoles are found in the cytoplasm, and an indication that the larger vacuoles are produced through the confluence of smaller ones is found in specimens where the chlorine ions are sedimentated with silver lactate. It is then sometimes possible to demonstrate that inside the large vacuoles the boundaries of several smaller vesicles are visualized by surface layers of sedimentated silver-chloride particles, which shows that the large vacuoles are built up by several small ones. Then it is further seen how vacuoles also open up into the intercellular spaces of the infoldings of the cell membrane.

MELVILL JONES: As always it is a very great pleasure and privilege to listen to Professor Dohlman. May I ask two questions: First, I am still not clear how the, as it were, wrong potential difference is generated by the electrolyte distribution. Second, could you give your views on how the standing generator potential, if one may call it that, is modulated by adequate or natural stimulation of the canal mechanism?

DOHLMAN: To your first question: The electrolyte potential of the endolymph should be about −50 mV. Honrubia has shown that the endolymph d.c. potential sinks to that value in a few minutes if the cochlea is made anoxic. The positive potential is therefore probably produced by the oxidative processes involved in the secretion of mucopolysaccharides and potassium in the same way and with the same result as in the salivary glands. To the second question: the d.c. potential, the summating potential, and cochlear microphonics are to a great extent independent of one another. It has been suggested by Von Békésy that the high positive d.c. potential should constitute an energy pool for the cochlea. However, this potential of the endolymph is so different in the vestibule and, as Fernández has shown, also different in different animals that it is difficult to relate the d.c. potential to a basic function of the hair cells.

HAWKINS: While we are talking about strange cells, I wonder if Professor Dohlman would care to comment on the Boettcher cells which are such a prominent feature of the basal turn of the cochlea. Although it is stated in a good many textbooks that these are absent in man, they are very much present in Dr. Johnsson's preparation of the temporal bone. I think previous implications to the contrary have been due to the deficiencies of the celloidin technique. These Boettcher cells look so much like the cells of the planum semilunatum that I wonder if you would care to speculate about their role.

DOHLMAN: I have no experience with this field. I have had very little experience with the mammalian cochlea. I have lately been working on the vestibular apparatus only and mainly on pigeons and frogs.

FERNÁNDEZ: I wonder if you have considered in your theory the possibility of active transport of ions across epithelial membranes such as Reissner's membrane. The equilibrium potential for Na^+, K^+, and Cl^- are out of equilibrium with the resting potential of the cochlea. For instance, the Cl^- concentration in perilymph is about equal to Cl^- concentration in the endolymph, but according to calculations, the voltage gradient will tend to increase the Cl^- concentration in the endolymph to about 2 moles. So, there must be an active transport of Cl^- pumping it out of the endolymph. In the utriculus the chlorine equilibrium potential is at equilibrium with the potential across utricular walls. I wonder whether the concentration of any ion in the endolymph could be a function of secretion and/or an active transport.

DOHLMAN: Yes, I did not go into the investigation by Rauch and others on that problem. He was able to show that if labeled potassium is injected into the perilymph, it is rapidly moved through Reissner's membrane into the endolymph. If sodium is injected into the endolymph, it passes this membrane in the opposite direction. Therefore, I believe that there is no question but that several parts of the labyrinthine membranous walls are engaged in a selective ion transport, beside the secretion of polysaccharides from special areas. Choo et al. have shown that systemically injected labeled potassium builds up the same specific concentration 30 times higher in the endolymph than in perilymph. This must involve an active transport in the plana semilunata, the stria vascularis, Reissner's membrane, and probably other membranous walls.

KHALIL: Can the movements of the endolymph on the cupular membrane and the lining of the membranous semicircular canals be responsible for the positive potential of the endolymph and for the opposite ionic distribution in the periotic fluid? Also, I would like to ask you whether there is any significance for the Reissner's membrane in the cochlea being placed in a special direction so that it remains almost vertical in the upright position?

DOHLMAN: It isn't vertical, and the position is different in different parts of the cochlear turns.

KHALIL: I meant the basilar and tectorial membrane are vertical.

DOHLMAN: Close to it, yes; sometimes, if you keep the head right, but we do not always do that. Regarding your question whether movements can have some influence on the potentials, it has been suggested that movements of the fluid could produce streaming potentials if that is what you mean.

KHALIL: Yes.

DOHLMAN: Well, that is very unlikely. The movements are very small and the mucopolysaccharides in the endolymph form a meshwork which probably will prevent any more extensive movements of the fluid capable of producing streaming potentials.

KHALIL: Recently, I have been interested in this point during my hemodynamics studies based on thermal dilution principles. In considering how this potential is produced, I came to the conclusion that the endolymph may be maintained in a continuous state of centripetal acceleration. Power generated from controlled ionic conduction between the positive potential of endolymph and the negative inner medium of the sensory hair cells may be partly responsible for this.

The Vestibular and Cochlear Aqueducts: Developmental and Adult Anatomy of Their Contents and Parietes[1]

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SUMMARY

An effort has been made to narrow the hiatus between the textbook descriptions of the statoacoustic apparatus and the accounts made possible by the use of the electron microscope. The results indicate, as might be expected, that our knowledge of anatomy of the ear in this middle zone of information is deplorably inadequate.

The present report is based upon the study of gross specimens of temporal bone (both unembalmed and skeletal), upon the examination of serially sectioned temporal bones and of reconstructions prepared therefrom. The following are the features of major interest:

The endolymphatic duct, far from being a simple quill-like tube with a mushroom-shaped intracranial expansion, is divisible into three segments—proximal and distal expansions, and an intermediate narrow portion. The distal part, the endolymphatic sac, is the most complex of the three, being either rugose or vesiculate. It occupies a correspondingly widened terminal part of the vestibular aqueduct, and extends beyond the external aperture of the latter to rest within the *dura mater encephali* in a foveate impression on the posterior surface of the petrous pyramid, just superior to the point of continuity of the jugular fossa and sigmoid sulcus.

The connective tissue around the sac, in the aqueduct, is continuous with that of the dural layer. It is rendered highly vascular by vessels that pass into the aqueduct from channels in the surrounding bone. The presence of capillary offsets arourd the membranous sac would seem to meet the requirements of a histological mechanism for exchange between blood and endolymph; and the nature of the interfibrillar spaces of the connective tissue could be regarded as a means of comparable exchange between endolymph and perilymph.

INTRODUCTION

Whether seated or standing, quiescent or spinning, we are normally (perhaps one should say "primitively") aware of our position; and, the while, we perceive sound in the surrounding air.

It seems remarkable that the mediating sense organs are local modifications of an epithelial labyrinthic system whose entire extent is less than the diameter of a 10-cent piece, and that, lacking the proper functioning of these specialized plaques (cristae, maculae, and spiral organ) and the physiological and physical integrity of two drops of fluid, we would be hopelessly vertiginous and deaf.

The functioning of this system calls for study as broad in its inclusiveness as the elements themselves are small.

This phase of the investigation is concerned with structure, an endeavor pursued with the

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undramatic use of serially sectioned temporal bones, of reconstructions prepared therefrom, and the employment of gross dissections of unembalmed and skeletal ("cleaned") specimens of temporal bone.

The cochlear aqueduct, unlike the vestibular aqueduct, does not contain a "duct"; the cochlear aqueduct is occupied by connective tissue similar to that in the vestibular channel, not by a part of the membranous labyrinthine system. Whatever service this aqueduct might lend to a process of exchange between the perilymph (in the tympanic scala) and the cerebrospinal fluid (in the subarachnoid spaces) would be owing, again, to continuity of interfibrillar spaces.

As would be expected, the cochlear aqueduct is devoid of blood vessels—there being no "visceral" element to require vascularization. The vein from the cochlea, contrary to statements in conventional textbooks, occupies a separate channel in the bone. The course of this conduit is close to that of the aqueduct; their apertures and their intermediate portions are close together, but nowhere confluent.

As stated in the summary of the present article, the aqueducts are similar in some respects, different in others. A major difference exists in the pattern of blood supply, a theme expanded in a subsequent paper (Barry J. Anson, David G. Harper, and Thomas R. Winch, "The Vascular Routes to the Temporal Bone: Developmental and Adult Anatomy").

In deference to the nature of the authors' two reports, source articles have been listed. The present accounts are expansions of portions of an inclusive otological investigation, now extended to cover the aspects of anatomy relevant to the purposes of this symposium.

The labyrinths, although encapsulated, are not locked away as if in stone. The osseous labyrinthine wall is the *pars petrosa* of anatomical terminology; but, contrary to the implication, it is quite unlike a rock. It contains many channels that transmit the vessels of osseous supply. Nor is the contained space completely discontinuous with that of the cranial cavity; there exist interconnections chiefly in the form of aqueducts.

Anatomical observation points to physical interdependence of the labyrinthine system, even though the chemical interrelation may continue to be the subject of debate. What may happen within the membranous labyrinth is, therefore, a matter of fundamental importance. Interpretation calls for revision of our knowledge of this inner one of the two labyrinthine systems.

In the current instance, as in so many others where phylogeny offers a connecting link among living creatures (even when they are of seemingly diverse sorts), comparative embryology aids in the attempt to explain otherwise baffling aspects of human anatomy.

Here we may draw a parallel: In an aquatic creature, the shark, the epithelium of the receptive organ for the equilibratory sense is derived from the ectoderm (fig. 1, upper left) just as it is in man (fig. 1, upper right).

In both *Squalus* and *Homo*, the embryonic placodes thicken and become auditory pits; enlarging and sinking below the surface layer, they assume the ovoid form characteristic of the auditory vesicles, or otocysts. Where the otocyst joins the ectoderm, a tubular process pushes out as a new growth: the endolymphatic duct. In selachian fishes, the endolymphatic duct opens permanently to the exterior. In man, the otocyst loses connection with the ectoderm. The internal ear, in order to become acoustic as well as equilibratory in function, is obliged (speaking teleologically) to reestablish an aqueous environment.

Accommodation entails the formation of two labyrinths, both of them closed to the exterior: an inner one derived from the otocyst (therefore having an epithelial wall); an outer one immediately surrounding and generally matching the shape of the inner one (and having an osseous wall). Each labyrinth becomes a fluid-containing system.

The canalicular side of the organ retains to a degree the fundamentally simple pattern of widely communicating chambers.

On the cochlear side, however, a complex mechanism must be built to bring the specialized sense organs of the membranous labyrinth into physical relationship with the outside world. With no new source of anatomical material for the putting together of a mechanism for hearing

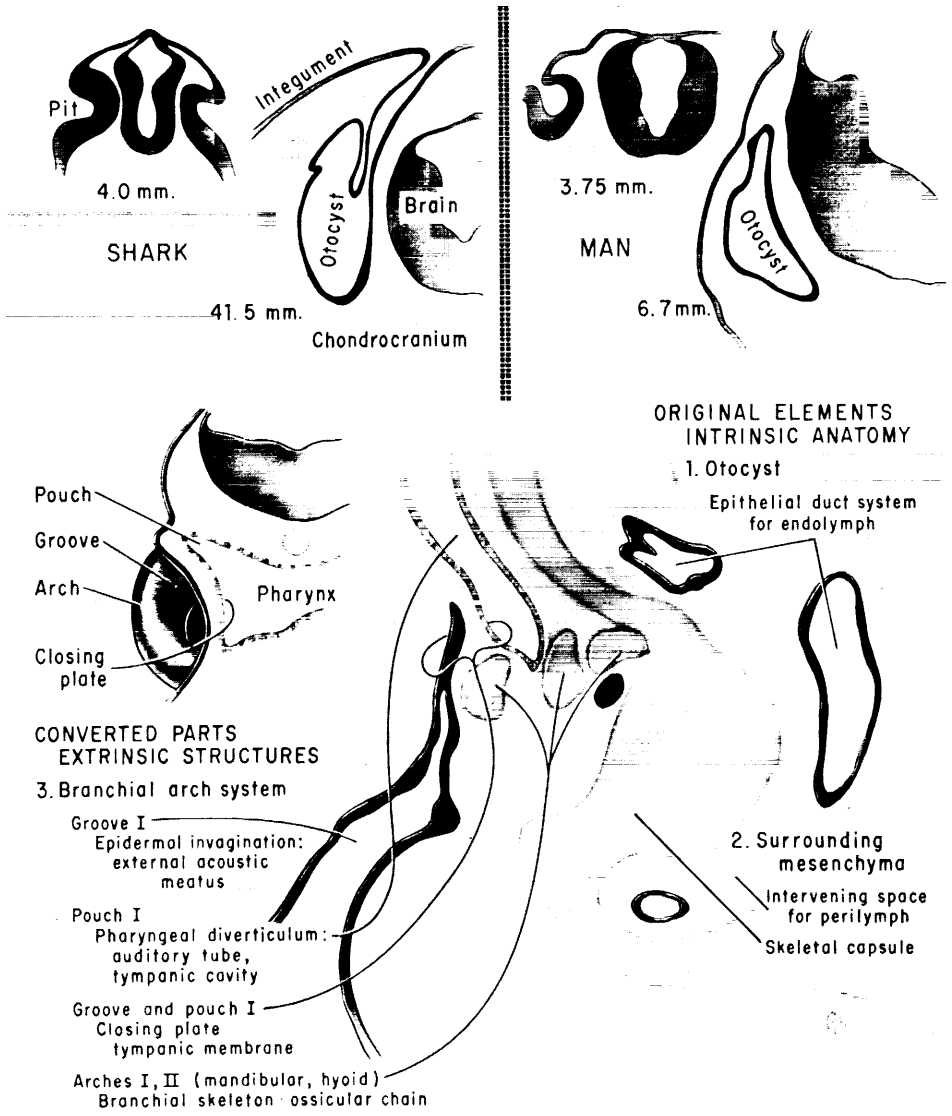


FIGURE 1.—*Comparative embryology of the ear. Primitive character of the otocyst and converted extrinsic structures requisite to service in a terrestrial environment. In its phylogenetically simplest form, the otocyst retains its original connection with the parent ectoderm. Thus, in the shark, after the auditory pit has become a vesicle, the contained fluid is one with the circumambient waters. In man, on the contrary, ectodermal continuity is lost in the early embryo. Thereupon a remarkable series of developmental events is initiated, through the operation of which the branchial arch system of the aquatic creature is "remodeled" to become the constituents of the external and middle ear of the terrestrial vertebrate. The otocyst gives rise to a membranous labyrinth around which the mesoderm contributes a capsule of precartilage. The tissue of this skeletal element undergoes resorption to form the matching spaces of the osseous labyrinth. An aqueous system is thus restored in which one fluid (the endolymph) is surrounded by another (the perilymph). The epithelial labyrinth, thus sequestered, could serve as equilibratory apparatus, but not in an auditory capacity. For the latter, a wave-transmitting mechanism is required to bring the sensory endings of the acoustic system into relation with the surrounding air. The converted parts of the branchial arch system are the external acoustic meatus, tympanic membrane, auditory ossicles, auditory tube, and tympanic cavity.*

in a terrestrial environment, the human embryo remodels a system for which it will have no other use; namely, the visceral arches of a respiratory system serviceable only in aquatic and amphibious creatures.

To the primordial system of epithelial ducts is added a series of converted structures, all of them derivatives of the branchial system. Elements come from the three embryonic germ layers through a most remarkable piece of morphological salvage (fig. 1).

From the ectoderm of the first pharyngeal groove come the external acoustic meatus and the epidermal (outer) layer of the tympanic membrane. From the entoderm of the corresponding pouch are derived the mucosal (inner) layer of the tympanic membrane, the auditory tube, the tympanic cavity and the pneumatic extensions therefrom.

The branchial arches (mandibular and hyoid) contribute the auditory ossicles. The mesenchyme surrounding the membranous labyrinth is converted into the otic capsule and the sparse tissue in the perilymphatic space.

Thus, there are primordial constituents (fig. 1, list at lower right) and converted parts (fig. 1, list at lower left).

The perilymphatic space, although within an osseous shell, is not segregated; it communicates with the cranial cavity by way of two aqueducts: cochlear and vestibular (figs. 2 and 3).

The cochlear aqueduct, contrary to conventional descriptions, transmits neither a vein nor an artery; from an early fetal stage and throughout life, the related cochlear vein is housed in a separate osseous channel. The vestibular aqueduct, unlike the cochlear, contains both arteries and veins that enter the connective tissue both from canals in the surrounding bone and from the cranial meninges.

The aqueducts are alike in being occupied by connective tissue. This tissue is as loosely textured around the endolymphatic sac as is the entire fibrous content of the cochlear aqueduct, the interstices of which constitute the so-called perilymphatic "duct." The tissue within the two aqueducts resembles that through which fluid generally moves in other parts of the body.

Two additional features are similar: Both aqueducts open internally upon the wall of the osseous labyrinth; both terminate externally in orifices situated on surfaces of the petrous pyramid. This means that both channels in

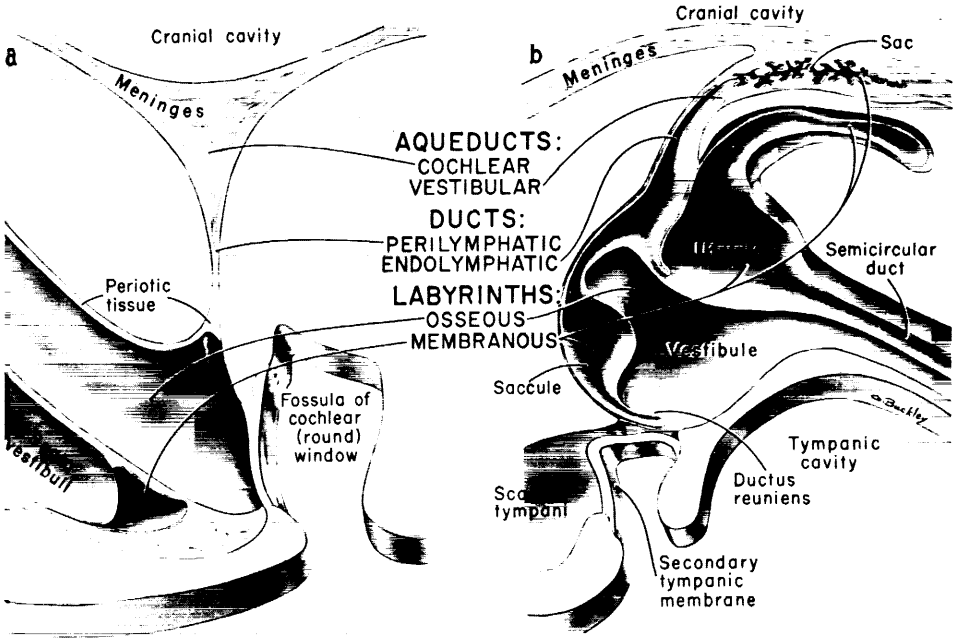


FIGURE 2.—*Comparison of the cochlear* (a) *and vestibular* (b) *aqueducts. The semischematic drawings are based on study of serially sectioned temporal bones, reconstructions and dissections. (From Laryngoscope, vol. 74, no. 7, July 1964, pp. 945–966.)*

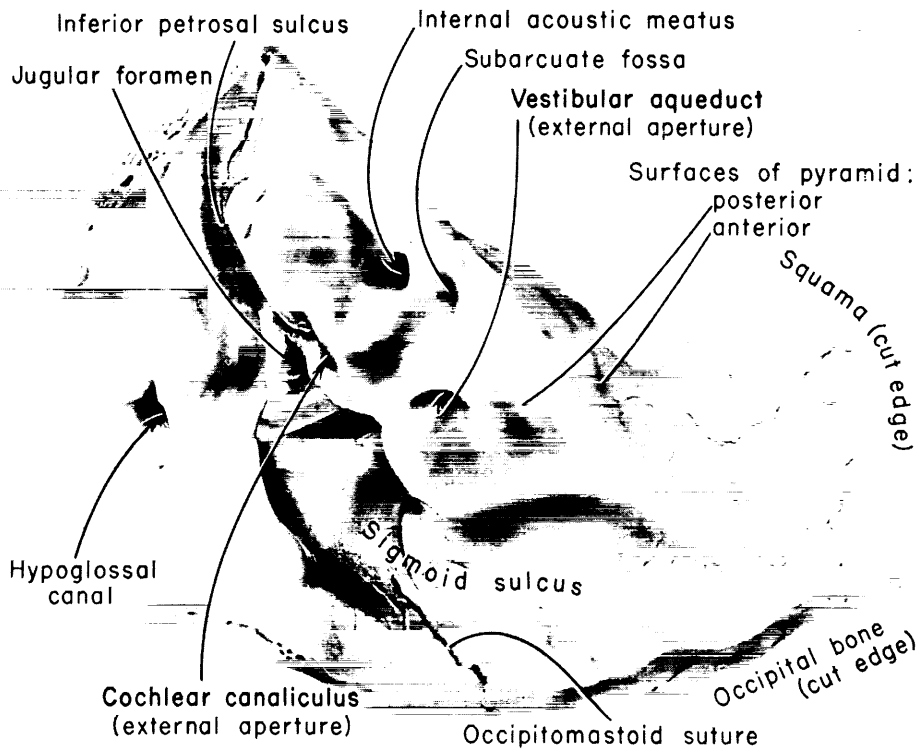


FIGURE 3.—*The medial surface of the temporal bone (skeletal preparation, undissected). The external aperture of the vestibular aqueduct and related structures on the posterior surface of the petrous pyramid are shown.*

the fresh state begin in periotic tissue and terminate in the meninges.

But there are also two differences: Developmentally the wall of the vestibular aqueduct is formed around a preexistent duct and sacculation of the membranous labyrinth, whereas the cochlear aqueduct is of secondary formation, produced through the resorption of precartilage of the developing otic capsule of the fetal ear; histologically, the vestibular aqueduct contains an epithelial duct and sac, together with related arteries and veins, whereas the cochlear duct contains none of these (the cochlear vein, as already mentioned, occupying a separate osseous channel adjacent to the aqueduct).

For further structural study, the primary need is for specimens which preserve the less "durable" meningeal layers; that is, *arachnoidea* and *pia mater*. Currently available histological material includes only that segment of the entire pathway which ends on the external aperture in the cranial *dura mater*.

THE POSITION, FORM, AND RELATIONS OF THE AQUEDUCTS

Gross Anatomy

The vestibular aqueduct opens into the posterior cranial fossa as a slitlike fissure located about midway between the internal acoustic meatus and the groove for the sigmoid sinus (fig. 4). This external aperture is overhung by a thin lip of bone. The internal aperture is situated behind and below the elliptical recess (housing the utricle) on the wall of the vestibule; it begins as a furrow, then becomes a canal that passes backward and downward to the posterior surface of the petrous pyramid.

When the "roof" of the aqueduct has been dissected away, it is found that the distal segment has the form of a triangle with the apex directed inward and upward toward the strikingly narrowed middle segment (fig. 4, at tip of arrow). As will be shown, the broadened seg-

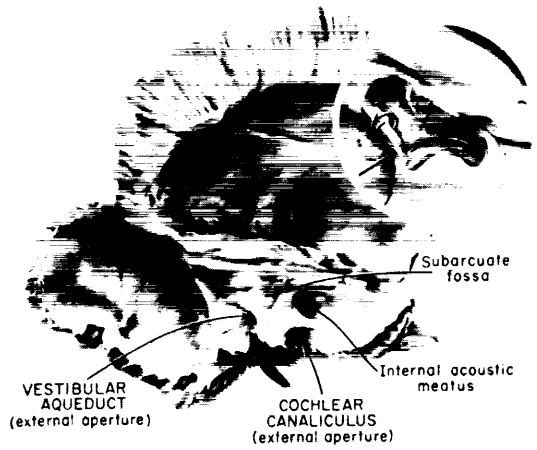


FIGURE 4.—*External aperture of the vestibular aqueduct. The specimen is shown intact and dissected to demonstrate the triangular form of the distal segment of the aqueduct. A bridge of bone (encircled) remains to mark the aperture. The long arrow points to the narrow intermediate segments.*

ment thereby exposed contains the endolymphatic sac, while the constricted part transmits the isthmus of the endolymphatic duct. Beyond the aperture (encircled margin) the posterior surface of the petrous pyramid is foveate for reception of the intradural part of the sac. Variations are numerous, sometimes departing from the typical to such a degree that they would be termed aberrant.

The cochlear aqueduct terminates on the inferior surface of the petrous pyramid anterior to the jugular fossa (fig. 5). It opens internally on the medial wall of the tympanic scala near the beginning of the latter (shown in photomicrographs, fig. 6).

The external aperture of the cochlear aqueduct is regularly funnel shaped. Although the opening is situated on the inferior surface of the petrous pyramid, it is visible from the medial surface where it appears as a notch at the posterior angle of the bone (fig. 4).

The vestibular aqueduct courses through the bone from the vestibule to the posterior cranial fossa. The narrow isthmus of the endolymphatic duct would occupy the constricted segment of the channel (fig. 6); the sac would be contained in the widened part of the aqueduct, and therefrom would be prolonged beyond the external aperture to the foveate impression on the posterior surface of the petrous pyramid.

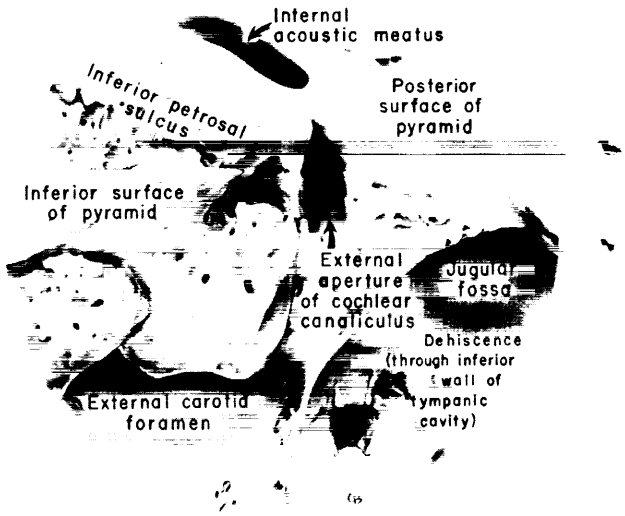


FIGURE 5.—*Inferior and posterior surfaces of the temporal bone. Three vascular routes are shown: the external acoustic meatus, the cochlear canaliculus (aperture), and channels opening into the superior petrosal sulcus. The dissection in figure 13 of the paper entitled "The Vascular Routes to the Petrous Part of the Temporal Bone: Developmental and Adult Anatomy" shows the nature of the underlying osseous tissue.*

Awareness of the form of the membranous labyrinth as a whole and of the relation of its parts to the surrounding osseous labyrinth is essential to an interpretation of the movement of fluids, blood, perilymph, and endolymph. This part of the discussion will be introduced by a review of the authors' recent studies on the membranous labyrinthine system.

The utricle is elongate and broadly continuous, L-shaped fashion, with the equally capacious common arm of the two semicircular ducts (fig. 7(*a*), at 1 and 2; see also figs. 18(*a*) and 18(*b*) and 19(*a*)). Together, the portions of the membranous labyrinth make up a widely open right-angled compartment. The utricle, therefore, might be regarded as an expansive kind of ampulla wherein the fluid is allowed to move freely across the acoustic maculae through the vestibular and canalicular subdivisions of the endolymphatic system. Unlike the utricle, the saccule, somewhat the smaller of the two vesicles, is offset from the endolymphatic duct and sac (fig. 7(*a*) at 3; see also fig. 19(*c*)).

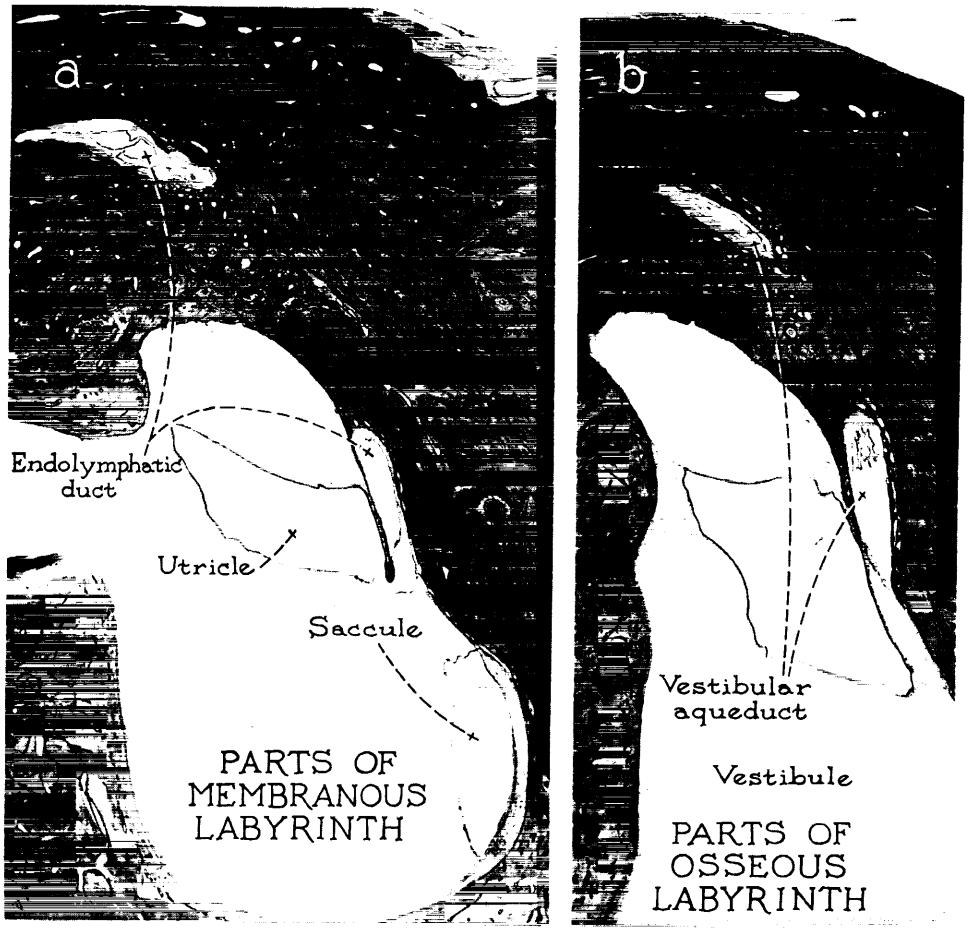


FIGURE 6.—*Vestibular and intraosseous course and relations of the endolymphatic duct and sac. Adult, 17 years of age. Transverse sections. Wisconsin Collection, series 25. 18×.* a: *The endolymphatic duct at the internal aperture of the vestibular aqueduct and the sac as it approaches the external aperture are shown. The saccule is lodged in the spherical recess of the vestibule. The sac is of vesiculate form. The endolymphatic fold, or "valve," is situated between the utricle and the sinus-like expansion of the endolymphatic duct. (Compare with fig. 5.)* b: *Proximally, the endolymphatic duct is a narrow channel. (See fig. 5, at isthmus.) The sac is sectioned at the approximate point of continuity with the narrow isthmus. The duct begins on the posterosuperior wall of the vestibule in a small depressed area of the elliptical recess (for reception of the utricle). It ends on the posterior wall of the petrous pyramid. (See fig. 14.) (The Vestibular System and Its Diseases. R. J. Wolfson, ed., University of Pennsylvania Press, 1966.)*

Whereas the utricle is broadly continuous with the semicircular ducts (fig. 7(*b*)); see also fig. 18(*a*)), the communication with the cochlear side is narrow (fig. 7(*c*)); see also figs. 19(*b*) and 19(*c*)). The ampullae are only half-partitioned by the shelflike cristae (figs. 7(*d*) and 8).

The endolymphatic sac is either rugose or vesicular (fig. 7(*e*)) and, contrary to earlier belief, it is a gross structure (fig. 9). The sac extends for a relatively great distance beyond the external aperture of the vestibular aqueduct (fig. 9 at labeled line). The sac occupies the foveate impression whose lower boundary is the sulcus for the sigmoid venous sinus (already shown in fig. (3)).

The segment of the sac situated within the aqueduct occupies the triangular space shown in the dissections. The sac narrows as it is traced inward, to become the isthmus of the endolymphatic duct at the deep, or apical, part of the aqueduct. Far from being a smooth-walled, mushroom-shaped terminal expansion or a quill-

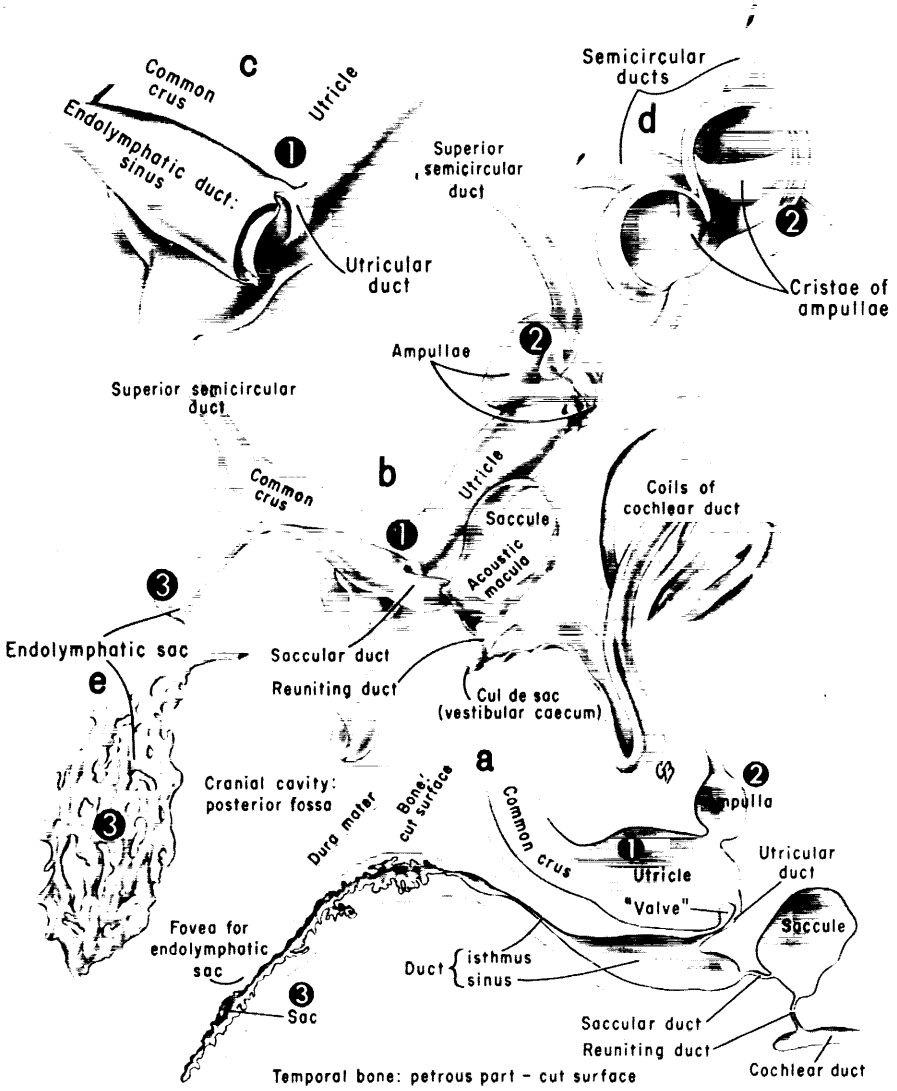


FIGURE 7.—*The membranous labyrinth based on reconstructions prepared from serially sectioned temporal bones. Far from being a succession of relatively simple tubes locally dilated (at ampullary, utricular, and saccular chambers), parts of the membranous labyrinth have distinctive character. The special modifications are illustrated here as they are demonstrated in a reconstruction of the epithelial duct-system in a newborn infant.* a *and* b: *In semidiagrammatic form and in detail, it is shown that on the canalicular side the utricle (at 1) is continuous broadly with the semicircular ducts (at 2); and that, on the contrary, toward the cochlear side, communication takes place through a narrow duct beneath a valve-like fold, into a channel that terminates in a rugose expansion in one direction (at 3), and is prolonged through narrow segments into the cochlear duct. Features are treated separately in the associated figures.* c: *The communication of the utricle with the endolymphatic duct is narrow, being "guarded," so to speak, by the utricular fold.* d: *Each semicircular duct is locally enlarged (at an ampulla); however, within each such expansion, a crista is present in the form of a half-partition across the lumen (unlike the conventionally pictured mound of histological preparations).* e: *The endolymphatic duct ends, not as a dome-shaped enlargement of a quill-like tube, but as a rugose sacculation prolonged from the vestibular aqueduct into the cranial cavity, there occupying a foveate impression on the posterior surface of the petrous pyramid.*

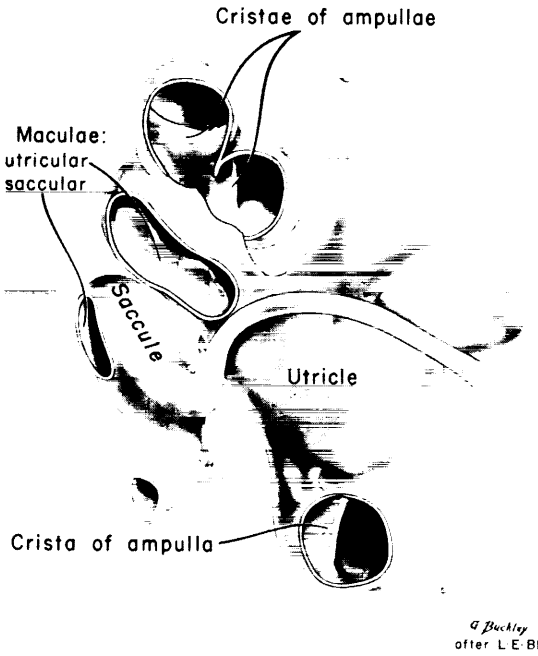


FIGURE 8.—*Reconstruction of the membranous labyrinth, with the saccule, utricle, and ampullae opened. Newborn infant (4-day premature). Wisconsin Collection, series 124. The form, size, and position of the maculae and cristae are demonstrated. The form of the cristae is especially striking; each has the form of a half-partition across its ampulla. In sections they appear to be mound-like. (Adapted from fig. 40, Bast, T. H.; and Anson, B. J.: The Temporal Bone and the Ear. Charles C Thomas, 1949.)*

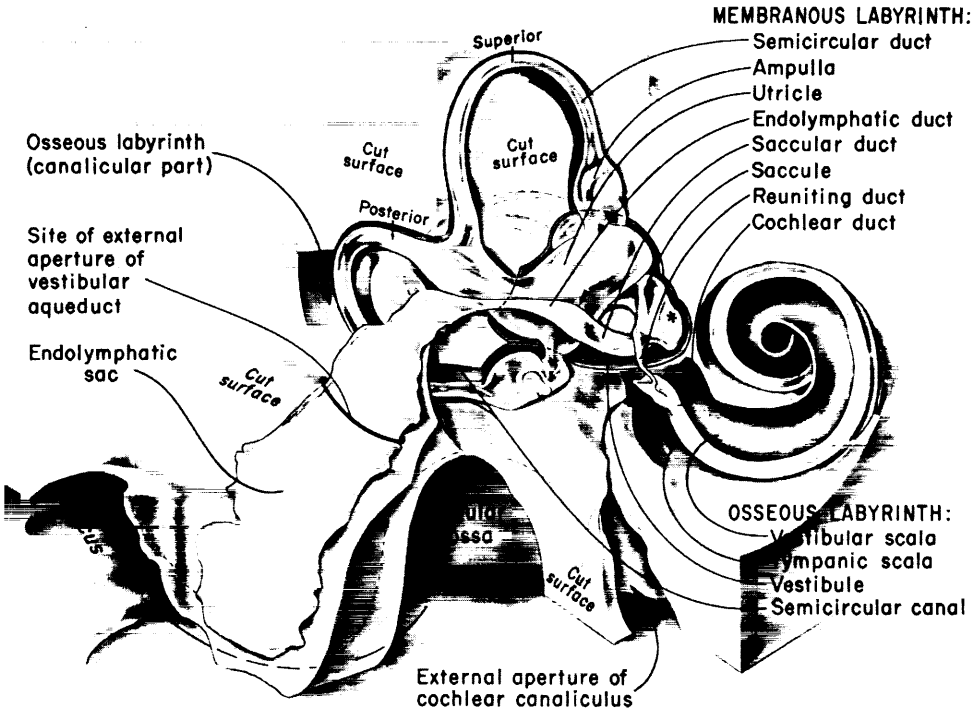


FIGURE 9.—*Reconstruction of the membranous labyrinth and related anatomy. Adult, 65 years of age. Wisconsin Collection, series 47. This was prepared especially to demonstrate the form and size of the endolymphatic sac and duct. The sac occupies a foveate impression; it is closely related to the bulb of the jugular vein and to vessels continued therefrom to the sigmoid venous sinus of the dura mater.*

FIGURE 10.—*Reconstruction of the space (lumen) of the endolymphatic sac. Adult, 36 years of age. Wisconsin Collection, series 40. The lumen is not a smooth-walled space. In this example of a rugose sac, the space is interrupted at several points, rendering the sac vesiculate.*

like tube, the endolymphatic sac is a complex structure; its epithelial wall is thrown into folds or vesiculate outpocketings, the lumen being correspondingly altered (fig. 10, lumen represented as a solid).

MICROSCOPIC ANATOMY

Vestibular Aqueduct

The epithelial wall of the sac is thrown into either plications or outpocketings, and the surrounding connective tissue is vascular (fig. 11). Channels from the bone open into the aqueduct (figs. 12(*a*) to 12(*c*) and 13(*a*) to 13(*c*)). This important matter of vascularity is referred to again in our subsequent paper (p. 259). For the moment, the account will be limited to consideration of the blood-vascular pattern in and immediately around the vestibular aqueduct.

A study of sections reveals the abundant presence of blood vessels in the tissue around the ductus and the saccus and their direct communications with vessels in the osseous wall of the aqueduct (figs. 12(*a*) to 12(*c*) and 13(*a*) to 13(*c*)). The endolymphatic sac falls far short of filling the space in the distal segment of the

FIGURE 11.—*Photomicrograph of a section through the endolymphatic sac, near the external aperture of the vestibular aqueduct. The level is indicated by the line in the preceding figure. Adult, 36 years of age. Transverse section. Wisconsin Collection, series 40. 24×.*

aqueduct. It seems highly probable that the interfibrillar spaces of the fibrous bed permit passage of perilymph and cerebrospinal fluid, just as comparable spaces elsewhere in the body permit the slow passage of tissue fluids. Were this true, the vestibular aqueduct would share in the function currently ascribed to the cochlear aqueduct.

The statement covering blood supply in the aqueduct applies to all series examined, whether they be fetal, infantile, or adult.

In histological material, vessels are not prominent in the *dura mater* around the part of the sac that extends into the posterior cranial fossa (fig. 14). This may be due to some vagary of preservation. The arrangement stands in sharp contrast to that around the intraosseous part of the sac where vessels are frequent offsets of sources in the wall. Their capillary extensions are found close to the duct and the sac.

Cochlear Aqueduct

The tissue of the cochlear aqueduct differs from the vestibular aqueduct in that it lacks vessels identifiable with use of the light microscope (fig. 15). This structural feature could have been predicted, since this channel does not transmit an epithelial tube. The aqueduct contains connective tissue, no "visceral" element. The vein from the cochlea occupies a separate channel.

The connective tissue within the aqueduct is like the periotic tissue that, in the 10-week fetus, fills the developing space between the carti-

laginous otic capsule and the membranous labyrinth.

MEMBRANOUS AND OSSEOUS LABYRINTHS

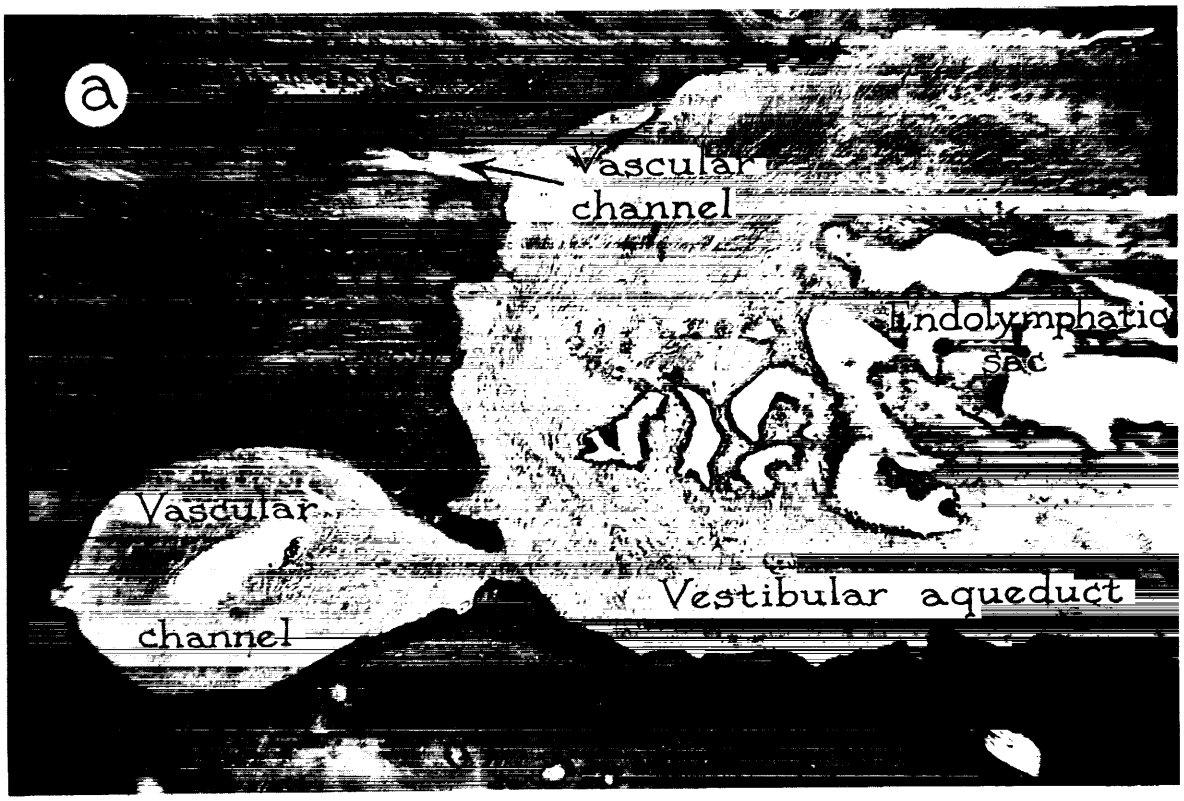
This relationship between a virtually avascular osseous labyrinth (containing the perilymph) circumambient to a membranous duct system is unique in bodily structure. The difference in capacity of the two labyrinths is striking. It is safe to assume that future studies on the physiology of the two fluid-containing systems will find significance in this relationship.

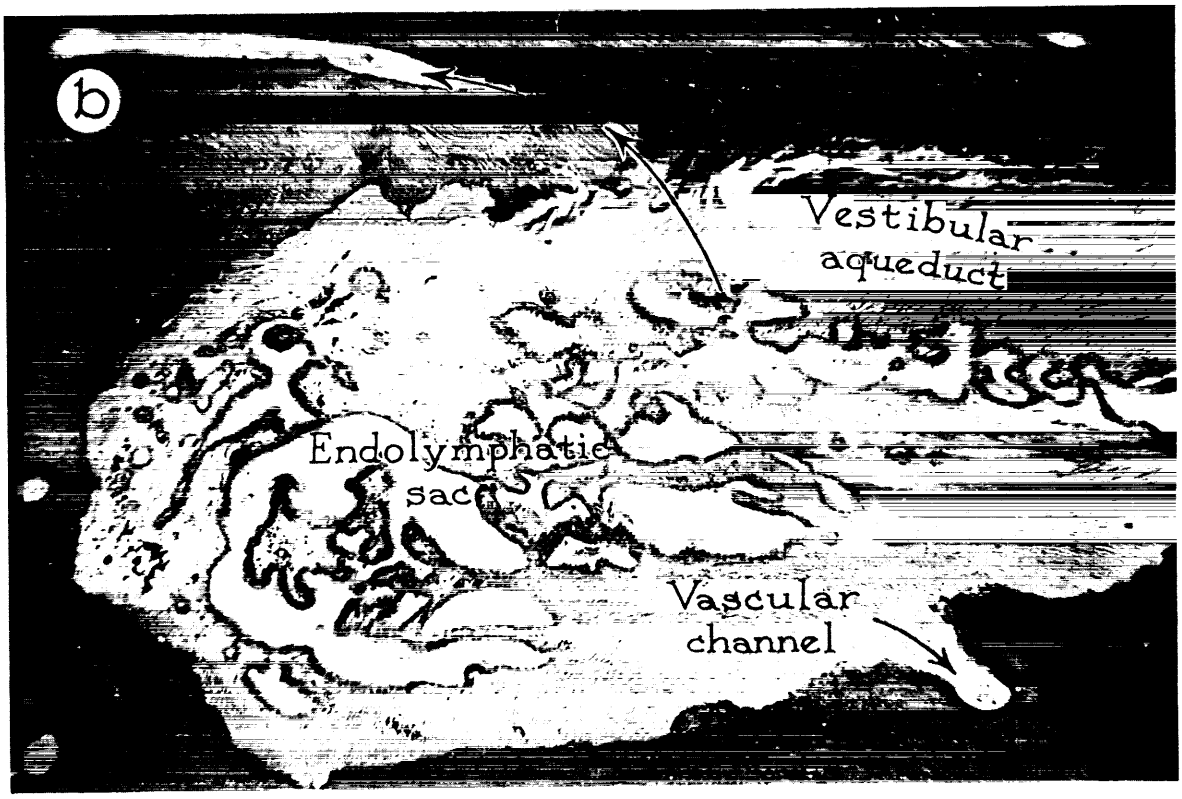
The relative total capacity of the perilymphatic and endolymphatic labyrinthic spaces is well demonstrated by the use of reconstructions (figs. 16 and 17).

The relationships are demonstrated with equal effect in photomicrographs of selected sections (figs. 18(*a*) to 18(*c*) and 19(*a*) to 19(*c*)).

On the cochlear side, the relative dimensions of duct and scalae are shown in the basal coil (fig. 19(*b*)). In the intermediate, or vestibular, area the spherical and elliptical recesses of the vestibule are occupied by the saccule and utricle, respectively. Here, the difference in capacity is striking in the area of broad continuity of the utricle with the common crus and semicircular ducts. The conspicuously greater capacity of the perilymphatic space, compared with that of the membranous duct, is evident in the area of continuity of the utricle with the common crus (figs. 18(*a*) and 18(*b*); 19(*a*)). Equally striking is the disparity in size of the labyrinths in the area of communication of the vestibule with the semicircular canals (figs. 18(*c*) and 19(*c*)).

The same statement applies also to the basal coil of the cochlea (fig. 19(*b*)).


a
Vascular channel
Endolymphatic sac
Vascular channel
Vestibular aqueduct


b
Vestibular aqueduct
Endolymphatic sac
Vascular channel

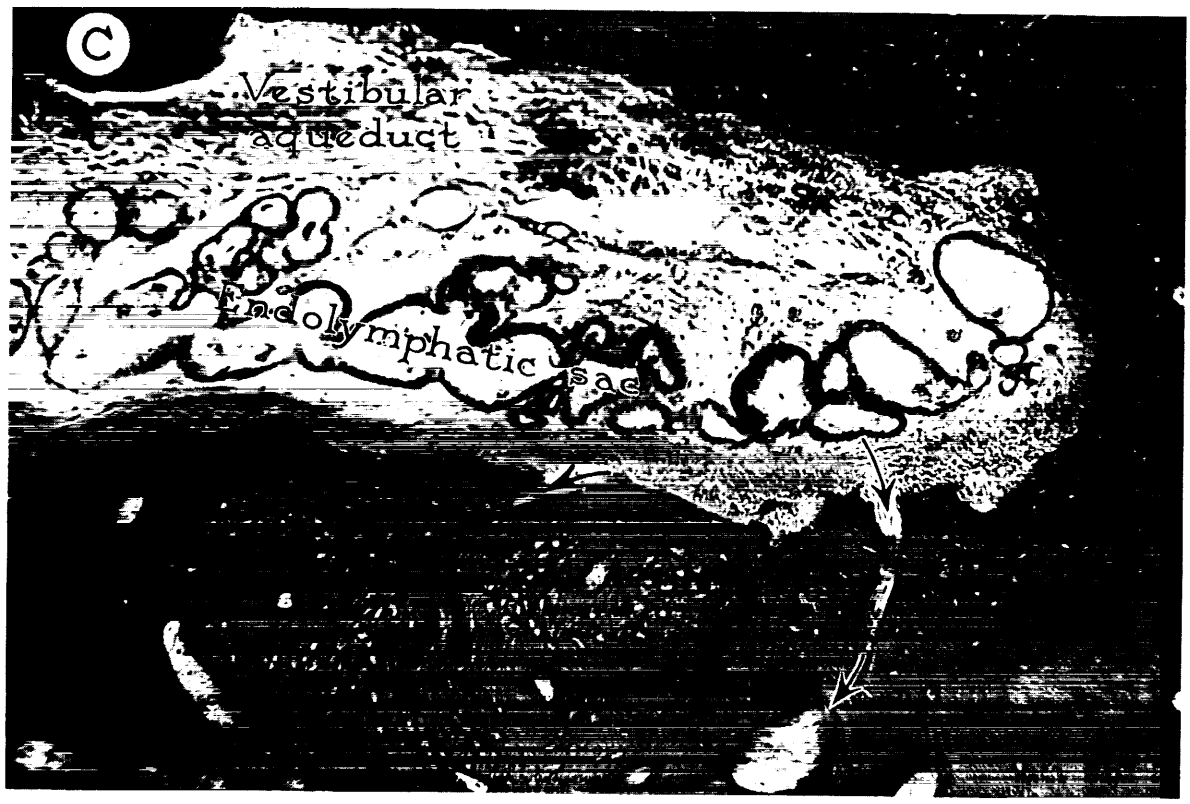


FIGURE 12.—*Form and blood supply of the endolymphatic sac.* (a) *Adult, 62 years old;* (b) *same specimen;* (c) *adult, 17 years. Transverse sections. Wisconsin Collection,* (a) *series 13,* (b) *series 13,* (c) *series 25.* (a) *93* ×, (b) *93* ×, (c) *100* ×. *In each instance the saccus is vesiculate in character. As reconstructions establish, these outpocketings, appearing separate in sections, communicate with a capacious central portion. (See fig. 10.) Vascular channels are numerous, sometimes relatively large, in the osseous wall. They send branches into the connective tissue around the sac. Some of these vessels are capillaries. As the external aperture is approached, the size of the aqueduct outbulks that of the contained sac. This circumstance spells increasing vascularity in the segment of the endolymphatic duct close to the cranial meninges.*

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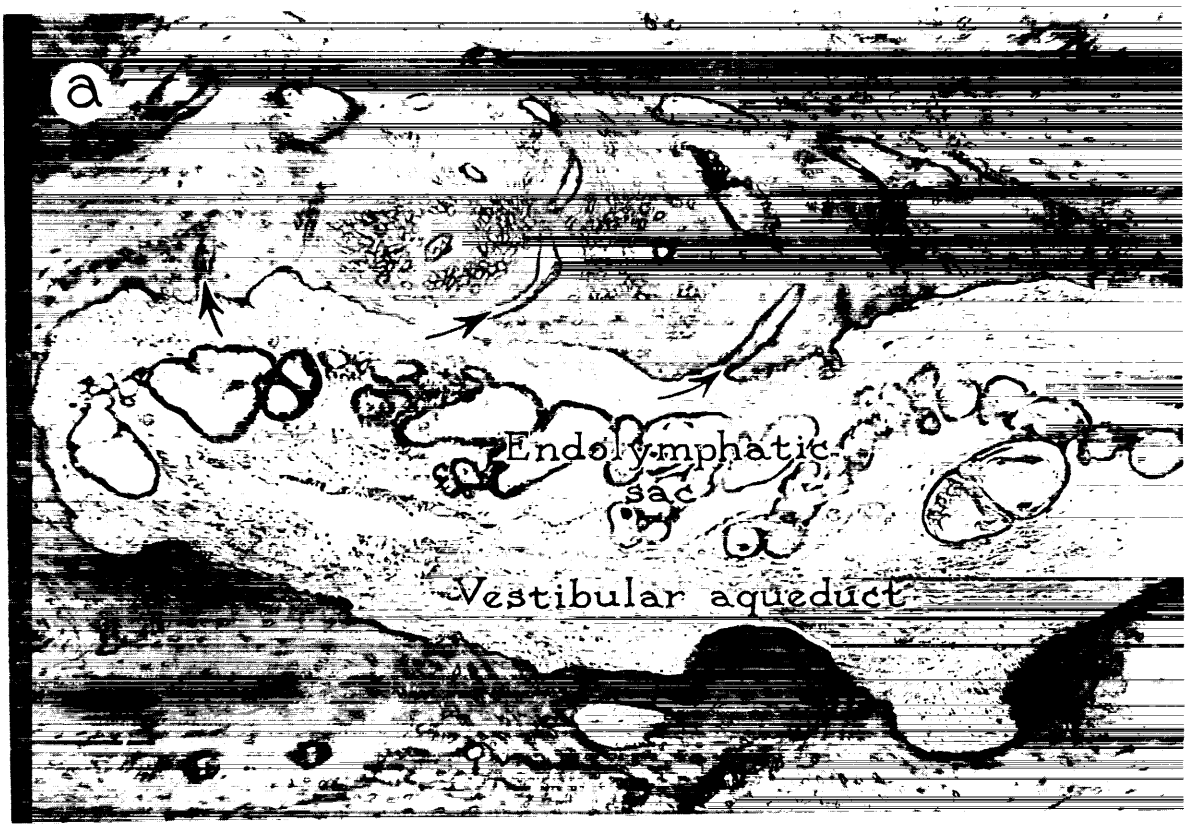
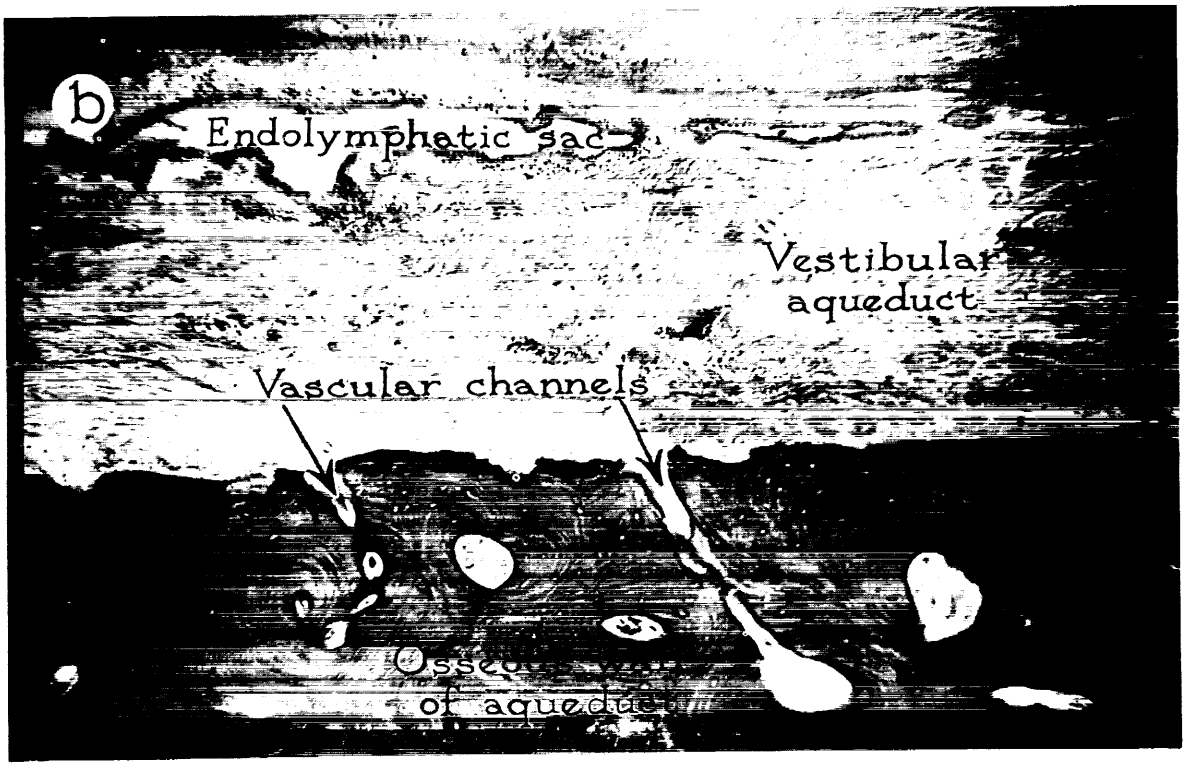

a
Endolymphatic sac
Vestibular aqueduct


b
Endolymphatic sac
Vestibular aqueduct
Vascular channels

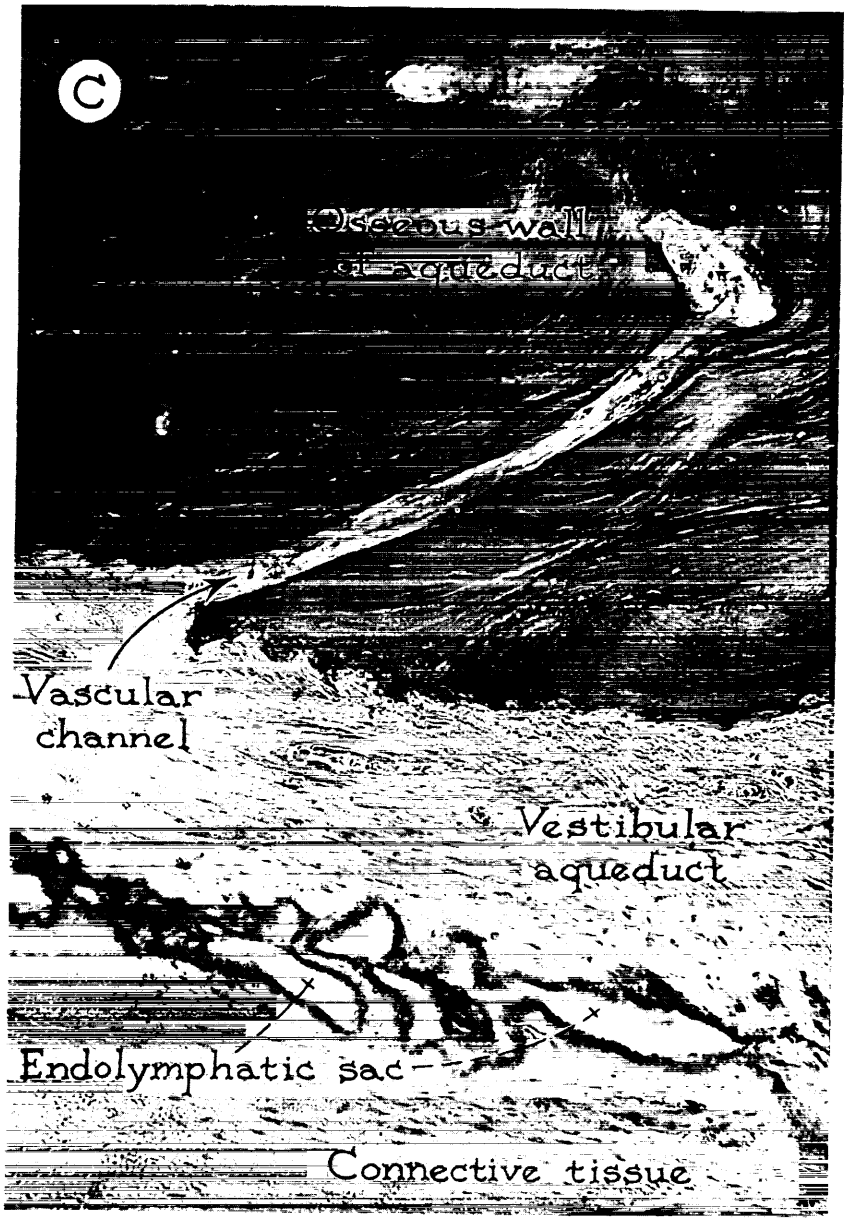


FIGURE 13.—*Form and blood supply of the endolymphatic sac.* (a) *Adult, 17 years of age;* (b) *adult, 62 years old;* (c) *adult, 55 years of age. Transverse sections. Wisconsin Collection,* (a) *series 25,* (b) *series 13,* (c) *series 6.* (a) *110×,* (b) *110×,* (c) *155×. The form of the sac varies from one individual to another and with the location in the same temporal bone. Usually its configuration is very complex where it lies in the depths of the distal segment of the aqueduct* (a), *less so as the external aperture is approached* ((b) *and* (c)). *Vascular channels are more numerous in the wall immediately surrounding the aqueduct than in the bone peripheral thereto. They open into the aqueduct at frequent intervals along its course, sometimes (at fortunate levels in the series) being traceable through a relatively long course. Their capillary extensions are encountered frequently in the loosely textured connective tissue near the epithelial duct. The strikingly rich blood supply of the vestibular aqueduct stands in striking contrast to the relative avascularity of the cochlear aqueduct.*

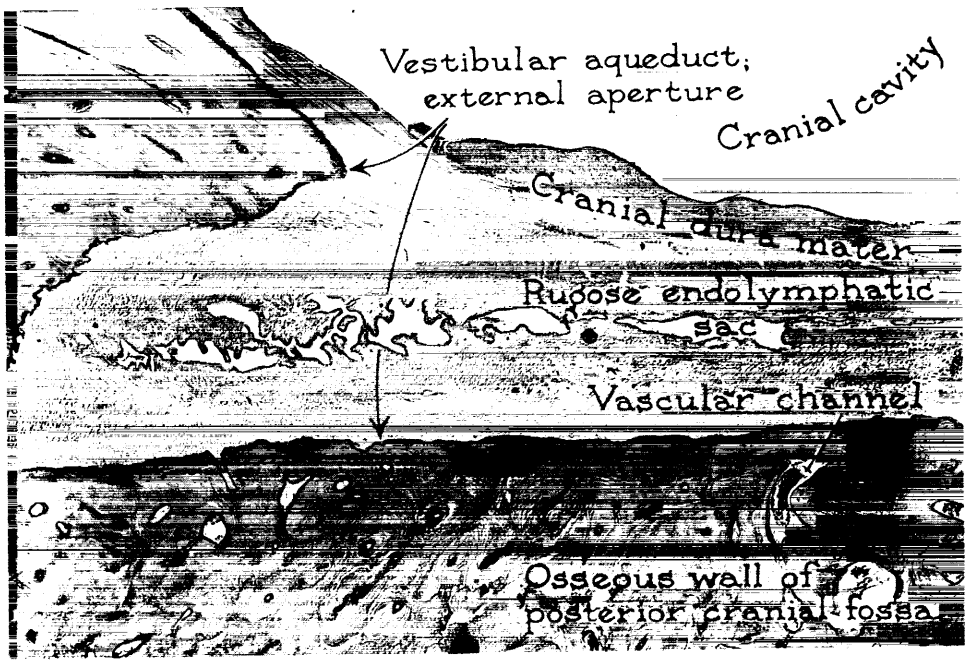


FIGURE 14.—*Form and relations of the endolymphatic sac. Adult, 62 years of age. Transverse section. Wisconsin Collection, series 13. 31×. The vesiculate character of the sac is demonstrated as it lies within the distal portion of the vestibular aqueduct and extends beyond the aperture of the latter into the posterior cranial fossa. The osseous wall contains many vascular channels from which fewer vessels are traceable into the* dura mater encephali, *and therefore to the sac, than in the case of the more proximal segment. (Compare figs. 12*(a) *to 12*(c) *and 13*(a) *to 13*(c).) *The sac occupies the shallow impression on the posterior surface of the petrous pyramid.*

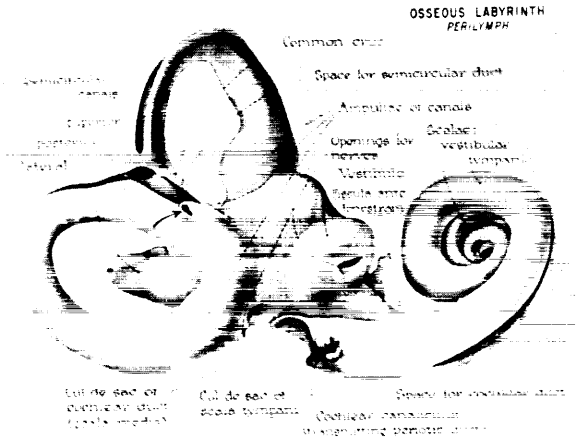


FIGURE 16.—*Reconstruction of the osseous labyrinth: the perilymphatic spaces are shown as solid, with sulci representing the position of parts of the membranous labyrinth. The unlabeled arrow points to the internal aperture of the vestibular aqueduct. Newborn (4-day premature). Wisconsin Collection, series 124. The fissula ante fenestram and the canaliculus cochleae (cochlear aqueduct) appear as perilymphatic appendages. The canaliculus is an outpocketing of the tympanic scala; the fissula is an extension of the space of the vestibule. The site of the secondary tympanic membrane is indicated by the asterisk.*

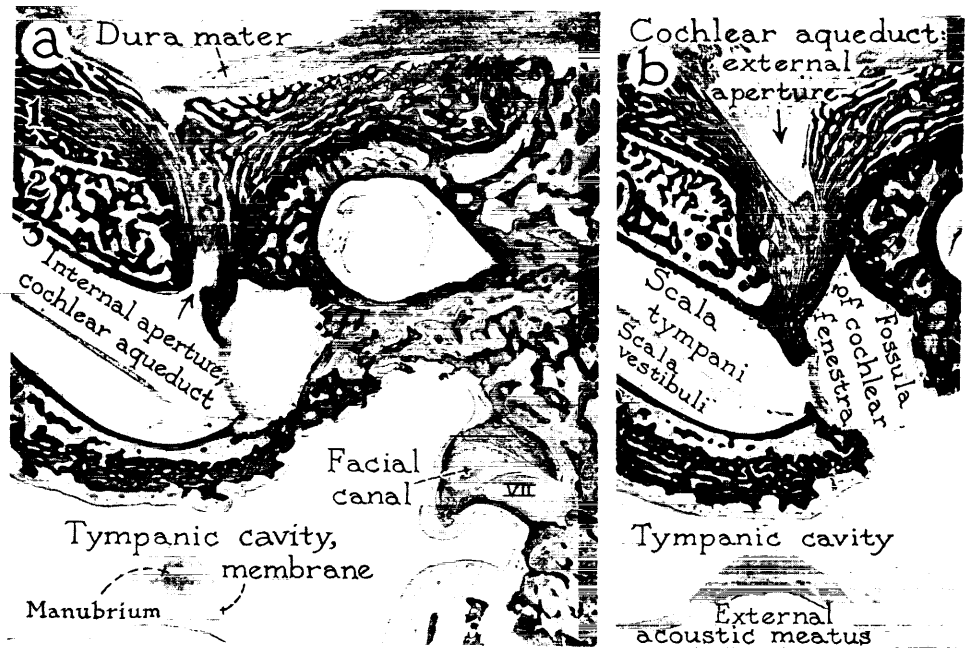


FIGURE 15.—*Cochlear aqueduct, or canaliculus; openings into the tympanic scala and cranial cavity. Newborn (4-day premature). Transverse sections. Wisconsin Collection, series 124. 8×.* a: *The internal aperture of the aqueduct, near the beginning of the tympanic scala. The opening is just anterior to the crest for the attachment of the secondary tympanic membrane, and by the latter is separated from the fossula of the cochlear fenestra (round window). Its tissue is continuous with the periotic tissue that covers the bone of the osseous labyrinth.* b: *The external aperture appears as a funnel-shaped opening on the inferior surface of the petrous pyramid, near the posterior angle of the bone. Here the contained tissue becomes continuous with the meninges. Contrary to familiar descriptions, the aqueduct does not transmit the vein from the cochlea. This vessel occupies a separate channel adjacent to the aqueduct.*

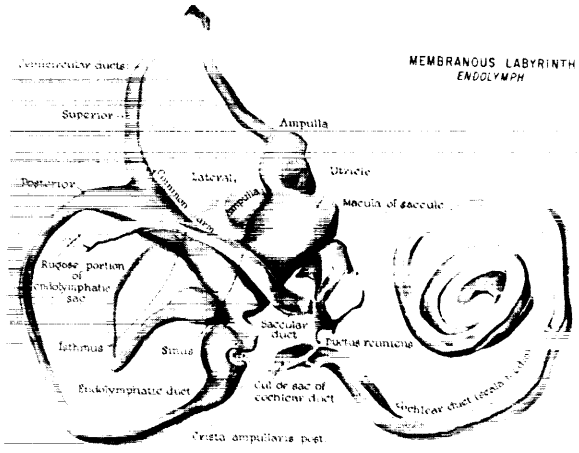
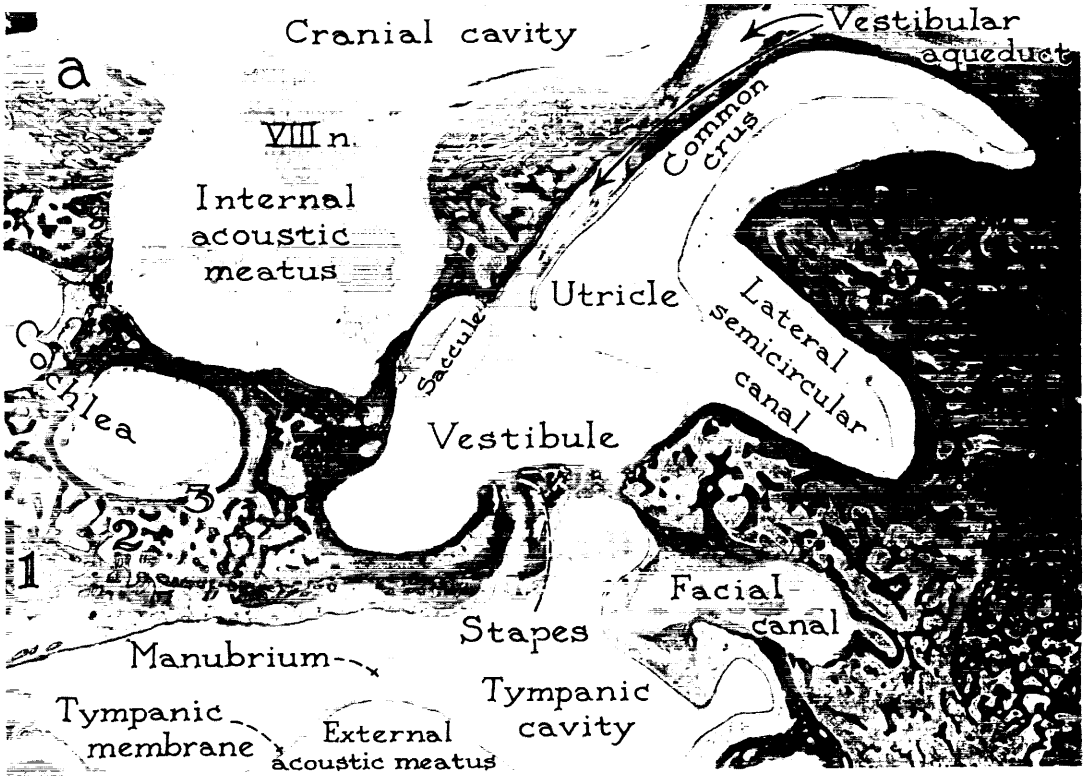
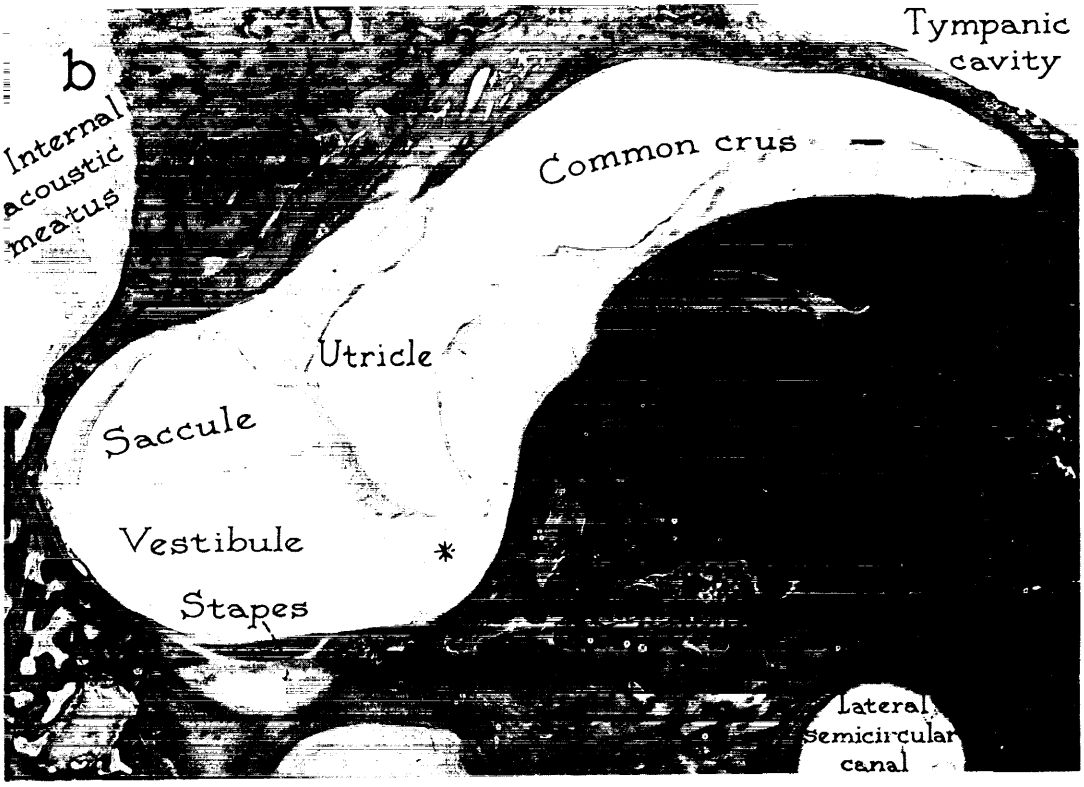


FIGURE 17.—*Reconstruction of the membranous labyrinth. The space of the labyrinthine duct-system is shown as a solid. Only the proximal portion of the sac is included in the reconstruction. Infant, 6 months old. Wisconsin Collection, series 121. The utricle opens widely into the semicircular ducts. Differing from such an arrangement, the communication with the cochlear duct is narrowed at two points. (See description with fig. 19.) The endolymphatic duct and sac are also strikingly different from the form customarily ascribed to them. (See fig. 7.)*


a
Cranial cavity
Vestibular aqueduct
VIII n.
Common crus
Internal acoustic meatus
Utricle
Lateral semicircular canal
Saccule
Cochlea
Vestibule
1
2
3
Facial canal
Stapes
Manubrium
Tympanic cavity
Tympanic membrane
External acoustic meatus


b
Tympanic cavity
Internal acoustic meatus
Common crus
Utricle
Saccule
Vestibule
Stapes
Lateral semicircular canal

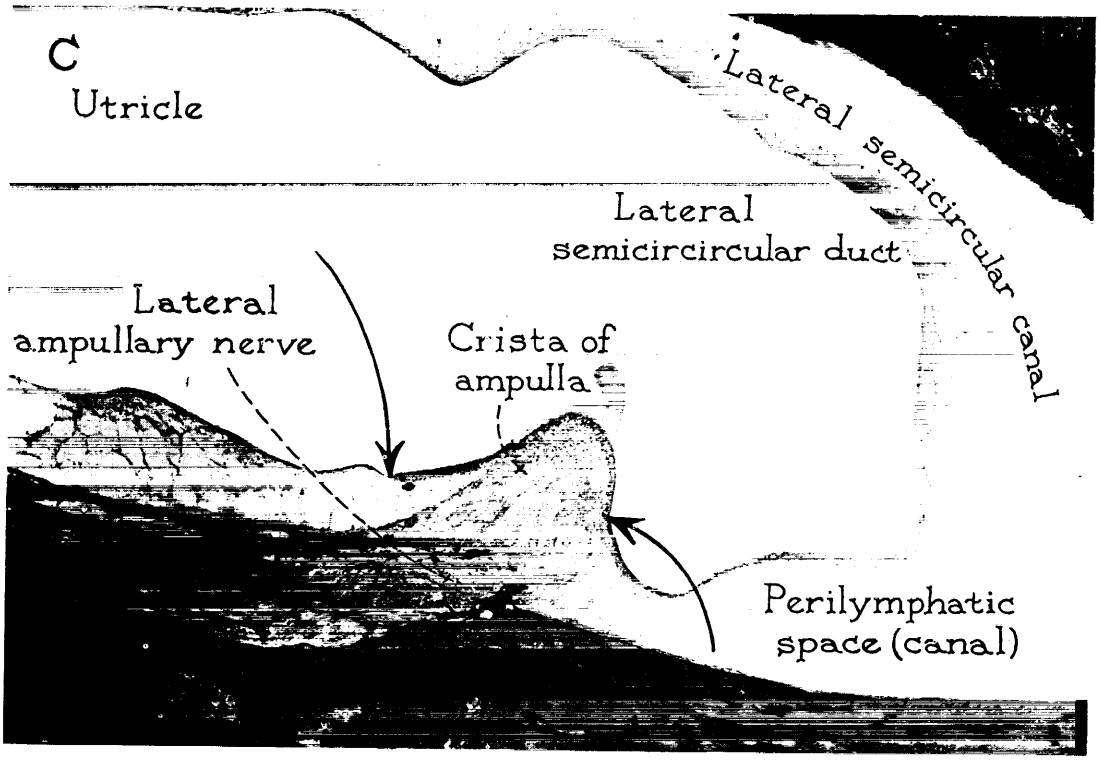
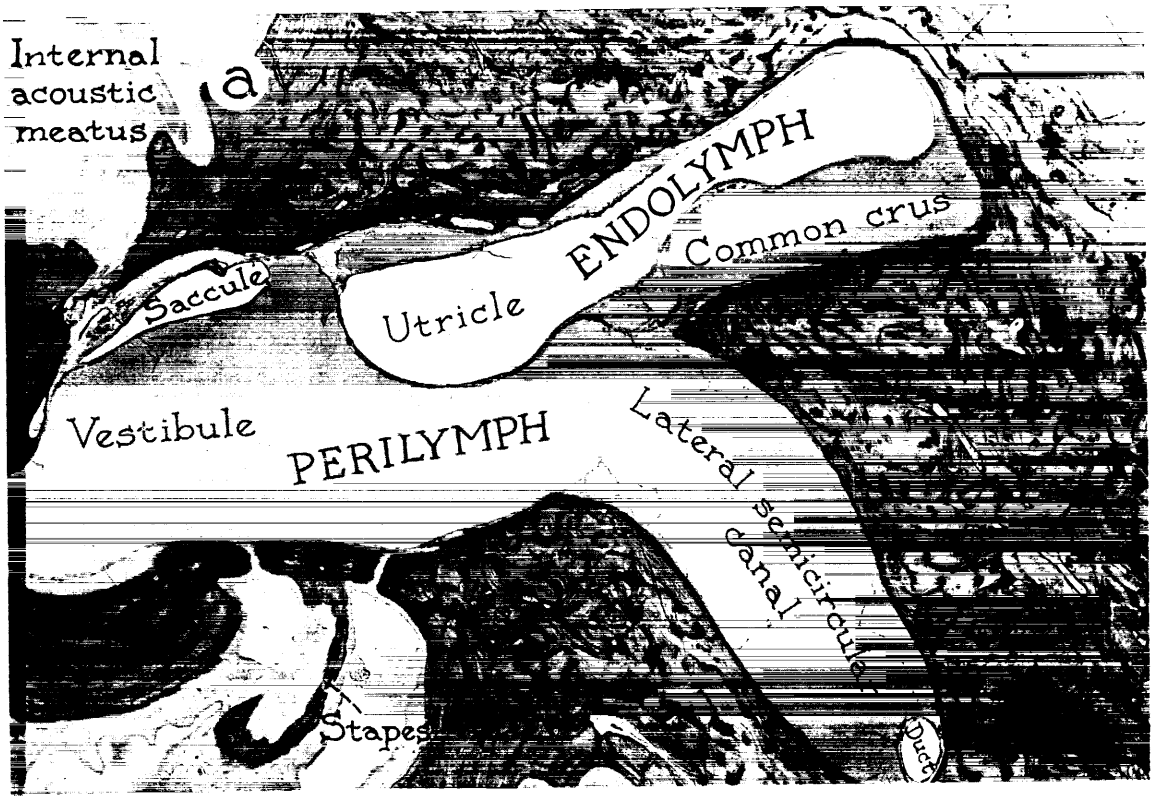
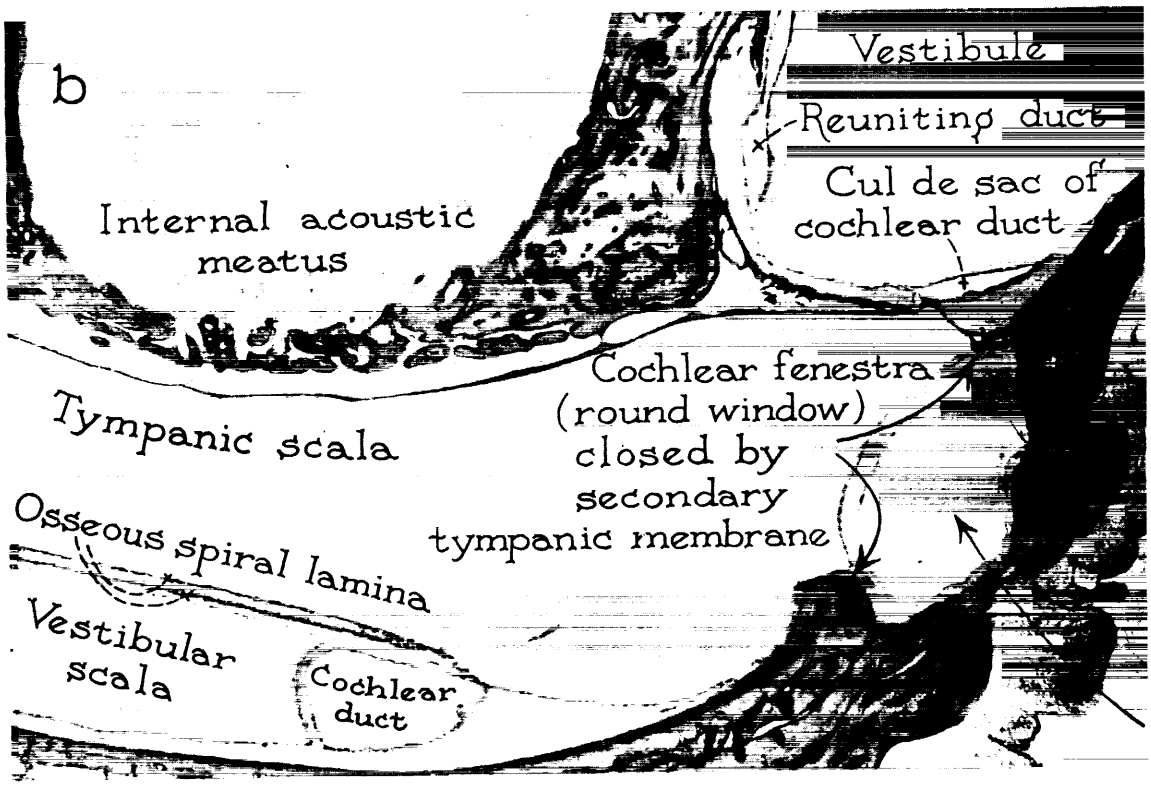


FIGURE 18.—*Utricle and semicircular ducts.* (a) *Newborn (4-day premature);* (b) *fetus at term;* (c) *adult, 19 years of age. Transverse sections. Wisconsin Collection, series 124, 123, and 29.* (a) 9×, (b) 16×, (c) 36×. a: *Showing the broad continuity of the utricle with the common arm of the superior and posterior semicircular ducts. The connection with the lateral duct appears in a neighboring section in the series.* b: *Similar communication with the common arm and the superior semicircular duct. The asterisk indicates supporting strands of periotic connective tissue.* c: *Continuity of the utricle with the ampulla of the lateral semicircular duct. Showing also the form of the crista and the course of the fibers of the upper terminal branch of the vestibular nerve (from the statoacoustic nerve) as they pass through canaliculi to the superior cribrose macula of the vestibule. Arrows point to the approximate limit of the crista.*


Internal acoustic meatus
a
ENDOLYMPH
Common crus
Saccule
Utricle
Vestibule
PERILYMPH
Lateral semicircular canal
Stapes
Duct


b
Vestibule
Reuniting duct
Cul de sac of cochlear duct
Internal acoustic meatus
Cochlear fenestra (round window) closed by secondary tympanic membrane
Tympanic scala
Osseous spiral lamina
Vestibular scala
Cochlear duct

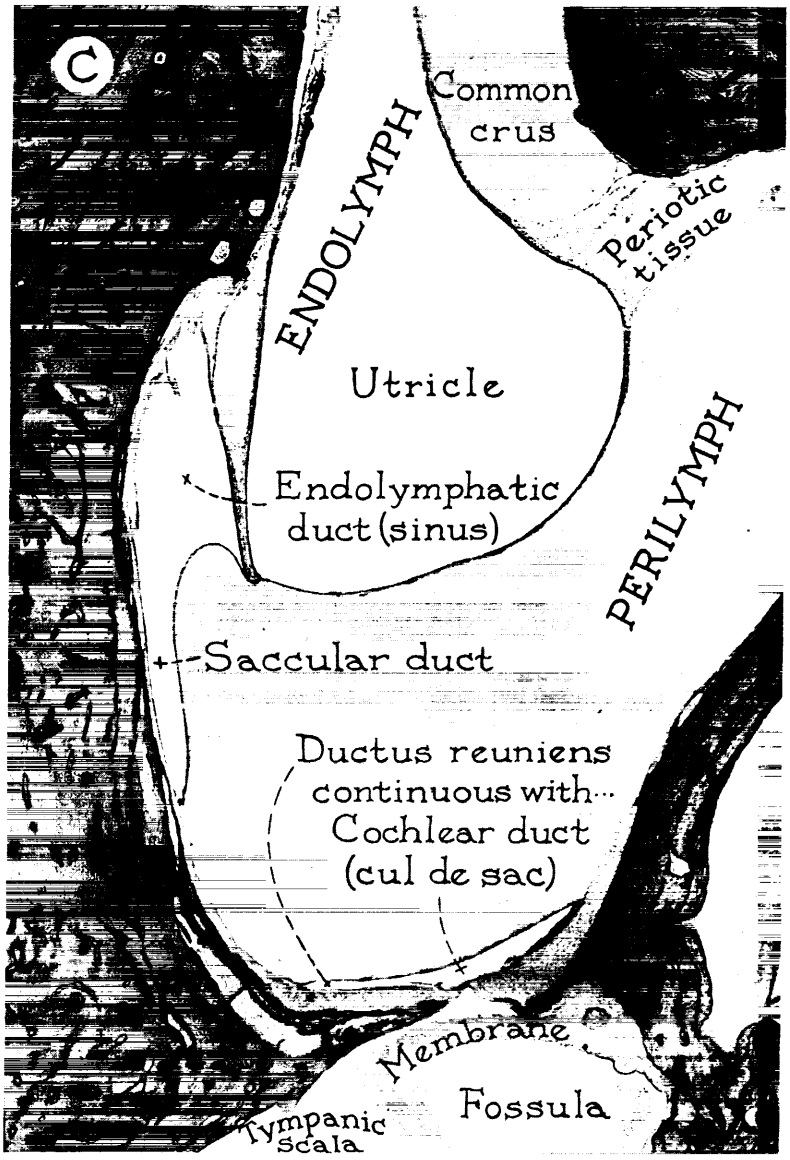


FIGURE 19.—*Membranous and osseous labyrinths; relative capacities in the areas of the vestibular (oval) and cochlear (round) windows. The space of the perilymphatic system is shown in darker tint.* (a) *Adult, 19 years of age;* (b) *infant of 6 months;* (c) *same series. Transverse sections. Wisconsin Collection,* (a) *series 29,* (b) *series 121,* (c) *series 121.* (a) *13* ×, (b) *22* ×, (c) *28* ×. a: *The labyrinthine spaces in the region of the vestibular fenestra, showing the vestibule and the area of continuity of the latter with the superior and lateral semicircular canals.* b: *The spaces occupied by the perilymph and endolymph in the vestibule and in the adjacent cochlea (basal coil, at the promontory) emphasizing that part of the system in which the utricle, by means of narrow intermediate ducts, communicates with the cochlear side of the labyrinth.* c: *The spaces for the labyrinthine fluids in the region of the cochlear fenestra, emphasizing that segment of the system in which the utricle communicates broadly with the canalicular part of the labyrinth.*

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ANSON, B. J.; DONALDSON, J. A.; WARPEHA, R. L.; AND WINCH, T. R.: The Vestibular and Cochlear Aqueducts: Their Variational Anatomy in the Adult Human Ear. Laryngoscope, vol. 75, Aug. 1965, pp. 1203–1223.

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DISCUSSION

DOHLMAN: Did I understand you correctly to say that there should be no blood supply to the membranous semicircular canals?

ANSON: Blood vessels rarely cross the perilymphatic space, from the wall of the canal to the epithelial duct.

DOHLMAN: I have also the same impression from sections of the canals. However, from preparations like those made by Dr. Johnsson and Dr. Hawkins, this demonstrates a very extensive vascular supply. However, from your picture I got the impression that the vascularization of the membranous walls is more extensive than should be required only for the nutrition of the perilymphatic tissue and the membranous walls. Dr. Fernández mentioned the ion transmission between the endolymph and perilymph, and in this connection I believe that we also have to take these highly vascularized areas into consideration. You mentioned some differences of the endolymphatic sac in different species; for instance, the selachiae without endolymphatic sac. In lampreys, you find that they have two endolymphatic sacs, one embedded in connective tissue like the dura, as in mammals, and the other one extending into the subarachnoid spaces as in frogs or in the pigeon where the endolymphatic sac lies inside the dura.

ANSON: Derivation would be important. Is the sac, in each of these instances, of ectodermal origin?

DOHLMAN: Both types are continuous with the membranous system and they seem to have the same function as a place for absorption. However, in frogs with their enormous endolymphatic sacs from the cisternae around the brain down along the spine, they seem to have also another function connected with the storage of calcium.

ANSON: My study in the fields of comparative embryology is limited to observations on the origin and early differentiation of the otocyst in mammals. There they follow a common pattern.

DOHLMAN: They seem to have the same function but they are so different.

ANSON: Perhaps they are functionally similar. Our observations have not been extended to the adult anatomy of the ear in mammals.

KHALIL: I came across a reference stating that there are longitudinal striations in the endolymphatic canal, especially on the wall adjacent to the periotic canal.

ANSON: Are these striations fibrous infoldings from the wall or within the substance of the epithelial duct system?

KHALIL: The infoldings between the membrana propria and the lining endothelium. This is a new edition of Gray's "Anatomy" in small print with an illustration, but I have not seen it elsewhere.

ANSON: I have not seen such structures in the ducts, utricle, or saccule. They are not among the features described in the 12th edition of Morris' "Human Anatomy."

SMITH: I had not realized before seeing your diagram, Dr. Anson, that the endolymphatic sac in the human ear was so large. When one considers the foldings of the epithelial surface and its rugosity, then the epithelial surface must be tremendous in size.

ANSON: Yes.

SMITH: Would you care to make an estimate as to its relative size in relationship to the rest of the membranous labyrinth?

ANSON: We shall be able to supply such information by the method of measurement of water displacement, using reconstructions of known magnification. It seems likely that the surface area of the endolymphatic duct and sac will be found to exceed that of the remainder of the labyrinthine system. The sac is relatively an enormous vesicle—relatively, of course, because all parts of the auditory and vestibular system are in the lilliputian category.

SPECIAL SESSION

N 68-29138

Labyrinthine Control of the Postural Muscles

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SUMMARY

The stabilizing reflexes operate according to the principle of minimizing undesired motion; muscles act as stiffer springs during elongation than they do when shortening. Analysis of this effect reveals the nature of the mechanisms available for postural adjustments, and the consequences of control messages in the alpha, gamma, and Renshaw control pathways. Nonlabyrinthine stabilizing reflexes involving several joints are briefly reviewed (supporting, stepping, hopping, propping, and sway reactions). The concept of a "behavioral vertical," with servo adjustment to bring the body into line, is discussed in relation to the roles of the various labyrinthine receptors. The positional reflexes from the labyrinth are shown to have a stabilizing function in contrast to the role attributed to them by Magnus. The new scheme presented here successfully predicts the reactions of an animal on a moving platform.

INTRODUCTION

It is implied in the notion of "posture" that the various parts of the body are actively maintained in a configuration which differs from that which they would otherwise assume. In particular, it is the activity of the postural muscles that is responsible for the development of appropriate forces to prevent the body of an animal from collapsing to the ground under the action of gravity. A movement of the body or of a limb, either as part of a locomotory act or in any form of voluntary activity, constitutes a change in posture. This involves adjustments, not only in the activities of the muscles in and around the part moved but also in the activities of many other muscles in other parts of the body. This is because the shift in the center of gravity in relation to the position of the supports entails a widespread redistribution of the forces acting between the various parts of the skeleton. In what follows I discuss the nature of the mechanisms by which the forces in different muscles are adjusted to appropriate values, and also the extent to which the various types of receptors in the labyrinth are concerned in these regulatory mechanisms.

NATURE OF THE REGULATORY MECHANISMS

In many animals, when they are standing on level ground in their normal erect posture, the center of gravity is carried at a height above the ground that is very much greater than the width of the area of support. This implies the continued performance of a delicate and complex balancing act. The individual bones of the skeleton are only loosely articulated together, and the various parts of the body are supported one upon another in a three-dimensional triangulated lattice structure, each triangle being made up of either two struts and a tie, or of two ties and a strut. The bones can act either as ties or as struts, but their lengths are necessarily constant. The muscles provide compliant ties, and it is by varying the degrees of activity in the various muscles, and thus altering the compliances of certain ties, that the animal is able to adjust its posture. The precise geometry of each of the triangles in the framework at any time is the result of a balance between the externally applied deforming forces and the forces developed in the muscular ties.

When the body is at rest on the Earth's surface,

the magnitude and direction of the resultant of all the forces acting between the body and the ground must, in general, be equal and opposite to the effect of the pull of gravity. Any inequality here will produce an acceleration, just as the withdrawal of all support will lead to a condition of freefall in which the body continues to accelerate toward the center of the Earth. Note that the expression "weightlessness" may sometimes lead to misunderstanding. In "freefall" it is not the force of gravity that has ceased to act; it is the opposing supporting force that has been withdrawn.

The fact that an imbalance of forces will lead to motion can be made use of in the mechanisms for adjustment of the ties, and this is the basis of postural control. The underlying principle is that undesired motion is reduced to a minimum. The restraints are temporarily relaxed in locomotion to permit controlled falling in a selected direction, interrupted by periodic checks during which the acquired momentum of the moving body is used, in conjunction with added muscular effort, to restore the center of gravity to its original height above the ground. The mechanism employed is not unlike that used in the pole vault.

Let us start our more detailed analysis by considering the triangulation of forces acting at the knee joint. The patella keeps the line of action of the tension in the quadriceps muscle away from the axis of rotation of the joint. Thus it acts with part of the epiphysis of the femur to form a short strut. The shaft of the femur, as a long strut, and the quadriceps muscle, as a tie, complete a triangle. The patellar tendon and the tibia act with the same short strut to form another triangle. These two triangles together stiffen the knee to resist the flexion which would otherwise occur under the combined action of the weight of the body applied downward at the hip, together with the supporting upthrust transmitted through the ankle from the foot. Thus, if the foot is on the ground, the weight of the body tends to rotate the femur about the knee in the direction of flexion, while the tension in the quadriceps tends to rotate the femur in the opposite direction. When the knee bends, the mechanical advantage of the downward force at the hip increases, because there is an increase in the offset. At the same time, because of the rolling action at the joint, there is also an increase in the offset of the line of action of the quadriceps. In addition, the quadriceps muscle is stretched.

The usual view is that it is this stretching of the muscle that generates, reflexly, enough force to prevent the muscle from being pulled out any further. There are, however, several variables that change simultaneously with change in joint angle, and it is quite possible to reach equilibrium at many different angles. It is even possible for the forces to remain in equilibrium in spite of a change in angle. What we need at the knee joint to minimize undesired motion is to arrange that the muscle behave as a stiffer spring when it is being stretched than when it is shortening. There are many ways in which this might be achieved, but we must first consider whether it happens at all.

Figure 1, which is typical of the behavior of many muscles, shows that the force developed at a particular length is, in fact, greater when the muscle is being lengthened than when the muscle is allowed to shorten. It has been shown (ref. 1) that the loops in such diagrams do not represent the effects of such viscous damping as may be implied in the well-known force/velocity relationship for muscle. They occur at low velocities and their width is not velocity dependent. Figure 2 shows what sort

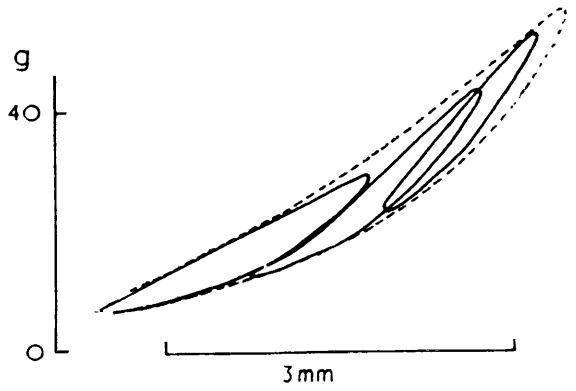

FIGURE 1.—*Plots of tension change against length change for the reflexly active soleus muscle of a decerebrate cat. When the applied tension was rhythmically altered over various ranges, the working point moved clockwise round the different loops shown. Note that the loops for the smaller ranges fit within the guide curves formed by the upper and lower limbs of the loop for the largest range.*

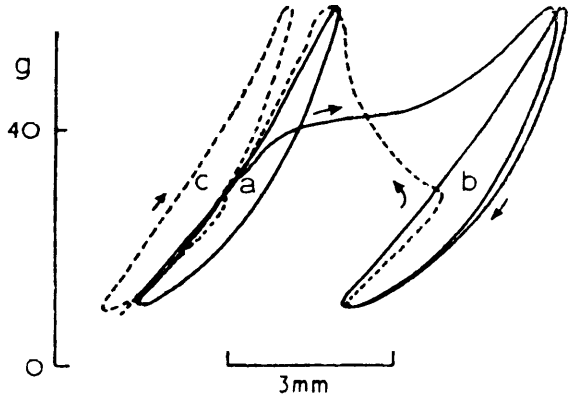

FIGURE 2.—*Continuous plot of tension change against length change (cat, soleus) during successive cycles of fluctuating applied tension. Between* (a) *and* (c) *the reflex was inhibited by applying electric shocks to the foot. The arrows indicate the direction of increasing time; the later parts of the record are shown as a broken line.*

of changes occur in the tension/length diagram when the limb is called upon to execute a reflex movement. In this case the reflex stiffness of the extensors is switched off to permit the limb to be flexed in a withdrawal movement.

In the course of studies of this kind it has come to light that there is a mechanism by which the animal can distinguish the relative compliance of the load into which each muscle is working. The nature of the reflex responses can be very different according to whether a muscle is being forcibly extended by a rigid device or is being subjected to predetermined tensions while free to take up its own length (ref. 1). The usefulness of this mechanism for the detection of compliance will be clear from an example. If a cat is in a tree, it is important to it to "know," so to speak, how much a particular branch will give way when the cat puts its weight on it, and whether the relative movements of the branches are due to the movements of the cat or to the action of the wind or of some other external agency.

For the source of the observed differences in tension on lengthening and shortening, we may look to the receptors which generate the stretch reflex activity; namely, the muscle spindles. When a spindle is subjected to a change in tension, as in figure 3, the time course of the change in its discharge can be seen to consist of a static component, related directly

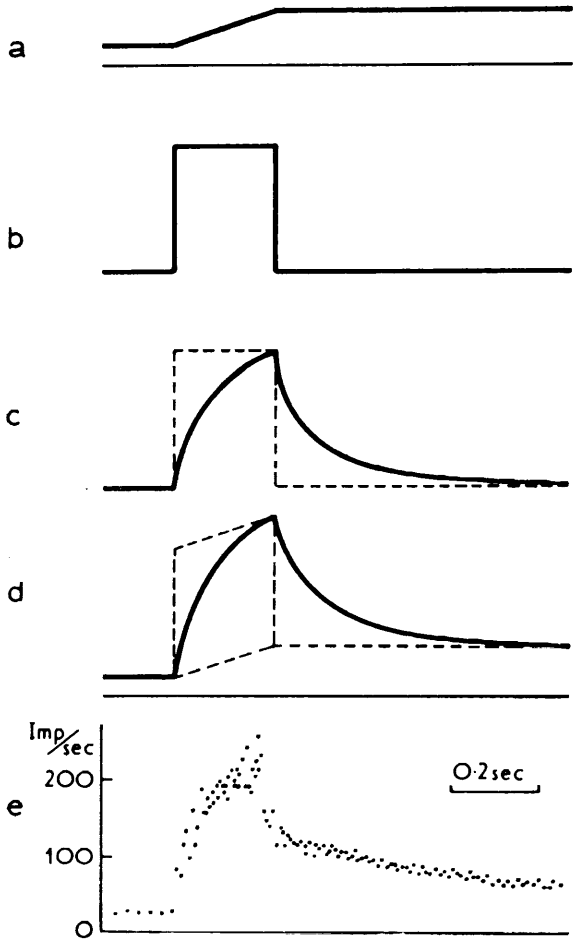

FIGURE 3.—*Scheme to illustrate how the discharge from a muscle spindle during a change in load may be considered as made up of a static component related directly to the instantaneous conditions of loading, together with a dynamic component corresponding to a sluggish response to rate of change of load.* (a) *Time course of tension change;* (b) *rate of change of tension;* (c) *sluggish response to* (b); (d) *sum of* (a) *and* (c); *and* (e) *spindle discharge.*

to the instantaneous conditions of loading, and a dynamic component which involves a sluggish response to rate of change of load. The decay of the dynamic component is what gives rise to the phenomenon referred to as "adaptation." Many deformation receptors exhibit comparable behavior, sometimes with several elements in the dynamic component of their response. For example, figure 4 shows separately the time courses of the different elements in the overall transfer function of a knee-joint proprioceptor (ref. 2). The presence of the dynamic com-

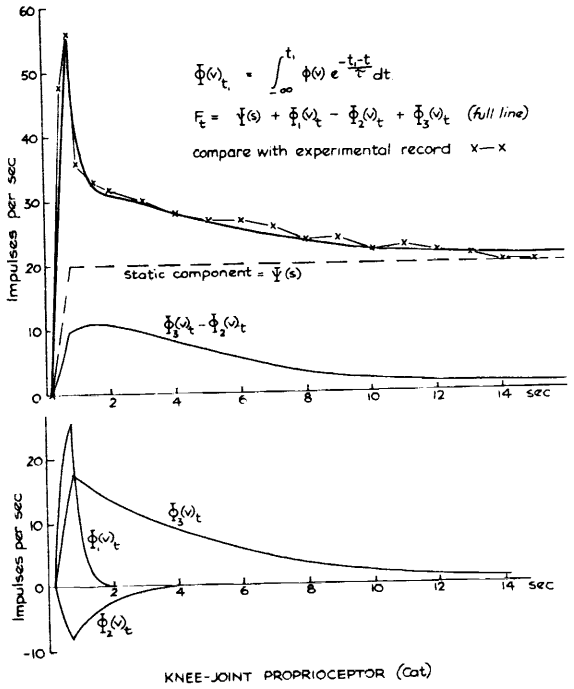

FIGURE 4.—*Time courses of the three elements of the dynamic component in the response of a knee-joint proprioceptor to a step change in joint angle.*

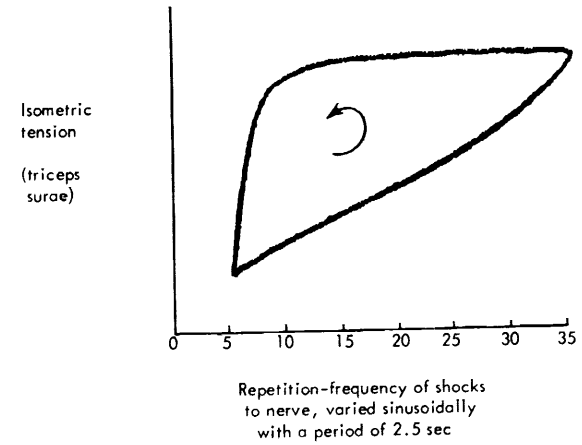

FIGURE 6.—*Experimental record to show that a tension, once developed, may be maintained in spite of a considerable reduction in the frequency of repetitive activation. During increasing frequency of shocks to the nerve, the muscle tension rises steadily in step with the stimulus frequency. When the shock frequency is falling, the tension at first remains high.* (*Partridge, L. D.: Signal-Handling Characteristics of Load-Moving Skeletal Muscle. Am. J. Physiol., vol. 210, 1966, pp. 1178–1191.*)

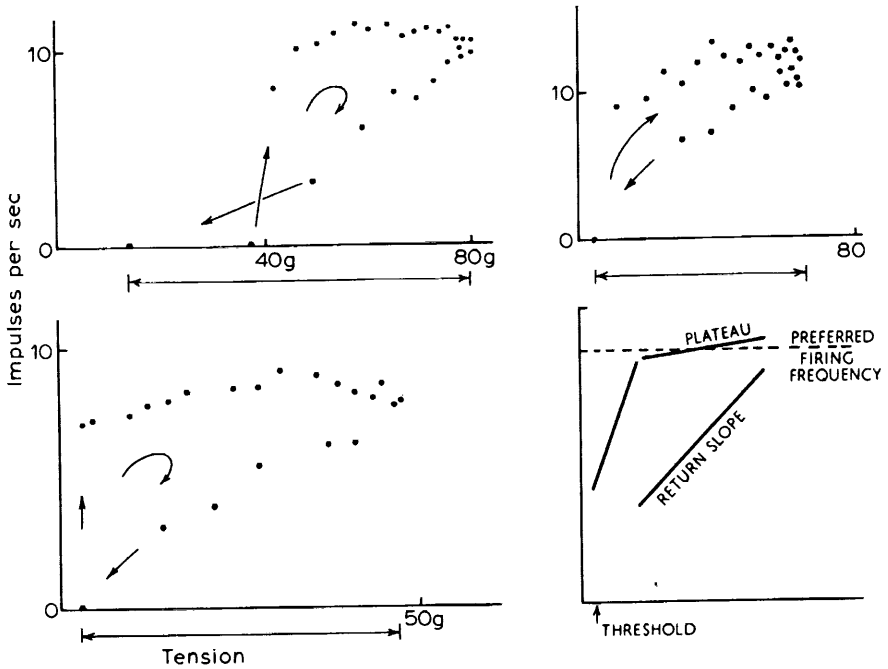

FIGURE 5.—*Representative plots of firing frequency against tension for different motor units in the cat's soleus muscle during rhythmically fluctuating applied tension. Each dot is produced by the arrival of an impulse; it indicates by its abscissa the prevailing value of the applied tension, and by its ordinate the reciprocal of the interval since the preceding impulse.*

ponent in the response implies that a spindle will generate a higher frequency of impulses at a particular tension if the tension is increasing than it will at the same tension if the tension is falling. It is reasonable to expect that the reflex activation of motor units will follow suit.

Figure 5 shows that the firing frequency of single motor units follows different time courses according as the tension is rising or falling. However, in the phase of rising tension, the firing frequency does not show a progressive increase with increasing tension. Each unit fires at its own preferred firing frequency or not at all, according to whether the appropriate tension threshold has or has not been exceeded (ref. 3).

To reconcile the fact that these frequency/tension diagrams show a clockwise loop while the corresponding length/tension diagrams (obtained from fig. 1 by interchanging the axes) show a counterclockwise loop, we need to remember that a muscle does not need such a high frequency of repetitive activation to maintain a particular tension once this has been developed by a high-frequency burst. (See fig. 6.)

The plateau in firing frequency seen in the discharge of the motor units (fig. 5) does not occur in the discharge from the spindles. Figure 7 shows how the static and dynamic components (each with its own threshold) combine to give the pattern of firing frequency observed when a spindle afferent is picked up in a dorsal root filament, the appropriate muscle being meanwhile subjected to fluctuating tensions. The transformation from this pattern to that seen in the motor units can be accounted for in terms of the known properties of the feedback loop through the Renshaw cells (ref. 4). The three sides of the triangle for the motor units are shifted independently or in combination during various conditions of convergent reflex drive. Some information about which pathways are being used can be inferred from the nature of the changes in each specific instance. A change in the threshold tension implies a change in the level of direct alpha bombardment; a change

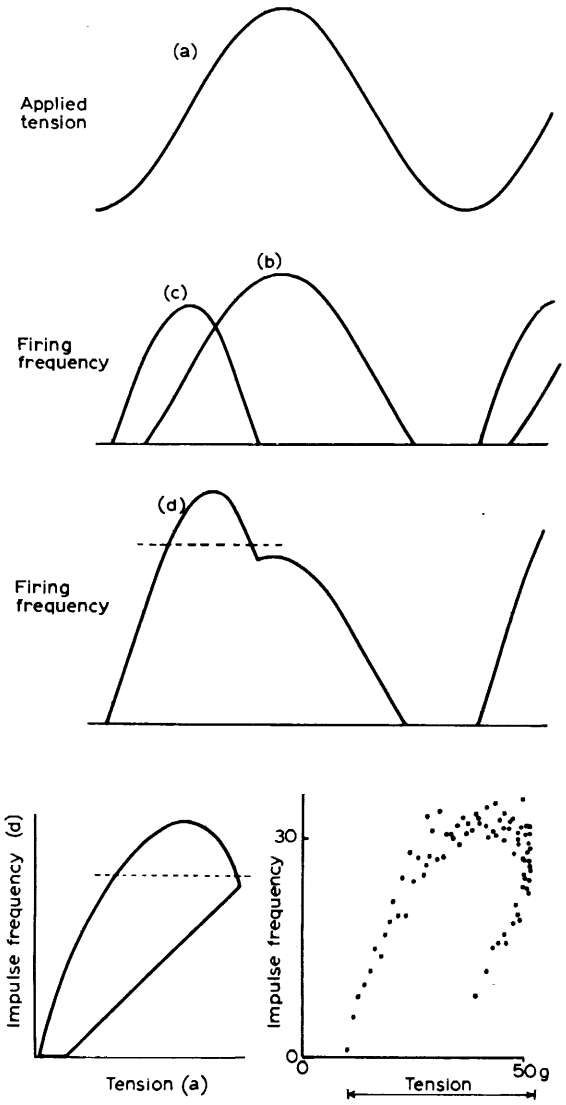

FIGURE 7.—*Scheme to show that a combination of static* (a) *and dynamic* (b) *components, each with its own threshold, can account for the observed time course of the discharge from a muscle spindle during rhythmically fluctuating applied tension.*

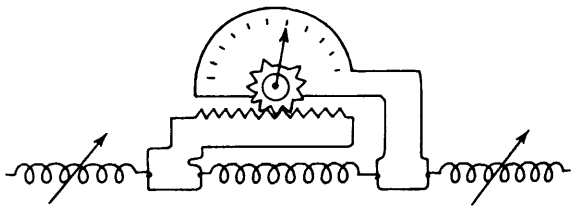

FIGURE 8.—*Schematic representation of some essential parts of a muscle spindle. The sensory ending is shown as a spring balance detecting the tension transmitted to it by the compliances of the polar parts of the intrafusal muscle fibers. These series compliances can be adjusted by fusimotor impulses in the gamma efferent nerve fibers.*

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in the plateau implies that the behavior of the Renshaw cells has been altered; a change in a sloping part of the triangle implies that different effects are occurring at different tensions, and the only way this change can be produced is by way of the gamma pathway involving fusimotor impulses to the intrafusal muscle fibers of the spindles.

The effect of fusimotor impulses can be explained by reference to figure 8. The generation of impulses by the sensory receptor depends on the local deformations occurring in the immediate neighborhood of the receptor itself. These deformations in turn reflect changes in the forces transmitted to the receptor region by the polar parts of the intrafusal muscle fibers. These forces can be altered either by changing the positions of the supports or by varying the mechanical properties of the intrafusal muscle fibers themselves. It is this last effect that is produced by the fusimotor impulses. It has been shown that different fusimotor axons have different effects on the receptor discharges. Some gammas increase the dynamic component in the response of the receptor to externally applied forces with little effect on the static component; some increase the static component while producing little change, or even a slight reduction, in the dynamic component (ref. 5). It is clear that fusimotor impulses in the gamma pathway, by changing the sensitivity of the spindles, can also alter the sensitivity of the stretch reflex; that is, they can change the reflex stiffness with which a muscle resists elongation.

POSTURAL STABILIZATION ACHIEVED WITHOUT THE AID OF THE LABYRINTHINE RECEPTORS

Up to this point we have been considering the repertoire of pathways by which the activity of the postural muscles can be varied and what sorts of changes can be expected to result from impulses in each of the pathways. Before proceeding to examine the role of the labyrinth, we need also to consider to what extent postural stabilization can be achieved without invoking the aid of the labyrinthine receptors.

We have seen that the geometry of each of the triangles which go to make up the lattice structure of the body depends upon a balance between the deforming forces and the forces developed reflexly in the muscular ties. The absence of continual oscillation, in what is essentially a springy structure, is achieved by the development of different forces according to whether each muscle is lengthening or shortening. Another important mechanism consists of the reflex interdependence of the conditions at neighboring joints. The increase in stretch-reflex activity that converts a limb into a stiff pillar in the supporting reaction depends on the splaying of the digits of the foot, and once this reaction has been elicited, the limb may be loaded with a wide range of forces without much change in its attitude, provided that the line of action of the loading forces remains roughly in line with the axis of the limb.

If the line of action of the loading forces on a limb is not in line with the limb, the load and the supporting reaction together will produce a resultant couple which will tend to rotate the limb so that the body moves over the foot. Next the supporting reaction is switched off, the foot is picked up and set down quickly in another position whereupon the supporting reaction reappears again. The direction of movement of the foot depends on the position of that foot in relation to the vertical projection of the proximal joint (hip or shoulder). If the body movement brings the projection of the proximal joint nearer to the foot, a hop will occur, carrying the foot farther away to improve the effectiveness of the limb as a prop and perhaps thus preventing further movement. If the body movement carries the projection of the proximal joint away from the foot, a stepping movement is executed, bringing the limb closer under the body. If the body movement, in either direction, is accompanied by a reduction in the magnitude of the couple, no step or hop occurs, and the limb continues to act as a prop. Meanwhile there are corresponding changes (sway reactions) in other limbs. (For further details, see refs. 6 and 7.)

The supporting, propping, hopping, stepping, and sway reactions can all be elicited in the absence of the labyrinths. The critical feature of the stimulus situation which leads to the choice of one or another of the reactions in

particular conditions appears to be the rate of change of joint angle. The operation of these reactions conforms with the principle of minimizing undesired movements. It is not clear how the nervous system separates out the velocity signal from the joint-receptor discharge. It does not seem to do so for the spindle discharge. We have already seen that the dynamic component is still present when the signal emerges from the central nervous system as the output to the motor units.

ROLE OF THE LABYRINTH IN THE REGULATORY MECHANISMS

At first sight, one might suppose that the labyrinthine receptors provide a separation between static and dynamic aspects of head position, the otolith organs being primarily static in function and the semicircular canals dynamic in function. In practice, it does not work quite like this.

So far as the otoliths are concerned, we may take the primary stimulus to be the couple which tends to rotate the jelly mass containing the otoconia in relation to the membranous wall of the organ. The couple is made up of an accelerating force exerted by the wall of the organ to keep the contents in place, together with a gravitational force on the contents tending to accelerate them toward the nearest large massive object, usually the Earth. These two forces are commonly not in line because the center of gravity of the contents of the otolith organ does not coincide with the center of its volume. These two points would only coincide if the contents of the otolith organ were uniform in density. It is the function of the otoconia to produce the necessary displacement of the center of gravity from the center of volume. Presumably the embedding of the hair processes of the neuromasts in the jelly mass of the otolith provides a restraining couple to prevent relative rotation of the otolith, and the neuromasts report the magnitude of this restraining couple.

We can alter the couple by tilting the skull while applying linear accelerations equal and opposite to those due to gravity (i.e., keeping the skull in place in the laboratory). Alternatively, we could apply linear accelerations of other directions and magnitudes, but we then need to apply similar accelerations to the whole of the laboratory or we lose touch with the preparation. Some electrophysiological experiments of this latter type have been reported by Gualtierotti and Gerathewohl (ref. 8).

Lowenstein and I have experimented with tiltings about various axes, using direct recording from the otolith organs of the skate (ref. 9), but we did not systematically explore rates of change of angle. These may be important, and perhaps we should look again at the various types of response with this in mind. There are several distinct types of receptors in the otolith organs. The characteristics of the different types are illustrated in figures 9 to 13.

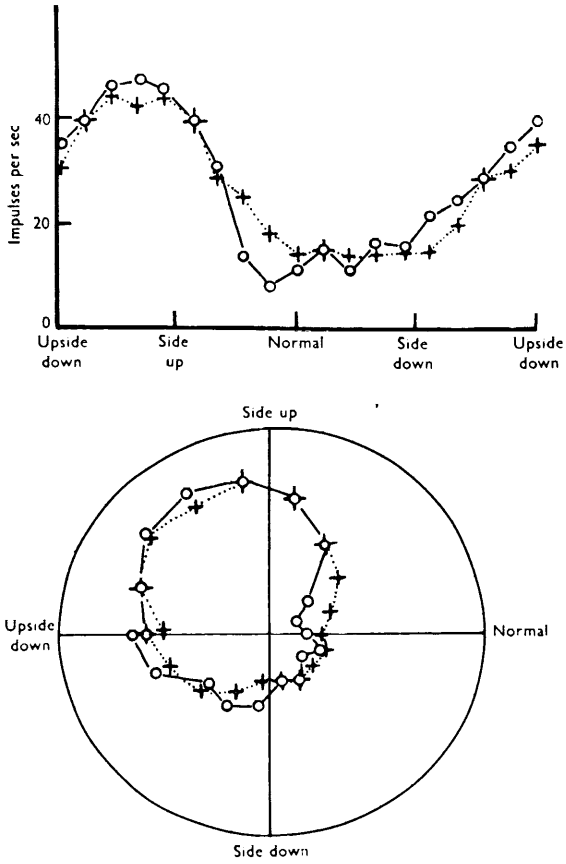

FIGURE 9.—*Rectilinear and polar plots of firing frequency against skull position for a position receptor in the utriculus of the ray during full-circle lateral tilts in opposite directions. The continuous line is to be read from left to right and clockwise; the dotted line from right to left and counterclockwise.*

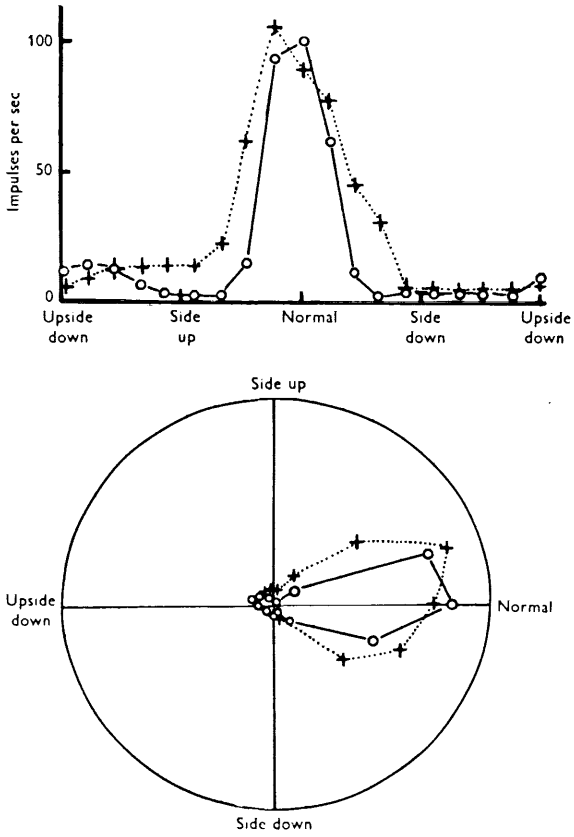

FIGURE 10.—*Rectilinear and polar plots of firing frequency against skull position for an "into-level" receptor in the lagena of the ray.*

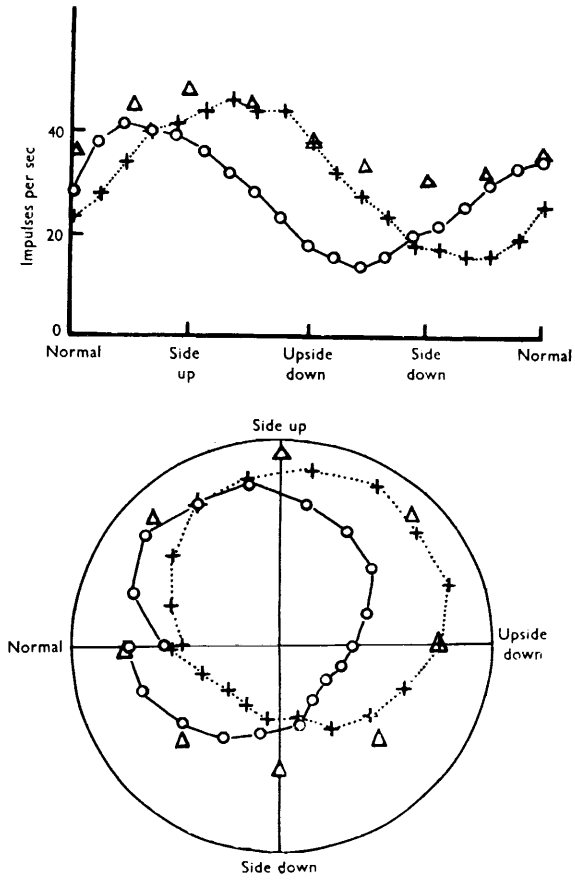

FIGURE 11.—*Rectilinear and polar plots of firing frequency against skull position for a position receptor (ray, utriculus) which showed a dynamic component in its response. The readings indicated by the triangles were taken during an interrupted full-circle tilt after 30-second rest in each position.*

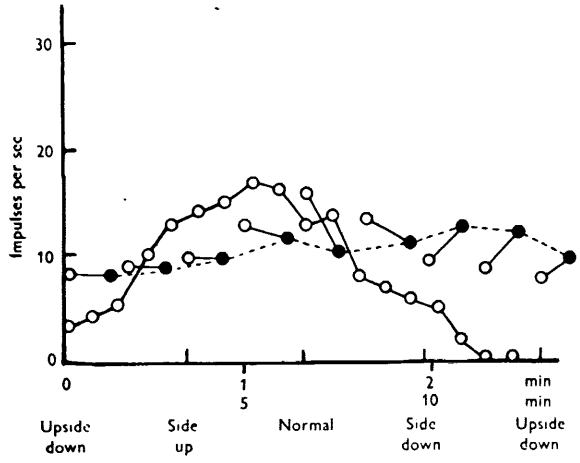

FIGURE 12.—*Plots of impulse frequency against time during one continuous and one interrupted full-circle tilt for a receptor (ray, utriculus) whose response shows a large dynamic component and only a very small static component. ○ = impulse frequency on first reaching that position. ● = impulse frequency after 2 minutes of rest in the position corresponding to the open circle linked to this filled circle. The time scales for the two tilts have been adjusted to bring the skull positions into coincidence.*

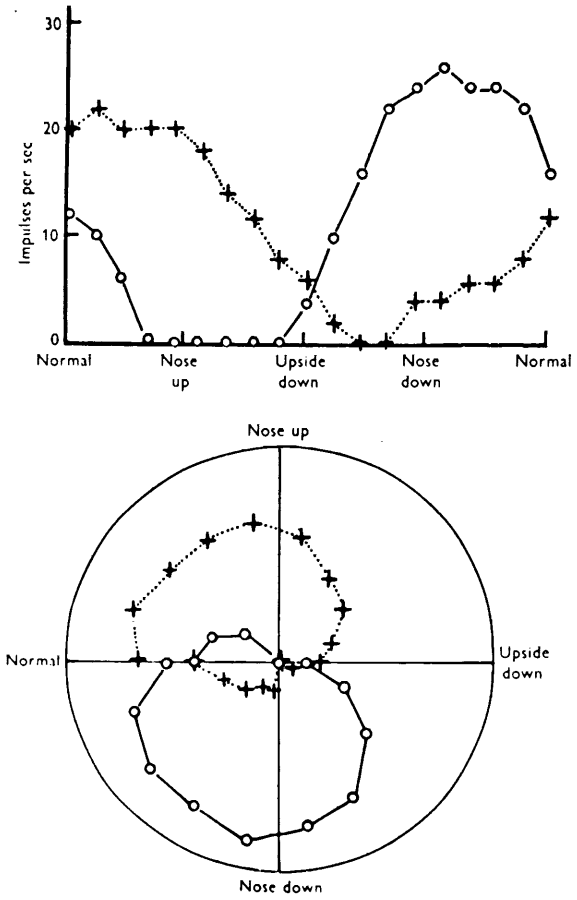

FIGURE 13.—*Rectilinear and polar plots of impulse frequency against skull position during two full-circle tilts in opposite directions for a "movement receptor" in the utriculus of the ray. The continuous curves are to be read from left to right and clockwise; the dotted curves from right to left and counterclockwise.*

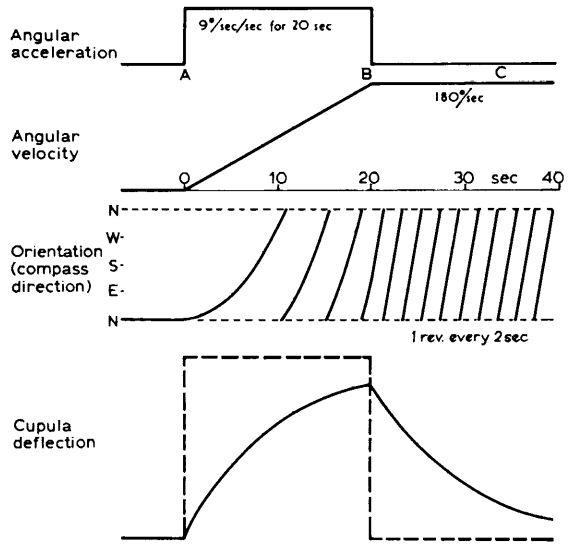

FIGURE 14.—*Time courses of angular velocity, orientation, and cupula deflection in a semicircular canal during and after a prolonged period of constant angular acceleration.*

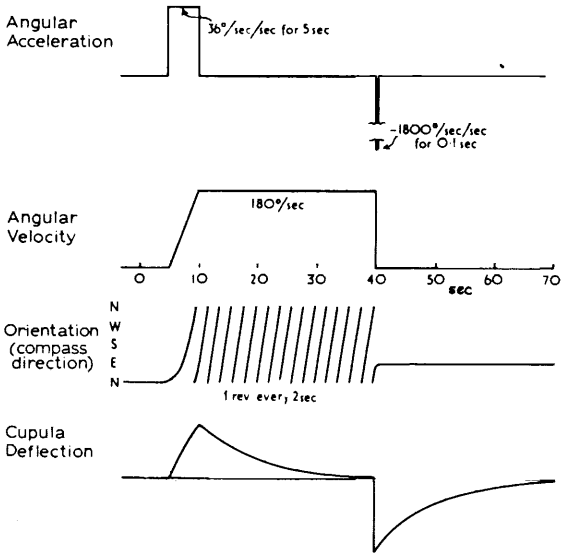

FIGURE 15.—*Time courses of angular acceleration, angular velocity, orientation, and cupula deflection during the procedure used for eliciting postrotatory effects by impulsive deceleration. Note that if the deceleration were to be spread out over 1 second (instead of 0.1 second as here), a smaller decelerating force would be needed, yet the cupula deflection would attain the same peak value as that shown.*

The types of receptors found in the canals are perhaps more straightforward in that they differ only in sensitivity and not in the nature of their responses. The deflections of the cupula appear to obey a second-order differential equation, and if we solve this with an analog computer for different types of input signal, a good picture of what the canals seem to be doing is obtained. Their basic design looks like that for a detector of angular acceleration, but the dimensions show that the system is very heavily damped. The diagrams of figures 14, 15, and 16 give an idea of what to expect.

Note that all these labyrinthine receptors are alike in one respect: They show a so-called "spontaneous" discharge when the skull is at rest, with deviations either in the direction of an increase or in that of a decrease in frequency. However, the head of an animal is seldom at

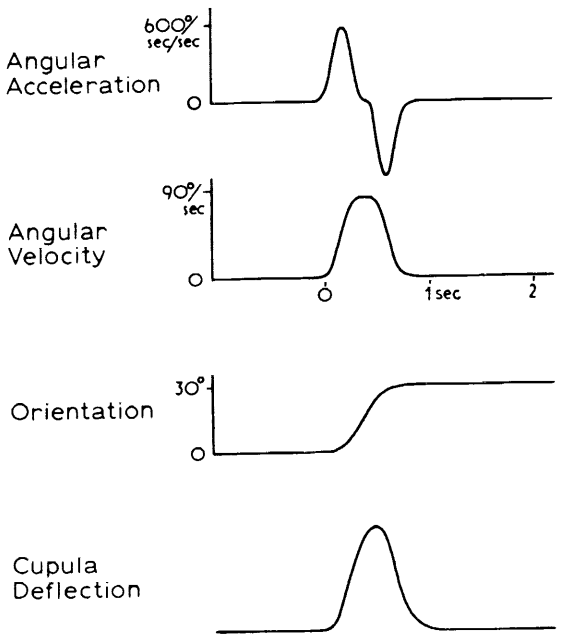

FIGURE 16.—*Time courses of angular acceleration, angular velocity, and cupula deflection to be expected during a typical naturally occurring movement. The uppermost curve was generated electronically by using parameters selected so that the curve for orientation obtained by double integration corresponded closely to the time course of an experimental record of a voluntary head movement. The curve for cupula deflection was obtained from the signal for angular acceleration by on-line analog computation using the differential equation given by Van Egmond, Groen and Jongkees (ref. 20).*

rest for long unless the animal is sleeping. This means that there is no such thing in the animal's experience as the "rest position" such as that which we set up in the laboratory by screwing the skull to a tilting apparatus and clamping it in an arbitrary position. Nevertheless in many animals, though not in all, careful observation can lead one to designate a particular head position as the "normal" position. It seems reasonable to take it that the midline plane of symmetry shall be vertical in the "normal" position. But how much noseup or nosedown is normal?

Photographs of lateral views of the head of animals engaged in characteristic activities can help to determine the "normal" position. This works particularly well for animals such as cattle where one can take the attitude of the head during leisurely forward locomotion and designate this as "normal." Girard (ref. 10) has dissected the labyrinths of a number of species, and he maintains that the "normal" attitude of the head corresponds to the position in which the lateral semicircular canals are in the horizontal plane.

If we can apply the argument in reverse to man, this means that the "normal" position for the head in man corresponds to the attitude for examining an object held in the hand, rather than the parade-ground attitude of "attention" usually designated as "normal" in anatomical texts.

The point about deciding on a "normal" attitude for the head is that it defines a "behavioral vertical" around which the supporting forces in the limbs are symmetrically disposed. When an animal is at rest on the Earth's surface, the resultant of the supporting forces has to be parallel to the direction of the pull of gravity, and it is economical to adjust the forces in the limbs to distribute the weight evenly. When the animal is on a moving support, the forces in the limbs are still maintained in symmetry about the behavioral vertical, but this direction is no longer necessarily parallel to the direction of the pull of gravity. The behavioral vertical is adjusted to lie along the line of action of the resultant of the acceleratory forces on the head. This is a matter of observation; that is, this statement describes what animals do. Now we need to consider what mechanisms are involved in producing this behavior.

We can apply our knowledge of servomechanisms to work out what might be useful and then examine the animal to see whether any of the relevant devices are employed. In a servomechanism, the control signal absorbs no power, and desired effects are brought about by regulating an auxiliary source of power according to the magnitude of the discrepancy between the achieved and the desired states. We first need a control signal, in this case to indicate the direction of the behavioral vertical in relation to the skull. There are difficulties involved, some of which have been mentioned previously. Nevertheless, it seems reasonable to suppose that such a signal might be available. The main difficulties arise when the animal wishes to hold its head in some inclined position. It would

be of no use to have the control signal anatomically defined because, if we did this, the head could not be moved out of the "normal" position; any attempt to do so would be met by reflex stabilizing forces.

From Brindley's experiments on dropping animals after periods of linear acceleration (ref. 11), it appears that a cat or a rabbit uses about 8 seconds of its past experience to decide on the direction of the behavioral vertical. His animals were put into boxes which had trapdoors in the floor. They were then subjected to linear accelerations either by sliding the box down an inclined track or by taking it in a motorcar driven in a circular path on an airfield. At an appropriate moment the trapdoor was opened, the animal fell out onto a cushion, and its attitude during the fall was recorded photographically. The animals orientate themselves symmetrically with respect to the behavioral vertical, which corresponds to the resultant linear acceleration, provided this has been constant for at least 8 seconds before the trapdoor is opened.

In addition to the control signal, we need a detector of the achieved state, in this case the prevailing orientation of the skull, in order to compare this with the direction of the behavioral vertical. The static position receptors in the otolith organs seem ideal for this. The auxiliary source of power and the effectors consist of the muscles of the limbs and neck. The comparator is inside the central nervous system, but the principle of minimal movement requires the addition of some kind of stabilization. A simple position servo operating on the inertia of the skull would be liable to oscillations just like those of a mass constrained by a spring. The restoring force after a perturbation would be related directly to the deviation, just as in a spring.

A well-known way of reducing unwanted oscillations in a mechanical system is to introduce viscous damping. In a servomechanism the same effect can be simulated by the use of output-velocity feedback. It is then appropriate to include input-velocity feedforward to eliminate the sluggishness inherent in viscous damping (velocity lag). Do we have any of these stabilizing signals?

The first thing that comes to mind is the action of the canals. They generate a signal which, in the short term at any rate, is related to rate of change of orientation of the skull (angular velocity). The sense of the reflex response to canal stimulation appears to be always to oppose the motion of the skull in space. The effect is not like that of damping between the skull and the body, although it is here that the muscular forces are developed. It is more like damping between the skull and space, so to speak. In some conditions it looks as though the reflexes were having the effect of increasing the effective inertia of the skull, but this is not quite right. In the postrotatory phase after impulsive deceleration, the skull tends to keep on moving; at the onset of motion the skull tends to stay behind. The effects on the eyes are similar: They behave as though they have added inertia and tend to stay looking in the same direction in spite of movements of the skull; after impulsive deceleration the eyes continue to turn in the same direction after the skull has been brought to rest. This inertia-like overshooting does not occur after naturally occurring movements because equal and opposite accelerations in rapid succession leave the cupula in an undeflected position (fig. 16).

For tilts about a horizontal axis we can consider each of the four vertical canals to be linked to the antigravity muscles of the limbs of the corresponding corners of the body. Thus if the skull starts to tilt over a diagonally placed horizontal axis to bring the right front corner downward, this angular acceleration will be in the ampulla-leading direction for the right anterior vertical canal, which therefore increases its discharge. The reflex response is an increased antigravity activity in the right forelimb, tending to oppose the tilt of the skull. Corresponding effects on the appropriate neck muscles have been recorded by Szentágothai in response to artificial displacement of the endolymph column in the canals (ref. 12).

The canals therefore provide output-velocity feedback to stabilize the position of the skull in space, in conformity with the principle of minimal movement. A single canal can generate damping reflexes in both directions, presumably by reciprocal innervation. Damage to a corresponding pair of canals (e.g., the right anterior

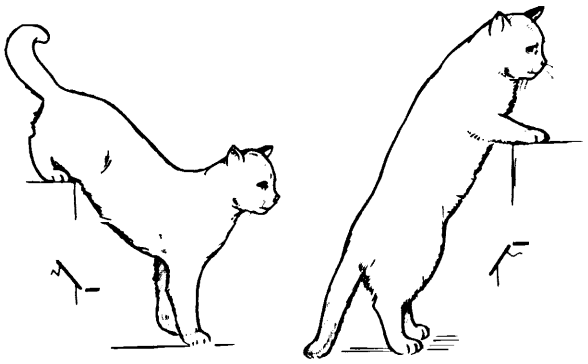

FIGURE 17.—*Neck reflexes acting alone in the cat. Note that the head is in the same position ("normal") in both cases.*

vertical and the left posterior vertical) is followed by pendular oscillation of the head in the plane of the damaged canals, as would be expected from the removal of damping (ref. 13).

Tilting the skull produces other effects besides those on the canals. If the skull is moved while the body stays behind, this will bend the neck and generate neck reflexes. We need to sort out positional reflexes generated by the labyrinth from positional reflexes generated from the neck. The nature of the neck reflexes has been admirably described by De Kleijn (ref. 14). In general, the response is in such a direction as to tend to transfer the deformation of the neck to the body; that is, to move the body so as to relieve the deformation of the neck. Thus, if the neck is ventriflexed, the neck-reflex response consists of flexion of the forelegs and extension of the hindlegs, tending to tip the body in the same sense as the head. We can see the effects in photographs of animals with their heads in the "normal" position, but with the neck bent (figs. 17 and 18). For other types of neck movement, the rule is "chin limbs extend," and vice versa. This works for lateral flexions (ear to shoulder) as well as for torsions about the long axis of the neck. Reflex torsion of the trunk is such as to put the whole of the vertebral column into a single smooth helix; thus clockwise torsion of the head on the neck produces clockwise rotation of the shoulders if the pelvis is held, or counterclockwise rotation of the pelvis if the shoulders are held.

The usual account of the positional reflexes from the labyrinth is the one given by Magnus (ref. 15). He emphasizes that there is a contrast between neck reflexes, which produce different effects on the limbs of the two sides or different effects on the forelimbs from those on the hindlimbs according to the direction of neck movement, and positional reflexes from the labyrinth, in which the effects on all four limbs are always equal. Magnus describes a position of minimum tone and a position of maximum tone, the tone in all four limbs varying simultaneously in the same sense between the two extremes. In my opinion a set of reflexes according to this scheme would be of no use in stabilizing the orientation of the head in relation to gravity. What is needed is that, if the head begins to tilt to one side, the antigravity muscles of the limbs and neck should push harder on that side to restore the normal attitude. Symmetrically

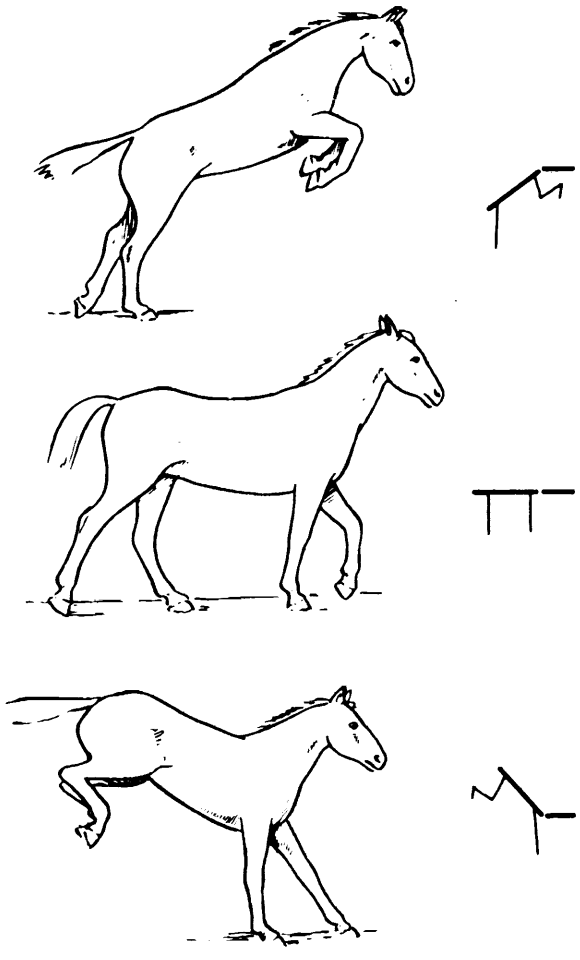

FIGURE 18.—*Neck reflexes in the horse.*

acting reflexes would not have the desired effect.

I have reinvestigated the positional reflexes in the cat. I have denervated the first three intervertebral joints in the neck and looked at the stretch-reflex sensitivity in various extensor muscles while tilting the head and holding the axis vertebra stationary with a clamp.

Figure 19 shows the response in the anconeus muscle, an extensor of the elbow, when the head is tilted toward the nosedown position. The forelimb extends. Figure 20 shows the responses in the soleus muscle also during fore-and-aft tilts. The hindlimb extends during noseup tilting and flexes during nosedown tilting. The responses in forelimb and hindlimb are in opposite senses, just as is required for stabilization. Figure 21 shows that the change in reflex sensitivity in the soleus muscle during head tilting can involve a shift in each of the three sides of the triangle in the plot of firing frequency against tension (fig. 5). That is to say, all three control pathways are involved. Figure 22 from the anconeus muscle shows that lateral tilting of the head produces unsymmetrical effects in the limbs of the two sides. The right foreleg is extended when the head is tilted toward right-side-down (about a horizontal longitudinal

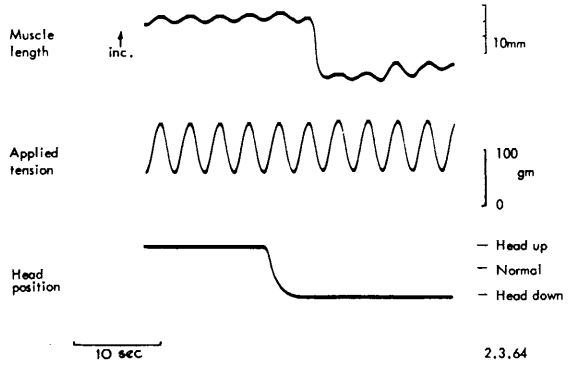

FIGURE 19.—*Increase in stretch-reflex sensitivity seen in a forelimb extensor of a decerebrate cat (neck denervated) in response to a nosedown tilt of the head.* C_1, C_2, *and* C_3 *are cut on both sides and the axis vertebra is immobilized in a clamp. The tendon of the anconeus muscle is dissected free and subjected to fluctuating tension (middle trace) which stretches the muscle (upper trace = length change). The muscle shortens when the head is tilted toward nosedown (signaled on bottom trace).*

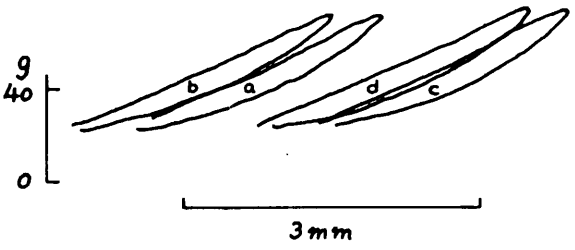

FIGURE 20.—*Tension/length diagrams for the soleus muscle of a decerebrate cat during fore-and-aft head tilting. Neck reflexes are eliminated by denervation and clamping.* (a) *Head in normal position;* (b) *head up;* (c) *head down;* (d) *normal. Note that the reflex sensitivity does not return precisely to its original value.*

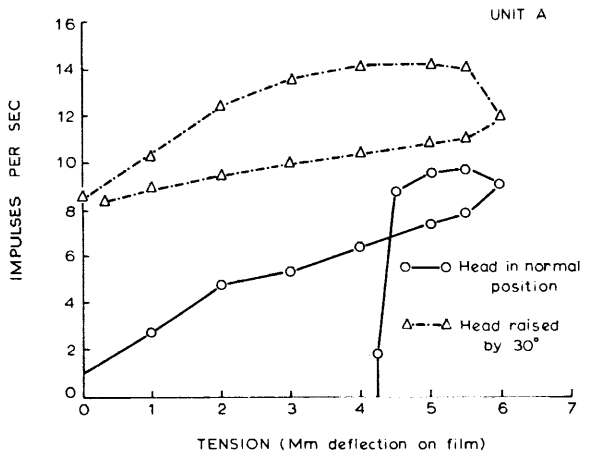

FIGURE 21.—*Plot of firing frequency against tension for a motor unit in the soleus muscle before (full line) and after (broken line) head tilting toward noseup. Neck reflexes have been eliminated by denervation and clamping.*

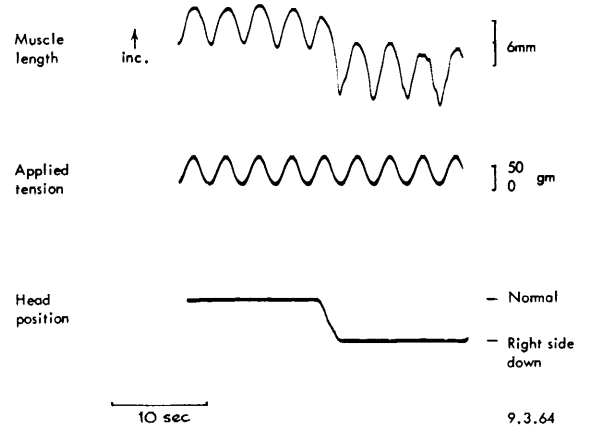

FIGURE 22.—*Record from the anconeus muscle (as in fig. 19) to show that the stretch-reflex sensitivity of the extensors of the right forelimb is increased when the head is tilted laterally toward right-side-down (decerebrate cat, neck denervated).*

axis); the right foreleg flexes and the left foreleg extends when the head is tilted toward left-side-down. Lateral rotations of the head in these conditions have no effect, because the neck has been denervated, and rotations about a vertical axis do not involve a change in otolith stimulation. The labyrinthine positional reflexes just described are sometimes in opposite senses to the neck reflexes.

We can see the labyrinthine reflexes acting alone in animals photographed when the head is in an inclined position with the neck straight, as in figure 23. Figure 24 demonstrates what happens when neck reflexes and labyrinthine reflexes are elicited simultaneously. Raising the head with the body stationary involves contrary responses from neck and labyrinth.

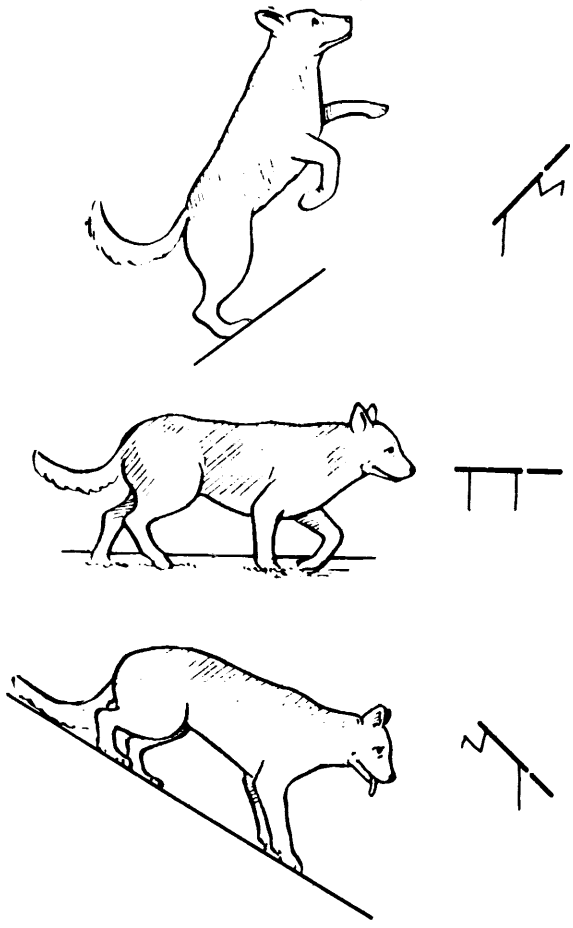

FIGURE 23.—*Tracings of photographs of a dog to illustrate the action of the positional reflexes from the labyrinth. The attitude of the neck is the same in each case.*

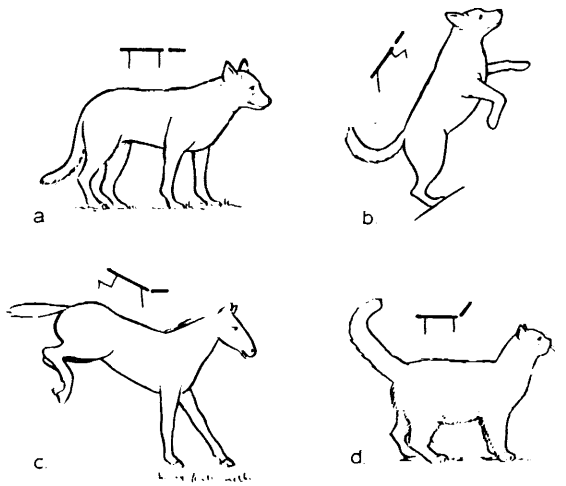

FIGURE 24.—*Characteristic poses to illustrate the interaction between labyrinthine and neck reflexes.* (a) *Normal;* (b) *head back, neck straight;* (c) *head normal, neck dorsiflexed;* (d) *head back, neck dorsiflexed.*

The dorsiflexion of the neck should produce forelimb extension and hindlimb flexion; the upward tilting of the head should produce hindlimb extension and forelimb flexion. The two effects cancel out, and the animal remains with its four limbs equally extended.

In the normal upright posture of man, either the head is tilted back a little from the true "normal" (as defined by the position of the semicircular canals) or the neck is somewhat ventriflexed. Both of these effects would lead to forelimb flexion and hindlimb extension, and it is interesting to compare the bipedal stance of man with that of the kangaroo (fig. 25). To bring a man into a neutral posture it would be necessary to tilt the head more forward (as in reading) and at the same time to lean the body over to relieve the flexion of the neck. This results in a posture like that often adopted by infants (fig. 25) in which the weight is evenly distributed over the four limbs.

A full set of the possible interactions between three positions for the neck and three positions for the labyrinths is given in figure 26 together with pictures of animals to illustrate the responses.

It appears, therefore, that the labyrinths are in fact able to generate unsymmetrical stabilizing responses of the kind we require, related to the achieved position of the skull in space. The

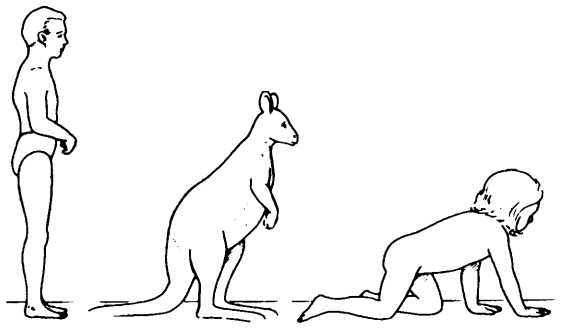

FIGURE 25.—*Man, kangaroo, infant.*

true position receptors in the otolith organs seem the most likely source for this signal, and we must presume that the central nervous system is in some way able to combine the position signal from the otolith organs with an assessment of the direction of the behavioral vertical, in order to generate a suitable error signal to drive the righting reflexes.

We have seen that the canals provide output-derivative feedback; is there any sign of input-derivative feedforward? Can we use for this the dynamic component seen in the response from some of the receptors in the otolith organs? A difficulty at once arises from the nature of the otolith discharge.

In the case of the stretch reflex, the whole of the spindle signal can be used as "error," and the dynamic component indicates the rate of change of error as is required for a servo-incorporating error-derivative feedforward. An error-derivative signal functions as a combination of output-derivative feedback to simulate viscous damping together with input-derivative feedforward for the elimination of velocity lag. In the otolith organ, we cannot use the whole of the signal as error, because the desired position usually corresponds to a condition in which the receptors will be generating a particular value of spontaneous discharge. This means that the dynamic component in the otolith discharge will be in positive feedback in some conditions and in negative feedback in others. It is not at present clear what advantages this arrangement confers.

We can imagine a role for those movement receptors that show the same response to tilting in opposite directions. These receptors show a decrease in their discharge when the head is tilted out of the normal position in either direction. If we suppose the otolith organs to drive the antigravity muscles, the effect of this type of response will be to allow the animal to sink down somewhat whenever a disturbance arises. This is, in fact, just what the animal does. The effect is to increase the stability by bringing the center of gravity nearer to the area of support and thus increasing the critical angle that must be exceeded before tipping will occur.

The function of the various labyrinthine reflexes appears to be to distribute the supporting forces in the limbs in such a way as to keep the center of gravity, as projected along the direction of the behavioral vertical, well within the area of support.

We have considered changes in the direction of the supporting force; what about changes in its magnitude? The couple which provides the stimulus to the otolith organs can be varied either by altering the direction of the supporting

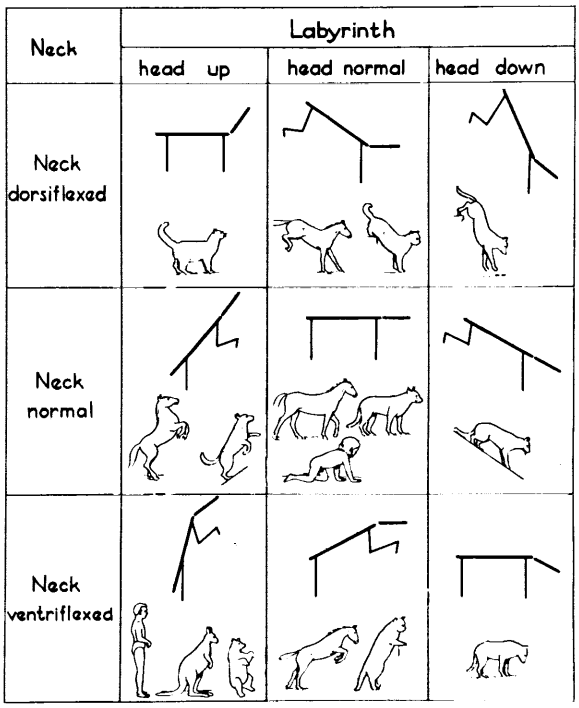

FIGURE 26.—*Scheme of the interacting effects of labyrinthine and neck reflexes on the limbs of various animals. The middle column shows the neck reflexes acting alone. The middle row shows the labyrinthine positional reflexes acting alone. In the top left and bottom right corners, the neck and labyrinthine reflexes are in opposition; in the top right and bottom left corners, they reinforce one another.*

force or by altering its magnitude. It follows that the otolith organs by themselves cannot unambiguously indicate a change in vertical acceleration. It is possible, however, for the canals to help. The occipital condyles are not usually vertically below the center of gravity of the skull when the head is in the normal position. This means that the skull must all the time be supported by the pull of the neck muscles. A change in vertical acceleration will alter the load on these muscles, causing the skull to rock. This generates angular accelerations which can be detected by the canals. It is this sort of conversion from linear vertical accelerations to stimulation of the vertical canals that seems likely to be implicated in the generation of motion sickness. It may be true that the canals are not sensitive to linear accelerations of the skull, but it seems very likely that, by this rocking mechanism, they may be useful in detecting linear accelerations applied to the body as a whole, when the head is supported on the neck. This type of signal will not be available if the head is resting on a pillow.

In considering the role of the signals from the labyrinth in a scheme for the servocontrol of the orientation of the animal in relation to the behavioral vertical, there is one feature that has been neglected. We have taken it for granted that the otolith signal supports the antigravity tone, in that a deviation from the desired position is reflexly corrected by an adjustment in antigravity tone with an increase on the appropriate side. However, in the direct recordings from the otolith organs, the increase in firing frequency occurs when the skull is tilted to bring that labyrinth uppermost. Some receptors showed an increase on noseup, some on nosedown, but all showed an increase on side-up tilting from normal. What we need is a signal which increases on side-down tilt. We must, therefore, suppose that the otoliths have crossed effects, and consequently that they are pitted against the effects of the canals of their own side. If we separate the otolith receptors into a group showing increases on noseup and a group with increases in discharge on nosedown tilting, we can set up a scheme such as that of figure 27 from which to predict their interaction with the canals. A downward tilt at the right front corner will produce a transient increase in antigravity tone in the right forelimb by the action of the right anterior vertical canal, and a sustained increase in tone in the same muscles from the effect of the nosedown receptors in the otolith organs of the left side.

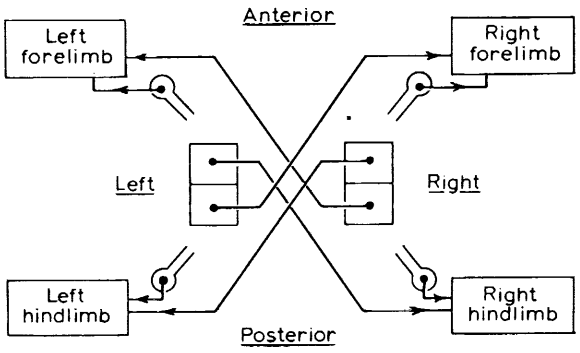

FIGURE 27.—*Scheme of the effects on the antigravity muscles of the four limbs generated by the two types of position receptors in the otolith organs, correlated with the effects from the vertical canals during angular accelerations in the ampulla leading direction.*

If the labyrinth is removed completely from one side, the animal comes to rest with the operated side down. From this we conclude that the effect of the resting discharge from the canals normally dominates over the effect of the resting discharge from the otoliths of the same side. With only one set of labyrinthine receptors, the otolith has to be tilted toward side-up in order to generate enough signal to balance the effect of the canals.

Animals having a hereditary defect of the otoconia on one side come to rest with the defective otolith uppermost (ref. 16), and this fits in with the notion that, in this position, the discharge from the intact otolith organs is reduced and the unbalance between the two labyrinths is at a minimum. The "uni-soli-utricular" animals of Tait and McNally (ref. 17) do not seem to fit in with this scheme; the reason for this has yet to be explained. Direct polarization of the utricular macula (ref. 18) gives effects that correspond to the scheme of figure 27, but does not decide the question about the crossed connections. The neuroanatomical details have still to be elucidated and perhaps this reflects the complexity of the pathways.

Great care will have to be exercised in any attempt to analyze the role of the various control

pathways—alpha, gamma, and Renshaw—in the labyrinthine reflexes because of the complications introduced by the intervention of the cerebellum, vestibular nuclei, and reticular formation. Recent studies (ref. 19) show that each of these three systems, as well as the VIIIth nerve itself, has access both to alpha and to gamma motor neurons in the spinal cord.

EXPERIMENTAL TESTS AND RESULTS

We may put together the information summarized in the preceding paragraphs in an attempt to predict what will happen when an animal stands on a moving platform, and we can then devise experiments to show up the salient features and test our predictions. The first expectation is that, when the platform starts to move, the head will tend to stay in the same place. This has been tested with a dog standing or sitting on a turntable that can be rotated by hand. Frame-by-frame analysis of lengths of ciné film show that the head does, in fact, remain stationary during the onset of turntable rotation.

If the axis of horizontal rotation does not pass through the head, the onset of rotation will involve a linear acceleration. This will alter the direction of the behavioral vertical, and the head should be tilted and the weight brought over to keep the center of gravity within the area of support (projecting the center of gravity in a direction parallel to the behavioral vertical). Propping and supporting reactions should then carry the animal round with the turntable. If the axis of rotation is arranged to pass through the head, there will be no linear accelerations. The body should get carried round while the head remains stationary. Eventually, neck reflexes should move the body over the turntable to relieve the lateral flexion of the neck, and the animal should walk over the moving turntable. What usually happens experimentally at this point is that the animal walks off the turntable or looks around, or otherwise confuses the observations. Apart from this, our expectations are fulfilled.

To avoid the effects of spontaneous movements which are almost inevitable in intact experimental animals, we may try the tests on man. The difficulty is that the subject quickly gets some

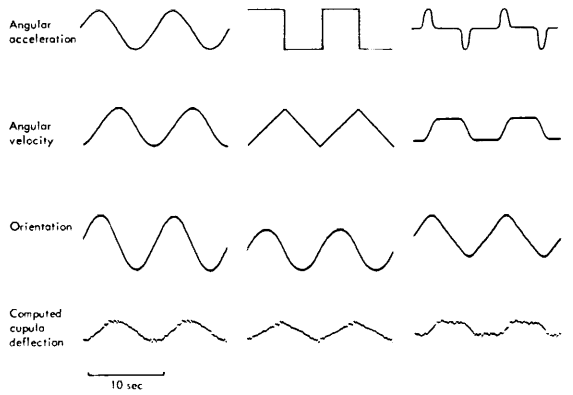

FIGURE 28.—*Time courses of various patterns of motion that can be imposed on the turntable by the use of a velodyne and a signal generator, together with computed cupula deflections expected when the skull moves with the turntable. Note that the superficially similar oscillatory motions involve quite different patterns of acceleration.*

idea (however erroneous) of what is expected of him, and he shows voluntary movements instead of reflex responses. Many subjects remain quite rigid on the turntable. One advantage of using man is that the subject can be made to carry various recording devices.

We have done some experiments with subjects standing unrestrained on a turntable which is driven by a velodyne to give oscillatory patterns of motion such as those shown in figure 28. The change in orientation of the head, both in space and in relation to the turntable, and the movement of the body in relation to the turntable are recorded. From the change in orientation of the skull we can compute, by on-line analog computer which solves the canal equation (ref. 20), the time course of the cupula deflection, which is the input signal to the central nervous system. The other two records give, by subtraction, the movement of the head on the body. By differentiating this remainder we get the rate of torsion of the head on the neck, and we can compare this with the time course of the expected cupula deflection, to see whether the reflex control of the neck muscles is similar to the control of the eye muscles. It is the rate of change of eye position in the skull (slow-phase velocity of vestibular nystagmus) that is related to cupula deflection.

This experimental arrangement has interesting possibilities. The head movement in space is

the stimulus to the canals; the movement of the head on the neck is the output from the labyrinthine reflex and the input to the neck reflex; the movement of the body over the turntable is the output of the neck reflex; and there is overall feedback over the whole system because both the movement of the body over the feet and the movement of the head on the neck are interposed between the externally applied movement of the turntable and the detectors in the canals. Up to now, we have done only a few experiments. Defects in the linkages for the movement recorders introduce a lot of noise which makes the differentiations unsatisfactory. Figures 29 and 30 illustrate the sorts of results that we are getting. Note that body, head, and eyes are all moving in this type of experiment, and it follows that no one of the movements can, by itself, exactly compensate for the turntable movement.

When the apparatus was set up for a demonstration to the Physiological Society, an unexpected result was recorded with one of our visitors acting as the subject. His attention had been caught by one of the fittings on the pillar attached to the turntable to support the recording devices. The resulting record is shown in figure 31. His head was moving round with the turntable to maintain visual fixation, and of course his feet were necessarily being carried round also. Meanwhile his body was executing extensive rotations in the opposite sense, and at one stage these rotations were more than sufficient to compensate for the movement of the turntable. The velocity of head movement on the body is again closely correlated with the cupula deflection, but it is now 180° out of phase.

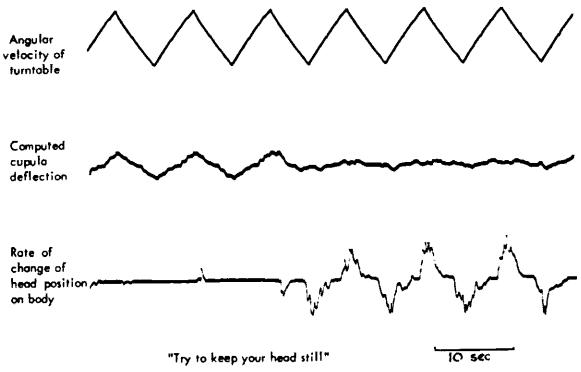

FIGURE 29.—*Time course of rate of change of head position on the body for a subject standing on a turntable which is undergoing alternating phases of constant angular acceleration. Note the similarity between the trace for neck rotation when the subject is trying to keep his head still and the earlier part of the trace for computed cupula deflection.*

This last experiment emphasizes the labile nature of the control mechanisms driven from the labyrinth and indicates that although some of the relevant questions have been answered, there are still many problems to keep us busy for some time to come.

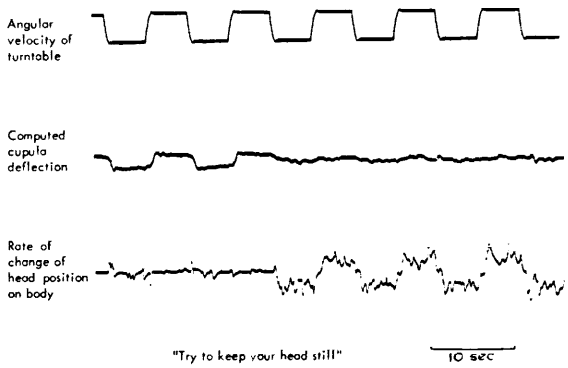

FIGURE 30.—*Time course of rate of change of head position on the body for a subject standing on a turntable which is undergoing alternating phases of constant angular velocity.*

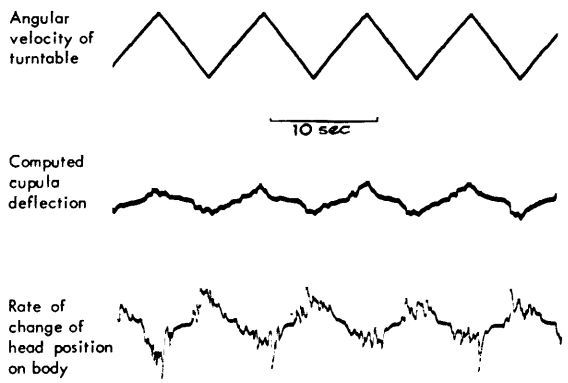

FIGURE 31.—*Records obtained in similar conditions to those for figure 29 except that, in this case, the subject was looking at a part of the apparatus that was rotating with the turntable. Note that the neck rotation follows a time course similar to that of the computed cupula deflection, but that these signals are now in antiphase. This means that while the feet (necessarily) and the head (by visual fixation) closely follow the motion of the turntable, the body is swung over the feet in the opposite direction so that, in fact, it remains almost stationary in space in spite of the movement of the supporting surface.*

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DISCUSSION

YOUNG: That is a very comprehensive and excellent review. My comment refers to the superposition of eye movements as a result of vestibular stimulation, neck stimulation, and visual fixation. I would refer you to some of Dr. Meiry's results which appear in our paper in NASA SP–115 and in NASA CR–628. The superposition holds very nicely.

My question concerns whether you would care to make a prediction about the outcome of an experiment that we are planning to do. It involves a task very much like postural control, namely, the orientation of a flight simulator, trying to maintain it vertical with no visual cues. It is programed as an inverted pendulum. The subject attempts to maintain the vertical based solely on nonvisual cues, which we have attributed to the vestibular system. We have determined that he can gain more rate information using the vestibular system than he can with just the visual display. We would like to do this experiment in a weightless condition on a parabolic flight where we expect we will receive no information from the otoliths, but only from the canals, and want to find out if we will get a decrement in performance because the subject has to rely solely on canal information for short-term postural reflex.

ROBERTS: I can tell you something about this in the way of a caution. I think that your expectation that you will get no information from the otoliths is not a reasonable one, because in all possible positions, as we have seen, the otolith organs generate a discharge. This discharge is what the central nervous system is interested in. If you imagine the otolith organ as a bag, as I do, with the jelly mass inside it loaded with otoconia, then the center of gravity of this mass will not correspond with its center of volume. Normally the effect of gravity acting on the mass in one direction and the supporting forces acting in the other direction together provide a couple which tends to rotate the jelly in relation to the otolith organ. Presumably the hairs projecting into the jelly mass provide a restraining couple, and the neuromast endings signal the magnitude of this restraining couple. You can alter the couple either by tilting, which alters the

relative direction of the gravitational field, if there is one, or you can alter the magnitude of the supporting force by producing accelerations or what have you. Now, if you remove the supporting force which is normally provided against gravity (that is what happens in parabolic flight), then all you are left with are the casual linear acceleration forces necessary to keep the otolith contents inside the cavity, and all of these forces will produce deflections of the hair cells according to the inertia of the mass. All of these deflections will count as significant signals and will presumably generate unknown reflexes.

MAYNE: It seems to us that the otoliths are used only to establish the vertical over a long-time smoothing period, as indicated by delays in the oculogravic illusion. Information about rapid movements is provided by visual, semicircular, and probably kinesthetic data. I would think therefore that, in the tests proposed by Dr. Young, there would be a gradual loss of the sensed vertical, but some righting reflexes controlled by semicircular sensory outputs. The proposed tests are very interesting and should throw further light on the division of labor between otolith and other sensory organs. Dr. Roberts, it is well known that a hand movement, as in picking up a pencil on a desk, can be carried out with the eyes closed once the position of the pencil has been ascertained. Presumably the motion is controlled by a program with inputs in the neutral centers and feedbacks through proprioceptive sensors. The eyes certainly do not enter in a continuous closed-loop control of the movement since they can be closed. Is the vestibule used like the eyes in the construction and selection of programs or does it operate continuously in the loop as do proprioceptive sensors? I wonder whether you have thought of this problem.

ROBERTS: I do not think that it is fair to regard the individual receptors in the labyrinth as acting independently, nor do I think it is fair to imagine that the central nervous system can look at any of the receptors individually. Because all of them are saying all sorts of things all the time, it is the overall pattern from all the receptors which generates the response. Is that sufficient?

MAYNE: We have given some thought to the matter and have not quite made up our mind. Obviously, the movement of the hand in picking up a pencil can only be carried out successfully if there exists information about the position of the hand and the position of the pencil. Information about hand position can be supplied by proprioceptive sensors; information about the pencil must be a memory in spatial representation, since the eyes can be closed during the movement. The question we have been wondering about is whether or not the vestibule supplies information continuously during overall body movements or whether it supplies it intermittently like the eyes to spatial representation, which is then utilized in setting up a coordinated program independently of the vestibule.

This is a rather difficult problem to resolve, as we cannot shut off vestibular signals as we can vision by simply closing the eyes, but I wonder whether you might throw some light on it.

ROBERTS: The question of the loop is an awkward one. I do not think that these things, like putting your finger on a button, can be regarded as simple servoloop responses. They involve a great deal of learned coordination. Whether or not the labyrinth comes in may depend on whether or not the body is free to move or whether you are sitting in a chair, whether the labyrinth is *relevant*. The principal things for finding your way about are almost certainly the joint receptors, for example, in getting your limb to the right place. In many situations the voluntary act that you produce is not dependent on the result. If follows that the "loop" is not a loop in the way you are thinking of it. You learn that certain patterns of motor command will result in certain positions of the limb. If you switch off the return pathway from the joint receptors by a cuff, which can be done for your fingers, by putting a cuff around the wrist, which will make the receptors in the hand anoxic and leave the muscles which move the fingers unaffected, and then test to see whether you can move to reproduce a particular movement, you will find that you can produce movements all right. If you can see what is happening, you will put your finger in the right place. If you cannot see what is happening, you cannot tell when somebody puts an obstacle in the way and prevents your finger from going to the right place. You think you have your finger at the right place, but it may, in fact, have been screwed down to the experimental apparatus. So there is no question about this type of voluntary movement depending on a servoloop.

Neural Reflection of Vestibular Mechanics[1]

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SUMMARY

Systematic analysis of response in vestibular neural units, selected for their specific dependence upon rotational stimuli in a particular canal plane, indicates close reflection of known physical properties of the semicircular canal. The dynamic response of similar units selected for their specific dependence upon simple linear acceleration suggests a much wider range of physical properties associated with sensory mechanisms in the otolith organs. However, the response of canal-dependent units to rotation of a linear acceleration vector without rotation of the animal appears to be relatively uniform and of significant magnitude. This suggests that the latter mode of stimulus may normally generate a meaningful component of information in the central nervous system during angular head movement in vertical planes, since such movement introduces rotation of the gravitational acceleration vector relative to the head. In the zero-gravity environment of space flight this component would be absent, thus introducing the potential hazard of discordant information in the central nervous system.

INTRODUCTION

Investigation of semicircular canal function has shown that during natural angular head movements, hydrodynamic components of the canal system perform one integration on the angular accelerations to which the canal is exposed, thus making angular-velocity-modulated information available for transmission to the central nervous system (refs. 1–7). Indeed, systematic analysis over a wide range of animal species has indicated that this essential end-organ property has been maintained, against natural growth trends, by very small but altogether appropriate adjustment of relevant canal dimensions (ref. 8).

With angular movements outside the natural range, for example, slow oscillatory rotation or steady-state rotation, "errors" enter into the velocity-modulated response of this mechanical system largely on account of elastic restoring forces which come into play whenever the cupula is displaced by relative fluid flow round the canal. Various authors have investigated the patterns of neural response in primary (refs. 5, 9, and 10) and subsequent (refs. 11 and 12) neurons in the vestibular system, and the results obtained suggest that at least some of these end-organ characteristics are reflected fairly faithfully in afferent neural channels.

Mechanical properties of the otolith organ are less well documented, although it has been shown that at least some components of neural response support the view that the response of the end organ is directly related to imposed linear acceleration (refs. 11 and 13). However, recent experiments conducted upon human subjects indicate that the accelerative stimulus may in some circumstances be transformed into a velocity-modulated response (ref. 14).

With introduction of combined stimuli, such as change in direction of the linear acceleration vector, the mode of end-organ response is still more uncertain. There is no doubt that this form of excitation can generate rational compensatory nystagmoid oculomotor response in humans (refs. 15 and 16) and other mammals (K. E. Money, personal communication; A. J.

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Benson, F. E. Guedry, and G. Melvill Jones, "Neural Response of the Semicircular Canal to Rotation of a Linear Acceleration Vector," in preparation). But the extent to which the observed responses are dependent upon canal and otolith stimulation can only be guessed at the present time.

The following account describes in brief résumé some provisional experimental findings selected from a series of recent investigations undertaken at the McGill Aviation Medical Research Unit. These investigations were conducted in collaboration with J. H. Milsum, director of the McGill Bio-Medical Engineering Unit (refs. 6 and 17–19), and A. J. Benson and F. E. Guedry of the RAF Institute of Aviation Medicine, Farnborough, England, and the Naval Aerospace Medical Institute, Pensacola, Fla., respectively (ref. 20). Other reports from these investigations are in preparation (G. Melvill Jones and J. H. Milsum, "Vestibular Neuronal Responses to Linear Accelerative Stimuli"; J. H. Milsum and G. Melvill Jones, "Vestibular Neural Responses to Adequate Stimulation of the Semicircular Canal"; A. J. Benson, F. E. Guedry, and G. Melvill Jones, "Neural Response of the Semicircular Canal to Rotation of a Linear Acceleration Vector").

Initially, investigation set out to repeat and extend previous observations on the neural response to adequate rotational stimulation of the canals. The fidelity with which some components of response in the vestibular nuclei reflected known mechanical properties of the canal suggested the possibility of using the neural response at this level to gain further insight into the mechanical nature of vestibular end-organ response to other modes of adequate stimulation; in particular, linear acceleration (G. Melvill Jones and J. H. Milsum, in preparation) and change in direction of the linear acceleration vector (A. J. Benson, F. E. Guedry, and G. Melvill Jones, in preparation).

METHODS EMPLOYED

The general approach in these experiments has been to make a systematic study of dynamic relations between a wide variety of highly controlled adequate stimuli applied to the end organ and the corresponding patterns of neural response obtained from units in the vestibular nuclei of intercollicular decerebrate cats. At this point it should be noted that unit responses from this level are probably derived from second-order neurons (refs. 21 and 22) which are liable to be under more than one neural influence. But this complicating feature was germane to the initial investigation which aimed to examine the fidelity with which the characteristic hydrodynamic response of the canal may be carried through the first neural relay into the central nervous system, bearing in mind how appropriately this end organ seems to have been evolved for the generation of angular velocity information during natural head movement (ref. 8). In this connection it is noteworthy that with a proven efferent innervation of the vestibular end organ, even primary afferent fibers are presumably not exempt from remote influence (ref. 23).

For stimulation of the semicircular canals, a servo-controlled turntable was employed capable of being driven by a wide range of signals derived from a low-frequency waveform generator. For linear accelerative stimuli, a parallel swing system was employed capable either of being oscillated vertically on a spring suspension, or horizontally in a linear parallel swing mode (ref. 17 and G. Melvill Jones and J. H. Milsum, in preparation). The parallel swing could also be made to describe a circular path without the platform itself rotating. In this mode of operation, referred to hereafter as "parallel swing rotation," a centripetal linear acceleration vector of constant magnitude sweeps round the animal without incurring angular movement of the animal (ref. 17).

Extracellular unit recordings were obtained from long, rigid steel microelectrodes, stereotaxically advanced by means of a hydraulic drive through a small occipital trephine and the intact cerebellum, into the region of the vestibular nuclei. Unit responses were recorded directly on a high-frequency-response ultraviolet galvanometer recorder which permitted immediate viewing of stimulus-response relations and signal quality. Simultaneously the frequency of action potentials was related to the stimulus waveform by on-line computation in a Burns averaging computer (ref. 24). Electrode position was

established by development of a "prussian blue" spot with ferrocyanide-formalin perfusion after electrolytic deposition of a minute quantity of iron from the electrode tip (ref. 25). The blue spot was anatomically located by examination of complete serial sections stained with cresyl violet and cut at 25-μ thickness after embedding the brainstem in paraffin. All recordings were obtained from intercollicular decerebrate cats.

The usual procedure was initially to suspend the animal platform in the parallel spring configuration and maintain multidegree of freedom of movement while advancing the electrode slowly through the floor of the IVth ventricle at the approximate anteroposterior level of VIIIth-nerve entry into the brainstem. Audible presentation of unit activity thus permitted identification of responses correlating with some mode of the imposed movement. After such identification the animal was exposed to sequential excitation in each of six degrees of freedom of movement (three rotational and three translational), thus permitting the choice of units responding to specific stimuli such as rotation in the plane of one pair of canals or linear acceleration in a particular direction. Units responding to multiple modes of excitation were discarded. In some circumstances, to be described in the following paragraphs, this functional diagnostic procedure was supported by further, more rigorous procedures.

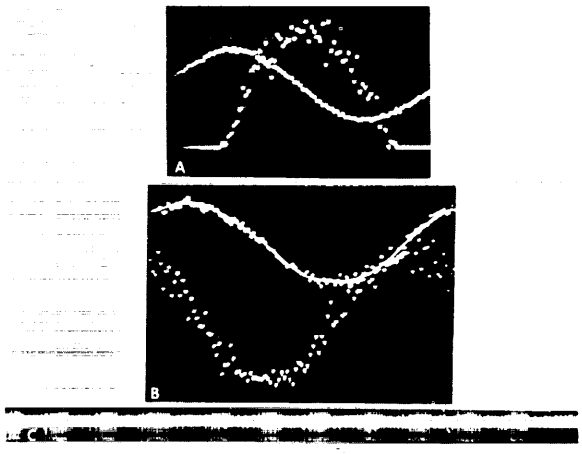

FIGURE 1.—*Vestibular unit responses to sinusoidal canal stimulation.* (A) *Original action potentials and averaged response of a unit in the medial vestibular nucleus to sinusoidal rotation in the plane of the left anterior canal (max. AP frequency = 52/sec; amp. = 3.3°; freq. = 1.7 cps).* (B) *Averaged responses of a cell sensitive to angular rotation in the plane of the left posterior canal (peak-to-peak AP frequency change = 44/sec). Note that the continuous line in each case represents the averaged waveform of stimulus position. (From ref. 26, and J. H. Milsum and G. Melvill Jones, in preparation.)*

EXPERIMENTAL FINDINGS

Responses to Angular Stimuli

Figure 1 (ref. 26) illustrates responses obtained from two cells located in the left medial vestibular nucleus during exposure to sinusoidal rotational movement in the planes of the left anterior canal (*A*) and the left posterior canal (*B*). A sequence of original action potential bursts associated with (*A*) is also illustrated. The average frequency of firing obtained from this cell over the sinusoidal sequence of stimulus is illustrated in the top-left photograph of this figure. The continuous curve gives the average angular displacement of the animal throughout the sine-wave of stimulus, while the dotted curve gives the average frequency of firing of that cell throughout the cycle, obtained over 120 consecutive cycles. Peak firing frequency was obtained approximately midway between the two peaks of angular position which corresponds to peak angular velocity of stimulation. In *B* the response was similar, the average response here being obtained over 205 cycles. The spontaneous level of activity in cell *A* was low, and hence during part of the cycle its response was cut off. However, the response of cell *B* can be followed throughout the cycle owing to its spontaneous firing frequency having been relatively high (21/sec).

Figure 2 (ref. 18) gives similar results obtained from a cell responding specifically to controlled angular velocity stimuli in the plane of the horizontal canals. Note that the continuous record of stimulus motion in this figure gives angular velocity, rather than angular position. At a period of 4 seconds per cycle, the frequency of firing of this cell was closely related to the angular velocity of stimulus (fig. 2(*A*)). But as the period was increased to 40 (fig. 2(*B*)) and 80 (fig. 2(*C*)) seconds, respectively, there was progressive phase advancement of the frequency of firing with respect to the angular velocity of stimulus.

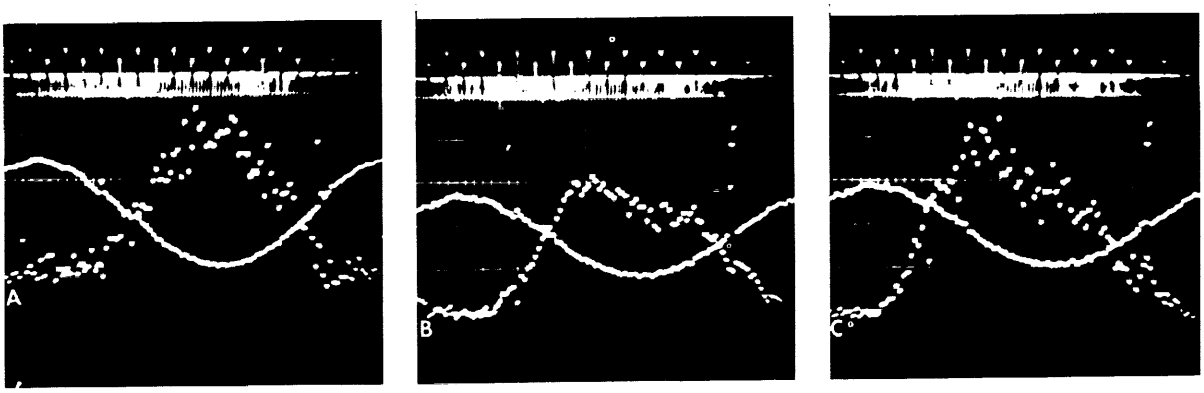

FIGURE 2.—*Dynamic responses of a single cell to sinusoidal horizontal rotation at various frequencies. Upper trace: bin location in the averaging computer. Continuous line: angular velocity in the horizontal plane. Dotted curve: averaged firing frequency of cell throughout the cycle.* (A) *4 sec/cycle, 67 deg/sec maximum angular velocity;* (B) *40 sec/cycle, 106 deg/sec maximum angular velocity;* (C) *80 sec/cycle, 106 deg/sec maximum angular velocity. Note particularly the correlation with angular velocity at 4 seconds/cycle and the phase advancement of the response with respect to the stimulus as the periodic time increases. Number of cycles averaged and maximum firing frequencies were* (A) *24 and 48;* (B) *2 and 52; and* (C) *1 and 62, respectively. (From ref. 18, and J. H. Milsum and G. Melvill Jones, in preparation.)*

The general patterns of response illustrated in figures 1 and 2 have thus far been associated with 18 cells selected by the procedure just described and held sufficiently long to permit observation over the full range of stimulus. These patterns of neural response conform well with the expected hydrodynamic response of a semicircular canal referred to previously. Thus whereas over the range of natural stimuli (presumably including one-fourth cps) fluid displacement in the canal would be expected to be in phase with angular velocity of stimulation, decrease in frequency of oscillation would be associated with progressive phase advancement of this mechanical response with respect to the stimulus. It seems that at least some components of neural response at this level in the central nervous system are related reasonably closely to the expected pattern of mechanical response in the semicircular canal. At the time this paper was written, a similar conclusion appears to apply to responses obtained from step (sudden change in angular velocity) and ramp (angular acceleration) changes in angular velocity (J. H. Milsum and G. Melvill Jones, in preparation), but a substantive verdict from these latter investigations must await completion of data analysis.

Response to Linear Stimuli

Figure 3 (refs. 18 and 26) gives results obtained from two cells responding to linear acceleration.

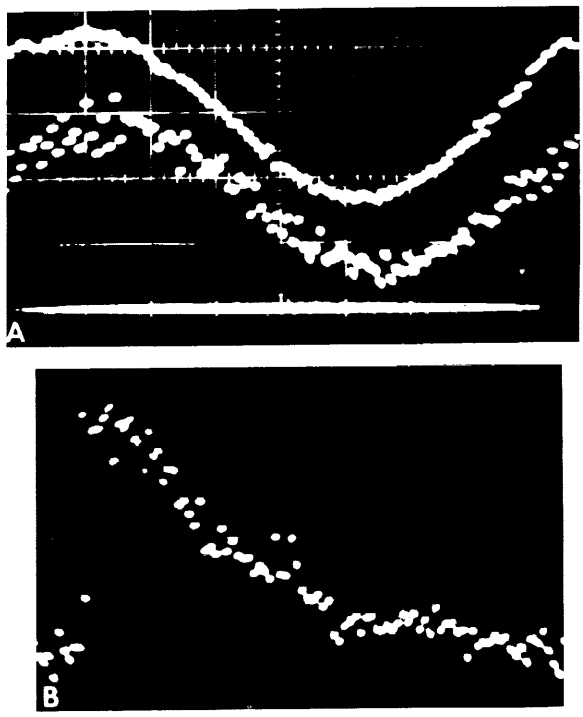

FIGURE 3.—*Averaged vestibular unit responses to otolith stimulation.* (A) *Sinusoidal vertical linear acceleration (116 cycles) amp. = 3.5 cm; freq. = 0.92 cps. Unit sensitive to vertical acceleration (maximum response on acceleration upward; sensitivity 233 AP/sec/g).* (B) *Sudden 8° tilt, left side down (6 cycles). Unit sensitive to horizontal acceleration. The response of* (B) *to sinusoidal acceleration was similar to that of* (A), *with maximum response on acceleration to right. (Initial AP frequency change in* (B) = *240 AP/sec/g.) (From refs. 18 and 26.)*

Figure 3(*A*) gives the average firing frequency of one cell in the medial vestibular nucleus of the left side during vertical linear oscillations obtained by suspending the animal platform in its parallel spring mode. The continuous curve gives the sinusoidal stimulus of imposed vertical acceleration, and the dotted curve again gives the average firing frequency of this cell correctly phase related to the stimulus. The straight line at the bottom of the photograph gives the base line (zero firing frequency) for this cell. Figure 3(*B*) shows the response of a cell which responded similarly to linear acceleration in the horizontal plane (not shown). But in this case the illustrated average response was to a stepwise sudden tilt of 8° left side down. Such a stimulus corresponds to stepwise application of steady acceleration. It can be seen that immediately after the step acceleration was applied, this unit responded vigorously, but with maintained application of stimulus the firing frequency decayed back to its original spontaneous level in about 25 seconds. A step response of this kind implies marked interference with the response to low-frequency waveforms of stimulus, so that although this cell followed the accelerative stimulus reasonably closely at 1 cps, this would probably not be the case for slow patterns of stimulus change. Indeed there appears to be considerable variability in the patterns of response obtained to stepwise changes in tilt which would suggest that even at a single frequency there could be a wide range of response characteristics between cells.

To further investigate the responses to linear acceleration, a mode of stimulus described as parallel swing rotation was employed, whereby the platform could be forced to describe a circular path without incurring angular movement of the animal platform. Figure 4 illustrates the averaged responses obtained from one horizontal linear acceleration sensitive unit exposed to this mode of stimulus. The upper curve gives the averaged dynamic response obtained on parallel swing rotation to the left. Zero degrees represents the point in the turntable rotation at which centripetal acceleration was directed posteroanteriorly along the long axis of the cat. The lower curve gives the response obtained during parallel swing rotation to the right. Both curves

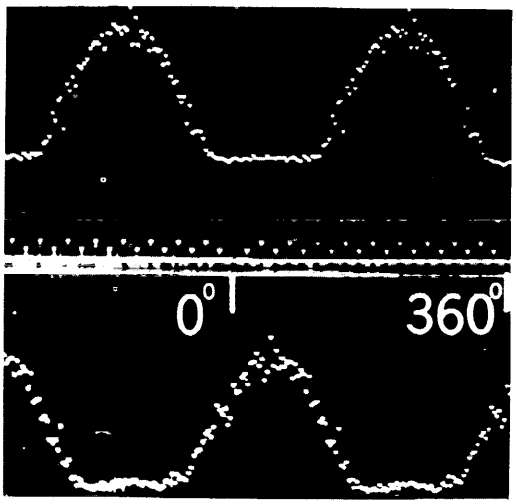

FIGURE 4.—*Vestibular unit responses to parallel swing rotation at 2.3 seconds/cycle. (50 cycles averaged in each case.) Upper trace: average action potential frequency during anticlockwise rotation of the linear acceleration vector (maximum frequency of firing 65/sec). Middle trace: computer bin location. Lower trace: averaged action potential frequency during clockwise rotation of the linear acceleration vector. (Maximum frequency 63/sec.) (From G. Melvill Jones and J. H. Milsum, in preparation.)*

represent the average firing frequency throughout the cycle obtained over 50 consecutive cycles of linear acceleration vector rotation at 2.3 seconds per cycle and 0.17 g. The average response is in each case written out for two cycles in order to display in an easily visualized way the response to parallel swing rotation to the right, since this crosses the zero mark.

Figure 5(*A*) illustrates in a pictorial way the points around the circuit of parallel swing rotation at which firing frequency was maximum for this cell during cyclical movement to the left and to the right, corresponding to the upper and lower curves, respectively, in figure 4. The results suggest that the line of maximum linear acceleration sensitivity for this cell lay midway between 144° (L) and 54° (R), which was indeed the case. In this event the semiangle between the two radial acceleration vectors presumably represents the phase advancement of the response of this cell relative to the imposed linear acceleration. Thus far in these experiments it has been striking to find how variable between cells this phase relationship proves to be. For example, figure 5(*B*) illustrates a corresponding

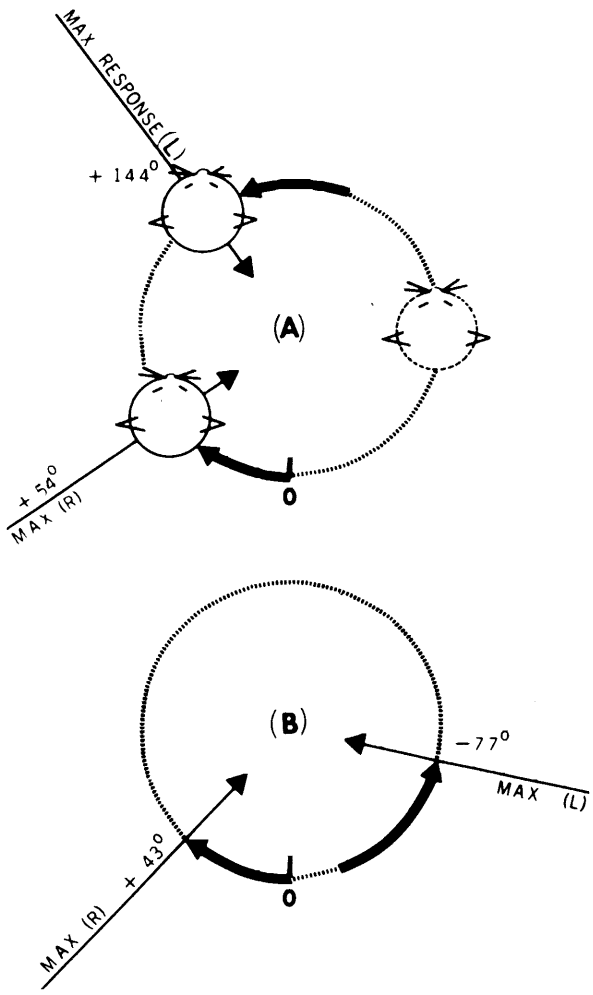

FIGURE 5.—*Pictorial representation of neural responses to parallel swing rotation for two cells.* (A) *Phase advanced unit; and* (B) *phase retarded unit. The thin arrows represent the direction of centripetal acceleration vector at the point of maximum firing frequency during angular movement of the linear acceleration vector in the direction represented by the associated thick circumferential arrow.* (*From G. Melvill Jones and J. H. Milsum, in preparation.*)

response obtained from a cell in which the neural response appeared to be phase retarded rather than advanced, relative to the imposed linear acceleration. Current experiments, not yet complete, indicate that such variability is the rule rather than the exception, and at this stage it is not possible to see the extent to which the patterns of neural response obtained can reflect the mechanical nature of the end organ. However, it is important to bear in mind the limitations imposed by constraining stimuli to a single frequency of sinusoidal stimulus. Indeed, responses thus far obtained on application of a wider range of stimulus waveforms suggest that this limitation may well conceal important generalizations in response characteristics. But again to avoid undue speculation, further comment must await completion of the current experimental series.

Response of Canal-Dependent Units to Rotation of a Linear Acceleration Vector

The parallel swing mode of stimulation, in which a linear acceleration vector sweeps round the animal, is not an unnatural mode of excitation. Any angular movement of the head having a component in the vertical plane must introduce relative angular movement of the linear acceleration vector attributable to gravity. Indeed it has recently been shown by independent investigators (refs. 15 and 16) that such rotation of the linear acceleration vector due to gravity can, when maintained, generate continued rational compensatory ocular nystagmus. The question then arises, To what extent can such response be attributable to otolith and semicircular canal components in the vestibular end organ? Certainly the responses of a single linear acceleration receptor such as those illustrated in figure 3(*B*) and in figures 4 and 5 cannot of themselves inform the central nervous system that a linear acceleration vector is rotating, since similar responses are obtained during translational oscillation of the parallel swing platform and during parallel swing rotation. Presumably in this case information associated with angular movement of the linear acceleration vector must be derived from suitable trigonometric coordination of sequential responses obtained from many otolith end-organ components. However, this complexity would not apply to a response obtained from a semicircular canal as a result of rotating the linear acceleration vector in its own plane. It is, of course, not at once obvious how such an excitation could be established. But Benson has suggested that such "artifactual" response may indeed be generated as a result of the rotating linear acceleration vector acting in some way as a circular pump generating pressure gradients around the endolymphatic circuit of the canal.

In this connection a particularly interesting response of a canal-dependent neuron to parallel swing rotation was observed by chance during earlier experiments (ref. 17). Relevant responses of this cell are summarized in the averaged records shown in figure 6. Figures 6(*A*) and 6(*B*) show the averaged responses of this cell to sinusoidal angular movement in the plane of the horizontal semicircular canals at periodic times of 4 and 64 seconds, respectively. These test results demonstrate the phase advancement with increasing periodic time which is to be expected from a strictly canal-dependent response. Figure 6(*C*) indicates the averaged response obtained from prolonged angular accelerations conducted consecutively to right and to left and extending over 64 seconds' continuous acceleration in each direction. Again the response to be expected from a canal-dependent cell is obtained; namely, a rise (shown to be exponential in other records) in firing frequency to an approximately steady state during angular acceleration in one direction and complete maintained elimination of response during angular acceleration in the opposite direction. Moreover, whereas response to rotational stimulation in the plane of the horizontal canals was in this cell very sensitive (threshold approximately 1.5°/sec), no correlated response was detected during angular stimuli in the planes of the vertical canals. Again, no correlated response was detected on exposure to translational accelerations in vertical and two orthogonal horizontal directions, imposed by oscillating linear motion in the parallel spring and parallel swing modes of table movement. Thus this cell appears to have been virtually solely under horizontal semicircular canal influence.

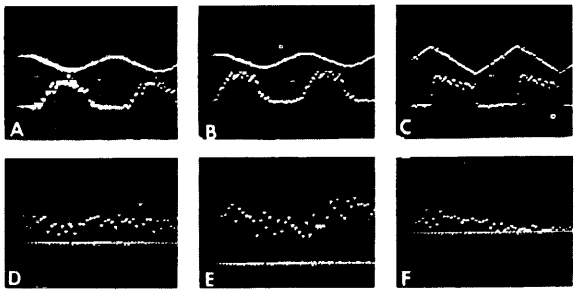

FIGURE 6.—*Averaged responses of "semicircular canal" unit to rotational and linear acceleration stimuli. Upper records give responses to angular stimuli. Lower records give responses to parallel swing rotation (i.e., rotation of linear acceleration vector). Sensitivity to angular velocity stimulus at 1/4 cps and 25°/sec amplitude = 0.66 action potentials (AP) per second per degree per second. Mean AP frequency on parallel swing rotation counterclockwise (left) = 17.8 AP/second, and clockwise (right) 2.9 AP/second.* (A) *Sinusoidal rotation at 1/4 cps (19 cycles);* (B) *1/64 cps (3 cycles);* (C) *rotational acceleration period 128 seconds (4 cycles);* (D) *spontaneous, AP freq. (7/sec);* (E) *parallel swing anticlockwise (50 cycles);* (F) *parallel swing, clockwise (50 cycles). (From ref. 17.)*

It was at this point that the idea of using parallel swing rotation (i.e., rotation of the linear acceleration vector without rotating the animal) for assessing the presence or absence of response to horizontal linear acceleration arose. But when this mode of stimulus was applied to this cell, a quite unexpected mode of response was obtained. From the audible presentation of action potentials, it was at once obvious that parallel swing rotation to left was associated with a persistent increase in firing rate, while parallel swing rotation to right was associated with a persistent decrease in firing rate. Figures 6(*E*) and 6(*F*) show the averaged firing rates obtained over 50 cycles to left and to right, respectively. These are to be compared with the corresponding spontaneous discharge rates presented in figure 6(*D*). Repetition of the stimulus sequence yielded almost identical averaged response curves.

Evidently this canal-dependent cell was responding as though the end organ were excited during parallel swing rotation to left and inhibited during parallel swing rotation to right, despite the fact that in this mode of excitation, there was no angular movement of the animal.

The observation was of sufficient interest to warrant formal experimental investigation (A. J. Benson, F. E. Guedry, and G. Melvill Jones, in preparation). After selection of canal-dependent units using the rigorous diagnostic technique outlined, cats were systematically exposed to parallel swing rotation of 2.2 seconds per cycle and centripetal acceleration 0.34 g. In every case parallel swing rotation in one direction led to a higher averaged frequency of firing than that obtained during parallel swing rotation

in the opposite direction. However, it was interesting to find that the spontaneous level of activity did not necessarily lie between these two responses, as was the case in the cell response illustrated in figure 6. Figure 7 illustrates the sequential determination of average firing frequency in one canal-dependent cell first during spontaneous activity, second during parallel swing rotation right, third during further spontaneous activity, fourth during parallel swing rotation left, and so on until four exposures had been obtained to right and to left, respectively, and nine spontaneous levels had been obtained. Averaging was conducted over 30-second durations in each case. Evidently this cell was consistently excited to a higher level of activity during parallel swing rotation to the right than to the left, but in both cases the activity was raised above the spontaneous level.

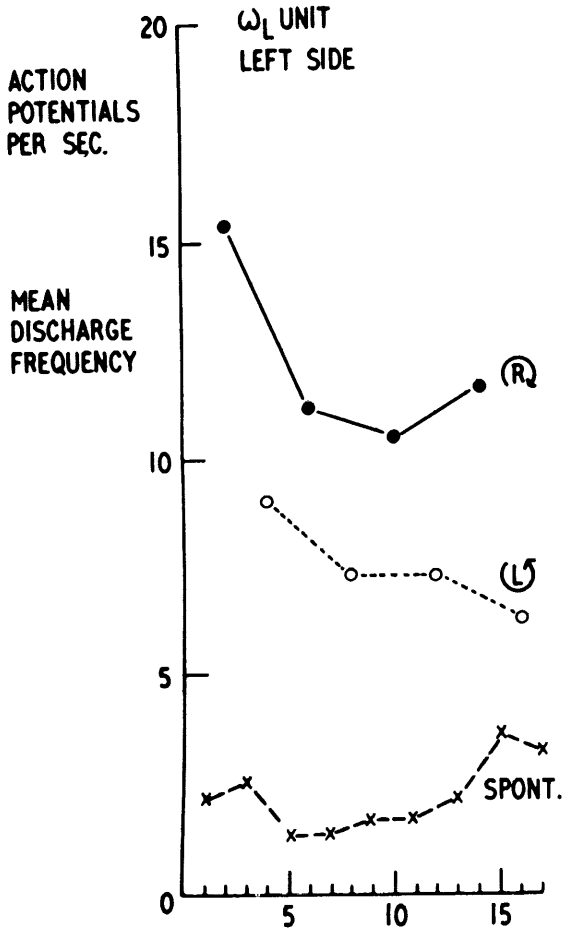

FIGURE 7.—*Effect of rotating linear acceleration vector on activity of a horizontal canal unit. This unit responded with high sensitivity to leftward angular velocity during sinusoidal horizontal angular velocity stimulus. Abscissa gives numerical sequence of tests. Continuous line: averaged firing frequency obtained during parallel swing rotation right. Open circles: parallel swing rotation left. Linear acceleration vector 0.34 g throughout. (From A. J. Benson, F. E. Guedry, and G. Melvill Jones, in preparation.)*

The cell whose response is given in figure 7 was on the left side of the skull responding positively to left angular velocity in the sinusoidal angular velocity mode of stimulation. Thus this cell may be described as an "Ewaldian cell" excited by ampullopetal flow in the ipsilateral canal during angular movement in the plane of the horizontal canals. In this case parallel swing rotation causing rotation of the linear acceleration vector in what might be described as an ampullopetal direction referred to the ipsilateral canal (one which would be likely to engender a tendency to fluid flow in the ampullopetal direction) led to greater excitation than during stimulus in the other direction. This general characteristic of response has proved consistent throughout all cells thus far examined.

As mentioned in the introduction, a cell in the vestibular nuclei could be under the influence of multiple end-organ structures. But over and above the evidence against this for the selected canal-dependent cells, it is hard to see how the observed maintained levels of change in cell activity could be brought about through mechanical stimulation of the otolith end organ. Thus it seems likely that the observed response was due to some mode of mechanical excitation of the semicircular canal. Such excitation could well give rise to rational compensatory patterns of oculomotor response, since these patterns of response would normally be derived from canal-dependent neural activity related directly to the velocity of angular movement.

CONCLUSIONS

From this brief résumé of some investigations of neural response characteristics in the vestibular nuclei, it seems that the angular velocity mode of information derived from the mechanical components in the semicircular canal is con-

ducted fairly faithfully into the central nervous system at least through some channels. Neural reflection of mechanical characteristics in the otolith organ does not appear to be so clear. However, the neural response of canal-dependent units to rotation of a linear acceleration vector does appear to reflect a mechanical response of the semicircular canal end organ to this type of stimulation. Presumably such stimulation, previously described as "artifactual," would be an everyday occurrence in natural life during angular movements of the head in a vertical plane.

If the resulting signal proves to be significant in the overall vestibular information pathway, it is of interest that in the zero-gravity environment of space flight, this mode of excitation would be absent, thus introducing the potential hazard of discordant vestibular information in the central nervous system.

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DISCUSSION

JONGKEES: I think we might find out a lot with this technique. Do you think that the stimulation of the cell as you showed it in the last pictures coincides with the movement of the cupula?

MELVILL JONES: My guess is that at least in part it does. My main reason for this is that without exception, the response behaved in the way one would expect from a physical model of the kind suggested by Benson. For example, a cell on the right side of the brain stem excited by ampullopetal flow in the ipsilateral canal would always be excited by anticlockwise rotation of the linear acceleration vector. According to Benson's hypothesis, this latter stimulus would itself be expected to generate a pressure gradient round the canal circuit leading to fluid flow in the ampullopetal sense. As I see it, the steady state would represent balance of forces generated by this pressure gradient and the resulting cupular elastic restoring force. Would you agree with this?

JONGKEES: I am not quite sure; there is one point I would raise before we can discuss it. When you move an animal placed on his side over a long distance with a strong acceleration, then he gets nystagmus too. He also gets that nystagmus when he has no canals and he does not get it when his otoliths are taken away. So the nystagmus in itself may be provoked by otoliths, I think. Thus, I do not feel so sure that there is a movement of the cupula. I do not know what the explanation will be. I think it is an extremely important thing. I am very interested in knowing what happens in a model of the labyrinth when you subject it to this movement.

Would it be possible for you to measure the indication time of this phenomenon, because the indication time of the otoliths is extremely short.

MELVILL JONES: Can you clarify indication time?

JONGKEES: Indication time is the time you find between the beginning of the stimulation and the maximum effect. That is much longer in the case of canal functions than in the case of otolith function. Perhaps that might help you out.

MELVILL JONES: I think measurement of the indication time would be particularly useful. For in the case of the rotating linear acceleration vector, if a pressure gradient were quickly established round the canal circuit, this would have to engender fluid flow against high viscous drag in order to deflect the cupula. In fact, one would, I suppose, expect an exponential pattern of cupular deflection if such deflection occurs, and it would be very interesting to examine this feature experimentally.

GUALTIEROTTI: First, I am pretty sure we are not dealing with a deviation of the cupula, because when you get a deviation of the cupula resulting in an inhibitory period, a rebound afterdischarge is always recorded at the end of the inhibition. It follows that if you had a cupula deviation provoking an inhibitory period, your responses could not have the characteristics that you have shown.

MELVILL JONES: What is the stimulus in that case?

GUALTIEROTTI: It does not matter what stimulus you have. If you have an inhibitory period, you always observe a rebound after discharge. This discharge is very similar to the one due to direct excitation, except perhaps is of shorter duration. This effect is very indicative and constitutes the main difference between an otolith unit and one from the semicircular canals. An otolith unit shows a pause in the firing when the stimulus is decreased, followed by a progressively slow increase of rate of firing, till normal value is restored. No excitatory rebound effect is present, whereas this rebound is typical of the semicircular canal response. In conclusion, during an alternative change from a positive to a negative stimulus, the semicircular canals usually respond with a high-frequency discharge, followed by an inhibitory period, followed by a rebound afterdischarge.

Now, for the second point. I do not know whether the mechanical system you used for applying a proper stimulus to the labyrinth is sufficiently accurate for quantitative studies, since you do not provide any direct recording of the acceleration involved. This seems rather crude. Our experience is that any motor-driven centrifuge or device, even if very carefully built, provides additional accelerations due to vibration and irregularities in the drive, especially through the gear junctions. The vestibular units are very sensitive to such parasitic accelerations, as you may see in figure D1. As shown, a quite small vibration is enough to set off a fast and complex response in this otolith unit. This is a very minor change in acceleration, of less than 0.01 g, and was provoked only by the effect of the teeth of the gears of the centrifuge. Without a highly sensitive accelerometer, such effect could not have been detected. Calculating the acceleration profile only by the rpm change may introduce a very large error. It is impossible to eliminate these kinds of artifacts, which are not really artifacts but additional acceleratory stimuli applied to the units. The only way out is to take such an acceleratory profile into account by measuring it directly with a proper system of accelerometers. In fact, to minimize this vibration we had to devise a complex hydraulic system mounted on a highly sophisticated anti-

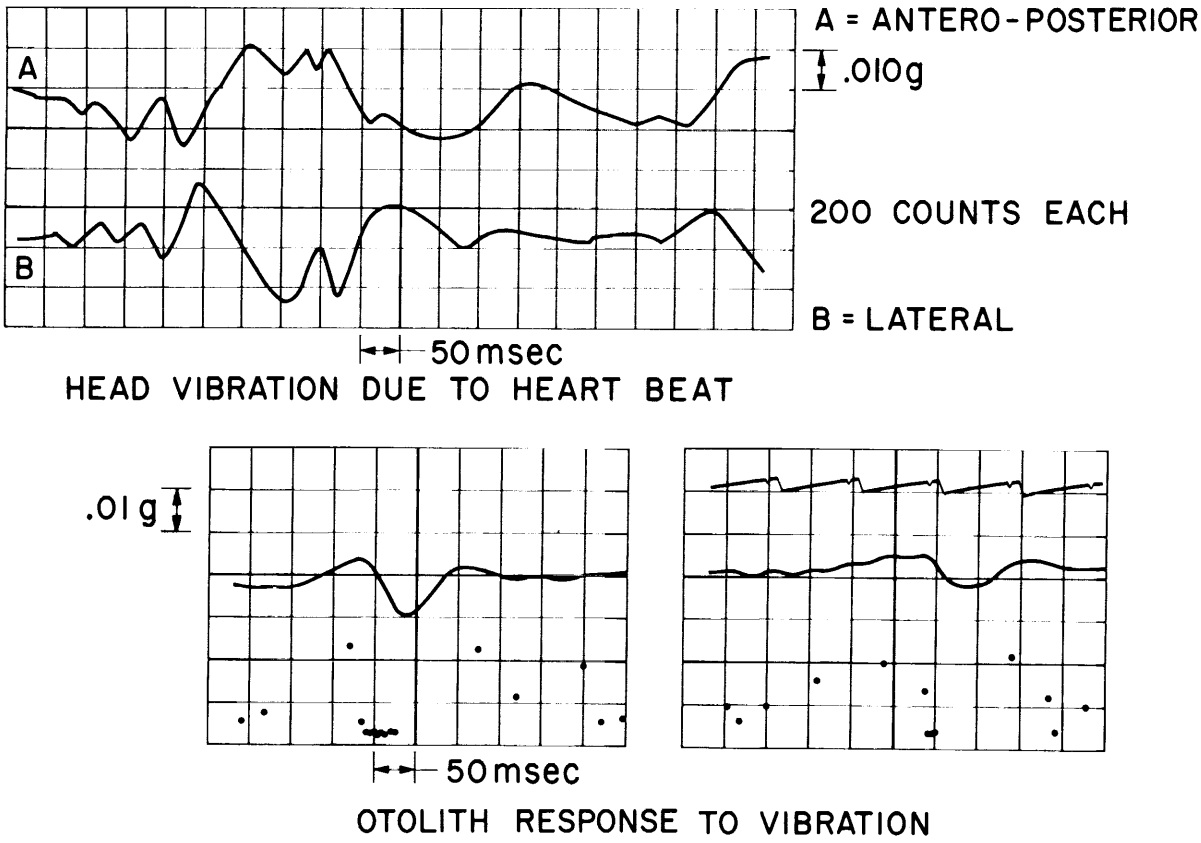

FIGURE D1.—Upper record: *Head vibration, measured at labyrinth level in man, due to heartbeat. The subject was sitting comfortably and his head was free. The mean curve of 200 sweeps is shown both from anteroposterior and lateral accelerometers.*

Lower records: *Two different responses to a vibratory stimulus similar to the head vibration in the upper record, recorded from a single otolith unit in the paralyzed frog. The consecutive intervals between spikes are computed as a distance from the base line and each black dot (calibration of the ordinate, 50 msec/div). Acceleration profile and time in the figure. Time marker, 100 msec.*

vibration pedestal. Even in this way, however, if you do not fix the head of the animal with extremely rigid clamps, you still have additional accelerations due to the natural vibration of the head following heartbeat. These accelerations, as you may see in the figure, show an intensity well above the threshold of the vestibular units. By the way, Dr. Bracchi and I are studying this particular problem of the head vibration due to heartbeat as being a stimulus for the labyrinth. Our conclusion is that it is a normal periodical background stimulation of the vestibule, maintained continuously, even in zero g. All these factors have to be taken into account when quantitative studies of the vestibular units are performed.

MELVILL JONES: Thank you very much, Dr. Gualtierotti. With regard to your first point, I am afraid I have to reiterate my original remark, namely, that response pattern must depend very much upon the pattern of stimulus. If one makes stepwise changes in angular position, then certainly the sudden angular swing in the *inhibitory* direction may be followed by a rebound burst of activity. But during a slow sine-wave stimulus this component of response will not manifest itself as a burst of activity on entering the inhibitory phase of the slow cycle. Rather, it will continuously modify the overall response, and it is such modifications which we look for in these experiments. So I do not feel yours is a really valid criticism in the context of these particular experiments. I am sure we would understand and agree with each other's views if we could discuss the matter together at length later.

With regard to your second point, I agree that the neural response to otolith stimulation is very sensitive. But I do not think this can of itself invalidate the maintained and averaged patterns of stimulus-response relations I have described. Perhaps I should add that the turntable employed is driven by a smooth friction drive and is therefore not subjected to the intermittent cogwheel influences you referred to.

CRAMPTON: This very beautiful set of data will keep us talking for many months, I am sure. Concerning the slosh-theory data, you made a point that, in all cases, rotation of the linear vector in one direction caused a greater discharge than it did with the rotation of the vector in the opposite direction and indicated that this fell in line with Ewaldian dogma. Is that not the implication?

MELVILL JONES: No. I was simply saying one particular cell responded that way. A non-Ewaldian cell would respond appropriately in the opposite sense.

CRAMPTON: In either case, however, the spontaneous discharge should fall between the two rates, should it not?

MELVILL JONES: Yes. One would have thought it should but it does not.

CRAMPTON: The second question concerns some data we collected very much like yours using long-duration ramps of 45 seconds or so. The response did not remain high and level but showed some adaptation or maybe an indication of overshooting. You had an example of each, I believe. Which do you find, no adaptation or overshooting, to be the usual case?

MELVILL JONES: At this stage it is difficult to say. To date I think we have roughly equal numbers showing overshoot, no adaptation, and adaptation. The "overshoot" case is the difficult one to explain, and since we have a number of such responses which are both very consistent and very marked, one feels a physiological explanation has to be searched for. My guess at present is that the continued pressure difference across the cupula may lead to yielding of tissue structures normally responsible for generating the elastic restoring force. In this case, one could imagine the cupula continuing to deflect slowly during the very prolonged steady angular acceleration. Then nonadapting cells would follow the cupula and give what you described as the "overshoot" response, while adapting cells would give a continuum of response ranging through the zero-change pattern to the highly adaptive pattern. Thank you very much for raising the point.

YOUNG: The second objection of Dr. Gualtierotti, I am sure, does not apply. If you had been recording from an otolith, you would have certainly detected it during your pure linear acceleration stimulus. Secondly, I would like to ask Mr. Steer to comment on the fluid dynamic analysis that he has been doing on just this problem. He is in our laboratory at MIT.

STEER: To support your conjecture that possibly the cupula is in fact deflected under the influence of counterrotating motion, I have been looking at the possibility that because the canal is a flexible structure, when it is put in the counterrotating field, a torque can be induced on the fluid. And to show that this is indeed a fact, I conjecture two simple experiments.

One is to take a glass of liquid, and start it from the center of a table, move it over to the side rather abruptly, and then start moving in this counterrotating motion. In a short period of time, stop the glass, and even though you have never at any time induced an angular acceleration, lo and behold the fluid is rotating in the glass. So a torque in fact has been induced on the fluid.

Take a jar that is full of fluid, cap it tight, and do the same experiment; you will never get a rotation of the fluid. This rotation of the fluid comes out of the fluid dynamic analysis because of the fact that you have a free surface. To carry that over to the case of the semicircular canal, certainly it is rigidly connected to the bony structure at the ampulla, but the canal duct itself is flexible and relatively unattached to the bony labyrinth. It has been shown that there are differences in the densities of the endolymph and perilymph, and Dr. Money has shown (in pigeons) that the canal duct itself is not of the same density as either the perilymph or endolymph. So indeed it is a flexible structure and in essence it has a free surface. To show this with analytical rigor is a horrible mess.

MELVILL JONES: Is it really so difficult?

STEER: It is tied up in the solution of Navier-Stokes equations with time-variable boundary conditions. It is a horrible mess, but we are getting there.

MELVILL JONES: Thank you very much indeed. What you say is most intriguing and certainly provides strong objective support for Benson's hypothesis that rotation of a linear acceleration vector can engender cupular deflection.

BENSON: George Crampton has hit on the main difficulty in interpreting these findings; namely, why do not all our units have their firing rate increased when the linear acceleration vector rotates in one direction, and decreased in the other? This is what we would predict on what George, disrespectfully, called the "slosh" theory. In 29 units which we studied, only some 20 percent behaved in this way. However, all showed a differential effect with increased firing in one direction of g-vector rotation and a decrease in the other. It is a fact that, during this type of stimulation, there is a large and changing gravireceptor stimulation which may raise the excitability of semicircular canal cells. This is one possible explanation, but we would like to know a good deal more about neural processes in the vestibular nuclei.

SESSION III: EFFERENT VESTIBULAR FUNCTION AND ANATOMICAL CONSIDERATIONS

Chairman: **BO E. GERNANDT**
Naval Aerospace Medical Institute

Nerve Endings in the Maculae and Cristae of the Chinchilla Vestibule, With a Special Reference to the Efferents[1]

CATHERINE A. SMITH
Washington University Medical School
AND
GRANT L. RASMUSSEN
National Institutes of Health

SUMMARY

The nerve endings in the maculae and cristae of the chinchilla's vestibule can be put into two general classes: calyciform and boutons. The calyciform terminals form chalices which completely encircle the hair cells except for their hair-bearing head. The boutons are subdivided into two types. The first type of bouton terminates only on the hair cells which often develop an adjacent synaptic bar, and its neuroplasm is similar to that of the chalices. These calicyform- and first-type bouton terminals are believed to belong to the vestibular nerve. The second-type bouton, the "vesiculated bouton," contains many small homogeneous vesicles and synapses sometimes by means of "en passant" boutons on hair cells, other boutons, chalice terminals, and nerve fibers. The vestibular nerve root to one ear was transected in six chinchillas. The animals were sacrificed at 2, 3, 6, 8, 32, and 35 days postoperatively. The 6- and 8-day animals yielded the most useful information regarding the efferent nature of the boutons. There were almost no normal vesiculated boutons present. Instead, some boutons were seen in these two animals which contained a fair number of dense vesicles, and these were interpreted as being altered vesiculated boutons. The studies strongly suggest that the vesiculated boutons are the terminals of efferent nerve axons.

INTRODUCTION

The organization and structure of nerve fibers and terminals in the vestibular labyrinth was the source of much interest around the turn of the century, and many outstanding investigators described their findings. Two different kinds of preterminal fibers were distinguished; some formed chalices about the sensory cells, and others appeared to end more diffusely. The early electron-microscopic studies of Wersäll, Engström, and Hjorth (ref. 1), Wersäll (ref. 2), and Smith (ref. 3) confirmed the observations made by means of silver stains, and added many details. All of these investigators emphasized that the hair cells could be divided into two groups with respect to their innervation, some having nerve chalices, others having bouton nerve terminals. Wersäll (ref. 2) first noticed that some of the boutons had more vesicles than others and suggested on this basis that they might be efferent in nature.

It had been demonstrated earlier (refs. 4 and 5) by Rasmussen that a well-defined bundle of nerve fibers (the olivocochlear tract) accompanied the VIIIth nerve and entered the cochlea. The question thus arose as to whether or not the vestibular nerve also carried some efferent nerve fibers along with it to the vestibular end organ. That it does indeed has been shown by a number of investigators. Rasmussen and Gacek (ref. 6) and Gacek (ref. 7) found that when the vestib-

[1] Supported in part by U.S. Public Health Service under Grant No. NB 00966.

ular nerve root was cut, or when lesions were made in the vestibular nuclei, there was selective Wallerian degeneration in some of the myelinated nerve fibers in 6 to 10 days after surgery. This was confirmed by McCabe and Gillingham (ref. 8). The Koelle stain for acetylcholinesterase has been used by Dohlman (ref. 9); Dohlman, Farkashidy, and Salonna (ref. 10); Ireland and Farkashidy (ref. 11); Rossi and Cortesina (ref. 12); and Gacek, Nomura, and Balogh (ref. 13) to study the presence of AChE-positive nerve fibers in the VIIIth nerve trunk and sensory regions. All these studies have shown that nerve fibers are present which can be stained by this method both within the nerve trunk and within the maculae and cristae. When the vestibular nerve was sectioned, the staining quality was lost.

It thus seems well established that there are some nerve fibers (far fewer in number than the regular VIIIth nerve fibers) present in both the nerve trunk and sensory regions which are chemically different from the vestibular fibers. Their reaction in this respect is similar to the efferent olivocochlear nerve fibers in the cochlea, and it might thus be inferred that Koelle-positive vestibular fibers are also efferents.

One of the questions that remains is whether the vesiculated boutons found by electron microscopy within the maculae and cristae by a number of investigators (refs. 2 and 14–16) belong to the efferent nerve fibers which accompany the vestibular nerve.

In a series of chinchillas in which the vestibular nerve root was cut specifically in order to follow the pathways of the cochlear efferents, we also had the opportunity to examine the vestibular end organs for degeneration of efferents there. The observations to be presented are the results of electron-microscopic studies of the vestibules from those animals.

MATERIAL AND METHODS

The ears from nine chinchillas were studied. Six of these animals had a unilateral vestibular root section. In order to sever all described efferent fibers (refs. 7 and 12) to the inner ear, it was planned to transect them where they pass outward, over, and through the descending root of the trigeminal nerve. The lesions were made with a thin knife and stereotaxic instrument as previously described by Smith and Rasmussen (ref. 17). The knife was inserted through the cerebellum at an angle indicated at 71 and 72 in figure 1. With one exception, only surviving animals in which the vestibular nerve was completely or almost completely cut were used for this study. The exception was animal No. 87 (fig. 1), the animal sacrificed 32 days postoperatively, whose lesion was misplaced some distance medial to the vestibular root. The survival times of the animals used in this series were 2, 3, 6, 8, 32, and 35 days. The unoperated ears from the 2-, 6-, 8-, and 32-day animals, from one other chinchilla whose experimental ear was not included in the study, and ears from two normal control animals were also examined. The ears were fixed by perfusion of 1 percent OsO_4 through the perilymphatic scalae of the labyrinth in the anesthetized animals, and after appropriate treatment embedded in Epon. Thin sections were cut with glass knives in an LKB Ultratome, stained with uranyl acetate and lead hydroxide or lead citrate, and photographed in a RCA EMU 3F electron microscope. One or more vestibular receptor organs were examined from each ear.

The brains were fixed in 10 percent formalin, and sections of the pons-medulla region stained with Sudan black B for study of the lesion.

FINDINGS

Normal Terminals in the Maculae Sacculi and Utriculi and in the Cristae Ampullares

Observations of normal terminals in the maculae sacculi and utriculi and in the cristae ampullares were made on the control ears from four experimental animals, plus ears from two unoperated normal chinchillas (figs. 2 to 10).

The nerve fibers destined for the maculae and cristae lose their myelin sheaths in the connective tissue, but retain their Schwann-cell sheaths until they pierce the basement membranes of the sensory epithelial structures. They have no specific sheaths within the maculae, but all the sensory regions of the vestibule are very compact, so that the nerve fibers are often rather closely invested by the supporting cells.

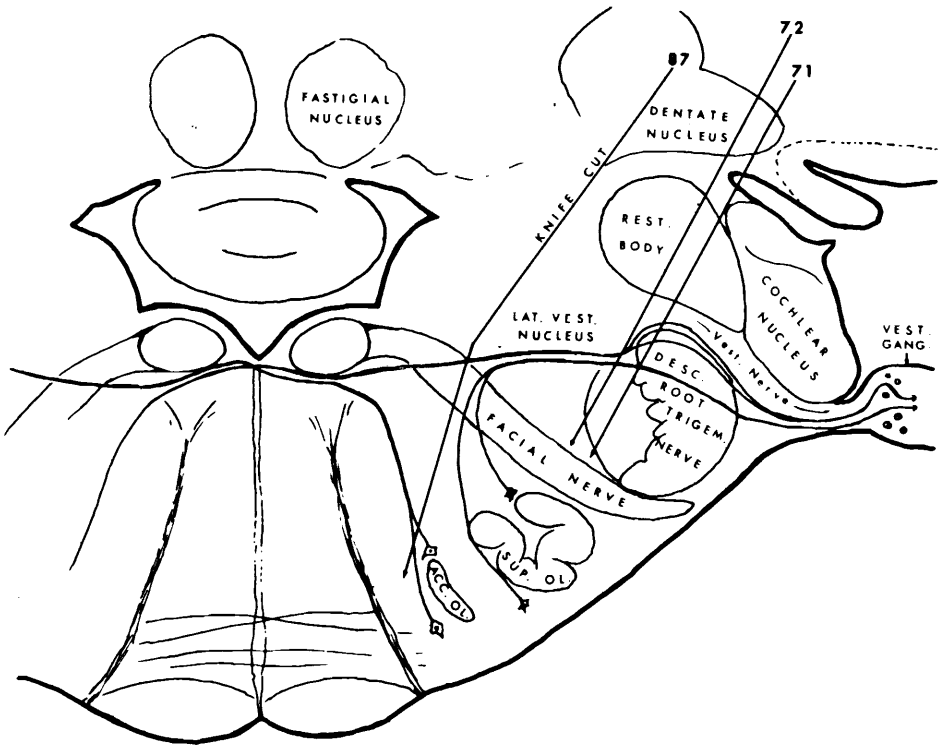

FIGURE 1.—*Diagrammatic drawing showing the experimental lesion made in the brainstem of chinchillas sacrificed 6 days (72), 8 days (71), and 32 days (87) postoperatively.*

The most peripheral extension of the myelin and Schwann-cell sheaths of the nerve fiber in figure 2 is seen below the basement membrane. The diameter of this nerve fiber in the macula is approximately 2 microns. It contains fine neurofilaments, a few vesicles of variable size, and some irregular cisternae and mitochondria. At the right a branch is visible, much smaller in size, which contains small vesicles of variable size. Other nerve fibers contain neurotubules and occasionally some branching tubular elements. It appears that these large nerve fibers terminate on the hair cells rather quickly after entering the maculae, although we have made no special studies in this regard.

The nerve terminals will be described as either calicyform or boutons. Some of the nerve endings are more clublike or fingerlike in form (and in fact what appears to be a bouton in a single section could be a cross section of one of the latter), but for simplicity, all will be termed "boutons."

Calicyform

Some of the larger nerve fibers expand at the bases of the hair cells and form the cups or chalices that completely envelop the sensory cells except for their hair-bearing heads (e.g., fig. 2). A single chalice may innervate one, two, or a number of hair cells, either partially or completely. Retzius (ref. 18) noted this and gave five cells as the maximum number of cells completely enclosed in one chalice. The thickness of the neural sheet investiture varies from 0.06 to 0.5 micron and is most often just below the latter. The nerve makes small invaginations (up to 1 micron in depth, and approximately 0.5 micron in diameter) into the basal part of the hair cell (fig. 2), and occasionally the sensory cell sends small spurs out into the nerve ending. The terminal's neuroplasm contains many mitochondria, fine filaments, vesicles of variable size, and irregular small cisternae which often have filamentous tails. The apical expanded lip of the chalice seems to be lacking in mitochondria.

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FIGURE 2.—*Macula utriculi, control ear. Two hair cells* (HC) *with chalice terminal* (C). *A myelinated nerve fiber* (M) *below penetrates the basement membrane* (BM) *and terminates as a chalice about the hair cell at left. A small branch* (arrow) *on the preterminal nerve fiber is at lower center.* S, *supporting cells. 1 micron shown by black line on this and each of the following electron micrographs, unless otherwise indicated.*

The gap between neural and receptor cell plasma membrane varies considerably. At the head of the cell it ranges from 175 to 490 Å (ref. 16). Around the basal bulb of the cell there are large areas where the gap is regularly wide (200 to 250 Å). Here the two cell membranes are straight and parallel. A dense material is interposed in the synaptic space and seems to be attached to the outermost layer of each synaptic membrane, but in two layers of constant width, separated from each other by a less dense layer (fig. 4). In some micrographs the dense layer appears to have a periodicity.

In the invaginations the gap is narrower and without the interposed granular material. It is very irregular, and this is due to small areas of what seem to be membrane fusions, or punctate tight junctions. No long areas of fusion were present in the material of this study. The invaginated neuroplasm sometimes contains a few vesicles.

Synaptic-bar structures are only rarely found adjacent to the chalices in the chinchilla vestibule, whereas they are often present inside the hair cells opposite the first type of bouton described in the following paragraphs.

Boutons

The other kind of nerve endings includes boutons of variable size (figs. 3, 5, and 7). Fingerlike and clublike terminals and boutons of the "en passant" type, that is, those connected together in a beadlike arrangement by slender nerve fibers, are also included. The boutons are of two general types in regard to their neuroplasmic contents. The first type terminates only on the hair cells. Its neuroplasm is similar to that of the calicyform endings in that it contains a few mitochondria, vesicles, and cisternae of variable size and fine filaments (figs. 5 and 7). The postsynaptic membrane may make some indentations into the sensory cell, but a quite regular synaptic gap is maintained. Often there are membrane thickenings on the presynaptic or postsynaptic side, or both, and synaptic-bar structures are adjacent within the hair-cell cytoplasm. Two or three bar structures are sometimes visible opposite one bouton. These are identical to the synaptic bars originally described in the cochlear hair cells (ref. 19). Sometimes small vesicles (not identifiable as a part of the bar structure) are lined up along the synaptic membrane inside the hair cell. Occasionally, the bristle-coated type of vesicle has been seen also adjacent to this type of ending that is characterized then by a neuroplasm containing only scattered formed elements and is associated with adjacent synaptic bars.

The second type of bouton contains many vesicles of homogeneous size (figs. 3, 6, and 9) and is not associated with an adjacent synaptic bar structure inside the hair cell. Any boutons on the hair cells which displayed a moderate number of vesicles, plus adjacent synaptic bars, were classified with the first group. The second-type bouton terminates on the hair cell (fig. 3), but may also make an apparent synapse with the first-type bouton (fig. 7), a chalice terminal (fig. 3), and/or another nerve fiber (fig. 8).

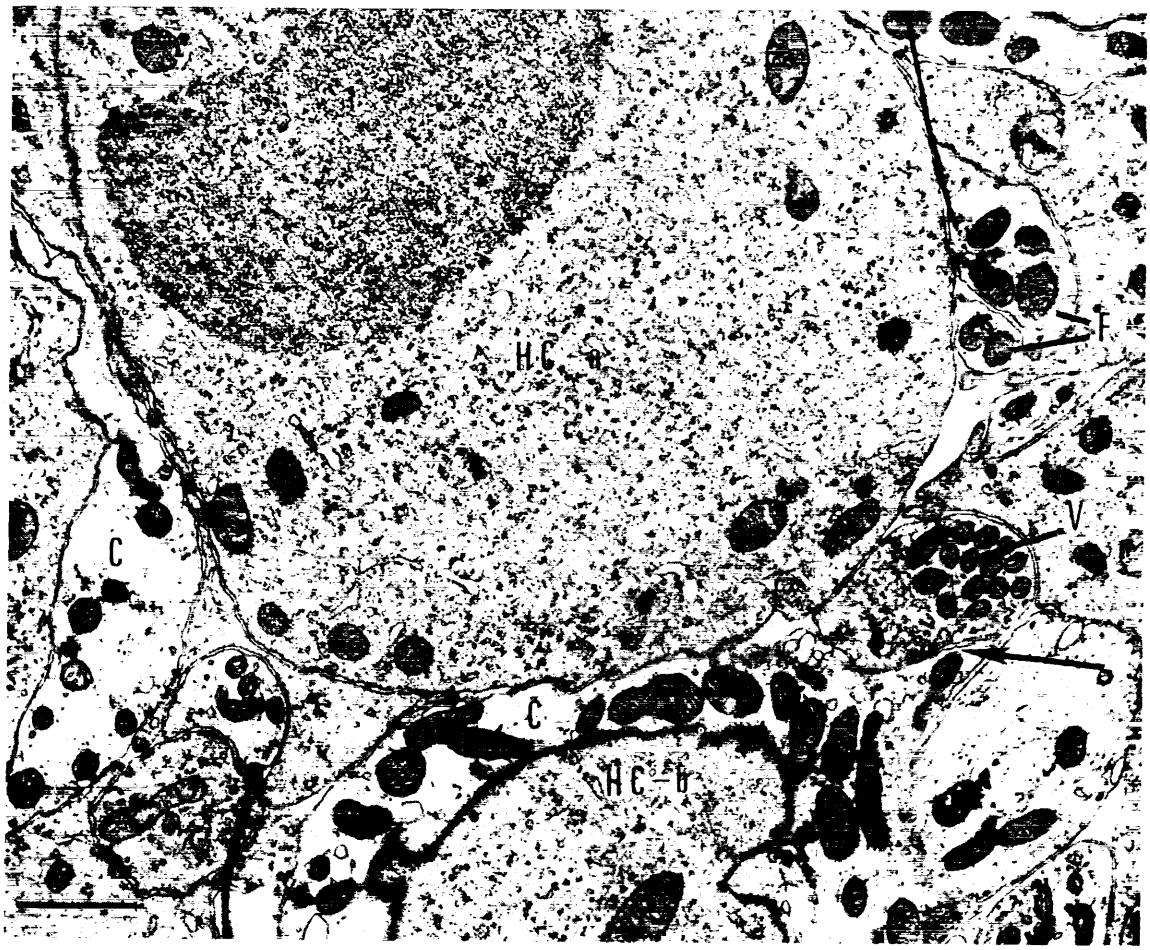

FIGURE 3.—*Macula utriculi, control ear. Two boutons of the first* (F) *and one of the second type* (V) *all at right, on a hair cell* (HC–a). *The vesiculated bouton* (V) *is also in contact with a chalice* (C) *terminal* (arrow) *where it displays a membrane thickening. The chalice which surrounds a second hair cell* (HC–b) *also synapses with the first hair cell. Another calicyform terminal is visible at extreme left.*

In addition to the numerous small vesicles, they also contain a few larger vesicles, mitochondria, and occasionally some filaments and tubules. "Vesiculated boutons" seems to be a good descriptive term by which to designate these terminals and will be used henceforth. Sometimes but not often they have thickened membranes at their synapses with the hair cells. (See fig. 11.) In an analysis of 44 boutons of this type in the maculae, 19 were found in apposition to hair cells and only two of these showed limited membrane thickenings. In the cristae, 17 were found at hair-cell bases, none of which had a well-defined thickening. From the total of 36 boutons on hair cells in maculae and cristae, only eight had any kind of subsynaptic cisternae within the adjacent hair-cell cytoplasm. This was usually a small cisterna of endoplasmic reticulum often with contiguous RNA granules. These are believed to be chance relationships. In one instance only, in an experimental ear, was there found a large subsynaptic cisterna comparable to those consistently found opposite the cochlear efferents. The vesiculated boutons may also make small irregular invaginations into the hair cell.

The second-type bouton also makes close contact with the nerve chalices (fig. 3) with other bouton endings (fig. 7), or with nerve fibers. From a total of 84 vesiculated structures studied,

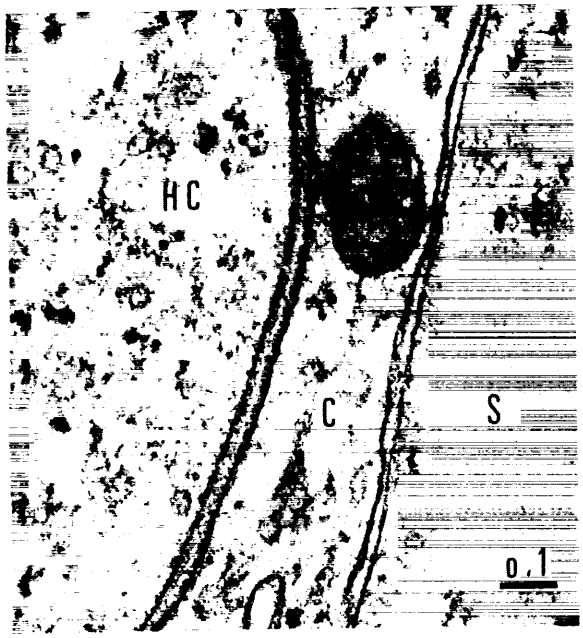

FIGURE 4.—*Macula sacculi, control ear. Detail of calciform* (C) *synapse on base of hair cell* (HC). *Synaptic gap indicated by arrow.* S, *supporting cell.*

21 were found to be closely apposed either to nerve chalice or nerve ending, or both, and 21 apposed to nerve fibers. Sometimes the apposition was multiple in that a single large neural process filled with vesicles made close contact with more than one nerve ending, with hair cell and nerve endings, or nerve fiber. In 12 of 36 instances, thickened membranes were present when the vesiculated endings were apposed to chalices or other type boutons (fig. 7). In 7 of 13 instances, thickened membranes were present if they were apposed to nerve fibers (fig. 8). Thus, membrane thickenings, plus associated regular gap and vesicular clusters, were more often found when the vesiculated boutons touched other neural structures than when they touched the hair cells.

The vesiculated boutons are usually found in the basal half of maculae or cristae. Here they have ample opportunity to synapse on nerve fibers and exert a postsynaptic influence on the vestibular nerve dendrites. They are often visible as enlarged bulbs on slender nerve fibers, and apparently make "en passant" synapses by this means (fig. 10).

Experimental Animals

Previous studies on the cochleas of these animals (refs. 17 and 20) showed that loss or clumping of vesicles, appearance of fine filaments, or mitochondrial changes were characteristic of the degenerating efferent terminals in the cochlea. We have examined the vestibules for similar features.

Two and three days postoperative.—The maculae from the ears of the two chinchillas sacrificed 2 and 3 days postoperatively showed few well-defined alterations. One or two nerve fibers contained a few dense bodies. Some vesiculated boutons were visible in the ears of both animals. Possibly some loss of vesicles may have occurred, but any changes present were too subtle to be used as reliable criteria for experimental degeneration. Most nerve fibers and terminals were normal in appearance.

FIGURE 5.—*Macula sacculi, control ear. The first type of terminal bouton* (F) *on a hair cell* (HC). *Two synaptic bar structures with circlets of vesicles* (arrows) *are present inside the hair cell. Visible thickening of postsynaptic membrane.*

Six days postoperative.—No boutons filled with homogeneous vesicles were found in the maculae of this animal. Some boutons were present which contained a moderate number of vesicles (fig. 12), but the vesicles were irregular and many were quite dense. A few nerve fibers contained dense bodies. Figure 13 shows a myelinated nerve fiber beneath the macula of the utricle containing dense bodies and large numbers of mitochondria.

Both the chalices and other boutons also contained an occasional large body; so, it would appear that all the cut nerve fibers (vestibular as well as efferents) were beginning to show results of the insult at this time. The cristae from this animal were not examined.

Study of the brainstem sections revealed that the vestibular nerve had been completely transected in this animal.

Eight days postoperative.—The 8-day animal showed a similar picture (with some variations) in that in all the sections examined from both maculae, only one or two normal appearing vesiculated boutons were found. A survey picture of the utricle (fig. 14) shows a number of hair cells and boutons. Some boutons have a moderate number of vesicles, but the vesicles are irregular in regard to density and size. We believe these to be altered vesiculated boutons. Figure 15 illustrates a similar bouton at higher magnification. In both this and the 6-day animal all boutons looked much alike, and it was necessary to consider other factors such as synaptic bars and location, as well as neuroplasmic characteristics, to get some hint as to which type of bouton they were. Those boutons with altered vesicles did not demonstrate any membrane thickenings. Figure 16 illustrates another bou-

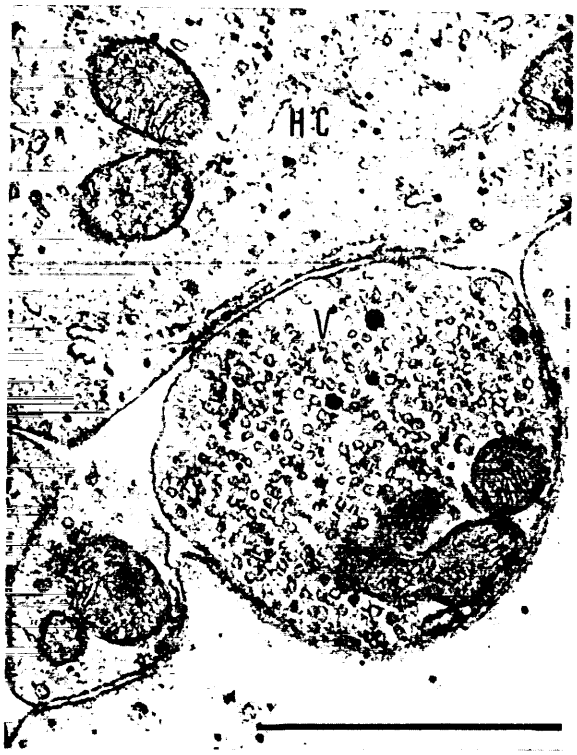

FIGURE 6.—*Crista ampullaris, control ear. Second-type bouton, the vesiculated bouton* (V), *in synaptic contact with a hair cell* (HC).

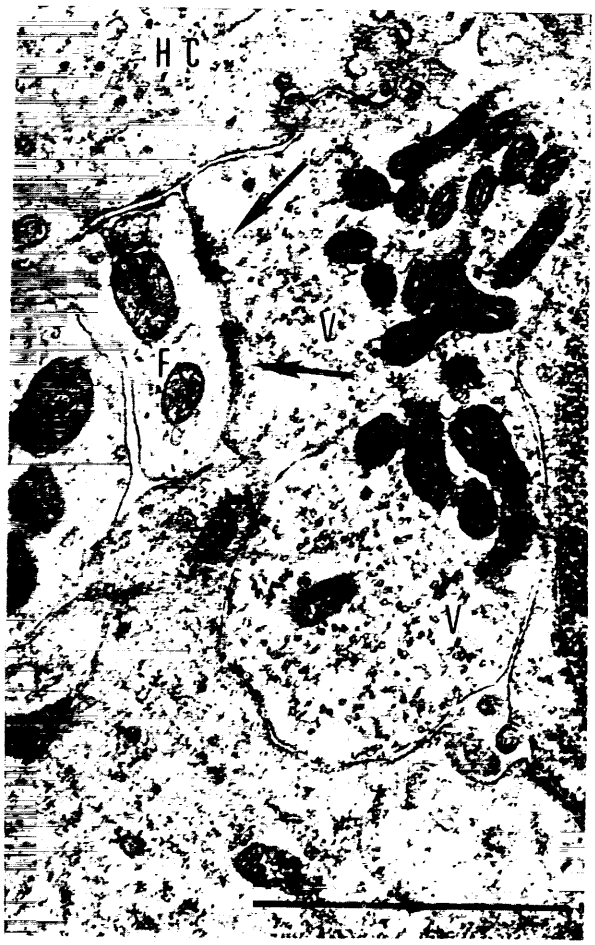

FIGURE 7.—*Macula utriculi, control ear. Two vesiculated boutons* (V) *at right. The upper one is in contact with the hair cell* (HC) *and also with the first-type bouton* (F). *Membrane thickenings at arrows.*

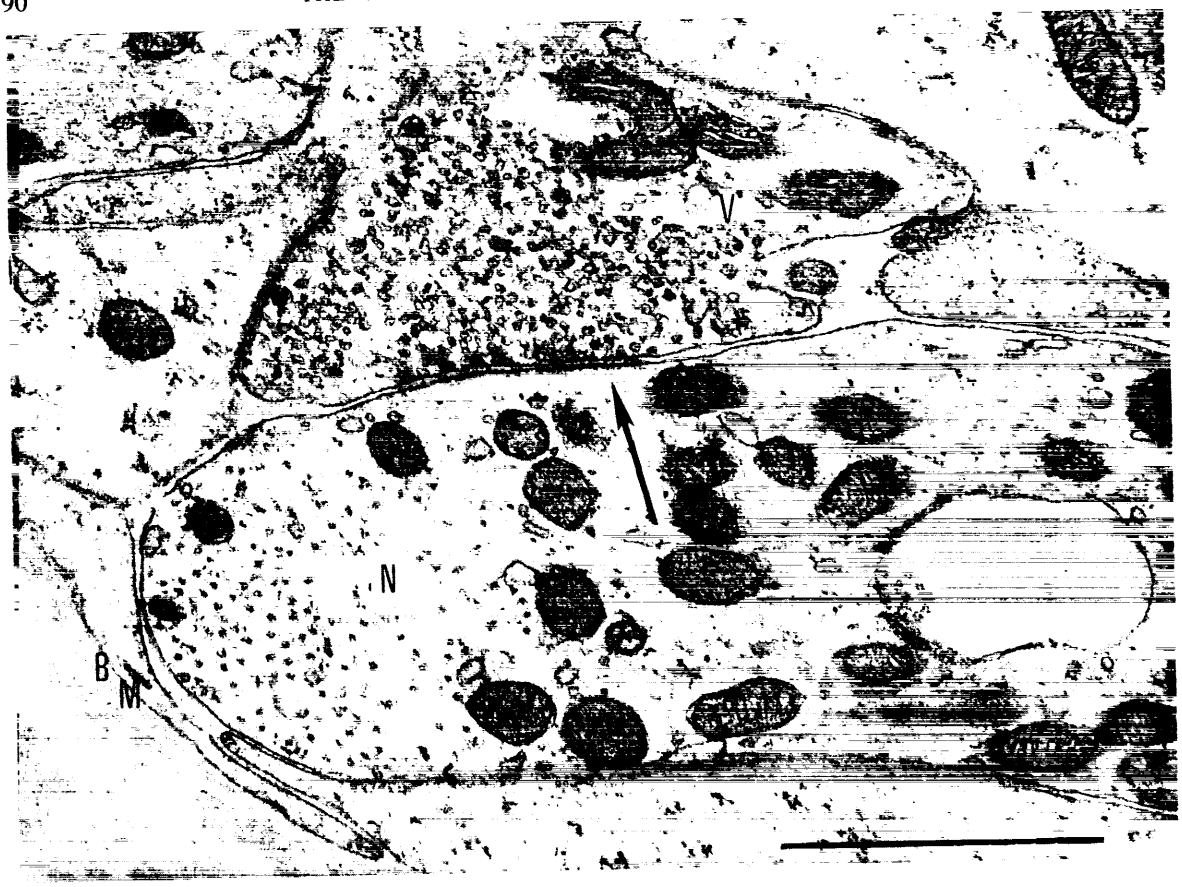

FIGURE 8.—*Macula sacculi, control ear. Vesiculated bouton* (V) *with apparent synapse on nerve fiber* (N). *Vesicular clusters and membrane thickenings at arrow.* BM, *basement membrane.*

ton which, because of its location (in contact with hair cells, chalices, and nerve fiber), leads one to believe it to be a degenerated vesiculated bouton. If it were judged on its neuroplasmic aspect alone, it might also be classed as a normal first-type bouton, with more than the usual number of vesicles. Therefore, it was difficult to identify with certainty altered vesiculated boutons. The fact remains that boutons with many homogeneous vesicles were for the most part no longer present.

Some nerve fibers within the maculae contained dense bodies and degenerating mitochondria.

The chalice terminals also revealed evidence for change in that some dense bodies were present in their neuroplasm. Some hair-cell–chalice units showed what might be evidence for a breakdown in normal hair-cell–synaptic activity (fig. 17). The synaptic gap at the basal portion of some cells showed irregular dilations which were filled with many small vesicles (300 to 400 Å) and some larger vesicles. Occasionally these made small outpockets (fig. 17) into the chalice. In normal ears, single vesicles have been seen infrequently in the synaptic gap, but not to the extent seen in this animal. In the 6-day animal also, there was some evidence for the same phenomenon, but to a minor degree.

The one crista which was examined from this animal's experimental ear showed marked swelling of nerve fibers and chalices, and lysosome changes in the sensory cells. Many of the hair-cell–chalice units showed the widened synaptic gap with interposed vesicles described previously in the maculae.

Some apparently normal vesiculated boutons of the "en passant" type were seen in the crista.

Study of the brain sections from the 8-day chinchilla revealed that some of the caudalmost fibers of the vestibular nerve were not cut.

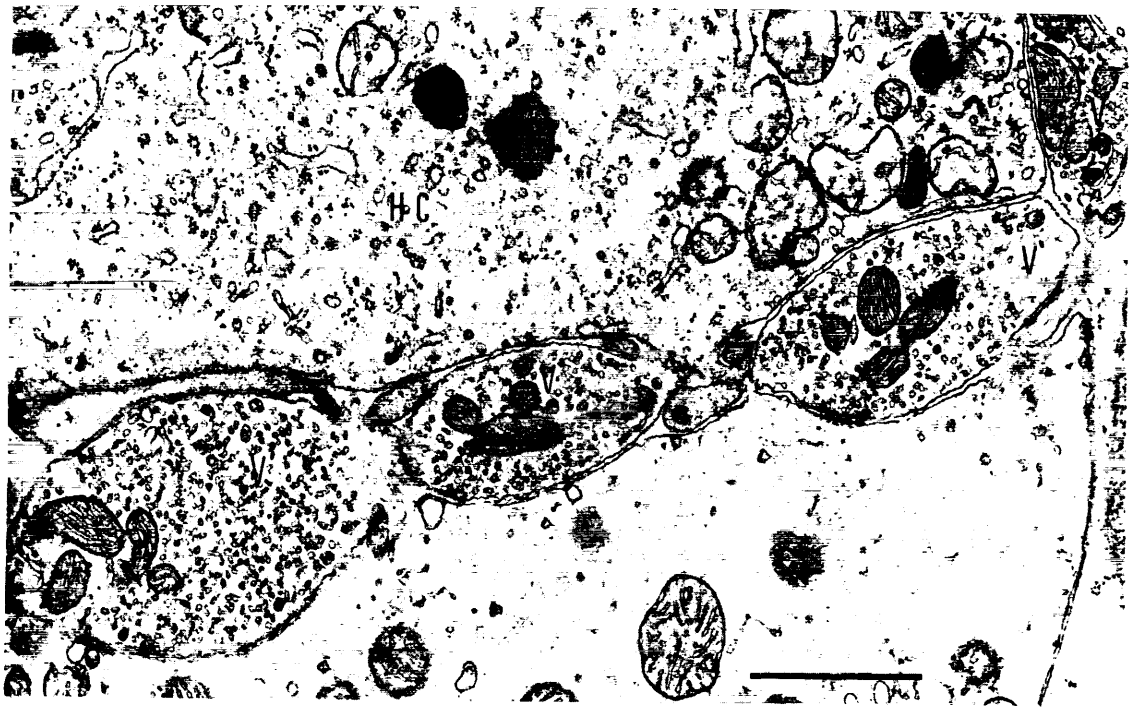

FIGURE 9.—*Crista ampullaris, control ear. Four vesiculated boutons* (V) *at side and base of hair cell* (HC). *These would probably be connected together and form "en passant" boutons.*

Thirty-two days postoperative.—The 32-day animal showed some altered boutons, but no changes in sensory cells or chalices. This was explained by a study of the brain sections which revealed that the lesion was made medial to the nerve root, so that the vestibular nerve was not cut at all. The knife passed through the lateral vestibular nucleus.

A number of small boutons in the utricular macula showed what appeared to be degenerative changes. The mitochondria were swollen and disorganized and the neuroplasm empty and almost devoid of formed elements (fig. 18). One bouton with the described features had an adjacent synaptic bar. There was also some swelling of the supporting cells. It is possible the changes found in this ear were preparation artifacts. Some vesiculated boutons were present.

The crista examined revealed two well-defined vesiculated boutons. Changes in other boutons were not marked enough to eliminate the possibility of artifact.

Thirty-five days postoperative.—The brainstem sections of the 35-day animal showed that most of the vestibular nerve root had been cut but that the caudalmost fibers again escaped the knife. The macula of the utricle from this animal showed marked changes in most nerve fibers and terminals. The chalice terminals were swollen; one was found to be exploded and broken with a resultant large hole in the macula. In another section a large body, more than 10 microns in diameter, filled with filaments, mitochondria, and myelin figures was found above the basement membrane. Another similar but smaller body was identified as an enlargement of a nerve fiber emerging from its myelin sheath. Large groups of nerve fibers displayed marked fibrillosis, shrunken or swollen mitochondria, and dense bodies. Obviously the preterminal parts as well as terminals of the vestibular nerve fibers had undergone considerable alteration by the time the animal was sacrificed. The boutons (of the first type) showed less alteration than the chalices, and some were fairly normal in appearance.

Among the greatly altered nerve fibers, some perfectly normal appearing vesiculated boutons were found.

FIGURE 10.—*Macula sacculi, control ear. Two "en passant"-type vesiculated boutons* (V) *in lower part of macula. One makes synaptic contacts with two hair cells* (HC). F, *first-type bouton.*

DISCUSSION

Previous observations on the maculae from the chinchilla's ear revealed (ref. 16) that there were two different kinds of terminal boutons in these vestibular structures. Extension of these studies to include the cristae have given additional information. The first type of bouton which terminated on the hair cells had a neuroplasm containing few formed elements similar to that of the calicyform endings. A synaptic-bar structure was often found adjacent within the hair-cell cytoplasm. We believe that this type of bouton belongs to the vestibular nerve. The associated synaptic-bar structure reinforces this viewpoint, because these structures have previously been found only adjacent to sensory nerve endings. The second-type bouton contained many small vesicles of homogeneous size. They often took the form of "boutons en passant" and made apparent synaptic contact with nerve fibers, chalices, and other boutons, as well as the hair cells. Boutons with these characteristics have also been found in guinea pig and squirrel monkey (ref. 15). Iurato and Taidelli (ref. 21) found the "en passant" terminals in the rat's crista. No synaptic-bar structures were associated with the vesiculated boutons. These nerve fibers were generally located in the basal half of the sensory-cell mass and seemed to form a plexus there.

The structure and synaptic relationships of the vesiculated boutons are similar to those of the chinchilla's cochlear efferents (ref. 20). Their location is in agreement with the acetylcholinesterase positive staining plexuses demonstrated by Dohlman, Farkashidy, and Salonna (ref. 10), and by Ireland and Farkashidy (ref. 11). The presumptive evidence thus is favorable for the efferent nature of the vesiculated boutons.

The experimental part of the study was initiated on the premise that those axons which are cut distal to their cytons will degenerate. It is also well known that retrograde changes occur in neurons whose axons are severed and that this is variable. Nevertheless, it would be expected that degeneration in efferent axons traveling with the vestibular nerve would occur before any changes, if present, were visible in the vestibular nerve fibers. This has been amply demonstrated previously, and in the vestibular nerve by Rasmussen and Gacek (ref. 6) and Gacek (ref. 7), who found degeneration of the myelinated portions of the efferents in 6 to 10 days' time after they were cut. The present studies indicated the reaction was somewhat different in the maculae and cristae, where naked nerve fibers course in a more or less compact tissue, more compact in the maculae than cristae. For one thing, the observable degeneration of the severed axon terminals was slow, even slower than in the cochleas of these same or comparable animals. For example, many of the olivocochlear efferent terminals were completely lysed in the cochlea of the 8-day animal (ref. 17). Furthermore, small changes were visible in the unmyelinated parts of the vestibular nerve and its terminals, as well as the

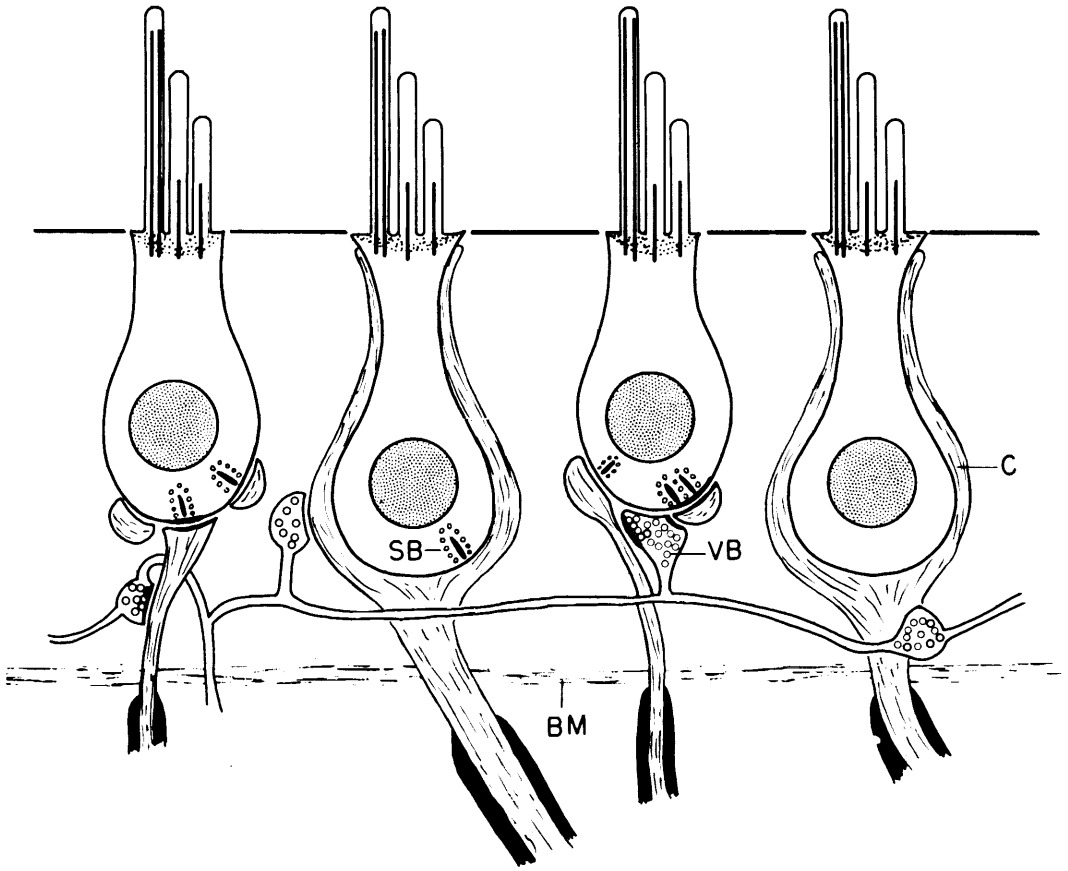

FIGURE 11.—*Diagrammatic drawing showing four hair cells and their nerve endings and the relationships of vesiculated boutons* (VB) *to hair cells, chalice terminals* (C), *other boutons and nerve fibers in the chinchilla maculae.* BM, *basement membrane;* SB, *synaptic bar. It is believed the efferent nerves form a sort of horizontal plexus as drawn.*

sensory cells at an early time, and were more marked at a later date. These factors have made the evaluation more difficult. They have also pointed out that generalizations about nerve degeneration are hazardous and that the course of change is regulated by the specific situation.

The most useful information regarding the efferent nature of the vesiculated boutons came from the animals sacrificed at 6 and 8 days. First, almost no boutons containing the many small vesicles were found in the 6- and 8-day maculae, whereas such boutons were readily found in control maculae. Many of the boutons present a week after transection contained irregular dense vesicles (rather granular in character), and these were interpreted to be altered vesiculated boutons. This interpretation has support from many other investigations on degenerating nerve endings (refs. 17, 22, and 23) which demonstrated that one characteristic feature of degenerating nerve endings is loss or alterations of synaptic vesicles. Second, the changes which had taken place by this time in the vestibular nerve fibers and their calicyform terminals were small enough so that, if the vesiculated boutons were branches of the vestibular nerve fibers, it seems unlikely they would have suffered the observed loss of vesicles. The results from these two animals strongly suggest that the vesiculated boutons, for the most part, are efferent terminals that course in the vestibular nerve.

The findings from the 32-day animal are difficult to interpret because there may be some artifactual changes present. This animal was of particular interest as the postoperative time lapse

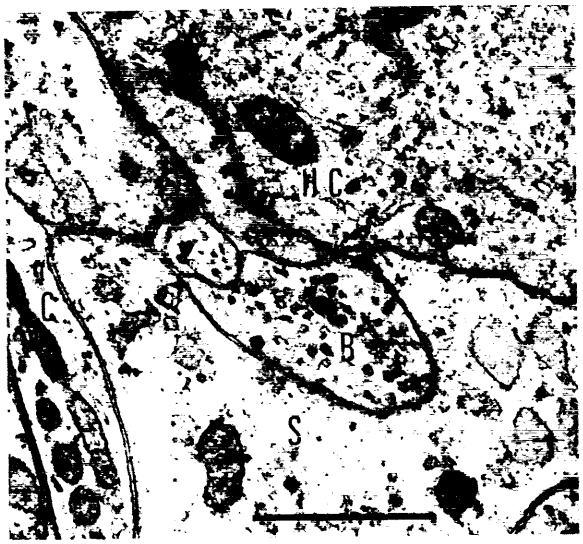

FIGURE 12.—*Macula utriculi, 6 days postoperative. Small bouton* (B) *at hair cell* (HC) *containing irregular dense vesicles interpreted as being an altered vesiculated bouton.* C, *chalice terminal;* S, *supporting cell.*

allowed a period for more complete degeneration of efferent boutons, but lacked the confusing vestibular-nerve degeneration (such as was present at 35 days) because this vestibular nerve had escaped the knife. If the animal is valid, then it would confirm the findings from the 6- and 8-day animals. Nevertheless, it must be emphasized that some other structures in the macula besides boutons were imperfectly preserved, and it is not possible to rule out a preparation artifact.

Why some few vesiculated boutons remained in the vestibules of the 8- and 35-day animals cannot be explained with certainty. Previous studies on the cochleas of these animals (ref. 17) indicated that all terminals do not degenerate simultaneously, and this might well explain the remaining normal-appearing boutons in the 8-day animal. For the 35-day animal, the caudalmost part of the vestibular nerve root was not cut; so, some of the efferents may have escaped section. This brings up the question as to the origin of the efferents. The previous studies by Rasmussen and Gacek (ref. 6) led those investigators to believe that the source in the cat of the vestibular efferents was the lateral vestibular nucleus. Rossi and Cortesina (ref. 12) more recently have given evidence of an "interposed" nucleus between inferior and lateral parts of the vestibular nuclei and that the reticular nuclei may also be involved. (For further details, see a subsequent paper by Giovanni Rossi entitled "Central Projections to the Vestibular Receptors.") The evidence from the 35-day animal suggests that at least some of the efferent fibers course in the caudalmost portion of the vestibular root and from the 32-day animal suggests that, in the chinchilla, some of the cells of origin may be located medial to the cut (which went through the lateral vestibular nucleus) rather than homogeneously scattered throughout this nucleus. The possibility that autonomic fibers coming in with the blood vessels or with the facial-vestibular anastomosis may synapse on the

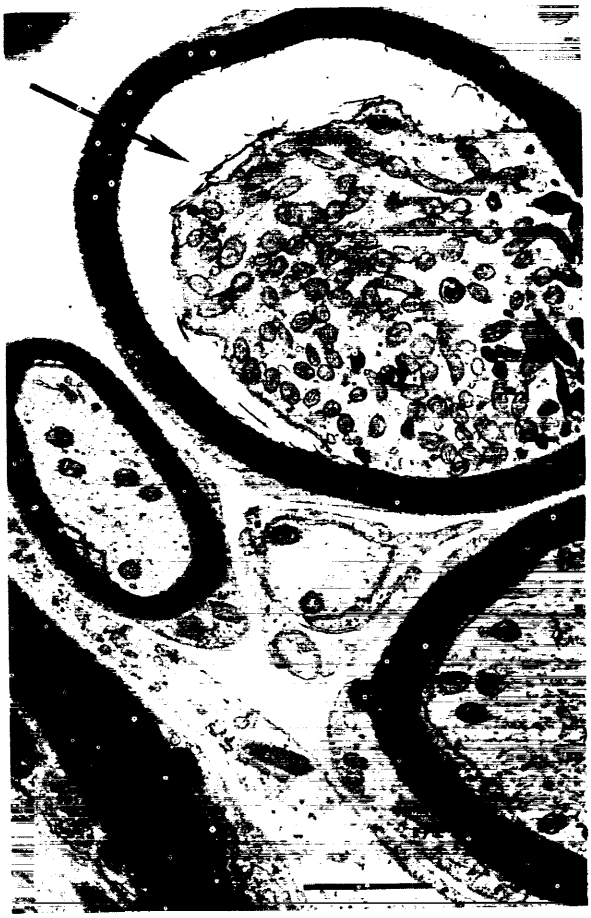

FIGURE 13.—*Macula utriculi, 6 days postoperative. Myelinated nerve fibers beneath macula, one* (arrow) *showing degenerative characteristics (dense bodies, many mitochondria, shrinkage); others are normal in appearance.*

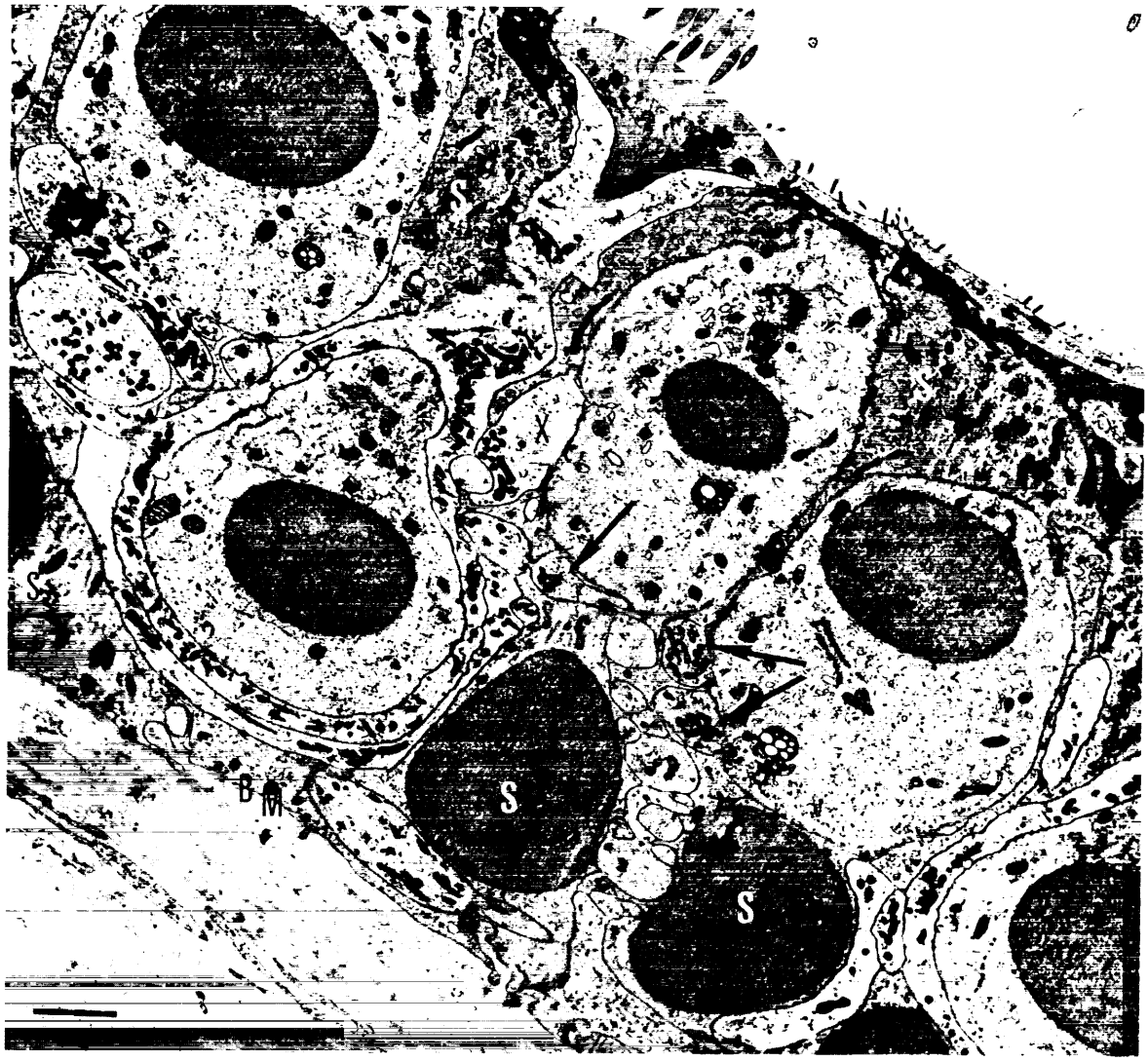

FIGURE 14.—*Macula utriculi, 8 days postoperative. Five hair cells with calicyform or bouton terminals on them. Some boutons, with a fair number of dense vesicles (arrows), are interpreted as being degenerated efferent boutons. No boutons filled with vesicles are visible.* S, *supporting cells;* BM, *basement membrane;* X, *see figure 16.*

hair cells or nerve fibers cannot be entirely excluded, but this seems unlikely.

The early alterations seen at 1 week in the vestibular nerve terminals are interesting, and point out the importance of the integrity of the complete neuron with its major processes intact. When the axon was interrupted, although on the central side of the neuron, the unmyelinated dendritic terminals reflected the injury. The abnormal accumulation of material within the synaptic cleft between sensory cells and chalice would bear further investigation. The normal reciprocal relationship between the two was apparently interrupted, or changed.

In the final analysis the following points can be brought out:

(1) Many vesiculated boutons, some in the form of "boutons en passant," are found on the hair cells and in apparent synaptic contact with vestibular nerve chalices, nerve fibers, and other boutons. They are generally to be found in the

FIGURE 15.—*Macula utriculi, 8 days postoperative. Small bouton* (B) *containing irregular dense vesicles and in contact with chalice* (C) *interpreted as being an altered vesiculated bouton. First-type bouton* (F) *at right.* HC, *hair cell;* S, *supporting cell. Higher magnification than that of figure 14.*

lower half of the sensory structures and probably constitute a horizontal nerve plexus.

(2) The findings in the experimental ears of which the vestibular nerve or nuclei had been transected strongly suggest that the vesiculated nerves are efferents and that for the most part they enter with the vestibular nerve. The series of animals is too small to come to any definite conclusions. To the authors' knowledge there is no other published similar study on the vestibule to which we might compare the present findings.

(3) No further definite information is available from these studies concerning the source of the efferents.

(4) The unmyelinated preterminal vestibular nerve fibers and their terminals also showed alterations as early as a week after the nerve root was cut. These changes were more marked after a month had elapsed.

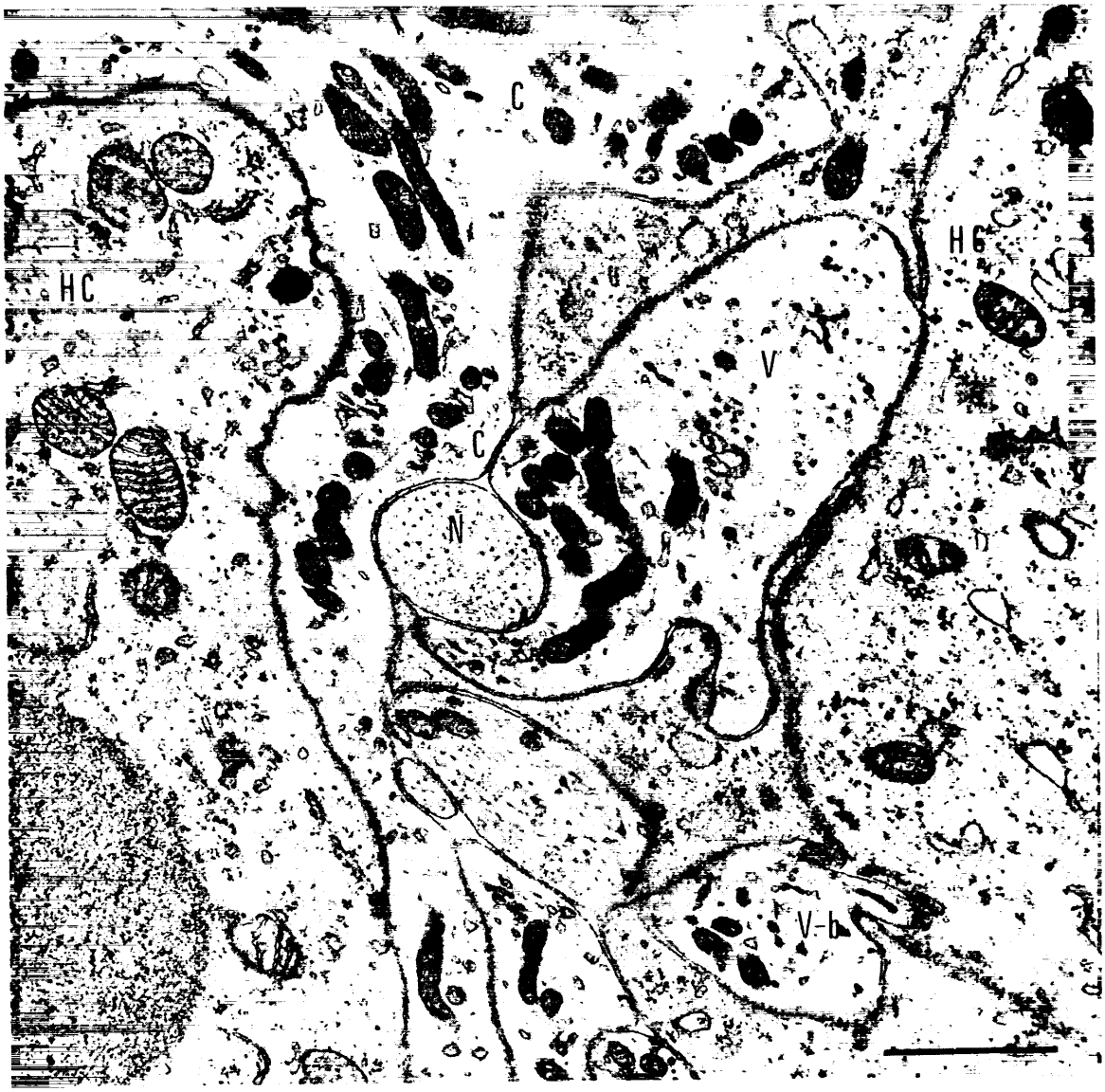

FIGURE 16.—*Macula utriculi, 8 days postoperative. Bouton at right center* (V) *containing a few scattered vesicles. It makes contact with a hair cell* (HC), *chalice* (C) *and partly encircles a nerve fiber* (N), *but without membrane thickenings. A bouton of similar structure at lower right* (V–b) *terminates on the hair cell. This is another section of the bouton at* X *in figure 14.*

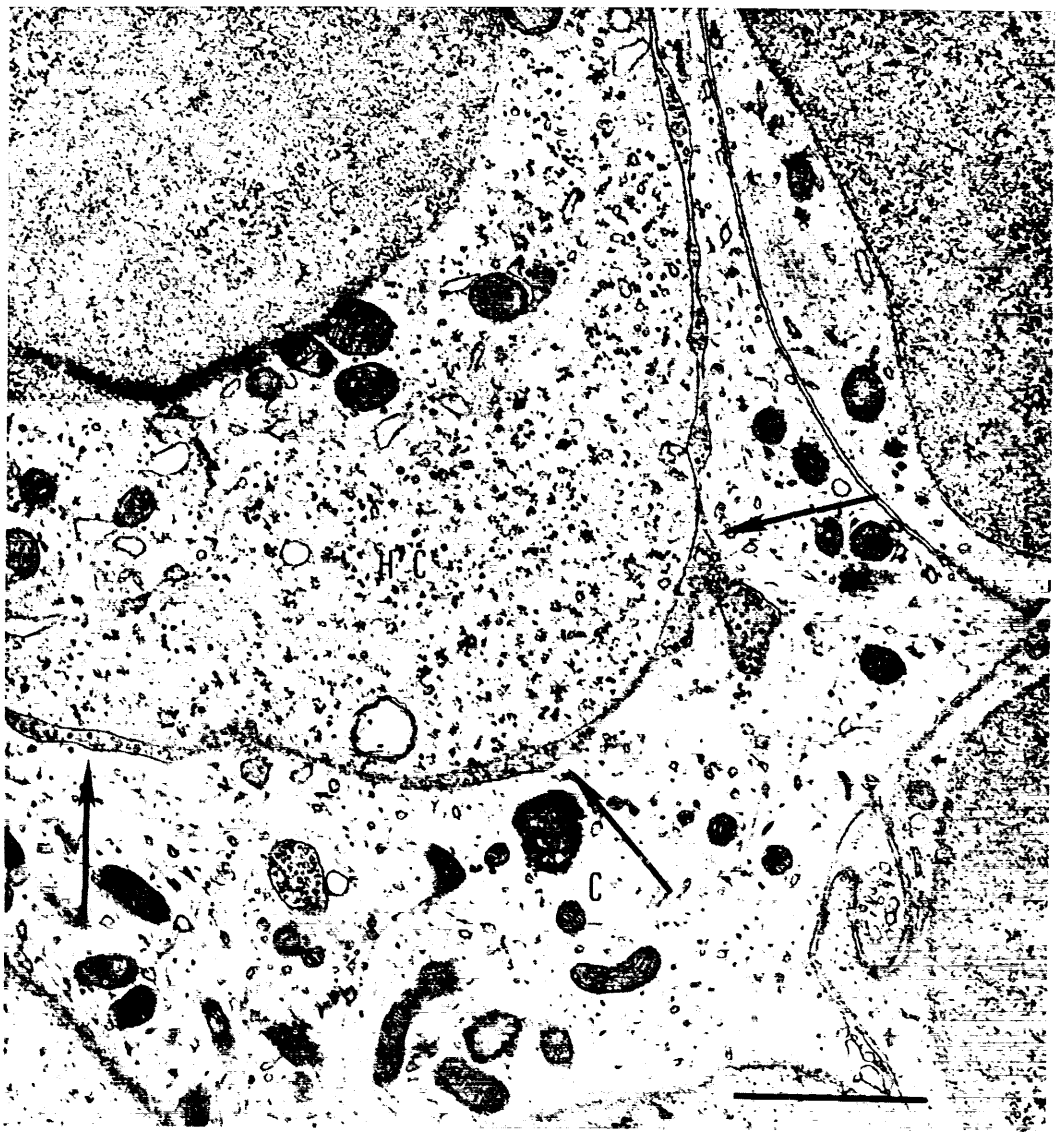

FIGURE 17.—*Macula sacculi, 8 days postoperative. The basal part of a hair cell* (HC) *with surrounding chalice terminal* (C). *Note the widened synaptic gap* (arrows) *with interposed small vesicles.*

FIGURE 18.—*Macula utriculi, 32 days postoperative. Hair cell* (HC) *with four boutons, one at left coming from a large nerve fiber* (N). *The bouton at right* (arrow) *is almost devoid of formed elements.*

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DISCUSSION

EAGER: By what criteria are you calling those light regions boutons?

SMITH: We do know these are nerve endings; they are very similar to the chalice nerve endings. They are similar in structure to other dendritic terminals, particularly in the cochlea. They do end as small boutons on the hair cell.

EAGER: I was curious because they are without vesicles.

SMITH: They contain only a few vesicles because they are not axons, but dendritic terminals.

TANG: Why did you not cut the section closer to the ganglion rather than so far inside that you left some tissues? There may have been some part left intact that might send some fibers which were not degenerated.

SMITH: The further the lesion was made from the ganglion, the less damage would be caused to the ganglion cells and their peripheral processes and terminals in the vestibule.

RASMUSSEN: If one made the lesions further laterally than we did, one would run the risk of causing trauma, possible interference with the blood supply to the vestibular ganglion which would seriously complicate interpretation of our experimental results.

MELVILL JONES: In your pictures of the vesiculated cells, all the vesicles seem to be nicely spherical. But I believe some individuals maintain that these really represent buddings off from tubular structures in truly presynaptic terminals. I wonder if you see any of these tubular structures? I did not notice any in your sections.

SMITH: Yes. This has been hypothesized from time to time. One sees no tubular structures in these nerve terminals themselves, but one sometimes can see them in the preterminal fiber, that is in the preterminal stalk. If some of these vesicles are broken off from the tubules, I do not know.

McDONALD: You mentioned that these ears were perfused, but I missed the type of perfusion fluid used. That would make a difference; if it is an aldehyde perfusion, particularly glutaraldehyde, the tubular structures come out more clearly.

Then the second question. Do you think the retraction of axons within the myelin sheaths is related to the preparative techniques?

SMITH: To answer the first question: the ears were perfused through the perilymphatic scalae with 1 percent osmic acid, while the animal was under anesthetic.

For the second question: axon retraction can be produced by faulty fixation, but the specimen illustrated was not fixation artifact. That particular axon was also filled with many mitochondria and dense bodies, characteristic features of axon degeneration. Other myelinated nerve fibers around it had a normal neuroplasmic content and no retraction from the myelin sheath.

HAWKINS: In some of your extraordinarily beautiful pictures, I thought I saw some altered mitochondria, just before the slides disintegrated, in the supporting cells and some unusually large cisternae in the hair cells. Were these the results of the denervation process?

SMITH: Were these in the experimental animals?

HAWKINS: Yes.

SMITH: Was it just in one or in all of them? If you remember, I said the one showed some artifact, and I did not know how to interpret that one.

HAWKINS: No. Several of the others.

SMITH: I have showed only those at 6 and 8 days. At this time there are some minor changes in the chalice nerves, and there may be some altered mitochondria in the chalice nerve because some early changes are evident.

HAWKINS: Were these in the cell bodies themselves?

SMITH: In the cell bodies.

HAWKINS: In the supporting cells and in the hair cells?

SMITH: One also sees some changes in the sensory cells. The crista from the animal sacrificed at 1 week showed changes in the sensory cells, but not particularly in the supporting cells. In the sensory cells, there were swollen mitochondria and also alterations in the lysosomes.

EAGER: I am sorry to go back to this problem of the terminal boutons.

SMITH: I did not know whether I understood your question in the beginning anyway and whether I answered it completely.

EAGER: Is it possible that the one species of bouton that you described, the one without vesicles, is rather a preterminal segment of axon rather than a true terminal bouton?

SMITH: It terminates on the hair cell.

EAGER: Without vesicles?

SMITH: It is a swelling and an enlargement; so I think it is not a preterminal axon. Did you mean the chalice, perchance? If you only see a part of the chalice, one might get this idea. No; the others are actually boutons and knob-like in character.

EAGER: But that is not always a justifiable criterion for calling it a bouton. What I am trying to obtain is some definition of bouton from a morphological standpoint. We tend to think of them as being occupied by vesicles.

SMITH: The only way in which you can be definitely certain would be to make certain serial sections and to follow it. Many of the vesiculated boutons, for example, are swellings and "boutons en passant," but these are on axons. This may be something of the sort you are talking about.

EAGER: Yes; I think that is perhaps what I am getting at.

SMITH: Many of the vesiculated endings are of this type. And if one follows them, it is evident that these are "boutons en passant" terminating on hair cells, terminating on chalices or on nerve fibers, but the other boutons which we believe belong to the vestibular nerve and which are like many other sensory boutons in that they do not contain many vesicles, are not boutons en passant. They are the typical swollen knoblike terminals ending on the hair cell. The criteria for a synapse of these sensory boutons would be membrane thickenings on both presynaptic and postsynaptic sides, and associated synaptic bar structures, besides the fact that they are terminal knobs. These are dendritic, not axon terminals.

EAGER: I should like to comment on the question raised about fixation and the forms of the vesicles one encounters. Recently at Yale, Dr. Fukami, working in the snake spinal cord, has found terminal boutons with a variety of elongated and rounded vesicle profiles and has asked the same question as to whether this might not be an artifact due to the glutaraldehyde perfusion which he was using at the time. So he ran a whole series of snakes perfused with osmium.

SMITH: These were all fixed with osmic acid; but I have used glutaraldehyde fixation also.

EAGER: Do you get the same picture?

SMITH: They are the same.

EAGER: Dr. Fukami gets absolutely the same picture. Following fixation with either glutaraldehyde or osmium, he has seen boutons side by side on a dendrite, one showing round vesicles and the other one showing elongated.

MONEY: Do you know of any species in which it would be possible to get a chronic animal with the efferents divided and the afferents not touched and the vestibular nuclei not damaged? Is this possible in any species?

SMITH: One could do this by making small lesions in various points where he believed the origin of the efferents to be in the brainstem.

MONEY: Are these lesions possible without going through the vestibular nuclei?

SMITH: Yes. This is what we almost accomplished by accident in one animal. That would be, I think, a better kind of lesion, particularly for the long-term animals, because then you would not get changes in the vestibular nerve which confuse the issue. All you would have is a more complete degeneration of the efferents.

MONEY: That one did have lesion in the lateral vestibular nucleus?

SMITH: Yes.

GERNANDT: Do you know by any chance how these vesicles discharge and how they become recharged again?

SMITH: I doubt if anyone really knows the answer to that question. In the cochlea I have seen "vesicular ghosts" that seem to be attached to the presynaptic membrane. I interpret these to be the remnants of vesicles which have discharged their contents on the presynaptic membrane. I doubt that the vesicles enter the synaptic gap, as has been sometimes hypothesized. They are probably "recharged" by an outward flow from the ganglion cell down through the axon to endings. Precisely where the vesicle itself is formed along this route, I do not know.

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Anatomical Evidence for an Efferent Vestibular Pathway

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SUMMARY

The pattern and distribution of the efferent vestibular innervation to the labyrinth are reviewed first as originally revealed by classical axon-degeneration techniques, Sudan black and the Nauta silver method. The histochemical method of AChE localization in efferent fibers was then used to demonstrate the system in an intact rather than a degenerated state. This enables one to form a better idea of the size and extent of the efferent fiber system. The origin of the efferent vestibular fibers is not entirely known, although some of the neurons appear to be located in the lateral vestibular nucleus. Precise termination is assumed to be on vestibular hair cells by small vesiculated endings, since the efferent cochlear fibers have been proven to terminate in the vesiculated endings on hair cells in the organ of Corti.

INTRODUCTION

During the last 10 years several studies have been reported representing direct or indirect evidence of an efferent nerve fiber system to the vestibular labyrinth (refs. 1–6). Increasing general acceptance of the concept of efferent (feedback) components in all sensory modalities has led to the current interest in this aspect of vestibular physiology.

The author had the good fortune to have been associated with G. L. Rasmussen in the early years of this interest in the vestibular efferent system. It was at this time that the first direct neuroanatomical evidence of the existence of this system (using Sudan black B) was reported from his laboratory.

This report reviews the direct demonstration of the efferent fiber system to the vestibular end organs of the cat by three techniques. The Sudan black and Nauta techniques are briefly discussed because it was by these time-tested classical methods that the course of the efferent neuron was first revealed. A newer method using acetylcholinesterase (AChE) in these fibers is presented in this report which confirms this very same pathway.

TECHNIQUES

Figure 1 summarizes the course and distribution of vestibular efferent fibers as demonstrated by axon-degeneration methods following transection of the vestibular root. These efferents travel along with the efferent cochlear fibers (refs. 7 and 8) within the vestibular root and nerve up to the area of the vestibular ganglion. Here the efferent cochlear fibers leave the vestibular nerve as the vestibulocochlear anastomosis to enter the cochlea. The vestibular efferent fibers diverge and disperse into the various vestibular nerve branches. Those of saccular and posterior semicircular canal nerves enter these nerves as scattered individual fibers which are evenly distributed among the afferent fibers. The efferent supply to the end organs of the superior division of the vestibular nerve leave the parent efferent bundle as several fascicles of fibers to travel in the proximal portion of the superior division. As these course distally in the division they break up into individual fibers in the nerve rami of the superior division; namely, the utricular nerve and the branches to the superior and the horizontal semicircular canal cristae. This system of fibers is thus more or less evenly

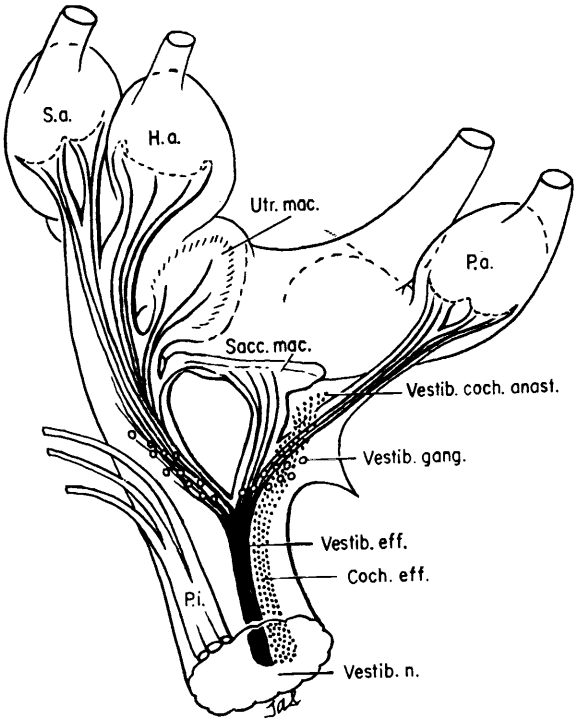

FIGURE 1.—*Diagram of the vestibular nerve and branches illustrating the course and distribution of the efferent vestibular fibers.*

distributed to all the vestibular end organs.

The Sudan black technique (Rasmussen) was originally used to demonstrate this pattern of axonal degeneration following brainstem lesions. The entire efferent vestibular system can be interrupted by transection of the vestibular root dorsolateral to the descending tract of the trigeminal nerve (fig. 2). After appropriate survival time for Wallerian degeneration (approximately 6–8 days), the cat is sacrificed by intravital perfusion with 10 percent formalin and the petrous bones with the labyrinthine nerve supply removed. These specimens are then stained in toto with Sudan black, decalcified, and the membranous labyrinth with its nerve supply dissected out under the operating microscope. Individual nerve branches can then be cut away from the specimen and embedded separately so that sections parallel to the nerve fibers can be made. In this way, the products of Wallerian degeneration can be best demonstrated in each nerve branch of the specimen. This technique, of course, demonstrates only myelinated fibers.

FIGURE 2.—*Photomicrograph of the cat brainstem showing a typical lesion* (arrow) *transecting the vestibular root.* CN, *cochlear nucleus;* VEST, *vestibular root;* V, *descending trigeminal root;* VII, *facial nerve. Sudan Black B stain.*

The same pattern of degeneration is revealed with a silver technique, the Nauta method (refs. 9 and 10), following vestibular root transection. Although generally used on central-nervous-system tissue to impregnate degenerating axons selectively, the method can be adapted for use on the nerve supply to the labyrinth. Since decalcification must be avoided to effect this technique, the vestibular nerve trunks and peripheral branches are dissected out of the undecalcified petrous bone by means of a dental drill and fine bone cutters. These nerve segments can then be embedded in gelatin and frozen sections cut. The gelatin is dissolved off and the nerve sections can be run through the usual Nauta technique.

Although there is some artifact from staining of normal fibers and Schwann cell nuclei, such sections are very useful in demonstrating the degenerating efferent fibers to the vestibular end organs. Although this silver method demonstrates the nonmyelinated portions of the degenerating axons, the number of fibers appeared only slightly increased over the number revealed with the Sudan black method. Moreover, with both methods it was more difficult to identify degenerating fibers as they traveled distally in the vestibular branches toward the

end organs. Presumably, this was related to the decrease in fiber diameter in this direction.

More recently, the histochemical method demonstrating AChE activity has been used to study the efferent system (refs. 11–13). In this study the acetylthiocholine iodide method (Gomori) was used on frozen sections cut from the entire petrous bone which had been decalcified in cold ethylenediamine tetracetate (EDTA). These bones were removed from cats, which had been sacrificed by an overdose of Nembutal, and were immediately placed in the cold EDTA. It was necessary to keep the cat petrous bone in the solution for about 40 days before decalcification was complete. Frozen sections were then cut at 20 microns in a cryostat and the sections mounted. These were then incubated according to the Gomori method. The technique is presented in detail elsewhere (refs. 14 and 15).

Control sections to rule out nonspecific reaction were incubated in a solution from which acetylthiocholine iodide was omitted but were otherwise treated identically. In some instances sections were preincubated in eserine (concentration 10^{-6} *M*) as a specific inhibitor of AChE activity.

In the normal cat ear this method selectively and clearly demonstrated the efferent fiber system to both the auditory and vestibular labyrinth. The pattern and distribution coincided with that revealed originally with the axon-degeneration methods (Sudan black and Nauta). With this method, however, the fiber system was depicted in an intact rather than degenerated state. In figure 3, which is a cross section of the VIIth and VIIIth nerves in the internal auditory canal, the combined vestibular and cochlear efferent systems are seen in the center of the vestibular nerve trunk proximal to the vestibular ganglion. As more peripheral sections are viewed, the efferent fibers to different end organs diverge from the parent efferent bundle and enter their respective nerve branches. Those vestibular efferents which innervate the posterior semicircular canal leave the common efferent bundle and course in the singular nerve as scattered individual fibers (fig. 4). Likewise, those efferents going to the saccule emerge and travel in the saccular nerve as scattered individual efferent fibers (fig. 5).

The vestibular efferents supplying the end organs of the superior vestibular division, however, split off as several fascicles of fibers which occupy a fairly localized position in the superior

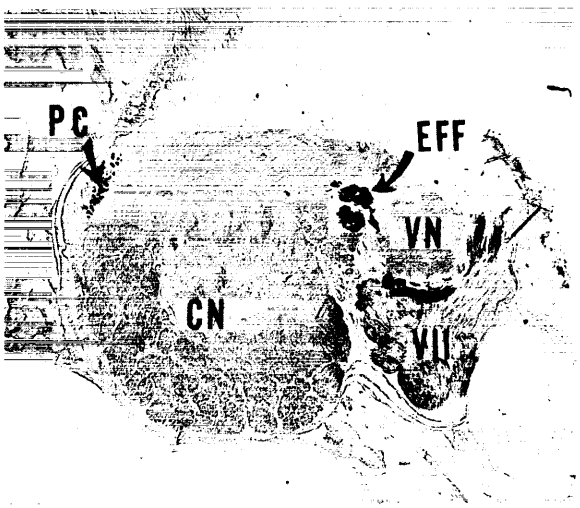

FIGURE 3.—*Photomicrograph of cross section of the nerves in the internal auditory canal of normal cat showing AChE localization in efferent fibers.* EFF, *parent bundle of cochlear and vestibular efferents coursing in the vestibular nerve* (VN); CN, *cochlear nerve;* PC, *portion of ganglion and nerve to posterior semicircular canal;* VII, *facial nerve.*

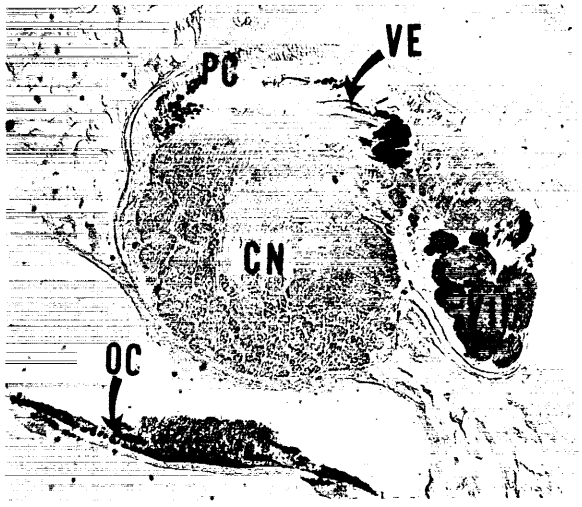

FIGURE 4.—*Photomicrograph more distally through nerves in internal auditory canal. Vestibular efferents* (VE) *to posterior canal nerve* (PC) *are beginning to split off from the parent efferent bundle.* OC, *intraganglionic portion of olivocochlear bundle;* CN, *cochlear nerve;* VII, *facial nerve.*

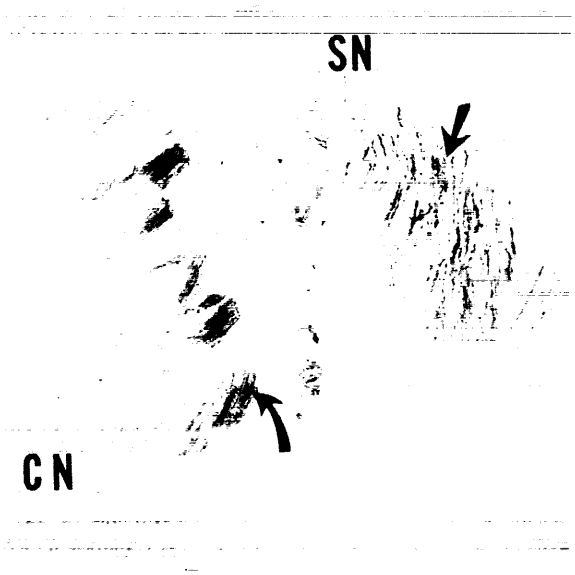

FIGURE 5.—*High-power photomicrograph showing vestibular efferents* (top arrow) *in saccular nerve* (SN). *Some branching of efferent fibers can be seen in saccular nerve. Several fascicles of cochlear efferent fibers* (bottom arrow) *coursing with basal turn cochlear nerve afferent fibers* (CN) *are also seen.*

vestibular division; that is, in that portion of the nerve nearest the membranous labyrinth (figs. 6 and 7). These bundles gradually break up into the individual fibers that then are evenly dispersed and distributed to the end organs

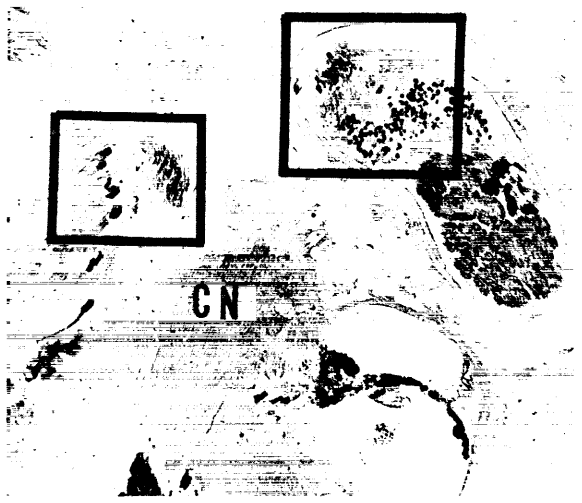

FIGURE 6.—*Photomicrograph through cochlea and superior vestibular division. Blocked out area at upper right is shown as figure 7 and area at upper left is figure 5.* CN, *cochlear nerve.*

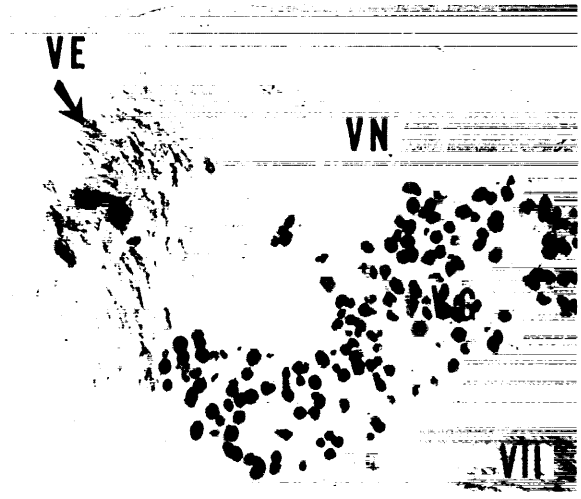

FIGURE 7.—*High-power photomicrograph showing vestibular efferent fibers* (VE) *traveling in medial portion of the superior division of vestibular nerve* (VN). VG, *vestibular ganglion;* VII, *VIIth facial nerve.*

supplied by the superior vestibular division (fig. 8).

Although the pattern and distribution of the efferent system as revealed by this histochemical technique were identical to those shown by the classical axon-degeneration techniques, experimental proof of their central origin is necessary.

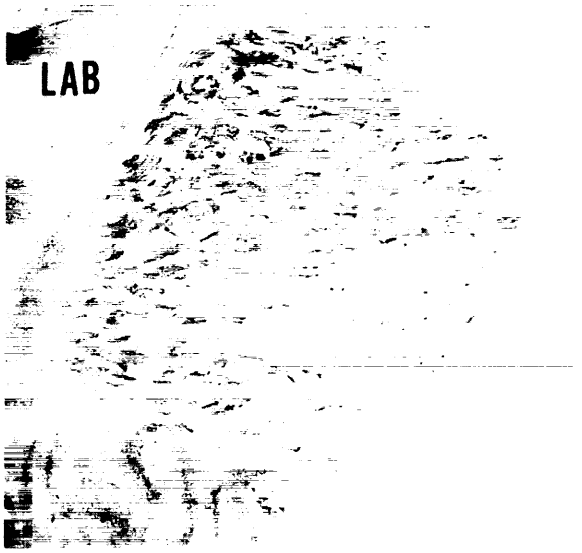

FIGURE 8.—*High-power photomicrograph of AChE activity in scattered efferents in very distal portion of superior vestibular division. Note how efferents remain in portion of nerve related to labyrinth* (LAB) *but gradually have become more scattered than in figure 7.*

FIGURE 9.—*Cat brainstem showing lesion transecting vestibular root* (arrows) *6 weeks previously.* VEST, *vestibular root;* CN, *cochlear nucleus;* SO, *superior olive;* V, *descending trigeminal root;* VII, *VIIth facial nerve.*

Such proof is obtained when unilateral vestibular root transection is performed to cause degeneration of the vestibular efferent system to one labyrinth (fig. 9). After appropriate survival times of 1 to 3 weeks, the animal is sacrificed by decapitation, and the brainstem and both petrous bones are placed in cold EDTA. The process as described earlier is carried out, and sections of both labyrinths are examined. The unoperated or control side shows normal AChE activity in the efferent fibers throughout the labyrinth. However, in the vestibular nerve and branches of the operated side, no AChE activity can be seen because the efferent fibers are completely degenerated (figs. 10–13).

It is readily apparent from the vestibular efferent system as demonstrated by this technique that there are slightly more efferent fibers than was demonstrated by the axon-degeneration techniques. It is also apparent from close examination of the vestibular rami that these efferent fibers branch as they reach the more distal portions of the nerve going to each end organ, and that in so doing their diameters decrease as they approach the end organ.

With all techniques used to demonstrate the efferent system, it is possible to trace these fibers to the basement membrane of the neuroepithelium in the end organ. The precise termination cannot be determined with any light microscopy method.

Under the electron microscope, small vesiculated nerve endings have been described around the hair cells or afferent nerve endings by several investigators (refs. 16–18). Similar vesiculated endings in the organ of Corti have been clearly shown to be the terminals of the efferent cochlear fibers (refs. 19–22). It is reasonable to assume that the same relationship holds true for the efferent vestibular system.

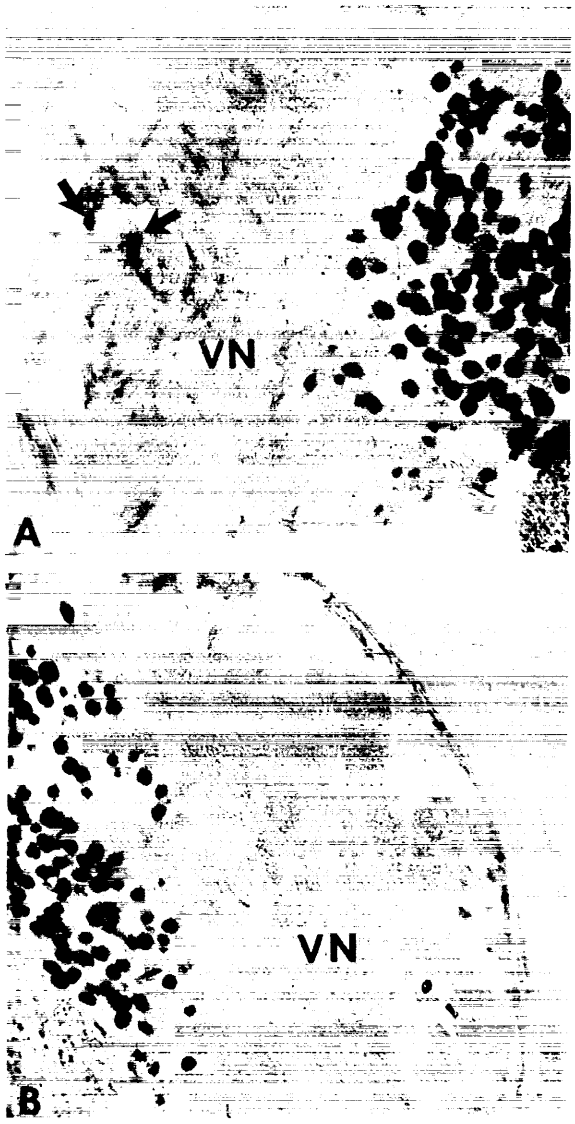

FIGURE 10.—(A) *Normal or control side of animal shown in figure 9. Normal AChE activity in efferent fibers in superior vestibular nerve* (VN). *Compare with figure 7.* (B) *Operated side of same animal. Note complete loss of efferent fibers of superior division.*

FIGURE 11.—(A) *Distal portion of superior vestibular nerve of control side in animal shown in figure 9. Normal complement of efferent fibers* (arrow). (B) *Comparable section through distal superior vestibular divisions of operated side showing complete loss of efferents as indicated by loss of AChE activity.*

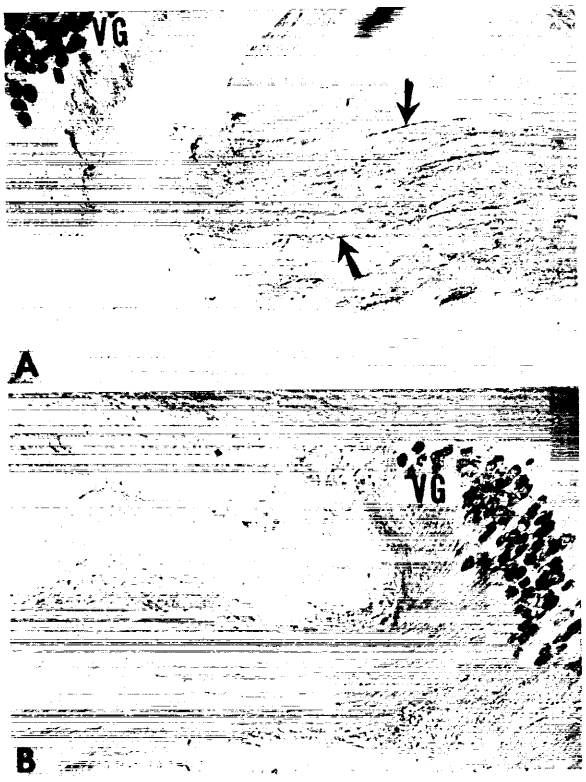

FIGURE 12.—(A) *Nerve to posterior semicircular canal showing normal AChE activity in efferent fibers* (arrows) *of normal side.* VG, *vestibular ganglion.* (B) *Posterior canal nerve of operated side showing complete loss of efferent fibers.*

CONCLUDING REMARKS

Comments on the site of origin of these vestibular efferents must be limited to information obtained from the results of degeneration from various lesions in the vestibular complex. Specific information has continued to be an unsolved problem in my experience.

Numerous experiments using the method of retrograde cell changes (ref. 23) following vestibular nerve section in very young kittens have failed to reveal unequivocal evidence of retrograde cyton reaction. The difficulty in determining such changes in small- and medium-sized neurons is well known.

A second method using the fact that injured neurons take up much greater amounts of methionine than normal cells was also employed using S^{35}-labeled methionine. This was injected into cats following labyrinthectomy, and autoradiographs were obtained after varying intervals.

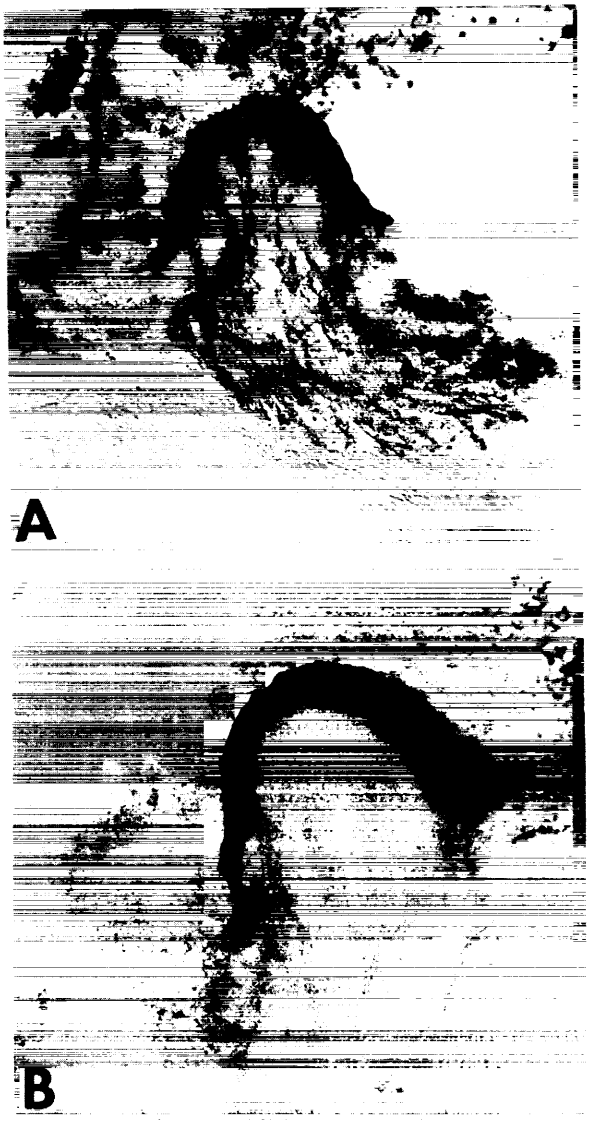

FIGURE 13.—(A) *Efferent fibers approaching crista of posterior semicircular canal on normal side, same cat as figure 9.* (B) *Crista of posterior canal on operated side showing loss of efferent fibers.*

Again, no definitely significant increase in uptake was noted in any cells or cell group.

From the various locations of lesions in the brainstem and the resulting degeneration of the efferent system, some areas in the vestibular nuclei complex have been ruled out as a source of efferents, while others remain good possibilities. Lesions of the superior vestibular nucleus, dorsal part of the medial vestibular nucleus, and cerebellum have failed to produce such degeneration in the vestibular nerve com-

plex. Lesions in the lateral vestibular nucleus do result in efferent fiber degeneration but cannot account for all the efferent component. It is very possible that other nearby sources such as the descending vestibular nucleus and reticular formation may contain some of these efferent neurons. Discrete lesions in these areas will yield helpful information on this point. I definitely feel that more reliable data on the origin of the efferent vestibular system will be obtained by correlating the resulting peripheral degeneration (perhaps as revealed by the histochemical method) with small localized lesions in the brainstem.

The function of the efferent vestibular system, as with efferent systems to other sense organs, is unknown. Current theories on its role are still purely speculation. Good data are available on efferents to other organs, for example, the cochlea, to show that such a system can exert an inhibitory effect on electrical phenomena at the sensory epithelium (refs. 24–26). Even in the auditory sense organ where most of the neurophysiological work has been conducted and where the precise anatomical connections of not only the peripheral efferent neuron but also of the entire descending chain are well known, the role of the efferent cochlear bundle in hearing is still speculative.

In the vestibular system, where the exact origin of the efferent component is not clear and where it is difficult to study the effects neurophysiologically of selectively stimulating or cutting the efferent system because they travel together in the vestibular nerve, there is less clear-cut evidence of the action of such a system. Function in vestibular mechanism is even more speculative here.

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DISCUSSION

JOHNSON: Two significant animal experiments have been reported which establish the presence of these efferent components of the eighth cranial nerve. Smith using the frog and Henriksson using the guinea pig as experimental animals were able to pick up nerve impulse potentials from the central end of the cut nerve when the contralateral end organ was stimulated.

GACEK: I might make a comment on the question posed to Dr. Smith in the earlier session. I cannot think of any way you could selectively transect or interrupt the efferent fibers without damaging the afferent fibers at this point, unless there is a far-removed nucleus giving origin to this bundle.

MONEY: Did you happen to see in your frozen sections of cat temporal bones whether the cupulae were well preserved? The second question: Would your technique show any occasional cell bodies in the posterior canal nerve, and did you happen to see any?

GACEK: In answer to the first question; no, the cupula was not well preserved. As far as ganglion cell bodies in the posterior canal or any of the nerves are concerned, I think they would show up very nicely if they were there scattered along the nerve. As you see, they stand out very prominently with this method.

EAGER: What concentrations of eserine were effective in blocking?

GACEK: The concentration was 10^{-6} *M*.

EAGER: So it was very low. I must congratulate you on this lovely demonstration. We have been looking at acetylcholinesterase activity in the cerebellar nuclei following cerebellar cortical lesions, rather massive lesions, and we find the opposite kind of picture; that is, no depletion of the esterase activity. It may be that these are not cholinergic pathways or that in this particular system the esterase stays around for a long period of time.

FERNÁNDEZ: Do you have an estimate of the number of vestibular fibers?

GACEK: When I had the good fortune to be associated with Dr. Rasmussen, I estimated the efferent fiber component to be about 200. When I first saw this material with the acetylcholinesterase method, I thought they were far greater in number. But now I think I was too generous, because in some of these fibers in horizontal section, not in cross section, I can see branching in some of them as they course out the nerve branches. To get an accurate estimate of the actual number of fibers, and not of collaterals near the end organ, I think I would probably have to count it in the vestibular nerve, where they are associated with the efferent cochlear bundle. So I think it is probably 200 or a little higher; that figure is probably more correct.

DAVEY: Can you give us an estimate of the ratio of these fibers to afferent fibers in the vestibular nerve?

GACEK: In the cat there are approximately 12 000 afferent fibers, myelinated fibers.

HAWKINS: Are all these fibers that show acetylcholinesterase activity myelinated fibers? Second, if they are myelinated fibers, where do they lose their myelin? Do they keep it all the way to the basement membrane?

GACEK: I do not know if they are all myelinated or not. The activity, of course, in cross section stands out as a solid dot rather than a ring. So I assume that the activity is more in the axon.

TOROK: Is there any advancement in the concept of the function of the efferent innervation of the vestibular system?

GACEK: I cannot answer that because there has been no convincing evidence of the nature of this efferent function.

GRAYBIEL: What are the relative numbers going to the macula of the utricle and the saccule?

GACEK: As compared to the canals?

GRAYBIEL: No; just the relative numbers, let us say, between these two otolith organs. Does one have a greater supply of the efferent fibers than the other?

GACEK: Yes; I think the utricular macula does. It is a larger nerve to begin with.

GRAYBIEL: Relative to their size then?

GACEK: Well, then, probably not.

GUALTIEROTTI: Do you have any evidence of the possible different kinds of efferent systems coming from a lateral branch of the sensory fibers like the one described in the *Limulus* retina? We have some physiological evidence that, in frogs, there is some inhibitory effect similar to the one found in the *Limulus* by Hartline and Ratliff. Also, what do you think is the physiological function of the efferent system here described?

GACEK: Your first question was whether there is any possibility of this efferent originating near the sulcus limitans, did you say?

GUALTIEROTTI: Besides the bundle coming from the centers of the system, is there any evidence of efferents originating as lateral branches of the sensory fibers?

GACEK: I am not clear on your question; I am sorry.

GUALTIEROTTI: Do you know the anatomical distribution of lateral inhibition in the horseshoe crab retina?

GACEK: No.

GUALTIEROTTI: Hartline and Ratliff described branches coming from some of the main afferents and reaching the body of the sensory cells or the terminals of the sensory fibers. They seem to be an inhibitory system. I think Dr. Smith can better answer this question. Do you have any evidence that there is a system like that in the cat vestibule?

SMITH: No. I do not have any evidence for the type of lateral inhibition as there is in the eye of *Limulus*.

GUALTIEROTTI: Do you have evidence that that is not the case?

SMITH: This might be accomplished by the "boutons en passant," because they are synapsing with different kinds of neural structures. I think possibly this type of a physiological activity could be set up by the efferent system.

GUALTIEROTTI: You mention the fact that together with the degeneration of the efferents you also observed some initial degeneration of the afferent fibers.

SMITH: Yes.

GUALTIEROTTI: If this is the case, it might be that some of the degeneration of the efferents is due to previous degeneration of the afferent fibers from which they branch out.

SMITH: This is doubtful, because the axon processes will degenerate before retrograde degeneration would occur in the vestibular dendrites.

Central Projections to the Vestibular Receptors

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SUMMARY

The efferent innervation of the vestibular receptors is discussed in the light of data from the literature and of the author's experimental findings.

INTRODUCTION

The study of the efferent innervation of the vestibular receptors has been approached from a very different angle from that of the study of the cochlear receptors. For the latter, the existence of the direct and the crossed olivocochlear bundles, proved by Rasmussen (refs. 1–5) between 1942 and 1960, has always constituted the point of departure for subsequent researches. For the vestibular receptors, on the other hand, the existence of an efferent innervation was at first deduced, as a working hypothesis, as well as from the close embryological, morphological, and topographical analogies existing between these and cochlear receptors, above all from the electron-microscopic features of the cupular and ampullary receptors.

In the case of the cochlear receptors, the aim was to describe the endings in the organ of Corti of the anatomically proved olivocochlear fibers, while for the vestibular receptors an attempt was made to establish whether the various characteristics of the nerve endings in the neuroepithelium were connected with a double innervation, afferent and efferent, of the receptor itself.

Many of the data concerning the efferent innervation of the cochlear receptors can be considered as definitely established. As regards the vestibular receptors, we are still awaiting further research to supply us with the elements still lacking before we can establish the existence of the identity between the efferent innervation of the cochlear and of the vestibular receptors.

ELECTRON - MICROSCOPIC FEATURES OF THE VESTIBULAR RECEPTORS AND ACETYLCHOLINESTERASE (AChE) ACTIVITY IN THE CRISTAE AND MACULAE

The studies of Wersäll (refs. 6 and 7) on the crista ampullaris of the guinea pig, the cat, and the rat, and those of Smith (ref. 8) on the utricle of the guinea pig, have proved the existence of two types of hair cells.

The vestibular sensory cells of type I, according to Wersäll (ref. 7), have a typical flask-shaped form and are almost totally enclosed in goblet-shaped nerve chalices (fig. 1). According to Engström (ref. 9), each chalice usually contains only one sensory cell, but in the utricular and saccular maculae there may be found several chalices which contain two, three, or even four sensory cells. The nerve chalice, which is formed by medium-sized-or-thicker fibers of the vestibular nerve (ref. 10), contains several synaptic vesicles only in its apical part (refs. 7 and 8). This is in agreement with Smith's hypothesis (ref. 8) that only the uppermost portion of the chalice represents the actual synapse

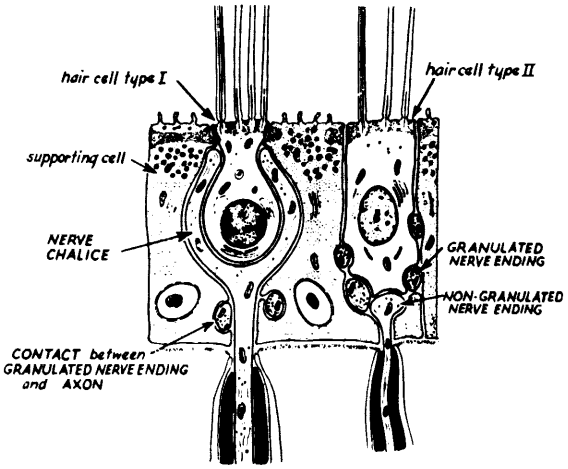

FIGURE 1.—*Schematic drawing of the hair cells in the vestibular sensory epithelium as it appears in the cat, guinea pig, and rat. (From ref. 10.)*

in the contact between the nerve ending and the sensory cell. The nerve chalice is surrounded by a plasma membrane separated from that of the hair cell by a synaptic space of about 150 Å (ref. 11). On the outside of the nerve chalice or the branch forming the chalice, there are always one or more "much granulated" nerve endings in synaptic contact with the chalice (ref. 12).

The vestibular sensory cells of type II, according to Wersäll (ref. 7), are cylindrical with a rounded base (fig. 1). They are surrounded in their infranuclear region by typical synaptic endings of two kinds. The larger number is of postsynaptic nature, but there are also several "much granulated" nerve endings containing large amounts of synaptic vesicles (refs. 7, 9, 10, and 12) with diameters of 200 to 400 Å, according to Wersäll (ref. 7), or of 300 to 1200 Å, according to Iurato and Taidelli (ref. 13), embedded in a sparse intermediate substance containing numerous mitochondria (ref. 13).

The synaptic bar was found only in the cellular areas of contact with the nerve endings of postsynaptic nature of both types of the vestibular sensory cells (refs. 14 and 15).

According to Engström (ref. 9), the majority of the vestibular sensory cells are of Wersäll type I and type II. However, one can find a few cells which represent a middle stage between types I and II. These cells are innervated by several small knob-shaped endings, which may be of either "much granulated" or "less granulated" variety, but there are also "less granulated" endings very much resembling one-half of a chalice. The form of these cells may represent a developmental stage between type II and type I, since in the more primitive animal species only cells of type II can be found (refs. 16–18).

According to Iurato and Taidelli (ref. 13), the "much granulated" nerve endings have a typical synaptic structure, as Engström (ref. 19) first observed, and are dilated synaptic areas alternating with thin presynaptic axonal pieces at distances from 0.5 to 4 microns. Each presynaptic fiber can have several synapses with the same "less granulated" nerve chalice as well as with large nerve fibers or vestibular cells of type II (fig. 2). The large majority of the "much granulated" nerve endings in the crista ampullaris of the rat are not true nerve endings; that is, boutons terminaux at the tips of axons, but dilated

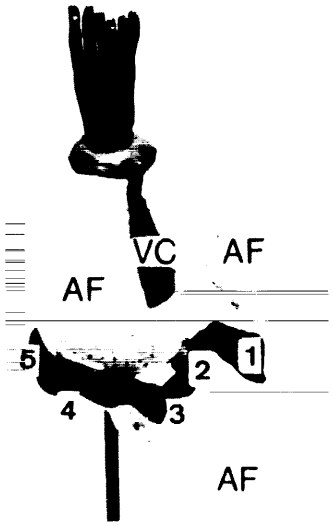

FIGURE 2.—*Three-dimensional reconstruction illustrating the relationships analyzed in a series of 17 sections. A presynaptic fiber shows five synaptic enlargements which are in contact, respectively,* (1) *with an afferent fiber* (AF); (2, 4, 5) *with the "less granulated" nerve chalice* (AF) *of a type I vestibular cell* (VC); (3) *and with a vestibular cell of type II. The reconstruction of the upper part of the "less granulated" nerve chalice was made by free hand. (From ref. 13.)*

synaptic areas, that is, boutons en passant along presynaptic fibers (ref. 13).

The existence of nerve fibers which exhibit AChE activity beneath the neuroepithelium of the semicircular canals and utricle of the pigeon was demonstrated for the first time by Dohlman et al. (ref. 20). These fibers were seen only in the parts of the membranous labyrinth where sensory epithelium is found. For this reason and because of their particularly intense AChE activity, the hypothesis was postulated that they were efferent cholinergic fibers (refs. 20 and 21).

The results of this research were confirmed by Ireland and Farkashidy (ref. 22), Rossi and Cortesina (refs. 23–25), Nomura et al. (ref. 26), Gacek et al. (ref. 27), and Vinnikov et al. (ref. 28). The researches of these authors have proved, moreover, the existence of fibers exhibiting AChE activity in the terminal tracts of the vestibular branch of the VIIIth nerve (fig. 3). This enzyme activity, according to Rossi's (ref. 29) research carried out in the guinea pig, is not present in the fetus, but appears only after birth.

The electron-microscopic research of Hilding and Wersäll (ref. 30) demonstrated the exact locality of the AChE activity in the vestibular sensory epithelia of the albino guinea pig. This enzyme activity is contained in the "much granulated" nerve endings on the outside of the nerve chalices of the hair cells type I and at the bottom of the hair cells type II.

FIGURE 3.—*Fibers positive to the Koelle and Friedenwald test for AChE in a peripheral rami of the vestibular branch of the VIIIth nerve. (Guinea pig; Koelle and Friedenwald, 70×.) (From the Journal of Laryngology and Otology, ref. 24.)*

The research of Ireland and Farkashidy (ref. 22), Rossi and Cortesina (refs. 23–25), and Gacek et al. (ref. 27) have also shown that when the efferent vestibular fibers are cut on the floor of the fourth ventricle (refs. 23–25) (fig. 4) or when the auditory nerve is cut, but the blood supply of the labyrinth is not disturbed (refs. 22 and 27), the AChE activity disappears

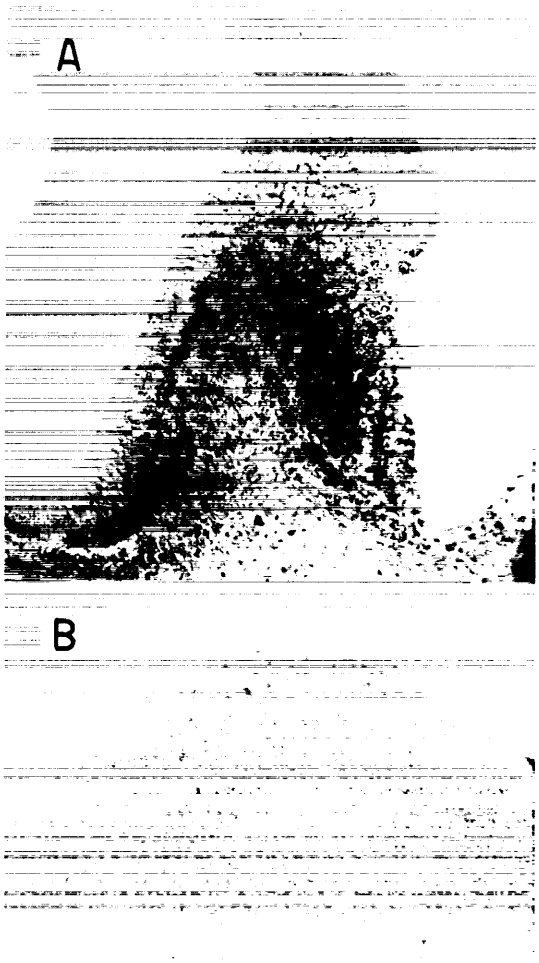

FIGURE 4.—*The two photomicrographs show, respectively, the left and right posterior labyrinths of the same animal, on which a sagittal incision was made in the lateral angle of the floor of the fourth ventricle, 4 days before it was killed. In* (A) *(labyrinth contralateral to the lesion) the crista ampullaris of the lateral semicircular canal appears markedly positive to the Koelle and Friedenwald test for AChE. In* (B) *(labyrinth ipsilateral to the lesion) the positivity of this side has completely disappeared. (Guinea pig; Koelle and Friedenwald, 90×.) (From the Journal of Laryngology and Otology, ref. 24.)*

from the otherwise intact peripheral vestibular receptors.

THE EFFERENT VESTIBULAR FIBERS

The existence of two types of nerve endings in the vestibular neuroepithelium has naturally raised the question of their function. In 1958, in a critical summary of the results of the electron-microscopic studies, Engström (ref. 19) put forward the hypothesis that the "much granulated" nerve endings with presynaptic morphological features belonged to a system of efferent fibers, while the "less granulated" nerve endings represented the terminal arborizations of the afferent dendrite.

The possibility that the vestibular receptors were also supplied with a double innervation, afferent and efferent, therefore seemed to be supported, at least as a hypothesis, by important, even though indirect, factors.

Actually the existence in the vestibular nerve of centrifugal fibers had been announced many years ago, but a critical evaluation of the results of the research of Bishoff (ref. 31) and of Lewandowsky (ref. 32) enables us to maintain that the fibers described by these authors, owing to their course and topographical relations, very probably belong to the system of the efferent cochlear fibers.

The papers of Leidler (refs. 33 and 34) and of Van Gehuchten (ref. 35) give us more significant data. Leidler observed in the rabbit the existence of a small bundle of fibers which degenerated after the destruction of the reticular formation near the median raphe, but which did not degenerate after the vestibular nerve had been cut. Some years later, Van Gehuchten confirmed in the rabbit the existence of a group of efferent vestibular fibers, part direct and part crossed, originating from cells in the reticular formation on both sides of the median raphe, at the level where the root of the Vth nerve enters the medulla.

The researches of Leidler and Van Gehuchten concern exclusively the existence of the efferent vestibular fibers in the brainstem, but the first demonstration of the existence of efferent fibers which reach the vestibular receptors was reported in a short paper delivered by Petroff (ref. 36) to the 68th annual session of the American Association of Anatomists. After observing a system of very thin nerve fibers near the neuroepithelium of the posterior labyrinth, Petroff carried out a series of experiments on the cat and monkey. In some animals he transected the VIIIth nerve and in others made an incision on the median line of the floor of the fourth ventricle. In both cases he noted the disappearance of thin nerve fibers. This disappearance was bilateral in the animals on which sagittal section of the floor of the fourth ventricle had been carried out; therefore, Petroff assumed that these fibers were crossed.

Rasmussen and Gacek (refs. 37 and 38) took up where Petroff left off, using cats and chinchillas for their experiments. In some cases they studied the Wallerian degeneration of the nerve fibers after electrolytically destroying small areas of the medulla corresponding to the sides of the various vestibular nuclei. In others, Wallerian degeneration was studied after a sagittal incision had been made in the floor of the fourth ventricle, at various points, depending on the particular cases: on the median line, at the level of the geniculum of the facial nerve; near the sulcus limitans, at the level of the vestibular nerve just before its emergence from the medulla.

Gacek (ref. 38) found degenerated fibers in the vestibular branch of the VIIIth nerve only in animals in which electrolytic destruction of an area of the medulla containing the lateral vestibular nucleus had been carried out and in animals in which the vestibular nerve had been transected before its apparent origin. Gacek was unable to corroborate the findings of Petroff as to the crossed course of these fibers; therefore, he regards them as uncrossed and suggests that "the lateral vestibular nucleus [is] the probable source of the efferent vestibular component" (ref. 38, p. 281). The results obtained with the method of retrograde-cell change after unilateral labyrinthectomy did not provide Gacek with any definitive information as to the origin of the efferent vestibular fibers.

Almost contemporaneously with the publication of the reports by Rasmussen and Gacek (ref. 37) and Gacek (ref. 38), Carpenter et al. (ref. 39) and Carpenter (ref. 40) announced the

results of a series of studies on the cat, carried out by means of the method of retrograde cell change after unilateral labyrinthectomy, and on the monkey after transection of the VIIth and VIIIth nerves. On the basis of their results, Carpenter et al. and Carpenter maintained that the fastigial nucleus, the medial vestibular nucleus, the superior vestibular nucleus, and a part of the inferior vestibular nucleus gave rise to efferent fibers connected with the vestibular nerve. They suggest that most of the fibers originating from the fastigial nucleus are crossed, while the fibers originating from the previously mentioned vestibular nuclei were for the most part uncrossed.

A systematic study of the central projections on the vestibular receptors has been carried out by Rossi and Cortesina (refs. 23–25) in the guinea pig and rabbit, using neuroanatomical and histochemical techniques. The efferent cochlear fibers are positive to the Koelle and Friedenwald (ref. 41) test for AChE, while the afferent ones are negative; this observation made by Rossi (ref. 42) in 1960 formed the point of departure for this research. This research was based also on the demonstration of the existence of Koelle and Friedenwald-positive fibers in the vestibular branch of the VIIIth nerve (refs. 23 and 29) as well as on the deduction that the AChE activity in the cristae and maculae must be related to a system of efferent fibers because it disappears when the vestibular branch of the VIIIth nerve has been cut (refs. 22 and 23).

The medulla oblongata of the guinea pig and rabbit was studied in sections submitted to the Koelle and Friedenwald (ref. 41) test for AChE, in Nissl stained sections, and in sections submitted to Cajal's reduced silver method of impregnation. Retrograde cell changes were also studied in guinea pig after intracranial section of the right VIIIth nerve and in the rabbit after electrocoagulation of the right vestibule and semicircular canals. The changes in the AChE activity in the membranous labyrinth caused by section of the vestibular nerve before its emergence from the medulla were also studied.

This research has allowed Rossi and Cortesina (refs. 23–25) to demonstrate the existence of two bundles of efferent fibers connecting the oblongata to the vestibular receptors. The first of these two bundles arises from a small nucleus first discovered during these studies on the guinea pig and rabbit (refs. 23–25) (fig. 5). This nucleus is composed of about 120 to 170 cells, some of small diameter, others larger and multipolar, the latter predominating. This nucleus is situated dorsally and medially to the most cranial part of the inferior vestibular nucleus and ventrally to the most caudal part of the lateral vestibular nucleus (figs. 6 and 7). It is additional to the four main vestibular nuclei and to the various cell groups related topographically to them. By reason of its position, Rossi and Cortesina termed it the "interposed vestibular nucleus." The hitherto unreported efferent bundle which arises from this nucleus (fig. 8) has been called by Rossi and Cortesina "direct ventral efferent vestibular

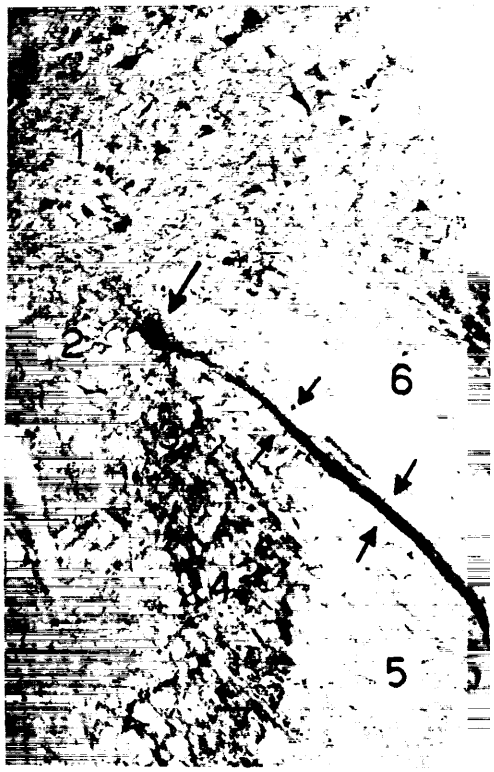

FIGURE 5.—(1) *Ventral part of the lateral vestibular nucleus;* (3) *inferior vestibular nucleus;* (4) *nucleus of descending root of the Vth nerve;* (5) *descending root of the Vth nerve; and* (6) *vestibular nerve. At* (2) *can be seen the "interposed vestibular nucleus" which gives rise to the "direct ventral efferent vestibular bundle" indicated by the arrows. (Guinea pig; Koelle and Friedenwald, 45×.) (From the Journal of Laryngology and Otology, ref. 24.)*

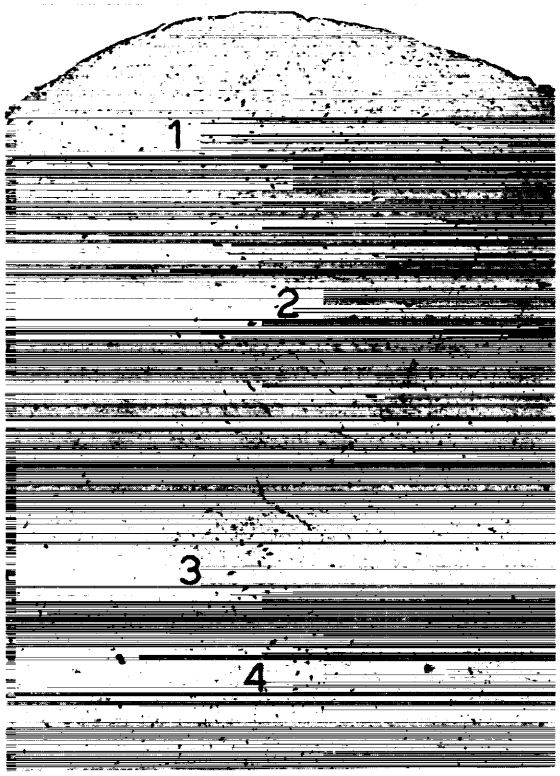

FIGURE 6.—(1) *Medial vestibular nucleus;* (2) *lateral vestibular nucleus;* (3) *interposed vestibular nucleus;* and (4) *inferior vestibular nucleus.* (*Guinea pig; Nissl, 45×.*) (*From the Journal of Laryngology and Otology, ref. 24.*)

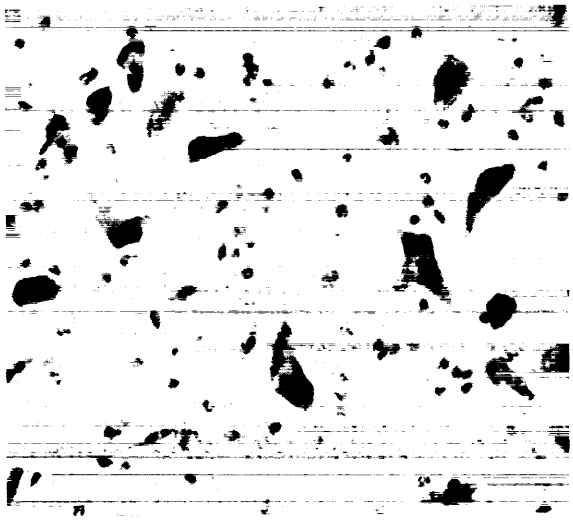

FIGURE 7.—*Detail at higher magnification of the area marked 3 of figure 6. Note the "interposed vestibular nucleus" with the morphological characteristics of its constituent cells.* (*Guinea pig; Nissl, 370×.*) (*From the Journal of Laryngology and Otology, ref. 24.*)

bundle." This bundle travels in a mediolateral direction and lies on a caudal plane with respect to the direct olivocochlear bundle, which, by contrast, travels downward in an oblique, mediolateral course. As this bundle crosses the dorsal part of the descending root of the Vth nerve, it sometimes divides into two bundles.

The second of the two bundles connecting the medulla oblongata to the vestibular receptors is clearly distinct from the bundle just described. Rossi and Cortesina (refs. 23–25) have called it "direct dorsal efferent vestibular bundle" and demonstrated for the first time its exact origin, course, and relations in the guinea pig and rabbit. This bundle arises from cells in the ventrocaudal

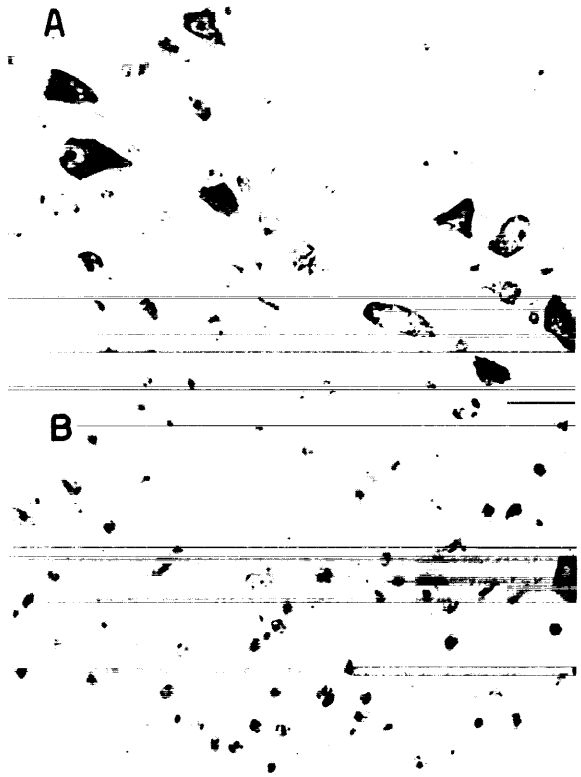

FIGURE 8.—A: *Interposed vestibular nucleus contralateral to the labyrinthectomy; the cells appear normal and bear no signs of retrograde change.* B: *Interposed vestibular nucleus ipsilateral to the labyrinthectomy; the cells display obvious signs of retrograde change. The two figures show the same section.* (*Rabbit; Nissl, 340×.*) (*Reproduced from Acta Anatomica, vol. 60, 1965, pp. 362–381, ref. 25, by permission of the publishers, S. Karger, Basel/New York.*)

part of the lateral vestibular nucleus (figs. 9 and 10) and lies around the dorsal margin of the descending root of the Vth nerve, before passing to the lateral margin and joining the other bundle of efferent vestibular fibers.

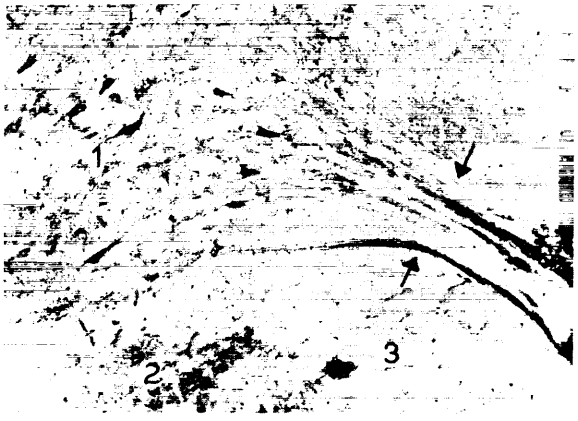

FIGURE 9.—(1) *Caudal region of the ventral part of the lateral vestibular nucleus;* (2) *nucleus of the descending root of the Vth nerve; and* (3) *descending root of the Vth nerve. The arrows indicate the Koelle and Friedenwald positive fibers originating from cells in the caudal region of the ventral part of the lateral vestibular nucleus and traveling ipsilaterally. These fibers give rise to the "direct dorsal efferent vestibular bundle." (Guinea pig; Koelle and Friedenwald, 49×.) (From the Journal of Laryngology and Otology, ref. 24.)*

Rossi and Cortesina (refs. 23–25) were also able to demonstrate that the efferent innervation of the cochlear, ampullary, and macular receptors includes fibers arising from cells lying at the side of the median raphe in the reticular formation of the pons and medulla in its posterior half, within the most cranial part of the medulla and the caudal part of the pons. These fibers, which are not crossed and which make up what Rossi and Cortesina called the "direct reticulocochlear and reticulovestibular bundle," travel ventrodorsally and join the fibers of the crossed olivocochlear bundle, after the latter has passed over the median line on the floor of the fourth ventricle (fig. 11).

According to recent data of Gacek et al. (ref. 27), the total number of the efferent vestibular fibers should be about 400 in the cat.

The general hypothesis formulated by Gacek (ref. 38) that the lateral vestibular nucleus appears to be the most likely source of the efferent vestibular fibers is corroborated by the discovery by Rossi and Cortesina (refs. 23–25) of two distinct bundles of efferent vestibular fibers, one from the lateral vestibular nucleus, the other from the quite separate and distinct nucleus called by Rossi and Cortesina the "interposed vestibular nucleus."

Only the existence of another component of efferent vestibular fibers, originating from a region other than the lateral vestibular nucleus, could account for Gacek's finding (ref. 38, pp. 278–280) that "the number of degenerated fibers was still greater when the vestibular nerve root was transected at various points before its emergence from the medulla" than in cases in which the area corresponding to the lateral vestibular nucleus was damaged. This is because only in these particular experimental conditions is it possible to affect the system of efferent vestibular fibers above the point of confluence and junction of the groups of fibers of which it is composed.

The investigations of Rossi and Cortesina (refs. 23–25), like those of Gacek (ref. 38), do not corroborate Petroff's finding in the cat and monkey of crossed efferent vestibular fibers, and contrast markedly with the observations of Carpenter and his colleagues who affirm that, in the cat and monkey, the efferent vestibular fibers arise from the superior vestibular nucleus, the medial vestibular nucleus, the inferior vestibular nucleus, and the fastigial nucleus and that some of these fibers are direct and some crossed.

The direct dorsal efferent vestibular bundle and the direct ventral efferent vestibular bundle, which are connected exclusively to the vestibular receptors; the direct reticulocochlear and reticulovestibular bundle, connected partly to the cochlear and partly to the vestibular receptors; the direct olivocochlear bundle and the crossed olivocochlear bundle, which are connected exclusively to the cochlear receptors, form, in rodents, a system of efferent fibers, the "efferent cochlear and vestibular system" (refs. 23–25) (fig. 12), connecting the medulla oblongata to the inner ear receptors. They are distinct in origin and course, but, on the lateral border of the descending root of the Vth nerve, they combine to form a single bundle which emerges from the oblongata together with the vestibular branch of the VIIIth nerve and

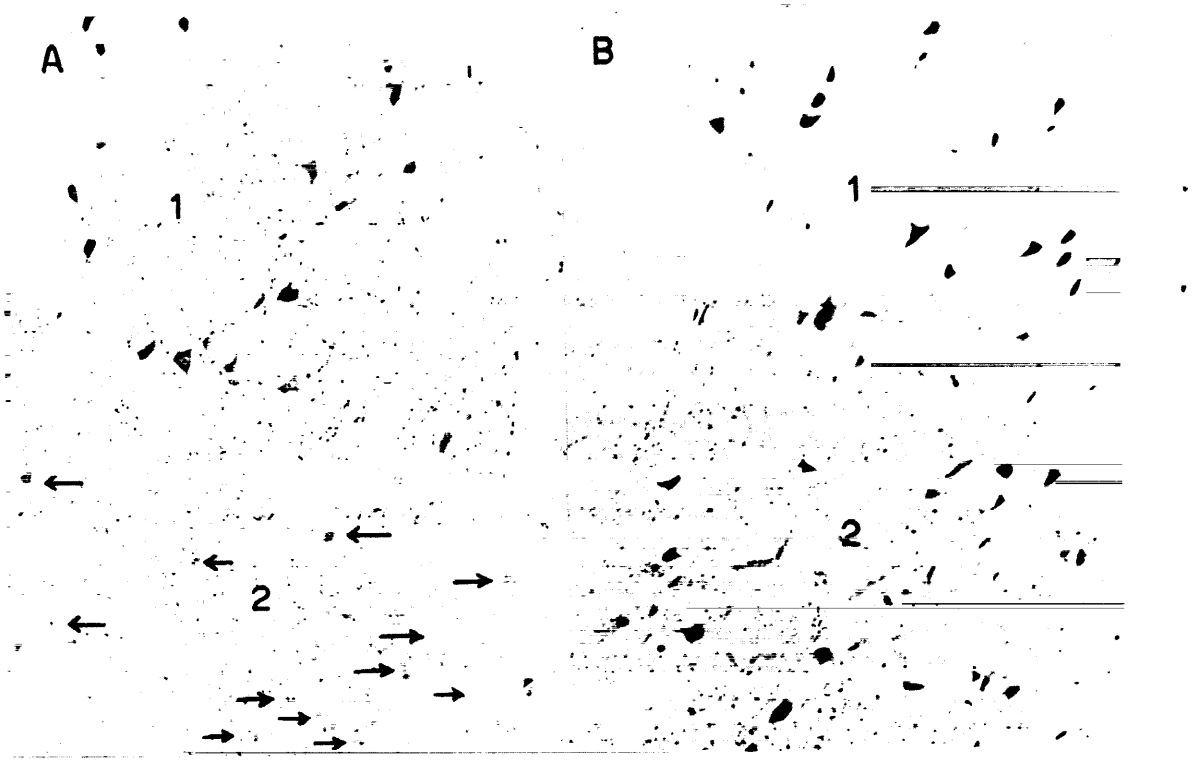

FIGURE 10. — A: *Lateral vestibular nucleus (caudal region) ipsilateral to the labyrinthectomy.* (1) *dorsal part of the lateral vestibular nucleus, the cells appear normal; and* (2) *ventral part of the same nucleus, cells with signs of retrograde changes (indicated by arrows).* B: *Photomicrograph of the same section shown in* A. *Lateral vestibular nucleus (caudal region) contralateral to the labyrinthectomy.* (1) *dorsal part of the same nucleus, cells appear normal; and* (2) *ventral part of same nucleus, cells appear normal, without signs of retrograde change. (Rabbit; Nissl, 90 ×.) (Reproduced from Acta Anatomica, vol. 60, 1965, pp. 362–381, ref. 25, by permission of the publishers, S. Karger, Basel/New York.)*

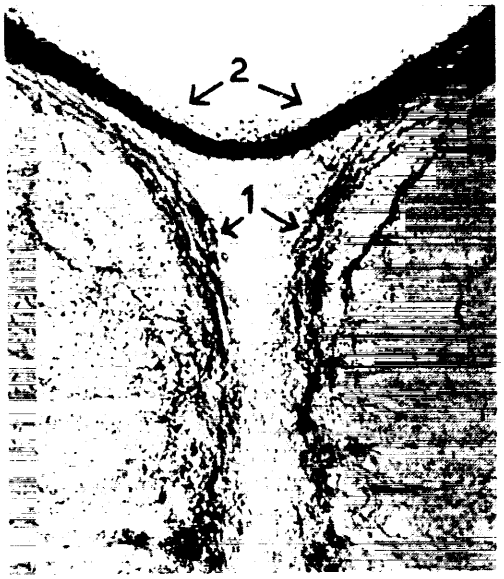

FIGURE 11.—*Section of the medulla just above the bulbopontine sulcus. Koelle and Friedenwald positive fibers originating from cells in the reticular formation lying at the side of the median raphe* (1) *join the bundle of crossed fibers* (2) *from the superior olivary complex. The bundle of fibers originating from cells in the reticular formation of the medulla and pons form the "direct reticulo-cochlear and -vestibular bundle." (Rabbit; Koelle and Friedenwald, 60 ×.) (Reproduced from Acta Anatomica, vol. 60, 1965, pp. 362–381, ref. 25, by permission of the publishers, S. Karger, Basel/New York.)*

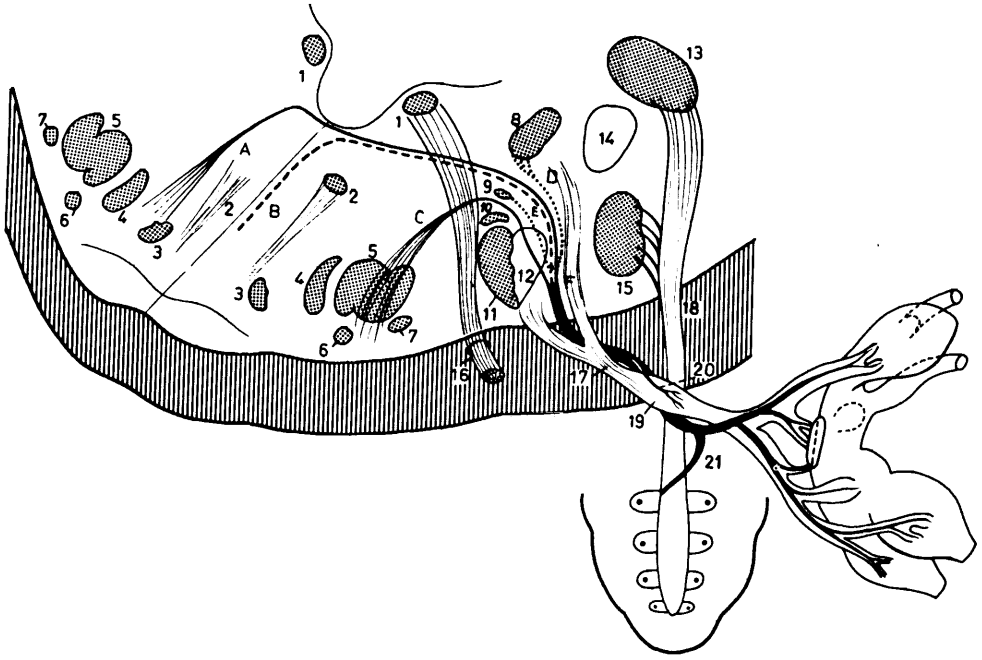

FIGURE 12.—*The "efferent cochlear and vestibular system" in rodents.* (1) *Geniculum of the facial nerve;* (2) *nucleus and root fibers of the abducent nerve;* (3) *nucleus of the trapezoid body;* (4) *accessory olivary nucleus;* (5) *superior lateral olivary nucleus;* (6) *medial preolivary nucleus;* (7) *lateral preolivary nucleus;* (8) *lateral vestibular nucleus;* (9) *interposed vestibular nucleus;* (10) *inferior vestibular nucleus;* (11) *nucleus of the descending root of the Vth nerve;* (12) *descending root of the Vth nerve;* (13) *dorsal cochlear nucleus;* (14) *restiform body;* (15) *ventral cochlear nucleus;* (16) *facial nerve;* (17) *vestibular branch of the VIIIth nerve with its two roots, superior and inferior;* (18) *cochlear branch of the VIIIth nerve;* (19) *Scarpa's ganglion;* (20) *a small bundle of efferent fibers terminating at the level of Scarpa's ganglion; and* (21) *Oort's anastomosis.* (A) *crossed olivo-cochlear bundle* (———); (B) *direct reticulocochlear and vestibular bundle* (– – – –); (C) *direct olivocochlear bundle* (———); (D) *direct dorsal efferent vestibular bundle* (.....); (E) *direct ventral efferent vestibular bundle* (.....); *and* (F) *bundle formed by the union of the various groups of efferent fibers. (Reproduced from Acta Anatomica, vol. 60, 1965, pp. 362–381, ref. 25, by permission of the publishers, S. Karger, Basel/New York.)*

radiates to the cochlear, ampullary, and macular receptors.

CONCLUDING REMARKS

The existence of a system of efferent vestibular fibers has by now been demonstrated by anatomical, histological, and histochemical research and also has been electrophysiologically confirmed (refs. 43–46).

The exact nature of the endings of these efferent vestibular fibers in the cristae and maculae is not yet definitely known, as the electron-microscopic investigations necessary to show which type of nerve ending degenerates after cutting of the efferent vestibular fibers have not been successful. In effect, the attempts to cut the efferent vestibular fibers, related by Wersäll and Flock (ref. 15), cause a complete degeneration of the afferent as well as the efferent nerve endings and deafferentation of the vestibular sensory cells.

In this connection we possess only indirect evidence which, however, leads us to believe that, as in the case of the cochlear receptors (refs. 47–52), the "much granulated" nerve endings in the cristae and maculae also belong to the efferent fiber system. In support of this hypothesis we must point out that these nerve endings have presynaptic characteristics (ref. 19), that the AChE activity in the cristae and maculae is confined to the "much granulated" nerve endings (ref. 30), and that it disappears after the section

of the efferent vestibular fibers on the floor of the fourth ventricle (refs. 23–25) or after the intracranial section of the VIIIth nerve (refs. 22 and 27). While awaiting a conclusive demonstration, it appears that we seem justified in assuming that the "much granulated" nerve endings represent the terminal arborizations of efferent fibers also in the vestibular receptors.

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DISCUSSION

JONGKEES: Did I understand from Dr. Rossi that a great percentage of the efferent fibers come from the lateral vestibular nucleus? Were there many connections between that lateral vestibular nucleus and the afferent fibers from the labyrinth, or did the feeding of the efferent fibers come from various parts of the brain?

ROSSI: The afferent vestibular fibers, according to studies of Brodal, Pompeiano, and Walberg, end on cells of the four main vestibular nuclei.

EAGER: You described chromatolytic cells in ventral parts, Dr. Rossi, but have you ever seen chromatolytic cells in dorsal parts of the lateral vestibular nucleus following labyrinthectomy?

ROSSI: No; only in the ventral part of the lateral vestibular nucleus in a small area within its caudal part.

EAGER: Were these the giant neurons?

ROSSI: Yes. These were the giant neurons.

HENRIKSSON: In connection with these fine anatomical data, I should like to report some experiments on vestibular efferent activity that we made a couple of years ago. One vestibular nerve of frogs was cut, and we recorded activity from the central part of the nerve during rotation. In this way we could study the efferent activity apparently originating from the opposite labyrinth.

GUALTIEROTTI: Was it a single unit activity or gross activity?

HENRIKSSON: It was gross recording. I would like to point out three properties of the efferent activity: First, the threshold for efferent activity is very high. There is no resting activity in the central part of the vestibular nerve. An acceleration of 6°/sec² for many seconds does not cause an efferent response, while an acceleration of 34°/sec² does cause a clear-cut response of apparently efferent activity. So, efferent activity differs very much from the afferent because of its high threshold.

DAVEY: Is 34°/sec² a threshold value?

HENRIKSSON: Somewhere in between 6°/sec² and 34°/sec².

GUALTIEROTTI: It might be possible that you do not see the beginning of the discharge because it is canceled by the noise.

HENRIKSSON: I do not think so. We made many experiments and we considered that possibility. Second, in an afferent, peripheral preparation no habituation can be seen even if the stimulations are repeated over and over again. The efferent activity has, however, a pronounced tendency for habituation. Such efferent activity seems to already diminish after one single stimulus and can even be totally abolished for many minutes. Third, efforts were also made to prove any effect of efferent activity. The response to rotation in a gross recording in the vestibular nerve with intact connection, both in the central and in the peripheral direction, will contain efferent as well as afferent activity. A comparison between this full activity with the pure peripheral response, without any connection with the brain, did not show any clear-cut difference. An expected inhibitory control by efferent activity thus could not be proven. Various experiments using various agents with anticipated effect on efferent activity were made, but all in vain.

MONEY: You used your large magnitude stimulation with that preparation, didn't you?

HENRIKSSON: Yes; we did.

Cerebellar Projections to the Vestibular Nuclei

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SUMMARY

The cerebellum gives rise to two major efferent pathways which terminate in the vestibular nuclei. One is formed by Purkinje-cell axons and projects directly to the lateral vestibular nucleus (Deiters). In the cat and rabbit the connections are homolateral and arise primarily from anterior lobe vermal and paravermal cortices. Direct fibers are traceable from posterior vermal regions of the cat cerebellum as well (lobules VI, VIIA, VIIB, VIII, IX, and X), but in the rabbit, lesions confined to lobule 3 of the posterior vermis result only in degeneration to the fastigial nuclei.

A second source of cerebellovestibular connections is the neurons of the fastigial nuclei. An uncrossed projection to all four vestibular nuclei arises from rostral parts of each fastigial nucleus, while the caudal one-third of the fastigius gives rise to a crossed pathway which passes, via the hook bundle, to the contralateral vestibular nuclei. In addition to its direct cortical projections to Deiters nucleus, the cerebellum can influence vestibular nuclear activity through fastigial nuclear relays. In addition to cortical vermal projections to fastigius, the paramedian lobule, posterior dorsal paraflocculus, and medial parts of crus II send fibers to fastigius, primarily to its caudal one-third.

Details of the terminations of the above pathways are discussed, as well as relevant information on the manner in which extracerebellar afferent pathways terminate in the vestibular nuclei. In addition, some new data on the fine structure of the lateral vestibular nucleus in the cat are presented, including the finding of axo-axonic synapses there.

INTRODUCTION

The vestibular nuclei, and particularly their efferent and afferent pathways, have been the subjects of an increasing number of experimental investigations in recent years, both anatomical and physiological. Much of the important experimental neuroanatomical data have come from the studies done by members of the Oslo group and their various collaborators, and excellent reviews have been published recently by Brodal, Pompeiano, and Walberg (ref. 1) and by Brodal (ref. 2).

The present discussion will be limited, for the most part, to a consideration of the anatomical relationship of the cerebellum to the vestibular nuclear complex and, particularly, to the manner in which the cerebellar cortex sends direct fibers to these nuclei. The fastigial nucleus of the cerebellum is an additional important source of vestibular afferents, and for that reason its various pathways and organization will be considered as well. Finally, in light of the greater need for more specific information regarding the manner of termination of the pathways under consideration, some of the cytological features of the various nuclei involved, especially of the lateral vestibular and fastigial nuclei, are discussed.

METHODOLOGY

Our data on cerebellar corticovestibular connections have been collected in experiments in the cat (ref. 3) and rabbit (ref. 4) by an analysis of the degeneration following small lesions placed in various areas of the cerebellar cortex of these animals. The Nauta-Laidlaw silver technique (ref. 5) or some modification of it (ref. 6) was used for this purpose on frozen sections of formalin-fixed tissues. Animals were sacrificed after a degeneration time of 1 week. While the Nauta technique allows only an approxima-

tion of the terminal degeneration on somata and dendrites in the nuclear regions examined, it is sufficient for the analysis of the general pattern of projection of one area to another in the central nervous system. For a more exact picture of terminal degeneration, one must resort to the electron microscope.

Tissues prepared for electron microscopy were fixed by glutaraldehyde perfusion, postosmicated, embedded in Maraglas, and thin sections cut on an LKB Ultratome. One-micron sections were cut from the same blocks, stained with toluidine blue, and photographed through a light microscope. These sections are especially useful for general orientation purposes and present a more faithful picture of a region than do tissues prepared by more conventional histological means.

DISTRIBUTION OF THE VESTIBULAR NUCLEI

Before discussing the details of afferent connections from the cerebellum, some features of the subdivision of the vestibular nuclei should be reviewed and considered in light of recent information on the manner in which primary vestibular fibers terminate within them (ref. 7).

Four major, and several minor, vestibular nuclear subdivisions are identifiable in the cat (ref. 8), and the same appears to hold true for the rabbit (ref. 9). Of most importance to the present discussion is the delineation of the lateral vestibular nucleus (Deiters) from the other three major nuclear groups (superior, of Bechterew; medial, of Schwalbe; inferior or descending). This is accomplished fairly easily in the cat by virtue of the presence within the lateral vestibular nucleus of the giant neurons which characterize it so well at all levels. One of these large neurons is shown in figure 1. There are, in addition to the large neurons, numerous cells of more modest dimensions scattered throughout the lateral vestibular nucleus (fig. 2), and they, in fact, constitute a majority of the neurons found in this nucleus. It is clear, from data yet to be discussed, that

FIGURE 1.—*Photomicrograph of a 1-micron-thick section showing a large neuron* (C) *in the lateral vestibular nucleus of the cat. Several small neurons* (c) *are also present in the field, as well as numerous myelinated fibers and glial cells. Tissues were fixed by perfusion with glutaraldehyde, postosmicated, and embedded in Maraglas. Toluidine blue stain. 996×*

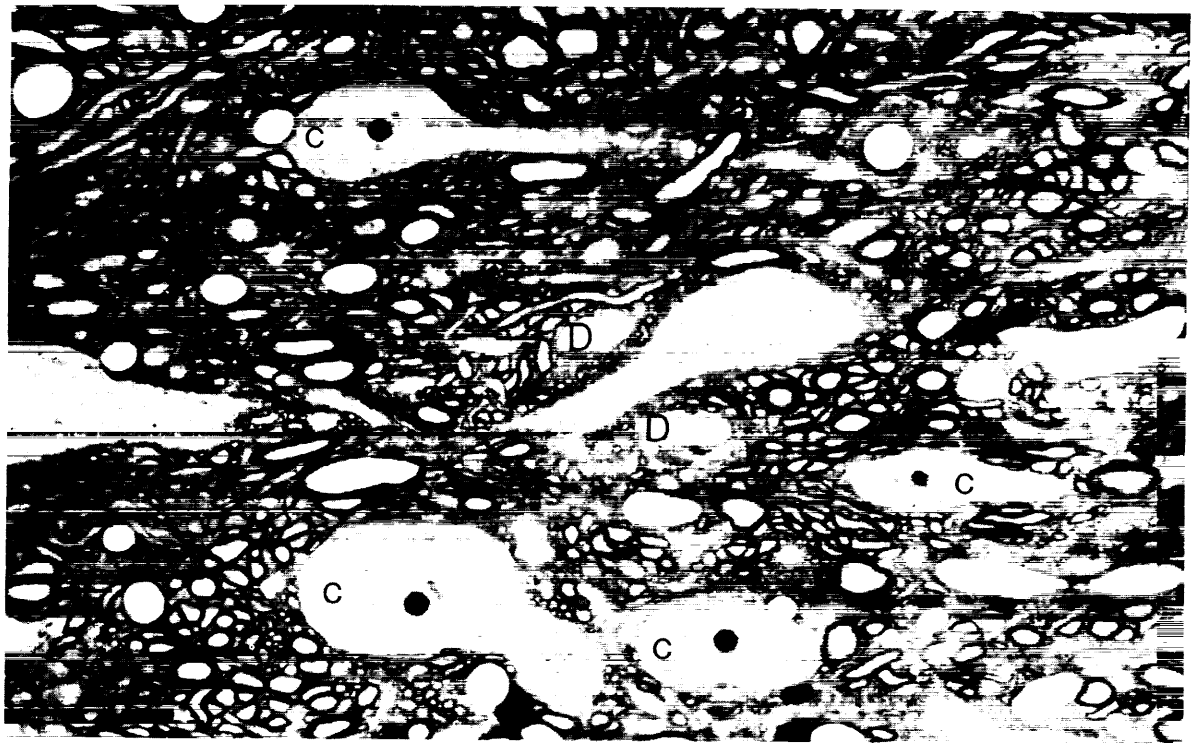

FIGURE 2.—*Photomicrograph of a 1-micron-thick section through the lateral vestibular nucleus of the cat showing a field of smaller neurons* (c), *myelinated fibers, and dendrites* (D) *cut in various planes. Fixation and staining as in figure 1.* 996×

in addition to a consideration of gross nuclear subdivision, an analysis of fiber terminations must include a consideration of a possibly more complex interaction with the variety of neurons found in these regions.

Primary vestibular afferent fibers reach all four major vestibular nuclei but do not terminate in all parts of them. Primary fibers to the superior nucleus terminate primarily in its central regions, while the medial and inferior nuclei receive primary vestibular fibers in their more lateral and medial areas, respectively (ref. 7). The lateral vestibular nucleus receives its primary vestibular fibers in a similarly restricted manner, with the projection being limited to rostroventral areas in the cat and, more specifically, to the small neurons found there (ref. 7). Similar observations have been reported from experiments in the rabbit (ref. 10). The data on primary vestibular projections to Deiters nucleus are especially important in light of the information on cerebellar cortical projections to this nucleus.

CEREBELLOVESTIBULAR PATHWAYS

Two cerebellar systems must be considered in any discussion of the possible influences of that organ on vestibular mechanisms. The first, composed of direct cerebellar cortical fibers (Purkinje cell axons), arises from limited areas of the cerebellar cortex, primarily from flocculonodular lobe (refs. 11 and 12) and vermis (refs. 3, 4, and 13), and terminates almost entirely in the lateral vestibular nucleus. A second, less specific, cerebellovestibular system is formed by the neurons of the fastigial nuclei which give rise to both crossed and uncrossed pathways terminating to greater or lesser extent in all four major vestibular nuclear subdivisions (refs. 14–16). And, of course, areas of cerebellar cortex can influence activity in all four vestibular nuclei indirectly via the fastigial nuclei (refs. 3, 4, and 17) so that the pattern of cerebellar corticonuclear projection becomes an important consideration as well.

DIRECT CEREBELLAR CORTICOVESTIBULAR PATHWAYS

In the cat and rabbit (refs. 3 and 4), a majority of direct corticofugal fibers emanate from the anterior lobe. These fibers come not only from the vermis of the anterior lobe, as has been suggested by recent studies (ref. 13), but also from paravermian and lateral regions.

The pattern of degeneration following a small lesion in anterior lobe vermal cortex (lobule V) of the cat is illustrated in figure 3. Such midline lesions result in bilateral degeneration traceable to both the fastigial and lateral vestibular nuclei. The latter show heaviest concentrations of preterminal degeneration in their more dorsal aspects. It should be noted that fibers on their way to terminations in Deiters nucleus pass through lateral portions of the fastigial nucleus, making it potentially difficult to lesion rostral portions of fastigius without inflicting some injury on the direct corticovestibular fibers.

Lesions placed more laterally in the anterior lobe of the cat (fig. 4) result in degeneration traceable to the ipsilateral interposed and lateral vestibular nuclei, again confined to dorsal regions of the latter. That the degeneration in Deiters nucleus is not a result of inadvertent vermal damage is manifest by the fact that the fastigial nuclei are free of degeneration.

Direct cerebellar corticovestibular fibers have been traced from several posterior lobe areas in the cat as well, including lobules VIIA and VIIB (ref. 3), and lobules VI, VIII, and IX (refs. 13 and 18) of the vermis. A few direct fibers to Deiters nucleus have degenerated following lesions in posterior paravermal cortex (lobulus simplex) in the cat (ref. 3), but these appear to be of insignificant number when compared with

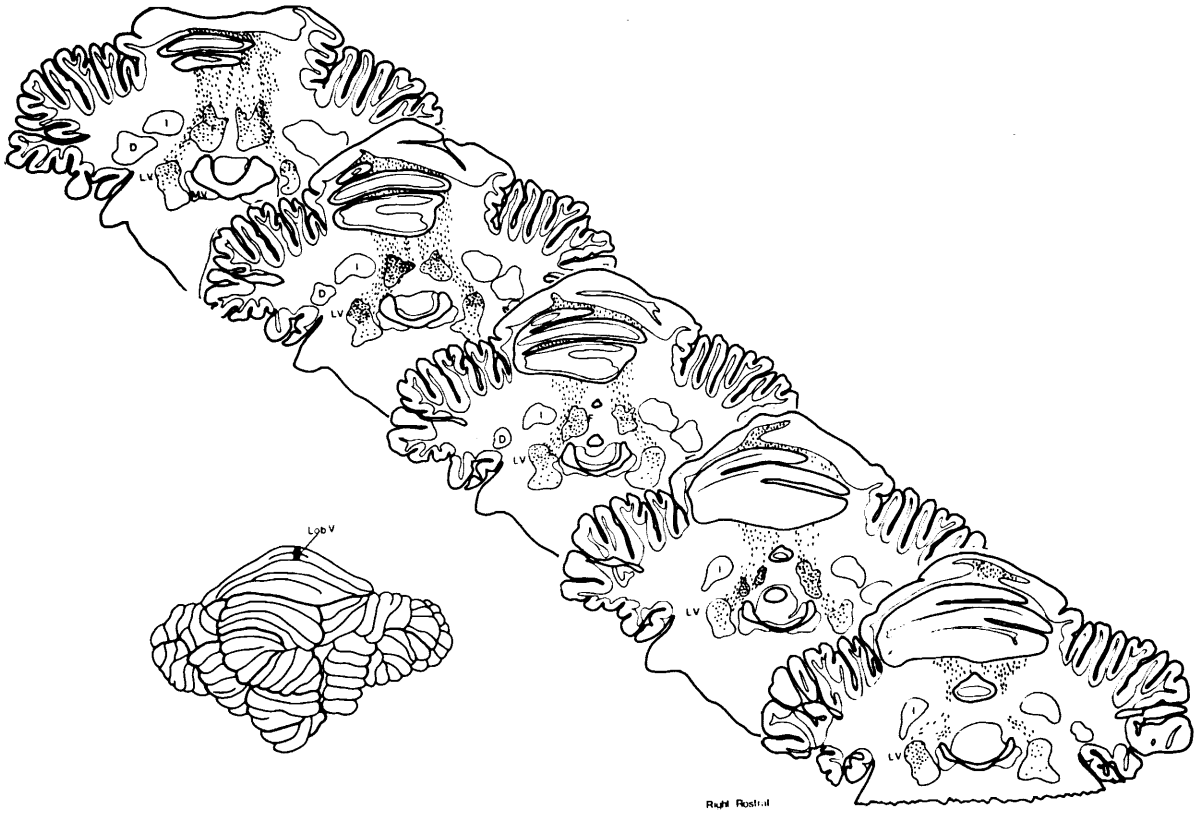

FIGURE 3.—*A series of projection drawings of transverse sections through cat cerebellum showing the pattern of degeneration following a lesion of anterior lobe vermal cortex* (lob. V). *Preterminal degeneration is depicted by dots and passing degeneration by dashes. Degeneration is distributed bilaterally to the lateral vestibular* (L.V.) *and fastigial* (F) *nucleus.*

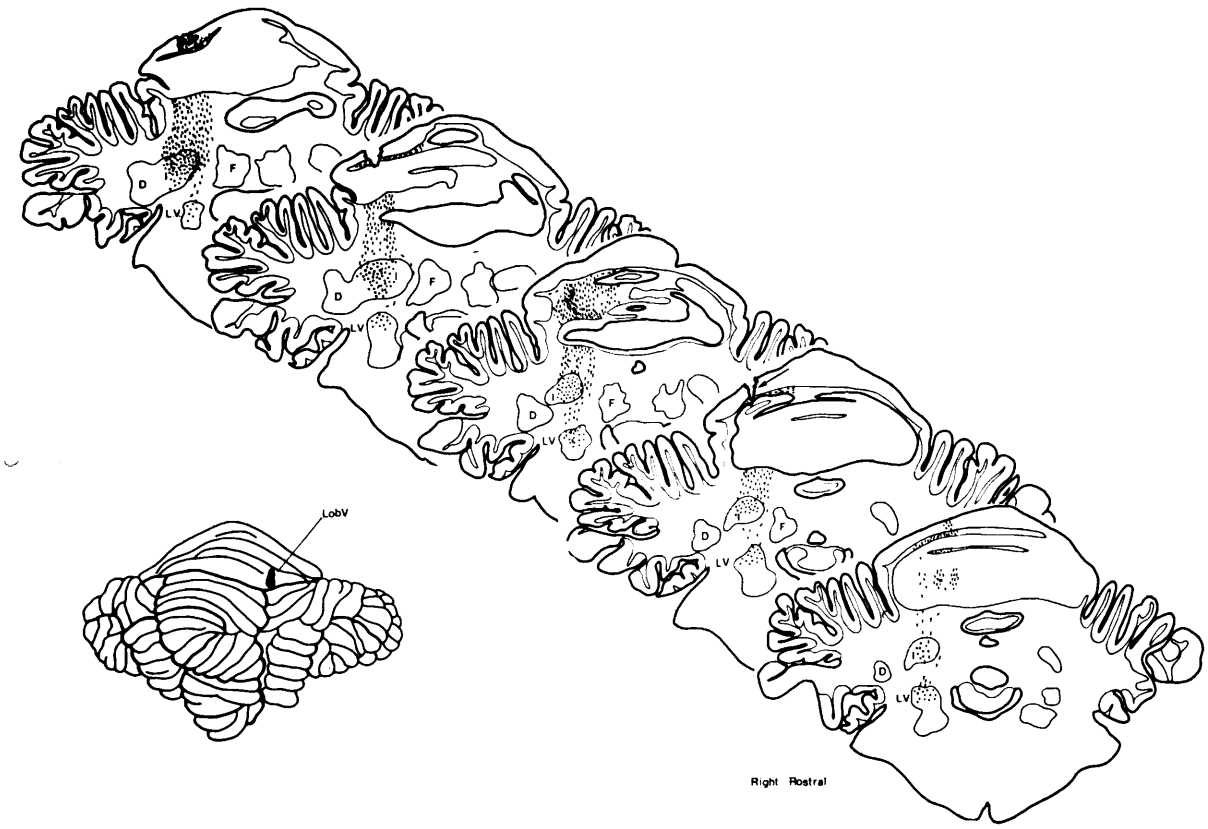

FIGURE 4.—*A series of projection drawings of transverse sections through cat cerebellum showing the pattern of degeneration following a lesion of anterior lobe paravermal cortex* (lob. V) *on the right side. Degeneration is confined to the right lateral vestibular* (L.V.) *and interposed* (I) *nuclei. Fastigial* (F) *and dentate* (D) *nuclei are free of degeneration.*

the projections from anterior and posterior lobe vermis.

The results of experiments in the rabbit (ref. 4) support, for the most part, the observations made in the cat. Lesions confined to the vermis of the anterior lobe (fig. 5) result in degeneration limited to the rostral fastigial nuclei and to dorsolateral areas of the lateral vestibular nuclei. In this case, the bilateral projection is the result of the midline nature of the lesion.

Anterior paravermal cortical areas in the rabbit also send direct fibers to Deiters nucleus, as well as to the homolateral nucleus interpositus. As in the vermal projections, degeneration is confined to dorsolateral parts of the lateral vestibular nucleus (fig. 6).

Posterior vermal lesions, when confined to lobule 4, in the rabbit, result in degeneration only in caudal regions of the fastigial nuclei (fig. 7) and, in our experience, no degeneration is traceable to any of the vestibular nuclei. This finding is in contrast to that of Jansen and Brodal (ref. 19) who have found degeneration in Deiters nucleus following lesions of this lobule in the rabbit.

FASTIGIOVESTIBULAR PATHWAYS

In addition to the direct cerebellar corticovestibular connections just described, the cerebellum can influence the vestibular nuclear complex via the fastigial nuclei. While the direct cerebellar cortical projections are limited, for the most part, to Deiters nucleus, the fastigiovestibular pathways terminate in portions of all four of the vestibular nuclei. The cerebellar cortex can, as a result, influence neuronal activity in all of the vestibular nuclei either monosynaptically or through a fastigial relay. The pattern of

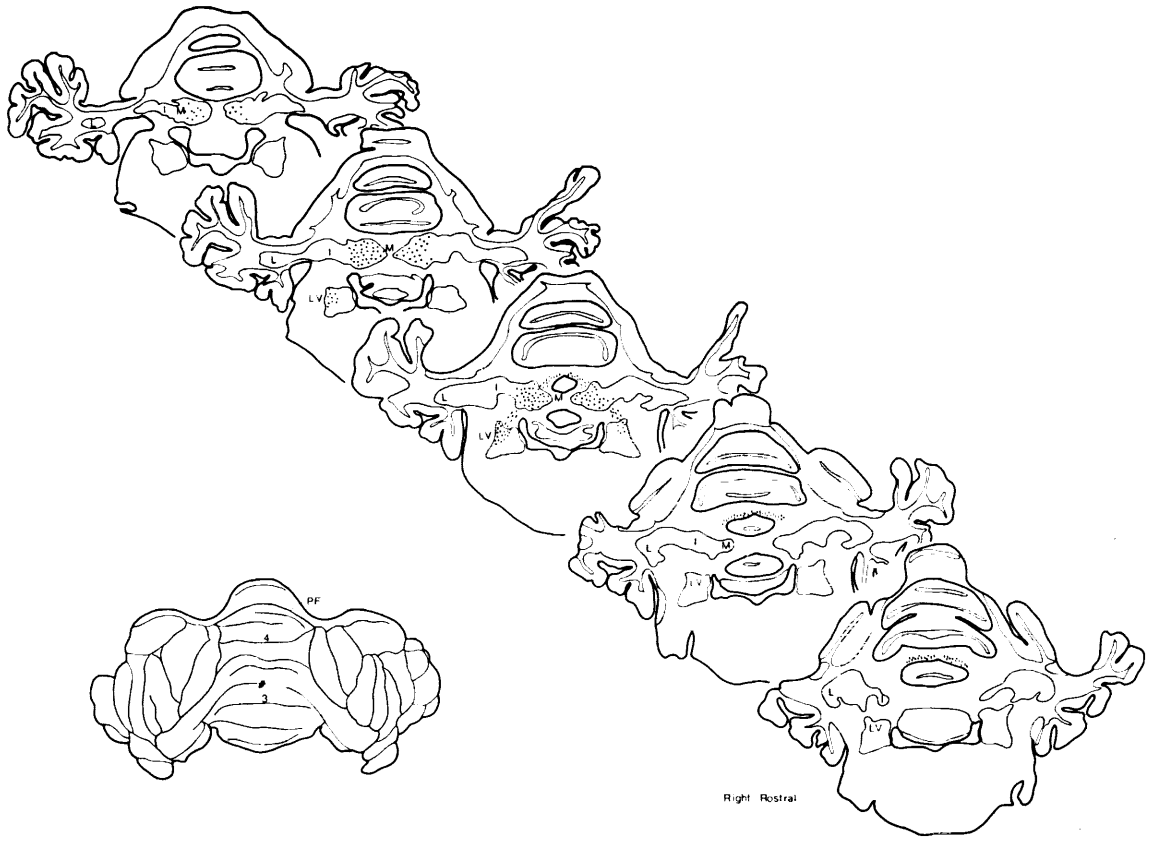

FIGURE 5.—*A series of projection drawings of transverse sections through the rabbit cerebellum showing the pattern of degeneration following a midline lesion of the anterior vermal cortex* (lob. 3). *Degeneration is distributed bilaterally to the medial* (M) *and lateral vestibular nuclei* (L.V.).

cerebellar cortical projection to the fastigial nuclei, then, assumes some importance in a consideration of cerebellovestibular organization.

Fastigial nuclear projections to the vestibular nuclei have been studied by a number of investigators but most recently by Walberg, Pompeiano, Brodal, and Jansen (ref. 16), and it is the results of their experiments in cats which will be considered next. Two distinct pathways emerge. One, which is uncrossed, originates from neurons in the rostral half, approximately, of the fastigius and terminates in the homolateral superior vestibular nucleus, in dorsal regions of Deiters nucleus, and in the medial and descending vestibular nuclei. A second, crossed, pathway, originates in the caudal one-third of the fastigius and passes, via the hook bundle, to the contralateral superior, medial, and descending nuclei and to ventral portions of the contralateral Deiters nucleus.

Cerebellar cortical pathways to the fastigial nuclei (ref. 3) in cat display some features which may be meaningful in the light of these data. While it is true that a majority of cerebellar cortical fibers terminating in the fastigial nuclei arise from neurons located in the vermis, it is equally true that the fastigius, and particularly its caudal one-third, receives fibers also from other cerebellar cortical areas. In the cat (ref. 3), the paramedian lobule sends a significant number of fibers to the fastigial nuclei on both sides. Ipsilateral connections have been traced to the fastigius from the dorsal paraflocculus and from medial portions of crus I and crus II of the ansiform lobule, and in each case, the projections have been limited to more caudal aspects of the nucleus. It is too soon to tell how the multiplicity of connections just described contributes to the results of the older physiological experiments (ref. 20), but it is clear that ablation of a

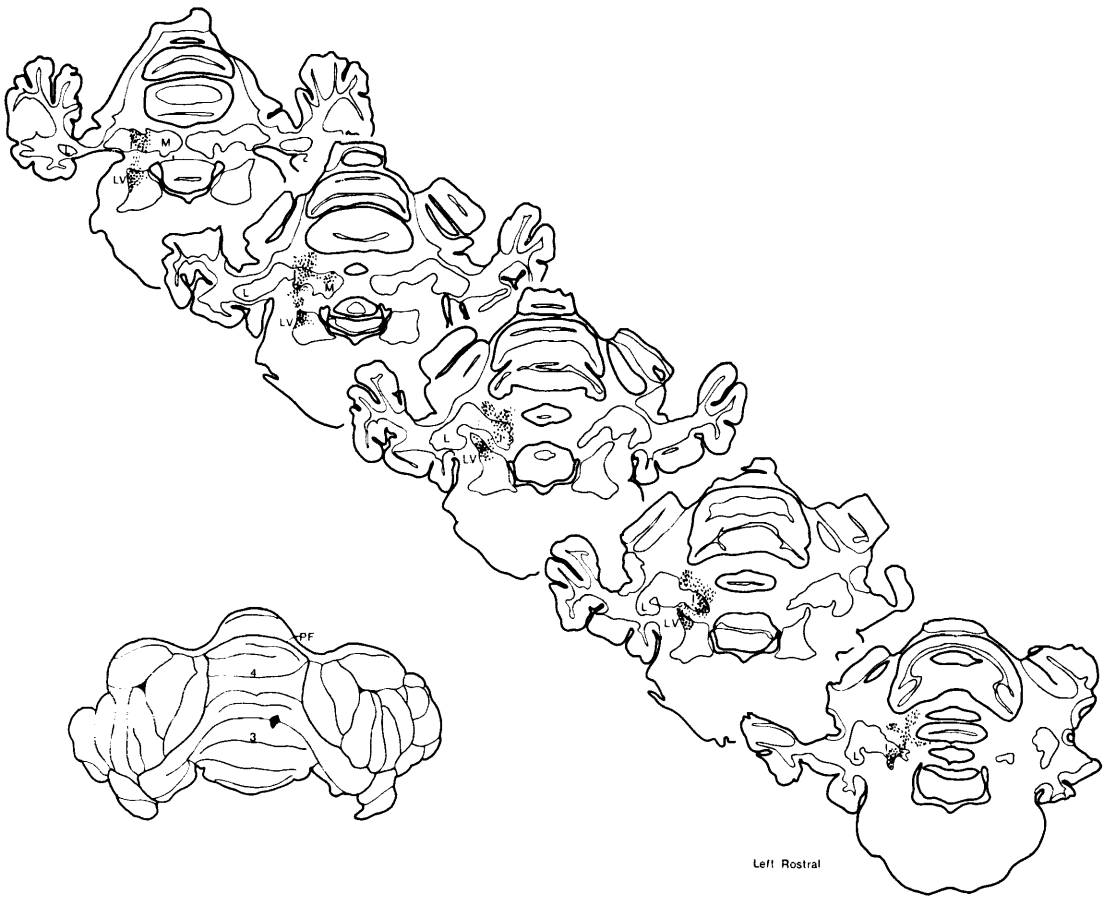

FIGURE 6.—*A series of projection drawings of transverse sections through the rabbit cerebellum showing the pattern of degeneration following a lesion of the left anterior lobe paravermal cortex* (lob. 3). *Degeneration is confined for the most part to left interposed* (I) *and lateral vestibular* (L.V.) *nuclei.*

single area of cortex, such as the paramedian lobule, could lead to the disruption of a number of neuronal connections any of which might result in the final postural deficit manifest after such a procedure.

THE MODE OF TERMINATION OF FIBERS IN DEITERS NUCLEUS

It is apparent from the review of the literature presented in the preceding paragraphs and from our own experimental experiences that the lateral vestibular nucleus not only receives a large and varied afferent input, but that it becomes, on the basis of the patterns of terminations, further subdivided into what appear to be special areas of interaction. It is also apparent, but the supporting data are less complete, that various afferent fibers terminate differently on the variety of neurons found in the areas under discussion. For example, direct cerebellar cortical fibers to Deiters nucleus end predominantly in dorsal parts of the nucleus and relate, as much as can be determined at a light microscopic level, to the giant neurons found there (fig. 8). Fastigial fibers to Deiters nucleus, on the other hand, whether they be to dorsal regions of the nucleus (from rostral parts of the fastigius) or to ventral parts of the nucleus (from the contralateral, caudal fastigius), show a greater relationship with the small cells of the respective regions and tend to avoid the giant neurons (ref. 1).

It is interesting to consider, too, the manner of termination of other afferents to Deiters nucleus. The spinal cord sends fibers to the lateral vestibular nucleus (primarily from lumbo-

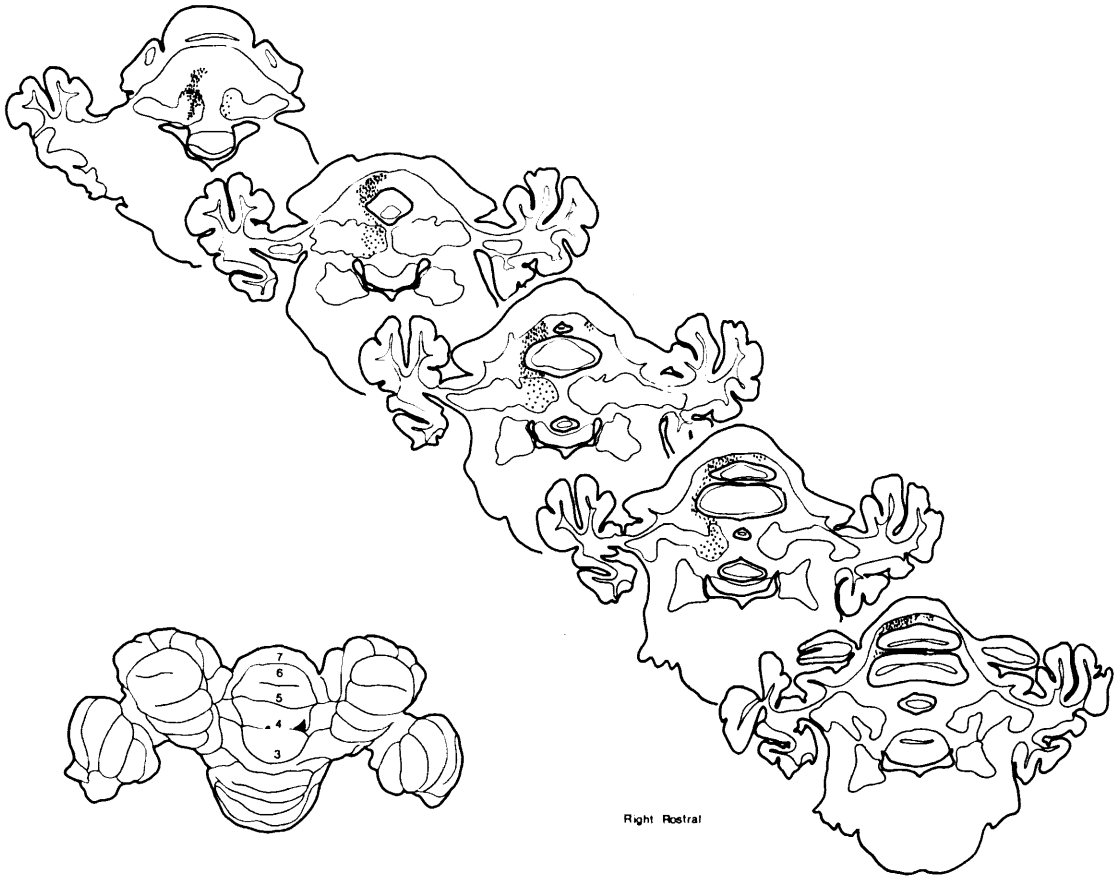

FIGURE 7.—*A series of projection drawings of transverse sections through the rabbit cerebellum showing the pattern of degeneration following a lesion of right posterior vermal cortex* (lob. 4). *There is no degeneration in either lateral vestibular nucleus, and the cerebellar nuclear degeneration is confined, for the most part, to the right nucleus medialis.*

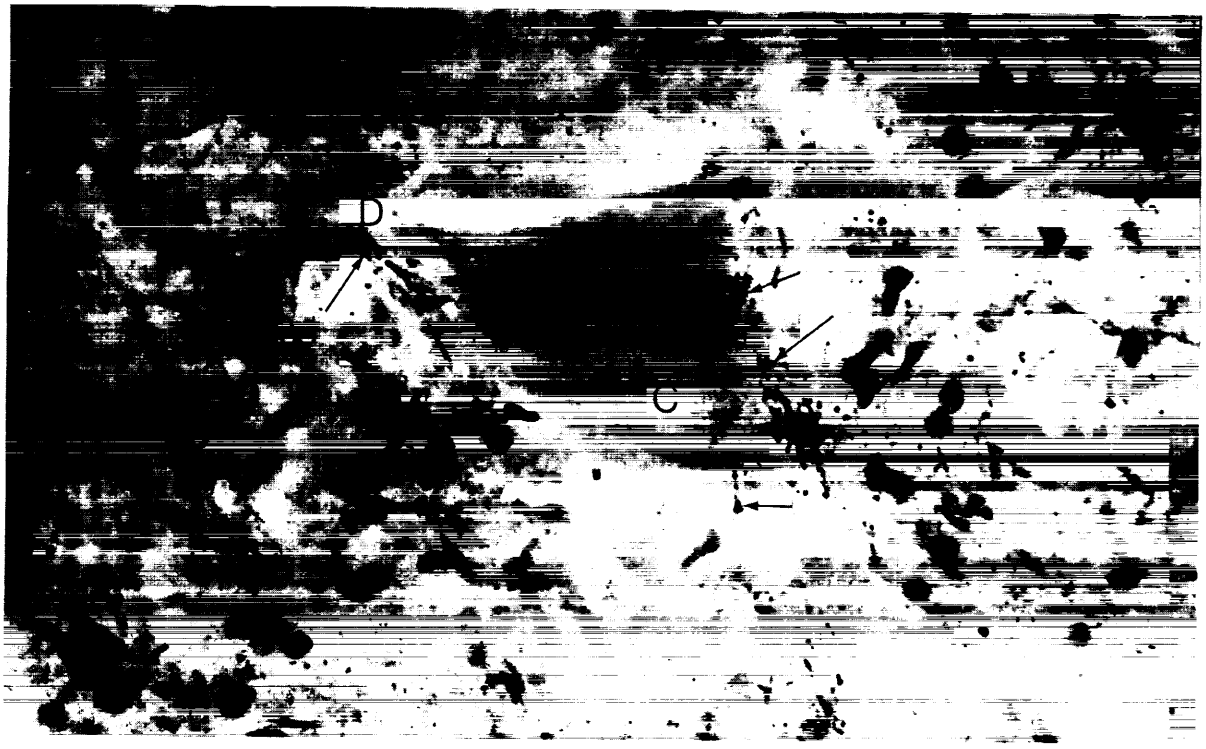

FIGURE 8.—*Photomicrograph showing degeneration* (arrows) *near cell body* (C) *and dendrite* (D) *of a large neuron in the lateral vestibular nucleus of the cat following a lesion of anterior lobe vermal cortex. Other degenerated fibers are scattered in the neuropil. Nauta-Laidlaw stain.* 996×

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sacral segments), and these end primarily in dorsal regions of the nucleus, in close relationship to the giant neurons (ref. 21). Primary vestibular projections to Deiters nucleus, however, are limited to ventral regions of the nucleus, and the degeneration following vestibular-nerve section appears to be limited to the small cells found there, avoiding the large cells to a considerable degree (ref. 7).

CONCLUSION

The conclusion seems inescapable that any further fruitful investigation of the vestibular nuclei, either anatomical or physiological, must take into account the fine specifics of neuronal interaction which are emerging from more recent investigations. For example, Ito and his coworkers (refs. 22–25) have found, from recording intracellularly in neurons of the cerebellar and vestibular nuclei, that the direct cerebellar cortical pathways to these neurons (Purkinje cell axons) are inhibitory. It would be important to know exactly how these fibers terminate on these neurons, and this can come only from an electron-microscopic analysis of degenerating terminals following cerebellar cortical lesions, work which is in progress in several laboratories (ref. 26, and R. P. Eager, "The Fine Structure of Terminal Degeneration in the Cerebellar Nuclei of the Cat Following Lesions of the Cerebellar Cortex," in progress). The same kind of

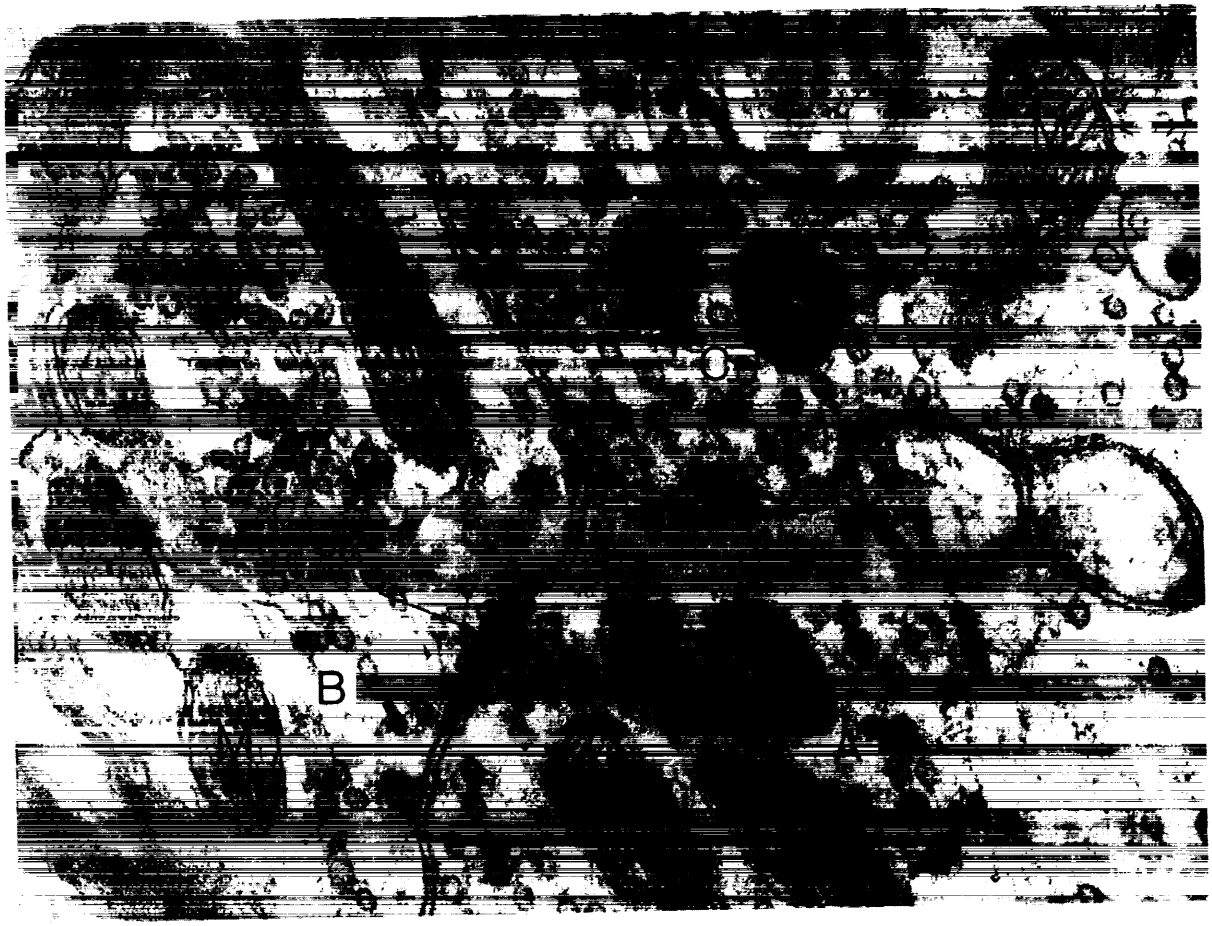

FIGURE 9.—*Electron micrograph showing a complex of three axon terminals* (A, B, C), *two of which* (A *and* B) *appear to be synaptically related* (arrow). *The specialization of apposing membrane between terminals* A *and* C *may represent another synaptic site, but more probably a zone of adherence. Note the clustering of synaptic vesicles along the presynaptic membrane of terminal* A. *Mitochondria* (M) *are present in all three terminals. Glutaraldehyde perfusion, postosmicated, and grids stained with lead citrate. 110 000×*

analysis is necessary, of course, for the other afferent pathways mentioned, and it is not unlikely that such studies will reveal a complexity of interaction which at the present time is only suggested by the preliminary work. Some observations on the normal fine structure of the lateral vestibular nucleus in the cat (ref. 26, and R. P. Eager, "The Normal Fine Structure of the Lateral Vestibular Nucleus in the Cat," in progress) have revealed a wide variety of different kinds of synaptic contacts, including axo-axonic synapses (fig. 9), and it is not unreasonable to believe that these may represent different afferent origins and functional capabilities.

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DISCUSSION

SMITH: In some of your figures there seemed to be a larger light area about the large ganglion cells than around the smaller cells. Does this mean there were more boutons on the soma of the large cells than on the small ones?

EAGER: This is quite true. There appear to be more somatic terminals on the large neurons than there are on the small, and this is one good way to distinguish them.

GOODMAN: I would like to ask two questions and make a comment. First, in the rabbit, did you find any differences in concentration for the direct corticofugal fibers; that is, was there a difference in concentration of fibers originating from the different lobules of the vermis? We found such differences in the rat.

My second question concerns species variation. What is the case in primates and is it different from the pattern in the lagomorph, carnivore, and rodent?

Lastly, a comment. Currently we have been talking and thinking about primary interactions of the cerebellum and vestibular complex in the vestibular nuclear complex and other medullary brain-stem systems. Recently, in fact during December 1966, Dr. Karl Achenbach and I found in the rat direct cerebellospinal fibers which were traced through spinal cervical region IV. This tract appears to continue caudad but, unfortunately, it was at this spinal level that we dissected out the brain and cord. We are presently preparing additional animals to assess the extent of these cerebellar efferent fibers. We know that the tract originates largely from caudal cerebellar nuclei and takes two routes into the spinal cord to terminate in Rexed's lamina VII of the ventral gray and in intermediate gray. My point is that spinal-cord regions also should be given consideration as a possible area of interaction between vestibular and cerebellar systems.

EAGER: I have not seen any difference in concentration, but perhaps they have not been prominent enough. As far as species differences are concerned, we are beginning to examine these projections in the squirrel monkey with the electron microscope and will have some information at the light microscopic level as well in the near future. You could provide some important information, I think, from your studies in the rat and bird. What patterns of degeneration to the vestibular nuclei have you seen in these animals?

GOODMAN: Our findings in the rat did present a gradient. There were more direct cerebellar efferent fibers to the dorsolateral vestibular region from the more caudally occurring vermal lobules than from other lobules of the vermis. Few fibers originated from the tuber-vermis-declive region, whereas a moderate number were traced from anterior lobe vermis. Nevertheless, it appears that in the three species representing different mammalian orders for which we have data, the pattern is generally the same.

A statement is made in Jansen and Brodal's book, "Aspects of Cerebellar Anatomy," which reaffirms the common assumption that as one goes phylogenetically up the scale in mammals, there should be a decrease in the number of direct or long cerebellar corticofugal fibers. If this is the case, then it would be expected that the inhibitory activity you suggest for these fibers would be of lesser consequence in primates. This is the reason I directed my question toward the pattern of these fibers in primates.

EAGER: As I recall, we saw very few direct cerebellar corticovestibular fibers in our experiments in *Macaca mulatta;* so, there may be some validity in this. Dr. Goodman has made a very important point with regard to the spinal cord, a point that I failed to emphasize, and that is that the spinal cord projects, via spinovestibular fibers, to the large neurons in dorsal parts of the lateral vestibular nucleus. So, in terms of that particular input to Deiters, there seems to be a very strong relationship in both directions.

FERNÁNDEZ: Perhaps you would care to comment about the projection of the flocculonodular lobe into the vestibular nuclei.

EAGER: We have had no personal experience, and the Oslo group have not done experiments specifically in the flocculonodular lobe either. There are only the older Marchi data of Dow who reported from both the flocculus and nodulus a rather large direct input into the vestibular nuclei.

ROBERTS: Would you like to speculate here about a conundrum arising in cerebellar physiology? One thinks of the cerebellum as an inhibitory organ, and when you stimulate various parts of the cerebellum, you get inhibitory effects. When you look at parts of the pathway, you find that the cortex has inhibitory effects at various stages all down the pathway.

Then there are experiments in which you have ablations of parts of the fastigial nuclei, and these experiments have to be interpreted as though these nuclei are producing facilitatory effects; for example, if you remove the caudal fastigial nucleus, you get crossed fastigial atonia. Where, then, are these facilitatory pathways? Also, do you have evidence of a pathway from the cortex of the cerebellum going through the region of the fastigial nucleus but with a relay there? Such a pathway would be necessary for interpreting some of these conundrums.

EAGER: Yes. There are two major efferent pathways that have to be considered. The direct corticonuclear and corticovestibular projections from cerebellum have been shown by Ito to be inhibitory, monosynaptically. The second major efferent pathway, that originating from neurons in fastigius and projecting also to the vestibular nuclei, has not been examined by means of intracellular microelectrode recording, but I should be very surprised if it, too, were an inhibitory pathway. And, of course, when one lesions the fastigial nucleus, one interrupts not only these afferent relationships but also the multiplicity of extracerebellar afferents terminating there. It is difficult, as you can see, to interpret the results, now, of some of the older stimulation and ablation experiments.

GOODMAN: With respect to the question of facilitatory effects of the cerebellum upon the vestibular nuclear complex, DeVito, Brusa, and Arduini in 1956 were the first to record with microelectrodes in the vestibular nuclei following stimulation of cerebellar cortex and nuclei. They obtained inhibition at 40 percent of the units, 30 percent were unaffected, and facilitatory effects were obtained from 30 percent

of the units tested. I do not remember whether they also did latency studies; nevertheless, they did find vestibular facilitation from cerebellar stimulation.

EAGER: I think this is an important point, because it is certainly true that there are reports in the cerebellar literature, especially from Moruzzi, Pompeiano, and others, that units in both cerebellar and vestibular nuclei can be both driven and inhibited upon cerebellar cortical stimulation. But you are quite right to invoke the possibility of other, perhaps multiple, synapses in the facilitatory activity. I raised this question to Ito in the last discussion we had and he is quite sure on the basis of intracellular recordings in many units, both in the cerebellar nuclei and vestibular nuclei, that Purkinje cells are acting in an inhibitory way in this regard, which makes us have to think about this system a little more carefully. You see how difficult it is to make any sense out of an ablation experiment. It is almost impossible.

GUALTIEROTTI: In this respect you are certainly aware of the long discussion of this particular problem, the inhibitory effect of the cerebellum, that took place in Tokyo at the International Physiological Congress. Eccles pointed out one factor that is not taken into account here, the feedback system reaching up the cerebellar cortex. You must be very careful when you draw conclusions from a stimulation experiment, because you might just stimulate the fibers that inhibit the inhibitory descendent pathways. It is therefore very difficult to be sure that the cortex, for instance, has points with inhibitory and points with facilitatory effect.

EAGER: You are quite right. There are all kinds of fibers running through these areas.

SESSION IV: BLOOD SUPPLY TO THE LABYRINTH

Chairman: CESAR FERNÁNDEZ

University of Chicago

N 68-29144

Vascular Patterns of the Membranous Labyrinth[1]

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SUMMARY

The vascular supply to the membranous labyrinth originates intracranially and is thus entirely separate from that of the middle ear. The *arteria cochleae propria* spirals about the cochlear nerve in the modiolus, giving off branches which first form the thin-walled glomeruli of Schwalbe and then divide to supply the structures of the lateral wall of the cochlea, on the one hand, and those of the spiral lamina, on the other.

Four separate capillary networks arranged in parallel supply the spiral ligament, stria vascularis, spiral prominence, and outer sulcus region. The capillaries of the spiral lamina form a stepped series of arcades within the substance of the limbus, beneath the tympanic lip, and under the pars arcuata of the basilar membrane. Pericapillary spaces and avascular channels are associated with many of these vessels, but not with those of the stria vascularis, which are closely invested by processes from basal and intermediate cells of the stria. The inner and outer spiral vessels are surrounded by extensive pericapillary spaces, which are sometimes connected by avascular channels. The pericapillary spaces of the inner spiral vessels communicate with the perineural spaces of the nerve bundles approaching the foramina nervosa in the habenula perforata, and thus with the interior of Corti's organ, to which they probably supply the cortilymph that fills it. The spiral vessels are innervated by unmyelinated fibers, which can be demonstrated by the Champy-Maillet zinc iodide-osmic acid technique.

The major capillary networks of the vestibular organs underlie the neural and secretory epithelia. Certain areas of the membranous canals and sacs are supplied by capillaries, whereas others, like Reissner's membrane, are avascular.

Quinine and sodium salicylate cause partial occlusion of the spiral vessels and other inner ear capillaries by swelling of the endothelial cells and pericytes. The ischemia thus produced is apparently responsible for the reversible ototoxic effects of these drugs.

INTRODUCTION

The blood vessels of the labyrinth have never received the same attention that has been lavished for the better part of a century and a half (to date the modern period of ear research, perhaps not altogether arbitrarily, from Huschke and Breschet (refs. 1 and 2)) upon its cells and membranes and their functional implications. Tracing the course of what Hamlet calls "each petty artery" is a labor that has no widespread occupational appeal, unless there are compelling surgical reasons for so doing. Comparatively few of the 19th-century microscopists devoted much space to the blood vessels of the ear. Even Retzius (ref. 3), primarily occupied as he was with problems of cytoarchitecture and innervation, had little to say about them, either in his detailed historical review or in his descriptions of his own findings. Most of his drawings are avascular, with the exception of two excellent illustrations of the vessels of the membranous labyrinth as they appear in a 5-month human fetus.[2]

Among the earlier authors who did mention in passing the blood supply of Corti's organ was the Copenhagen neuroanatomist Hannover (ref.

[1] This investigation was supported by PHS research grants NB-05065-03 and NB-05785-02.

[2] Pl. xxxiv, figs. 12 and 17 of ref. 3.

4), who published a drawing of the inner and outer spiral vessels at the edge of the osseous lamina on the tympanic side of the basilar membrane. Hannover seems, incidentally, to have been the first to demonstrate the parallel, radial fibers of the membrane, likening them, some 20 years before Helmholtz, to the strings of a piano ("som Strengene i et Claveer"). Another Dane, Ibsen (ref. 5), described the canalis vasculosus spiralis modioli, containing an artery from which almost all of the other arteries of the cochlea arise. Corti (ref. 6) devoted a page or more to his bande vasculaire or stria vascularis, with its unusual capillary bed. Because of its position he was tempted to infer a certain rapport between it and the secretion of the endolymph. Hensen (ref. 7) characterized the spiral ligament itself as "ausserordentlich gefässreich," and called attention to a longitudinal vessel, the vas prominens, which he assumed to be venous in nature.

Winiwarter (ref. 8), while still a medical student at Vienna, published a long article based on the examination of stained sections of the cochlea in the guinea pig and rabbit. He described various vascular features, including the arterial "glomeruli" of the modiolus, the vessels of the spiral ligament, the capillaries of the stria, and the vas spirale enclosed within the substance of the basilar membrane. Voltolini, of Breslau, devoted two shorter papers (refs. 9 and 10) to a discussion of vascular loops in the spiral limbus. He found this structure "recht gefässreich," although others had considered it to be avascular.

The first attempt to fit these fragments of information into a general schema of cochlear circulation was made by Schwalbe (Strassburg) in the chapter he contributed to the 1877 Festschrift for Carl Ludwig (ref. 11). There he devoted special attention to the arteries of the modiolus (tractus spiralis arteriosus), which wind around the nerve. Their numerous branches, seen at regular intervals, coil upon themselves to form the glomeruli, which Schwalbe illustrated and likened to those of the kidney. These modiolar glomeruli, he supposed, reduce the pressure at which the blood is delivered to the cochlea and thus protect the organ of Corti against disturbance by arterial noise and pulsation. Further protection is presumably afforded by the unique arrangement of the vessels in the walls of the cochlea, since only the scala vestibuli, separated from the organ of Corti by Reissner's membrane, is exposed to the effects of arterial blood flow in its walls. The scala tympani is surrounded only by veins.

Still more comprehensive treatments of the labyrinthine vessels were those of the Leipzig anatomist Eichler (ref. 12) and the Basle otolaryngologist Siebenmann (ref. 13). Eichler confined his study to the cochlea, with special attention to its capillary beds in spiral lamina and spiral ligament, as well as to the course of its arteries and veins. Siebenmann followed the internal auditory artery in its various branches to both cochlear and vestibular structures. Between them these two authors give such complete and superbly illustrated accounts of the major vascular patterns of the labyrinth that later investigators (refs. 14 to 19), although more often cited, have in fact been able to add little to the story other than confirmation. They have, however, supplied important data concerning the form and distribution of the various capillary networks.

DISTRIBUTION OF THE INTERNAL AUDITORY ARTERY

Although we have nothing new to report about the gross anatomical aspects of the blood supply to the membranous labyrinth, it may be helpful to glance briefly at the general arrangements of the arteries and veins that are involved. Figure 1 shows the general schema of the arterial and venous systems of the monkey, according to Nabeya. This blood supply originates within the cranial cavity and is thus entirely separate from the vessels that supply the otic capsule and the tympanic cavity, with which Anson and his colleagues have dealt in important recent publications (refs. 20 and 21).

Blood reaches the inner ear by way of the internal auditory artery, which usually arises as a branch of the inferior anterior cerebellar artery, but which may spring directly from the basilar artery itself. The much-discussed question of its origin, and the views and findings of previous authors, have recently been reviewed by Walker (ref. 22). After entering the internal meatus it divides into three main branches: the

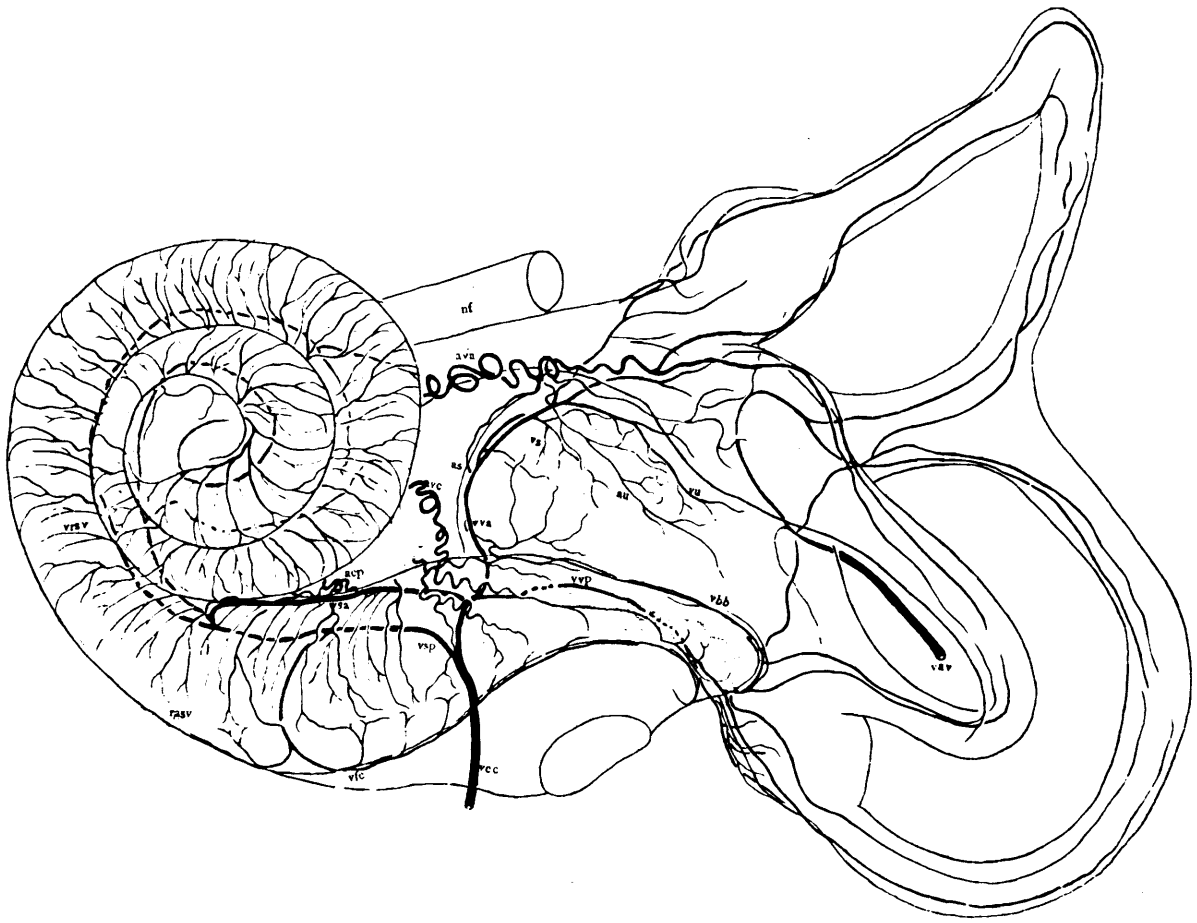

FIGURE 1.—*The arterial and venous systems of the monkey* (Macaca fuscata) *according to Nabeya (ref. 15).*

ava—Arteria vestibuli anterior
acp—Arteria cochleae propria
au—Arteria utricularis
rasv—Radiating artery on the scala vestibuli
vav—Vena aquaeductus vestibuli
vcc—Vena canaliculi cochleae
vs—Vena saccularis
vsp—Vena spiralis posterior
vva—Vena vestibuli anterior
avc—Arteria vestibulo-cochlearis
as—Arteria saccularis
nf—Nervus facialis
vrsv—Venae radiatae scalae vestibuli
vbb—Vestibular blind branch
vfc—Vena fenestrae cochleae
vsa—Vena spiralis anterior
vu—Vena utricularis
vvp—Vena vestibuli posterior

arteria vestibularis anterior, the arteria vestibulo-cochlearis, and the arteria cochleae propria. The latter two vessels may have a common stem, the arteria cochleae communis. The arteria vestibulo-cochlearis divides into the arteria vestibularis posterior and the ramus cochlearis. The usual distribution of these vessels may be outlined as follows:

Arteria vestibularis anterior to—
- Macula of utricle
- Cristae of lateral and superior ampullae
- Membranous canals
- Superior surfaces of utricle and saccule

Arteria vestibularis posterior to—
- Macula of saccule
- Nerve and crista of posterior ampulla
- Membranous canals
- Inferior surfaces of utricle and saccule

Ramus cochlearis to—
- Cecum vestibulare
- Modiolus
- Lower one-third of basal coil of cochlea

Arteria cochleae propria to—

- Entire cochlea, except for lower third of basal coil
- Modiolus
- Spiral ganglion
- Spiral ligament and stria
- Spiral lamina, limbus, and basilar membrane

Among the terminal branches of these arteries, there are extensive anastomoses. Major capillary networks are found in relation to the various end organs and to the membranous walls of the labyrinth.

VENOUS OUTFLOW

The veins of the inner ear do not necessarily accompany the arteries, but tend to go their separate ways. Blood from the spiral ligament and spiral lamina of the apical and middle portions of the cochlea is collected by the anterior and posterior spiral veins in the floor of the scala tympani, and these drain with numerous anastomoses, by way of the vena aquaeductus cochleae, and by way of the internal auditory veins into the internal jugular vein. The basal portion of the cochlea is also drained by the vena aquaeductus cochleae, which lies in a bony canal paralleling the cochlear aqueduct, into the inferior petrosal sinus.

Venous drainage from the vestibular structures is largely by way of the vestibular vein, which descends in the medial wall of the vestibule, collecting blood from the utricle and saccule and from the three ampullae. It runs toward the cecum vestibulare in the region of the round window, where it finally empties into the vena aquaeductus cochleae. A second route is by way of the smaller vena aquaeductus vestibuli, which receives tributaries from the utricular wall and the semicircular canals, especially from the common crus, and passes through the vestibular aqueduct to empty into the lateral sinus.

CAPILLARY BEDS OF THE COCHLEA

Among the vessels of the labyrinth, our major interest lies of course in those tiniest and most numerous of "petty arteries," the arterioles, capillaries, and venules of the cochlear and vestibular end organs. We have studied them by stereomicroscopy and bright-field or phase-contrast microscopy in three types of preparations:

1. *Unstained preparations.*—The blood vessels are delineated by the color of the blood that they contain. The specimen is fixed with 4 percent buffered paraformaldehyde and examined without further processing. The vascular pattern of the stria is especially well displayed. If the tissue is washed and transferred to a graded series of alcohols, the red color fades immediately and the contrast is lost.

2. OsO_4-*stained preparations.*—The tissue is stained, in buffered 1.0 percent OsO_4 solution, with or without previous paraformaldehyde fixation. This type of preparation is useful for phase-contrast study of the vessels of the spiral ligament and stria and the spiral vessels beneath the basilar membrane. The pericapillary spaces and the avascular channels, which are described below, are easily visualized.

3. *Benzidine-stained preparations.*—The vessels are stained by virtue of the peroxidase reaction of the blood they contain, in accordance with the method of Pickworth (ref. 23). After paraformaldehyde fixation, the cochlea and vestibule are opened widely for staining, and the specimens can be examined as surface preparations without the need for making frozen sections. The method is more valuable, however, for studying the patterns of the various capillary beds by stereomicroscopy than by the higher magnifications available with phase-contrast or bright-field microscopy. Figure 2 shows the inner ear of a guinea pig stained in this way. Much of the bony capsule has been removed in order to display the vessels within.

We have not used intravascular precipitation of Prussian blue or lead chromate to demonstrate the vessels. Injections of contrast material such as india ink would seem to have important advantages for differential staining of the arterial and venous systems, but, as seen in Agazzi's photomicrographs (ref. 24), the vascular patterns often appear incomplete because of failure of the fluid to fill all of the capillaries.

FIGURE 2.—*Guinea pig cochlea, blood vessels stained with benzidine. The bony capsule and spiral ligament have been removed from one side. In the apical turn arterioles can be seen descending in the roof of scala vestibuli to the spiral ligament and stria, and along the surface of the modiolus to the spiral lamina. In turn 3 the spiral vein is seen in the floor of scala tympani, receiving tributaries descending in the wall of scala tympani and in the modiolus.*

The Cochlear Plexus

On the arterial side the specialized arrangement of the cochlear blood supply is apparent in the tractus arteriosus, which spirals about the cochlear nerve in the modiolus. Here the arteria cochleae propria runs in a band of tissue to which it supplies numerous capillary twigs. Balogh and Koburg (ref. 25) found that the tissue contains cells of epithelial type and resembles the choroid plexus. Their autoradiographic studies demonstrated a lively protein metabolism, and oxidative enzymes were found in abundance. Because of its similarity to the choroid plexus, Balogh and Koburg have called this tissue the cochlear plexus and have ascribed to it a secretory role in the formation, not only of the fluid which fills the perivascular spaces of the modiolus and passes along the nerve fibers to the spiral ganglion, but perhaps also of that which reaches the interior of the organ of Corti. Thus the cochlear plexus may prove to be one important source of the cortilymph.

Further evidence of the significance of this tissue is the presence of a large number of unmyelinated nerve fibers, which we have demonstrated with the Champy-Maillet zinc iodide–osmic acid technique (ref. 26) and which apparently constitute the vasomotor nerve supply to the smaller vessels.

Branches from the arteria propria cochleae, while still within the bony confines of the modiolus, form the well-known convolutions or glomeruli of Schwalbe. These glomeruli are thin walled, and are surrounded by wide perivascular fluid spaces. The vessels then leave the modiolus to pass radially through channels in the thin septum of bone which serves as the roof of scala vestibuli and the floor of scala tympani of the turn above. In this way they reach the upper border of the spiral ligament, where they divide into several separate capillary networks that supply the tissues lining the inner surface of the outer wall of the three cochlear scalae: the spiral ligament, the stria vascularis, the spiral prominence, and the region of the outer sulcus.

Capillaries of the Outer Wall

The complicated patterns formed by these vessels can best be seen by direct examination under the stereomicroscope. Figure 3 shows portions of the wall of the first three turns of the guinea pig cochlea. It is clear that the complexity increases from the upper turn downward, but the general patterns are the same in all three turns. The main features are the following:

The radial arterioles divide as they reach the upper margin of the spiral ligament. Branches from the majority of them give off capillaries which form a network supplying that portion of the ligament above Reissner's membrane. Other branches descend more or less vertically in the ligament behind the stria. These vessels are the so-called arteriovenous shunts. Although they do not usually divide any further, they form S-shaped loops immediately behind the cells of the outer sulcus. They then pass below

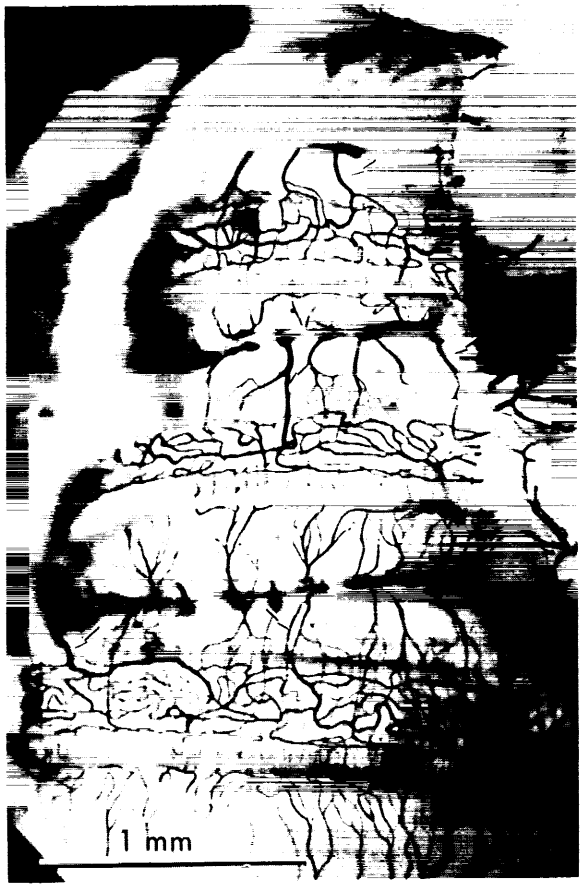

FIGURE 3.—*Vascular patterns of the spiral ligament and stria vascularis in the guinea pig cochlea, turns 1 to 3. Most of the radiating arterioles pass behind the stria as so-called arteriovenous shunts, form S-loops behind the outer sulcus, and then run for a short distance beneath the attachment of the basilar membrane, before descending as venules in the wall of scala tympani. Only the largest arterioles supply the stria. One such vessel can be seen in turn 3, and two each in turns 1 and 2. Note the increasingly complicated pattern of the strial vessels from above downward. Benzidine stain; composite of three photomicrographs of the same specimen.*

the line of attachment of the basilar membrane, where they turn to pursue a short longitudinal course, before descending to join the venules draining the wall of scala tympani.

In the guinea pig only a minority of the radial vessels, i.e., the largest of them, supply the stria vascularis. In figure 3 there is only one vessel entering the stria in the third turn, and two each in the second and first turns. Often such a large vessel will also give off a branch which descends vertically behind the stria to the system of longitudinal capillaries supplying the spiral prominence. On the other hand, we have not seen any evidence of a direct connection from the capillaries of the stria to those of the spiral prominence or from the capillaries of the spiral ligament to either of these systems. We can therefore distinguish four capillary networks, which are arranged in parallel, apparently without any connections in series. These are approximately the same capillary networks described by C. Smith and by Scuderi and del Bo, but to our knowledge they have not previously been recognized as exclusively parallel circuits.

1. *Capillaries of the vestibular portion of the spiral ligament.*—The smaller radial arterioles arching over the roof of the scala vestibuli give off branches which form a network of capillaries running more or less longitudinally in the thinner portion of the spiral ligament above the attachment of Reissner's membrane. They are surrounded by well-defined pericapillary spaces (fig. 4), and these spaces are often interconnected by avascular channels, which are clearly seen when surface preparations of the spiral ligament are examined by phase-contrast illumination. Such channels are present in several other cochlear tissues of the guinea pig and of other species including man, but they have not to our knowledge been noted previously.

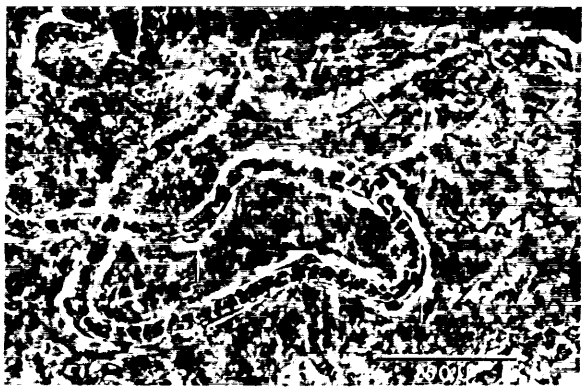

FIGURE 4.—*Pericapillary spaces (vertical arrows) and an avascular channel (diagonal arrow) from the vestibular portion of spiral ligament. Guinea pig, surface preparation,* OsO_4 *staining, phase contrast.*

This network of capillary and avascular channels appears to stand in much the same relation to the scala vestibuli as do the vessels of the stria vascularis to the scala media. Capillary pressure is presumably high enough so that fluid moves by filtration outward from the vessels. A substantial part of the perilymph may have its origin here.

2. *Capillaries of the stria vascularis.*—The strial vessels usually enter it just below the insertion of Reissner's membrane. They are capillaries of large caliber which form a complicated network of many anastomoses within the epithelium of the stria (fig. 5). So closely are they invested by multiple layers of the intermediate and basal cells of the stria that there appears to be no pericapillary space around them (fig. 6). The marginal cells, which make up the endolymphatic surface of the stria and send their basal processes between the capillaries, appear to be separated by at least a thin layer of intermediate-cell cytoplasm from direct contact with the endothelial cells. To this extent our observations may be at variance with those recently reported by Rodriguez Echandia and Burgos (ref. 27).

The strial capillaries are often found tightly packed with red cells. The blood in them shows a remarkable degree of hemoconcentration, indicating an unusually active process of fluid transfer from the stria. Perlman (refs. 28 and 29) has observed that the blood flow here is relatively slow.

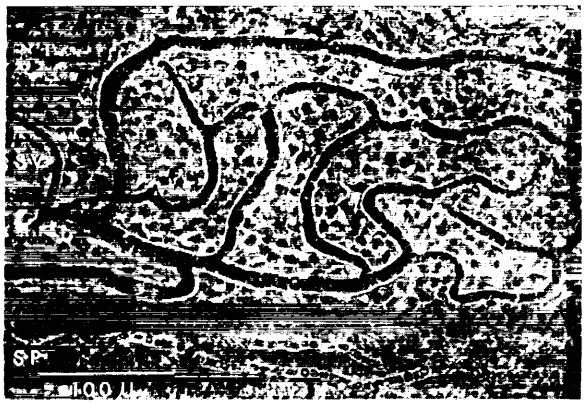

FIGURE 5.—*Capillaries of the stria vascularis,* SV, *and spiral prominence,* SP. *Polygonal outlines of the marginal cells of the stria are seen between its anastomosing capillaries. Note differences in pattern, caliber, and degree of filling of the capillaries of the stria and the spiral prominence. Guinea pig, surface preparation,* OsO_4 *staining, phase contrast.*

FIGURE 6.—*Capillary of the stria vascularis closely surrounded by intermediate and basal cells. Processes of darker marginal cells extend inward from the endolymphatic surface, where occasional microvilli and vacuoles are seen. The basal layer of cells separating the stria from the spiral ligament appears to be continuous with the epithelium of Reissner's membrane and the superficial cell layer of the spiral prominence. Electron micrograph,* OsO_4 *staining.*

3. *Capillaries of the spiral prominence.*—The spiral prominence is often supplied by a descending branch of the same large arteriole that supplies the stria. The capillaries of the prominence run a relatively short longitudinal course, sometimes singly but often paired, before turning down to join the venules of the wall of scala tympani. They are usually well filled with red cells, but they do not show evidence of the extreme hemoconcentration that is typical of the strial vessels (fig. 5).

4. *Capillaries descending vertically behind the stria vascularis.*—These capillaries are similar

to those of the spiral ligament above Reissner's membrane. Their walls consist of a single endothelial layer, and they generally have a pericapillary space surrounding them (fig. 7). They sometimes lie close to the thin layer of basal cells that form the boundary between the stria and the spiral ligament, but they do not pass this barrier to enter the stria. Below the lower border of the stria, these vessels make a double hairpin turn under the epithelium of the outer sulcus before they continue their downward course. In the basilar crest, immediately below the insertion of the basilar membrane, they turn again to run longitudinally for a short way before descending to join the other venules draining the spiral ligament. These are the vessels described by Scuderi and del Bo (ref. 19) as "venous loops of the spiral crest which appear to form a spiral vessel."

FIGURE 7.—*Capillary of the spiral ligament behind stria vascularis near its lower margin. Note simple endothelial wall and pericapillary spaces. Electron micrograph,* OsO_4 *staining, same section as figure 6.*

Capillaries of the Spiral Lamina

From the modiolar glomeruli, other arteriolar branches descend along the surface of the modiolus (as seen in fig. 2, top coil) and enter the spiral osseous lamina to supply the spiral ganglion, the nerve fibers, the limbus, and the arcuate portion of the basilar membrane. As seen in figure 8, these vessels form a stepped series of arcades in the substance of the limbus, beneath the tympanic lip, and beneath the pars arcuata of the basilar membrane.

Although the basilar membrane as a whole has no direct blood supply other than the outer spiral vessels, and its pars pectinata is avascular, it is surrounded by capillaries on either side, both above and below its insertions in the spiral limbus and the spiral ligament. This

FIGURE 8.—*Capillary patterns of the spiral ligament and stria* (S) *and the arcades of the spiral lamina and limbus* (L) *on either side of the avascular portion of the basilar membrane (zona pectinata).* PSV, *posterior spiral vein, receiving tributaries descending from spiral ligament. Guinea pig, basal coil, benzidine stain.*

FIGURE 9.—*Capillary patterns in the cochlea of the squirrel monkey. The basal turn has been dissected to show, at left, the spiral ligament and stria vascularis with radiating arterioles over scala vestibuli; between arrows and at upper left, the capillaries of the spiral lamina and the tympanic portion of spiral ligament, and, at upper right, the venous drainage in the wall of scala tympani. Apical termination of the art. cochleae propria is seen through the helicotrema at upper center. Benzidine stain.*

disposition of capillaries on either side of the basilar membrane is also clearly seen in the squirrel monkey (fig. 9). Here, as well as in macaques and man, single vessels occasionally cross the tympanic face of the basilar membrane and link the spiral vessels with those of the spiral ligament.

Capillaries of the Limbus

These vessels form a series of arcades in the substance of the limbus. They approach the bases of the interdental cells but do not enter the region of Huschke's teeth. Perivascular spaces are not evident, but avascular channels can be demonstrated (fig. 10).

The Spiral Vessels

Much has been written about the spiral vessels, but no attempt will be made here to review

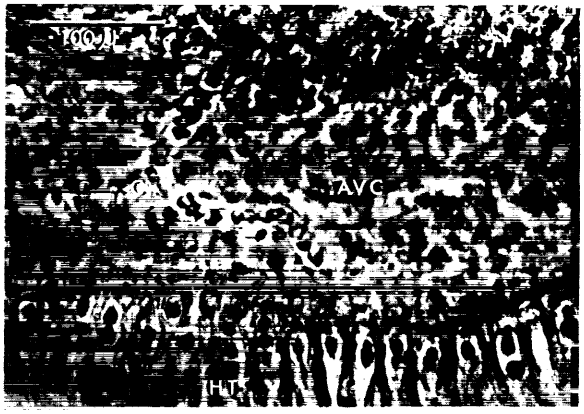

FIGURE 10.—*A capillary* C, *near the margin of the spiral limbus, with avascular channel,* AVC. HT, *Huschke's teeth with interdental cells between them. Guinea pig, "thick" horizontal section of Araldite-embedded specimen,* OsO_4 *staining, phase contrast.*

the various and often conflicting opinions that have been expressed about their function and significance. If they are observed as in figures 8 and 9, they make much more of an impression than they do when seen in conventional midmodiolar cross sections. Lawrence (ref. 30) has recently shown that localized occlusion of the spiral vessels is more damaging to the organ of Corti than localized interruption of the blood supply to the spiral ligament and stria.

The inner spiral vessels run along the tympanic surface of the osseous lamina and beneath the habenula perforata. In the guinea pig they are surrounded by wide pericapillary spaces (fig. 11). The individual arcades are relatively short.

FIGURE 11.—*Inner* (ISV) *and outer* (OSV) *spiral vessels:* ISV *at the tympanic crest of the spiral lamina near habenula perforata,* HP, *and myelinated nerve fibers,* N. OSV *beneath the basilar membrane, showing* T*-junction. Pericapillary spaces,* PS, *are clearly seen, especially in relation to* ISV. G, *granules surround* OSV. *Guinea pig, surface preparation,* OsO_4 *staining, phase contrast.*

The inner vessels are closely related to the myelinated nerve fiber bundles in the habenula, and there is direct communication between their pericapillary spaces and the perineural spaces (fig. 12). These channels appear to be identical with the "perilymphatic pores" in the osseous lamina that Schuknecht and El Seifi (ref. 31) have described as linking the fluid inside the organ of Corti and the perilymph in scala tympani. They communicate, however, not directly with the perilymph, but with the filtrate in the pericapillary spaces of the inner spiral vessels, which are shut off from scala tympani by an extension of the tympanic lamella.

FIGURE 12.—*Relation between inner spiral vessel and nerve fiber bundle, with myelinated and unmyelinated fibers and Schwann cells, near habenula perforata. The vessel is surrounded by an extensive pericapillary space, which communicates with the perineural space of the nerve fiber bundle. Guinea pig, electron micrograph,* OsO_4 *staining.*

The outer spiral vessels form a more-or-less continuous series of arcades in the guinea pig, with T-junctions communicating with vessels in the interior of the limbus (fig. 11). These junctions become less frequent in the lower basal turn, so that in the so-called hook region the outer spiral vessel may run for long distances (> 1 mm) between T-junctions.

In the cat the outer spiral vessel is usually absent in the upper turns, as shown by C. Smith (ref. 18), and in the primates that we have examined it is not infrequently interrupted, at least for short distances. Corti's organ obviously does not depend upon a single set of vessels for its supply of oxygen and nutrients, but upon all of the capillary networks that border it on either side. The outer spiral vessels are surrounded

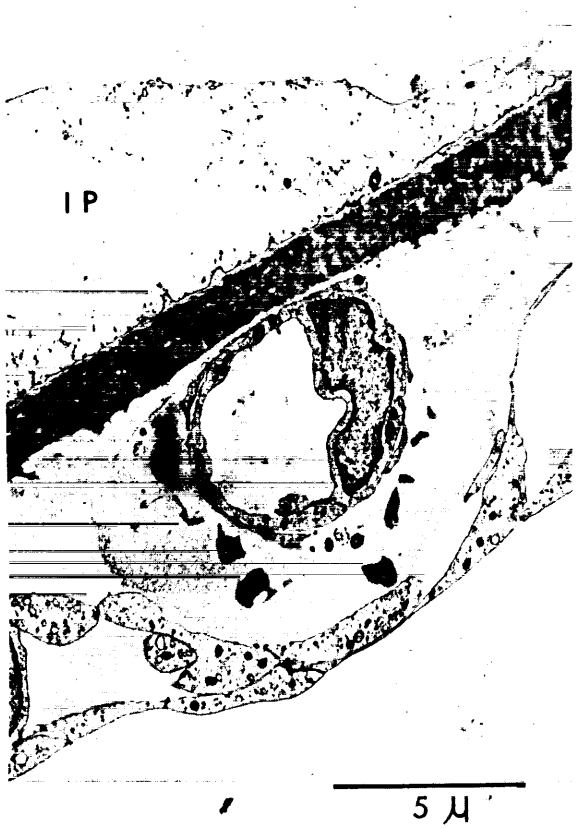

FIGURE 13.—*Outer spiral vessel beneath basilar membrane, showing surrounding pericapillary space bounded by mesothelial cells of the tympanic lamella.* IP, *footplate of inner pillar. Note precipitate surrounding the vessel, and darker bodies which apparently represent the granules seen in surface preparation. Guinea pig, electron micrograph,* OsO_4 *staining.*

FIGURE 14.—*Outer spiral vessel beneath basilar membrane, in longitudinal section.* PC, *pericyte. Guinea pig, electron micrograph,* OsO_4 *staining.*

FIGURE 15.—*Outer spiral vessels* (OSV), *with avascular channel,* AVC, *in series between them. Granules are seen surrounding the* OSV. *Guinea pig, surface preparation,* OsO_4 *staining, phase contrast.*

by perivascular spaces, which are bounded by the basilar membrane above and tympanic lamella below (figs. 13 and 14), and these may be linked by avascular channels either in series (fig. 15) or in shunt (fig. 16). These avascular channels of the basilar membrane are commonly seen in man as well as in the guinea pig.

The outer vessels are closely applied to the tympanic side of the basilar membrane. Immediately about them, at least in the guinea pig, there are dark granules (figs. 11, and 13 to 15) of an unidentified material, which we have not seen associated with capillaries elsewhere and which appear structureless under the electron microscope.

Pericytes (fig. 14) are numerous on both inner and outer spiral vessels. Vasomotor innervation is supplied by unmyelinated fibers that accompany the myelinated cochlear fibers but

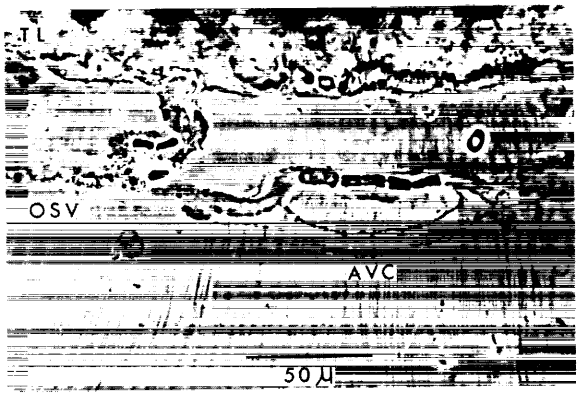

FIGURE 16.—*Outer spiral vessel* (OSV), *with pericapillary space and avascular channel* (AVC) *in shunt. The organ of Corti has been removed, and only the tympanic lip,* TL, *and the basilar membrane with its radial fibers (pars pectinata) are seen. Guinea pig, surface preparation,* OsO_4 *staining, phase contrast.*

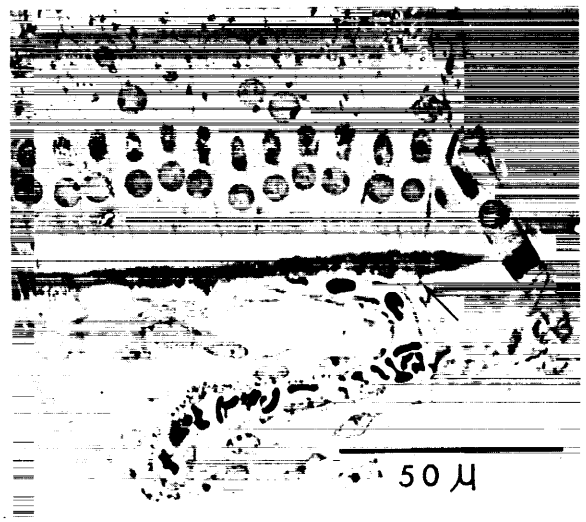

FIGURE 17.—*Nerve fiber (diagonal arrow) passing between footplates of outer pillars to pierce basilar membrane and end on outer spiral vessel. Guinea pig, "thick" section, Araldite embedding,* OsO_4 *fixation, basic fuchsin stain, phase contrast.*

descend to pierce the basilar membrane (fig. 17) and terminate on the vessels. These fibers are readily demonstrated with the Champy-Maillet zinc iodide–osmic acid technique (fig. 18).

BLOOD SUPPLY TO VESTIBULAR ORGANS

The small arteries that supply the vestibular end organs enter the maculae and cristae after coiling upon themselves in much the same way as the small arteries of the modiolus which form the glomeruli of Schwalbe. They enter the end organs along with the nerve fibers and soon divide to form capillary networks, the densest portion of which corresponds to the sensory area and lies immediately beneath the basement membrane in both the maculae and the ampullar cristae.

These various capillary nets have been carefully described and pictured by Catherine Smith for the guinea pig and by Scuderi and del Bo for man. The present study adds little of importance to their findings.

For the purpose of orientation, figure 19 shows a partial dissection of the vestibular structures of the guinea pig and their relation to the cochlea, in which some of the vascular arrangements already described can be distinguished. The dense capillary networks beneath the maculae of the utricle and saccule are illustrated in figures 20 and 21. Figure 20 also shows the distribution of vessels in the membranous wall of the utricle, and an avascular area which is regularly found opposite the opening of the common crus. The vessels of the semicircular canals are confined to lesser curvature (fig. 22), whereas the greater curvature is avascular, as C. Smith

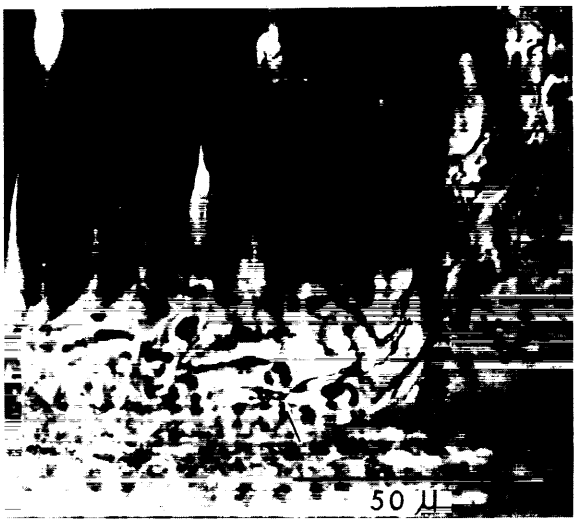

FIGURE 18.—*Unmyelinated nerve fiber (diagonal arrow) running parallel to inner spiral vessel, with nerve endings en passant. Guinea pig, Champy-Maillet* OsO_4-ZnI_2 *stain. "Thick" section, Araldite embedded. Bright field.*

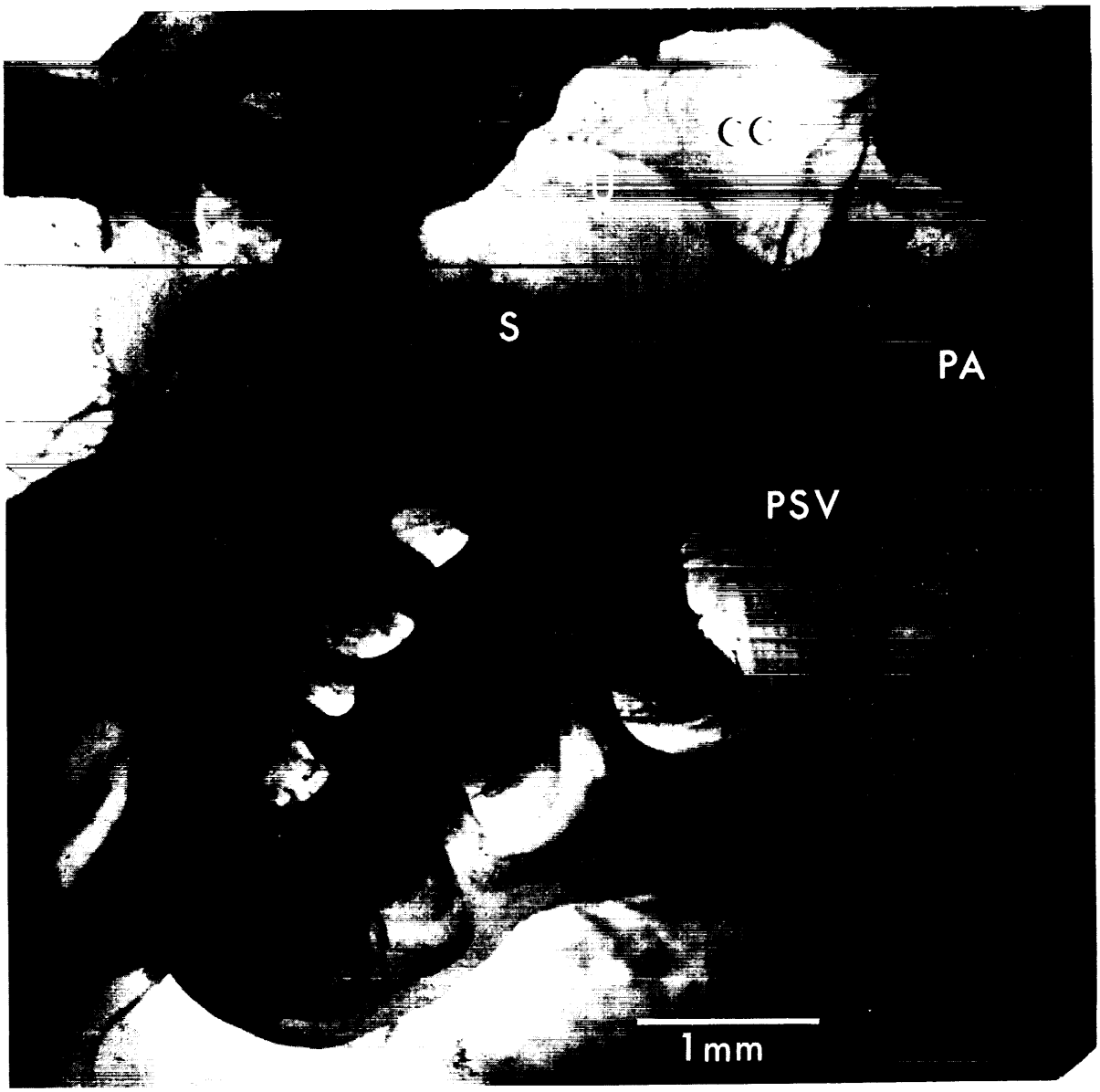

FIGURE 19.—*Partial dissection of left vestibule and cochlea in guinea pig with vessels stained by benzidine.* U, *utricle;* CC, *common crus.* PA, *posterior ampulla.* S, *macula of saccule.* PSV, *posterior spiral vein.*

has already pointed out. The cells of the greater curvature are reminiscent of those of Reissner's membrane, and fibrous attachments of the trabeculae of the perilymphatic space are absent. Like the capillaries of the maculae of the utricle and saccule, those of the crista lie for the most part directly beneath the basement membrane of the epithelium (fig. 23). From the network of the crista, capillaries radiate to supply the planum semilunatum (fig. 24).

AVASCULAR CHANNELS

The presence of avascular channels has already been alluded to in the spiral ligament above Reissner's membrane, the spiral limbus, and the pars arcuata of the basilar membrane. Similar channels have been seen in the spiral ligament behind the stria, and in the spiral prominence. They have been less extensively studied in the vestibular portion of the membranous

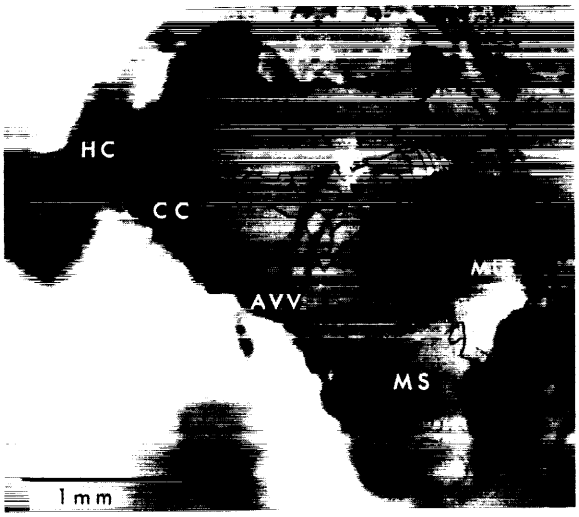

FIGURE 20.—*Vessels of the membranous utricle and the macula utriculi. Note the avascular area which is opposite the opening of the common crus,* CC. MU, *macula of utricle with its capillary plexus;* MS, *macula of saccule.* HC, *mouth of horizontal canal;* AVV, *anterior vestibular vein. Guinea pig, benzidine stain.*

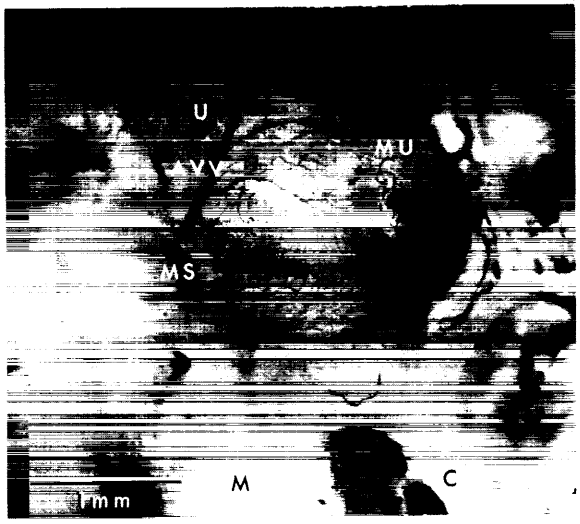

FIGURE 21.—*Capillary plexus of the macula sacculi,* MS. U, *utricle; with macula* MU; AVV, *anterior vestibular vein;* M, *modiolus;* C, *cochlea, basal turn. Guinea pig, same specimen as figure 20, benzidine stain.*

labyrinth, but they have been seen in the walls of the membranous canals (fig. 25), and they probably occur elsewhere. Their origin is not clear, but it is possible that they represent the perivascular spaces of much more extensive capillary networks that are present in fetal life. They presumably help to provide for an increased

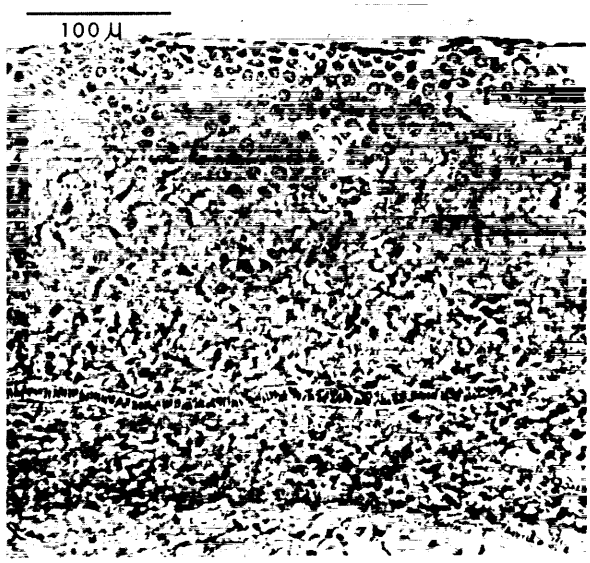

FIGURE 22.—*A portion of a semicircular canal. Longitudinal vessels and fibrous tissue are confined to the lesser curvature (below), whereas an epithelium with cells resembling those of Reissner's membrane occupies the greater curvature. Guinea pig,* OsO_4 *staining, whole mount, phase contrast.*

extravascular circulation of fluid within the walls of the membranous labyrinth.

VASCULAR REACTIONS TO QUININE AND SALICYLATES

The ototoxic effects of quinine and salicylates have been recognized for many years, but no satisfactory demonstration of the histopathological basis of their action has been given. Since the hearing impairment, unlike that due to kanamycin and other basic antibiotics related to streptomycin, is often reversible, Silverstein et al. (ref. 32) have attributed the temporary hearing loss to metabolic changes in the cells of Corti's organ. In acute experiments in guinea pigs, in which single doses of either drug caused loss of the Preyer reflex and severe ataxia, we have found a widespread vasoconstriction of the small vessels of the middle and inner ear after single doses of both drugs. Phase-contrast examination of surface preparations has shown constriction of strial capillaries and partial occlusions of the spiral vessels by swollen endothelial cells and pericytes (figs. 26 and 27) after single doses of quinine dihydrochloride and sodium salicylate, 250 mg/kg. The same dose of

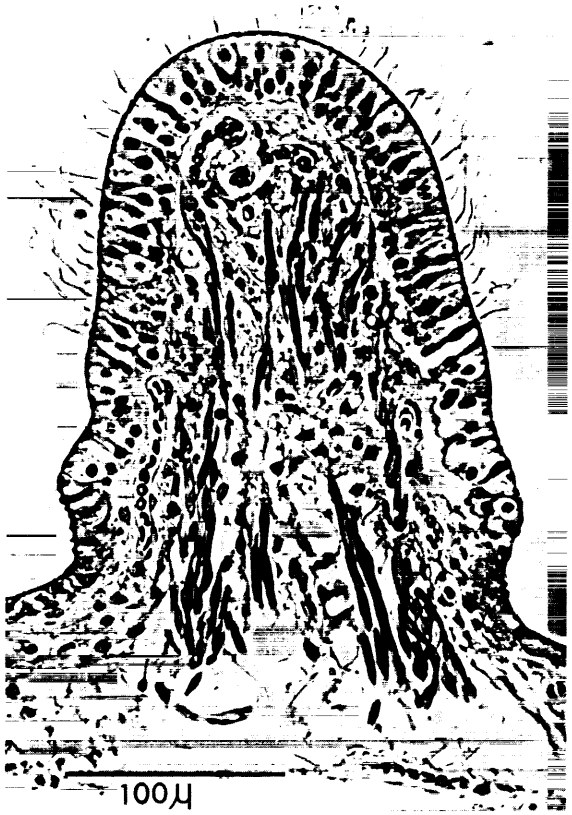

FIGURE 23.—*Crista of semicircular canal in cross section, showing portions of capillary plexus beneath the secretory epithelium (at left) and beneath neuroepithelium (near summit). Guinea pig, "thick" section, Araldite embedded,* OsO_4 *staining, phase contrast.*

FIGURE 24.—*Capillaries radiating beneath the planum semilunatum of an ampullar crista. Guinea pig, surface preparation,* OsO_4 *staining, phase contrast.*

FIGURE 25.—*Capillary with adjoining avascular channel* (AVC) *from the wall of a semicircular canal. At right, the Reissner's membranelike epithelium of the greater curvature. Guinea pig, surface preparation,* OsO_4 *staining, phase contrast.*

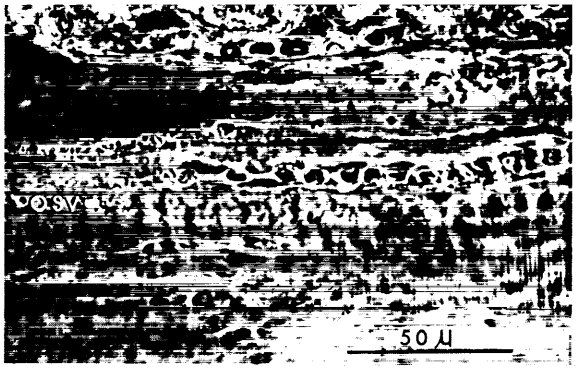

FIGURE 26.—*Spiral vessels of quinine-treated guinea pig, showing partial occlusion of outer spiral vessel* (OSV) *by endothelial cells, and apparent distention of its pericapillary space. Quinine dihydrochloride 250 mg/kg s.c., sacrificed 1 hour later. Surface preparation,* OsO_4 *staining, phase contrast.*

FIGURE 27.—*Basilar membrane (tympanic side) of salicylate-treated guinea pig, showing empty outer spiral vessel* (OSV) *with swollen endothelial cells and pericytes.* OP, *bases of outer pillars. Sodium salicylate, 500 mg/kg s.c., sacrificed 30 min later. Surface preparation,* OsO_4 *staining, phase contrast.*

sodium salicylate in operant-conditioned monkeys (ref. 33) caused a threshold shift of 20–25 dB, with recovery in 24 hours.

Our findings clearly support the conclusion of Gradenigo (ref. 34) and Wittmaack (ref. 35) that the hearing impairment caused by quinine is due to cochlear ischemia, similar to the retinal ischemia readily produced by this drug in experimental animals. The salicylate effect on hearing seems to be explicable on the same basis.

DISCUSSION

The capillaries of the inner ear are arranged in patterns that appear to favor the localized exchanges of water, ions, and metabolites upon which both the rigid control of its internal environment and the transducer activities of its end organs depend. The vestibular end organs have capillary networks immediately underlying the neuroepithelium, and the organ of Corti is surrounded by the capillary beds of the membranous spiral lamina on one side, and by those of the spiral ligament, spiral prominence, and stria on the other. These are sufficient to maintain a somewhat precarious supply of oxygen to the hair cells and their supporting structures. Any reduction in blood supply, as seen after quinine and salicylates, is sufficient to impair sensory function.

The source of the cortilymph that fills the tunnel and the Nuel spaces of Corti's organ has not yet been identified by experiment, but it seems most likely that this fluid comes mainly from the plasma filtrate of the inner and outer spiral vessels. The "perilymphatic pores" that have been said to exist in the osseous spiral lamina, and to connect the interior of Corti's organ with the perilymph in scala tympani, appear in reality to be communications between the pericapillary spaces of the inner spiral vessels and the perineural spaces of the bundles of cochlear nerve fibers approaching the foramina nervosa. The cochlear plexus of the modiolus may also supply a part of the cortilymph, by way of the perivascular spaces of the modiolar glomeruli and the perineural spaces of the cochlear nerve. The functions of the specialized tissue of the cochlear plexus and of the modiolar and vestibular glomerular vessels are largely unknown and obviously deserve further study.

Although filtration appears to be a prominent feature, especially in the capillaries of the spiral ligament and in the spiral vessels, none of the capillaries that we have encountered show fenestrations like those of the glomerular capillaries of the kidney (cf. ref. 36). Those that we have examined appear to have a complete, continuous basement membrane or basement lamina (ref. 37). Most of them lack a complete pericapillary cellular investment interposed between the parenchymal cells and the capillary (cf. ref. 38), but those of the stria do have such a covering. In the latter tissue, secretion rather than filtration seems to be the rule, and the marginal cells appear to be designed for active transport of ions between the blood and endolymph.

Direct observation and cinematography of the microcirculation of the inner ear in the living animal, especially in the beautiful series of studies by Perlman and Kimura (ref. 29), have given important information concerning the dynamics of the blood flow in the spiral ligament and stria. Similar studies of the vestibular portions of the membranous labyrinth should prove equally rewarding.

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DISCUSSION

DOLOWITZ: This has been a beautiful demonstration of the cochlea and organ of Corti. In your demonstration you showed the Reissner's membranes covering two walls of the triangle. What did you find when you examined the third wall?

HAWKINS: We think that it extends behind the stria; and at the point that we can call the lower edge of the stria, it comes out once more to cover the spiral prominence. There we seem to lose it. Where it has gone from there, I do not know, but it seems to end at the Cladius cells in the region of the so-called root cells. We shall have to make some developmental studies to find out whether this notion is true and just exactly what happens to it; in other words, whether it becomes the basilar membrane as we suspect.

SMITH: The avascular channels that you showed between two capillaries, what are they formed by? Are they formed by endothelial cells?

HAWKINS: When we see these pericapillary spaces around the spiral vessels in the electron micrographs, they seem to be formed by the tympanic cover layer cells, i.e., the mesothelial cells. We have not actually seen the avascular channels yet in the electron microscope.

SMITH: There was one other question regarding the processes that you showed around the capillaries in the stria vascularis. Have you considered the possibility that these might be extensions of the stria vascularis cells? In electron micrographs I have observed that the cells of the stria vascularis do extend about the capillaries in the stria.

HAWKINS: These cells seem to be similar in character to those that I described as going behind the stria. I forget how they are referred to in the Echandia paper, the recent one on the stria. They are the same ones that we are equating with Reissner's membrane cells. I think that the processes are extending from behind rather than from the marginal cells at the endolymphatic surface.

WOOD: Did the salicylates appear to have the same effect on the endothelium as quinine?

HAWKINS: So far as I can say, they are not distinguishable. Certainly in terms of dose, they might be. We have not gone, as I recall, over 250 mg/kg with quinine. We have gone up to 500 mg/kg with sodium salicylate. It was with the salicylate that we treated the monkeys that recovered so nicely from the hearing loss.

WOOD: It is the same mechanism?

HAWKINS: Yes; so far as we can see in the preparations of the basilar membrane, it is exactly the same.

The Vascular Routes to the Petrous Part of the Temporal Bone: Developmental and Adult Anatomy [1]

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DAVID G. HARPER
AND
THOMAS R. WINCH
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SUMMARY

Basic to consideration of applied anatomy of any organ, or organ system, is knowledge of the pattern of its blood supply. In a preceding paper ("The Vestibular and Cochlear Aqueducts: Developmental and Adult Anatomy of Their Contents and Parietes," by Barry J. Anson, David G. Harper, and Thomas R. Winch), this feature was considered with reference to the structure of the endolymphatic duct and sac. It has been expanded in the present report to include the entire petrous part of the temporal bone.

At least nine channels conduct blood vessels to or from the interior of the petrous pyramid. They have been described and illustrated as seen in dissections, in serially sectioned specimens, and as demonstrated by reconstructions prepared from the latter. In each instance the description of the adult form has been introduced by an account of developmental anatomy.

These routes are the following: the spiral foraminous tract of the cochlea; the vestibular areas (superior and inferior) of the fundus of the internal acoustic meatus; the subarcuate fossa; the vestibular aqueduct; the petrosal sulci; the facial canal; the fissula ante fenestram; and the channel for the cochlear vein (near the cochlear aqueduct).

For the innervation of the sensory elements in the cochlear duct, of the utricle and the saccule in the vestibule, and those of the ampullae in the semicircular canals, the routes traversed are the foraminous tract and the vestibular areas in the fundus of the meatus; the statoacoustic (VIIIth) nerve, in division and subsequent arborescent spread, is accompanied by blood vessels of neural supply.

The vascular pattern of the surrounding capsule belongs in a wholly different category; the vessels are separate from those that supply the spiral organ, the maculae, and the cristae. The capsular arteries, derived from parent stems in the mucous membrane of the labyrinthine wall of the tympanic cavity and the meningeal investment of the posterior surface of the petrous pyramid, vascularize the bone, but do not (so far as observed) pass through the inner periosteal layer to reach the membranous labyrinth. In another respect, the capsular differs from the neural supply: In the former case, arteries are accompanied by veins; in the latter, veins (of essentially diploic character) form an independent system.

In short, then, the blood supply to the *pars petrosa* and its labyrinthine contents is divisible into neurovascular and capsular parts. The former is associated with the brain, the latter with the skull. This arrangement finds its genesis in embryonic germ-layer sources: The membranous labyrinth, like the brain, is an ectodermal derivative; the capsule, with the skull in which it is lodged, is derived from the mesoderm.

[1] Carried out with the support of the Central Bureau of Research of the American Otological Society, Inc., and the U.S. Public Health Service of the National Institutes of Health (grant No. NB-03855-05).

CERVICAL SOURCES OF BLOOD SUPPLY

The regular concepts of blood supply to parts of the skeletal system generally do not apply to the pattern of vascularization of the *pars petrosa* of the temporal bone, even though the arterial sources are familiar (fig. 1).

The arterial sources are: subclavian (at 1), external carotid (at 2), and internal carotid (at 3). When once their branches reach the temporal bone, they are conveyed to parts of the middle ear and inner ear where the architecture belongs in a very special category. The pattern of venous drainage is equally unusual.

Three features prepare the investigator for the observed oddities: the arterial supply is, in part, an offset of the cerebrocerebellar system; returning venous blood is collected into capacious sinuses in the dural layer; diploic anastomoses bring the vessels in the temporal bone into communication with the vast system lodged between the plates of the skull.

DEVELOPMENTAL AND ADULT ANATOMY

As seen in medial (or meningeal) view, four openings lead into the petrous pyramid: the internal acoustic meatus, the subarcuate fossa, the vestibular aqueduct, and the cochlear aqueduct or canaliculus (fig. 2). The first three transmit blood vessels; the cochlear aqueduct is matched in its course by a channel for a vein.

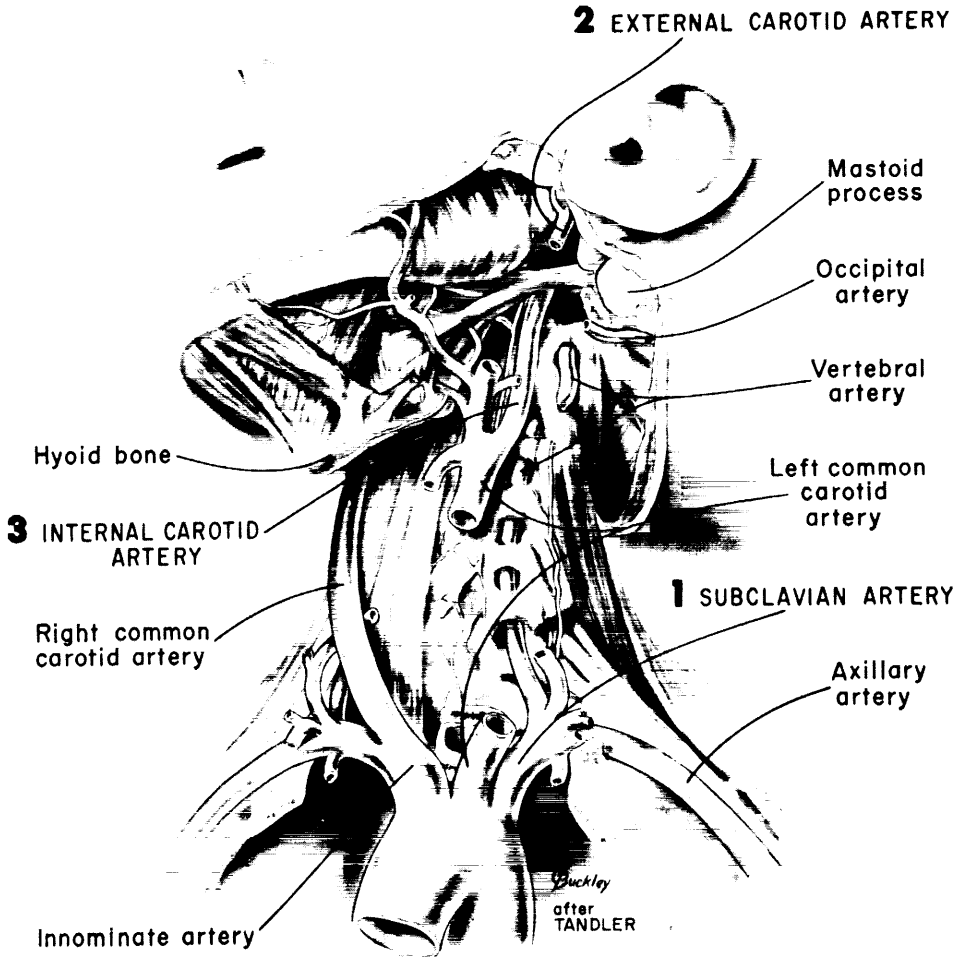


FIGURE 1.—*Deep dissection of the neck which shows the subclavian and carotid sources of arteries that supply the temporal bone.* (*Ann. Otol., vol. 75, Dec. 1966, pp. 921–944.*)

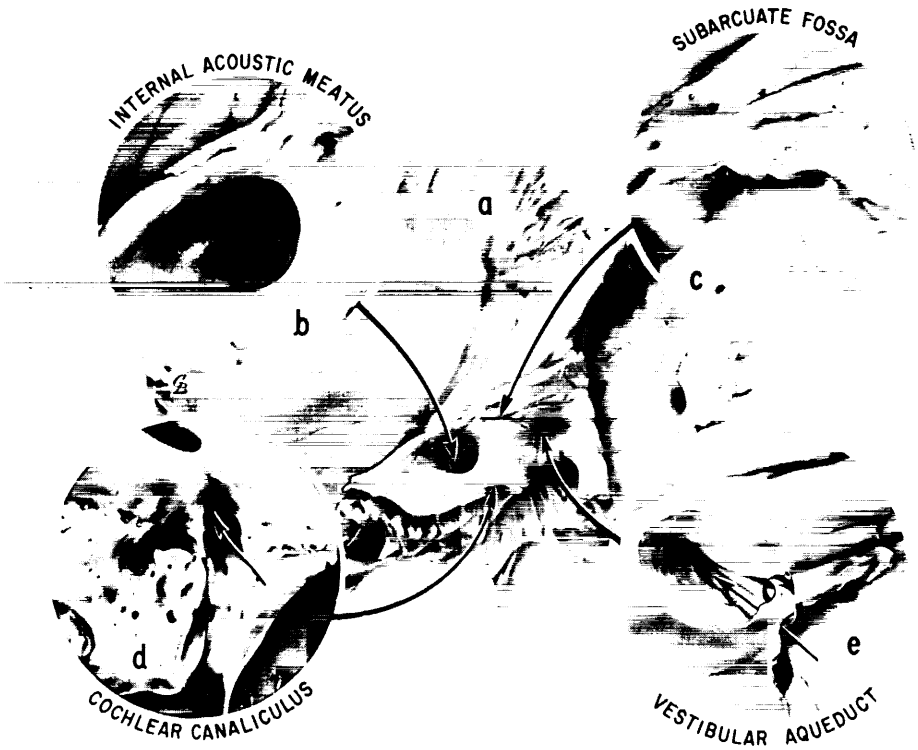


FIGURE 2.—*Medial surface of the temporal bone (skeletal preparations). The following channels through which blood vessels reach the labyrinths within the petrous part of the temporal bone are shown: internal acoustic meatus* (b), *subarcuate fossa* (c), *and vestibular aqueduct* (e). *The site of the external aperture of the cochlear canaliculus, or aqueduct,* (d) *on the inferior surface of the bone is visible in this view as a notch at the posterior angle* (a). *The minute channel for the cochlear vein reaches the inferior surface near the aperture of the canaliculus. Numerous small openings are distributed over the posterior surface. They transmit veins from the meningeal surface to the interior of the bone (to diploic tissue). In many specimens similar openings occur on the "floor" of the superior and inferior petrosal sulci (fig. 5 of the paper entitled "The Vestibular and Cochlear Aqueducts: Developmental and Adult Anatomy of Their Contents and Parietes" and fig. 12 of this paper).*

On the opposite or lateral (tympanic) side, the prominent channel for carriage of blood supply is the facial canal (fig. 3). Smaller openings conduct the several tympanic vessels to an anastomosis on the promontory. These lesser channels are the following: the caroticotympanic, the hiatus of the facial canal, and the *fissula ante fenestram.*

All of the channels are unlike the more familiar nutrient foramina through which typical long bones of the human skeleton receive their blood supply. Their unusual adult course and distribution are due to the special nature of the steps through which the ossification centers pass in attaining maturity. Fourteen such centers contribute to the formation of the otic capsule around the labyrinth. The first appears at about the 4-month stage, the last at about the middle of the fifth month. In a short period of 6 weeks, the capsule has changed from cartilage to bone.

Toward the close of the period, capsular growth and differentiation are evident in striking form: Under the arch of the superior semicircular canal, vascular buds from the meningeal tissue invade and spongify the cartilage, thereby permitting, for a limited period, expansion of the arcs of the semicircular ducts. The invasive vessels are derived from the internal auditory artery and vein. These subarcuate vessels will be accounted for hereinafter as traversing one of the several im-

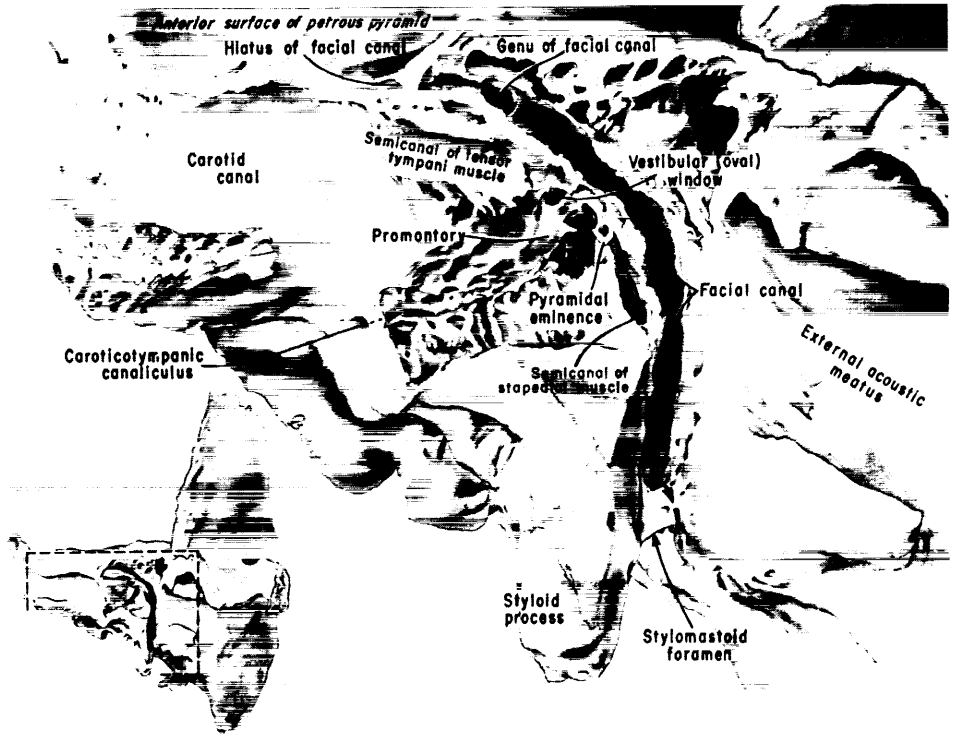


FIGURE 3.—*Temporal bone: dissection to expose the labyrinthine (medial) wall of the tympanic cavity. Five of the several routes by which blood vessels reach the wall in the area of the promontory to contribute to the tympanic plexus are shown. These vessels are named for their position (anterior, posterior, superior, and inferior). The posterior tympanic, a branch of the stylomastoid (the latter from the posterior auricular) leaves the facial canal through the canaliculus of the* chorda tympani. *The superior tympanic from the middle meningeal (the latter a branch of the internal maxillary) goes through the tympanic canaliculus (in the cochleariform process) to the promontory. The inferior tympanic, from the ascending pharyngeal, also enters the middle ear through the same canaliculus to ramify on the promontory. The anterior tympanic, from the internal maxillary, enters the middle ear through the petrotympanic fissure. The caroticotympanic canaliculus transmits small branches of the same name, derived from the internal carotid artery. The natural orifice of the stylomastoid foramen is marked by a remnant of the wall (encircled). The asterisk indicates the site of an air-cell. The dissections also demonstrate the subdivisions of the facial canal. (Compare with fig. 16*(b).*) (Ann. Otol., vol. 75, Dec. 1966, pp. 921–944.)*

portant vascular channels through the *pars petrosa* of the adult bone.

The following additional features of development contribute to the complexity of blood supply:

(1) The cochlear and canalicular divisions of the otic capsule are governed by different and independent timetables of morphogenesis and growth, the cochlear being chronologically the more advanced.

(2) The ossification centers, with expansion and fusion peripherally, leave no histological evidence of their primordial independence.

(3) Each ossification center is made up of three layers. They, too, have their separate developmental timetables. None ever attains Haversian structure.

(4) Since the capsule has a boxlike form, there are no groupings of vascular conduits of the sorts regularly encountered in typical long bones of the skeleton; that is, there are no nutrient foramina.

Internal Acoustic Meatus: Cochlea

Prior to the onset of ossification in the otic capsule, the vascular pattern of the cochlea is

well established. In the 4-month fetus, the branches of the internal auditory artery, following the statoacoustic nerve, enter the internal acoustic meatus (fig. 4(*a*), at 1), pass to the modiolus (at 2), reach the tympanic and vestibular scalae (at 3 and 4), and ultimately reach the vascular *stria* on the wall of the cochlear duct.

At the beginning of ossification, the vessels are even more striking here in the 5-month fetus. They may be traced from the meatus, through the modiolus (fig. 4(*b*), at 1), to the attached margin of the future osseous spiral lamina (at 2), to the wall of the vestibular scala (at 3), and the tympanic scala (at 4), and to the spiral ligament (at 5).

One month later, in the 6-month fetus, readily identifiable channels transmit vessels from the tympanic plexus (in the future submucosal layer) through the outer and into the middle layer of the capsule.

No two of the three layers are alike (figs. 5(*a*) and 5(*b*)). The outer periosteal layer will thicken, and concurrently become more dense. The middle layer, now quiescent, will grow rapidly in late fetal and early prenatal stages. Together they will attain petrous fabric. The inner periosteal layer, long since a mature stratum, will remain unchanged.

So far as can be determined with the light microscope, no vessels (in the adult capsule) pass from the labyrinthine wall of the middle ear to the sensory elements in the cochlear duct. They seem to be sealed off as elements in a neurovascular complex.

The density of the layers is evident in sections from late fetal, infantile, and adult temporal bones (figs. 4(*c*) and 5(*c*)). Whereas the tympanic wall is petrous, the way into the cochlea on the meningeal side is a widely open aperture.

Subarcuate Fossa

The distance between the internal acoustic meatus and the subarcuate fossa is about 2 to 5 mm. A sulcus sometimes connects them to accommodate the subarcuate branch of the internal auditory artery and the corresponding vein.

As already described, the vascular buds from the subarcuate artery render spongy the canalicular division of the cartilaginous cochlear capsule, entering beneath the arch of the superior canal. This process is prominent in the fetal capsule in the early stage of ossification (fig. 6(*a*)).

After the arcs of the semicircular ducts have attained full expanse, the fossa undergoes reduction in size concurrently with retreat and atrophy of the vascular tissue. This advancing stage in ossification is demonstrated in the temporal bone of the newborn infant (fig. 6(*b*)).

In the adult the fossa persists, but with greatly reduced capacity (fig. 6(*c*)). Gross specimens demonstrate its relatively large size in the newborn (fig. 7(*a*)).

Typically the fossa is reduced to a pinpoint in specimens of adolescent and adult skulls (figs. 7(*a*) and 7(*b*)). It is small, but so is every other structure in the temporal bone.

The developmental history of the temporal bone explains the capaciousness of the subarcuate fossa in the fetus and in the infant. Although regularly minute in the adult, occasionally it may be larger than normal. The fossa may be a vertical opening at the accustomed site of the external aperture of the vestibular aqueduct. Small emissary apertures may occur as accessory to the fossa itself.

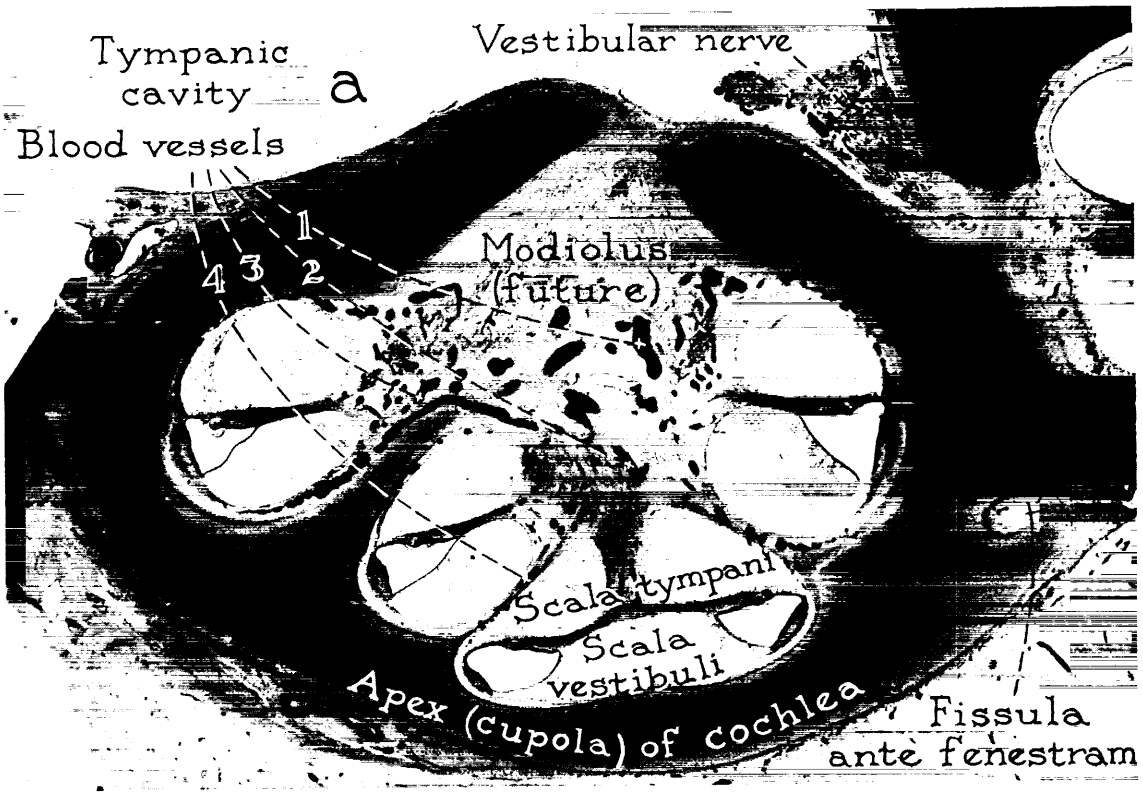
In the adult temporal bone, a tract of petrous air cells regularly follows the general course of the subarcuate fossa, passing under the arch of the superior semicircular canal (fig. 8, tract opened by dissection).

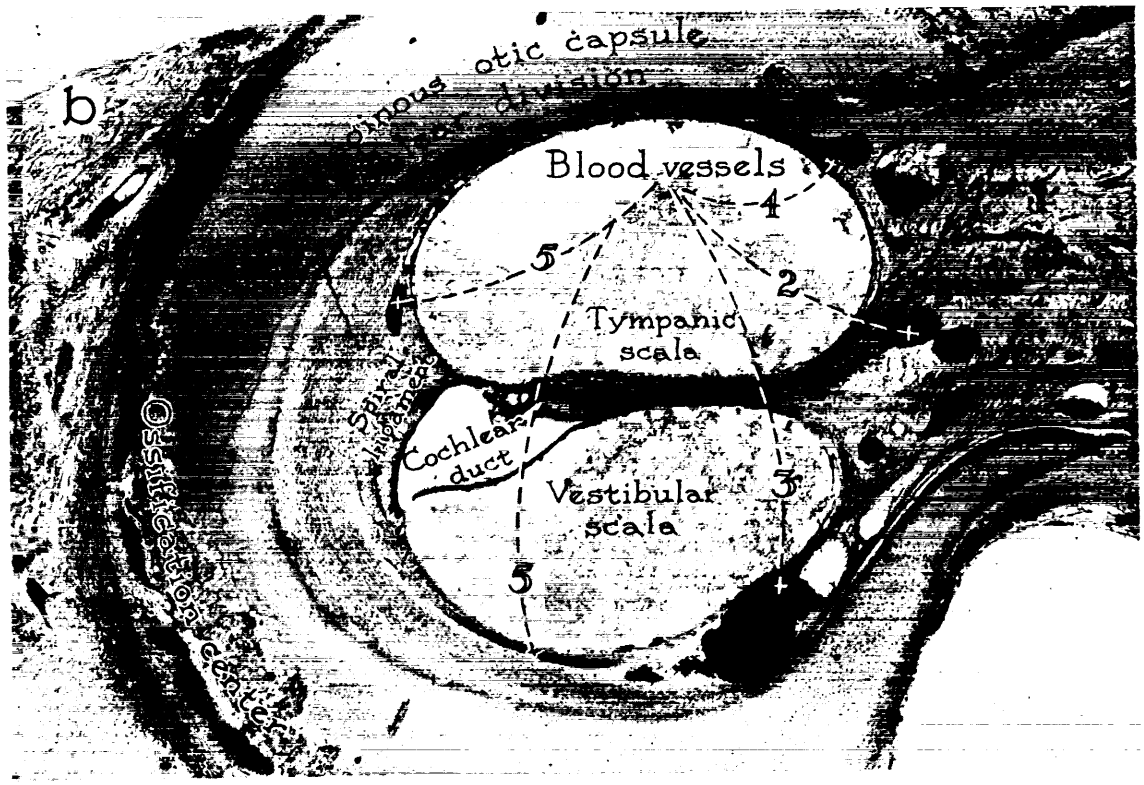
Upon entering the bone through the subarcuate fossa, the blood vessels spread in a complex ramifying pattern within the submucosal tissue of the air cells. This arrangement stands in sharp contrast to that of the cochlear supply. In the latter instance, as already demonstrated, there is a direct route through the internal acoustic meatus.

It remains to be determined by what tortuous course the vessels pass to the interior of the petrous pyramid.

Vestibular Aqueduct

The vestibular aqueduct is an important channel for the passage of blood vessels between the cranial cavity and the vestibule. On the way, numerous connections are made with vessels transmitted by vascular channels in the encompassing bone. The communications constitute a veritable plexus around the endolymphatic sac and duct.


Tympanic cavity
a
Vestibular nerve
Blood vessels
1
2
3
4
Modiolus (future)
Scala tympani
Scala vestibuli
Apex (cupola) of cochlea
Fissula ante fenestram


b
Blood vessels
1
2
3
4
5
Tympanic scala
Cochlear duct
Vestibular scala
Osseous spiral lamina
Osseous otic capsule

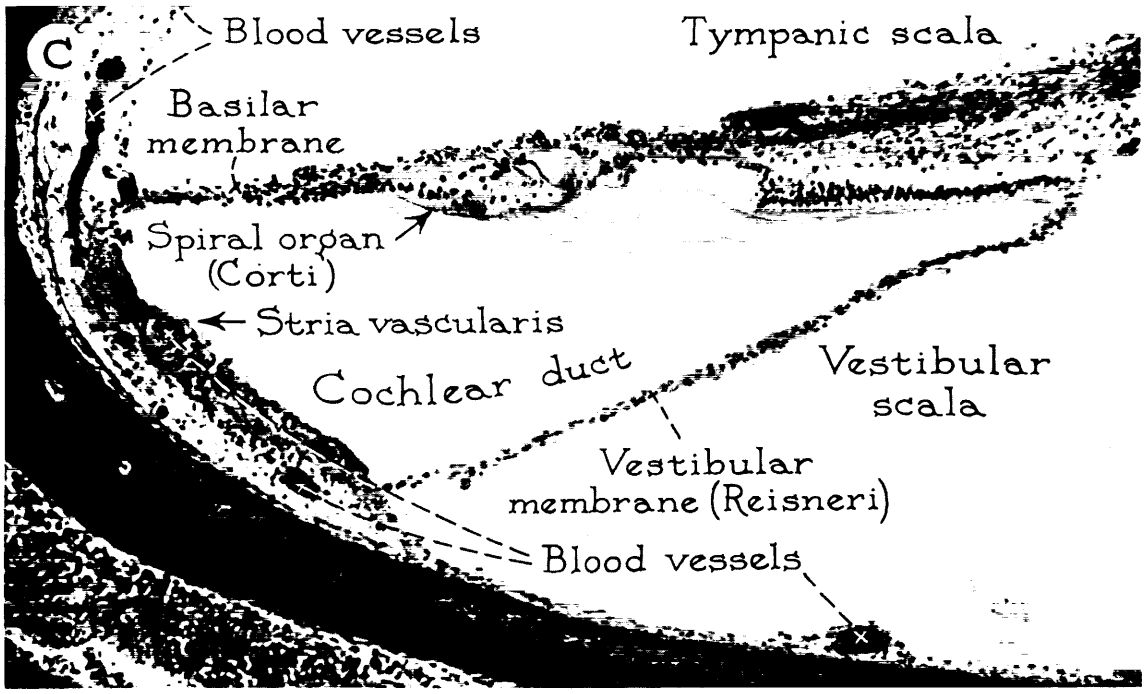


FIGURE 4.—*Establishment of the internal auditory artery as the source of supply to the cochlea.* (a) *Fetus of 16½ weeks (126 mm crown-rump length);* (b) *fetus, 19½ weeks (161 mm);* (c) *newborn (4-day premature). Transverse sections. Wisconsin Collection, series 11, 13, and 124, respectively.* (a) *18×,* (b) *18×,* (c) *135×.* a: *Vessels pass through the internal acoustic meatus to the modiolar area (at 1 and 2), then along the walls of the* scala tympani *and* scala vestibuli *on the way to the* stria vascularis *of the cochlear duct.* b: *Vessels are traced from the margin of the developing osseous spiral lamina (at 2) to the walls of the vestibular scala (at 3) and tympanic scala (at 4) toward and into the spiral ligament (at 5).* c: *Vessels are present in the periotic tissue of the vestibular scala, spiral ligament, and vascular stria.*

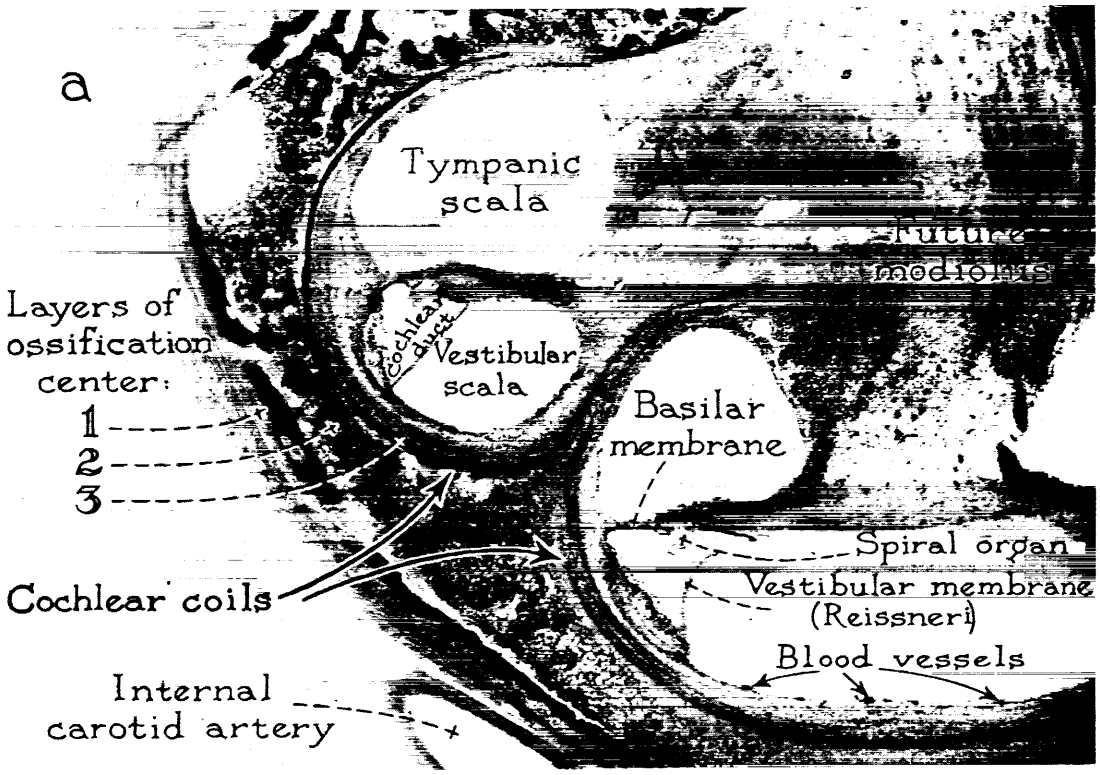
The gross form, size, and relationships of the distal segment of the aqueduct and of its external aperture call for introductory consideration. Typically, the aperture is elongate and oblique, situated approximately midway between the superior petrosal sulcus and the jugular fossa, just below the subarcuate fossa (fig. 9).

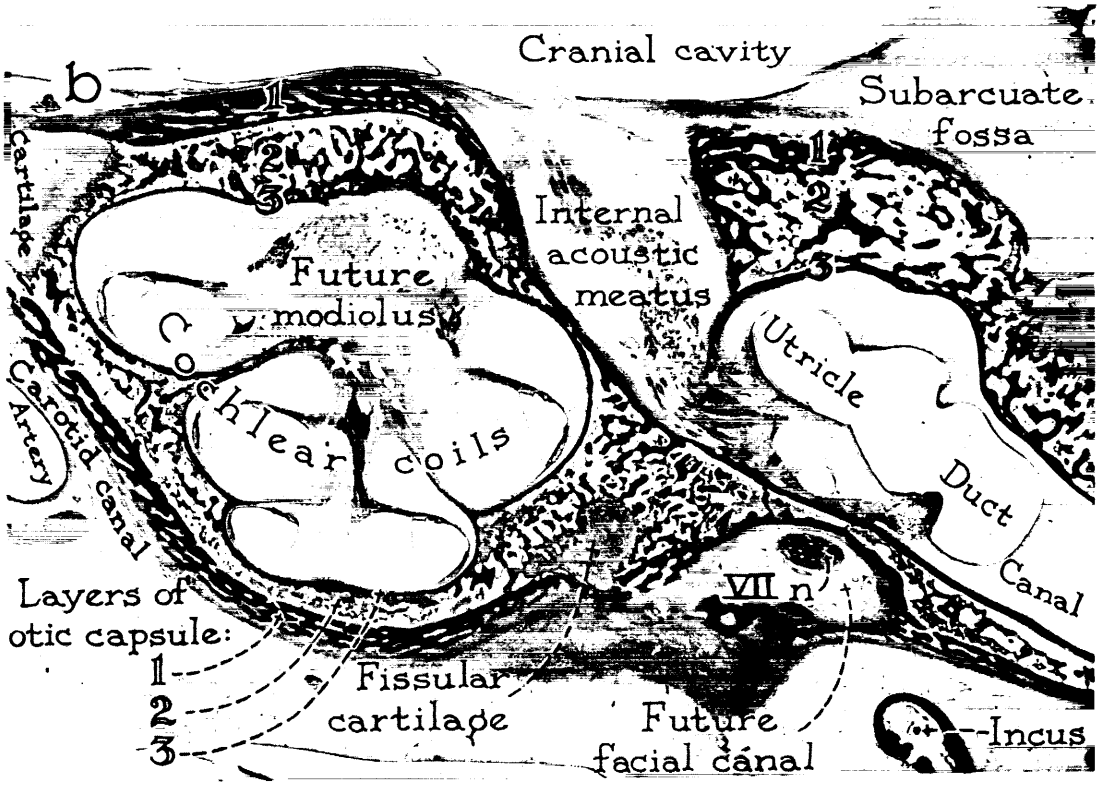
The distal segment is wide at the aperture; it narrows toward an apex (figs. 2(*a*) and 2(*e*)). The configuration matches that of the contained *saccus*, which is broad as it approaches the intradural position, slender as it goes inward to the vestibular aperture (fig. 7(*a*) of the paper entitled "The Vestibular and Cochlear Aqueducts: Developmental and Adult Anatomy of Their Contents and Parietes").

As demonstrated in that report, the *saccus* is relatively wide and rugose or vesiculate as it expands toward the external aperture of the aqueduct. It narrows inward as the smooth-walled isthmus, beginning at the apex of the distal segment of the aqueduct. The duct widens again after emergence from the internal aperture of the aqueduct. In the form of a sinuslike expansion, it is contiguous with the utricle, the latter occupying the elliptical recess of the vestibule.

The vessels that enter the vestibular aqueduct are rami from the posterior meningeal branch of the occipital. They are elements in a complex whose sulci are frequently encountered in skeletal specimens of temporal bone (fig. 10). Such sulci may course toward the subarcuate fossa and the vestibular aqueduct.

Vascularization is established early in the vestibular aqueduct (fig. 11(*a*) at arrow). In the 5-month fetus (that is, at about midterm) the mesenchymal tissue around the endolymphatic duct and sac contains blood vessels (fig. 11(*b*)). This is the stage at which ossification of the cartilaginous otic capsule begins.


a
Tympanic scala
Future modiolus
Layers of ossification center:
1
2
3
Cochlear duct
Vestibular scala
Basilar membrane
Spiral organ
Vestibular membrane (Reissneri)
Blood vessels
Cochlear coils
Internal carotid artery


b
Cranial cavity
Subarcuate fossa
Cartilage
Internal acoustic meatus
Future modiolus
Cochlear coils
Utricle
Duct
Canal
Carotid Artery
Carotid canal
VII n
Layers of otic capsule:
1
2
3
Fissular cartilage
Future facial canal
Incus

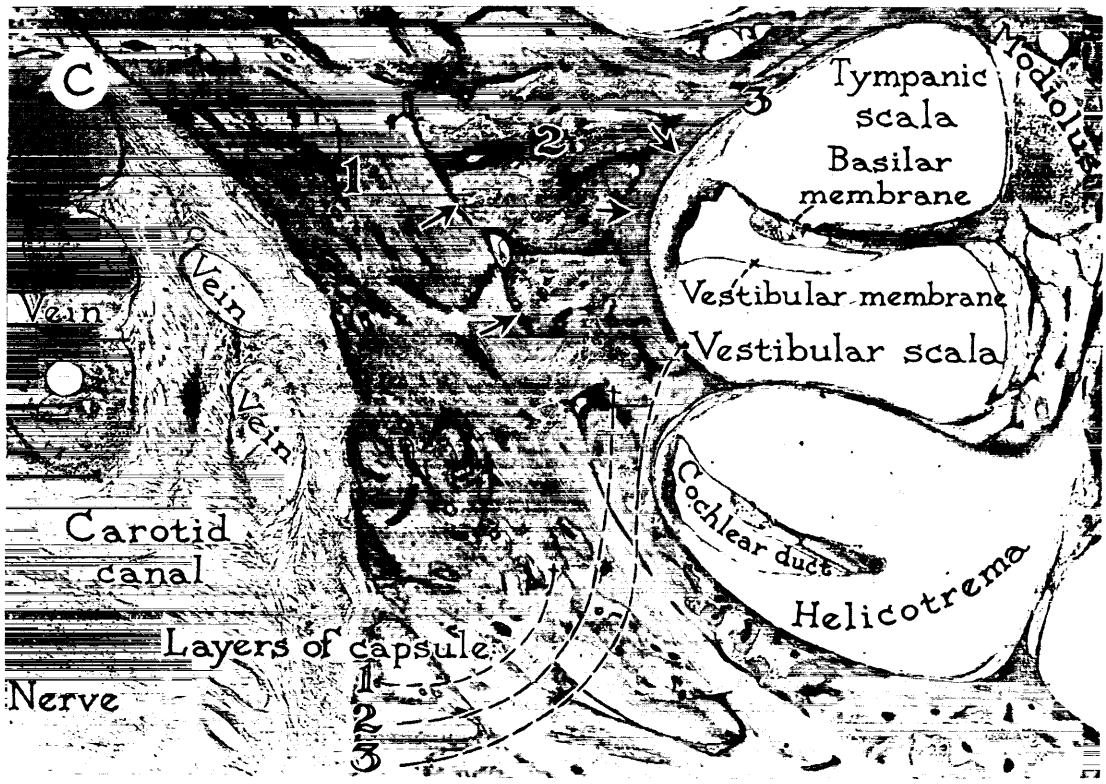
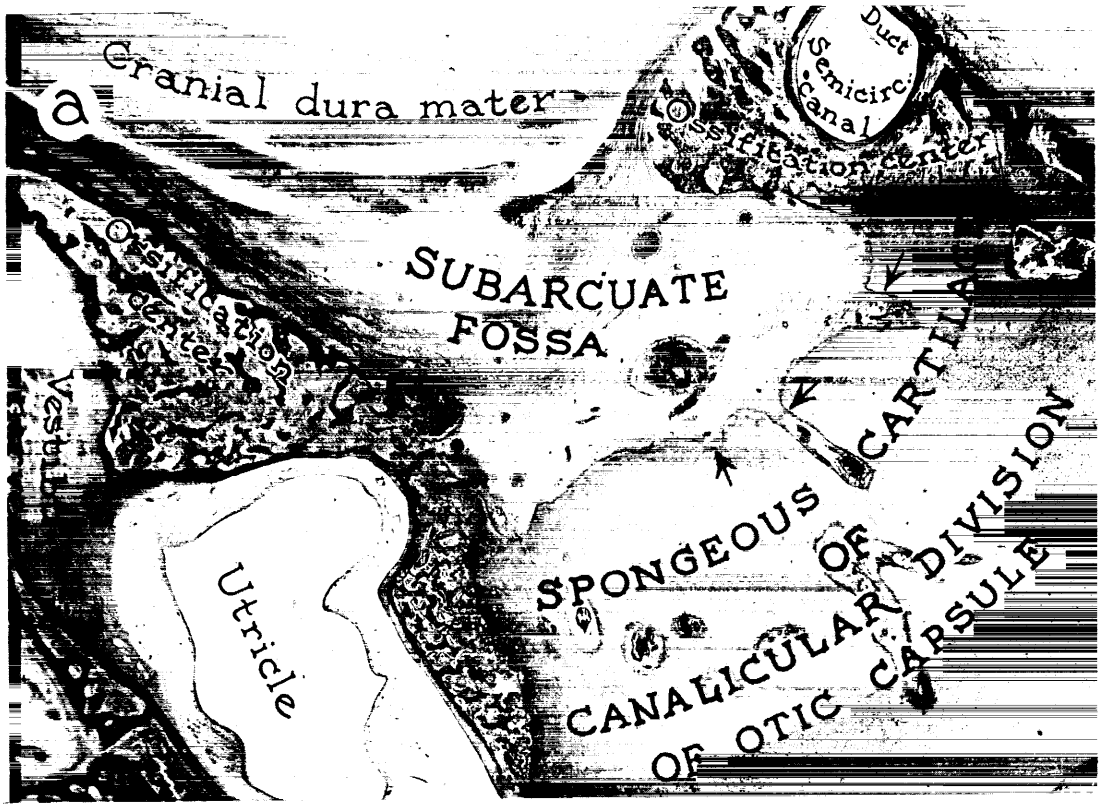
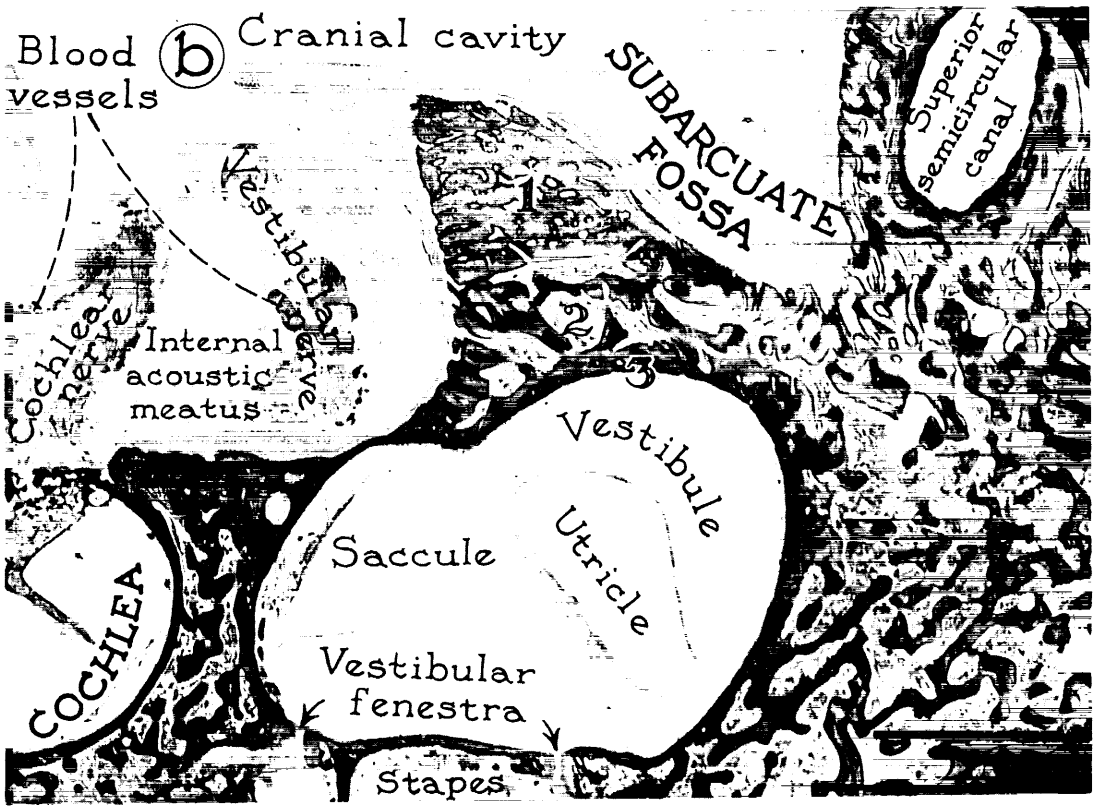


FIGURE 5.—*Developmental and adult structure of the osseous capsule of the cochlea.* (a) *Fetus of 19½ weeks;* (b) *fetus of 21 weeks;* (c) *adult, 19 years of age. Transverse sections. Wisconsin Collection, series 41, 21, and 28.* (a) *21×*, (b) *14×*, (c) *33×*. a: *In the fifth month, the three typical layers are present in the ossification center at the base of the cochlea. The outer periosteal lamina (at 1) consists of plates which do not yet form a continuous shell. The inner periosteal layer (at 3) is excessively thin, yet where present is an uninterrupted sheet. The middle layer (at 2) is still largely cartilaginous. Areas of intrachondral bone are beginning to appear. Each of these "islands" consists of calcified cartilaginous matrix in which osteogenic buds excavate large spaces, replace the necrotic cartilage cells, and lay down bone within the lacunae. Excavation, however, is never complete; large islands and bars of calcified cartilage remain osteoblasts (Bast, 1930), then deposit endochondral bone on the outer surface of these* globuli interossei. *As deposition progresses, the marrow spaces become smaller, ultimately accounting for the petrous character of the pyramid. Unlike skeletal elements generally, the layers of the capsule are not reexcavated and rebuilt.* b: *In the fetus at the 5-month stage, the external periosteal layer is developing rapidly, on the way to becoming a prominent part of the otic capsule. The inner periosteal layer is now a complete, but thin, shell for the cochlear coils. Growth in the middle layer has been slow, and will continue so until the last week of fetal life.* c: *In the temporal bone of the adult, the three layers remain identifiable. The cartilage islands, unfailingly present, serve to set off the external and internal periosteal strata.*

Here, as elsewhere in the body, an epithelial tube acquires a blood supply early in the course of its morphogenesis. In the cochlear aqueduct (which lacks such content) the tissue is virtually avascular.

As developmental events prove, the schema of vascular pattern in the vestibular aqueduct of the preosseous stage is predictive of the blood supply to the endolymphatic duct and sac in the adult. Blood vessels course through the connective tissue that surrounds the epithelial duct and in channels of the surrounding bone (fig. 11(*c*); see also figs. 12(*a*) to 12(*c*), 13(*a*) to 13(*c*) in a preceding paper entitled "The Vestibular and Cochlear Aqueducts: Developmental and Adult Anatomy of Their Contents and Parietes"). Other vessels enter directly from the meninges.


a
Cranial dura mater
Semicirc. canal
Duct
Ossification center
SUBARCUATE FOSSA
Ossification center
Vestibule
Utricle
SPONGEOUS
CANALICULAR
OF OTIC
OF
CARTILAGINOUS
DIVISION
CAPSULE


Blood vessels
b
Cranial cavity
SUBARCUATE FOSSA
Superior semicircular canal
Vestibular nerve
Cochlea nerve
Internal acoustic meatus
Vestibule
Utricle
Saccule
COCHLEA
Vestibular fenestra
Stapes

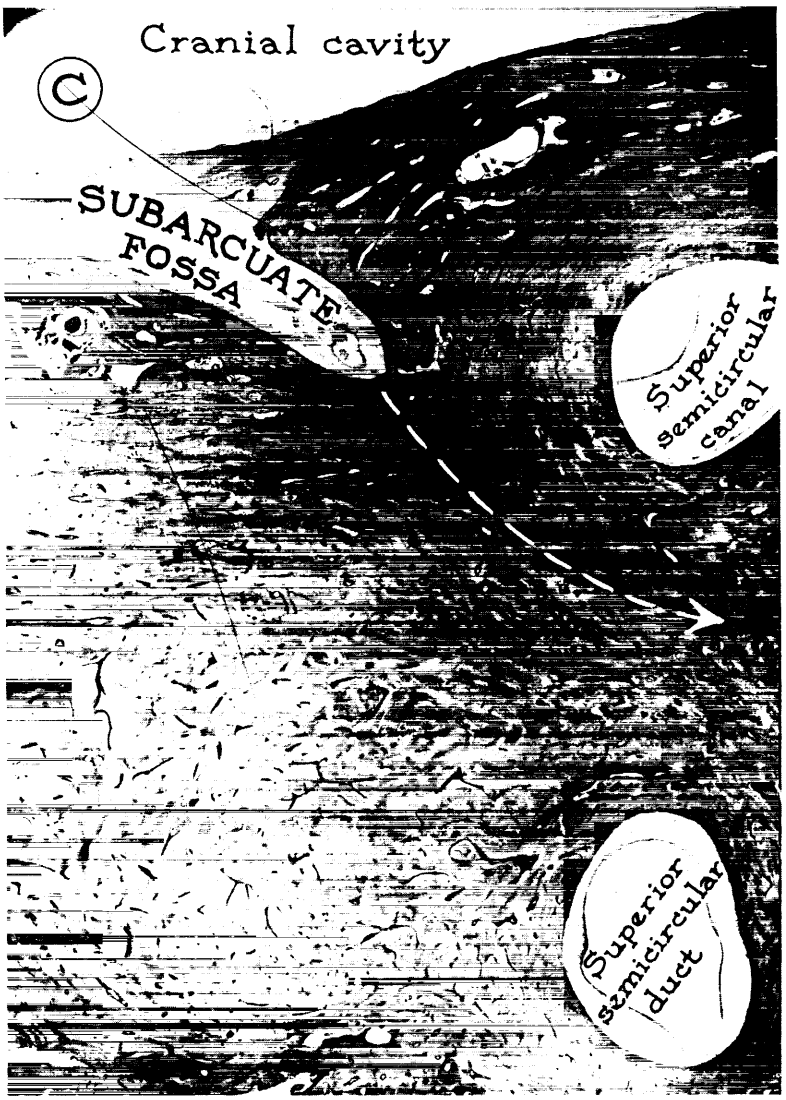


FIGURE 6.—*Developmental and adult anatomy of the subarcuate fossa.* (a) *Fetus of 21 weeks (183 mm);* (b) *newborn (4-day premature);* (c) *adult, 62 years of age. Transverse sections. Wisconsin Collection, series 94, 124, and 13, respectively.* (a) *24×,* (b) *18×,* (c) *16×.* a: *At this fetal stage, vascular tissue, invading the canalicular part of the capsule has reached the height of its growth. Ossification, rapidly advancing in subsequent stages, converts the cartilage into bone. The vascular buds (at arrows) render the cartilage spongeous, thereby permitting expansion of the arcs of the semicircular ducts. The blood vessels, entering from the cranial cavity, are represented in the adult by the small subarcuate branches of the internal artery and vein.* b: *The fossa has been reduced in depth through growth of bone of the middle layer (at 2). Concurrently with continuing increment of the latter, growth of the outer periosteal layer (at 1) will further reduce the size of the fossa (compare with gross specimens in fig. 7). The inner periosteal layer (at 3) will remain unaltered.* c: *In the temporal bone of the adult, the fossa persists as a channel of greatly reduced capacity. The original course of the fossa through the bone may remain histologically distinguishable from the surrounding tissue, here indicated by the arrow.*

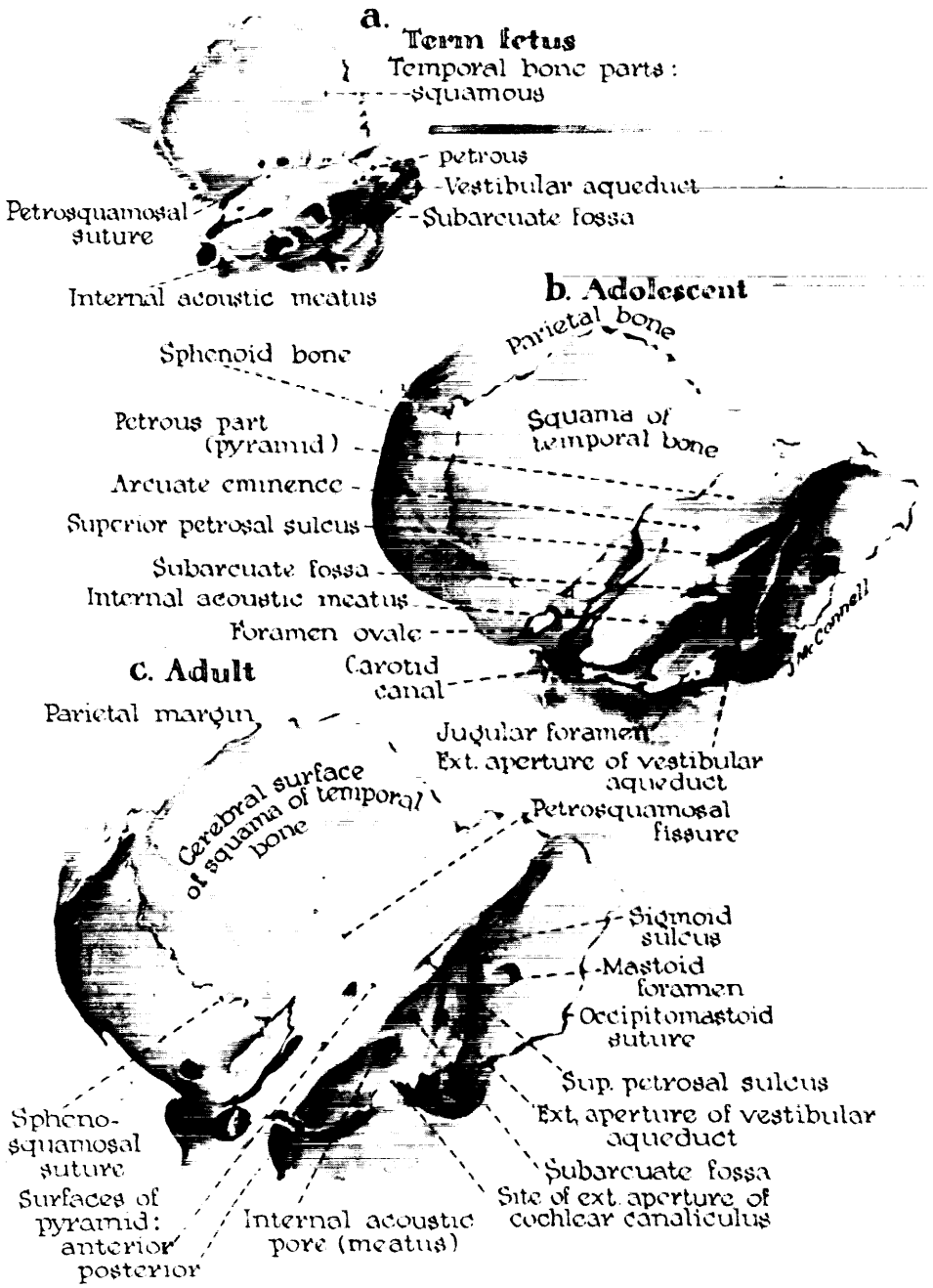


FIGURE 7. — *Medial surface of the temporal bones (skeletal preparations). Specimens selected to demonstrate the decrease in size of the subarcuate fossa.* a: *In the newborn infant and in the fetus at term, the subarcuate fossa is still a channel with an aperture approximately as large as that of the internal acoustic meatus.* b: *Reduction in capacity takes place gradually. The temporal bone of the adolescent is less than half the size of the channel in the newborn.* c: *In the adult, the aperture is usually of pin-point dimensions. However, variations occur. In some specimens the aperture is a transverse or vertical slit near the superior petrosal sulcus, in others an opening at the posterior angle of the petrous pyramid close to the sigmoid sulcus.*

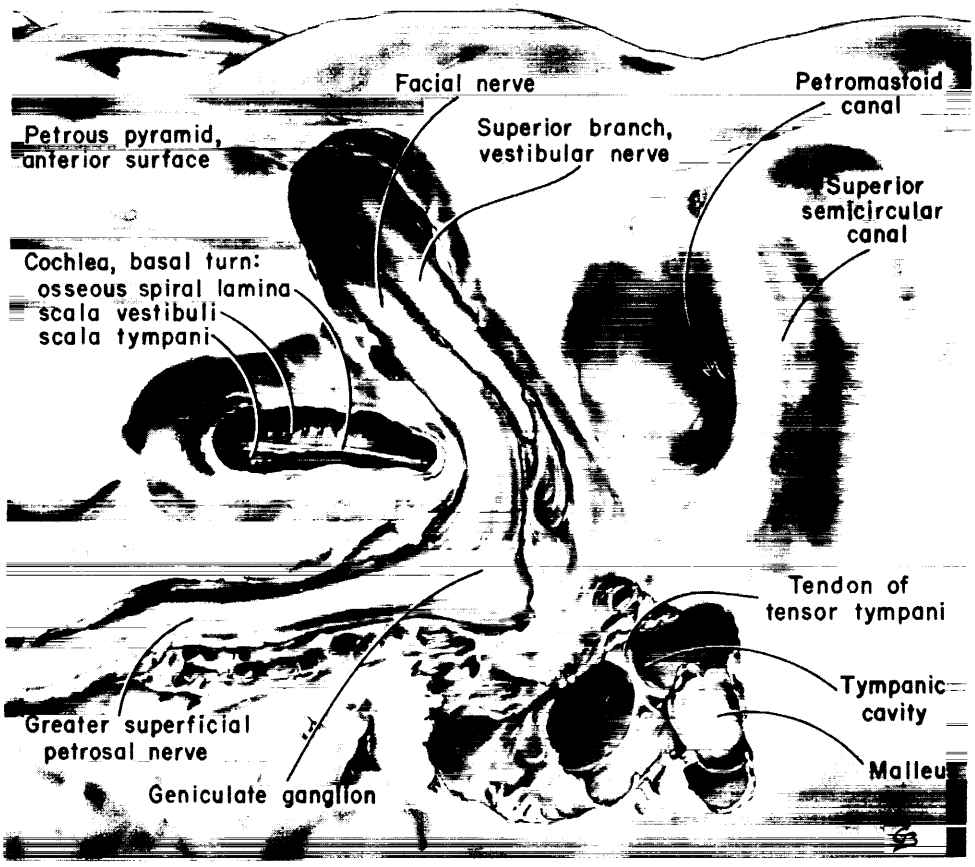


FIGURE 8.—*Anterior surface of the temporal bone (dissection of an unembalmed specimen). This figure demonstrates specially the petromastoid canal and related anatomy. The canal passes beneath the arch of the superior semicircular canal, matching the original course of the subarcuate fossa. It becomes continuous with the pneumatic spaces of the posterior part of the petrous pyramid (developmental stages in figs. 6*(a) *and 6*(b)*). The internal acoustic meatus, facial canal, and cochlea are also shown. The internal auditory vessels reach the modiolus of the cochlea from the meatus; branches thereof follow the utricular and saccular divisions of the vestibular nerve through the foramina in the wall of the fundus to reach the vestibule (supplying the acoustic maculae).*

Cochlear Aqueduct

The cochlear aqueduct (or canaliculus) opens upon the inferior surface of the petrous pyramid in a funnel-shaped depression between the external carotid foramen in the front and the jugular fossa behind, near the medial compartment of the jugular incisure (fig. 12(*d*)).

Nearby are the tympanic canaliculus for a tympanic artery and the caroticotympanic canaliculus for vessels of the same name (fig. 12).

The cochlear canaliculus in the adult is occupied by connective tissue which appears to be avascular, as examined with the light microscope.

The "duct," improperly so termed, can be nothing more (as a conveyer of fluid) than the interfibrillar spaces everywhere present in connective tissue. Upon the existence of such spaces depends any service that it might perform in the capacity of a carrier of fluid between the perilymphatic *scalae* and the arachnoidal meshwork.

The aqueduct passes from the wall of the tympanic scala at the *crista* for attachment of

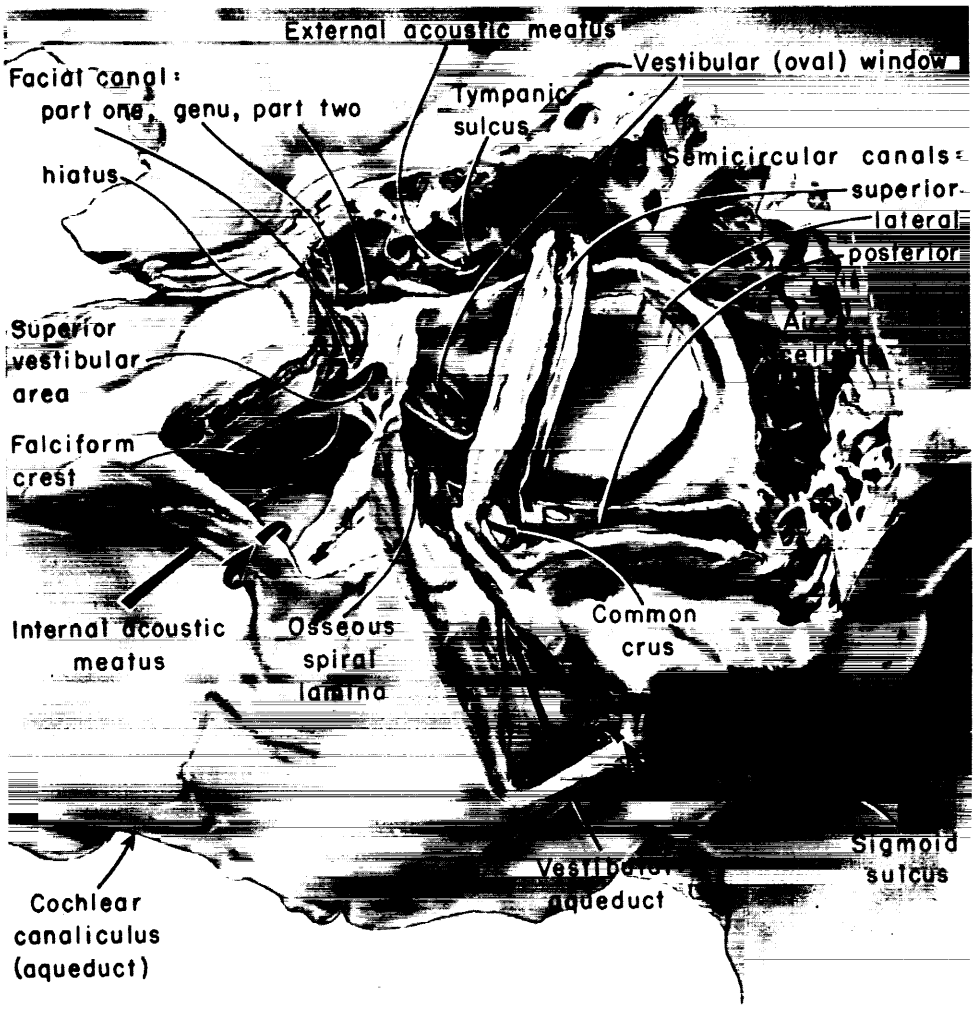


FIGURE 9.—*Temporal bone viewed from the medial aspect. In this selected specimen, representative of many others, the external aperture of the vestibular aqueduct is an oblique slit overhung by a thin ledge of bone. Distal to the aperture, between the latter and the sigmoid sulcus, the surface of the pyramid is foveate for reception of the intradural segment of the endolymphatic sac. Here the distal segment of the aqueduct has been exposed by removal of its "roof" except at the aperture, where a portion of the bone (encircled) remains as a topographical landmark. The course of the sac, toward the narrow segment of the aqueduct, is marked by the large curving arrow. The related structures, at deep level, are also shown by dissection. These include the internal acoustic meatus, the semicircular canals and vestibule, and air-cells in the posterior portion of the pyramid. (Dissection by Raymond L. Warpeha.)*

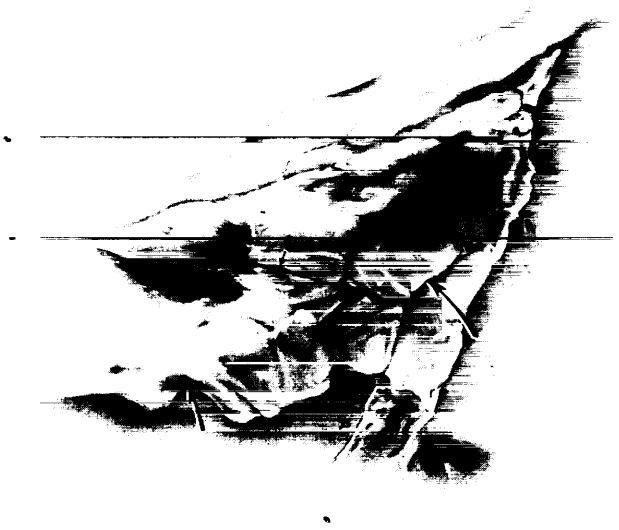


FIGURE 10.—*Temporal bone viewed from the medial aspect. The vascular sulci on the posterior surface of the petrous pyramid leading to the subarcuate fossa and the* porus *of the internal acoustic meatus (arrow, upper left), and to the external aperture of the vestibular aqueduct (right) are shown. Although the external aperture of the cochlear aqueduct (or canaliculus) terminates on the inferior surface of the pyramid, it appears as a notch at the posterior angle of the petrous part (lower arrow).*

the secondary tympanic membrane through the bone to the inferior surface of the petrous pyramid. At the internal aperture its tissue is continuous with that which lines the wall of the osseous labyrinth. At the external aperture the tissue merges with the *dura mater encephali.*

Contrary to the standard description, it does not transmit the cochlear vein. The channel for the latter vessel merely follows the aqueduct through the bone.

This feature is evident in the cochlear aqueduct of the 5-month fetus (fig. 13(*a*)). Already the channel for the cochlear vein is being separated from the developing perilymphatic "duct" (of the aqueduct) by spread of bone from an ossification center. In the 6-month specimen, division is complete (fig. 13(*b*)).

Retaining the relationship established when ossification began, the cochlear vein occupies an independent channel (fig. 13(*c*)).

Petrosal Sulci

It is clear from what has gone before that the diploic veins must be considered as elements in the blood supply of the *pars petrosa.* This is the wholly neglected source of temporal bone blood supply.

Some of these vessels, leaving small openings of emissary nature in the inferior petrosal sulcus, empty into the bulb of the jugular vein. They are frequently numerous (fig. 12, to reader's left). The underlying bone is occupied by air cells or marrow spaces. On the basis of present knowledge, it would appear that the vessels are lost in this intricately patterned bone. None can be found entering the inner periosteal layer of bone around the semicircular canals.

Internal Acoustic Meatus: Vestibule, Canals

Among the regularly disregarded routes for the passage of blood vessels to the membranous labyrinth are the foramina in the partition between the fundus of the internal acoustic meatus and the vestibule of the osseous labyrinth (fig. 14).

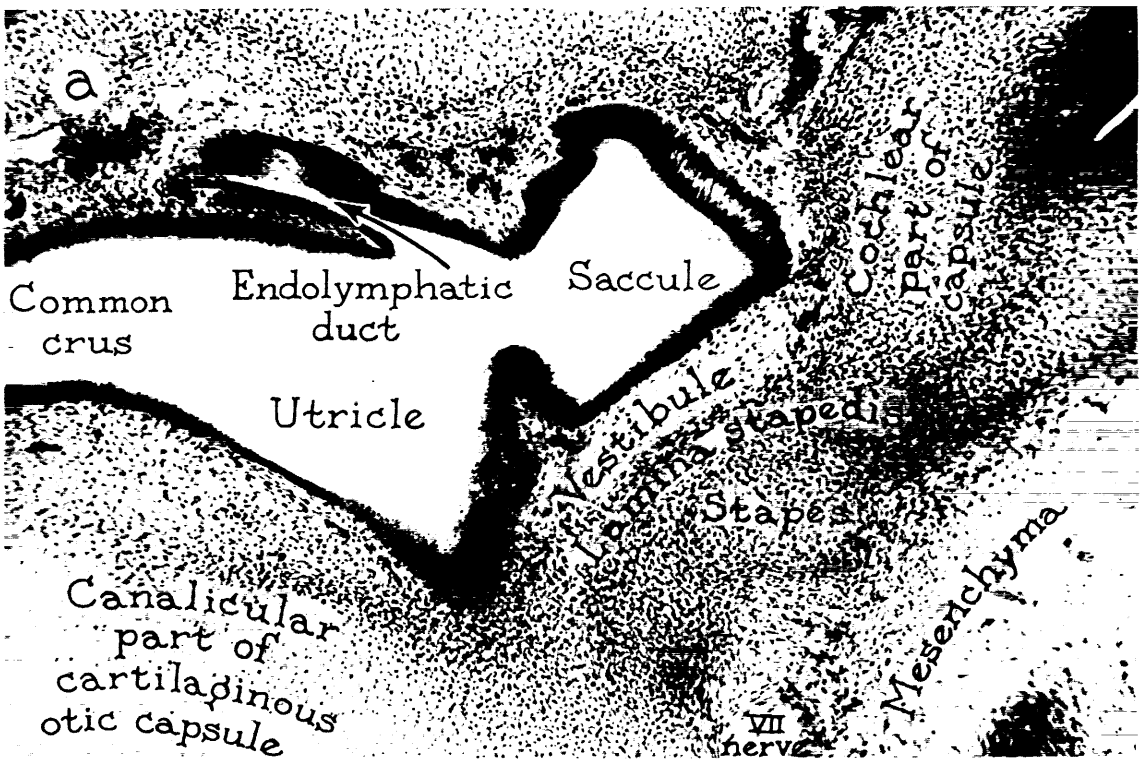
The vestibular areas (superior and inferior) and the singular foramen of the fundus serve to transmit arteries and veins as well as fibers of the statoacoustic (VIIIth) nerve. Such vessels appear prominently in the fetus of approximately 6 months (23 weeks) in association with the vestibular nerve.

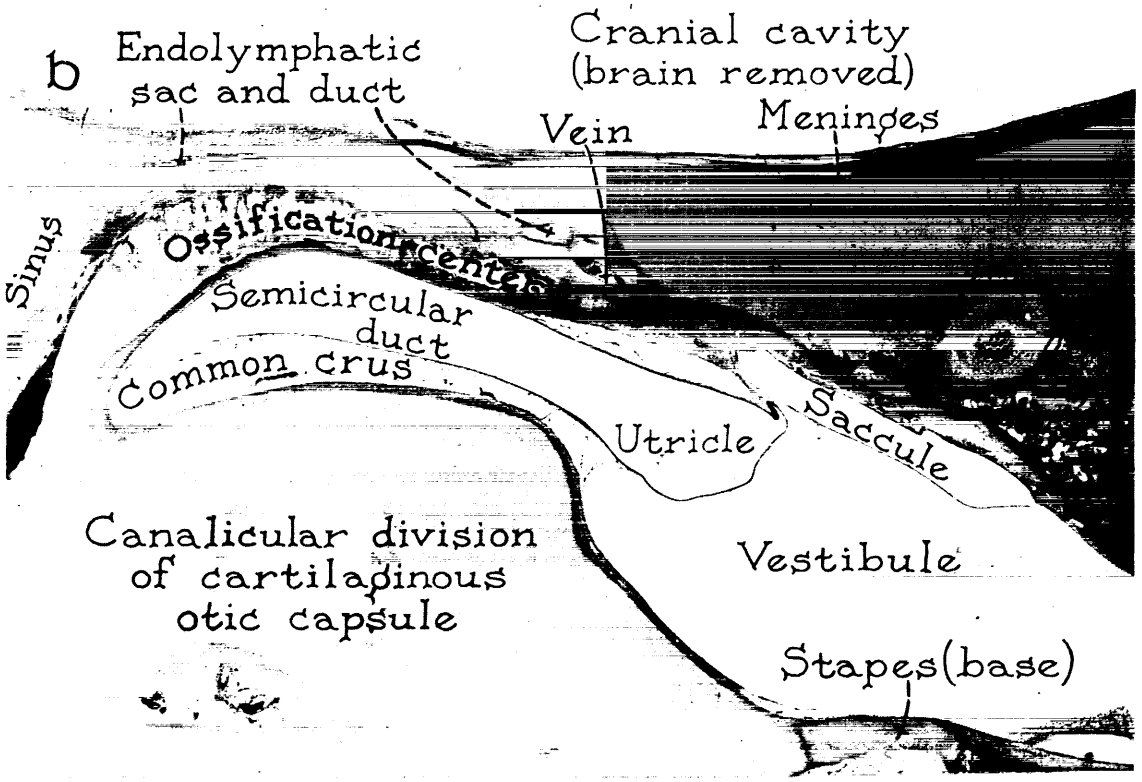
Blood vessels appear at the inferior vestibular area of the fundus and the cribrose macula of the saccule in the wall of the spherical recess (fig. 15(*a*)).

In a similar way vessels pass with the nerve bundles from the vestibular area to the cribrose macula of the utricle in the wall of the elliptical recess of the utricle (figs. 15(*a*) and 15(*b*)).

The fibers of the posterior ampullary nerve are likewise accompanied by vessels which enter the osseous ampulla through the inferior cribrose macula. They have come through the singular foramen of the fundus of the internal acoustic meatus.

As already mentioned, this is seemingly the only way in which blood vessels reach the contents of the labyrinth. This relationship


a
Common crus
Endolymphatic duct
Saccule
Cochlear part of capsule
Utricle
Vestibule
Lamina stapedis
Stapes
Canalicular part of cartilaginous otic capsule
Mesenchyma
VIII nerve


b
Endolymphatic sac and duct
Cranial cavity (brain removed)
Vein
Meninges
Sinus
Ossification center
Semicircular duct
Common crus
Utricle
Saccule
Canalicular division of cartilaginous otic capsule
Vestibule
Stapes (base)

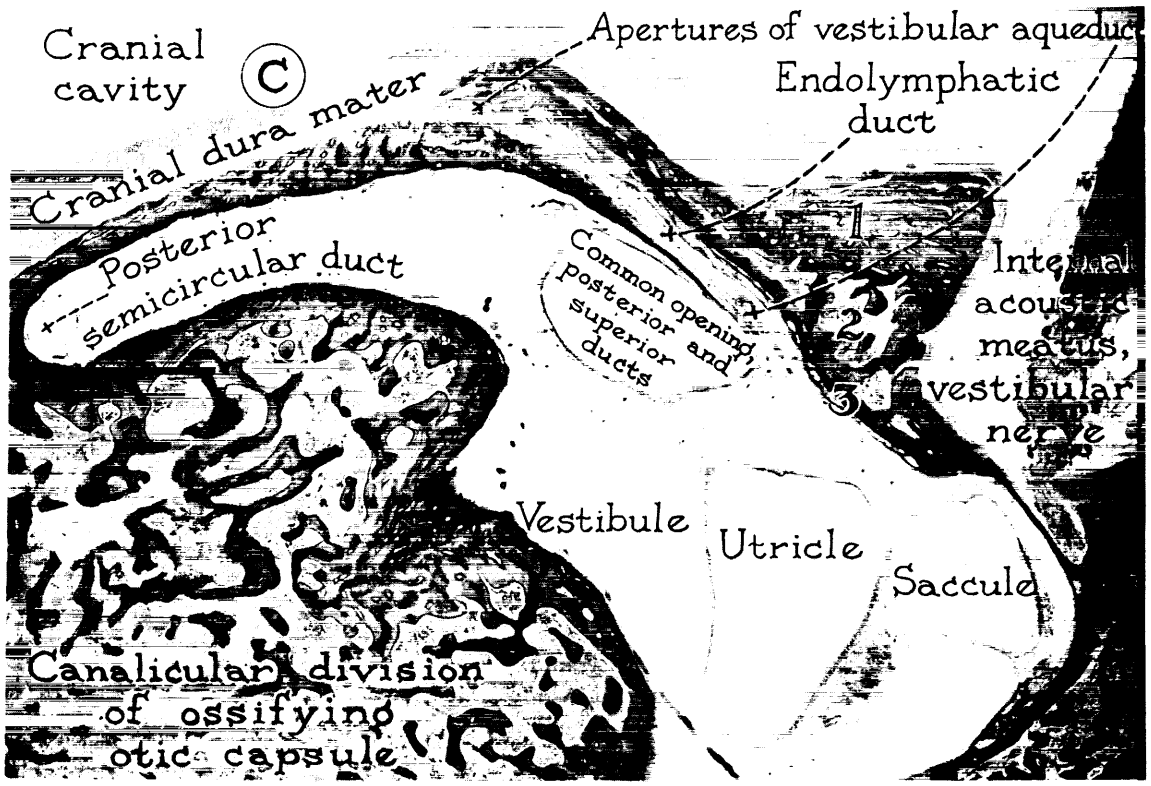


FIGURE 11.—*Stages in the development of the otic capsule in the region of the vestibular aqueduct.* (a) *Fetus of 8½ weeks (28 mm);* (b) *fetus of 20 weeks (167 mm);* (c) *newborn (4-day premature). Transverse sections. Wisconsin Collection, series 158, 105, and 124, respectively.* (a) *18×,* (b) *15×,* (c) *15×.* a: *At this early stage, while the otic capsule is still in the precartilaginous stage, blood vessels are present around the endolymphatic duct. Here the precartilage is undergoing retrogressive change, preparatory to change into connective tissue.* b: *Blood vessels are present in the mesenchymal tissue around the endolymphatic duct and sac while the surrounding cartilage of the primordial aqueduct is undergoing ossification.* c: *The aqueduct is sectioned through its length to emphasize the nature of the wall of the aqueduct. The capsular layers are: outer periosteal (at 1); middle layer of endosteal and intrachondral bone (at 2); inner periosteal layer (at 3). The middle layer will increase in bulk to assume petrous consistency.*

between nerves and vessels is established early and is retained, as far as is known, as the mature scheme of vascularization. Further study is in progress in which the vascular channels of the middle and inner capsular layers will be demonstrated by reconstructions.

Facial Canal

The facial nerve is, of course, not the sole occupant of the canal that bears its name (figs. 16(*a*) to 16(*c*)). The facial canal houses the stapedius muscle and transmits the superficial petrosal branch of the middle meningeal artery and the stylomastoid vessels from the posterior auricular branch of the external carotid.

From the level of the geniculum to the first part of its vertical course, it passes between the vestibular (oval) window above and the prominence of the lateral semicircular canal below. At the beginning of its descending course it lies behind the pyramidal eminence.

The canal already houses the facial (VIIth) nerve; the stapedius muscle; and, of special interest here, blood vessels (capacious stylomastoid veins and smaller corresponding arteries). The surrounding mesenchyma shows early evidence of differentiation into connective tissue. Branches leave the primitive "canal" to supply the capsule as they do in the adult temporal bone.

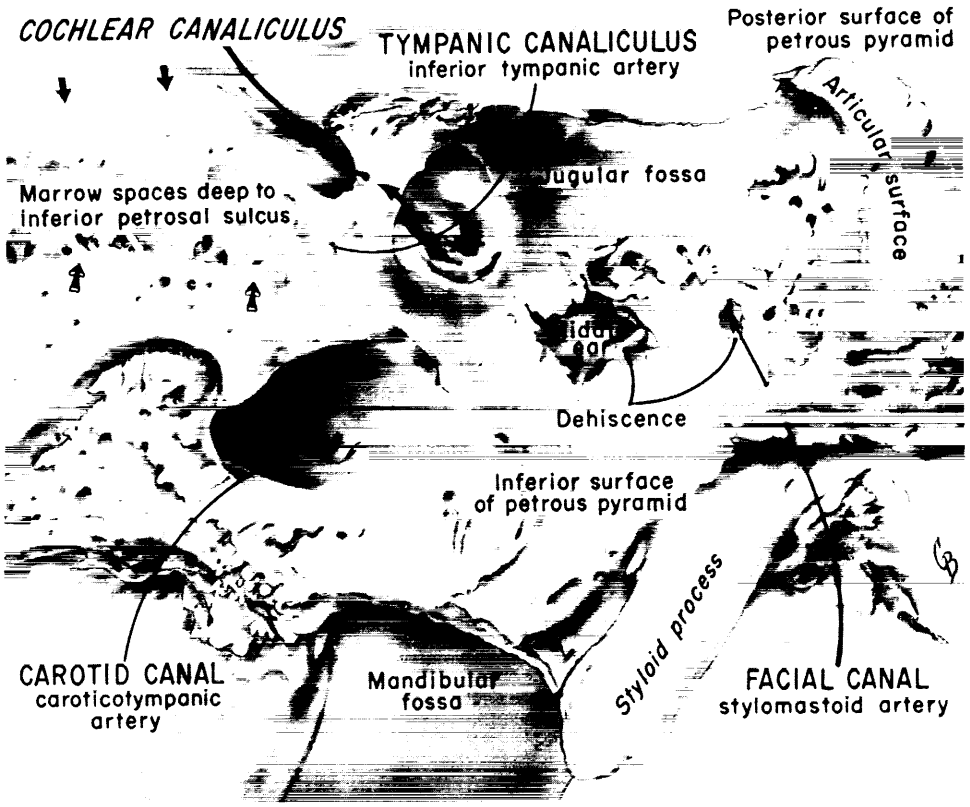


FIGURE 12.—*Inferior surface of the temporal bone. This dissection shows spaces whose vessels (in the natural state) would be in communication with the superior petrosal sulcus. Two other vascular routes are shown, namely, the carotid canal and the facial canal. This is a dissection of the specimen shown in figure 5 of a preceding paper entitled "The Vestibular and Cochlear Aqueducts: Developmental and Adult Anatomy of Their Contents and Parietes." (From Anson, B. J.; and Donaldson, J. A.: The Surgical Anatomy of the Temporal Bone and Ear. W. B. Saunders, 1967.)*

When ossification of the otic capsule begins, the future facial canal is merely a sulcus in the tympanic wall of the canalicular division of the otic capsule. Its appearance is early, the development precocious, and grouping of contents established before the fetus reaches midterm.

The facial sulcus of the 9-week fetus becomes a canal through overgrowth from the outer periosteal layer of the otic capsule (fig. 17(*b*)). Adult structure is soon established (fig. 17(*c*)). The contained connective tissue is highly vascular.

It is a matter of more than passing interest that the facial canal, in the vertical segment, is partially subdivided into semicanals: vascular, myological, and neural (fig. 16(*b*)). This is a striking feature in dissections as well as in sections.

The blood vessels are not confined to the vertical part of the facial canal. They are present prominently in the horizontal part, as seen in this specimen of an adult, 57 years of age (fig. 16(*a*)).

In the vertical part of the canal there is more space than contents. This is strikingly evident in the segment above (that is, superior to) the point at which the stapedius tendon quits the canal in passing into the tympanic cavity by way of the pyramidal eminence (fig. 16(*c*)). Blood vessels are numerous in the connective tissue around the nerve. In previous studies it was determined that the veins form a rich circumneural plexus.

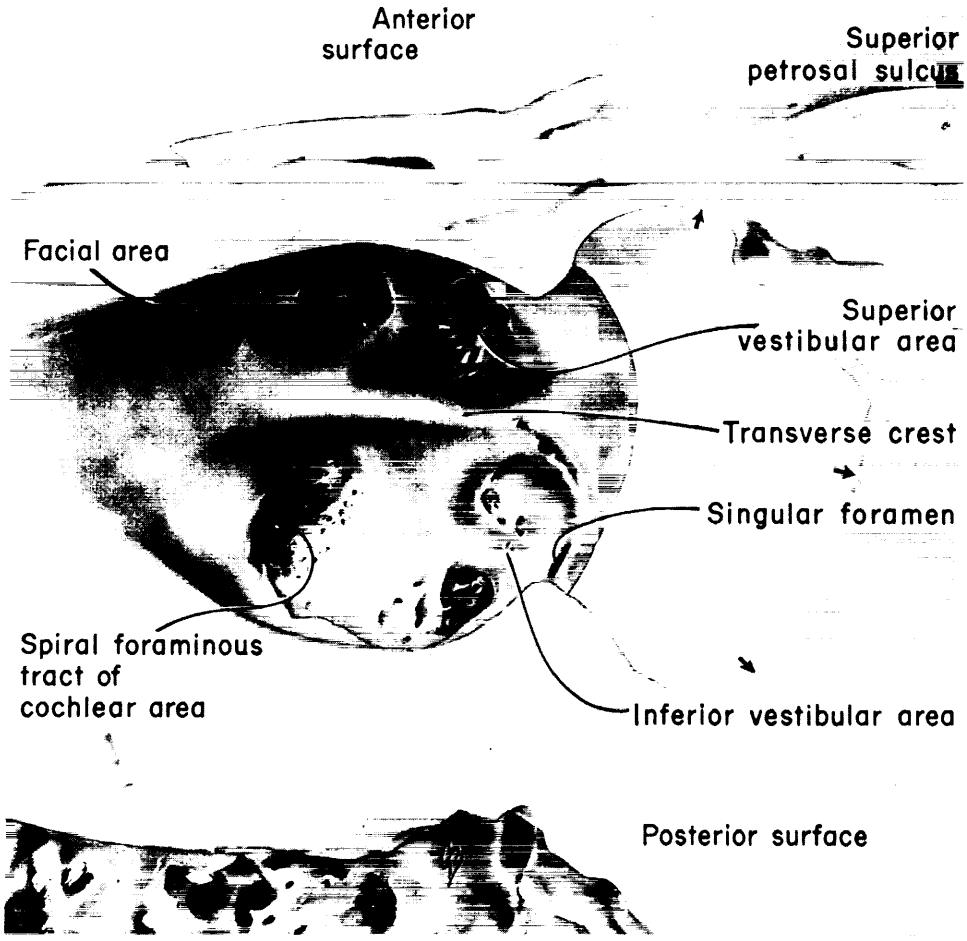
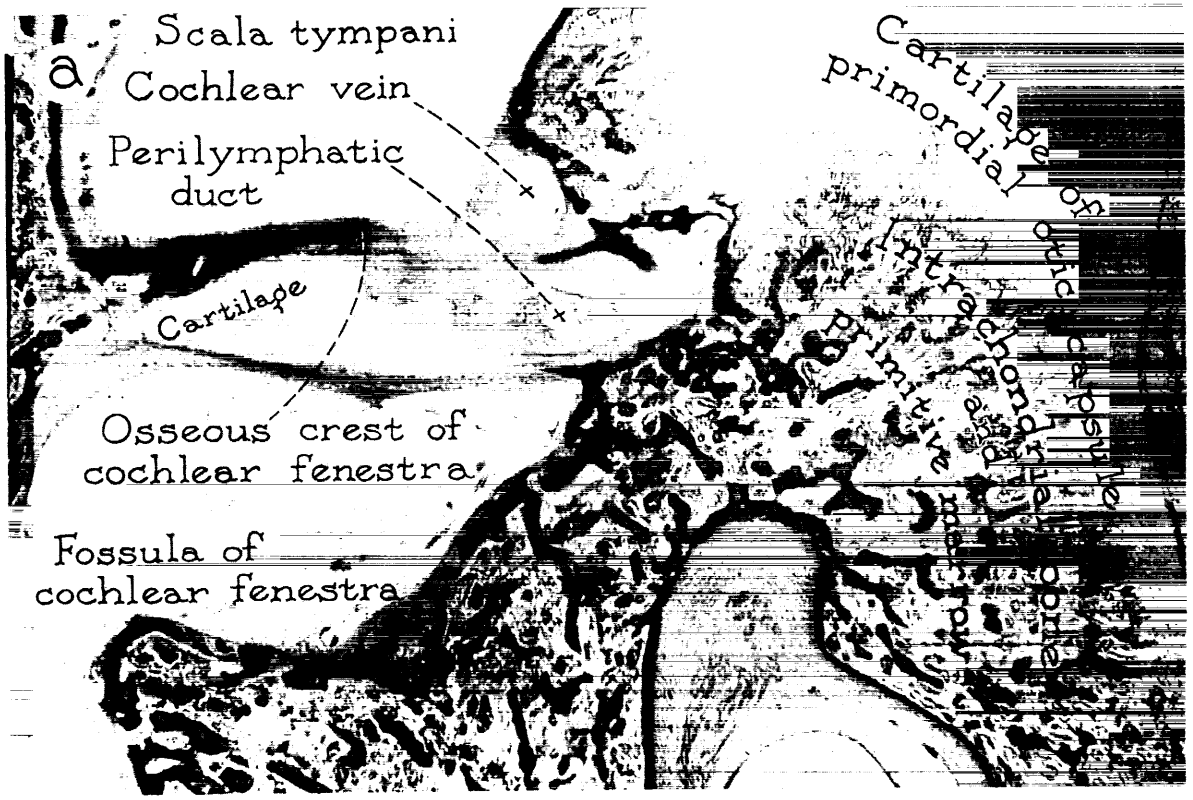
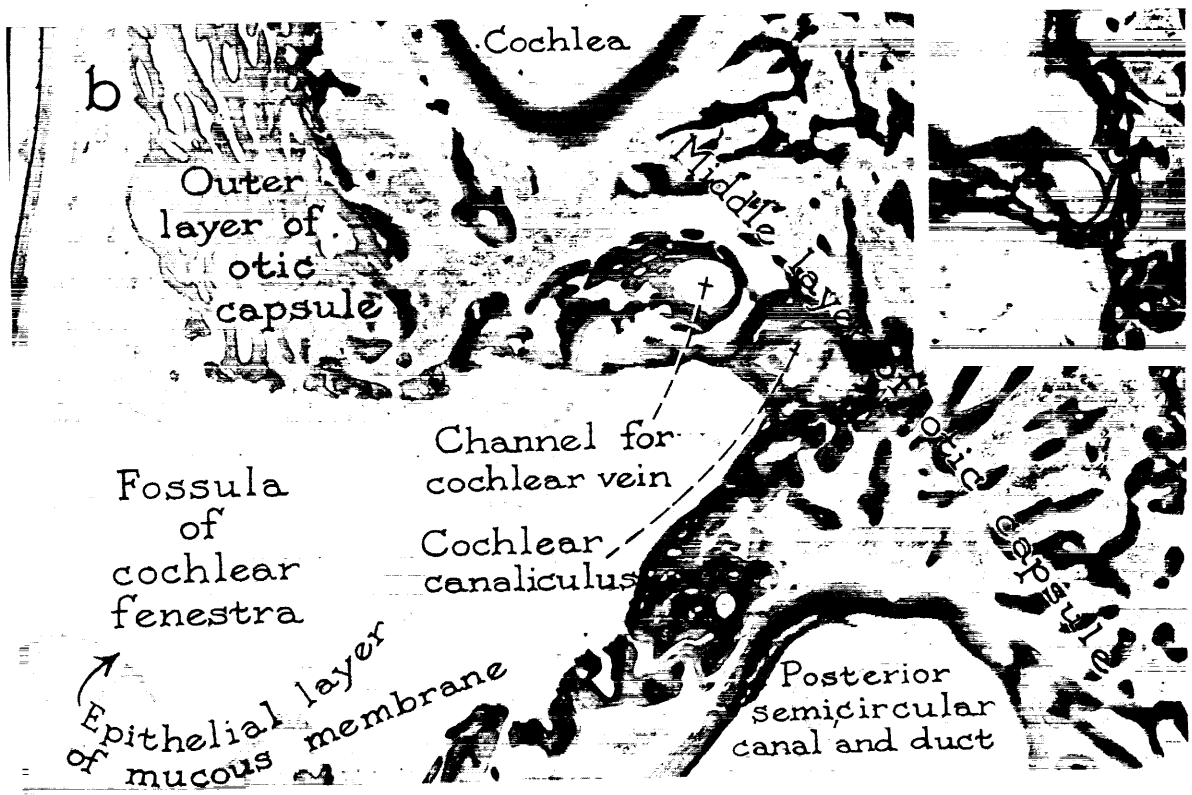


FIGURE 14.—*Medial surface of the temporal bone. The foramina in the fundus of the internal acoustic meatus are shown. Through these openings, constituting the vestibular areas and the spiral tract of the cochlea, small vessels travel with the nerves to the sensory elements. In addition, vessels in the horizontal segment of the facial canal (fig. 16*(a)*) communicate with those accompanying the facial nerve in the internal acoustic meatus. (From Anson, B. J.; and Donaldson, J. A.: The Surgical Anatomy of the Temporal Bone and Ear. W. B. Saunders, 1967.)*


a
Scala tympani
Cochlear vein
Perilymphatic duct
Cartilage
Osseous crest of cochlear fenestra
Fossula of cochlear fenestra
Cartilage of primordial otic capsule
Intrachondral portion of primitive otic capsule


b
Cochlea
Outer layer of otic capsule
Middle layer
Channel for cochlear vein
Cochlear canaliculus
Fossula of cochlear fenestra
Epithelial layer of mucous membrane
Otic capsule
Posterior semicircular canal and duct

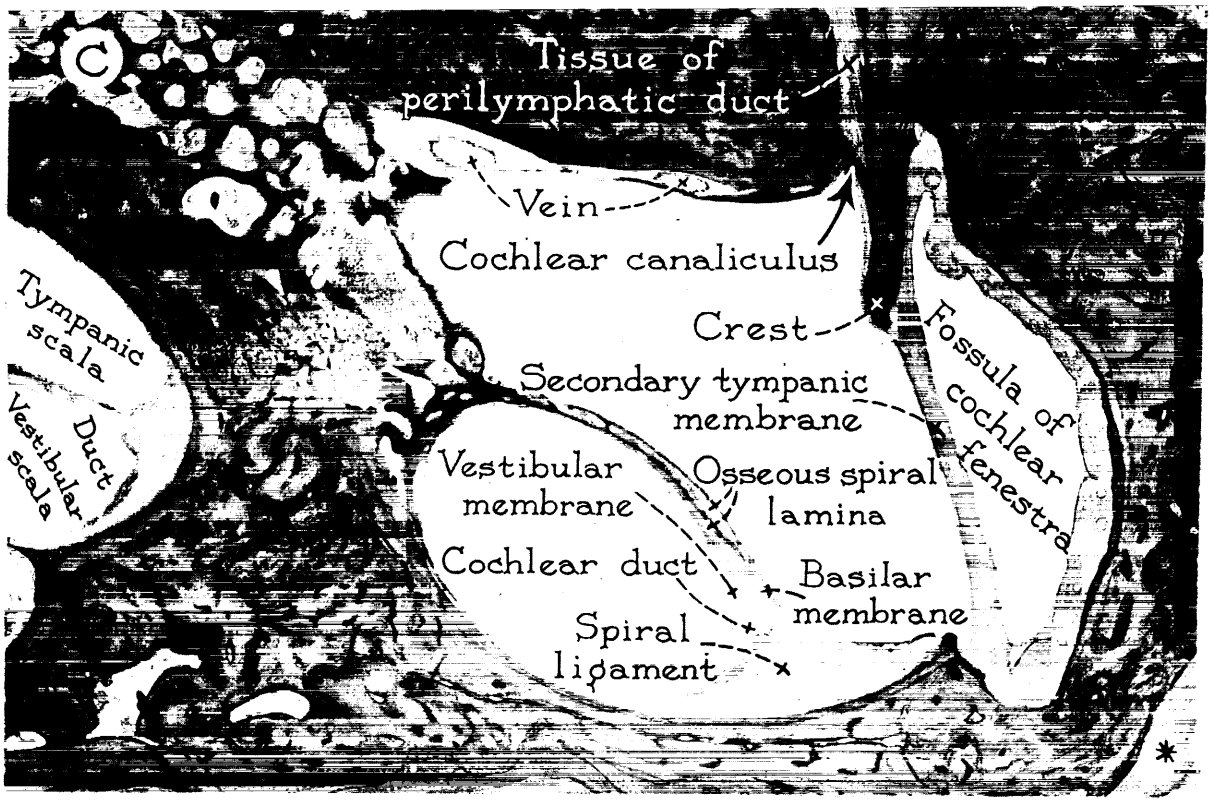


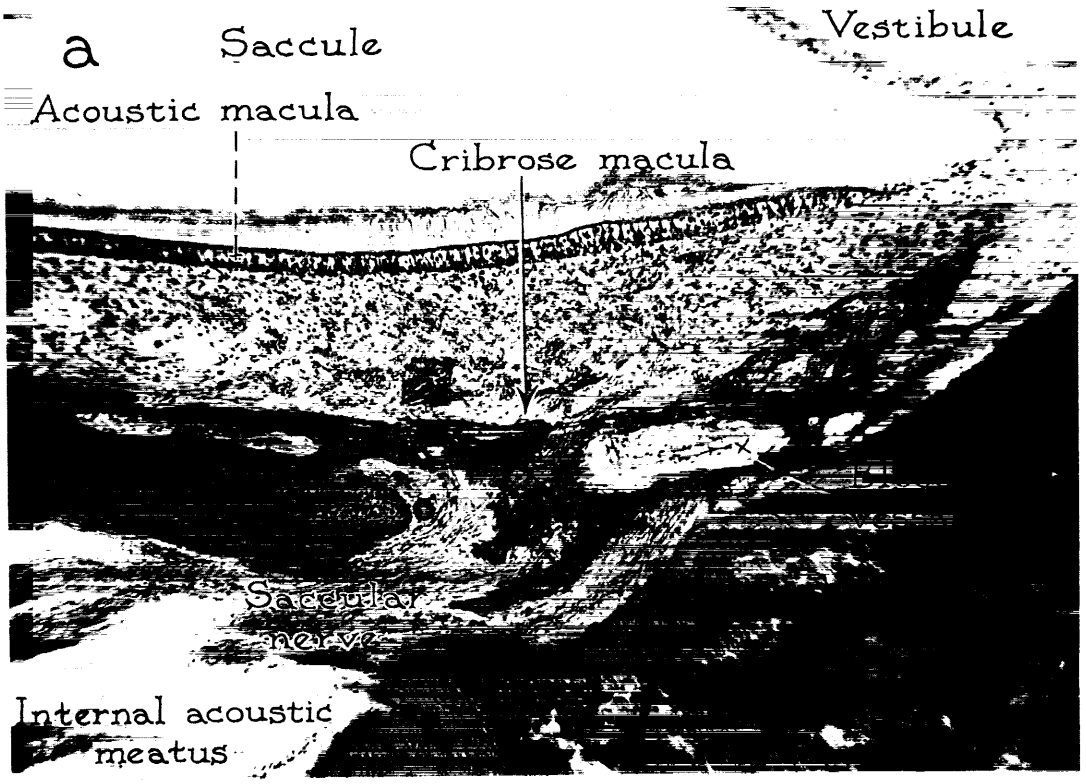
FIGURE 13.—*Developmental and adult anatomy of the cochlear aqueduct, or canaliculus.* (a) *Fetus of 20 weeks (167 mm);* (b) *fetus, of 24 weeks (215 mm);* (c) *child, 2½ years. Transverse sections. Wisconsin Collection, series 105, 62, and 88, respectively.* (a) 27×, (b) 27×, (c) 23×. a: *The aqueduct, formed through retrogressive change in the cartilage, is being separated from the cochlear vein by growth of bone of the outer periosteal layer of the otic capsule. The connective tissue in the aqueduct has been termed perilymphatic (or periotic) duct. This tissue is apparently avascular. (Acta Oto-Laryngol., Stockh., vol. 59, 1965, pp. 140–151.)* b: *Complete osseous enclosure of the aqueduct and the channel for the vein.* c: *The cochlear vein, here within the wall of the tympanic scala, courses through the bone in a channel near, but wholly independent of, the cochlear aqueduct.*

Fissula Ante Fenestram

Last in the list of vascular routes, and the least important, is the *fissula ante fenestram.* It is, from the time of its inception, a fibrous tract across the otic capsule (fig. 18(*a*)). Like the so-called perilymphatic duct, it is formed by resolution of precartilage already part of the capsule. It is, therefore, to be described as an appendage of the perilymphatic spaces of the developing osseous labyrinth, which are produced in the same manner.

In midcourse and at the vestibular extremity, the *fissula ante fenestram* is like the cochlear aqueduct (fig. 18(*b*)). It was similarly formed in the fetus; it contains similar tissue. However, the fissula differs from the aqueduct in terminating at its external aperture in mucous membrane (that of the labyrinthine wall of the tympanic cavity), and in being the predilective site of formation of otosclerotic bone. The fissula transmits a small artery or arteriole from the mucous membrane of the tympanic cavity to the periotic tissue that lines the adult vestibule.

In the adult temporal bone it is a minute channel (fig. 18(*c*)). It is therefore to be regarded as a negligible source of capsular blood supply.


a
Saccule
Vestibule
Acoustic macula
Cribrose macula
Saccular nerve
Internal acoustic meatus


b
Blood vessel
Utricular nerve

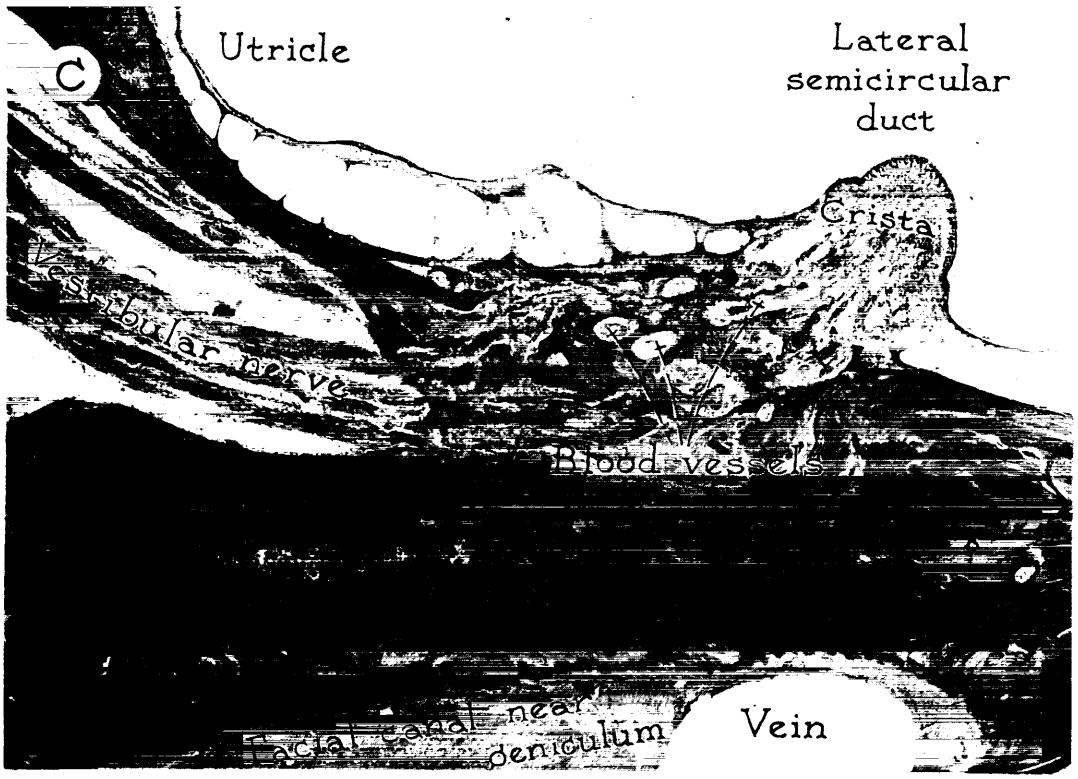


FIGURE 15.—*Neurovascular routes from the internal acoustic meatus to the acoustic maculae and the cristae.* (a) *Adult, 19 years old;* (b) *newborn (4-day premature);* (c) *adult, 57 years. Transverse sections. Wisconsin Collection,* (a) *series 29,* (b) *series 124,* (c) *series 32.* (a) 92×, (b) 88×, (c) 40×. a: *The lower terminal branch of the vestibular nerve (from the acoustic or statoacoustic) passes (as the saccular nerve) from the inferior vestibular area of the fundus of the internal acoustic meatus through the middle cribrose macula of the vestibule to the acoustic macula of the saccule. Branches of the internal auditory vessels accompany the nerve bundles to reach the tissue in the spherical recess, between the saccule and the foraminous wall of the vestibule.* b: *The other (upper) terminal branch of the vestibular nerve courses (as the utricular nerve) from the superior vestibular area through the bone to the superior cribrose macula of the vestibule to the acoustic macula of the utricle. As in the former instance vessels are present, free among the nerve bundles and in small vascular channel of the bone that separates the foramina.* c: *Fibers of the lateral ampullary nerve pass through the same cribrose macula to the crista in the lateral membranous ampulla. Numerous vascular channels are present in the bone; branches of the contained vessels appear among the nerve fibers. Examination of serial sections shows that some of these channels begin in the wall of the fundus, separate from the foramina occupied by the nerves; then, traversing the bone between the meatus and the vestibule, they open into the foramina where the latter constitute the cribrose maculae. This means that the blood supply to these neural sensory elements is derived from the internal auditory vessels (that is, from the meningeal aspect of the petrous pyramid, not from the mucosal, or tympanic, side).*

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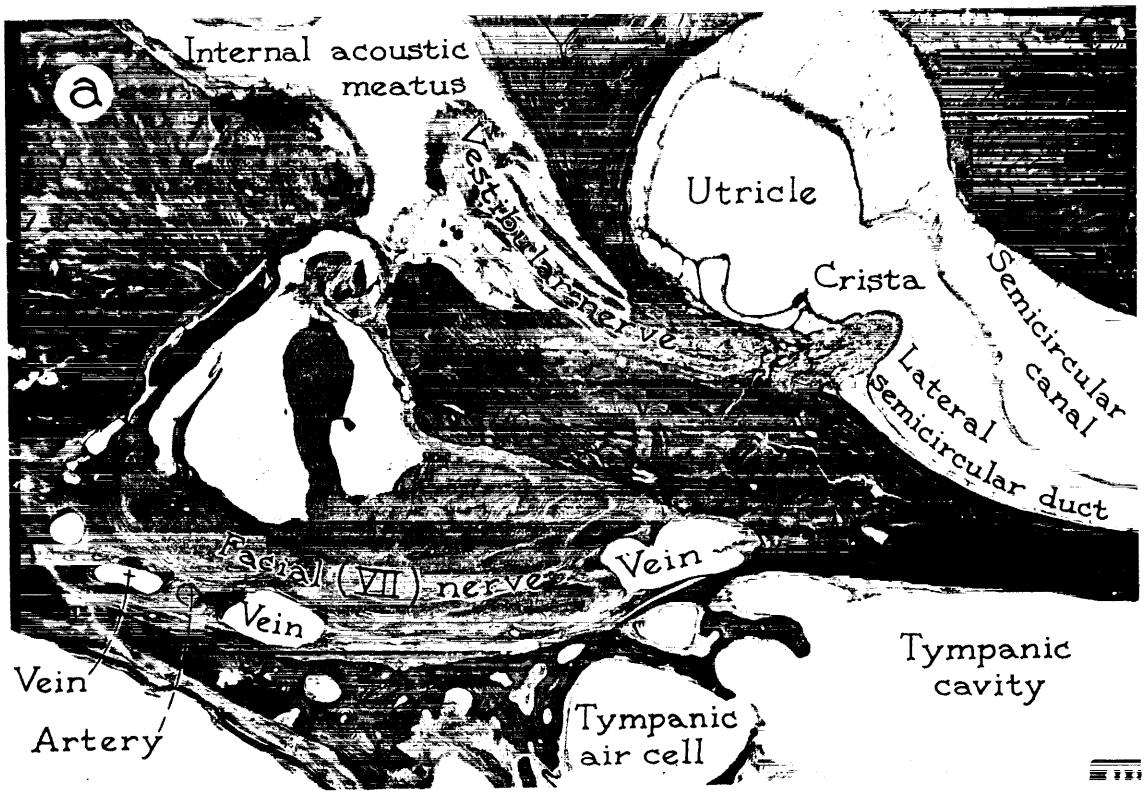
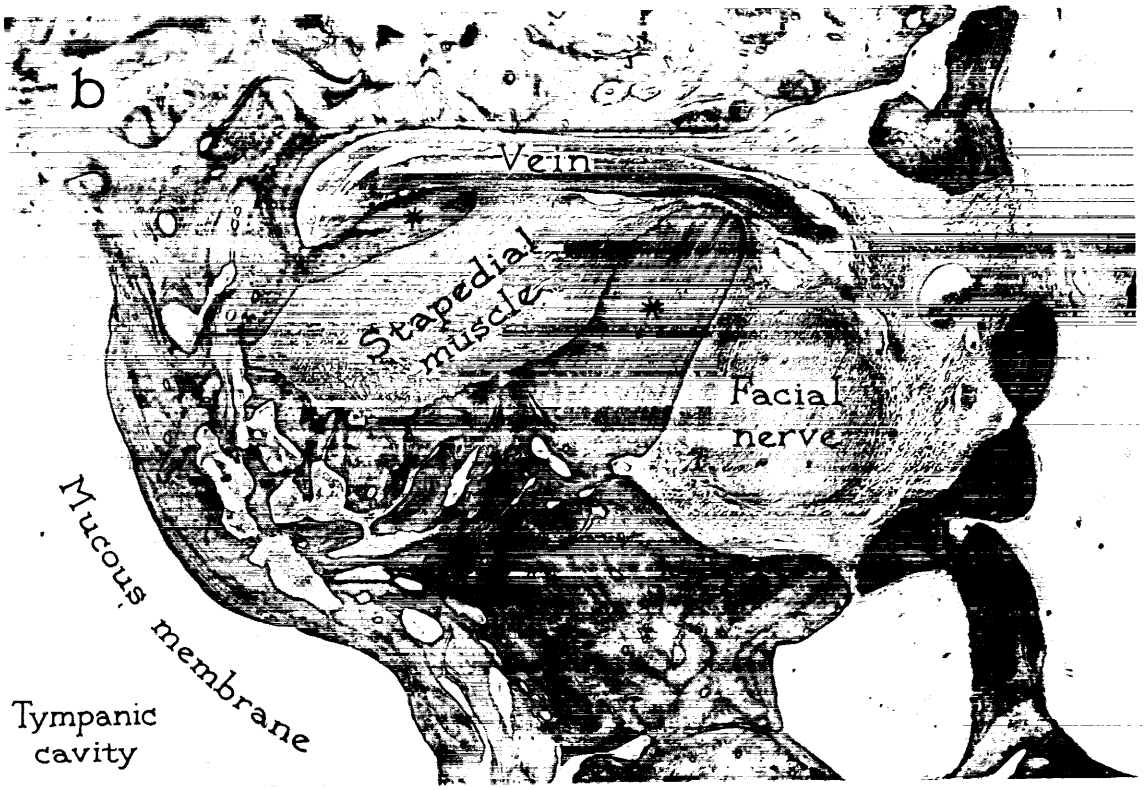

a
Internal acoustic meatus
Vestibular nerve
Utricle
Crista
Semicircular canal
Lateral semicircular duct
Facial (VII) nerve
Vein
Vein
Vein
Artery
Tympanic cavity
Tympanic air cell


b
Vein
Stapedial muscle
Facial nerve
Mucous membrane
Tympanic cavity

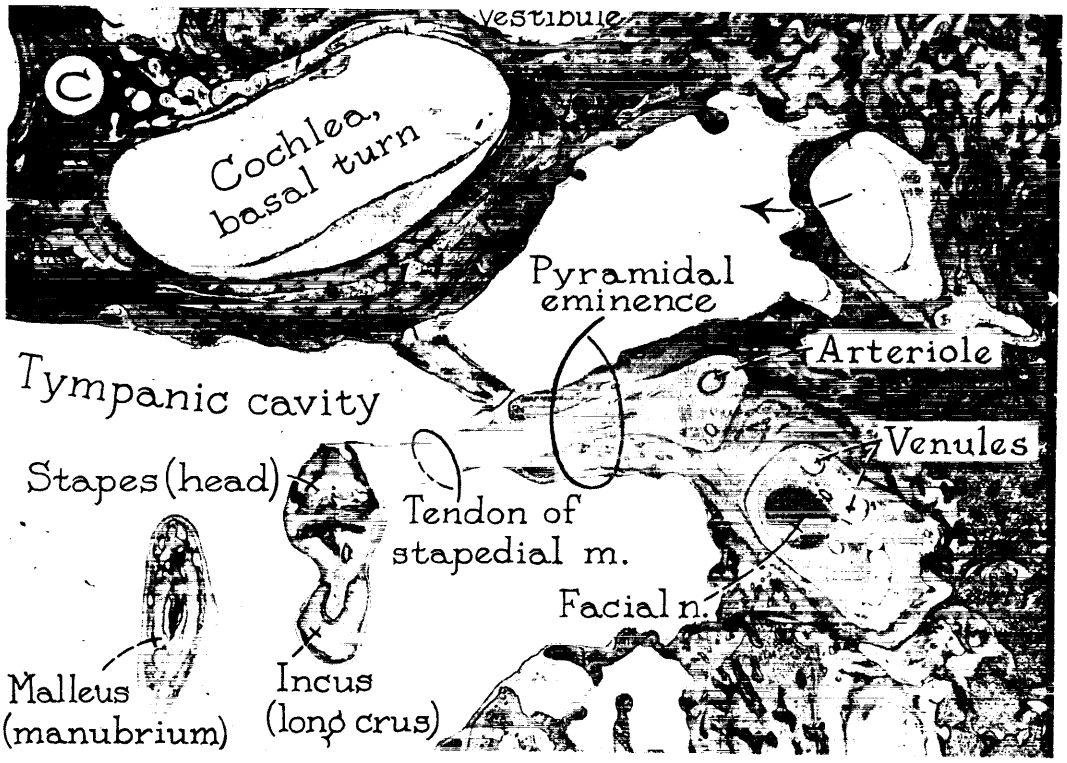
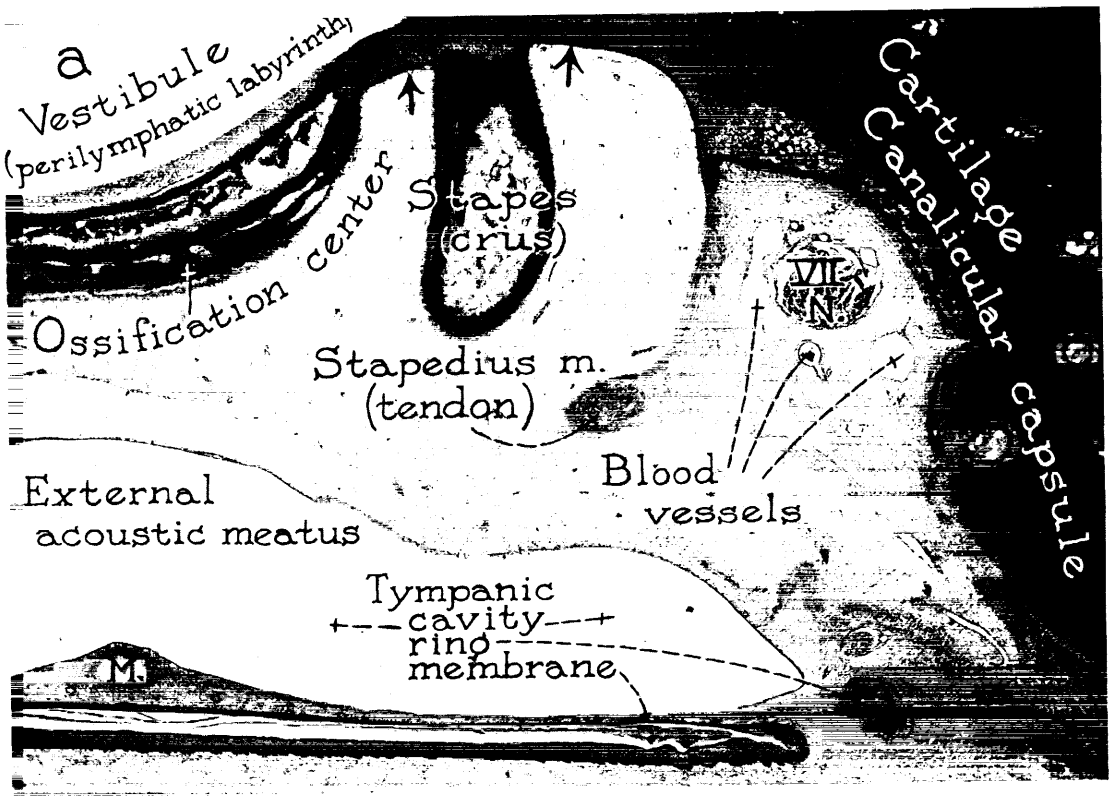
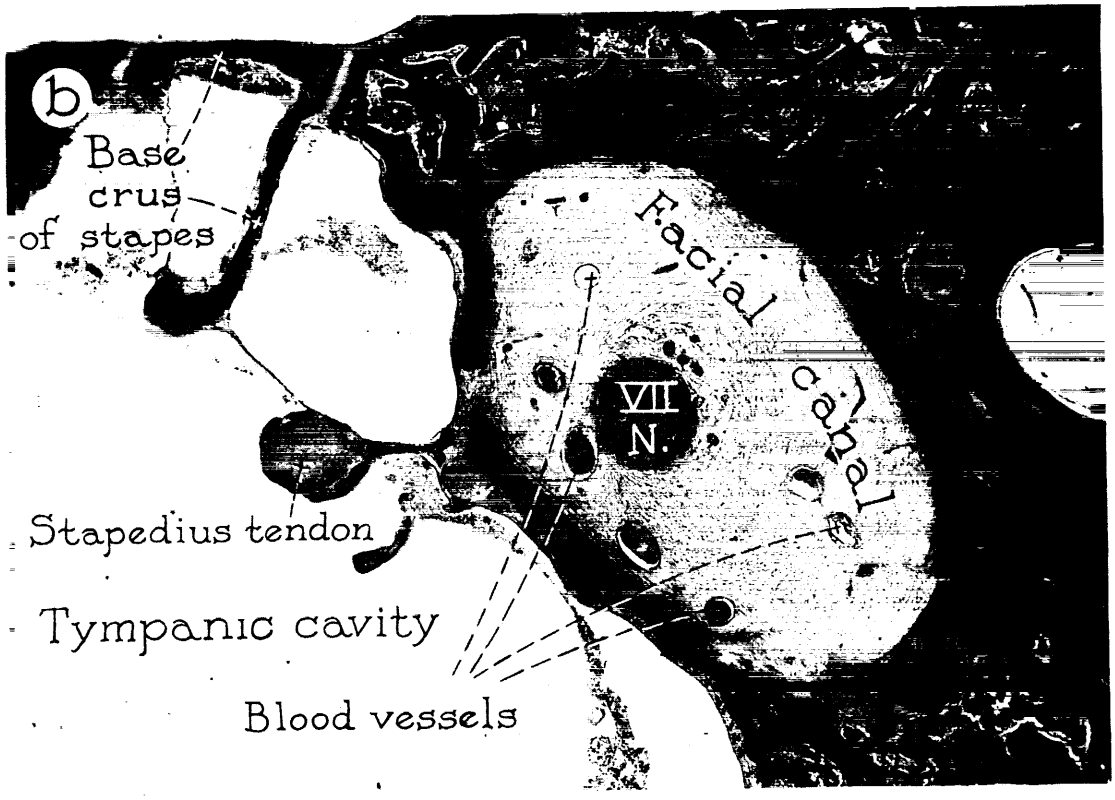


FIGURE 16.—*Contents in the segments of the course of the facial canal.* (a) *Adult, 57 years of age;* (b) *child of 14 months;* (c) *infant of 10 weeks. Transverse sections. Wisconsin Collection, series 32, 93, and 83, respectively.* (a) *15×*, (b) *26×*, (c) *14×*. a: *Arteries and veins accompanying the nerve in the horizontal part of its course.* b: *Vein, stapedius muscle and facial nerve in the vertical segment of the course. They occupy "semicanals" separated by osseous ledges (at asterisk) from the wall of the main conduit.* c: *Contents of the facial canal at the horizontal level of the pyramidal eminence. The canal transmits tributaries of the stylomastoid vein and branches of the corresponding artery. The veins may form a plexus around the nerve. Arteries and veins follow the stapedius tendon into the tympanic cavity; others enter the bone of the canalicular division of the* pars petrosa.


a
Vestibule
(perilymphatic labyrinth)
Ossification center
Stapes
(crus)
VII
N.
Cartilage
Canalicular capsule
Stapedius m.
(tendon)
Blood
vessels
External
acoustic meatus
Tympanic
cavity
ring
membrane
M.


b
Base
crus
of stapes
Facial
canal
VII
N.
Stapedius tendon
Tympanic cavity
Blood vessels

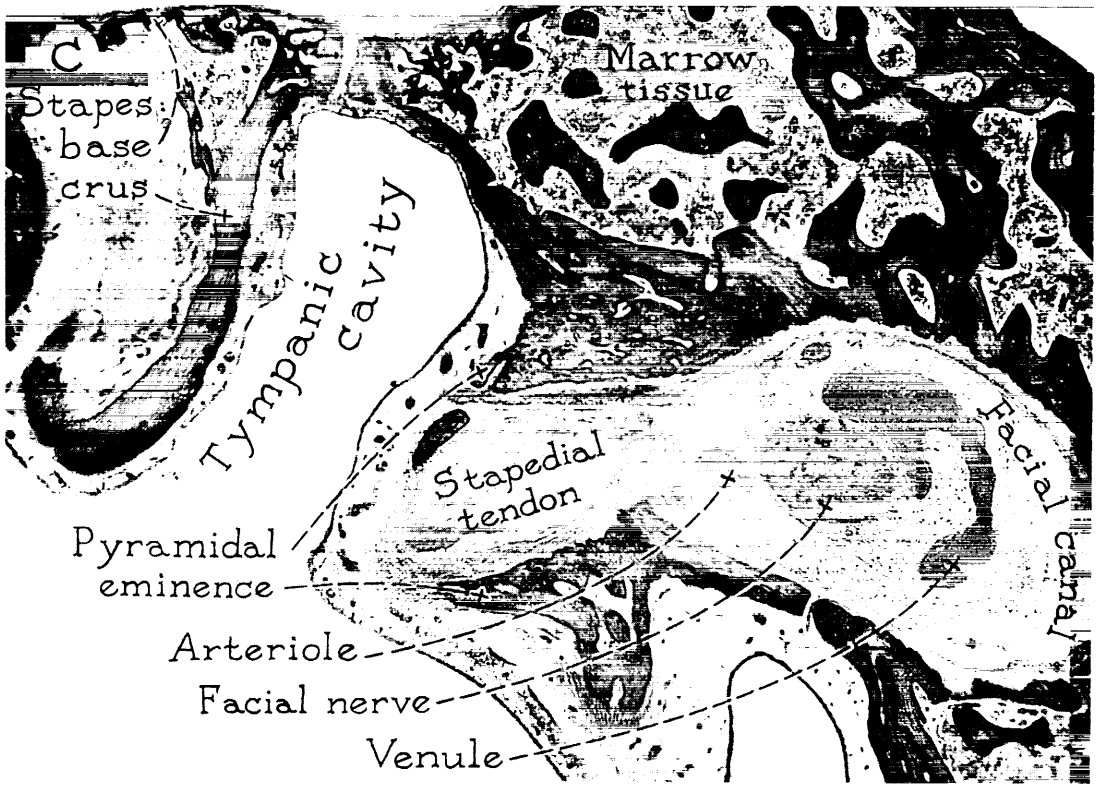
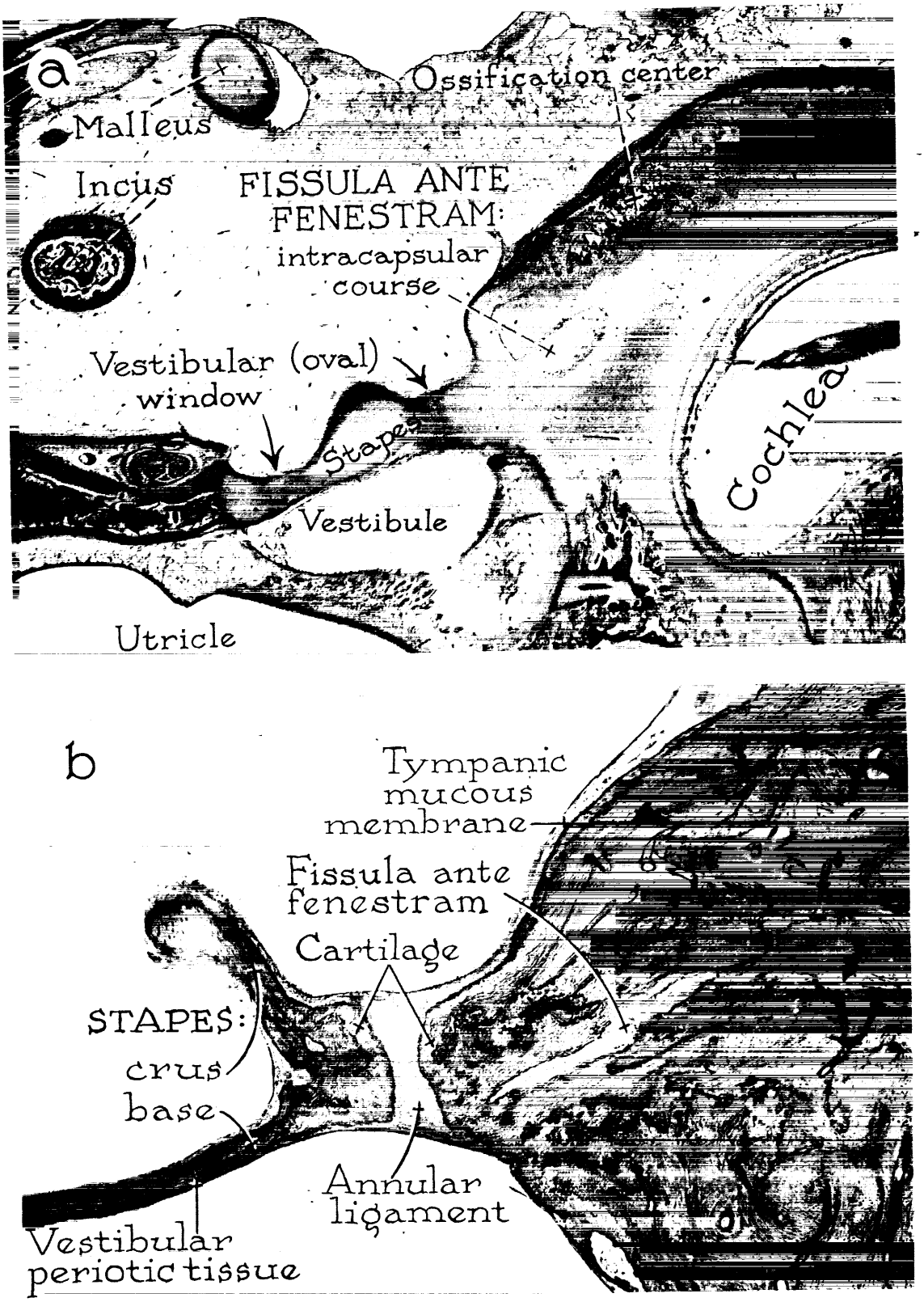


FIGURE 17.—*Developmental anatomy of the facial canal and its contents.* (a) *Fetus of 21 weeks (183 mm);* (b) *fetus of 34 weeks (310 mm);* (c) *newborn (4-day premature). Transverse sections. Wisconsin Collection, series 21, 34, and 124, respectively.* (a) *23 ×*, (b) *23 ×*, (c) *18 ×*. a: *The "canal," in the vertical segment, is a sulcus in the canalicular part of the cartilaginous otic capsule. The triad of structures is already present: facial (VIIth) nerve; stapedius muscle; blood vessels. The vestibular (oval) window is indicated by arrows.* b: *At this level in the descending portion, the capacity of the canal is far greater than required by the contained nerve and accompanying branches of the stylomastoid artery and vein. The stapedius tendon, having emerged from the pyramidal eminence (at a more inferior level), is crossing the tympanic cavity on the way to attachment on the stapes. The hiatus in the tympanic wall of the canal transmits ossicular blood vessels.* c: *The nerve is accompanied by branches of the stylomastoid vessels. Together the structures take up less than one half of the space of the canal. The stapedius tendon is passing through the pyramidal eminence on the way to a tympanic course to the head of the stapes. The veins are elements of a plexus that follows the facial nerve to the stylomastoid foramen.*


a
Malleus
Ossification center
Incus
FISSULA ANTE FENESTRAM:
intracapsular course
Vestibular (oval) window
Stapes
Vestibule
Cochlea
Utricle
b
Tympanic mucous membrane
Fissula ante fenestram
Cartilage
STAPES:
crus
base
Annular ligament
Vestibular periotic tissue

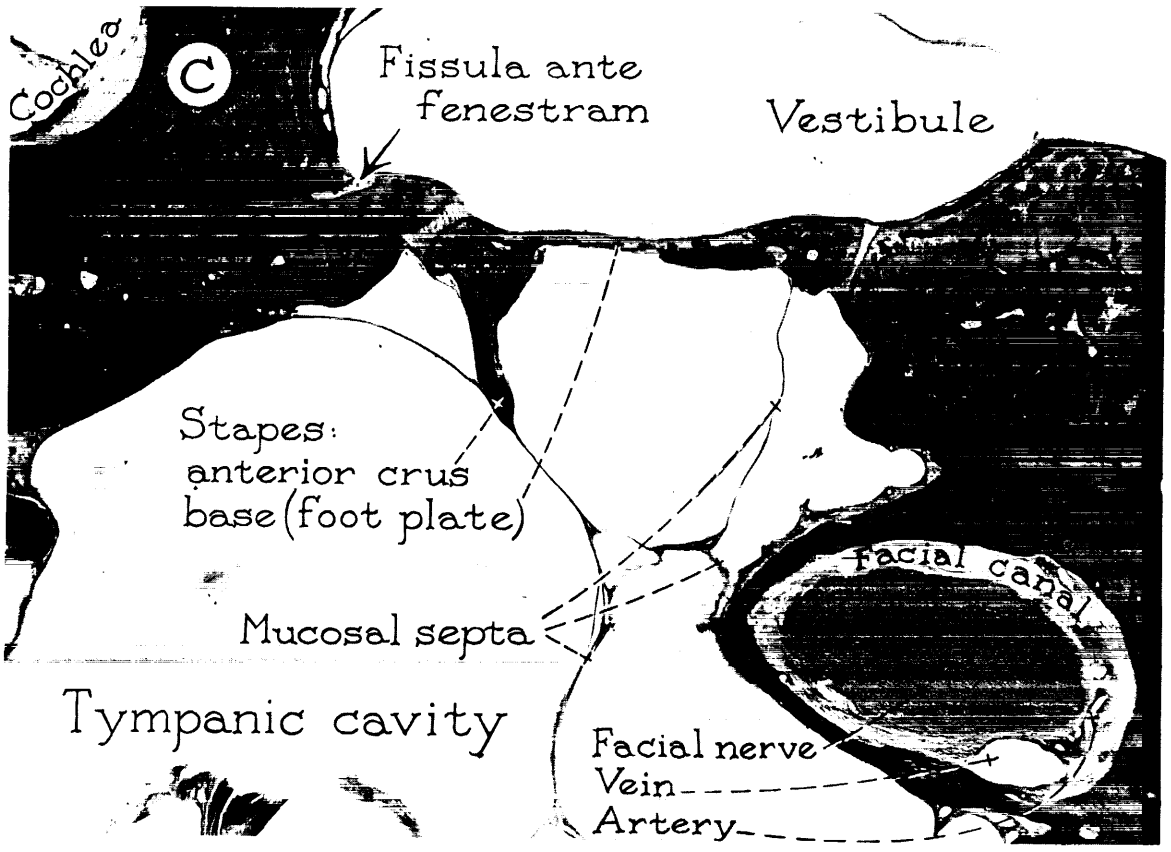


FIGURE 18.—*Developmental and adult anatomy of the* fissula ante fenestram. (a) *Fetus of 19 weeks (161 mm)*; (b) *child 14 years old*; (c) *adult, 19 years of age. Transverse sections. Wisconsin and Northwestern Collections, series 13, 9/23/35, and 29, respectively.* (a) *20×*, (b) *50×*, (c) *18×*. a: *This antefenestral tract is formed through resolution of precartilage, a process similar to that which produces the perilymphatic spaces of the osseous labyrinth. It may, therefore, be regarded as a perilymphatic appendage (in the category with the perilymphatic "duct" in the cochlear aqueduct). The internal aperture opens into the vestibule where the contained tissue becomes continuous with the periotic layer that lines the osseous labyrinth. The external aperture ends on the labyrinthine wall of the tympanic cavity, where its content meets submucosal tissue. The fissula contains only minute vessels that could be of minimal importance in blood supply to the* pars petrosa. b: *Here the fissula approaches the internal aperture on the wall of the vestibule.* c: *At the vestibular extremity, the fissular tract appears as a minute channel occupied by tissue which is continuous with that lining the labyrinthine wall. At the opposite end (not shown) its fibrous content merges with the submucosal tissue of the tympanum.*

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Cochlea

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Subarcuate Fossa

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DISCUSSION

MELVILL JONES: Sometime ago, when investigating pressure changes in the middle ear due to introduction of foreign gases (such as oxygen during descent in flying personnel), it was found that such changes can generate quite marked vestibular stimuli. One searched for ways in which middle-ear-pressure change could be transmitted to the vestibular system so as to generate objective physiological stimulation of the semicircular canal; and blood vessels, of course, came to mind. Can you suggest likely vascular pathways through which relevant pressure changes could be transmitted?

ANSON: I have no comment. Our studies on blood supply are, as you see, in progress. Determination of routes of pressure change await the combined efforts of anatomist and physiologist.

Autoregulation of Strial Blood Flow Effect of Increased Expiratory Resistance: Hyperventilation [1]

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SUMMARY

Short periods (15 to 30 sec) of graded abrupt drops in carotid pressure were produced by graded increases in expiratory resistance. Strial flow rates were correspondingly reduced. With longer periods (120 sec) of increased expiratory resistance, strial blood flow dropped during the first 30 seconds but returned to normal at between 60 to 120 seconds, while carotid pressure remained low. Immediately after terminating the short and longer increases in expiratory resistance, carotid pressure returned toward normal while strial flow rate was supernormal for about 60 to 180 seconds. Hypocapnia produced by hyperventilation reduced strial flow rates without significant change in blood pressure. Hypercarbia and hypoxia increased strial flow rate.

These findings support the concept that intravascular pressure as well as arterial oxygen and carbon dioxide tension directly affects vascular smooth muscle of cerebral and cochlear resistance vessels and thereby influences cochlear blood flow. In this way cochlear blood flow can adjust to physiological stresses (physical and metabolic) so that cochlear function can be sustained.

INTRODUCTION

Factors that influence inner ear blood flow have been under investigation in our laboratory. Strial vessels exposed by fenestrating the apical coil of the guinea pig cochlea have been used in these studies. Unlike peripheral vascular beds, this vascular bed appears to be remarkably free of vasomotor activity, either spontaneous or secondary to direct sympathetic nervous stimulation or to drugs acting at nerve endings in vascular smooth muscle. As expressed by Harper (ref. 1) for all vascular beds, strial blood flow is dependent on the interplay of two factors: the pressure gradient between artery and veins of the blood perfusing the stria and the resistance offered to the blood flow by these vessels, particularly the arterioles. There is considerable evidence that even completely denervated blood vessels are not passive conduits for the blood flowing through them. Their smooth muscles respond directly to stretch and to some chemical stimuli; that is, oxygen, carbon dioxide, and metabolites. The behavior of vessels to such stimuli has been widely studied, as it reveals the capacity for autoregulation of blood flow. Haddy (ref. 2) points out that the venous blood coming from an organ during autoregulation shows changes in the concentration of many naturally occurring vasoactive chemical substances. Besides oxygen and carbon dioxide, they include the hydrogen ion, potassium, magnesium, calcium, adenyl compounds, and others. Autoregulation has been defined in a limited sense as the intrinsic tendency for an organ to maintain constant blood flow despite changes in arterial perfusion pressure.

[1] This work was aided in part by grant NB-00269 from the U.S. Public Health Service and the Douglas Smith Foundation for Medical Research of the University of Chicago.

In a broader sense, Green et al. (ref. 3) state:

> Autoregulation includes all processes which operate locally in a vascular bed to maintain some factor constant in the face of various externally or internally produced stresses.
>
> The factor that is kept constant, the control variable, may be blood flow, or the tissue concentration or tension of some nutrient (O_2, etc.) or some metabolite (i.e., CO_2).
>
> Autoregulation has been studied by subjecting isolated or semi-isolated organs to stresses, such as changes in arterial perfusion pressure or blood gas content or by altering tissue metabolism while recording change or lack of change in blood flow, change in venous gas content, or change in the content of other metabolites. Most theories of autoregulation are based on active response of vascular smooth muscle to some aspect of the stress.

Autoregulation has been found in many organs: kidney, skeletal muscle, myocardium, intestine, and brain. Circulatory homeostasis in response to physical and metabolic stresses even in an isolated, denervated organ may thus be achieved. Pressure-flow relationships, direct observation of blood vessels, and changes in many venous blood constituents have indicated this autoregulating phenomenon. Since the labyrinth receives its blood supply from cerebral blood vessels, pertinent to the consideration of autoregulation in cochlear blood flow is the evidence for autoregulation of cerebral blood flow. In man the capacity of the cerebral vascular bed to maintain blood flow constant at different levels of blood pressure has been indicated by blood-flow studies in hypertension and in drug-induced hypotension. In animals the evidence is conflicting and appears to depend on the experimental methods used. Isolation of the brain, extensive surgical trauma, and use of perfusion pumps have resulted in preparations that reveal a linear relation between cerebral blood flow and arterial perfusion pressure. With more physiological preparations, and autoperfusion with blood of normal pCO_2 and pO_2, the ability of the cerebral vascular bed to maintain a constant blood flow over a wide range of arterial pressures is clear (ref. 1). In addition to physical factors (pressure), metabolic products and nutrients (i.e., CO_2, O_2) in the blood perfusing the brain have been shown to be particularly important in controlling blood flow by affecting the smooth muscle of the resistance vessels (arterioles).

Thus despite insignificant neurogenic control of cerebral vessels, the brain achieves metabolic and hemodynamic homeostasis through locally operating feedback controls of tension in the vascular smooth muscle of the resistance vessels.

Our previous studies of the cochlear vascular bed and blood flow have indicated behavior closely similar to that of the cerebral vascular bed. Further consideration of autoregulation in cochlear blood flow seems indicated. Moving-picture analysis of strial blood flow while recording changes in physical (pressure) and in chemical (CO_2 and O_2) factors of the blood and tissue as well as cochlear function afford some opportunity to study this problem. Two factors were studied: One was the strial blood flow response to a brief, abrupt drop in perfusion pressure and the other was the response to a brief reduction in the pCO_2 of the blood. Some effects of hypercapnia and hypoxia on strial flow were also examined.

METHOD

The method for exposing and illuminating the strial vessels of the guinea pig for motion-picture recording of blood flow has been described (ref. 4). The vessels in this terminal vascular bed range from about 5 to 10 microns in diameter. Through suitable transducers and electrodes, simultaneous monitoring of carotid blood pressure, end tidal pCO_2, pO_2 of the perilymph, cochlear function (microphonic output), and electrocardiogram, some control of the physiological state of the whole animal as well as of the cochlea is possible (fig. 1).

The method for measuring flow velocity in the exposed strial vessels by moving-picture analysis has also been described. Abrupt brief drops in arterial perfusion pressure were produced by raising the expiratory resistance. The curarized 250-g animal, anesthetized with Dial and urethane, is respired with a pump at 42 strokes per minute and 2.5-cc stroke volume. To effect an abrupt, reversible drop in blood pressure, brief measured increases in the expiratory resistance were produced by submerging tubing from the expiratory line below water to depths corresponding to pressures of 2, 4, 8, and 12 mm Hg. To effect a rapid, brief reduction in the pCO_2 of the blood, the animal was hyperventilated. In the hyperventilation experiment,

both increased stroke volume (5 cc) and increased stroke rate (92 per minute) were used. For the production of hypercapnia (8 percent CO_2 in air) or hypoxia (5 percent oxygen in 95 percent nitrogen), flow of these gases at several hundred cubic centimeters per minute was delivered to the intake port of the respirator through tubing from gas cylinders.

FINDINGS

Increased expiratory resistance: Graded abrupt sustained drops in carotid pressure were produced with 15- and 30-second periods of increased expiratory resistance of from 2 to 12 mm Hg (figs. 2 and 3). This was associated with a drop in strial blood flow rate. This initial flow rate drop was, in general, proportional to the drop in carotid pressure. The blood-pressure drop was sustained with expiratory resistance continued even for 120 seconds. However, despite this drop in blood pressure sustained for 120 seconds, strial flow rate did not remain depressed but began to rise within 60 seconds, approaching preexposure levels at 120 seconds and exceeding them for a few minutes after removing the expiratory resistance (fig. 4).

Longer periods of increased expiratory resistance could not be used for this study, since they were associated with reversal of blood-pressure drop with return to normal pressure in 6 to 7 minutes (fig. 5). Expiratory resistance of 8 and 12 mm Hg was used in most experiments, but smaller elevations (2 and 4 mm Hg) also produced drops in pressure. On terminating the short exposures (15 to 120 sec) there was a prompt return of blood pressure toward the initial value, while blood flow rates at this time exceeded preexposure values (fig. 6). Flow velocity returned to normal values within about 3 minutes. With this method the drop in carotid blood pressure could be controlled and the drop in strial flow rates could be varied. With maximum reduction (over 50 percent) in

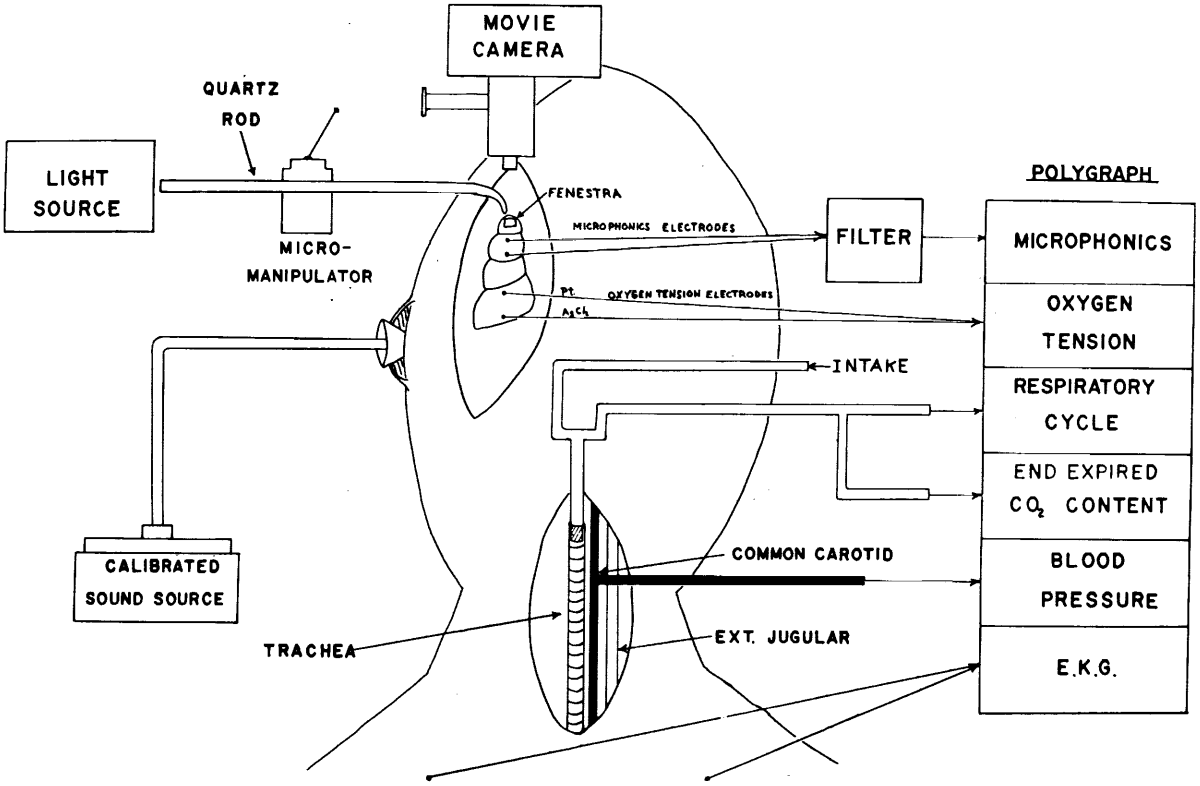

FIGURE 1.—*Diagram of surgical field and associated equipment used for simultaneous recording of cochlear blood flow, cochlear function, and cochlear oxygen tension along with carotid blood pressure and end-tidal carbon dioxide.*

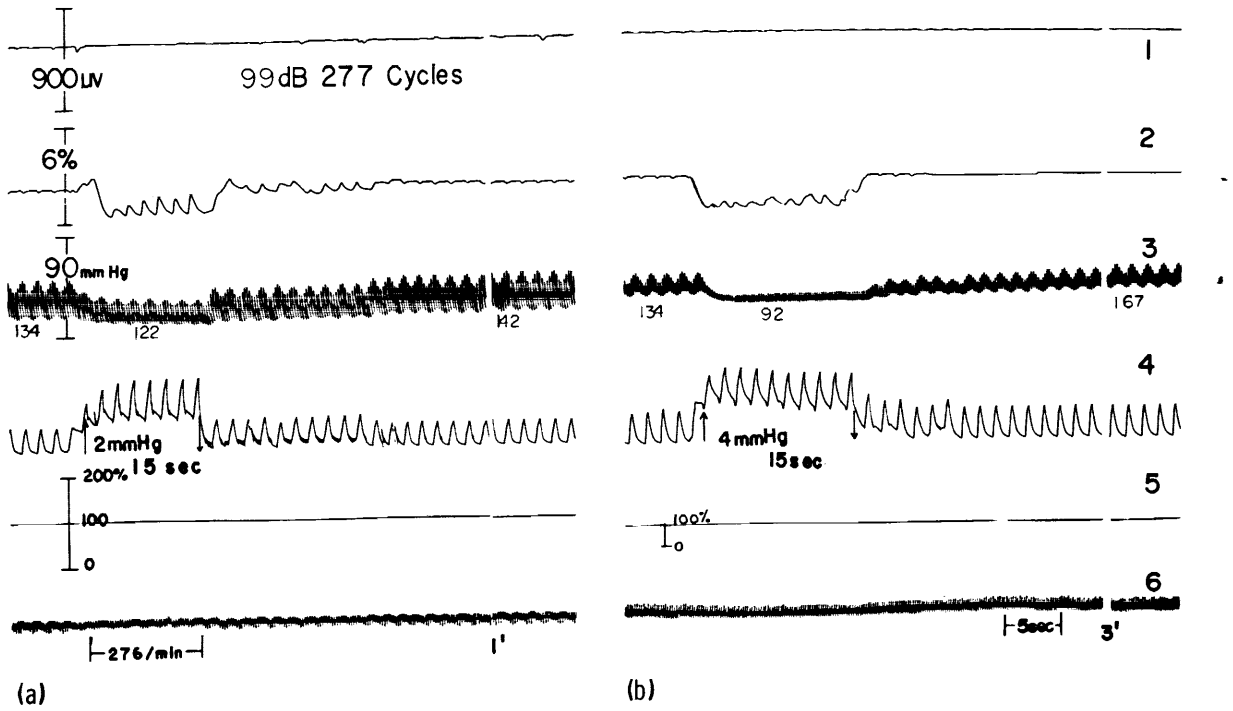

FIGURE 2.—*Effect of 2 mm Hg elevation in expiratory resistance for 15 seconds* (a). *Flow velocity* (μ/sec) *in strial capillary indicated below blood pressure channel* (3). *Record of experiment with 4 mm Hg elevation in expiratory resistance for 15 seconds* (b). *Channel:* (1) *cochlear microphonic output;* (2) *end-tidal* pCO_2; (3) *carotid blood pressure;* (4) *respiratory pressures;* (5) *cochlear oxygen tension; and* (6) *electrocardiogram.*

TABLE 1.—*Carotid Pressure, Strial Blood Flow, Cochlear Function, and Cochlear Oxygen Tension Before, During, and After 15 Seconds of Elevated Expiratory Resistance (12 mm Hg)*

	Micro μv	Blood pressure, mm Hg					O_2 tension, percent	Heart rate/ min	Blood flow velocity, μm/sec					
		Max	Min	Mean	Percent change	Pulse P			AVA	Percent change	St. cap	Percent change	RA	Percent change
Control	320	60	40	50	0	20	100	336	294	0	133	0	343	0
12 mm Hg:														
During 15 sec	260	22	18	20	−60	4	87	336	59	−80	20	−85	154	−55
1 min after	320	50	34	42	−16	16	97	336	370	+26	183	+36	528	+54
3 min after	320	60	40	65	0	20	+120	336	535	+82	284	+110	635	+85
10 min after	320	60	40	50	0	20	100	336	291	−2	131	−2	378	+10

strial flow rate a transient, slightly delayed drop in microphonic output and cochlear oxygen tension were recorded (tables 1 and 2). Lesser degrees of reduced flow in the strial vessels were not associated with depression in cochlear function or oxygen tension (tables 3 and 4). When the initial blood pressure was very low (i.e., 25 mm Hg) due to the animal's poor condition, values as low as 10 mm Hg systolic and zero diastolic were sustained during 2 minutes of increased expiratory resistance of 8 mm Hg. Strial blood flow was severely reduced throughout this period of very low pressure, unlike in the normal animal where recovery of flow was noted despite sustained reduced carotid pressure (fig. 7). Brief (15 to 120 sec) exposures of the

TABLE 2.—*Effect of Elevating Expiratory Resistance by 12 mm Hg for 30 Seconds. Data as in Previous Table*

	Micro μv	Blood pressure, mm Hg					O_2 tension, percent	Heart rate/min	Blood flow velocity, μm/sec					
		Max	Min	Mean	Percent change	Pulse P			AVA	Percent change	St. cap	Percent change	RA	Percent change
Control	300	60	40	50	0	20	100	324	294	0	133	0	343	0
12 mm Hg:														
During 30 sec	200	22	18	20	−60	4	57	(a)	53	−82	17	−87	86	−75
1 min after	300	52	36	44	−12	16	105	324	632	+122	346	+140	816	+138
3 min after	340	56	36	46	−8	20	134	324	853	+190	394	+195	+1029	+200
10 min after	300	60	40	50	0	20	100	324	353	+20	147	+10	412	+20

[a] Irregular.

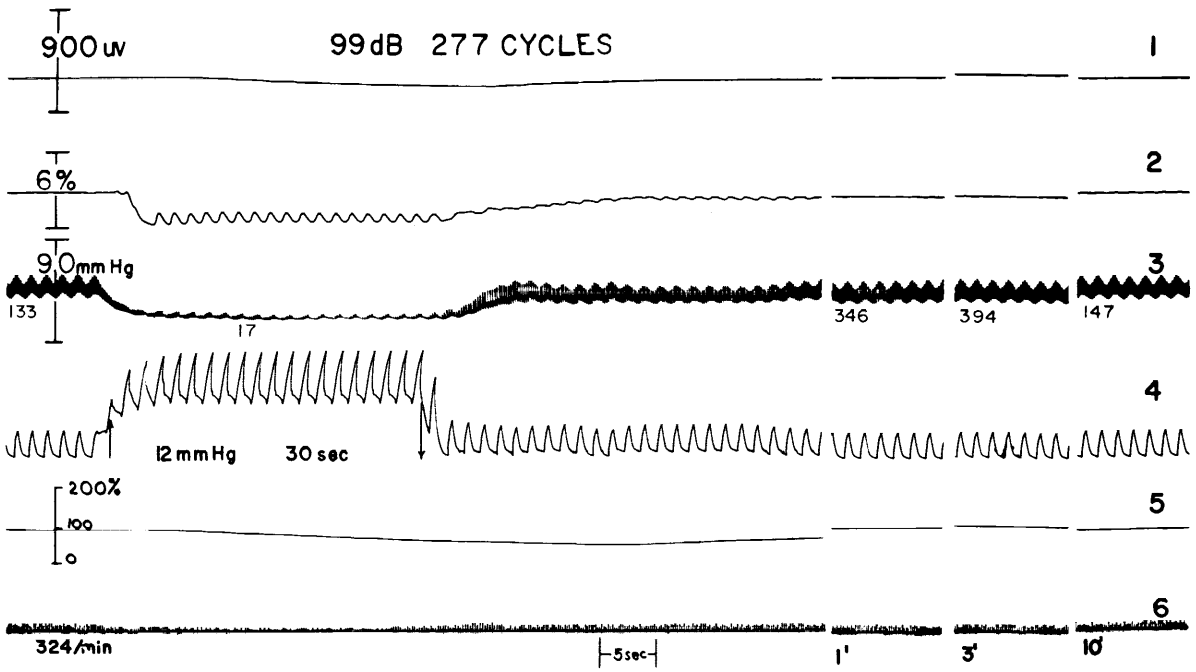

FIGURE 3.—*Record of experiment relating to data in table 2. Effect of 30 seconds of increased expiratory resistance of 12 mm Hg. Results similar to those recorded in figure 2 but more pronounced. Flow velocity (μ/sec) in strial capillary indicated below blood pressure channel* (3).

animal to increased expiratory resistance of 8 mm Hg could be repeated (i.e., six times) at frequent intervals with rapid recovery from each and with no evidence of deterioration of the animal. Unlike the normally respiring condition, abrupt fall and recovery of the carbon dioxide values in expired air recorded during increased expiratory resistance did not reflect the changes in pCO_2 of arterial blood since, with increase of the functional dead space, the position of the alveolar portion of the air column moving out of the lung on expiration is shifted when expiratory resistance is increased. The position of the sampling tube for carbon dioxide analysis in the expiratory line remains fixed and is now probably in relation to the tidal air with lower carbon dioxide values.

When the expiratory resistance was increased during periods of hypoxia (5 percent O_2) or hypercapnia (8 percent CO_2), flow rate changes were minimal. However, the initial strial flow rates were now markedly increased by the

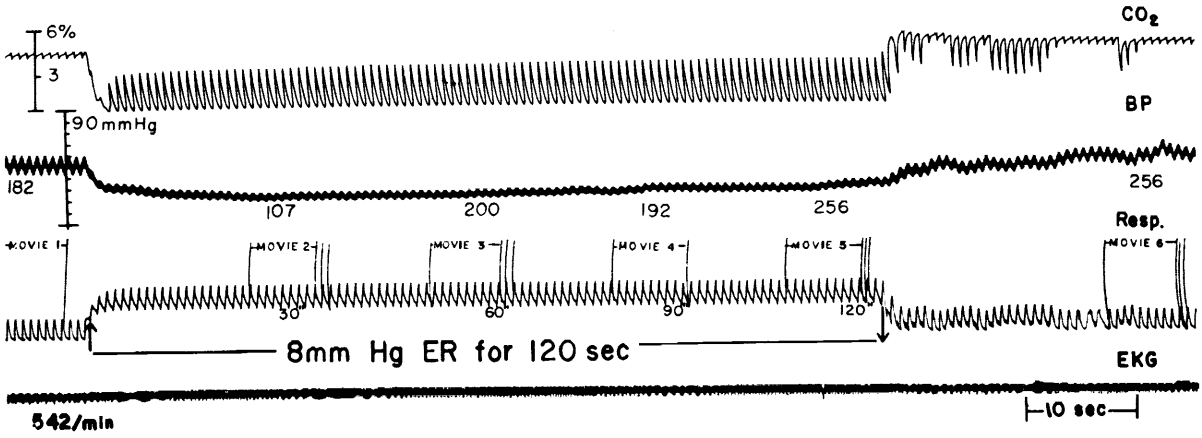

FIGURE 4.—*Record of carotid pressure response during 2 minutes of increased expiratory resistance. Flow velocity (μ/sec) in strial capillary indicated below blood pressure channel* (3). *Note reversal of velocity values despite a sustained drop in carotid pressure (autoregulation).*

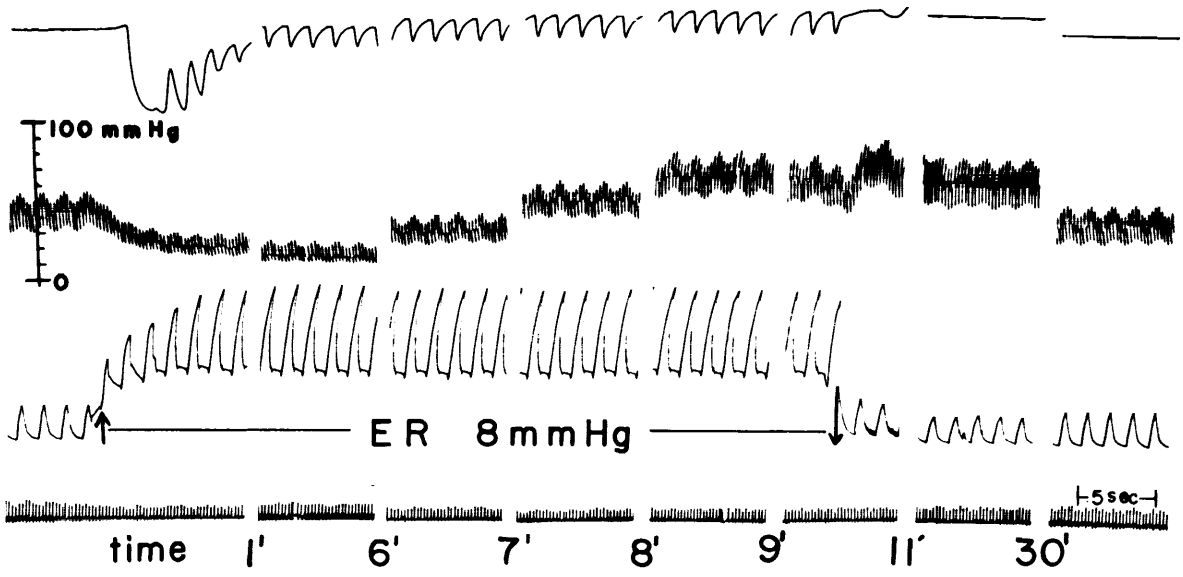

FIGURE 5.—*Record of carotid blood pressure response to prolonged (10 min) elevation of expiratory resistance (8 mm Hg) showing abrupt initial drop and gradual elevation to supernormal values after 7 minutes.*

hypoxia and by the hypercapnia. In the hypoxia experiment, carotid pressure was not elevated, while during the hypercapnia experiment, blood pressure was elevated about 100 percent.

Hyperventilation.—Short periods (15 to 90 sec) of respiration at double (5 cc) the normal stroke volume (fig. 8) or at increased rate (92 per min) with normal stroke volume (fig. 9) were associated with a small drop in carotid pressure but with a clear reduction (up to 50 percent) in strial blood flow. This reduction was sustained throughout the period of exposure. Normal flow rates followed immediately after terminating the hyperventilation.

The recorded carbon dioxide content of end tidal air during hyperventilation with normal stroke volumes showed an abrupt, sustained drop and abrupt recovery on termination of hyperventilation and closely paralleled the reduced pCO_2 of the arterial blood. There was

TABLE 3.—*Effect of a Brief (15 Sec) Rise in Expiratory Resistance of 2 mm Hg on Carotid Pressure, Strial Blood Flow, Cochlear Oxygen Tension, and Cochlear Function*

	Micro μv	Blood pressure, mm Hg					O_2 tension, percent	Heart rate/min	Blood flow velocity, μm/sec					
		Max	Min	Mean	Percent change	Pulse P			AVA	Percent change	St. cap	Percent change	RA	Percent change
Control	580	52	16	34	0	36	100	276	235	0	134	0	252	0
2 mm Hg:														
During 15 sec	580	34	14	24	− 30	30	100	276	202	− 1.4	122	− 9	190	− 25
1 min after	580	52	16	34	0	36	100	276	245	+ 4	142	+ 6	280	+ 11
4 mm Hg:														
During 15 sec	580	24	20	22	− 40	4	80	276	174	− 26	92	− 31	204	− 19
1 min after	580	52	30	41	+ 21	22	100	276	334	+ 42	185	+ 38	333	+ 32
3 min after	580	54	28	41	+ 21	26	100	276	305	+ 30	167	+ 25	328	+ 30

TABLE 4.—*Effect of a Brief (15 Sec) Rise in Expiratory Resistance of 8 mm Hg on Carotid Pressure, Strial Blood Flow, Cochlear Oxygen Tension, and Cochlear Function*

	Micro μv	Blood pressure, mm Hg					O_2 tension, percent	Heart rate/min	Blood flow velocity, μm/sec					
		Max	Min	Mean	Percent change	Pulse P			AVA	Percent change	St. cap	Percent change	RA	Percent change
Control	400	48	38	43	0	10	100	318	294	0	133	0	343	0
8 mm Hg:														
During 15 sec	400	28	22	24	− 45	4	93	318	178	− 40	66	− 51	153	− 55
1 min after	400	56	46	59	+ 37	14	119	318	382	+ 30	181	+ 36	535	+ 56
3 min after	400	56	46	52	+ 21	12	119	318	444	+ 51	199	+ 50	525	+ 53
10 min after	400	48	38	43	0	10	100	318	290	− 2	131	− 2	402	+ 17

TABLE 5.—*Effect of Hyperventilation (Stroke Volume Unchanged but Rate Increased to 92/min) on Strial Blood Flow and Other Values*

	Micro μv	Blood pressure, mm Hg					O_2 tension, percent	Heart rate/min	Blood flow velocity, μm/sec								
		Max	Min	Mean	Percent change	Pulse P			AVA	Diam (μ)	Percent change	St. cap	Diam (μ)	Percent change	RA	Diam (μ)	Percent change
42/min: Control	280	70	30	50	0	40	100	240	312	4	0	115	7	0	355	4	0
92/min:																	
During	280	48	26	37	− 26	22	100	240	218	4	− 30	49	6	− 58	232	4	− 35
1 min after	280	70	30	50	0	40	100	240	318	5	+ 2	112	0	− 1	360	6	+ 2

no significant change in the diameter of the exposed strial vessels at this time. Unlike the findings with increased expiratory resistance, comparable reductions in strial blood-flow velocity achieved by hyperventilation were not associated with reduction in microphonic output or cochlear oxygen tension (table 5). Hyperventilation with increased stroke volume was also effective in producing short periods of reversible reduction in strial flow rate provided values of 5 cc were not exceeded (table 6). With larger stroke volumes, overexpansion could produce permanent damage to the lung.

REMARKS

The relation of blood pressure to blood flow has been examined for evidence of autoregulation by producing brief, sudden, reversible changes in blood pressure with clamps or pumps and

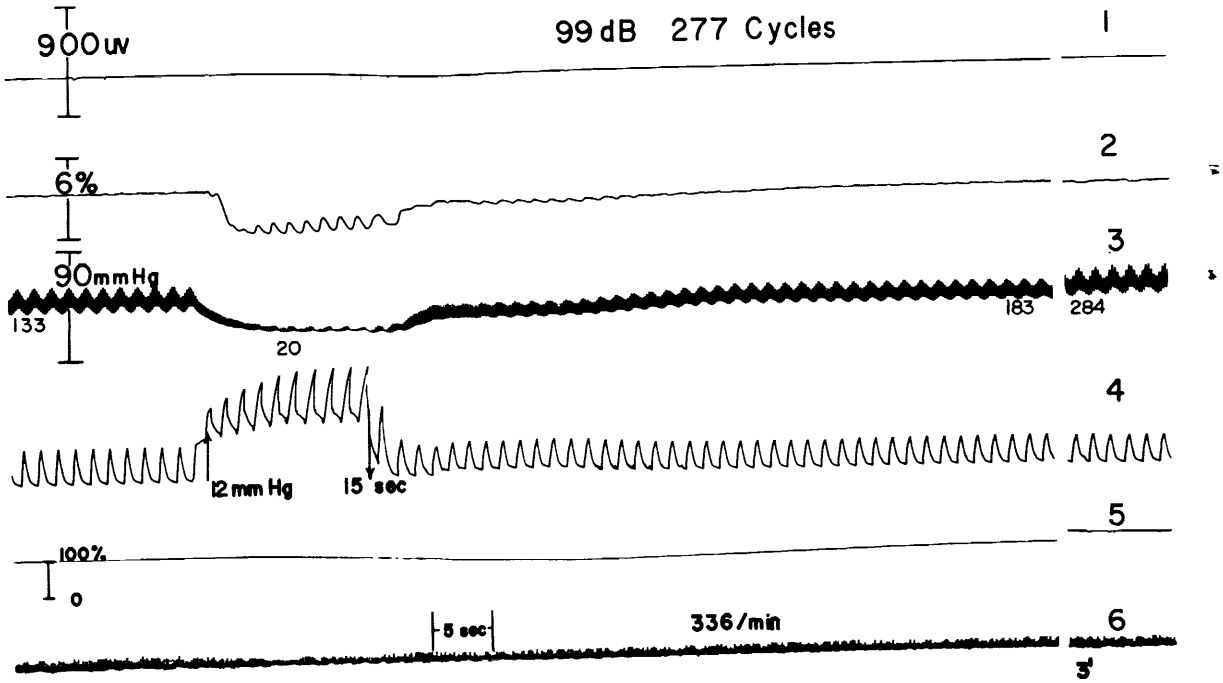

FIGURE 6.—*Record of experiment before, during, and 3 minutes after 15-second elevation of expiratory resistance (12 mm Hg). Flow velocity (μ/sec) in strial capillary indicated below blood pressure channel (3). Note drop in carotid pressure, cochlear blood flow, microphonics, and oxygen tension.*

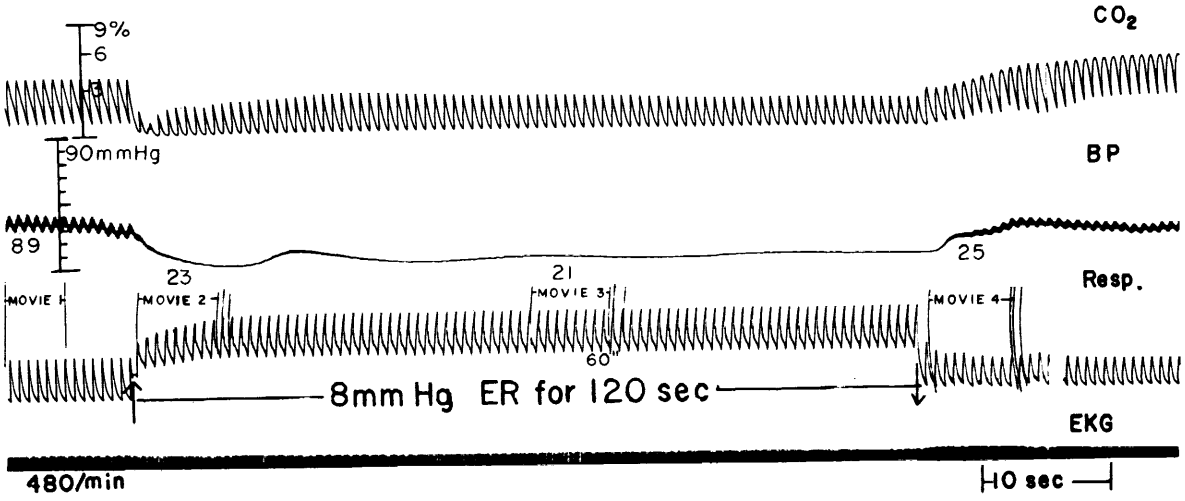

FIGURE 7.—*With profound drop in carotid pressure sustained during increased expiratory resistance (8 mm Hg) strial blood flow remains depressed (even stops) throughout period of low blood pressure (absence of autoregulation). When expiratory resistance is removed, blood pressure rises and flow returns toward normal values in all vessels. Strial blood flow velocity (μ/sec) indicated below blood-pressure channel (3).*

TABLE 6.—*Effect of Hyperventilation (Rate Constant but Doubling Stroke Volume) on Strial Blood Flow, Vessel Diameter, Cochlear Function, Cochlear Oxygen Tension, and Carotid Pressure*

	Micro μv	Blood pressure, mm Hg					O_2 tension, percent	Heart rate/min	Blood flow velocity, μm/sec								
		Max	Min	Mean	Percent change	Pulse P			AVA	Diam (μ)	Percent change	St. cap	Diam (μ)	Percent change	RA	Diam (μ)	Percent change
2.5 cc: Control	550	46	18	32	0	28	100	276	290	4	0	92	6	0	327	5	0
5.0 cc:																	
During	540	38	12	25	−23	26	73	276	228	4	−21	58	6	−37	245	5	−25
1 min after	550	46	18	32	0	28	100	276	292	4	+2	89	6	−3	320	5	−2

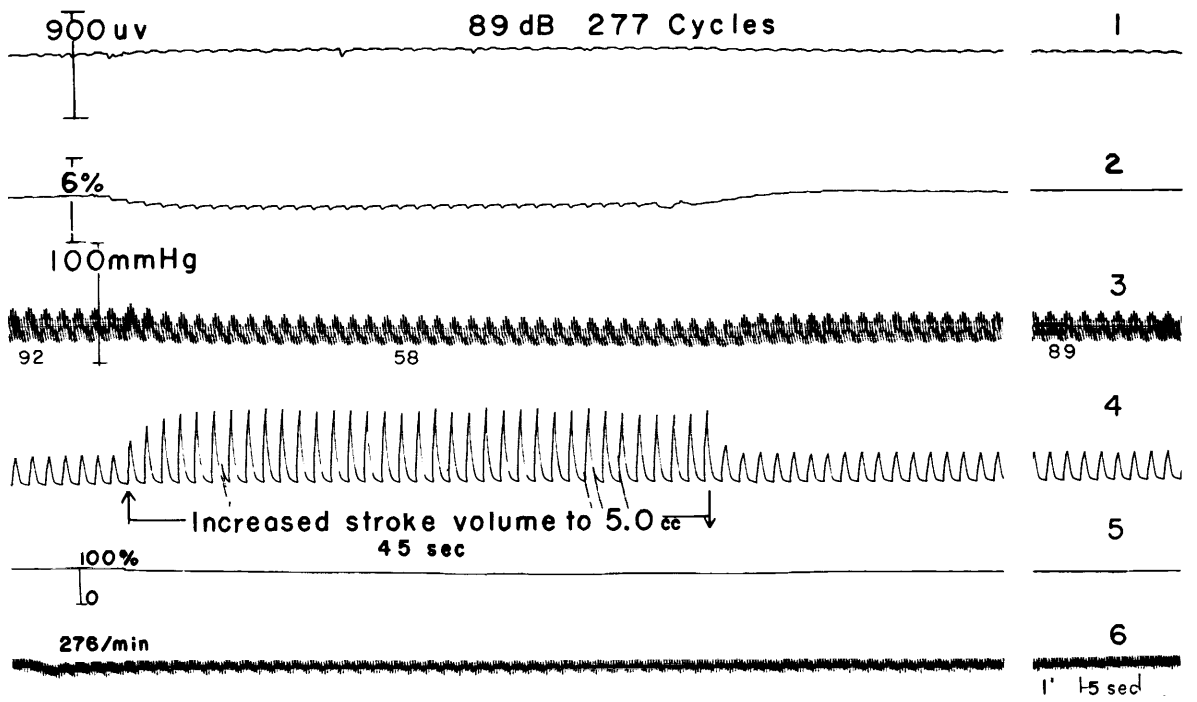

FIGURE 8.—*Record of hyperventilation experiment detailed in table 6. Strial blood flow measured before, during, and 1 minute after 45 seconds of respiration with 5-cc stroke volume. Carbon dioxide content of alveolar gas dropped from about 3 percent to about 2 percent (flow velocity (μ/sec) in strial capillary indicated below blood-pressure channel (3)).*

recording flow rate changes with flowmeters on larger arteries or veins. Similar changes in pressure can be produced by sudden increase in expiratory resistance. When expiratory resistance is briefly elevated, cardiac stroke volume is promptly reduced as return of blood to the heart is impeded. A sudden drop in arterial pressure results and is sustained throughout these brief exposures. Pressure is immediately reversed to preexposure levels on return to normal resistance. During increased expiratory resistance, strial flow rate can be recorded at 15- to 30-second intervals by moving pictures and compared with flow rates immediately before and immediately after exposure. Despite limitations of the method which preclude detection of continuous changes in flow, the initial drop in strial flow followed by rise in flow to normal values, despite a sustained reduction in carotid pressure, is clearly evident both by direct observation of the strial vessels and by moving picture analysis (table 7). Flow in all vessels in this terminal vascular bed exposed by fenestration is affected: capillary, arteriole, and arterio-

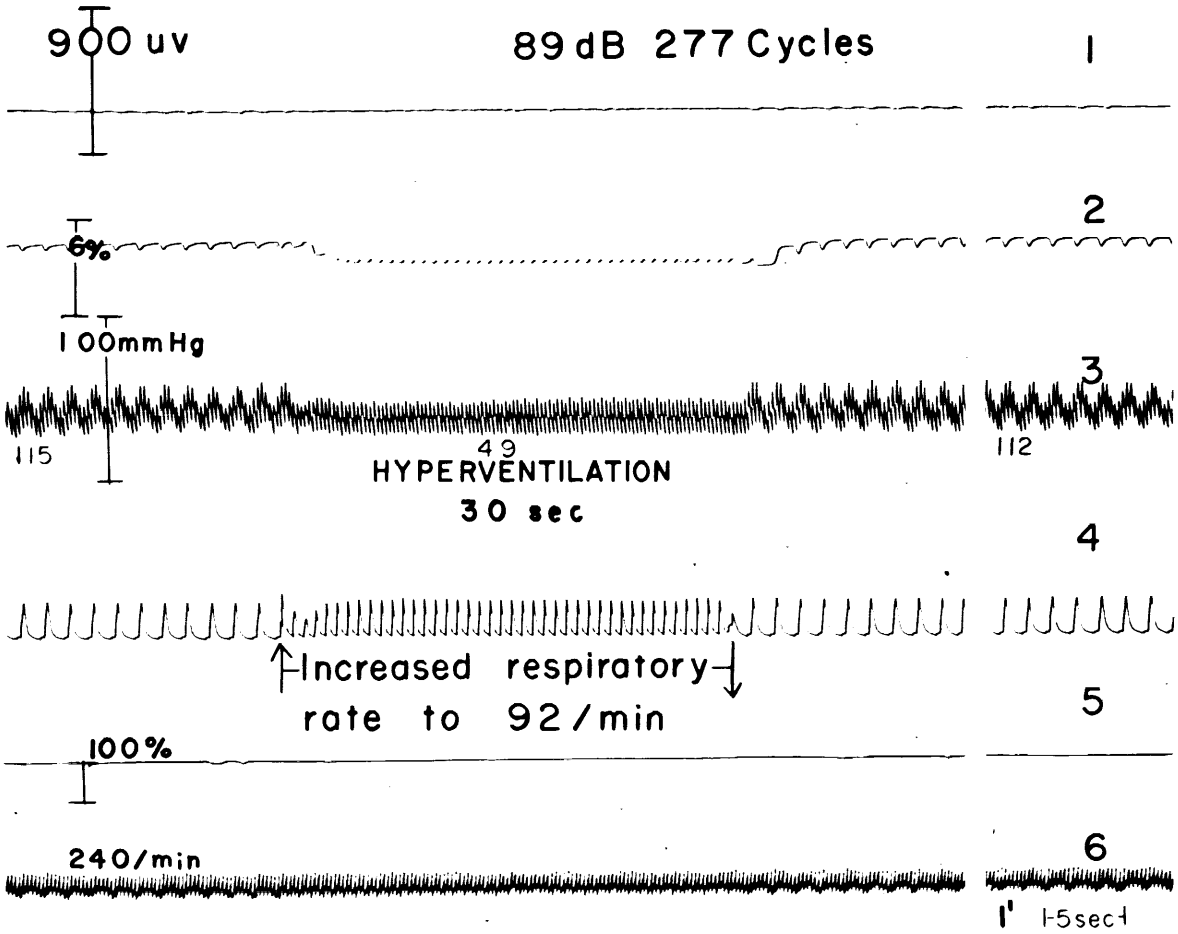

FIGURE 9.—*Record of hyperventilation experiment detailed in table 5. Blood flow recorded before, during, and 1 minute after respiration with 2.5-cc stroke volume at 92 per minute. Flow velocity (μ/sec) in strial capillary indicated below blood pressure channel (3). Note drop in alveolar carbon dioxide content during hyperventilation.*

venous arcade. The degree of change varies with the type of vessel and the particular geometry of the vascular channels in each animal. The measured drop in cochlear oxygen tension associated with increased expiratory resistance at 8 and 12 mm Hg and the unknown values for arterial pCO_2 make it difficult to clearly separate these chemical factors from the physical factor of decreased pressure in relaxing arteriolar smooth muscle to increase strial flow rate. In normal animals and man, evidence for autoregulation of the cerebral circulation to changes in blood pressure has been obtained by Harper (ref. 1), by Rapela and Green (ref. 5), by Lassen (ref. 6), and by Carlyle and Grayson (ref. 7). All investigators stress the importance of maintaining normal physiological conditions; that is, normal pO_2 and pCO_2 of arterial blood perfusing the brain and other factors that prevent marked dilation of cerebral blood vessels. Harper showed that when pressure-flow relations were examined with the perfusing blood at double the normal arterial pCO_2 values, the flow rate varied directly with pressure (showed no evidence for autoregulation) unlike the relations with normal pCO_2 when cerebral blood-flow rate remained stable between pressures of 70 to 180 mm Hg. Below 70 mm Hg perfusion pressure, autoregulation is lost and flow rates decreased linearly as pressure drops. Lassen

TABLE 7.—*Blood Flow Velocity in Microns per Second in Strial Vessels*

[(R) Radiating arteriole; (C) Capillary; (A) Arteriovenous arcade. Velocity values in strial vessels, before, at onset, and at end of 120-sec expiratory resistance of 8 mm Hg and at 1 minute and 3 minutes after. Note initial drop in flow and return toward normal flow before expiratory resistance is terminated, and a brief period of supernormal flow immediately after terminating expiratory resistance]

	Control			Onset			End			Post 1			Post 2		
	C	A	R	C	A	R	C	A	R	C	A	R	C	A	R
N	21.0	20.0	8.0	13.0	13.0	7.0	8.0	8.0	3.0	12.0	13.0	6.0	8.0	8.0	4.0
Mean	164.4	311.5	265.1	91.8	165.2	145.7	201.1	247.7	321.7	234.1	317.8	484.8	174.9	260.9	365.2
Standard deviation	44.9	111.6	68.4	28.2	43.6	38.6	91.9	116.4	159.4	98.9	147.2	194.1	57.9	72.9	56.9

(ref. 6) pointed out that anoxia also abolishes cerebral autoregulation. In both cases, marked dilation of cerebral arteries is produced. He suggested that the mechanisms involved in autoregulation include transmural pressure gradients and accumulation of metabolic products in the perfusing blood, including carbon dioxide to which the smooth muscle of the resistance vessels (cerebral arterioles) is uniquely sensitive. Autoregulation of cerebral blood flow is a physical adjustment of arteriolar smooth muscle tonus to maintain a stable internal environment for nerve cells.

In the dog, Rapela and Green (ref. 5) found that with abrupt 60-second reductions of carotid and vertebral blood pressure, an initial fall in cerebral blood flow was not sustained but was followed by a rise to normal values within 30 seconds. Sudden return of pressure while vessel dilation was still present caused a brief overshoot of flow. They consider that both pH and pCO_2 as well as pO_2 may act as regulators in a feedback control system of smooth muscle tonus. Schneider (ref. 8) pointed out that with slow changes in pressure, cerebral blood flow was constant for perfusion pressures from 200 down to 60 mm Hg, but with rapid drops in pressure through this range, flow drops proportionately. However, below this level of pressure, cerebral blood flow drops linearly with falling blood pressure whether slowly or rapidly produced.

Meyer et al. (ref. 9) found that slow reduction in internal carotid pressure down to 70 mm Hg by bleeding did not affect cerebral flow rate (autoregulation). With reduced intraluminal pressure or because of reduced pO_2 or pCO_2 in the tissues, the tonic constriction of arteriolar smooth muscle decreases and the vessel dilates. When pressures were reduced further by continued bleeding, flow rates dropped due to inadequate dilation of vessels. Meyer et al. pointed out that the response of cerebral vessels to stretch and to chemical stimuli is not counteracted by autonomic nervous control. On the other hand, they observed that the rich sympathetic supply of the external carotid counteracted these vasodilator forces to produce flow rates in the external carotid proportional to pressure even above 70 mm Hg.

Harper (ref. 1) also reported that cerebral blood-flow rates remained constant in the normocapnic dog with pressure reduced by hemorrhage until pressures dropped below 80 mm Hg. Increases in cerebral venous pressure (internal jugular) to 23 cm H_2O had little effect on cerebral blood flow. With arterial pCO_2 held constant, anoxia did not cause a rise in cerebral blood flow until oxygen saturation fell below 75 percent (oxygen tension 40 mm Hg).

With abrupt rise in pressure, Yoshida et al. (ref. 10) also found autoregulation of cerebral blood flow in the monkey. This could be abolished with 5 percent carbon dioxide. Harper reported that while in the normotensive dog, hypercapnia produced a marked increase and hypocapnia a marked decrease in cerebral blood flow, in the hypotensive dog this effect was decreased or absent. He believed that cerebral blood flow is regulated to maintain a constant brain pCO_2 in response to changes in arterial pCO_2 and, secondly, the diameter of cerebral blood vessels is regulated to maintain constant flow despite fluctuations in systemic blood pressure.

Harper found, as did Reivich (ref. 11), that cerebral blood flow was very sensitive to pCO_2, so that flow changed 2.5 percent for every mm

Hg change in pCO_2 in the range between 30 and 60 mm Hg. In contrast to the observations of Rapela and Green, Harper reported that pH alone did not alter cerebral blood flow if Pa CO_2 was kept constant by adjusting ventilation rate. In contrast to Harper, Häggendal (ref. 12) found that even a moderate degree of hypoxia as well as hypercapnia and drugs seems to abolish autoregulation as maximum dilation of the cerebral vessels is produced. The physiological changes associated with increased expiratory resistance including the Valsalva maneuver have been widely studied in anesthetized animals and in unanesthetized human subjects. In the anesthetized, vagotomized dog exposed to 18 mm Hg positive pressure breathing for 1 minute, Marotta and Harner (ref. 13) measured an initial drop in femoral artery blood flow. This flow recovered partially at 1 minute despite a sustained low (50 percent of normal) femoral artery pressure. Immediately after exposure, flow was supernormal although femoral artery pressure was not fully recovered (85 percent of normal). Flow and pressure returned to normal 1 minute later. In anesthetized dogs, Lenfant and Howell (ref. 14) reported a 50-percent fall in cardiac output with 26 cm H_2O expiratory pressure. Similar changes for anesthetized man were reported by Ernsting (ref. 15). Salzano and Hall (ref. 16) found an increase in alveolar and arterial carbon dioxide tension during continuous pressure breathing, even in anesthetized hypothermic dogs.

Information on cerebral blood flow during pressure breathing is limited. In humans syncope can be produced by pressure breathing and resembles that of fainting. It is associated with a precipitous drop in blood pressure and peripheral pooling that reduces the effective blood volume by 800–1200 cc, according to Ernsting (ref. 15). He discussed in detail the physiology of pressure breathing from the standpoint of aviation and stated that pressure breathing itself probably reduces cerebral blood flow. In man, Meyer et al. (ref. 17) found that elevation of intrathoracic pressure during the Valsalva maneuver decreased cerebral blood flow. The decreased flow resulted from a reduction of the cerebral perfusion pressure gradient as arterial blood pressure dropped to minimum levels in 5 to 10 seconds and venous pressure arose.

The importance of oxygen in autoregulation was pointed out by Guyton et al. (ref. 18). They found that oxygen deficiency hyperemia is as great as reactive hyperemia following release of arterial obstruction and that oxygen was necessary for recovery from reactive hyperemia. Without oxygen, flow rates remained supernormal. Thus no vasodilator substance had accumulated that could be washed out by the returning circulation and permit return to normal flow. They believe that oxygen is the most nearly flow limited of all common physiologically important substances transported by the blood. Blood can transport normal amounts of carbon dioxide from tissue when cardiac output falls as low as one-tenth normal. It can transport normal amounts of glucose, protein, and fat to the tissue when cardiac output falls as low as one one-hundredth normal and transport adequate amounts of urea away from the tissue when blood flow falls as low as one one-hundredth normal. They observed that with a normal workload on smooth muscle (i.e., arterial pressure of 100 mm Hg), the degree of constriction and dilation varied with the pO_2 as it changed from 100 to 30 mm Hg. Häggendal and Johansson [2] found that severe anoxia abolishes autoregulation of canine cerebral blood flow and suggest that vascular smooth muscle requires oxygen to respond to pressure changes.

Guyton (ref. 19) found a threefold increase in blood flow through small (1/2-mm diameter) arteries when the arterial pO_2 was lowered from 100 to 30 mm Hg and, therefore, a corresponding decreased resistance in the isolated vessel.

Shepherd (ref. 20) pointed out that resistance vessels dilated after release from obstruction even in a sympathectomized, atropinized, and denervated vascular bed so that the reactive hyperemia after a period of no flow (zero pressure) is a local effect on the vascular smooth muscle. It is not affected by pretreatment with antihistamines. The marked temporary increase in strial flow rate observed immediately after

[2] Häggendal, E.; and Johansson, B.: Effects of Arterial Carbon Dioxide Tension and Oxygen Saturation on Cerebral Blood Flow Autoregulation in Dogs. Acta Physiol. Scand., suppl. 258, 1965, pp. 27–53.

release of the experimentally occluded internal auditory artery reported earlier (1959) by Perlman et al. (ref. 21) is an example of this local dilation effect on the vascular smooth muscle, probably due to reduced pressure, anoxia, and accumulation of carbon dioxide, and is evidence for autoregulation of blood flow by the inner ear vessels.

Similarly, the abrupt increase in strial flow from subnormal values in the self-respired, hypothermic animal at about 22° C before carotid pressure drops may also indicate autoregulation probably due to hypoxia and hypercarbia affecting arteriolar smooth muscle tonus (ref. 22).

The effect of hyperventilation on cerebral blood flow in man and animals has been thoroughly examined. Direct observation of cerebral blood vessels in monkey and cat by Meyer and Gotoh (ref. 23) indicate constriction of larger vessels (50- to 100-micron diameter) along with reduced blood flow from control value of 53 cc/100 g/minute to 38 cc/100 g/minute during hyperventilation and with a minimal drop in blood pressure.

In man during hyperventilation, Fazekas et al. (ref. 24) measured a decrease in the pO_2 of jugular blood with no change in cerebral oxygen consumption or arterial pressure, indicating increased vascular resistance and reduced cerebral blood flow. Cerebral blood flow dropped from a normal of 60 cc/g/minute to 35 cc/100 g/minute during hyperventilation.

In the monkey, Handa et al. (ref. 25) found that hyperventilation reduced flow rates equally in the internal carotid and vertebral arteries without a significant fall in blood pressure.

Gotoh et al. (ref. 26) reported that cerebral tissue becomes anoxic during hyperventilation, mostly because cerebral vessels are constricted as arterial pCO_2 is reduced.

In the monkey with prolonged hyperventilation, cortical pO_2 (polarographic electrode) was reduced from an initial value of 15–35 mm Hg to 2 mm Hg, while the change in blood pressure was minimal.

The cerebral hypoxia was partly the result of decreased flow and partly the result of a decrease in dissociation of oxygen from alkaline hemoglobin (Bohr effect).

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DISCUSSION

VON GIERKE: Did you observe any change in cochlear circulation as a result of auditory stress alone?

PERLMAN: We did this in an earlier experiment and found that the auditory stress had to be very great in order to produce a measurable increase in flow velocity, in the order of 134 to 150 dB at the 277-cycle frequency that we used. Below that level we saw no change in flow velocity. We interpreted the findings to indicate that the increased metabolic activity of the end organ below 134 dB was achieved by increased extraction of oxygen and metabolites from the capillaries. In experiments by others with constant flow rates through heart, kidney, and brain, arteriovenous differences in oxygen may vary with functional activity.

HAWKINS: Where do you locate the smooth muscle elements that you mentioned? I am not sure that they are present in the vessels of the modiolus. Perhaps they are in the bony channels crossing the roof of the scala vestibuli. We do not seem to see them in the vessels coming down in the upper part of the spiral ligament or in the capillaries of the stria itself. I wonder whether a good part of this peripheral resistance might not be in the capillary endothelium itself at localized points, as we have seen it in the spiral vessels under the basilar membrane due to swelling of the endothelial cells and the pericytes. With quinine, we do see in the stria itself as well as in the spiral vessels evidences of vasoconstriction in our static preparations.

PERLMAN: The evidence for smooth muscle on blood vessels in the inner ear is based on examination of histologic sections of the temporal bone and staining smooth muscle with methylene blue in the living cochlea. In the exposed stria and spiral ligament, we find what we think are smooth muscle on the radiating arteriole and arteriovenous arcade only one cell layer thick, both in the histologic sections and with this vital stain. These vessels and the larger vessels in the modiolus do have smooth muscle. Compared with the peripheral vessels, the muscular layer is very thin. Even the internal auditory artery has very little smooth muscle, similar to the findings in cerebral vessels.

As regards the endothelial thickening, the only reason that we have not considered this as a factor in controlling blood-flow resistance is the fact that we do not see any change in the width of the blood column as if it were distorted by a swollen endothelial cell. I have seen a temporary narrowing of the blood column in a radiating arteriole in one instance following a large dose of histamine, but not in these experiments.

McDONALD: We have been interested in the small blood vessels of the sensory nerves to the inner ear. We have noted some marked similarities at the electron-micrograph level of the capillaries of the nerve underlying the macula of the saccule and the utricle. We have not examined cochlea in this regard, but I notice some of Dr. Hawkins' micrographs seem to be consistent with our findings in the vestibule. These capillaries in these areas have a marked similarity to the capillaries in the brain. They have a thick continuous endothelium, a fairly thick basement membrane, in the rabbit on the order of 80 millimicrons. Often a perivascular cell is present, around which the basement membrane also passes. These structural features are shown in figures D1 and D2.

These structural features are quite different from those of capillaries, say, for example, in the kidney, where the endothelium is discontinuous. In the viscera generally the basement membrane is not quite so thick, but the capillary endothelium is discontinuous. In the liver both basement membrane and the endothelium are discontinuous. I think the similarity of capillaries in the brain and these nerves is worth noting. I feel that probably the response of smooth muscle of larger vessels is the main thing that is causing the effects observed in cochlear blood flow and similarly in brain blood flow. Since the capillary bed is so similar in the brain

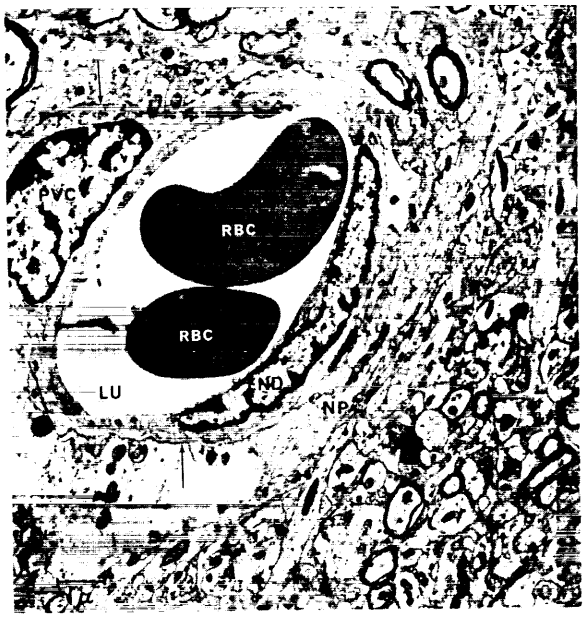

FIGURE D1.—*Electron micrograph of capillary from the sensory cortex of a rabbit. The endothelium covering the basement membrane is continuous.* PVC, *perivascular cell nucleus;* RBE, *erythrocyte;* LU, *lumen;* END, *endothelial cell nucleus;* NP, *neuropile; arrows indicate basement membrane. 6300×.*

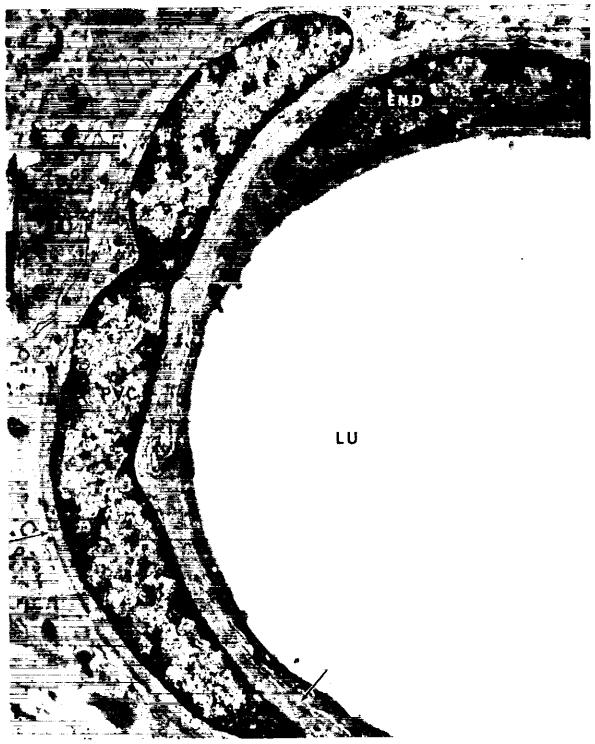

FIGURE D2.—*Electron micrograph of capillary from vestibular nerve beneath the macula utriculi. Labels are the same as in figure D1. Note the structural features are the same as in D1. 8560×.*

and cochlea, it is likely that the smooth muscle mechanism behaves similarly to regulate blood flow in these two sites.

PERLMAN: The problem of vasomotion and vascular resistance in cerebral and labyrinthine blood vessels is complicated. Direct observations of the strial vessels and blood flow during sympathetic nerve stimulation or during administration of adrenergic drugs do not indicate vasoconstriction or reduced blood flow. Similar observations on cerebral vascular bed show minimal changes and only of larger vessels. Altogether the evidence from direct observation for significant vasomotion of cerebral or labyrinthine vessels is very limited; i.e., spasm of a large vessel near a bleeding aneurysm noted in the angiogram. Nevertheless, on the larger blood vessels of the cochlea and the internal auditory artery, both silver stains and fluorescent stains reveal nerve endings which look like adrenergic nerve endings. They must have some function. The question is: How are you going to demonstrate it?

HENRIKSSON: From a clinical point of view, do you think that we can expect any possible effect from drugs upon the circulation of the inner ear?

PERLMAN: The circulation of the inner ear is similar to that of the brain. Our experiments indicate that we can increase cochlear blood flow by increasing the CO_2 tension in the blood; by drugs that relax vascular smooth muscle, i.e., papaverine; and by drugs that elevate the carotid blood pressure, i.e., epinephrine.

Whether this information can be applied to specific clinical problems remains to be determined.

SESSION V: TESTS OF OTOLITH FUNCTION

Chairman: **W. J. McNALLY**
Montreal, Canada

N68-29147

On the Otoliths: Their Function and the Way to Test Them

L. B. W. JONGKEES
University of Amsterdam
The Netherlands

SUMMARY

A description is given of the topography and microscopic anatomy of the otolith organs. The importance of the topographic arrangement of the kinocilia for their function is discussed. Some hypotheses about this function seem more or less certain: stimulation of the otoliths is produced by linear accelerations or higher derivatives. The transmission of mechanical into nervous energy is caused by shearing forces acting on the cilia of the sensory cells. The effects of stimulation are sensation of position and reflexes involving the trunk, neck, extremities, and eyes. It is of no importance whether the accelerations act as gravity, "progressive movements," or centrifugal force. The resultant of all forces acting at the same moment is the decisive stimulus. Both utriculus and sacculus have a vestibular function, but they also respond to low-frequency vibrations.

Some data indicate the existence of cooperation between semicircular canals and otoliths; for example, otolith stimulation influences nystagmus provoked by canal stimulation. On the other hand, it has been proven that linear accelerations can provoke nystagmus, but only under certain conditions.

Both sensations and reflexes can be used as indicators in tests of otolith function in man for clinical purposes or as means of examining the degree of vestibular normality.

The tilt chair, the centrifuge, and the parallel swing seem to be the most appropriate instruments for these kinds of tests. Untrained subjects seem to find it rather difficult to judge sensations of position (compared to the vertical) and of change in position. Trained subjects can give some, but limited, information; even subjects without labyrinthine function get a certain amount of information about their position.

Eye reflexes, especially compensatory rolling of the eyes on the tilt chair (afterimage measurements), and horizontal or vertical displacements of the eyes (electronystagmography) on the parallel swing can be used for the investigation of patients and untrained persons. It seems probable that the absence or presence of otolith function on one or both sides can be found with these tests.

Up to the present time there has been insufficient experience with these tests to prove their practical value as routine procedures.

ANATOMY

The otolith organs are found in the vestibule of the bony labyrinth between the three semicircular canals and the cochlea. The utriculus is part of the pars superior, and the sacculus belongs to the pars inferior of the membranous labyrinth (fig. 1). The three semicircular canals arise from the utricle and return to it. The pars superior is separated from the pars inferior by the membrana limitans (refs. 1–8).

The maculae of the otolith organs of man are more or less oval in shape. According to Corvera et al. (ref. 4), the utriculus is about 4.2 mm² and the sacculus 2.2 mm². Their major and minor axes are, respectively, 2.8/2.1 and 2.2/1.1 mm. The anterior portion of the utricular macula consists of a narrow zone, demarcated from the large, flat, main portion by a sharp inclination upward. No separate medial portion was found by Corvera et al. (ref. 4). The saccular macula has no sharp lateral inclination of the anterodorsal part, but a marked dorsal expansion. The maculae of the utriculus and sacculus are formed by a broadening of the epithelial layer. They contain the perceptive elements and the supporting cells. The sensory cells are of two types (ref. 9), but each cell of both types carries a varying (60 to 70) number of cilia. In this group one kinocilium is placed at

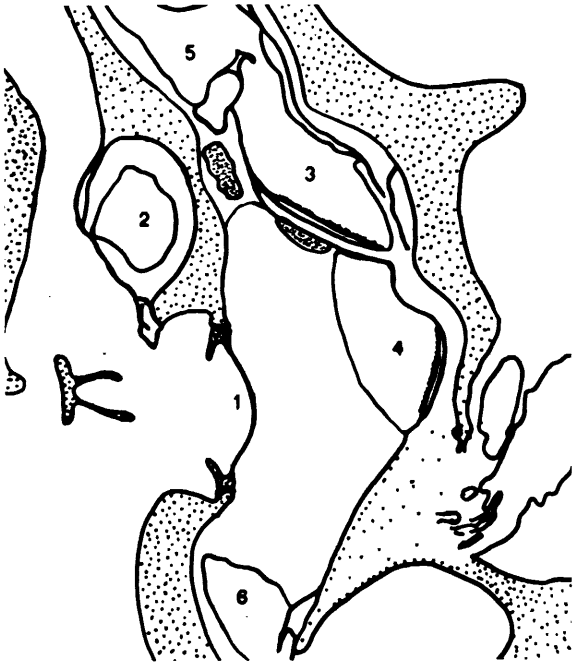

FIGURE 1.—*Microscopic section of the inner ear of a rabbit (half schematic).* (1) *Stapes;* (2) *facial nerve;* (3) *utriculus with macula on top of the membrana limitans, below it the utricular nerve;* (4) *sacculus with macula;* (5) *ampulla of the superior semicircular canal; and* (6) *cochlea.*

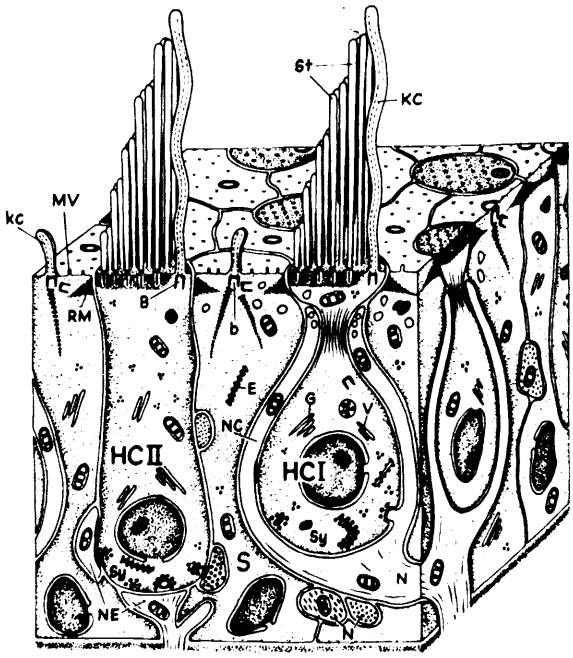

FIGURE 2.—*Schematic drawing of an area from a vestibular sensory epithelium with the two types of haircells* (HC I *and* HC II). KC, *kinocilia;* St, *stereocilia. (Courtesy of H. Spoendlin.)*

the border of the hair bundle of stereocilia (fig. 2). According to Lowenstein et al. (ref. 10), the topographic arrangement of these kinocilia between the stereocilia appears to be of functional significance. Lowenstein et al. postulated that this position within each hair bundle is related to the direction of excitatory and inhibitory displacement in the course of mechanical stimulation of the sensory cell.

The hairs protrude into a gelatinous mass containing a great quantity of mucopolysaccharides, and the otoliths are embedded in this mass. The otoliths in mammals are not stones but are small conglomerations of neutral polysaccharides, proteins, and calcite (calcium carbonate) crystals, the so-called otoconia. Their density is 2.7 as compared to 1.02 to 1.06 of the endolymph. The ligaments in which the otoliths are suspended originate in the cells at the margin of the sensory epithelium (ref. 5). The whole structure seems more suitable for tangential stimulations than for perpendicular ones. Damping seems to be effected by the surrounding endolymph which is quite viscous because of the mucopolysaccharides it contains.

From an anatomical point of view, the sacculus appears to be the locus of predilection for acoustic damage. This damage, especially of the otolithic membranes, is actually found in practice (refs. 11 and 12). On the other hand, Perlman (ref. 13) described a reinforced portion of the saccular wall in man. This area is situated so that variations in pressure caused by normal movement of the stapes are largely prevented from reaching the saccule.

The sensory nerve fibers from the labyrinth come together in the eighth cranial nerve whose component parts are the cochlear and the vestibular nerve. These two nerves are connected again by a small nerve bundle, the ramus Oort. A small ramus Hardy leads from the cochlear nerve to the saccule. The ramus Voit (fig. 3) connects the two branches (anterior and posterior) of the vestibular nerve. The ganglion Scarpae is found in the vestibular nerve. In the anterior part of the vestibular nerve the fibers originate in the horizontal and posterior ampullae

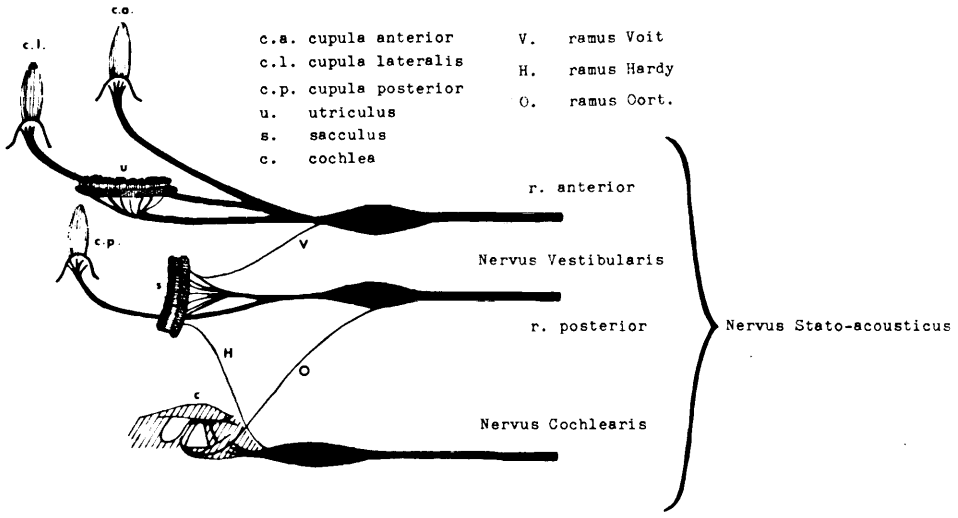

FIGURE 3.—*The nervus statoacousticus and its branches.*

and in the utricle. The posterior part joins the fibers from the sacculus and posterior ampulla. It does not seem justifiable to draw conclusions about the function of the various parts of this complicated organ from its neuroanatomy, since they all originate from the same placode.

Van Egmond (ref. 5) stressed that the macula sacculi rests on a bony layer, but the macula utriculi on a membrane between utriculus and cisterna perilymphatica.

The exact position of the various planes of the otoliths has been a point of discussion between the school of Quix and that of Magnus and De Kleyn, since both tried to prove their point of view about pressure or traction of the otoliths as the physiological stimulus of the maculae. The results were not quite identical, but nevertheless they served to prove the points of the defendants of the theories. Based on the very careful calculations of Miller (ref. 7), we know that shearing forces acting on the four maculae of the otolith organ can explain very precisely the ocular movements (counterrotation) in man rotated about a dorsoventral axis (fig. 4). For the purpose of this paper it seems sufficient to use the suggestion of Quix (ref. 14) and to depict the position of the otoliths by the position of the hands (fig. 5). The planes usually used to describe the maculae otolithicae are not really planes. These organs are somewhat bowl shaped, and their "planes" are nearly perpendicular to each other. In the normal position of the head, the macula saccularis is more or less vertical and the utricular macula is about horizontal. The utriculi seem to be synergists, the sacculi antagonists (ref. 5).

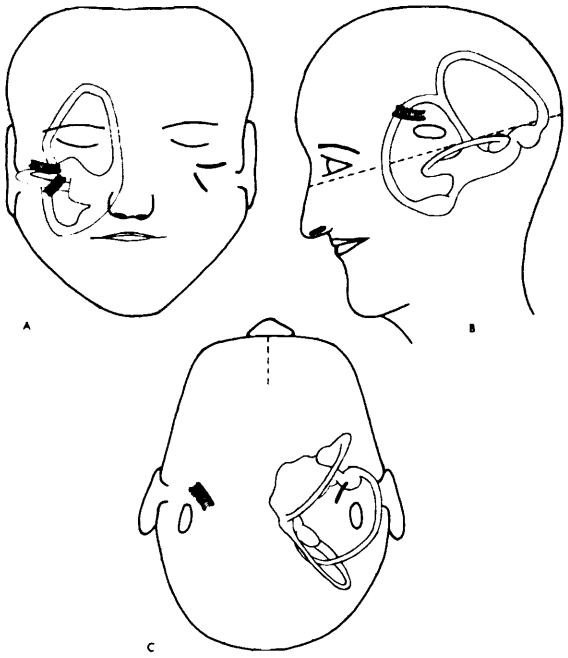

FIGURE 4.—*Schematic drawing of the position of the otolith maculae in the skull. The semicircular canal system in thin lines, the planes of the maculae in thick ones.* (A) *Frontal;* (B) *lateral; and* (C) *from above. (Free after Quix.)*

FIGURE 5.—*Position of the hands indicating the position of the maculae when the horizontal semicircular canal lies in the horizontal plane.* (A) *Maculae utriculorum; and* (B) *maculae sacculorum.* (*Free after Quix.*)

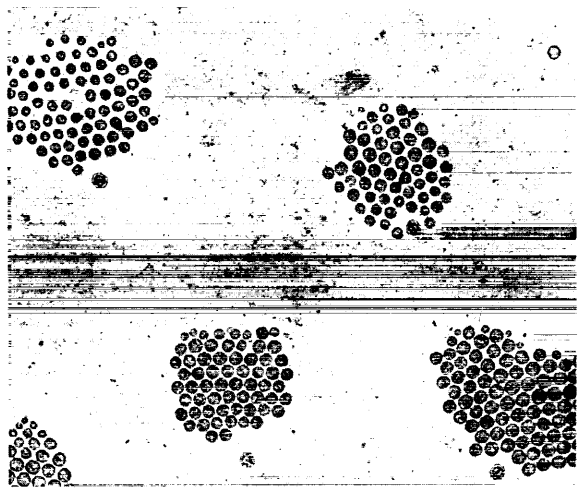

FIGURE 6.—*Horizontal section through several hair bundles just above the cell surface. Each bundle belongs to one cell and contains one kinocilium among 60 to 70 stereocilia.* (*Courtesy of H. Spoendlin.*)

Spoendlin (ref. 15) examined the distribution and spatial arrangement of the stereocilia and kinocilia of the sensory hairs (fig. 6) by phase-contrast and electron microscopy. The polarization of the kinocilia in the maculae appears to be such that the utricular—

polarization spreads fanlike from the medial and anterior part up to a curved boundary line beyond which the polarization of the sensory hairs is reversed. The kinocilia on either side of this dividing line are facing each other. A very similar pattern of polarization is observed in the maculae sacculi. Here too we find a curved dividing line going through the entire sensory epithelium on either side of which the polarization of the sensory hairs is opposite. In the saccule, however, they are facing away from each other (figs. 7(*a*) and 7(*b*)). A positive stimulation with increased neuron activity would always arise when the sensory hairs are deviated towards the kinociliar pole of the sensory cells.

These anatomical data agree with various experimental findings (refs. 16–18).

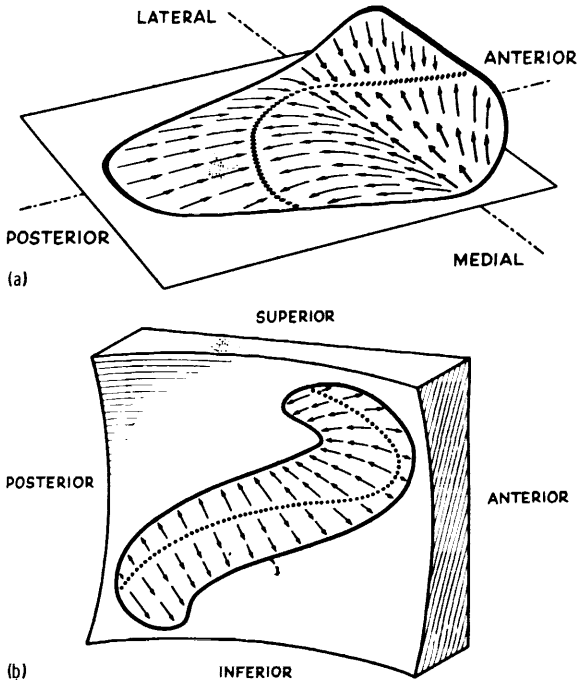

FIGURE 7.—*Schematic representation of the direction of the sensory hairs.* (a) *In the macula utriculi; and* (b) *in the maculi sacculi.* (*Courtesy of H. Spoendlin.*)

PHYSIOLOGY

The Stimulus

It has been known since the work of Flourens in 1842 (ref. 19) that the labyrinth has a function in the realm of equilibrium and since the work of

Breuer in 1874 (ref. 20) and of Mach (ref. 21) that the semicircular canals react to rotatory accelerations. The function of the otoliths (or statoliths if we want to express their function in a name), however, has been discussed for a long time and only now, it seems, the discussion has come to an end. Though Breuer and Mach had already proposed the hypothesis that rotatory accelerations were the stimuli for the semicircular canals and rectilinear ones the physiological stimuli for the otoliths, Magnus, De Kleyn (refs. 22–24), and their school defended another hypothesis. They divided the stimuli for the labyrinth into static and dynamic stimuli; that is, the effect of gravity and the effect of movements, respectively. Under their hypothesis the effects of gravity, linear accelerations (progressive movements), and centrifugal accelerations were placed in different categories and those of "progressive movements" and rotatory stimuli in the same category. This implied that one and the same organ detects one group of stimuli and that a different perceptive organ had to be present for each group of stimuli.

I think that today no one doubts the superiority of the hypothesis of Breuer and Mach, since there is no real qualitative difference among the actions of linear accelerations either in gravity, in linear accelerated movements, or centrifugal accelerations. All three provoke a reaction of inertia which alters the position of the otolith mass in relation to the maculae of the otolith organs and causes sensations and reflexes. It is impossible for any instrument, even the finest, to differentiate between the influence of gravity, linear acceleration of movements, or centrifugal influence. Only differences in direction, magnitude, and duration can be recorded.

It might still be possible to imagine that one and the same organ is capable of perceiving both linear and angular accelerations, but a great many experiments in animals and some in man indicate the difference between the activity of the semicircular canals, on the one hand, and of the otoliths, on the other. Jongkees and Groen (ref. 25) found that the time of indication [1] of the canal system is approximately 40 seconds (ref. 26). The time of indication in response to linear accelerations was found to be of the order of 0.1 second (refs. 27–29). The time of indication for both kinds of stimuli differs by a factor of 300 or more. Even physiologically this distance cannot be bridged. Consequently, at least two different kinds of organs are required to produce the reactions and sensations known thus far to originate from the vestibular labyrinth.

[1] The time required to obtain a maximal deviation, action or sensation, when the system is exposed to a constant stimulus, or the time required by the system to return from a stimulated condition to the equilibrium position, when the stimulus suddenly stops its action.

Linear Accelerations and the Effects They Provoke

On the basis of theoretical considerations, the conclusion is unavoidable that all linear accelerations must have the same effect on a perceiving organ and, therefore, are bound to give the same reactions and sensations to the subject whom they affect.

To examine this question it is necessary first of all to know the sensations and reflexes caused by linear accelerations. The difficulty of this investigation lies in the continuous activity of the gravitational acceleration; therefore, other accelerations should always be investigated in connection and cooperation with gravitational acceleration. Jongkees and Groen (ref. 25) demonstrated that the sensations provoked by linear accelerations in a centrifuge at constant angular velocity and during swinging on a parallel swing not only give the same sensations qualitatively, that is, the sensation of inclining toward the direction of the resultant force (refs. 21 and 30–33), but also quantitatively. By comparing the apparent position of the body under the influence of centrifugal force or accelerations on a parallel swing (fig. 8) with the angle given to a position chair (ref. 34) to obtain the same sensation, it has been shown that the experienced angle was exactly the same quantitatively as the angle between the resultant and gravity.

As stated, the otolith organs are stimulated by linear accelerations, and this stimulation causes both a perception of the position of the body in relation to the vertical and reflexes which counteract the effect of the stimulating acceleration (refs. 35–37).

A decrease of the (gravitational) acceleration in the vertical direction elicits an extension of the extremities, a raising of the chin, and a downward movement of the eyes; an increase provokes a

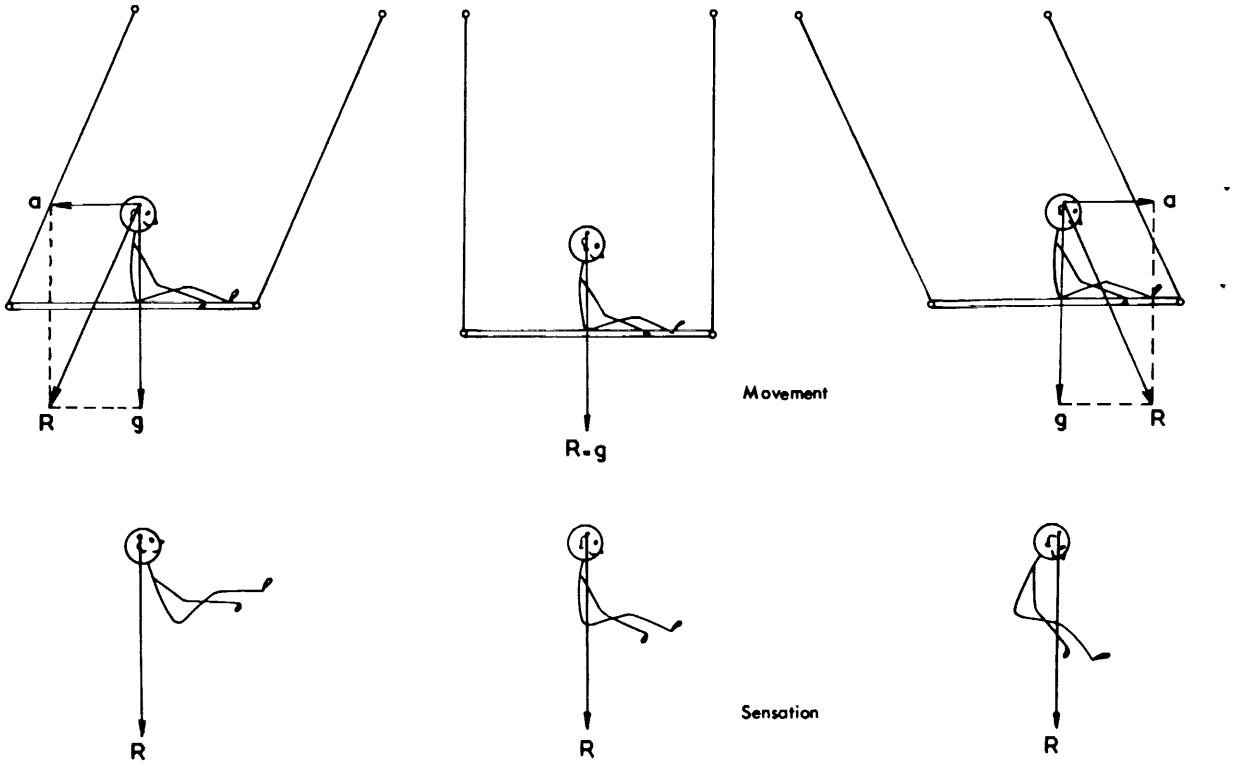

FIGURE 8.—*Scheme of the parallel swing, its movement, and a parallelogram of forces acting during the movement.* a, *Acceleration of the swing;* g, *gravitational acceleration; and* R, *resultant, sensation of position felt by the test subject.*

flexion of the extremities and of the neck and an upward look of the eyes (fig. 9). In linear acceleration acting from side to side an abduction of the extremities and of the eyes is found in a compensatory direction (fig. 10). They all seem to be defense movements of equilibrium against movements acting from the outside. Slow-motion films of jumping horses led Quix to these conclusions long before electrophysiological experiments were made to support his view. Zum Gottesberge and Plester (ref. 38) submitted the sacculi of patients to changes in pressure during stapedectomy operations. This caused sensations of change in position or a sensation of falling sideways.

Counterrotations of the Eyes

An objective effect of stimulation of the otoliths, which has been studied for more than a century, is counterrotation of the eyes (refs. 28 and 39–41). Benjamins and Huizinga (ref. 42)

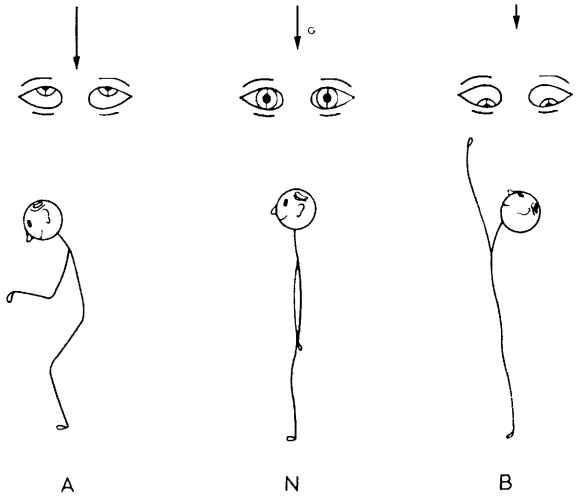

FIGURE 9.—*Reflexes on body, extremities, and eyes provoked by an increase* (A), *and decrease* (B), *of the gravitational acceleration as compared with the normal condition* (N). *The arrow indicates direction and size of the acceleration* (g, *gravity*).

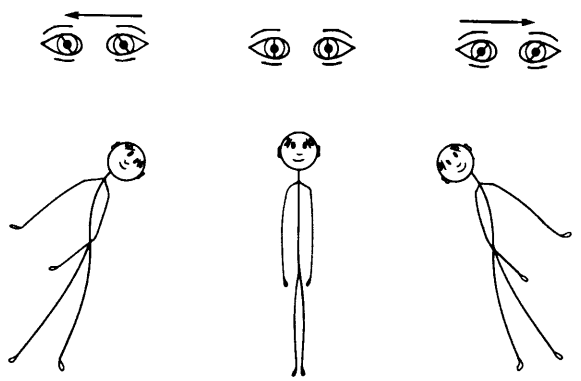

FIGURE 10.—*Reflexes of body, extremities, and eyes under the influence of an acceleration from one side, indicated by an arrow at the top of the figure.*

found that pigeons lost this phenomenon after destruction of the saccule, and clinical investigation of De Kleyn and Versteegh (ref. 43) and of Woellner and Graybiel (ref. 44) indicated that, in patients with lesions of the superior part of the labyrinth, counterrotation of the eyes remained intact, whereas it disappeared in lesions of the inferior part (refs. 7 and 45–51).

Plugging or destruction of the semicircular canals does not alter the reaction to changes in position or to linear accelerated movements (ref. 52), but after destruction of both labyrinths they disappear. Philipszoon (refs. 53 and 54) found compensatory eye movements in rabbits after unilateral labyrinthectomy and either heterolateral sacculus extirpation or destruction of the utricular nerve. When both the sacculus and the utricular nerve were destroyed, the response to rotatory stimuli was still normal, but compensatory eye movements could no longer be provoked. Nevertheless, one has to be very careful in drawing quantitative conclusions (fig. 11).

In patients with complete ophthalmoplegia some counterrotation of the eyes can still be found, according to Kompanejetz (ref. 55). This indicates that a purely mechanical factor can have some effect. Fleisch (ref. 56), who very carefully measured counterrotation in rabbits, came to the conclusion that there is a certain tendency of the muscles to maintain an existing position. Not only the last position but also the preceding one influences to some extent the countermovement of the eye. These facts must

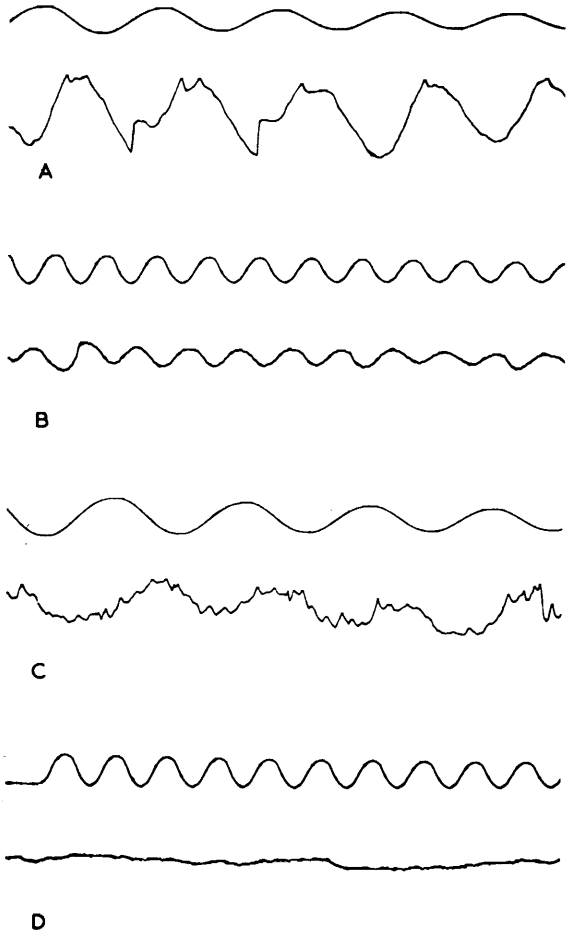

FIGURE 11.—*Compensatory eye movements on the parallel swing before and after selective otolith destruction.* (A) *Rotatory test before operation;* (B) *parallel swing before operation;* (C) *after operation; and* (D) *after operation.*

be kept in mind when measurements of the compensatory rotation of the eyes are used as a basis for determining the origin of the stimulation of the maculae of the otolith.

Pressure and Shearing Force

Benjamins and Nienhuis (ref. 57), Brandt and Fluur (ref. 30), Miller (ref. 7), Quix (ref. 8), and Sullivan et al. (ref. 50) made such measurements in man, but their conclusions differ. The same results were used both to prove that either positive or negative local pressure of the otoliths on the maculae had to be the physiological stimulus of the otolith macula, and to explain that it had to be a shearing force acting parallel to the surface of the macula.

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It seems unnecessary to go into a discussion of this problem, since Von Békésy (ref. 27) has so clearly explained that the question is not well put, that pressure perpendicular to the surface and shearing force along the macula both can always be seen as two components in a parallelogram of forces, and that the parallel component has the best chance of being the active one as a pressure gradient is needed to produce sensation. Where there is a pressure gradient, shearing forces will always be present. The experiments of Von Holst (ref. 58) gave excellent support to the ancient theory of Breuer (ref. 59) that shearing forces are essential for the transmission of the mechanical stimulus toward the nerve receptors. Support for the shearing-force theory came from studies with increased gravity action in a centrifuge and the position which freely moving fishes took under the combined influence of light and resultant forces of gravity and centrifugal force. Other investigators came to the same conclusion while studying other animals and humans (refs. 37 and 60–64).

In patients with only one functioning labyrinth, the threshold for the perception of the sinusoidal movements of the parallel swing is lower when the normal labyrinth is underneath (ref. 18). Experiments on a parallel swing showed that, when rabbits are submitted to linear accelerations in the reverse position, the threshold for eye movement is lower than in the normal position. When the same stimulus is given, the effect is stronger in the reverse position. This proves that the stimulus is more effective when the otoliths are free from their maculae and indicates shearing forces (refs. 16, 65, and 66) (fig. 12).

Though Ruysch (ref. 67) did not succeed when he tried to find displacements of the otoliths due to gravity by making X-rays in various positions, De Vries (ref. 68), and G. Vilstrup and T. Vilstrup (ref. 69) could demonstrate these displacements with the same technique. They only found them parallel to the macula (15 μ for 1 g in the spiny dogfish) and not perpendicular to it. The movements of the otoliths seem to be (almost) critically damped. Though all these data seem very conclusive, there still remain some difficulties. Jongkees (ref. 35), who introduced a small steel ball into the inferior part of the inner ear, provoked reflexes away from the pressure of this steel ball on the sacculus when it was pulled against it by an ophthalmologist's magnet or pushed against it by centrifugal force. Ogino et al. (ref. 70), examining action currents in the utricular nerve, got the strongest effect when linear accelerations were acting in a direction perpendicular to the surface of the maculae, and Yamagata (ref. 71) saw that his rabbits no longer reacted to lateral linear accelerations after destruction of their sacculi. Another problem lies in the fact that when man is upright, he is extremely well informed as to the position of the whole body in respect to the Earth, but when he is in the inverted position the orientation is poor or nil (refs. 14, 33, and 72). In this case the pressure theory of Quix provides an easy explanation. After unilateral labyrinthectomy,

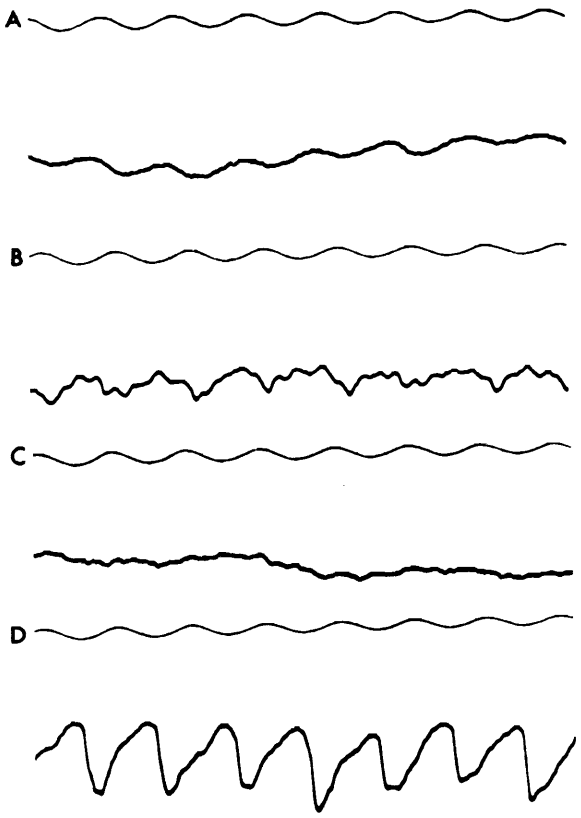

FIGURE 12.—*Parallel-swing test in a rabbit after left-sided labyrinthectomy.* (A) *Prone position;* (B) *on the right side;* (C) *on the left side; and* (D) *supine. Upper curves: movements of the swing. Lower curves: movements of the eyes. When the intact labyrinth is underneath, the reaction is stronger. In the supine position the reaction is stronger than in the prone position.*

counterrotation of the eyes is found only when the intact labyrinth is uppermost (refs. 49, 57, and 73). Finally there is one expression of otolith function which still lacks a rational explanation. Why falling or jumping animals should land on their four legs, even when they start the fall from various positions, is not explained by any of the theories regarding the action of the otoliths upon the maculae. During free-fall, theoretically, the otolith exercises the same pressure at all positions of the head; that is, no pressure. Nevertheless, even a blinded cat will turn in midair as long as its labyrinths are intact. Pressure gradients, memorized stimulation patterns, air resistance, and the polarization of the sensory hairs of the maculae are suggested to explain these phenomena.

Linear Accelerations and Nystagmus

The general opinion has long been that stimulation of the otoliths could not provoke nystagmus. Versteegh (ref. 74) did not find it in his experiments after destruction of the sacculus or severing of the utricular nerve, and Jongkees (ref. 35) corroborated these findings. Ulrich (ref. 51) and Szentágothai (ref. 75) were able to elicit eye movements by direct stimulation of the otoliths, but not nystagmus. Fernández et al. (ref. 76), however, found spontaneous nystagmus after section of the utricular nerve in cats, but could not provoke it by stimulation of the nerve. Some other investigators (refs. 49 and 77–79) came to the conclusion that directional preponderance and positional nystagmus were based on pathology of the otoliths. Nevertheless, most workers in this area have agreed with McNally (ref. 48) that there was no evidence for this supposition.

Apart from counterrolling of the eyes, other eye movements have been found; for example, Sjöberg (ref. 80) in a lift, Fleisch (ref. 56) by linear accelerated movements, Jongkees and Groen (ref. 25) on the parallel swing, Jongkees (ref. 81) during vertical sinusoidal movements, and Miller (ref. 7) and De Wit (ref. 82) during tilt, but Jongkees and Philipszoon were able to provoke nystagmus regularly when stimulating rabbits and men by purely linear accelerations. Linear acceleration applied to rabbits on a small cart produced nystagmus, and nystagmus could be provoked in both rabbits and men on a parallel swing if they were not in the normal position (fig. 13). To show nystagmus, rabbits have to be in a lateral position and men have to look sideways (fig. 14). In both instances it seems that a preceding deviation of the eye is necessary to reach the threshold of the rapid phase of nystagmus. McCabe (ref. 84) could demonstrate nystagmic eye movements in rhythmic linear vertical accelerations in cats, chinchillas, and man. This nystagmus was found to be altered by acoustic trauma and to be lost after labyrinthectomy, but it remained intact in cats administered streptomycin to the point of loss of canal function.

Sacculus Function

One other point of theoretical importance must be discussed before practical tests for the examination of the otoliths can be discussed; that is, the function of the sacculus.

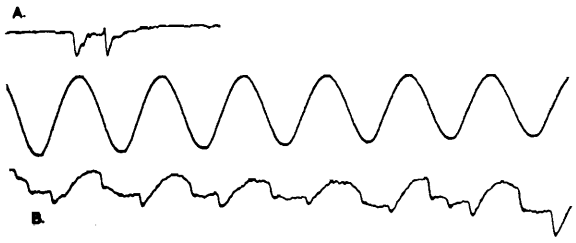

FIGURE 13.—*Linear accelerations and nystagmus.* (A) *Two nystagmus beats in a rabbit in lateral position moved on a cart with great linear acceleration; and* (B) *many nystagmus beats in a rabbit in lateral position on the parallel swing.*

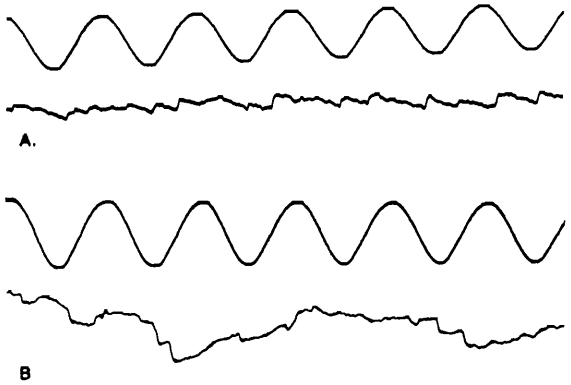

FIGURE 14.—*Nystagmus in a human subject lying on the parallel swing in normal position being moved from side to side.* (A) *Fixing the eyes to the right; and* (B) *to the left.*

Before microscopic operations on the labyrinths of test animals became possible, various investigators tried to damage the otolith organs by centrifuging animals at high speeds for short periods of time. The forces had to be very great (about 100 times gravitational force), otherwise no damage was found. Spoendlin (ref. 85) found no morphological changes in the maculae of monkeys after exposures of up to nearly 11 g.

The results of these experiments, though suggestive, were not conclusive because changes in other parts of the vestibular organs proved to be inevitable, and regeneration was fairly rapid (refs. 47 and 86). Compensatory eye movements and lift reactions generally disappeared more or less completely (ref. 87). After Versteegh (ref. 74) experimentally found no changes in the vestibular reflexes in rabbits following destruction of one or both maculae sacculi, it was generally accepted that the saccule plays no part in the maintenance of equilibrium; many investigators thought the sacculus to be a sound perceiving organ (refs. 11–12 and 88–90).

Anatomic data and sound damage as well as sound perception in fishes and related species led to these conclusions. The utricle was raised to the rank of the only static perceptor. However, other points have been brought out to indicate that the saccule plays a part in the regulation of equilibrium. Benjamins and Huizinga (ref. 42) had proved that counterrolling of the eyes of pigeons disappeared after destruction of the saccule, but not after destruction of the utricle. Also, anatomical data did not really support the acoustic theory. In Versteegh's own experiments, so-called progressive reactions and counterrotation of the eyes were still partly intact (ref. 47) after destruction of the utricular nerve.

In 1933 Lorente De Nó (ref. 91) stated:

> An acoustic function [of the saccule] cannot be accepted because, although it has connections with the centers and pathways involved in the regulation of equilibrium, it has no connections with the pathways and centers involved in hearing.

Von Békésy (ref. 27) was able to produce head movements in subjects who were listening to very loud beats. The movements were synchronous with the beats and were explained as produced by a fluid eddy pressing on the saccule.

Hasegawa (ref. 87) noted disappearance of reactions to dorsoventral accelerations after destruction of the sacculi in frogs and guinea pigs (refs. 37, 49, and 92). The experiments of Jongkees (ref. 35), McCabe (ref. 84), Philipszoon (ref. 53), Schöne (ref. 63), and Smith and Johnson (ref. 93) provided new arguments that the saccule was an organ of equilibrium. The real proof of an equilibrium function came from the investigations of electrical effects in the nerves of the various parts of the labyrinth and in the brainstem (refs. 17, 61, and 94–98). Sense organs in the maculae were seen to show a resting discharge the frequency of which was altered by positional changes. Both utriculus and sacculus responded to lateral tilt and to fore-and-aft tilt.

In addition to reactions which the maculae have to "static" stimuli, they also respond to vibrational stimulations. It appears from the experiments of Lowenstein and Roberts (ref. 17) that particularly the lateral part of the saccular macula reacts to low-frequency vibrations (together with the posterior part of the utricular macula). Trincker and Partsch (ref. 99) found in the guinea pig that the nerve cells of all the labyrinthine organs can be stimulated both by static displacement and by the whole frequency spectrum of mechanical oscillations. Owada and Shizu (ref. 49) stimulated the saccular macula and its nerve electrically; they found an upward movement of one eye and a downward movement of the other. All in all, it can no longer be doubted that the saccule has a vestibular function. However, the functional ranges of utricles and saccules overlap (ref. 98), as has been proven by measurements of the spontaneous potentials derived from their nerve endings in the thornback ray.

The Interaction of Otoliths and Semicircular Canals

The labyrinth is a small organ derived from one placode, and it is probable that its various parts will not act completely independently of each other, as already described for the four otolith organs.

Benson and Bodin (ref. 100) found that strength and duration of the resultant linear acceleration on a human centrifuge had an effect on the duration of postrotational nystagmus. They recorded nystagmus during rotation at constant speed

about a horizontal cephalocaudal axis. Guedry (ref. 101) recorded that the after-nystagmus postrotation about a cephalocaudal axis was shorter when this axis was horizontal than when it was vertical. Smith and Johnson (ref. 93) suspected an effect of the otoliths on nystagmus and were supported by the works of McNally (ref. 102) and Tait and McNally (ref. 103), who found the reaction of the vertical canals to be very strong after utriculus destruction and assume a "crossed partnership" (see also (ref. 104)).

Milojevic and Voots (ref. 105) reported that, though the horizontal canal did not show any difference with respect to caloric effects in the 135° and 45° positions, nevertheless, the duration of the caloric test is shorter at the latter position; 135° is the position for otolith activity. Bergstedt (ref. 106) was able to show a clear influence of linear acceleration on preexisting positional nystagmus.

In 1960 Owada and Shizu (ref. 49) found that pressure on the utricular macula provokes directional preponderance to the homolateral side. After section of the utricular nerve, directional preponderance to the heterolateral side is found. After section of the horizontal-canal nerve, spontaneous nystagmus changed in magnitude following change in position of the head. After section of the utricular nerve, this influence disappeared. Direct pressure on the utricular substance also influenced the spontaneous nystagmus.

In other papers, Owada et al. (refs. 49 and 107) showed that pressure on the macula sacculi suppresses spontaneous nystagmus to the homolateral side. (See also ref. 108.) Bos et al. (refs. 16 and 65), however, warned against rules attributing certain eye movements to lesions of the vestibular organs. On the other hand, Ledoux (ref. 96) stated explicitly that the action potentials from the canal nerves are not influenced by the action of linear accelerations, and Graybiel et al. (ref. 109) found no effect of linear accelerations on the oculogyral illusion.

In conducting experiments with subjects in the upside-down or lateral positions, not only the effect of position on the otoliths but also its effect on blood distribution in the body and on various sense endings in the internal organs must be taken into consideration before conclusions from these experiments can be accepted (ref. 110).

Adaptation

Adaptation in the semicircular canal system is well known and important, but, until now, proof of the existence of adaptation in the otolith organs has not been found (ref. 58). The effect of constant gravity remains the same, but changes either in force (centrifuge) or in direction cause an alteration in the number of action potentials which remains constant until the next change (refs. 97, 98, and 111). Every position of the animal is linked to a certain frequency (ref. 61). Nevertheless, the otoliths do provide some information. Afferent potentials have been found by Bertrand and Veenhof (ref. 112) in their experiments with rabbits in the parallel swing, and most people adapt themselves to the movements of a ship. As seasickness seems to be mainly of otolithic origin, this suggests some adaptation (adaptation pattern of Groen (ref. 113)).

The Response of the Autonomic Nervous System

Responses of the autonomic nervous system to labyrinthine stimulation have been mentioned very often, but have seldom been the target of examination. Wojatschek (ref. 114) changed the position of the head of his patients (chin upward), after abruptly stopping rotation, provoked Coriolis forces in this way, and tried to classify the reactions in four groups. Hulk and Henkes (ref. 115) found that stimulation of the semicircular canal by rotation does not alter the retinal blood pressure as measured with Baillart's ophthalmodynanometer, but stimulation of the otoliths on the parallel swing does. This finding corroborates the hypothesis that motion sickness arises in the otoliths (refs. 14, 80, and 90), though canal stimulation and Coriolis actions cannot be denied a part in its causation. The fact that a nystagmus is never seen in seasickness and that linear accelerations are manifested by the movements of a ship on a turbulent sea support the otolithic theory.

Otoliths and Reflexes of the Muscles of Body, Neck, and Limbs

Reflexes appear not only in the eye muscles but also in the muscles of trunk and extremities (refs. 14, 35, 42, 50, 74, and 90). After destruc-

tion of the utricle, general loss of tone of skeletal muscles of the neck, trunk, and limbs on the operated side is found.

Quix (ref. 14) described an influence of the otoliths on past pointing. Sasaki et al. (ref. 37) declared that the mechanism of linear kinetic reflexes of the healthy adult consists of the increase of tonus of the flexor and the decrease of tonus of the extensor muscles under the influence of an "ascending acceleration action"; a forward acceleration increases the tonus of flexor muscles of the extremities and decreases the extensor tonus. In case of a backward acceleration, the effect is reversed. Acceleration to one side increases the tonus of the homolateral extensors and of the contralateral flexors. (See figs. 9 and 10.)

Since the days of De Kleyn, Magnus, and Versteegh (refs. 22–24, 43, 47, and 86), the drop test and the so-called "Sprungbereitschaft" and righting reflexes have been used to provoke muscular reflexes from neck, body, and limbs in cats and rabbits. They are not affected by deficient canal function (ref. 52).

Van Eyck (ref. 116) used electromyography in pigeons to demonstrate that the postural tone of the craniodorsal muscles and of the extensors of the legs depends upon intact utriculi. Von Holst (ref. 58) and his school influenced the position of fishes in a centrifuge and concluded that in this way the fish kept the shearing vector constant in relation to the utricle. This shearing vector S depends upon the angle α between the direction of the stimulus and the surface of the macula ($s = f \sin \alpha$). Jongkees (ref. 35) provoked postural changes in rabbits in which a steel ball was caused to exert pressure on the saccule, and Von Békésy (ref. 27) produced movements of the head in normal test subjects when they were subjected to very strong sound (beats). These movements were synchronous with the beats (3–5 seconds).

Conclusions

In judging tests of otolith function, it is essential to keep the following points in mind:

(1) The otoliths are stimulated by linear accelerations (or their higher derivatives), and it is of no importance whether this linear acceleration is presented as that of gravity, during centrifugal activity, or as "progressive movement." The essentials are strength, duration, and direction of the resultant.

(2) The otoliths are sense organs: In response to a well-defined stimulus (linear acceleration) they react with adequate responses which consist of a sensation of position in the surrounding world and reflexes. (A sensation of displacement has only been proven to exist as the result of a linear acceleration (resultant) changing its direction. (See "Parallel Swing."))

(3) The sensation of position is provided by perception of the direction of the resultant acceleration in its representation of the vertical.

(4) The reflexes are movements of the eyes (counterrotation, up-and-down movements) and those of trunk, neck, and extremities (action of extensors and flexors).

(5) Responses of the autonomic nervous system accompany otolith stimulation.

(6) Otolith stimulation seems to influence canal function.

(7) Under certain conditions nystagmus can be brought about by linear acceleration.

TESTS FOR OTOLITH FUNCTION

In the preceding part of this paper a description was given of all kinds of ingenious ways to investigate the function of the otoliths. However, only a few can be used in man and still fewer can be used routinely. A discussion follows about those tests that may give insight into human behavior in general and into sometimes different tests appropriate for examination of individual subjects.

As has been shown, sensations and reflexes are the result of stimulation of the otoliths. However, in some cases there is no unanimous opinion about the origin of the reflex or the sensation. For this reason, spontaneous or toxic positional nystagmus, directional preponderance in the caloric test, postural vertigo, Coriolis forces, and the complicated past-pointing experiments of Quix will not be discussed because there is no proof of sufficient weight that the results are elicited completely, or even mainly, by the condition of the otolith organs (e.g., ref. 48). Another examination that will not be discussed, although linear accelerations are used to examine equilibrium reactions, is the "stability index" which is

found by subjecting men in the Romberg position in a small cart to linear accelerations and noting the threshold of their loss of equilibrium (ref. 117). It appeared that the loss of equilibrium depended upon canal reflexes caused by the incipient falling, which provokes rotatory accelerations.

In the proposed tests the influence of the direction of the resultant linear accelerations is investigated. The effect of gravity upon the otolith maculae is difficult to avoid. As long as we remain on the Earth, this effect is absent only during falling and jumping. In space-flight laboratories it is possible to examine the influence of weightlessness (ref. 72) by very intricate instruments, but up to now it has seemed easier to examine the otoliths with less-complicated instruments. This examination has been carried out for a very long time by the investigation of sensations of position. The results of these measurements have become much more accurate, but they have hardly shed any essentially new light on the problem of the tests of the labyrinth.

Sensation of Position

Linear acceleration acting on the otoliths provokes in the subject a sensation of "verticality." This sensation is not an effect of gravity alone, but it depends on the final resultant force, although the subject will feel only a change in position of the resulting acceleration and no sensation of displacement. Linear accelerations have never been proven to cause sensations of movement through mediation of the otoliths.

The Sensation of Position on a Tilt Chair

Aubert (ref. 118), Delage (ref. 119), and Grahe (ref. 120), but above all Quix and Eysvogel (ref. 121), have already done experiments on the sensation of position of human beings in various positions. In 1926 Quix constructed a "position chair" (fig. 15) movable about Cardan joints so that the head could be brought into any desired position without a change in the position of body, neck, and head in relation to each other. This is necessary to avoid neck reflexes.

In positions near the normal vertical one, the "orientation" is precise (yellow spot of the otoliths according to Quix). In lateral positions it is much poorer, and in the upside-down position

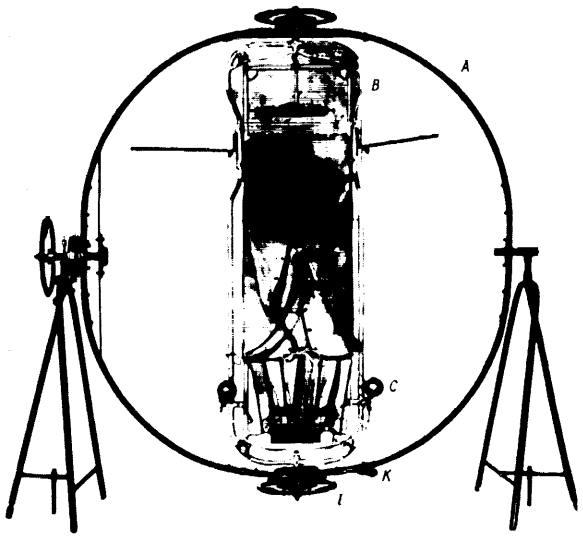

FIGURE 15.—*Position chair of Quix.*

(more than 120° in any direction from the zero upright starting point) it is nearly nil (blind spot of the otoliths). The Aubert phenomenon (ref. 118), that is, that the perceived angle of inclination is smaller than the actual inclination from zero positions, and the reverse, the Müller phenomenon (ref. 122), depend upon the size of the angle between the position of the subject and zero. A certain misconception about zero position plays a part in it too (ref. 121). The sensation of being upright is felt when the main parts of the utriculus and the horizontal semicircular canals are horizontal (subjective zero position).

The Sensation of Position in a Centrifuge: The Oculogravic Illusion

In the last two decades a number of new experiments have been done by Graybiel and his coworkers (refs. 33 and 123–125). When a subject is exposed to the influence of linear acceleration in various positions in total darkness, he notices under suitable conditions apparent changes in position of a barely supraliminal visual stimulus; they named this phenomenon the oculogravic illusion. They tested subjects on a human centrifuge and found that the resultant force has essentially the same influence as gravity. It gives rise to a sensation of displacement from the true vertical. These experiments showed that the observer orients himself to the resultant force acting on the body as if it were the true vertical.

The initial movement is rapidly indicated; for the final portion there is a lag, but there is little or no overshoot. They confirmed the views of Quix (ref. 8) and also the observations of Jongkees and Groen (ref. 25), who compared the action of the resultant force to the action of gravity alone. These experiments prove again that it is impossible to separate one kind of linear acceleration from the others. It is only the resultant force which is perceived by the otoliths and of value to the subject (ref. 30). This remains perfectly true when the resultant force is increased (ref. 63). Even after elimination of visual (darkness) and tactile (underwater) stimuli, the perception of position remains unchanged. According to Schöne (ref. 63), this indicates that, in the situation investigated, the perception of position is almost exclusively determined by the activity of the otoliths. One difficulty, however, lies in the fact that people with loss of two labyrinths are still able to indicate fairly well their position in space even with closed eyes (refs. 32, 126, and 127).

The experiments of Van Dishoeck, Spoor, and Nijhoff (ref. 128) dealt with the importance of the visual target used for evaluating sensations provoked by vestibular stimulations. They investigated the relations between the oculogyral illusion, sensation, and nystagmus and found that the illusion had no relation to the movements of the eyes but was related to the sensation of rotation. It seems acceptable that the same is true for the oculogravic as well as for the audiogravic illusion (ref. 129). Vogelsang (ref. 130) stated that these illusions can be considered as a tendency to correlate optical, vestibular, and other cues as an expression of a cerebral correlative function.[2]

Not only has the perception of the subjective in relation to the true vertical been investigated but also the position of the subjective horizon (refs. 2, 50, 63, 82, and 124). The eyes deviate upward as the head tilts forward and downward, and deviate downward in response to backward and upward tilting. In this case visual fixation has to be avoided. The subjective horizon does not change position when the resultant force is increased as long as the subject is in the normal position, while in other positions it does. This leads to a change of the surrounding world whenever the subject changes the position of his head under the influence of increased g. Groen (ref. 113) remarked:

> These results are obtained under laboratory conditions. It appears that the sensitivity of the otoliths, or their influence on the different parts of the body, is considerably reduced if the measurements are done during flight in an airplane. This may be ascribed to the disturbing effect of the airplane, to the reduced oxygen pressure, or to mental strain, or to a combination. Even a deviation of 5° from the vertical seems very difficult to observe, corresponding to a linear acceleration of about 80 cm/sec^2.

The same is true for the canal organ. In all the experiments with instruments built to provoke linear accelerations, one warning is necessary. If rotations below the threshold for stimulation of the semicircular canals are used for stimulating the otoliths, one has to be very careful. This threshold is probably below the values often used. (See Sullivan et al. (ref. 50).) Ek, Jongkees, and Klijn (ref. 131) found αt values down to 0.5°/sec still giving measurable reactions to rotatory stimuli in the pigeon.

Sensations on the Parallel Swing

For practical purposes the investigation of sensation of position is not a very dependable one. It has given support to the shearing-force theory, but it does not appear to be able to give us a stable basis for the appreciation of individual otolith function. The instruments may be kept simple (tilt chair), but are sometimes extremely costly and complicated (centrifuge). There is, however, another way to investigate the sensations caused by linear accelerations. If we subject a person to sinusoidal movement in a horizontal plane, the cooperation with gravity will cause a changing direction of the resultant force. This leads to a sensation of to-and-fro or up-and-down rotation, dependent upon the direction of the movement of the swing, and no sensation of linear displacement appears when the experiment is performed in the dark.

The instrument, a very simple one, is the parallel swing (refs. 21 and 114). Jongkees

[2] When counterrolling of the eyes is discussed, one point, that of the importance of the resultant force, its direction, and size (centrifuge), will again be found to be essential, and an important cooperation between the four otolith organs will be apparent.

and Groen (ref. 25) gave a detailed description, analyzed the movements and sensations, and used it to determine the threshold of perception. This appeared to be of the order of 2 to 6 cm/sec^2 and to be considerably higher in patients with loss of the two labyrinths (ref. 132). Walsh (refs. 18 and 66) found that the threshold for sensation is not noticeably influenced when the subject is immersed in water or in more viscous fluids. The sensations are disturbed when the patient's head is brought into the position of Quix's blind spot of the otoliths; that is, head-down position. High thresholds up to 20 cm/sec^2 were also found in deaf children with nonfunctioning labyrinths. Hereditary deafness with intact pars superior of the labyrinth also led to a higher threshold, but not so high as the nonfunctioning labyrinths did (ref. 43). In Walsh's study the threshold appeared to be normal in patients with one labyrinth destroyed as long as they lay on their backs, but the sensitivity was consistently reduced when the patient lay with his damaged side downward. Since the parallel swing is a very simple instrument (ref. 73), these examinations might be of practical use for estimating otolith function in patients.

The Examination of Reflexes Caused by the Influence of the Resultant Linear Acceleration

Reflexes on Body, Neck, and Limbs

As described in the foregoing, the otoliths influence the muscular reflexes of neck, body, limbs, and eyes. The influence of position on the "Stellreflexe" according to Magnus (ref. 22) can be detected on Von Stein's (ref. 133) goniometer (refs. 134 and 135) (fig. 16). Subjects having intact labyrinths can remain upright on an inclined plane; those with disturbed vestibular function fall easily.

Quix and Eysvogel (ref. 121) examined the reflexes on the neck in their "position chair." The patient's body was fixed but his head could be moved freely, while he was led into various positions in space. Countermovements of the head about the craniocaudal axis were found regularly when the body was rotated about the sagittal axis. They appeared to be inconstant

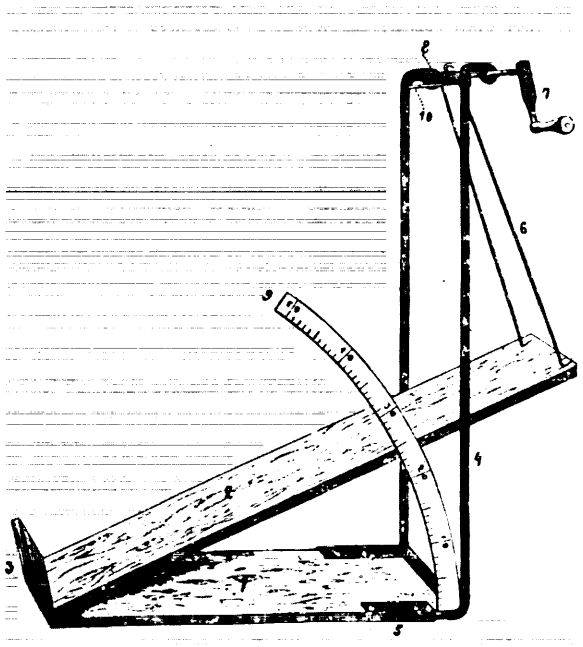

FIGURE 16.—*Von Stein's goniometer.*

and certainly not compensatory in normal subjects. The same authors investigated past pointing under the same conditions and concluded that past pointing was normal as long as the saccular otolith was over its macula, but quite disturbed when this was not the case. The effect is homolateral and coincides with Quix's so-called blind spot of the otoliths.

Reflex Actions of the Muscles of the Eyes

The examination of body, neck, and limb reflexes does not seem to be very promising. Better results are obtained by investigation of the compensatory movements of the eyes under the influence of changes in the position of the body. The best known compensatory movement is the ocular counterrolling when the subject's head is tilted laterally with respect to gravity. It seems essential to use an instrument which makes it possible to tilt the subject without bending his neck since, otherwise, reflexes coming from nuchal receptors (e.g., Bos, ref. 136) may arise. The patient must look straight forward since, otherwise, unwanted elements are introduced (ref. 137). Visual fixation does not seem to have any influence. The effect of a change in position is maintained as long as the stimulus does not

change direction.[3] A tilt of approximately 60° is sufficient to provoke a maximal counterrotation of the eyes. (See fig. 17.) It can be examined

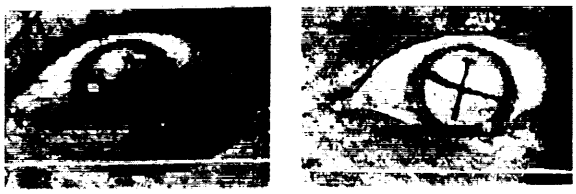

FIGURE 17.—*Counterrotation of the eyes of a patient measured by putting an egg pellicle marked with a cross on the cornea. Test subject in* (A) *normal position; and* (B) *tilted 60° to the right side.*

by using natural or applied landmarks on the eyes, observed or photographed (ref. 45), or by way of the afterimage of a vertical line of light (ref. 32). With the latter method the patient can indicate and mark the position of the afterimage on a piece of white paper in relation to the original vertical, which moves together with the tilt chair (refs. 73 and 132) (fig. 18). The line drawn immediately indicates the counterrolling of the eyes. In normal cases it is of the order of 10° when the patient is tilted over 60° and identical on both sides. The examination takes place in an almost dark room and gives reproducible results. Patients without labyrinthine function show no or hardly any compensatory rolling of the eyes. There appears to be good agreement between loss of counterrolling and loss of the oculogravic illusion (ref. 44). In cases of unilateral destruction of the labyrinth, it is present only when the intact labyrinth is tilted upward. This method can be used for routine examinations. It is not too complicated, and the necessary instruments are not expensive. (See fig. 19.)

Counterrolling under the influence of increased resultant forces has also been examined (refs. 30, 60, and 138). It appears to increase substantially when the magnitude of the stimulus is increased on a centrifuge (directly proportional to the magnitude of the resultant).

The investigations of counterrolling has one disadvantage. It cannot easily be recorded

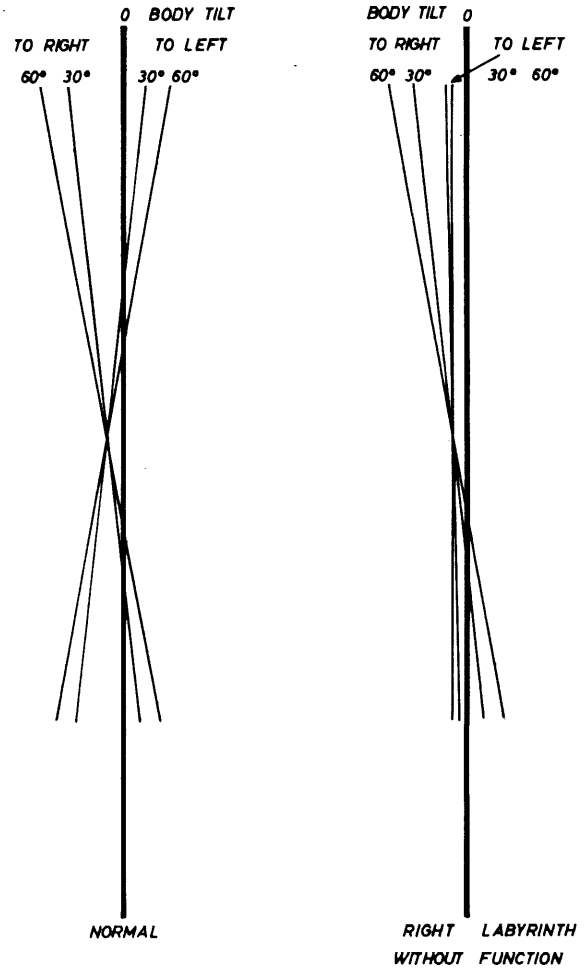

FIGURE 18.—*Counterrolling of the eyes indicated by the direction of an afterimage (Fischer).*

because the rotation of the eye about a dorsofrontal axis does not change the potentials around the eye (electronystagmography). Perlman (ref. 139) mistakenly thought that, behind closed eyelids, counterrolling did not appear, but Dodge (ref. 45) successfully used a small mirror on the closed eyelids to record the compensatory movements by photographing them; on the whole, however, this technique of recording has not become popular. It is more practical to film the eye movements.

Parallel Swing and Countermovements of the Eyes

The countermovements of the eye which are caused by the sinusoidal movements of the parallel swing are not all of the normal rotatory type. They are also movements about a bitemporal

[3] It is a mistake to call this continuous vestibular reflex tonic, since it has nothing to do with muscular tonus (refs. 1 and 135).

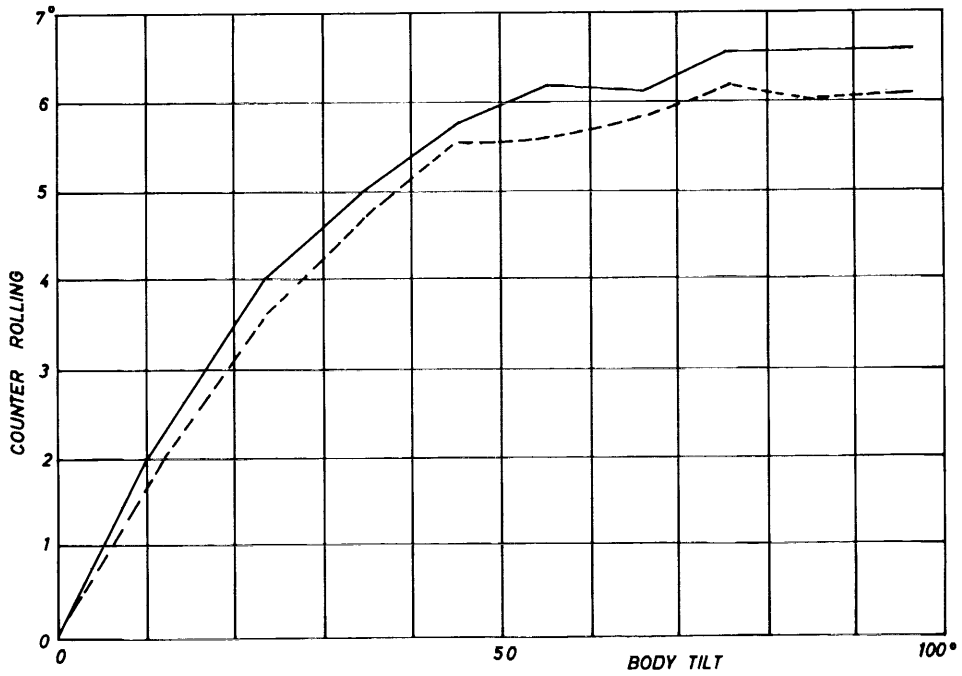

FIGURE 19.—*Counterrolling after Mulder 1874.*

axis (vertical) or about a craniocaudal axis (horizontal). De Wit (ref. 82) was the first author to describe clinical studies of them. He used the afterimage of a horizontal line and made the patient (who was moved slowly about a bitemporal axis) indicate continuously with a piece of chalk the position of the afterimage on a blackboard. In normal people a large white square is made which nearly covers the entire blackboard. In patients with disturbed otolith function, the line remains on the same level all the time. In this way De Wit found disturbed otolith function in streptomycin intoxication long before other labyrinthine symptoms could be detected.

In contrast to the rotation of the eyes about a dorsoventral axis, this vertical movement can be easily recorded with the aid of nystagmography, especially when use is made of a parallel swing which provokes sinusoidal responses of the eyes when the recumbent patient is moved in a bilateral or longitudinal direction. The technical problems of the parallel swing and the recording by electronystagmography have been described by Jongkees (ref. 73) (fig. 20). Though the parallel swing is an easy and cheap apparatus with which to record the reaction of the otoliths to

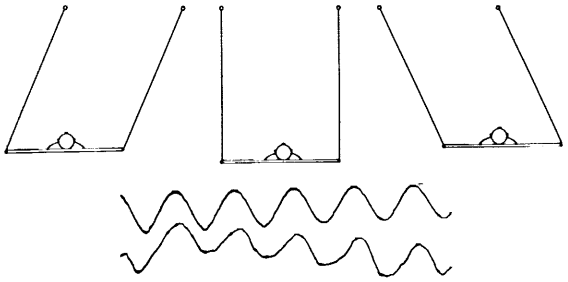

FIGURE 20.—*The routine parallel-swing examination: The patient is lying on his back and moved from side to side. Fixation of the patient's head during the test is necessary. Upper curve: movements of the swing. Lower curve: movements of the eyes.*

linear stimulation with the aid of electronystagmography and though it indicates the presence or absence of otolith function (fig. 21), helps to investigate the physiology of the otoliths, and to study the effect of drugs on the otoliths (fig. 22) (e.g., Philipszoon (ref. 53)), it is not yet the last and only answer to the problem of otolith testing. For unilateral otolithic disease its value is still uncertain. The investigations of Walsh (refs. 18 and 66) may lead to a further increase in the value of the parallel-swing test. The sensations

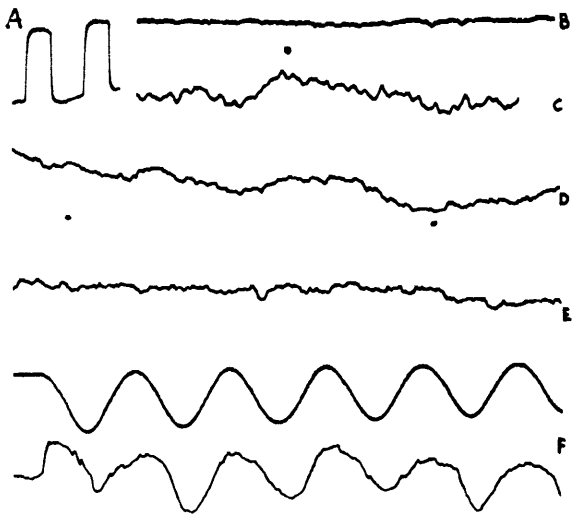

FIGURE 21.—*Labyrinthine tests in a patient with bilateral fenestration operation.* (A) *Calibration;* (B) *rotation test for horizontal canals;* (C) *same for vertical canals;* (D) *fistula sign;* (E) *caloric test; and* (F) *parallel-swing test. All the canal tests are negative. The otoliths react normally.*

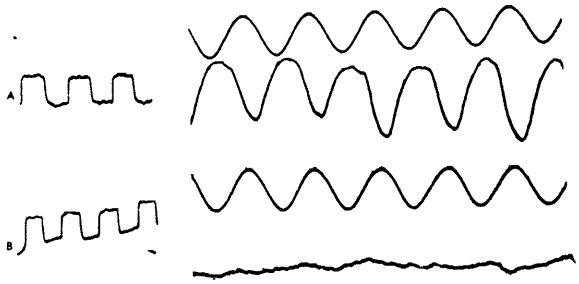

FIGURE 22.—*Upper curves: movement of the swing. Lower curves: movement of the eyes.* (A) *Normal reactions of rabbit on parallel swing; and* (B) *after 250 mg of Cinnarazine. Complete absence of eye movements. On the left: calibration.*

of body movement (illusions according to Graybiel's terminology) have a lower threshold when a patient with unilateral loss of labyrinthine function lies with the damaged side up and is consistently reduced when he lies with the damaged side downward. In rabbits with one destroyed labyrinth, Jongkees and Philipszoon (refs. 140 and 141) found the same influence of position on the magnitude of the eye movements. When the damaged side is up, the reactions are considerably smaller.

We have examined a limited number of patients with unilateral labyrinthine destruction and formed the impression that the same phenomenon appears in human beings. This would promote the parallel swing to a still more important position in the domain of otolith testing. But the examiner has to be careful. The influence of light perception may spoil the test, and in some patients the eyes show a spontaneous sinusoidal movement. The correlations of the movements of the swing with those of the eyes must be certain; if necessary, the frequency of the swing can be altered (figs. 23 and 24).

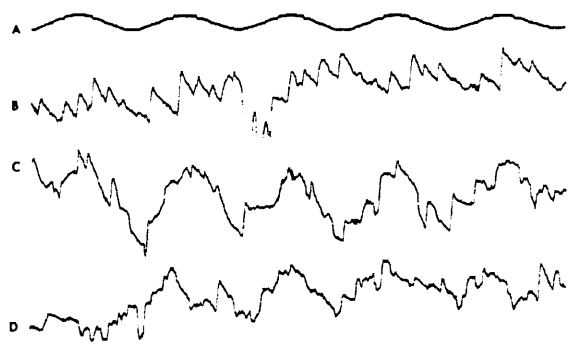

FIGURE 23.—*Parallel-swing test in a patient with a dead labyrinth on the left side.* (A) *Movement of the swing;* (B) *eye movements of the patient in supine position;* (C) *same in right-side position; strongest reaction, intact labyrinth uppermost; and* (D) *same in left-side position. The spontaneous nystagmus does not mask the otolithic effects.*

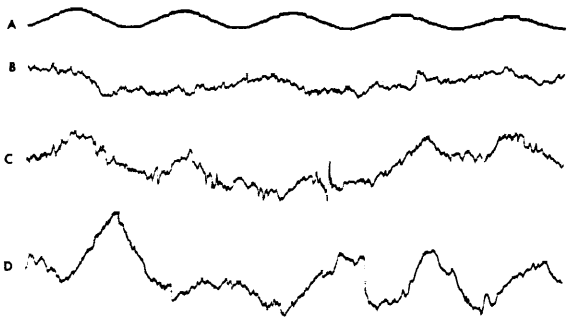

FIGURE 24.—*Parallel-swing test of a patient with a dead labyrinth on the right side.* (A) *Movements of the swing;* (B) *eye movements of the patient in supine position;* (C) *same in right-side position; and* (D) *same in left-side position. Strongest reactions, intact labyrinth uppermost.*

Vertical Movements

In some publications, vertical, sinusoidal accelerations are described. Here the same phenomena (refs. 81 and 82) appear. Nothing

new is added, but the necessary apparatus is much more complicated than the parallel swing (fig. 25).

Conclusions

It appears that both sensations and reflexes can be used for testing otolith function in man. The sensation of changed position or displacement can be used successfully for scientific experiments, but for routine examinations it seems too difficult for untrained subjects.

Reflexes of body, limbs, and neck are not suitable for routine examinations either, but the otolith reflexes of the eyes (compensatory eye movements) can be used for the purpose of routine examination.

It seems that the parallel swing combined with the electronystagmograph is the easiest, safest, and quickest way to become informed about otolith function. The measurement of compensatory eye position on a tilt or position chair during movements about a dorsoventral axis seems to be a good second. When afterimages are used to indicate the rotation of the eyes, it is also workable for institutes which do not own expensive apparatus.

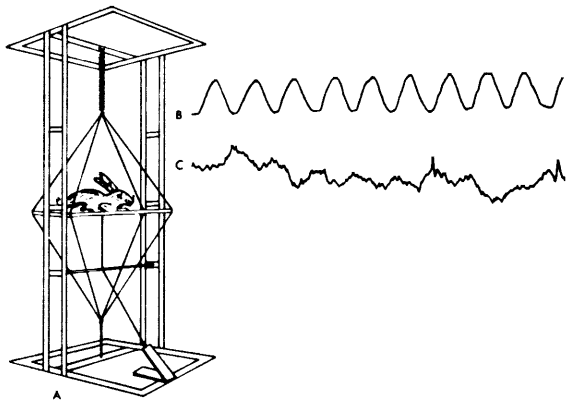

FIGURE 25.—*Sinusoidal vertical linear accelerations.* (A) *Instrument to make them;* (B) *movements of the animal; and* (C) *movements of the eyes.*

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DISCUSSION

KELLOGG: I did not understand how the tilt platform operates that you showed, where the subject falls over.

JONGKEES: A platform starts horizontal, then one side of it is pulled upward, so an oblique position results. In this way a patient's support is rotated. At a certain moment he cannot correct it any more..

KELLOGG: In reference to the figure showing counterrolling with the crosshair on the eyes, what was the method of putting the crosshair on? I assume it was a human eye? It looked like one.

JONGKEES: It was a human eye. You cut a piece of pellicle from a hard-boiled egg, put a cross on it, and place it on the eye.

KELLOGG: Does it stay there?

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JONGKEES: Yes.

KELLOGG: In position?

JONGKEES: Yes.

GUEDRY: You mentioned that you occasionally found nystagmus and occasionally found the sinusoidal eye motions. We have observed the same thing on the parallel swing. I wonder if you have some idea about why you have nystagmus sometimes and why you have the smooth sinusoidal eye movements at others?

JONGKEES: You only get nystagmus when you put a rabbit on its side. And you only get nystagmus in man when you ask him to look sideways. So it seems that a certain position of the eye in the direction of the nystagmus is necessary. You get it under the influence of the otoliths in a rabbit and under the influence of will in man.

GUEDRY: We have made a similar observation and had the impression that the mental activity of the person influenced the occurrence of nystagmus and smooth counterrolling. Mental arithmetic and keeping the person mentally active seemed to potentiate the saccadic eye movements and a tendency toward nystagmus, whereas a relaxed state potentiated sinusoidal eye movements.

We have done a number of experiments with the parallel swing with people who we believed not to have labyrinthine function and compared these results with those obtained from people who have normal labyrinthine function. During the side-to-side oscillation, people without labyrinths reported a great deal of tilting. This could be because these people have undergone a large number of experiments at Pensacola where they were required to report tilt, although we did not set them in that direction for this experiment. However, our subjects with normal labyrinths tended to report linear movement, sensations of linear velocity, much more prominently than they reported tilt. When they were asked to estimate angles of tilt, the angles were grossly underestimated. I believe that Walsh in his reports has dealt primarily with sensations of linear velocity. It is well known that on the centrifuge or in a tilt chair, you can estimate tilt accurately, but this is done with a prolonged maintenance of position. If we oscillate at higher frequencies without concomitant synergic canal information, it appears that sensations of linear velocity are much more prominent than sensations of tilt.

JONGKEES: I get the impression that it is more or less the same with the sensation threshold as it is in hearing. The first thing you hear is something, and you have no idea what it is. In my opinion, and I have also done a lot of experiments on the parallel swing, the first thing you feel is a certain rhythm, but you do not know what it is, whether it is a displacement or a rotation. Something happens in a certain rhythm and you say, "That is the threshold." That is what Walsh found also. Personally, I think the better you fix the patient, the fewer movements he feels and the more he feels rotation. We tried back injections of Novocain, but movement of the intestines and the like cannot be stopped. That is the difficulty with all the examinations of sensation. That is why I do not feel very strongly in favor of examination of sensations for this kind of work.

The Oculogravic Illusion as a Test of Otolith Function

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SUMMARY

This paper presents a review of recent literature on the oculogravic illusion and an evaluation of the illusory effect as an indicator of otolith function. The evidence presented indicates that normal observers are highly susceptible to the oculogravic illusion, that it varies widely with the specific testing situation, and that several sensory processes may contribute to the effect. Individual differences are substantial, particularly among naive unselected observers. Marked differences between normal and labyrinthine-defective observers, for both the static and dynamic components of the oculogravic illusion, have been reported in many studies. It is concluded that under very specific testing conditions, the oculogravic illusion may be an indicator of otolith function.

INTRODUCTION

The relationship between orientation to gravity and orientation to the visual horizon is one of the classical problems of aviation psychology and aviation medicine. Consequently, during the past 25 years a substantial number of experiments have been carried out with the general purpose of attempting to understand the interaction of visual and gravitational cues in human orientation in space. At Pensacola this work was originally instigated as a part of a long-term study of orientation and disorientation in pilots (refs. 1 and 2). Current investigations still have implications for the classical problems of orientation in aircraft and spacecraft operations, but they also have broader implications for understanding the vestibular mechanism and the more general problem of the interaction of visual and postural information. It is with this latter problem that this report is concerned.

Early studies of space perception in aircraft led to the observation that during certain maneuvers involving increased acceleration, such as climbs and turns, observers viewing a visual target in darkness, reported apparent motion and change of position of the visual field. The effect was characterized by high velocity, large displacement, and long duration (refs. 1 and 2). Concurrent laboratory investigations revealed that these apparent movements could be divided into two well-known phenomena which Graybiel labeled the oculogyral illusion (ref. 3), associated primarily with stimulation of the semicircular canals, and the oculogravic illusion (refs. 4 and 5), which was believed to be a function of stimulation of the otolith organs. In more recent years both of these phenomena have been widely used as indicators of vestibular stimulation. In some laboratory situations, as in the air, these effects are inseparably intertwined, but by suitable experimental arrangements in the laboratory, each effect can be studied individually. It is the purpose of this paper to review briefly some of the work on the

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oculogravic illusion and to evaluate it as an indicator of otolith function.

THE OCULOGRAVIC ILLUSION DEFINED

A working definition of the oculogravic illusion is presented by merely defining the operations involved in a typical experimental situation. No attempt will be made at this point to delineate the specific sensory mechanisms involved, since they are highly complex and not clearly established in all of their details. The oculogravic illusion may be defined as an apparent motion and an apparent displacement of a fixed, visual field when an observer is exposed to a change in magnitude and direction of gravitoinertial force (refs. 4–6). The sense of the apparent motion and the magnitude of the apparent displacement are related to the changes in gravitoinertial force (GIF). The oculogravic illusion involves two related components: (1) an apparent motion which is typically a smooth, regular change and constitutes the dynamic aspect of the phenomenon, and (2) a displacement from one position to another in space which involves the static aspect of the illusion. It should be noted that these two components may occur together or separately (ref. 4).

The oculogravic illusion may be demonstrated by two somewhat different effects which are dependent upon the direction of GIF with respect to the observer (fig. 1) (refs. 4 and 5). In the typical experiment the observer is seated on a carrousel some distance from the center of rotation while he observes an isolated visual target in darkness. If the direction of the added accelerative force is eyeballs right, the observer will report that he is tilted to his right and that the visual target appears to rotate clockwise. To aline the field, or say a luminous line, with the horizon, he merely rotates the line counterclockwise about its center point. Similarly, if the added accelerative force is eyeballs-in, he will perceive himself to be tilted backward, and the visual target will be perceived to move and be displaced upward. To make the target level, he displaces it downward (refs. 4 and 7). The amount of the rotation and the vertical displacement give a measure of the observer's perception

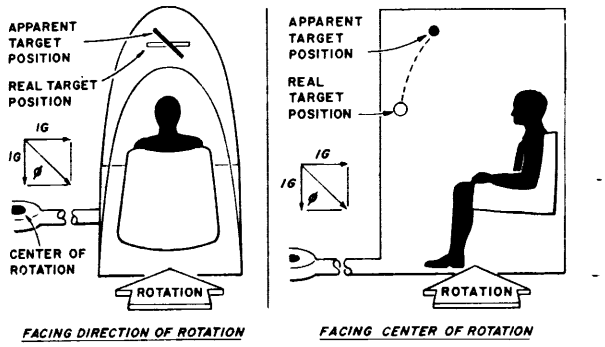

FIGURE 1.—*Apparent displacement of a visual target when observer is exposed to a change in gravitoinertial force.*

of the illusion. The oculogravic illusion has been demonstrated in rotating devices (refs. 4–6), in elevators (ref. 8), in aircraft during complex maneuvers (refs. 1 and 2), and during simple linear acceleration (ref. 9). A special case of the oculogravic illusion, or at least a related effect, has been demonstrated during short periods of near-zero gravity in aircraft (refs. 10 and 11). Gerathewohl and Stallings (ref. 10), who first described this phenomenon, called it the oculo-agravic illusion. The oculo-agravic illusion involves apparent motion and displacement of a real target which is opposite to that observed during increases in g-force (refs. 1 and 2) (fig. 2). These phenomena have also been called the elevator illusion (refs. 8 and 12).

It is worth noting that there have been some criticisms of the method of studying visual space perception by placing the observer at some distance from the center of rotation of a carrousel and using the oculogravic illusion as the indicator of the phenomenon (refs. 13 and 14). It has been argued that the physical effects in a tilting chair and on the rotating platform are

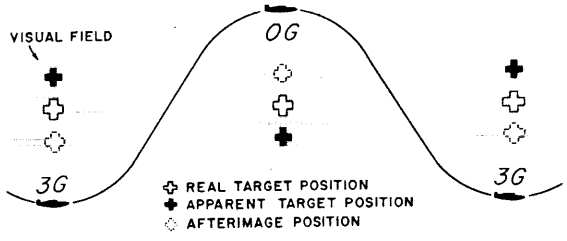

FIGURE 2.—*Apparent position of a real target and an afterimage during a parabolic maneuver.*

identical and that the observer cannot distinguish between the experience of the displaced direction of gravitoinertial force during rotation and the displacement of gravitational force during simple tilting. Of course, it is an elementary principle of physics that centrifugal force and gravitational force have the same general effects on the body. On the other hand, there are obvious differences in other physical events between the two situations, and they lead to very different experiences from the observer's point of view, as Witkin (ref. 14) has pointed out. Witkin believes that the observers use all of the relevant information available to them and that this information is very different in these two situations. Furthermore, he argues that they use varied cognitive styles which lead to marked individual differences among them. Moreover, since the oculogravic illusion results from a highly complex stimulus situation, the total proprioceptive stimulation is dissimilar in these two situations; for example, the semicircular canal stimulation and the g-level are not the same. The observer has no difficulty whatever in distinguishing between the two conditions, and they yield different perceptual responses (refs. 4 and 15–18).

RESULTS OF EXPERIMENTS ON THE OCULOGRAVIC ILLUSION

The effects of changes in the direction of GIF on visual space perception have been studied systematically for well over 100 years, and in the last 25 years there have been an increasing number of these studies (refs. 4–6 and 19). This section presents a review of recent studies of this phenomenon with some emphasis on studies relevant to the effect as an indicator of otolith function.

Sensitivity to Changes in Magnitude and Direction of GIF

It is well known that observers are able to set themselves to the postural vertical with an average error of only 2° to 3° in a tilting chair (ref. 20). It is no surprise, therefore, that their perception of the visual horizontal and vertical is extremely sensitive to changes in GIF. With the observer seated erect with respect to gravity, thresholds of sensitivity measured by the apparent motion and displacement of a luminous line in darkness have been reported to be of the order of 1.5° (refs. 7 and 21). With the observer on his side the thresholds turn out to be much greater (approximately 9°), while with the observer upside-down, it is very difficult to establish thresholds (refs. 6 and 21). With the observer erect on the centrifuge, this means that an increase in magnitude of centripetal acceleration of only 0.0003 g is perceived. Similar data have been obtained in flight for short-term linear accelerations with the thresholds being of the order of 0.07 g (ref. 9). It is quite clear from these data that the oculogravic illusion measured under optimum conditions is a highly sensitive indicator of changes in magnitude and direction of GIF.

Some Effects of the Nature of the Vestibular and Visual Stimulus on the Oculogravic Illusion

Several studies have shown that the static phase of the oculogravic illusion is a function of the change in magnitude and direction of GIF, and for normal, sophisticated observers approximates the change in direction of GIF for changes up to about 30° (refs. 6, 15, 16, 22, and 23). But for larger changes the illusion tends to increase more rapidly than the change in GIF, producing what Graybiel has termed the "magnitude effect," and the illusion may be nearly double the change in the direction of GIF (refs. 4 and 5). When the rate of change is slow, for example, 30° in 6 minutes or more, it has been shown that the oculogravic illusion also increases slowly in close accord with the change in direction of GIF. On the other hand, when the change is rapid, for example, reaching its maximum value in 3 to 6 seconds, the oculogravic illusion reaches its maximum value only after 50 to 100 seconds. If the observer views a horizontal line during this period, he will report that it rotates slowly and becomes displaced to a new position. This slow, apparent motion constitutes the dynamic component of the oculogravic illusion and has been termed the "lag effect" (refs. 17 and 22). Two studies (refs. 15 and 16) were conducted to investigate factors which contribute to the "lag effect." It has been shown that the character of the preexposure visual field immediately before a change

in GIF occurs has little or no influence on the "lag effect" nor on the final magnitude of the illusion. On the other hand, if there is a delay in presenting the luminous target following a rapid change in GIF before settings are made, a major, systematic increase in the "lag effect" and a reduction in the level of the static component of the illusion occur.

After the oculogravic illusion has reached its maximum value, adaptation effects are minimal (refs. 4, 5, 17, and 22). Early work showed that the oculogravic illusion exhibited no systematic changes from its maximal value in normal observers up to 15 minutes of continuous exposure to centripetal force producing eyeballs-right (ref. 22), while more recent data showed no further systematic changes up to 4 hours of constant rotation (refs. 23 and 24).

It is interesting to note that the visual acuity necessary to perceive the oculogravic illusion is quite low. A study of partially blind observers from the Florida State School for the Blind and Deaf showed that they set a luminous line to the gravitational horizontal with great accuracy. Furthermore, all of them perceived the oculogravic illusion very much like that seen by normal observers (ref. 25).

Effects of Head and Body Position

It is well known that, under static conditions, the perception of the visual horizontal is very accurate and that when the head and body are passively tilted, constant errors occur (refs. 7 and 26). This is also true under conditions of increased g (refs. 27 and 28). Similarly, during exposure to centripetal acceleration with a change in direction of GIF of 6° to 12°, the oculogravic illusion is perceived with the observer seated or kneeling with the head and body erect (ref. 26). But with the observer's head and body in an unusual position to invert his head, or with the observer on his side, the oculogravic illusion is not readily perceived. In other words, with head and body erect the seated observer is well oriented to the GIF; whereas, when he is inverted or on his side, he is disoriented with respect to GIF. There is some evidence that when the observer is inverted by rotating him to the head-down position in a simulator cockpit, he does perceive the oculogravic illusion (ref. 29). Conversely, the oculogravic illusion does not appear during various head and body tilts with the observer standing on a rotating platform set at the gravitoinertial horizontal (ref. 30).

Observations in Flight

The oculogravic illusion has been reported in its various forms during flight, although in flight maneuvers it is difficult to isolate the effects of linear or centrifugal acceleration and angular acceleration since both are involved in aircraft maneuvers. Clark and Graybiel (ref. 9) have reported rotation of a visual target during acceleration and deceleration during flight with the observer facing to the left in the aircraft. Upward displacements as great as 60° have also been reported during increased g, for example, in coordinated turns and dives (refs. 1 and 11). The reverse of these effects has been reported when afterimages were used as targets. Observations under zero-g conditions produced the opposite effects (refs. 10, 12, and 31) (fig. 2). In a related study, Hammer (ref. 32) reported increased errors in setting a luminous line to the vertical in darkness under zero-g conditions, but both the constant and the average errors were quite small.

Interacting Perceptual Processes

Late in the 19th century Mach (refs. 33 and 34) expressed the view that it "is indeed quite certain that absence or loss of the labyrinth sensations can be, to a large extent, replaced by the other space perceptions. . . ." Similarly, as a result of the ubiquitous character of gravitational forces, many sensory processes are stimulated by them, and interaction effects also occur with the vestibular receptors intact (refs. 18, 28, and 35). Both tactile and proprioceptive cues appear to be potential sources of information for the oculogravic illusion, but the relative influence of each is difficult to determine. Tactile cues appear to be promising sources of information because touch is so constituted that it can transmit highly complex information (refs. 36 and 37). This has been well known for many years; for example, Rousseau suggested 200 years ago that it would be possible to construct a tactile language, and recent attempts

have been made to code optical signals on an optohapt (ref. 36). Much discussion continues regarding the priority of vision over touch and the various proprioceptors (e.g., see Rock (ref. 38)), who continues to emphasize the priority of vision), but the basic question of concern here is: How do the various sources of information interact in the perception of the oculogravic illusion (ref. 39)?

With a full visual framework present for the observer during rotation, the oculogravic illusion has been shown to be minimal or absent; that is, with discrepant visual and gravitational cues, the full visual reference predominates (refs. 4, 5, and 40). If, however, the observer is exposed to a full visual framework during prolonged constant rotation and the room lights are subsequently turned out leaving only an isolated, luminous line viewed in darkness, the line will appear to rotate slowly to produce the oculogravic illusion (refs. 15 and 23). The effect increases fairly rapidly for about 60 seconds and then more slowly for an additional 60 seconds. This gradual increase in the illusion is in marked contrast with the apparent change in the position of the luminous line when the room lights are turned on. Under these conditions the illusion disappears almost immediately. This second type of "lag effect" associated with the oculogravic illusion does not occur as smoothly as the "lag effect" associated with the sudden onset of a centripetal force. It has also been demonstrated during the observation of the A-phenomenon which increases in the same way when the room illumination is turned off (ref. 18).

The importance of tactile information in the perception of the oculogravic illusion has been suggested in a study which compared normal and labyrinthine-defective (L–D) observers while they stood in a rotating room (ref. 30). These observers set a line to the horizon in darkness in four different head and body positions. The oculogravic illusion was not present for the normal observers with head and trunk in the position expected to produce the effect in seated observers. Furthermore, there were no significant differences between the two groups. These results suggest that tactile information in combination with proprioceptive information leads to a more veridical perception. This view is supported by the fact that the same observers did not exhibit the E-phenomenon when they stood and actively tilted the head and body rather than being passively tilted (ref. 41). These data support the notion that the perception of the visual horizontal or vertical is an end product of a highly complex perceptual interaction.

Individual Differences

Since several sensory mechanisms undoubtedly interact to produce the oculogravic illusion, it is not surprising that substantial individual differences have been reported (refs. 6, 15, 23, and 40). Witkin (ref. 40), in a study of 258 observers during rotation, found marked individual differences among completely naive, unselected observers in setting a luminous line to horizontal or vertical. These differences occurred both with room lights on and in darkness, the standard deviation in darkness being 6° to 7°. A number of studies at Pensacola (refs. 6, 15, and 23) have also reported appreciable, but somewhat smaller, individual differences among observers who were highly sophisticated with regard to the observations and carefully selected to have normal vestibular function. Since Witkin's observers were both naive and of unknown vestibular function, individual differences would be expected to be greater in his group.

In evaluating the importance of the vestibular mechanisms in space perception, a comparison of the performance of normal and L–D observers offers a crucial test. Consequently, comparisons of these two groups have been made by many students of vestibular function, although the accurate selection of observers for the two groups presents certain difficult problems. Normal and L–D observers have been shown to perform quite differently on several tests presumed to indicate otolith function (refs. 27, 42, and 43); for example, on the parallel swing. These two groups also show gross differences in their perception of the oculogravic illusion (refs. 4, 6, and 19). One recent comparison (ref. 6) of normals and L–D's indicates that L–D's: (1) show higher variability, (2) show a different pattern of response, (3) perceive a smaller illusory effect, and (4) do not perceive

the full dynamic components of the illusion. Additional evidence on the issue has been reported by Graybiel (refs. 19 and 44) who rotated normals and L–D's while they were submerged in water to reduce tactile cues to a minimum. Under these conditions the normals showed a typical oculogravic illusion, while the L–D's perceived practically no illusion (fig. 3) (ref. 44). This not only supports the notion that the oculogravic illusion is an indicator of otolith function, but it also suggests that a comparison of the data in and out of water for the L–D's gives some measure of the contribution of the nonotolith cues to the oculogravic illusion. Additional evidence on the issue is to be found in the fact that L–D observers do not perceive the elevator illusion (ref. 8). As noted previously, normals report that a real target moves upward with increasing g and downward with decreasing g (refs. 1, 8, and 12), while L–D's do not observe this effect. Graybiel and Johnson (ref. 45) have shown that L–D's report less tilt of the visual field than normals in a counterrotating room with the lights on. A comparison of normals and L–D's during constant exposure to centripetal acceleration for 1 hour has also shown the importance of nonvestibular information in producing the illusion. The comparison demonstrated marked, significant differences between the normals and the L–D's for the first 10 to 15 minutes, but at the end of 1 hour the differences were not significant (fig. 4) (ref. 24). Hence, the duration of the testing period is an important consideration.

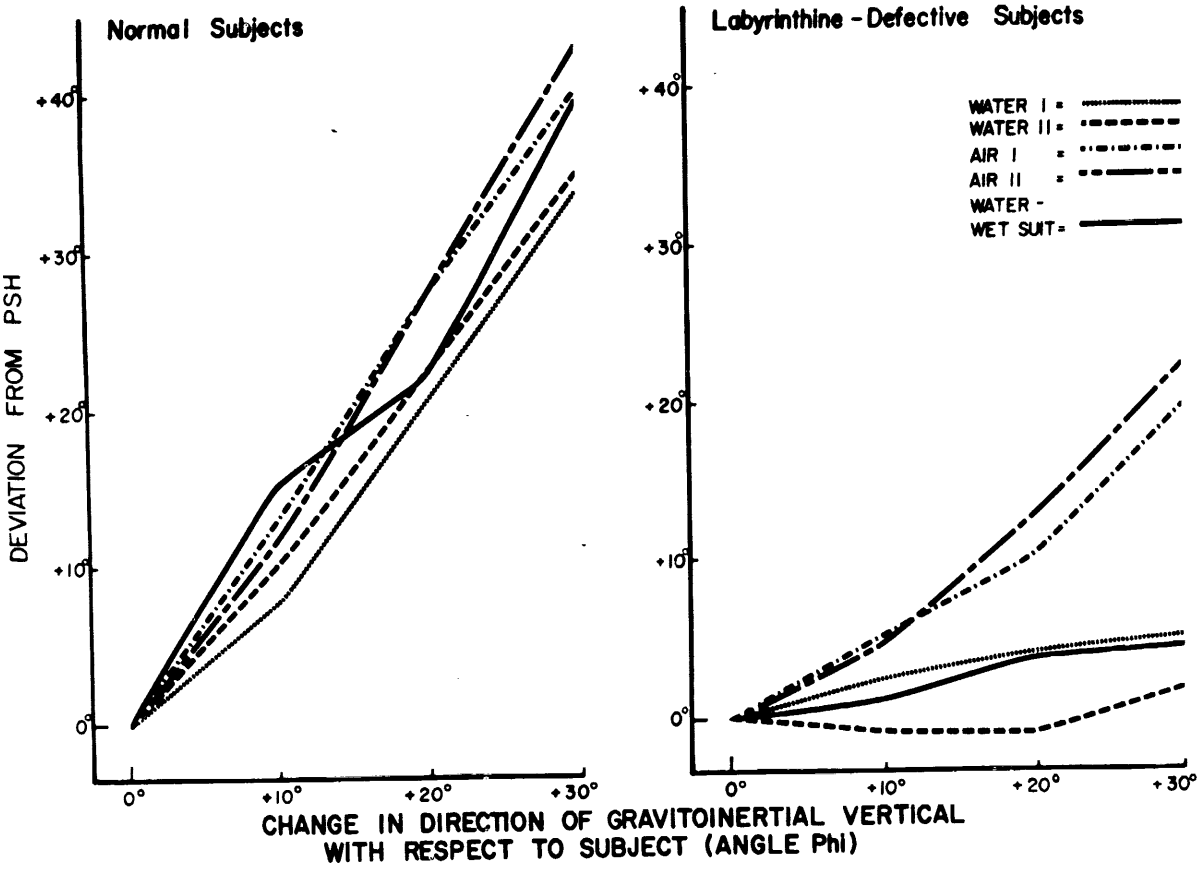

FIGURE 3.—*The oculogravic illusion with observers rotated in water.* (*From ref. 44.*)

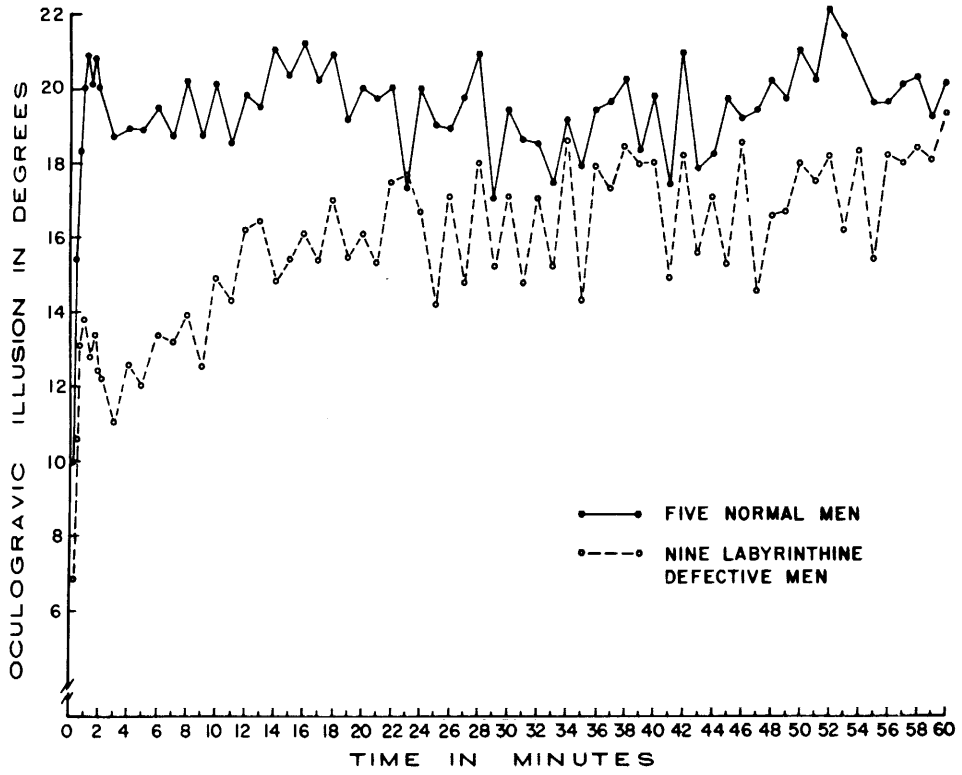

FIGURE 4.—*Change in the oculogravic illusion during 1 hour of continuous rotation. (From ref. 24.)*

TESTING CONDITIONS FOR THE PERCEPTION OF THE OCULOGRAVIC ILLUSION

With the results of these experimental observations in mind, an attempt may be made to consider the oculogravic illusion as an indicator of otolith function. At the outset it can be noted that normal observers are extremely sensitive to the effect, and that the illusion is dependent on complex perceptual processes. The oculogravic illusion varies considerably with the particular testing situation. Furthermore, as is the case with other tests of otolith function, nonvestibular perceptual processes are inextricably involved by the very nature of the situation. The most significant type of evidence on the matter stems from the repeatedly observed differences between normals and L–D's in their perception of the illusion. Overall, the data support the notion that if the oculogravic illusion is used as an indicator of otolith function, it must be observed under very specific testing conditions which tend to produce a maximum effect in normals and at the same time reduce the effects of certain nonotolith cues. These optimum testing conditions are:

(1) The observer is seated with head and body erect and suitable restraining equipment is used, or he is rotated with his body under water.

(2) The observer views a dim, luminous line in darkness or in a ganzfeld.

(3) The observer begins to make his observations after at least 1 minute of constant rotation and 1 minute of darkness.

(4) The centripetal acceleration is moderate to produce a change in the direction of GIF of 20° to 25°.

(5) The duration of a constant centripetal acceleration does not exceed 5 to 10 minutes.

(6) The observer is given practice in the rotation device and in the observation of the oculogravic illusion.

(7) To observe the dynamic aspects of the illusion, the observer remains in darkness for 1 minute before rotation begins.

In his early reports, Mach (ref. 33) expressed the view that what is now called the oculogravic illusion is closely related to otolith function. At the same time he pointed out the importance of other sensory processes in producing the phenomenon. The results of the studies of the oculogravic illusion in the past 20 years tend to support Mach's view, but with the limitation that the test be made under very specific conditions. With these limitations in mind, the oculogravic illusion may be considered to be a valid indicator of otolith function.

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DISCUSSION

KELLOGG: You got no reaction at all from the labyrinthine defective subjects in terms of the perception of illusion under water?

CLARK: Dr. Graybiel did the study.

KELLOGG: I was going to suggest that there might be a ranking order of the sensitivity of the illusion with reference to counterrolling, because counterrolling can be picked up, I think, in all the L-D subjects we have tested, which would imply that the threshold for this illusion would be higher. I would take it to mean that. Dr. Graybiel might want to make a comment.

GRAYBIEL: We found a small amount of counterrolling in all. We tested 11 or 12 subjects repeatedly and carefully, and at least 9 of them demonstrated a significant amount of counterrolling, but this did not overlap the normal. In estimating the amount of apparent motion, some of the subjects, on brief exposure, not only were inconsistent but demonstrated "improvement" with practice. While an abnormally low index was nearly always associated with an abnormally low estimate of the illusion, within these low ranges the score on one test was not a good predictor of the score on the other. Estimates of the illusion made by four L-D subjects submerged to neck in water were reduced; the exposure time was brief. Whether long exposure would affect the estimates similar to that demonstrated under dry conditions remains to be tried. Centrifugation with subjects

submerged might yield highly consistent estimates of the illusion which would be valuable for correlation with other tests of otolith function. As Dr. Clark pointed out, it has very severe limitations as a routine test.

CLARK: Yes. Not very many people can rotate their patients under water, I would suspect.

MELVILL JONES: I would like to ask whether you think the processes involved in arriving at the final end product over a 50- to 100-second period are similar to those involved in establishing the change of orientation "set" in cats described by Brindley and referred to by Dr. Roberts in his presentation. It seems to me they might be similar, but there is a wide discrepancy in durations; namely, 50 to 100 seconds in your case and 6 to 7 seconds in Brindley's.

CLARK: I would think not. But I see Dr. Roberts is shaking his head a little anyway. I would think that it is quite clear, as Dr. Jongkees has pointed out, that the latency to firing, or the indication time, is quite short with the otoliths. It seems to me quite clear that it cannot be peripheral. I would merely say that it is a function of the central nervous system orientation to the situation. I might add in addition that the same sort of effect can be produced with the E-phenomenon. Dr. Miller and Dr. Graybiel have produced similar lags just with the subject lying on his side and turning off the lights, and then the A-phenomenon occurs in about the same amount of time. A couple of my students have found the same result. I think that the phenomenon is a rather general one related to a change in orientation from visual information to the postural information. I might point out finally that the reverse, however, is quite rapid, as I am sure you know. If the subjects are asked to make a judgment with the lights on again, then it is very quick; at least it is hard to measure it.

BERGSTEDT: Concerning the lagtime, it is of certain interest that it is about the same as for positional nystagmus. Positional nystagmus is a clinical phenomenon in certain patients and in normals after drug intoxications, such as alcohol and so on. We do not consider for certain that it is triggered from the otolith organs. It has not really been shown, but there are quite strong indications. I made some centrifuge studies with results in that direction, and the lagtime is of about the same magnitude as for these oculogravic illusions.

ROBERTS: In connection with these oculogravic illusions, it would be, I think, relevant to bring in some of the ideas that Dr. Whiteside has been thinking of in this connection. He is not here to speak for himself and I may be misrepresenting him, but my impression is that he has come to the conclusion that the oculogravic illusion, like the related autokinetic illusion, arises not so much from the otolith or labyrinthine stimulation but from correcting movements made for some presumably central reason, to correct for what he calls labyrinthine drift. If, for example, you are in a particular position in which you have made a definite assessment of the behavioral vertical, then all is well, and you can have a clear idea of where the external world is. If you are now held in this position for some time, your labyrinthine noise may build up. Eventually you have to make small correcting movements of the eyes, so to speak, to restore them to where you think they should be for central fixation. It is this type of correcting movement of the eyes, bringing them back toward the center, which gives you the impression that the visual field is moving, as though your correcting eye movements had been necessary to follow a moving visual field. So that an accumulation of noise over this 100-second period and a general subsiding of the state of confidence as to what is the behavioral vertical, are the sorts of things which might be thought of as accounting for this very long time course, rather than some physical property of lag or viscosity or what not in the otolith organs.

MAYNE: We have suggested in a series of reports to NASA that the oculogravic delay is simply a smoothing function to cancel out transient accelerations and retain constant gravitational force. This engineering concept can probably be reconciled with Dr. Roberts' intuitive comments. A similar operation occurs in a simple airplane autopilot in the determination of the vertical. The greater delay experienced with L-D subjects may be the result of the noisier kinesthetic sensory data requiring longer smoothing time.

Effect of Drugs on Ocular Counterrolling[1]

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SUMMARY

Ocular counterrolling, a specific indicator of otolith activity, under controlled conditions was measured before and at various times after the oral administration of one of several selected drugs or a placebo. A pool of nine normal subjects participated, and from four to six were used in each experimental trial. Alcohol, 1 cc/lb body weight, had a significant and progressive depressant effect on the amount of eye roll during the intoxication period; complete recovery was recorded 6 hours after its ingestion. Scopolamine, chlordiazepoxide hydrochloride, meprobamate, meclizine, acetylsalicylic acid, *d*-amphetamine, and diphenidol, given in twice the usually recommended doses, had no significant effect.

INTRODUCTION

The effect of various drugs on labyrinthine functions has been investigated using eye-movement responses as specific and motion-sickness symptoms as nonspecific indicators (refs. 1 to 10).

The purpose of the present study was to explore in a preliminary way the specific effect upon otolith activity of several drugs, including drugs which have been found to be effective in reducing motion sickness symptoms (refs. 7 to 10). Objective determination of otolith organ activity in man can be accomplished by the measurement of ocular counterrolling which has been well established as a specific indicator of otolith function when certain experimental procedures are followed (refs. 11 and 12). Developments in technique (refs. 11 and 13) have greatly improved the accuracy of the measurements and have made the use of this reflex for studying the function of the otolith organs more practical.

A reflex change in ocular counterrolling normally correlates with a change in direction or magnitude of linear acceleration including gravity acting upon man (refs. 14 and 15). If the gravitoinertial stimulus is kept constant, such as was done in the present study by holding the subject in a given tilt position, the effect of factors other than this stimulus upon otolith activity can be studied. The parameter used in this investigation was acute alteration in the internal bodily environment as effected by drugs. A significant increase or decrease in ocular counterrolling which might occur following the administration of a specific drug and correlate with its known temporal mode of action would be evidence of the extent and type of effect upon the otolitho-ocular reflex arc. In selecting drugs for the present study, several categories were chosen, but emphasis was placed on those drugs which were known to influence general or specific response to vestibular stimulation (refs. 1 and 8 to 10).

[1] Work performed under T-47557(G) for the Biomedical Research Office, Manned Spacecraft Center, NASA.

METHOD

Subjects

The subjects were nine young healthy Navy men ranging in age from 18 to 20 years. Special tests of the labyrinthine organs made on each of these men had demonstrated that semicircular canal response as elicited by thermal stimulation (ref. 16) and otolith organ activity as determined by the standard test (ref. 13) of ocular counterrolling were within normal limits. Four of the subjects were tested with each of the drugs and the placebo used in this study, while the others, due primarily to military obligations, were unavailable for testing with the entire drug list shown in table 1.

PROCEDURE

Each subject was tested according to the standard method of measuring counterrolling used in this laboratory, which involves photographically recording the natural iris landmarks of a subject positioned upright, and tilted laterally to one of four positions: $\pm 25°$ and $\pm 50°$. The subject's eye when properly fixating the center of a ring of light was photographed, as a rule six times at each of the five body positions. The counterrolling tilt apparatus and specific procedures for its use have been described in detail in other communications (refs. 11 and 13). Three standard tests were made prior to the day of the experimental trials to determine whether the individual had normal otolith organs as well as to provide baseline counterrolling data for comparison with the results obtained at the time of testing when the subject was under the influence of a drug.

Table 1 lists the particular subjects tested with each of the drugs (including a placebo), the drug dosage, and the times at which the standard counterrolling test was started following oral administration of the drug.

Alcohol (80-proof vodka) was administered in the proportion of 1 cc/lb body weight; in all other drugs the dosage was twice that usually recommended. When it could be determined from standard pharmacological manuals, the absorption and excretion or destruction rates of a given drug formed the general basis for the test schedule. A period of at least 30 minutes separated test sessions to allow adequate time for conducting the ocular counterrolling test as well as for resting the subject.

Immediately prior to administration of the drug as well as the time of predicted termination of its effect, the subject was tested twice (predrug trials) in succession by the standard counterrolling method; during interim times, only one such test was given. The subject was removed from the tilt device and allowed to rest

TABLE 1.—*Experimental Schedule Used for Investigating the Effect of the Oral Administration of Each of Several Drugs and a Placebo Upon Ocular Counterrolling Responses*

Drugs	Dosage [a]	Time of CR test after drug administration, min	Subjects receiving drugs
Placebo (lactose), mg	750	60–180–240–300	BU, CH, HA, WI
Alcohol (vodka, 80 proof), cc/lb	1	30–60–90–150–360	CH, HA, WH, WI
Scopolamine (Hyoscine), mg	1.2	30–60–420	BU, CH, HA, LA, WI
Chlordiazepoxide hydrochloride (Librium), mg	50	4th day	CH, GL, LA, WH
Meprobamate (Miltown), mg	400	60–90–120–420	BU, CH, GL, HA, WI
Meclizine (Bonamine), mg	100	30–60–90–420	BU, CH, CO, HA, LA, WI
Acetylsalicylic acid (aspirin), grains	25	30–60–120–300	BU, CH, HA, WH, WI
d-Amphetamine (Dexedrine), mg	20	30–60–90–420	BC, BU, CH, GL, HA, WI
Diphenidol (Vontrol), mg	100	60–90–120–420	BU, CH, HA, LA, WI

[a] Each subject listed for each drug received only 1 dosage except for that of chlordiazepoxide hydrochloride which was given to each of 4 subjects once for 3 consecutive days.

following each of the single or double counterrolling tests of a given time period. This general procedure was followed for the placebo and all drugs except in the case of the drug chlordiazepoxide hydrochloride which was administered on 3 consecutive days to take advantage of its cumulative action, and several standard counterrolling tests were made on the fourth day without regard to time.

On the day of the drug or placebo test, the subject did not eat breakfast but was fed approximately 2 hours after administration of the drug. A period of from 48 to 72 hours elapsed between drug tests for any one subject.

RESULTS

The mean counterrolling values of the nine subjects which were determined for upright and the four body-tilt positions (±25°, ±50°) in the baseline test series are portrayed in figure 1. By definition, the mean value obtained

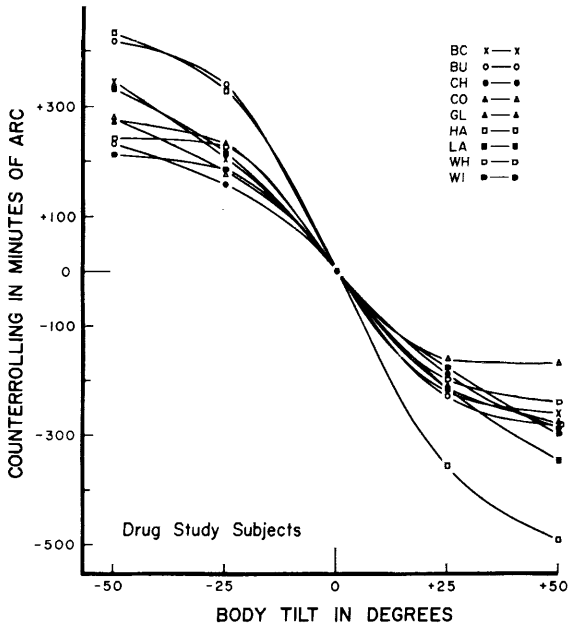

FIGURE 1.—*Baseline mean counterrolling response of each of the nine subjects.*

with the subject in the upright position represents zero counterrolling as shown in this figure. Each subject exhibited substantial counterrolling relative to his basic eye position, a valid indication that he had normal otolith organ function. The subjects' overall response patterns were qualitatively and in most cases quantitatively similar to each other and to those of previously tested subjects (ref. 12).

In an attempt to present the counterrolling data of this study in a more graphic form than the one depicted in figure 1 and one which would allow ready visual comparisons among the results, measurements at each of the two magnitudes of tilt (25° and 50°) were averaged without respect to the clockwise (+) or counterclockwise (−) direction (or algebraic sign) of the counterrolling response. This data reduction procedure also decreases the amount of artifact introduced by spontaneous physiological changes in eye-roll position, changes which are frequently found among successive recordings of counterrolling in the same subject as well as between tests conducted under apparently identical experimental conditions. Although such variations in roll position of the eye for a given angle of body tilt usually are small, amounting only to several minutes of arc, they occasionally may exceed 1° or 2°. The influence of these physiologic changes on counterrolling upon the results of the present study is by no means eliminated by averaging the measurements, since it is still quite evident that there was physiologic variability in the composite results of the placebo trials of four subjects (fig. 2) and that there were differences in group measurements obtained in certain of the baseline and predrug trials (figs. 2 through 10). Each curve shown in figures 2 through 10 is derived from the measurement of several hundred photographic recordings and represents the mean measurements of the counterrolling data as averaged for the 25° and 50° bodily tilts. Shown are the data collected in the baseline tests, and in those tests conducted just prior to and following the administration of each drug.

For technical reasons the counterrolling recordings of one baseline trial of certain subjects were unusable; this accounts for the fact that for the placebo, *d*-amphetamine, and diphenidol (figs. 2, 9, and 10), only two baseline trials are plotted. Where there are differences in magnitude of counterrolling, the predrug trial data probably serve better than the baseline values, obtained days and weeks in advance, as a stand-

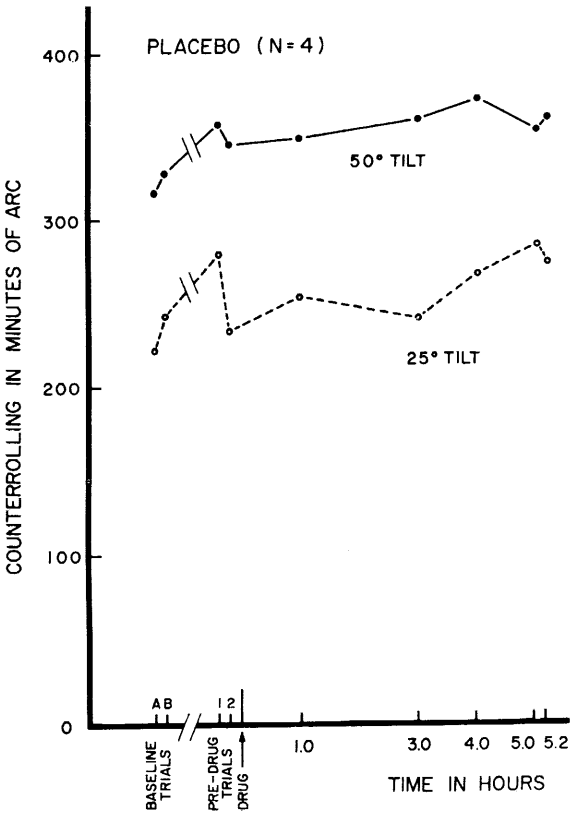

FIGURE 2.—*Effect of a placebo upon the ocular counterrolling response of four of the subjects.*

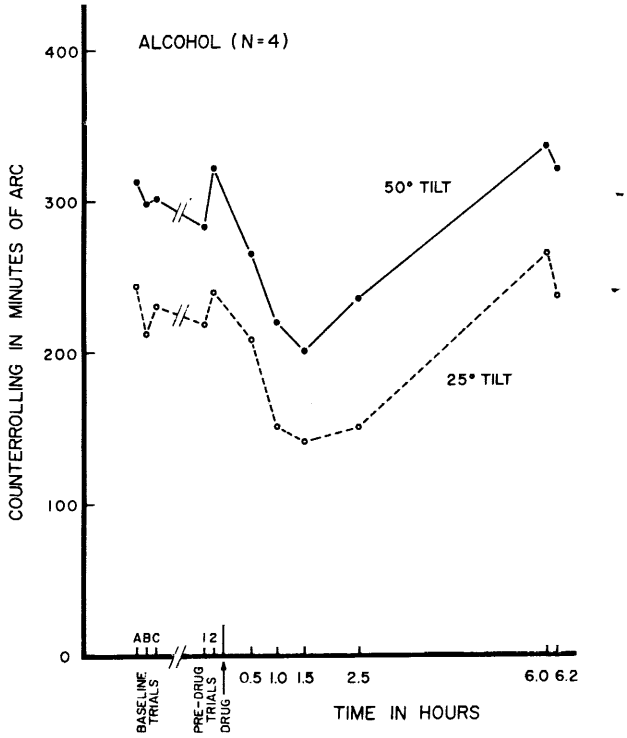

FIGURE 3.—*Effect of alcohol upon the ocular counterrolling response of four of the subjects.*

ard against which postdrug values may be compared. Spontaneous day-to-day variability of other compensatory eye movements have been reported and recognized as a complication in the demonstration of a pharmacological effect (ref. 1).

DISCUSSION

In interpreting the results, it was necessary to differentiate between a measured change in ocular counterrolling which was the result of the experimental variable, in this case drug action, and the change due to spontaneous variability or "noise" of the system caused by many other factors which contribute to the tonicity of the extraocular muscles. Differentiation was made possible by imposing three main requirements that had to be satisfied before a change in magnitude of counterrolling was accepted as a specific indication of drug action upon this reflex mechanism: (1) the magnitude of the change had to differ significantly from

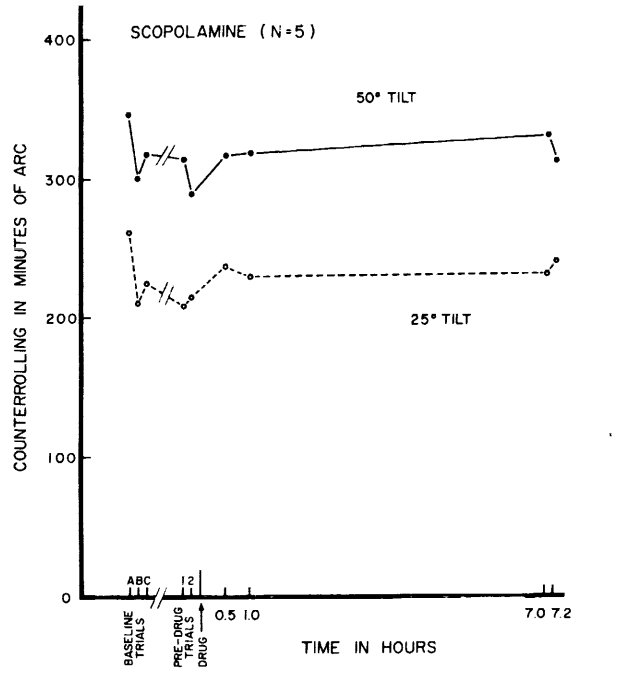

FIGURE 4.—*Effect of scopolamine upon the ocular counterrolling response of five of the subjects.*

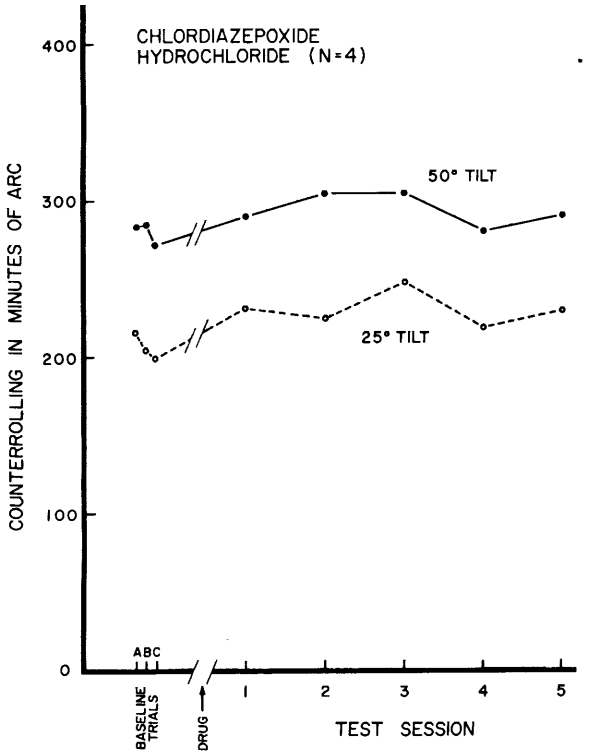

FIGURE 5.—*Effect of chlordiazepoxide hydrochloride upon the ocular counterrolling response of four of the subjects.*

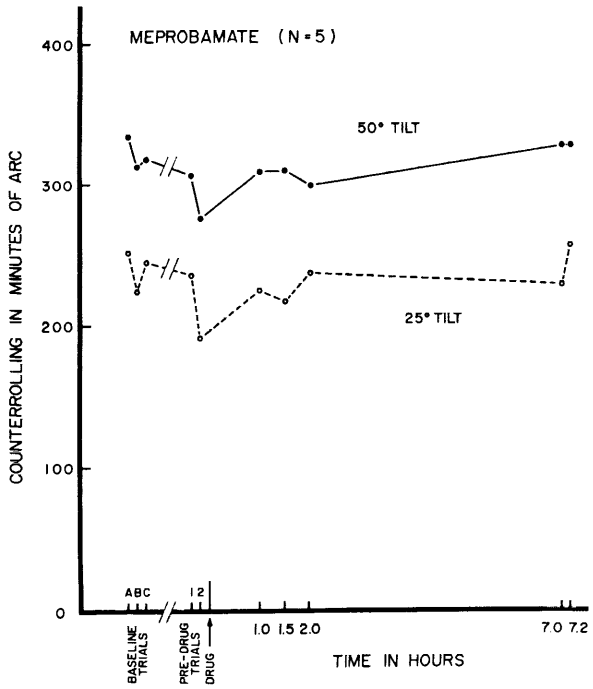

FIGURE 6.—*Effect of meprobamate upon the ocular counterrolling response of five of the subjects.*

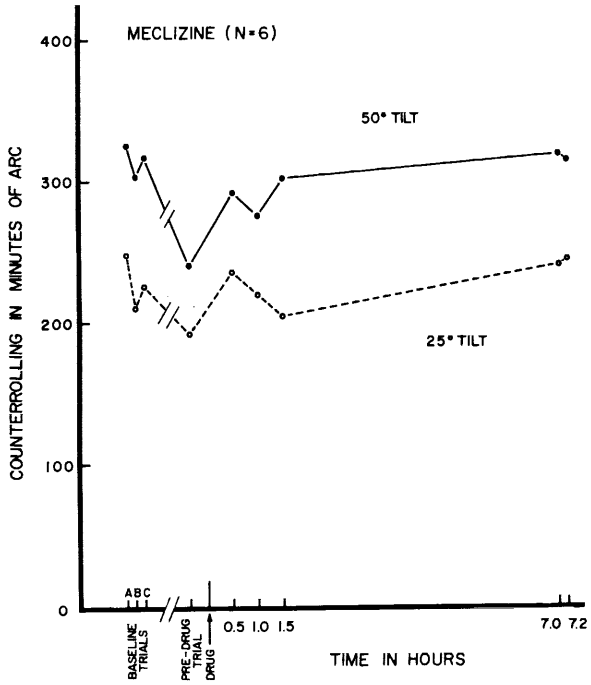

FIGURE 7.—*Effect of meclizine upon the ocular counterrolling response of six of the subjects.*

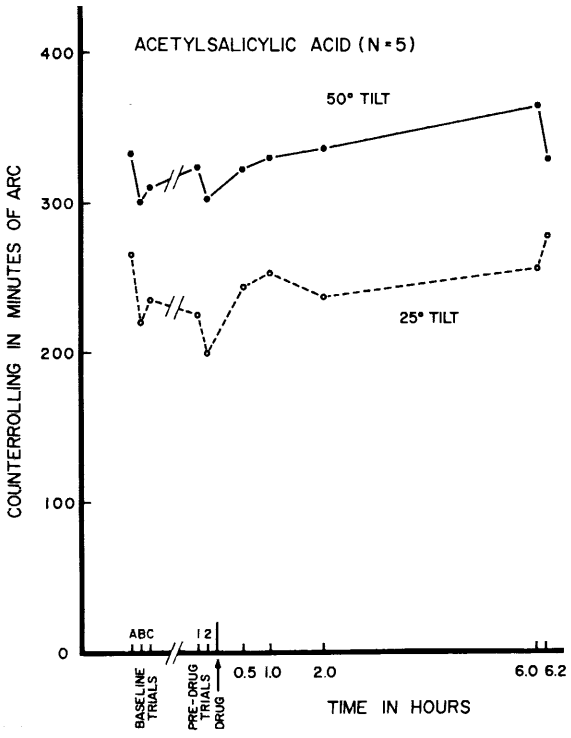

FIGURE 8.—*Effect of acetylsalicylic acid upon the ocular counterrolling response of five of the subjects.*

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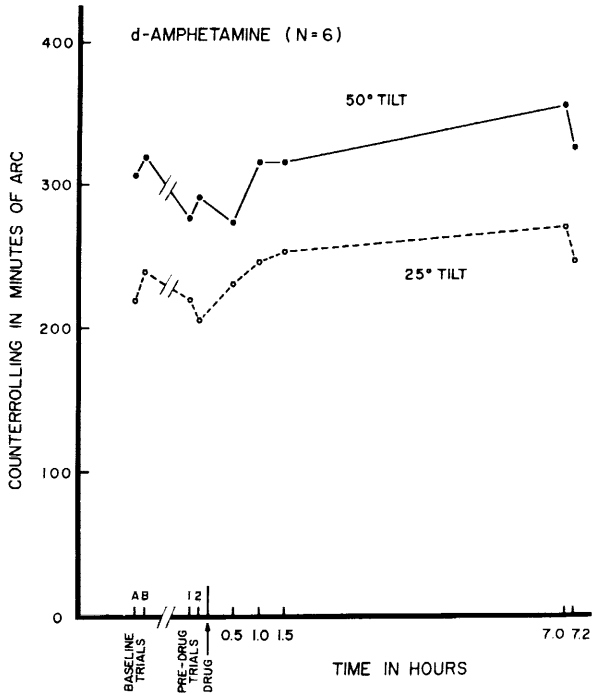

FIGURE 9.—*Effect of* d-*amphetamine upon the ocular counterrolling response of six of the subjects.*

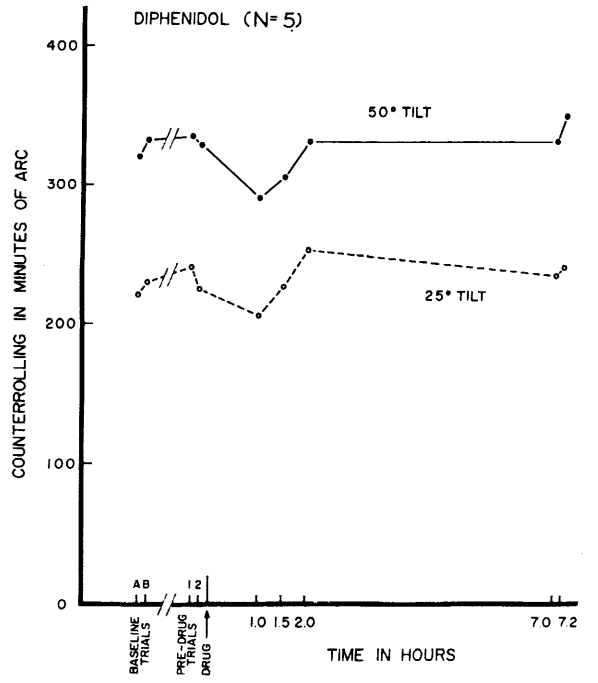

FIGURE 10.—*Effect of diphenidol upon the ocular counterrolling response of five of the subjects.*

that found in the predrug test made on the same day, (2) the response had to correlate in some fashion with the known temporal aspects of drug effectivity, and (3) the responses for the 25° and 50° body tilts had to be essentially in parallel.

Physiological variability of counterrolling as of other biological system responses occurs at random, under a given set of conditions, and within certain limits. This fact and the fact that the three requirements set forth above were not met are illustrated by the experimental trials in which a placebo was substituted for a drug (fig. 2). Among the five placebo-test sessions distributed similarly in time to the test schedules of the various drugs, the amount of counterrolling tended to rise and fall several minutes of arc at random. The average deviation of the response for 25° and 50° body tilt equaled 18 and 9 minutes of arc, respectively. No longitudinal trend with regard to change in counterrolling or correspondence between the 25° and 50° body tilt values was apparent.

Similarly, for several of the drugs used, namely, scopolamine, chlordiazepoxide hydrochloride, meprobamate, meclizine, and acetylsalicylic acid, no clear-cut effect upon the average counterrolling response was found. Further study is required to determine why meclizine, although structurally related to Cinnarazine, had no depressant effect upon the otoliths, as has been reported for the latter drug (refs. 1 and 4). It would seem that these particular drugs in this study were not specific for the otolitho-ocular system, and the well-recognized beneficial effects against motion sickness provided by scopolamine and meclizine cannot be attributed to any direct action upon the otolithic receptor organs or nervous pathways leading ultimately to the extraocular muscles. Furthermore, Jongkees and Philipszoon have reported that scopolamine had no effect on otolithic type compensatory eye movements of rabbits (ref. 1).

On the other hand, counterrolling was influenced by each of the other drugs used. The response curves obtained in conjunction with the administration of *d*-amphetamine suggested, if anything, a slight enhancement of the counterrolling reflex. In the case of the antihistamine-type drug diphenidol, a definite decrease in

counterrolling was measured within the 90-minute period after the drug was taken. Beyond this initial period the magnitude of the response at 50° tilt returned to, and at 25° tilt was slightly higher than, the baseline values. The final measurements were essentially the same as those of the predrug trials. Among all drugs tested in this study, the greatest change in counterrolling was found with alcohol. It can be seen from figure 3 that a progressive and rather rapid fall in counterrolling was measured in all subjects at both angles of tilt after their ingestion of alcohol. The lowest level was reached at about 90 minutes into the intoxication period. This rather rapid reduction in the magnitude of counterrolling was followed by a slower return to base level and perhaps slightly above it after about 6 hours. It is interesting to note that this sequence is not unlike the characteristic temporal changes in blood alcohol concentrations (ref. 17) as well as the concomitant manifestation of positional alcohol nystagmus (PAN, phase 1) (ref. 17) and ataxia (ref. 18), although no direct comparisons with these factors can be made since they were not tested concurrently.

Alcohol, by some unknown mechanism, acts to release positional nystagmus, and from the evidence of this study also suppresses otolith organ activity. Whether or not these findings are physiologically related must await further investigation. From the substantial evidence that otolith organs play a predominant role in PAN (refs. 17 and 19), the possibility exists that a change in the modulating influence of the otolith organs may be involved.

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DISCUSSION

BERGSTEDT: Some years ago when I made positional alcohol studies, I was searching for evidence that the otolith organs in one way or the other would be involved in this phenomenon, and I checked the counterrolling effect after giving alcohol. I followed the subjects both during the intoxication period and during the hangover period in comparison with the same schedule for the positional nystagmus. I also found a decrease in counterrolling during these first periods. However, I continued the study beyond the 6 hours in which Dr. Miller studied the effects and found a slight increase in the counterrolling effect, like a reverse action. It is not so pronounced as in the first period, but there is, however, as far as I could find out, an increase in the action. This could speak in favor of the fact that positional alcohol nystagmus is really triggered or released via the otolith organs. We know that alcohol influences eye movements in two ways, however. We can get a nonvestibular nystagmus, when you look aside from the normal eye position, beating in the direction you are gazing which exactly follows the blood alcohol curve. This appears when the alcohol level is about 0.06 percent. It depends a little on the individual as well as on fatigue, and so on. It disappears when the blood alcohol level decreases. Positional alcohol nystagmus is only related to the increase in blood alcohol level which gives first a faceup positional nystagmus followed by a period of decrease, with a lagtime of 5 hours.

MILLER: Of the four subjects used in this study, one subject did indicate that his counterrolling was rebounding, as it were, after 6 hours; but at this time we just cannot say anything more than that about this possibility.

YOUNG: I would like to ask either Dr. Miller or Dr. Bergstedt what is known about the motion-sickness effects following alcohol; that is, in that 1- to 2-hour period of decrease in counterrolling sensitivity, is there a decrease in motion sensitivity?

MILLER: I cannot answer that; perhaps someone else can.

BERGSTEDT: During centrifuge studies I attempted to get as high a blood alcohol level as possible to obtain a perfect positional nystagmus, but a level which would be under the one at which vomiting and motion sickness would be easily released, because as soon as vomiting or a nausea feeling appeared, positional alcohol nystagmus absolutely disappeared. My impression is that as soon as nausea is felt by the subject, a decrease in nystagmus intensity, both from the presumed otolith stimulation and from cupula stimulation, will be seen. I have not studied seasickness in humans, but my impression from the nausea-induced sickness in the centrifuge speaks in favor of the fact that the lack of nystagmus in seasickness studies can be partly dependent on the nausea effect. Nausea depresses nystagmus, as far as I can find out, but I have not made just exactly the study you asked for.

DOLOWITZ: Dr. Hiebert and I have done some work with antihistaminics measuring their effects on the semicircular canal. We also found a depression and then a raise in the activity of the cristo-ocular and cristospinal reflexes. It has occurred to me maybe we are missing something. Do you think there is a possibility we have a diurnal variation in our normals, and by hitting peaks and dips we are perhaps obtaining false effects?

MILLER: Possibly, yes. These physiological variations of substantial magnitude may mask a real effect. Because of this variability it has been necessary in this discussion where slight changes were involved only to suggest that the drug caused an increase in the counterrolling (or otolith) response. In order to deal appropriately with these and other findings, we must learn much more about normal variation in ocular counterrolling which might include, as you say, a diurnal pattern.

MONEY: I was interested in the results of alcohol in counterrolling because I have done some tests with alcohol in cats and found that after a large dose of alcohol, the durations of postrotatory nystagmus, using a simple angular impulse test, are increased by about 50 percent. So apparently there are very different actions of alcohol on otolith function and canal function.

BENSON: We have been working on the effect of hyoscine on postrotational nystagmus. It is very clear when people have had hyoscine for the normal postrotational nystagmic response to be very much suppressed; yet, the nystagmus returns when the subject is aroused by mental arithmetic. To what extent did arousal effects alter counterrolling responses in your study, and did you make any control of the behavioral states of your subjects?

MILLER: We did not take any special account of this since we were interested in a relative change in counterrolling. We assumed individuals were just about as alert each time they were tested. They were taken out of the device after each counterrolling test, rested, and were put back essentially in the same way to be retested by the same procedure. It is possible that the individual may have been a little more anxious at the start than at the end of the test, but this was not apparent. Certainly, state of arousal is one of the things that we must explore in determining why we have these fairly large physiological variations which are well beyond our measuring error of only a few minutes of arc.

BENSON: Does heightening the level of arousal increase it?

MILLER: We have not investigated this systematically as yet.

JONGKEES: Did you try the antihistaminic drug, Cinnarazine? I am afraid, however, that you cannot get it here.

MILLER: That is correct.

JONGKEES: But have you not tried sleeping drugs?

We tried barbiturates and found that they have some effect on the otolithic reactions, though you have to put the patient nearly to sleep.

MILLER: We want to extend our studies to include these and other drugs which have not been investigated using counterrolling. Dr. Graybiel now is trying to obtain Cinnarazine which you found so effective in reducing, actually abolishing, the nystagmic response to parallel swing accelerations. We are very interested in this drug and anxious to try its effect on counterrolling.

ROBERTS: One complication occurs to me which might be possible to solve with your apparatus. When a person is tilted, there will be changes in the eye position, first of all presumably resulting from the canals and then later from the otolith organs. Do you have any time courses of the rotatory movements of the eyes, and do these drugs perhaps act on the earlier stages of the response more than they do on the final deviation?

MILLER: The standard counterrolling test which we use does not take into account the earlier dynamic phases of counterrolling. We tilt the man very slowly up to position and maintain this position for 30 seconds to 1 minute before we even begin to make the first eye record. It would be interesting, of course, to explore these dynamic responses to see if they are affected, whereas the static are not.

Tests of Semicircular Canals and Otoliths in Cats

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Defence Research Medical Laboratories

A film was shown to illustrate the fast tilt test of the semicircular canals and the slow tilt and the dropping platform tests of the otoliths in cats (ref. 1). Normal cats, labyrinthectomized cats, and cats with the semicircular canals discretely plugged were tested while blindfolded (a total of more than 70 cats). Normal cats retain the upright posture after fast or slow angular displacements, and they extend the limbs with toes spread on the falling platform. Labyrinthectomized cats fall after fast or slow angular displacements and they do not extend the limbs or spread the toes on the falling platform. Cats with the semicircular canals plugged fall after fast angular displacements but not after slow angular displacements, and they exhibit the normal response on the falling platform.

It was concluded that the semicircular canals contribute to bodily equilibrium by initiating corrections for fast angular displacements from the normal orientation. The otoliths initiate corrections for slow angular displacements about horizontal axes and initiate the responses to dropping.

To hold the cat's head for the counterrotating room test, or for standard angular impulse tests, the Chicago technique of clamping a wire passed through holes in the canine teeth is supplemented with a stainless-steel post which is continuous with a stainless-steel plate. The plate is implanted in the skull with four stainless-steel screws, 3 months before immobilization of the head is required (fig. 1).

Otolith function can be studied, without interference from the vestibular receptors of angular accelerations, in cats with all the semicircular canals plugged. Histological confirmation of the successful elimination of single semicircular canals, without damage to other canals or the otoliths, was obtained (figs. 2–6).

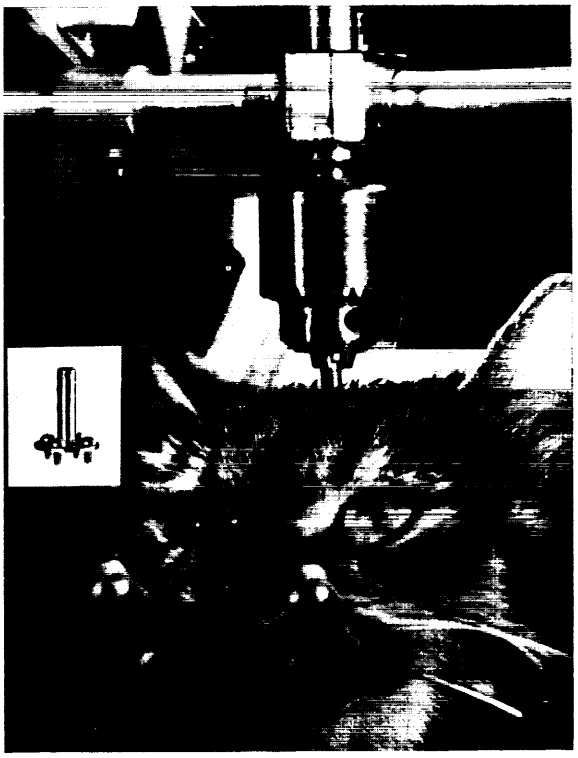

FIGURE 1.—*Technique for immobilizing the head of cat.*

REFERENCE

1. MONEY, K. E.; AND SCOTT, J. W.: Functions of Separate Sensory Receptors of Nonauditory Labyrinth of the Cat. Am. J. Physiol., vol. 202, 1962, pp. 1211–1220.

FIGURE 2.—*A plugged anterior (superior) semicircular canal is shown in cross section. The canal is completely blocked. Cat 219, right ear, 46×.*

FIGURE 3.—*The ampulla of a plugged horizontal semicircular canal. Part of the plug of bone chips is visible in the duct of the canal at the place where the plane of the section leaves the plane of the duct. The ampulla has normal appearance. Cat 219, right ear, 42×.*

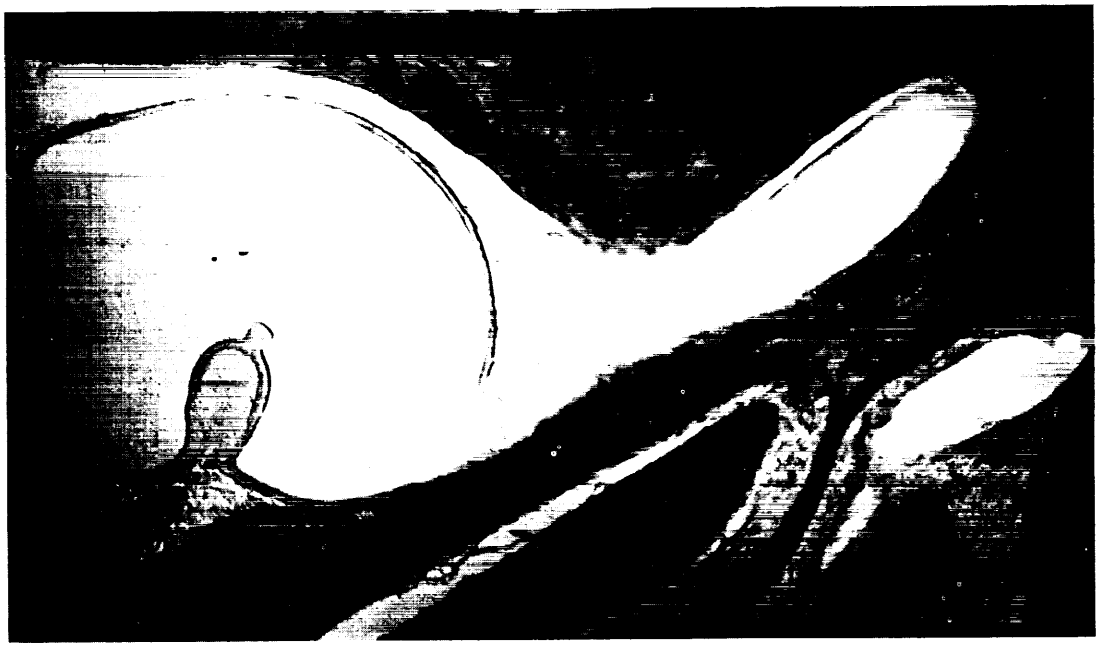

FIGURE 4.—*The ampulla of another plugged horizontal canal. The plug is not in the plane of the section. The plugging of a canal, in cats, not only leaves the other canals and the otoliths functional, it even leaves normal, morphologically, the ampulla of the canal which is plugged. Cat 234, right ear, 42×.*

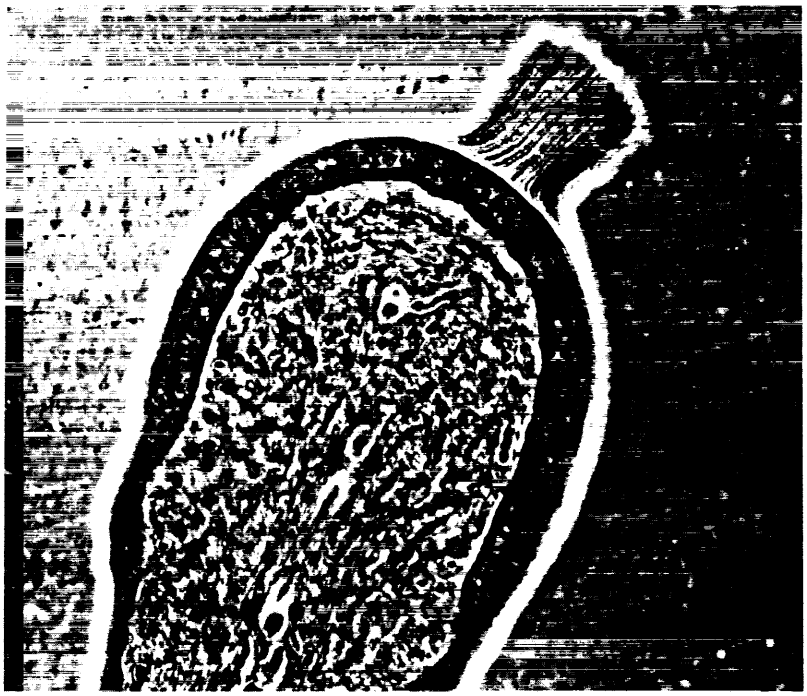

FIGURE 5.—*The crista of the ampulla shown in figure 3. The crista has the same appearance as those of the normal unoperated cats in the series. Phase-contrast photograph of stained section. Cat 234, right ear, 216×.*

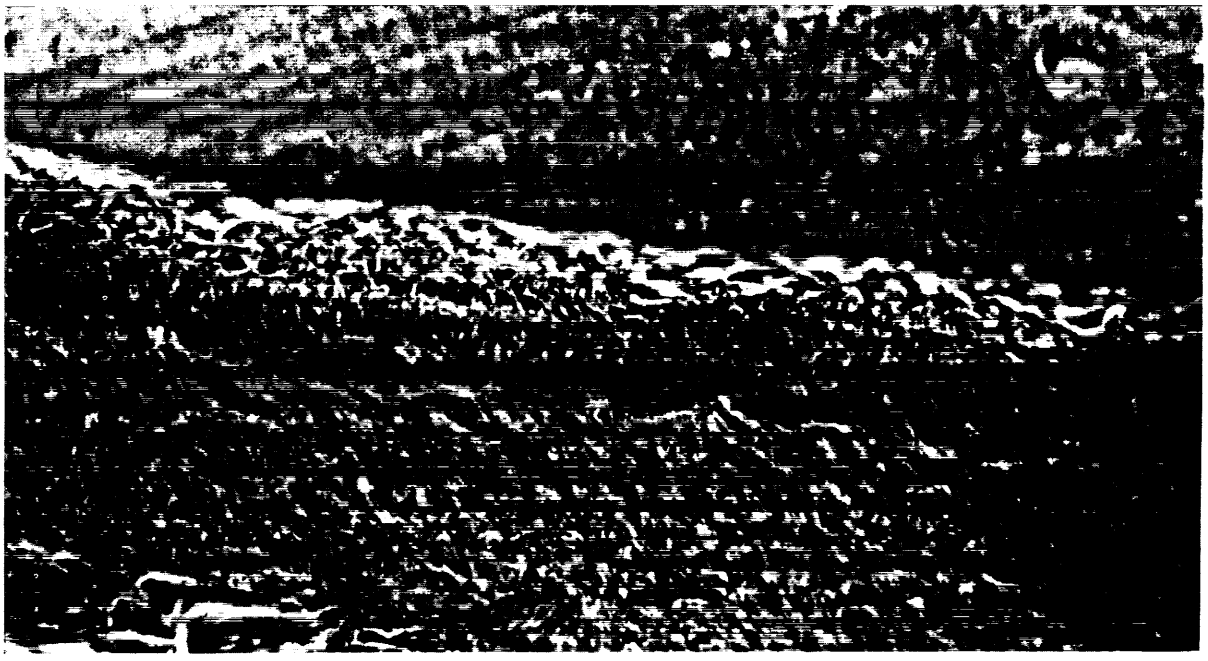

FIGURE 6.—*The utricular otolith of the same ear as shown in figure 3. The otolithic macula and membrane are morphologically normal. Phase-contrast photograph of stained section. Cat 234, right ear, 297×.*

Some Physiologic Responses to Vestibular Stimulation[1]

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SUMMARY

Although it has been well established that strong stimulation of the organ of balance can readily result in incapacitating motion sickness and disorientation effects, much remains to be understood of the probable widespread physiologic effects which are evidenced in part at least by the symptoms of pallor, perspiration, and nausea.

In an attempt to clarify our understanding of some of these effects, human and animal experimentation was carried out in regard to: (*a*) cardiovascular effects, (*b*) autonomic reactivity changes, and (*c*) intracranial blood flow changes.

The results indicate that vestibular stimulation sufficient to cause nausea just short of emesis results in decreased peripheral blood flow and greatly increased skeletal muscle vascularity to such a degree as to be similar to vasovagal syncope in its effects. Further evidence of such incapacity was obtained by measurement of intracranial vascularity changes, probably mediated by autonomic nervous system activity.

INTRODUCTION

Most research in vestibular physiology has been concerned with the processes governing the maintenance of spatial orientation under normal or unusual environmental conditions. Furthermore, it has been well established by several authors (e.g., refs. 1 to 3) that appropriate disturbances of vestibular activity can readily cause incapacitating motion sickness as well as disorientation effects. Such incapacity is certainly of great significance in aerospace travel (ref. 4), and much remains to be understood as to the widespread physiologic basis of the disturbances which are evidenced by such external objective signs as pallor, perspiration, yawning, vomiting, etc. It is the object of this presentation to describe some of the preliminary research that we have been concerned with in our attempts to understand pertinent physiologic effects.

CARDIOVASCULAR EFFECTS

Our interest here was motivated by the observation of skin pallor as a consistent sign or symptom of motion sickness. It should be pointed out that, from our experience, certain other signs characteristic of vasovagal syncope (antidiuresis, nausea, and sweating) are also seen in motion sickness after vestibular stimulation, whereas still others (bradycardia and fall in blood pressure) appear to be absent or at least inconsistent. In our experiments, it was decided to investigate the etiology of the cardiovascular response which results in skin pallor,

[1] This study was carried out in association with the Defence Research Medical Laboratories, Toronto, and the Institute of Aviation Medicine, RCAF.

and for this purpose the flow of blood in the forearm was monitored. This procedure was chosen because of its technical feasibility under the experimental conditions available, with the hope that the results might be applicable to interpretation of general systemic changes.

Forty-six healthy young men between the ages of 18 and 41 years served as subjects. Strong vestibular stimulation was induced by applying multiplanar angular accelerations with the device illustrated in figure 1.

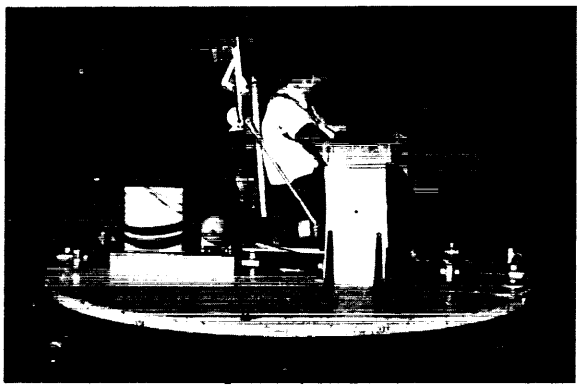

FIGURE 1.—*Turntable, showing the plethysmograph and arrangement for moving the head.*

The subjects, placed centrally on the turntable to minimize centrifugal acceleration, were rotated in the normal sitting position and with concomitant nodding head movements. Attached to the back of the seat was a motor-driven head holder designed to maintain the subject's head in a predetermined position relative to the turntable and to move it in the sagittal plane in a controlled manner. From its original position the head was moved forward and downward through an angle of approximately 45° in 6 seconds, held in this position for 6 seconds, returned to the original position during an additional 6 seconds, and allowed to remain at rest for 6 seconds before the cycle was repeated. When the turntable is in motion, such a cyclic angular displacement of the head, in the plane at right angles to that of the rotation of the turntable itself, is a very violent vestibular stimulus, causing vertigo. Nausea (motion sickness) rapidly ensues in all but the most resistant subjects.

The turntable was fitted with electrical slip-rings to allow the output of instruments on the turntable to be recorded on stationary apparatus; similarly, apparatus on the turntable could be controlled externally. Blood flow in the forearm was measured by a venous occlusion plethysmograph that was unaffected by accelerations of the turntable. An arterial occlusion cuff was placed around the wrist and the venous occlusion cuff around the arm above the elbow. Changes in the circumference of the forearm were sensed by a modified Whitney's mercury-in-rubber strain gage, consisting of a double length of soft-rubber tubing that contained a very small continuous core of mercury which formed one arm of a Wheatstone bridge. Changes in the circumference of the arm following venous occlusion changed the length of the core of mercury, altered its electrical resistance, and caused an imbalance in the bridge; the resulting electrical output of the circuit was amplified and recorded by a Sanborn recorder. The rate of swelling of the arm was represented by the slope of the record, which was taken as an index of blood flow. The sensitivity of the recorder was adjusted so that the 15° slope at a paper speed of 15 cm/min represented approximately 1 ml of blood flow per 100 ml of forearm volume. In preliminary experiments values obtained with this method were checked against values obtained by the methods of Barcroft and Edholm (ref. 5) and found to be quite comparable. Within the range of results reported here (15° to 17°), the blood flow was proportional to the slope; i.e., a slope of 30° represented a blood flow of approximately 2 ml/min per 100 ml of forearm volume. Blood-flow readings were obtained every 15 seconds; the venous occlusion cuff was inflated to 70 mm Hg, then allowed to deflate, and then the cycle was repeated automatically. The arterial occlusion cuff at the wrists was inflated continuously to a pressure of 250 mm Hg during each period in which a series of blood-flow determinations was made. Figure 2 (top) depicts the arrangement of the apparatus used and (below) a set of measurements thus obtained.

In a few experiments the blood pressure was measured by arterial puncture and recorded continuously; in others it was estimated with a sphygmomanometer and by auscultation before and after rotation. The heart rate was recorded by an electrocardiogram or cardiotachometer.

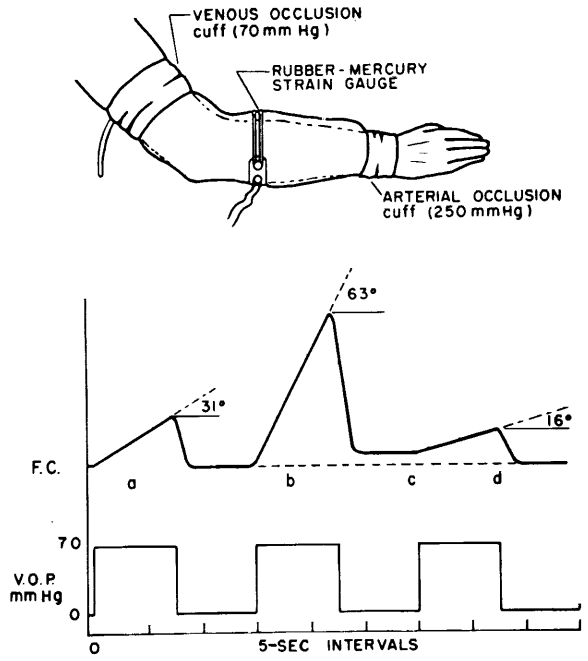

FIGURE 2.—*Measurement of forearm blood flow. Upper: Apparatus in place. Lower: Results obtained by procedure.* F.C. = *Forearm circumference.* V.O.P. = *Venous occlusion pressure.* a: *Prestimulus.* b: *Response in a subject sensitive to vestibular stimulation.* c: *Failure of forearm circumference of sensitive subject to return to baseline when venous occlusion pressure released.* d: *Poststimulus response.*

At the start of an experiment the procedure was explained to the subject, and he was secured in the seat with safety belts. A strap was placed around his forehead to secure the head in its holder, and he was instructed to allow his head to move passively with its holder, but not to attempt any active movement. When all the instruments had been attached and adjusted, the subject was blindfolded, and the room darkened. To minimize vestibular stimulation, the turntable was accelerated as slowly as the controls would allow, but the subject usually had a gentle sensation of rotation while the speed of rotation was increasing. The sensation ceased shortly after the maximum (constant) speed of 30 rpm was obtained, and at this stage measurement of blood flow was begun. In the control tests (those without superimposed head movement) rotation and measurement of blood flow both were continued for 5 minutes. Some of the subjects reported disorientation and nausea during the control experiment. In the experimental tests the superimposed movements of the head were begun as soon as stable blood flow was established. The subject was requested to signal verbally when he became nauseated to the point that he believed further stimulation (head movement: vertigo) would cause him to vomit. On this signal, head movement was stopped, but, whenever possible, rotation of the turntable at 30 rpm was continued until a total of 5 minutes at this speed had elapsed. In all experiments, deceleration was carried out as slowly as the controls permitted, again with the purpose of minimizing vestibular stimulation.

In figure 3 are shown the forearm blood-flow index, forearm circumference, and heart-rate responses of a motion-sickness-susceptible subject and of a nonsusceptible subject before, during, and after 2 and 5 minutes, respectively, of vestibular stimulation. In the subject with a low tolerance to vestibular stimuli (nausea to limit of tolerance after 2 minutes of head movement), there was an immediate twofold to threefold increase in forearm blood flow. As the head movement continued, there was also an increase in the circumference of the arm between the periods of venous occlusion (interim arm circumference), and this was taken to indicate an increase in blood volume. The heart rate increased sharply, but immediately returned to normal levels even though the forearm blood flow and interim arm circumference remained above normal. There was a slight drop in arterial blood pressure (125/75 to 110/65 mm Hg). In the subject with a high tolerance to vestibular stimulation (not nauseated after 5 minutes of head movement), there were no important increases in the forearm blood flow, interim arm circumference, or heart rate. There was a slight increase in blood pressure (110/50 to 120/55 mm Hg). Two other subjects, in whom blood pressure was recorded continuously through a needle inserted into the brachial artery, showed no significant changes in blood pressure or heart rate, although both subjects were unequivocally nauseated.

In figure 4 are illustrated the blood-flow indexes on four subjects who tolerated head movements during rotation for 3½, 3, 5, and 5 minutes,

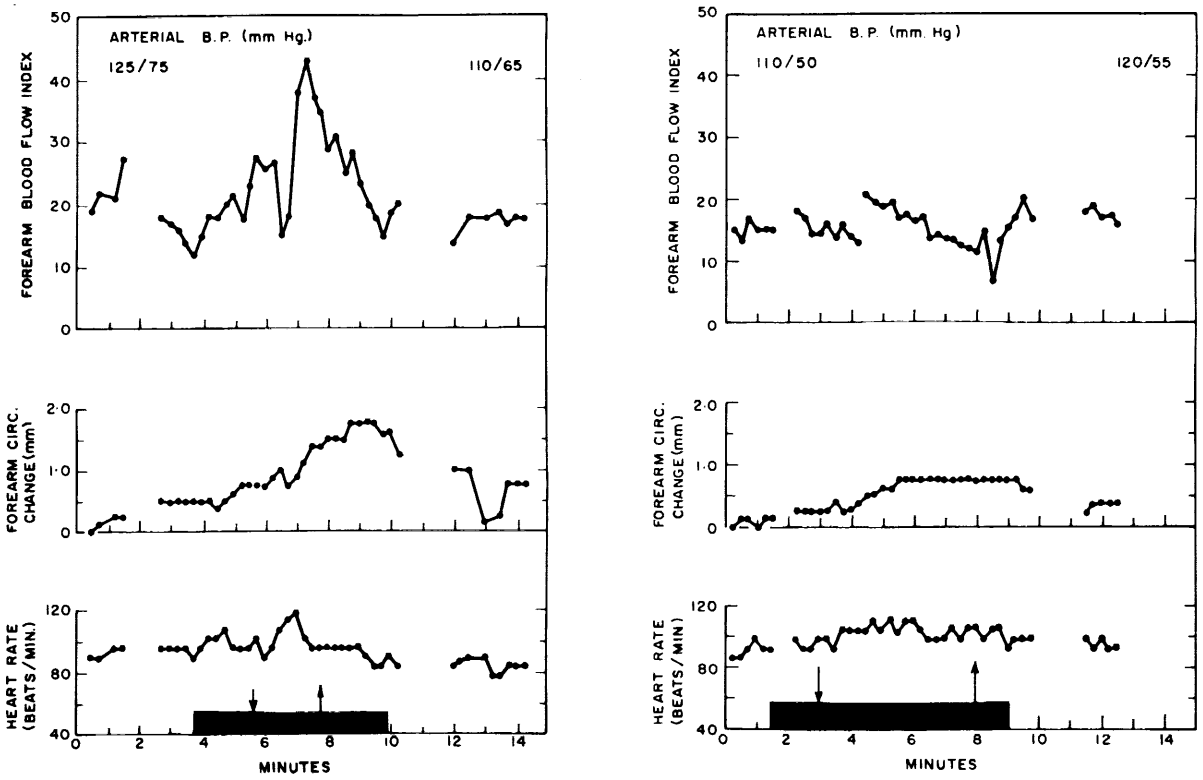

FIGURE 3.—*Forearm blood flow, forearm circumference, heart rate, and blood pressure during vestibular stimulation.* ■, *turntable in motion (30 rpm);* ↓, *start of head movement;* ↑, *end of head movement. Left: Susceptible subject—motion sick after 2 min of vestibular stimulation. Right: Nonsusceptible subject—no motion sickness after 5 min of vestibular stimulation.*

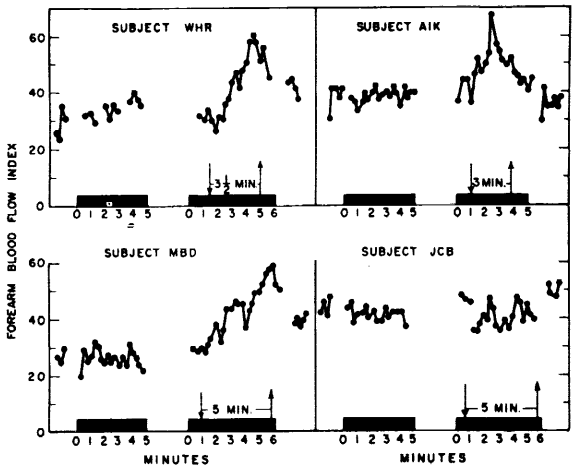

FIGURE 4.—*Forearm blood flow in subjects representative of the series (see text).* ■, *turntable rotating at 30 rpm;* ↓, *start, and* ↑, *stop of head movements.*

respectively. These responses are representative of those observed in the entire series. During the 5-minute control period at 30 rpm without head movement, no appreciable increase in forearm blood flow was recorded in any subject, nor were there any complaints of disorientation or nausea. Subjects WHR and AIK, who were nauseated to a limit of tolerance after 3½ and 3 minutes, respectively, of superimposed head movement, showed marked increase in forearm blood flow. Subjects MBD and JCB denied having any sensation of nausea after 5 minutes of superimposed head movement. In subject MBD the forearm blood flow increased gradually throughout the period of superimposed head movement. Although this subject admitted to no symptoms of nausea, sweating of his forehead was observed. In subject JCB the forearm blood flow remained constant within the limits of the method, and he exhibited no signs of motion sickness.

In table 1 the frequencies of increase in forearm blood flow and interim arm circumference

TABLE 1.—*Frequency of Increase in Forearm Blood Flow and Circumference as Related to Duration of Head Movement by 46 Subjects While Rotating at 30 rpm*

Duration [a] of superimposed head movement, min:sec	Number of subjects	Increase in forearm blood flow			Increase in forearm circumference		
		Definite	Questionable	No change	Definite	Questionable	No change
0:00–0:59	4	4	0	0	4	0	0
1:00–1:59	7	7	0	0	5	1	1
2:00–2:59	13	11	2	0	10	2	1
3:00–3:59	6	5	1	0	4	1	1
4:00–4:59	2	0	2	0	1	1	0
5 min +	14	4	2	8	4	3	7

[a] The superimposed head movements were discontinued when the subject became nauseated to the degree that emesis was imminent, or after a maximum of 5 minutes.

are tabulated in relation to duration of head movement necessary to cause nausea of such a degree that emesis was imminent. The effects upon blood flow and arm circumference were graded as "definite" or "no change"; all other responses were graded "questionable." It is interesting to note that all subjects with less than 3 minutes' tolerance showed some degree of increased blood flow, that is, showed "no change" responses, whereas of the 14 subjects whose tolerance was 5 minutes or more, 8 showed "no change" in blood flow. A similar correlation can be seen between tolerance and increase in "interim arm circumference" of the forearm.

The sensations described by the subjects exposed to a potent vestibular stimulus varied from a mild vertigo to severe vertiginous disorientation and nausea, occasionally threatening emesis. Although there were some exceptions, the magnitude of the changes in the forearm blood flow correlated with the severity of the symptoms. By observing the blood-flow recordings it was often possible to predict when the subject would signal that he would vomit if the stimulation was not discontinued. Incidences in which the blood flow was not increased in proportion to subject's degree of nausea were the exceptions, and are difficult to explain. Blood-flow measurements in these subjects may have been in error, but it is more probable that some subjects either exaggerated or minimized their symptoms.

It is difficult to quantify with absolute confidence the changes in the blood flow and in arm circumference shown by the Whitney strain gage plethysmograph, and for this reason we have sought other means of verifying these results and of excluding artifacts. Simultaneous measurements in both forearms and one calf have shown increases of blood flow during vestibular stimulation of subjects susceptible to motion sickness. This indicates that effects are not confined to one limb. Similarly, when three strain gages were used on one forearm (one at the wrist, one at the point of maximum circumference, and one midway between these two), vestibular stimulation in subjects susceptible to motion sickness caused an increase in the circumference of the forearm at all three sites. However, deliberately clenching the fist to cause a shifting of the muscle mass of the forearm, and to simulate changes in muscle tension that might reasonably be expected to result from vestibular postural reflexes, invariably resulted in the recording of a decrease in circumference of one or two of the strain gages. It may, therefore, be assumed that changes of the blood flow occurred in all extremities, probably involving most of the skeletal muscles; moreover, the changes in the limb volume (or circumference) were not due to artifact of shifting muscle mass caused by changes in muscle tension.

The results reported here do not establish the mechanism of the increase in blood flow or

limb blood volume. It appears unlikely that increase in epinephrine output is significant because there was no consistent change in heart rate or blood pressure. In a few cases in which increased heart rate was evident, the increase was transient, and the rate returned to normal while the blood flow remained elevated. It is unlikely that our observations can be attributed to the effects of hyperventilation (ref. 6); e.g., hypocapnea. Although an increased respiratory minute volume has been observed during subsequent experiments in this laboratory to be a regular concomitant of vestibular stimulation, the increase in peripheral blood flow in a respiratory minute volume occurs simultaneously and often within seconds of the start of vestibular stimulation. From this evidence we conclude that, although the two phenomena may have a common source, the increased peripheral blood flow is not caused by hypocapnea because the former occurs before the increased respiratory minute volume can result in hypocapnea.

The association of the symptoms of motion sickness with vestibular stimulation induced on the turntable or by other procedures has been described (refs. 7 to 9). A marked antidiuretic response due to motion sickness has been demonstrated by Taylor et al. (ref. 7). The antidiuretic response to vasovagal syncope is well known (refs. 10 and 11). Barcroft and Edholm (ref. 5) have shown that there is a marked increase in forearm blood flow and a concomitant vasoconstriction of the hand during fainting as a result of hemorrhage. They concluded that the increased flow in the forearm occurred in the muscle. Intravenous injection of Pitressin into the human subject caused an increased vasodilatation and skin vasoconstriction with no consistent change in arterial blood pressure. Collectively, these findings indicate a close similarity between the signs and symptoms of the vasovagal syndrome and also of vestibular stimulation and motion sickness. The results of the present study offer further evidence of this correlation.

In general terms, an increase in blood flow through one part of the body must be compensated either by decreased flow elsewhere or by an increase in cardiac output, or reduced arterial blood pressure will result. The human forearm is 85 percent muscle by volume, and the skeletal muscle represents about 50 percent of the total body mass. By calculation, blood flow through the muscle would represent about 15 to 16 percent of the cardiac output. If one can assume that blood flows in the forearm and calf are representative of the total body skeletal body muscle blood flow, then a slight increase in these flows must be compensated by a prompt substantial cardiovascular adjustment if normal blood pressure is to be maintained. The evidence from our study is that the increase in blood flow is more than slight. Since there was little or no apparent change in blood pressure or heart rate concomitant with increased flows, in order to maintain this blood pressure one or both of the following adjustments must have occurred:

(*a*) An immediate increase in the cardiac output by increase in stroke volume (because heart rate did not change significantly); or

(*b*) An increased vasoconstriction in other regions of the body.

The latter is certainly evident by the marked pallor observed in sick subjects. Skin blood flow is between 2 and 13 ml/100 ml tissue/minute, the figure chosen depending on which of the various reported values is accepted. Skin being about 5 percent of the total body mass, the total skin blood flow would be calculated to be 30 to 50 percent of the total muscle blood flow under resting conditions. The total cessation of skin blood flow should, therefore, compensate for only a small part of the twofold to threefold increase seen in our experiments.

These results may have a bearing on aerospace flight during turning manuevers that cause vestibular stimulation and increased g. In some individuals under certain conditions, failure of one or more of the compensatory mechanisms can result in a fall of the peripheral resistance below an already critical level. As a result, there would be a decrease in arterial blood pressure, and, among other effects, a decrease in g-tolerance, and possibly a loss of consciousness due to cerebral anemia. It is suggested that this is another physiological stress that may lead to flying accidents and that it also applies to accelerations likely to be encountered during space flight.

AUTONOMIC REACTIVITY EXPERIMENTS

The purpose of this study was to compare certain cardiovascular changes which occur after experimental vestibular stimulation with those following exercise and during carotid sinus and eyeball pressure. A comparison was then made between those susceptible to laboratory-induced motion sickness and those not affected.

Fifty-nine aircrewmen in training, between 17 and 27 years of age, were tested by turntable rotation (sitting position) with concomitant nodding head movements—a well-established laboratory method for inducing motion sickness (ref. 9). Perspiration was the most consistent untoward sign, being present in all 34 members of the motion-sick group. Thirty-two members of this group experienced pallor, 31 nausea, and 2 vomiting. Of the 59 subjects, 41 were able to withstand the full 5 minutes of rotation; 16 of these showed some sign of sickness during this period. Eighteen subjects could only tolerate shorter periods of rotation (from 4½ minutes to 1 minute (in a single case)), and all experienced some degree of motion sickness. Two members of the group vomited, one after 4½ minutes and the other after 3½ minutes of turntable rotation.

Although there were some differences between the motion-sick susceptible and nonsusceptible individuals in mean heart rate and other electrocardiographic findings, the results cannot really be considered as significant, especially when one realizes that some anxiety is always involved. When the heart rate changes before and after exercise (Master double two-step test) were compared in the two groups, no great differences were seen. The same conclusions apply to the greater decrease seen in mean heart rate of the susceptible subjects after carotid sinus pressure. However, a higher-than-normal rate was found in the laboratory in these subjects; cause of this was attributed to anxiety.

Another test of autonomic reactivity was carried out, using as an index the value of mean eyeball pressure withstood by the subjects until the pain became unbearable (value measured by means of a tonometer). The mean eyeball pressure withstood by the motion-sick group reached only 207 mm Hg, with a mean duration of 9.6 seconds, compared to 222 mm Hg for 10.4 seconds in the more resistant group.

Another finding of significance concerns pulse-pressure change when the two groups before and after strong vestibular stimulation are compared. Although the motion-sick subjects did show signs of anxiety, the fact remains that they showed a decrease in pulse pressure of 20 mm Hg from the resting level as compared to an increase of 6 mm Hg in the nonsick individuals.

With exercise the pulse pressure and heart rate were more elevated in the motion-sick group. This suggests that the cardiac output and perhaps efficiency of the heart may have been decreased in the motion-sick group during vestibular stimulation on the turntable.

The cardiovascular reaction pattern established in the motion-sick as compared to the nonsick group indicates some increased autonomic reactivity in individuals susceptible to motion sickness. However, no definite conclusion concerning the role of these autonomic cardiovascular responses in the etiology or pathogenesis of motion sickness can be made, and further research along this line is indicated.

INTRACRANIAL BLOOD FLOW EXPERIMENTS

As indicated in the first part of this report, in some individuals under certain conditions, failure of one or more of the compensatory mechanisms could result in a fall in the peripheral resistance to below an already critical level. As a result, there could be a decrease in arterial blood pressure and, among other things, a decrease in g-tolerance and possibly a loss of consciousness due to cerebral anemia.

In order to obtain more direct evidence of such a possibility, some experiments were carried out to determine whether intracranial blood flow would change after vestibular stimulation. Due to the risks involved, experimental animals were used instead of human subjects.

The procedure consisted of the intravenous injection of some of the animal's own serum, the albumin of which had been made radioactive with I^{131}. An appropriate radiation counter with a focusing collimator was directed toward

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the animal's head at such a position as to give a scan of the brain. Counts of gamma rays per 15-second intervals were then recorded by a digital "readout." Analog displays of these counts plotted against time were used to indicate changes in intracranial vascularity in that measurements were made before and immediately following vestibular stimulation (rotation of 30°/sec for 10 turns, followed by sudden stops which occurred within 0.5 second). The animals used were monkeys (Rhesus), dogs, rabbits, and rats.

The results indicated that brain vascularity can be quickly and markedly altered following vestibular stimulation. In the monkeys and dogs, the gamma radiation count per unit of time dropped promptly following stimulation, but this was immediately followed by a sudden increase in count to a value exceeding the prespin count, possibly indicative of a sudden physiologic change to offset this apparent drop in vascularity. In the rodents, however, the postrotatory effect was a prompt increase in brain vascularity. It is possibly significant to note that monkeys and dogs can be made motion sick while this is not so for rodents. In all cases the radiation count from the brain remained constant if no rotation occurred. Caloric stimulation produced the same effects as did rotation, while negative-g exposure (centrifugal force directed toward the head) caused increased brain vascularity as did the intravenous injection of a cerebral vasodilator drug; these findings all attest to the validity of the test procedure. It is realized, however, that these procedures do not measure intracranial blood flow, and a more direct procedure is required before a full understanding of this interesting physiologic relationship can be fully understood.

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A Revised Dynamic Otolith Model[1]

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SUMMARY

The application of control theory to analysis of vestibular function has yielded mathematical models of the semicircular canals and, more recently, the otoliths. A proposed dynamic otolith model is based on "input-output" experiments including dynamic counterrolling, subjective perception of velocity during sinusoidal linear oscillation, and threshold to constant acceleration. This model is consistent with electrophysiological data and includes a low-frequency lag term to permit a steady output to sustained tilt or acceleration.

INTRODUCTION

The dynamic otolith model proposed by Meiry in 1965 was based on observed relations between perceived direction of linear motion and horizontal acceleration (ref. 1). Although this model correctly predicted phase of perceived velocity for lateral oscillation and time to detect motion under constant acceleration, it failed to account for at least two observations:

(1) Behavioral and electrophysiological data indicate a sustained steady otolith output to sustained tilt angle (refs. 2–5). The model's perceived acceleration or tilt output decayed to zero with a time constant of 10 seconds.

(2) Dynamic counterrolling data agree with the model at higher frequencies. The experimental counterrolling at zero frequency, however, indicates a static component of otolith output with no phase lag referred to acceleration, whereas the model had no static output and approached 90° of lead at zero frequency (ref. 6).

REVISIONS

At the suggestion of Von Gierke, a static component was included in the otolith model. The revised linear model, which allows steady-state response to acceleration, is shown in figure 1.

This revised linear model will act approximately as a velocity transducer over the mid-frequency range ($0.19 < \omega < 1.5$ rad/sec). The transfer function from specific force to perceived tilt or lateral acceleration has a static sensitivity of 0.4.

The amplitude ratio and phase versus frequency for the revised model is shown in figure 2, along with Meiry's experimental phase data on the relation between perceived linear velocity and actual horizontal sinusoidal velocity. The fit to the experimental data is excellent, although it clearly indicates the need for additional experiments at frequencies below 0.2 rad/sec to verify the predicted drop in phase lead. (Because of the low frequencies and the requirement for maintaining accelerations clearly above threshold level, linear simulator tracks longer than those currently available would be required for exten-

[1] The original model was developed by J. L. Meiry under NASA Grant NsG–577. Present work was done under Air Force Contract AF33(615)–5038, Biosystems, Inc., Cambridge, with Aerospace Medical Research Laboratories, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, Ohio.

This paper has been identified by Aerospace Medical Research Laboratories as AMRL–TR–66–209.

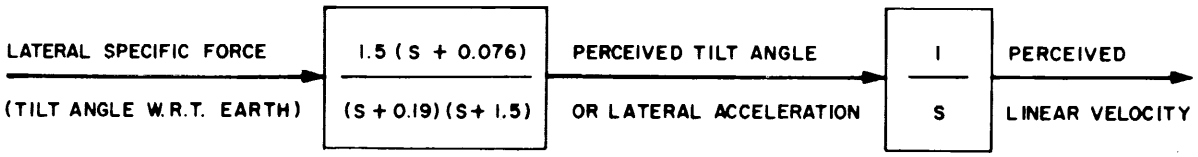

FIGURE 1.—*Revised otolith linear model.*

sion of the experimental data to much lower frequencies.)

The placement of the center-frequency position and "alpha" of the low-frequency lead-lag network is somewhat arbitrary for this data fit, and the lead-lag break frequencies can easily be changed to incorporate new low-frequency data.

Recent supporting evidence for this model was provided by Kellogg (personal communication), based on dynamic counterrolling experiments. The magnitude and phase lag of the torsional rotation of the eye was measured versus lateral head tilt for constant velocity rotation about a horizontal axis at various rates. Since the instantaneous component of g-force acting on the otoliths and stimulating the counterrolling is a sinusoid, the data may be compared directly with the otolith model frequency response. The counterrolling points shown on figure 2 were taken from Kellogg's curve fit data for two subjects, each rotated clockwise and counterclockwise at rates from 5 to 30 rpm. Notice the overall agreement of the counterrolling phase-lag data with the otolith model over the region tested. The amplitude ratio of the counterrolling data, related to the otolith model by an arbitrary counterrolling index, shows a decrease in the vicinity of the model break frequency at 1.5 rad/sec. Extension of the dynamic counterrolling data to the region 0.1 to 2.0 rpm would be exceedingly useful. The known zero phase lag for static counterrolling has already been mentioned as a reason for model revision.

The acceleration threshold in the revised model raised the problem of its physiological interpretation. On the one hand, the lead term in the

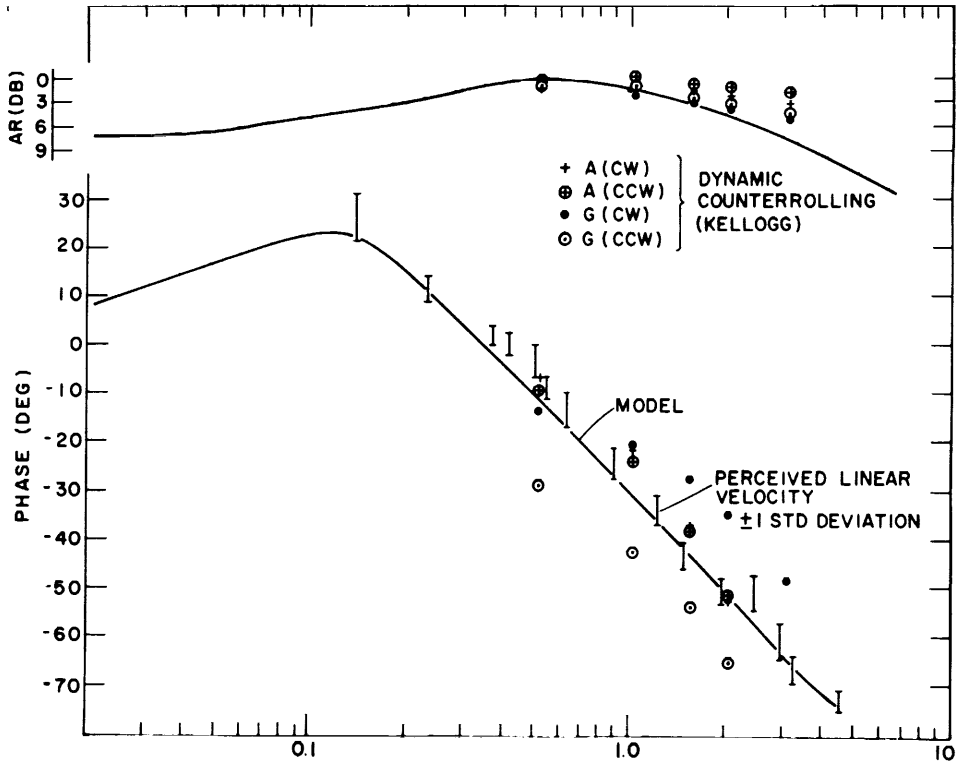

FIGURE 2.—*Perceived velocity frequency response.*

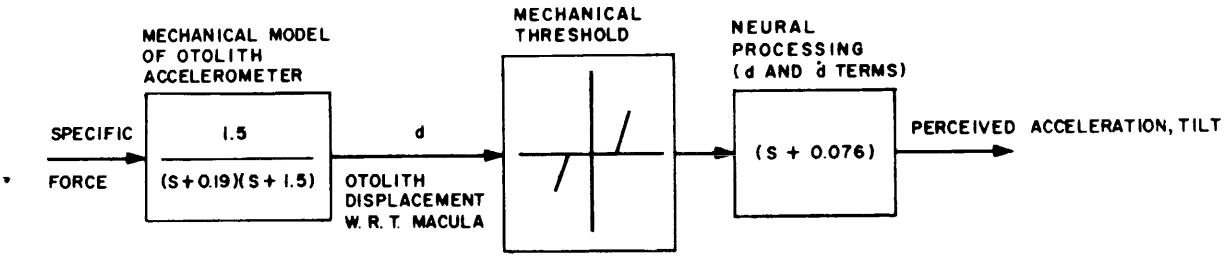

FIGURE 3.—*Revised nonlinear otolith model.*

transfer function could be attributed to a more complex mechanical model of the otolith, perhaps including the effect of a second mass-spring-dashpot combination representing movement of the macula with respect to the bony structure. Mayne has independently explored this avenue and suggested a possible mechanical otolith model which combines aspects of a conventional accelerometer and an integrating accelerometer (ref. 7). On the other hand, the lead term could be attributed to the neurological end, either in central processing of otolith displacement signals or through the presence of two types of hair cells in each macula, one responding to otolith displacement or hair bending, and the other responding to rate of change of otolith displacement or rate of change of hair bending. Similarly, the hair cells could produce the lead term if they were of the slowly adapting type postulated by several researchers.

Because of its compatibility with the time-to-threshold data, we favor the explanation of the lead term on the basis of neurological adaptation or processing of otolith displacement, rather than attributing it to the mechanical structure. The revised nonlinear otolith model is shown in figure 3. The threshold is here shown as based on a minimum deviation of the otolith with respect to the macula rather than a minimum output of the total model. The threshold level may be related to specific force, but not to otolith displacement at this time.

The ability of the nonlinear model to match data on latency time for perception of constant horizontal linear acceleration is shown in figure 4. The model assumed an absolute threshold of approximately 0.005 g, which placed the 0.01-g latency time at 5 seconds as per the data point. The remainder of the model prediction fits the data exceedingly well.

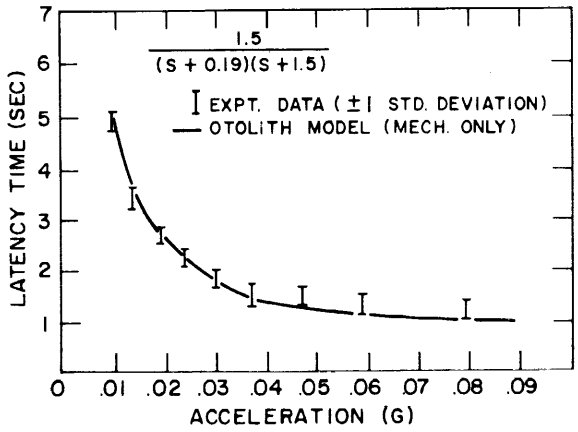

FIGURE 4.—*Time for perception of constant linear acceleration—model and experiment.*

An analog-computer simulation of the revised otolith linear model was performed using the setup of figure 5. In this simulation, potentiometers a and b independently determine the two denominator break frequencies. Potentiometers a and c determine the lead break frequency. The response to a unit step is given by the following equation, which yields a steady-state output of 0.4:

$$f(t) = 1.5[-0.457(1-e^{-0.19t}) + 0.724(1-e^{-1.5t})]g/g$$

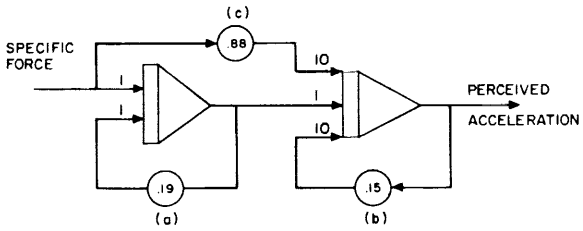

FIGURE 5.—*Analog-computer simulation of linear portion of otolith model.*

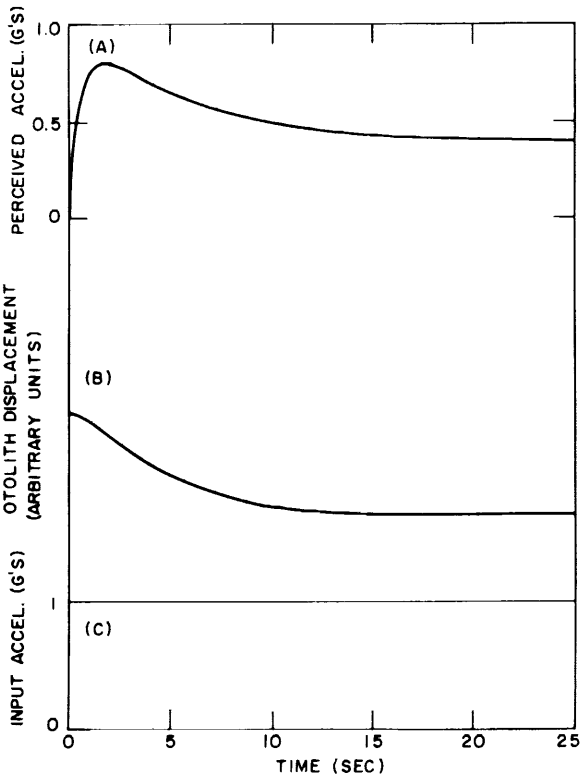

FIGURE 6.—*Step response of linear model:* (A) *Perceived acceleration or tilt;* (B) *otolith displacement; and* (C) *acceleration or tilt step input.*

The step response of this system is shown in figure 6 in which a simulated acceleration step, or step of angle with respect to the vertical, appears in the lowest trace. Trace *B*, otolith displacement, rises slowly to its steady-state value, dominated by the 5.3-second time constant. Model latency predictions are based on this curve. The upper trace is the model output, indicating perceived acceleration or angle of tilt as a function of time, and showing a rapid rise followed by slow decay to a positive steady-state value. It is interesting to note that this curve agrees, qualitatively at least, with the calculated slow-phase eye movement attributed to the otoliths for a steplike input acceleration.

CONCLUDING REMARKS

The adoption of Von Gierke's suggestion has resulted in a revised linear and nonlinear otolith model which successfully matches all of the experimental data on which the older model was built and provides correct zero-frequency sensitivity and phase as well. Furthermore, it is supported by recent data made available on the phase lag associated with counterrolling eye movements. This model is being incorporated in a physical simulation of the vestibular system currently being developed. Although many questions remain to be answered, the development of a comprehensive model for dynamic space orientation appears within grasp (ref. 8).

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DISCUSSION

VALENTINUZZI: First of all, I want to say that I like the model on which Drs. Young and Meiry are working very much. Dr. Fernández, Dr. Fox, and I are working on a labyrinth problem in which this model might be useful. We

are subjecting cats to two combined rotations: one about a vertical axis, another about a horizontal axis. The theoretical prediction was that we should obtain a nystagmic output responding to a sine or a cosine function. That is, the vertical nystagmus component should follow a cosine function because of the participation of the vertical canals, and the horizontal nystagmus component should follow a sine function due to the participation of the horizontal canals. The experiments have given something which fits this theoretical prediction, and something else; that is, the amplitude of nystagmus, supposing that we start the rotation at zero degree, follows either a sine or a cosine law, and there is a reversal of nystagmus direction, as predicted for each component. What have we found which was not expected? That frequency and amplitude of nystagmus change when the animal is upside down. Furthermore, we found a modulation of the baseline. Therefore, nystagmus becomes modified by three modulations: amplitude modulation, frequency modulation, and baseline modulation. We started to think of some interpretations. The first guess has been that the otoliths participate in this response in such a way that the shearing force follows a sine function, but that this shearing force is also combined with Coriolis force which is oscillating as well. We are working on the analysis of the recordings and also performing more experiments. We have to consider the otoliths as subjected to the variable gravity action composed with an oscillatory Coriolis force, according to the canal or the nystagmus component we take into account. I think that the model proposed by Drs. Young and Meiry will be useful, as is a paper by H. L. de Vries on the mechanics of the labyrinth otoliths (Acta Oto-Laryng., Stockh., vol. 38, 1950, pp. 262–273).

YOUNG: Thank you for your comment. I hope it will be useful. Perhaps rather than considering just the Coriolis force, if you consider that you have a sinusoidally varying compression force on the otolith, that is a possible explanation for the modulation frequency.

MAYNE: I was very much interested to hear about the proposed otolith model and was pleased to note that a concept similar to ours has been derived. Our own model was covered in a series of three reports issued over a year ago under contract NAS9–4460 between the NASA Manned Spacecraft Center and Goodyear Aerospace Corp., Arizona Division. In the performance of our 1-year program we seem to have gone through a thought process similar to that described by Dr. Young. From various experimental data it appeared to us that the otoliths had to provide data for both velocity and acceleration in making it possible to estimate both body displacement and the direction of the vertical. Of course the otoliths could have detected only acceleration, and this value could have been integrated *once* for velocity and *twice* for displacement in higher centers. But symmetry with semicircular canals suggested the likelihood of an overdamped linear transducer. We looked toward publishing data on otolith single-fiber responses for clarification of this point.

We found the most complete and beautiful records in this regard in an early paper by Lowenstein et al. The data were taken at the periphery, and we took them to represent unprocessed otolith signals in a fish preparation. Gravity in this case acted on the otolith as an acceleration. Whatever processing may be performed to separate the effect of these two forms of acceleration must take place centrally and, in part, by synergetic interaction with semicircular signals, as discussed in our papers. The data of Lowenstein et al. included various curves for continuous rotation, steady response in various positions, and sudden rotation from one position to another. In the case of a sudden turn of the head corresponding to a step acceleration impressed on the otolith, the response increased instantaneously, then decayed to a constant value generally higher than the initial one. For continuous rotation representing a sinusoidal acceleration input, the response was also sinusoidal but led the acceleration in phase. Obviously such a response was not velocity, as velocity should lag the acceleration. It occurred to us that the dilemma may be resolved if the otoliths were assumed to consist of two transducers incorporated into one, an underdamped and an overdamped transducer measuring, respectively, acceleration and velocity. The arrangement would be such that the overall response would be the difference between the individual outputs. Naturally, the velocity transducer could be replaced by a central integration in accordance with Dr. Young's suggestion, if I understood it properly. However, this would not account for the peripheral response obtained by Lowenstein. We suggested two possible otolith configurations to produce the type of observed response. These, however, are only tentative hypotheses requiring further investigations. The mathematical representation in our reports shows a vector representation of the responses of the two transducers for a sinusoidal input and their vector addition to make up the overall response.

We represented our model mathematically as follows:

$$Y(S)=\frac{K^2\omega_0^2}{S^2+2\zeta\omega_0 S+\omega_0^2}-\frac{K_2\varphi\beta}{(S+\alpha)(S+\beta)}$$

For relatively low frequency, the response becomes approximately

$$Y(S)=K_1-K_2\frac{\alpha}{S+\alpha}$$

where

$Y(S)$ = transfer function for an acceleration input
K_1 = a constant related to underdamped transducer
K_2 = a constant related to overdamped transducer
$1/\alpha$ = time constant of overdamped transducer

Various overall responses to a step acceleration for various values of K_1 and K_2, in different fibers, are shown in figure D1. I assume this representation is similar to that proposed by Dr. Young.

We applied our mathematical model to Lowenstein's data on both sinusoidal and step inputs. But this is a bit too complicated to discuss here; so, I will refer those interested to our papers.

With a little reflection it appeared to us that the otolith signal was beautifully adapted to the control of body movements. Velocity within an appropriate frequency is given by the difference between (*a*) and (*b*) or (*c*); acceleration or gravity is given by (*a*) at practically all frequencies. We suggested that the whole response such as (*b*) or (*c*) may be

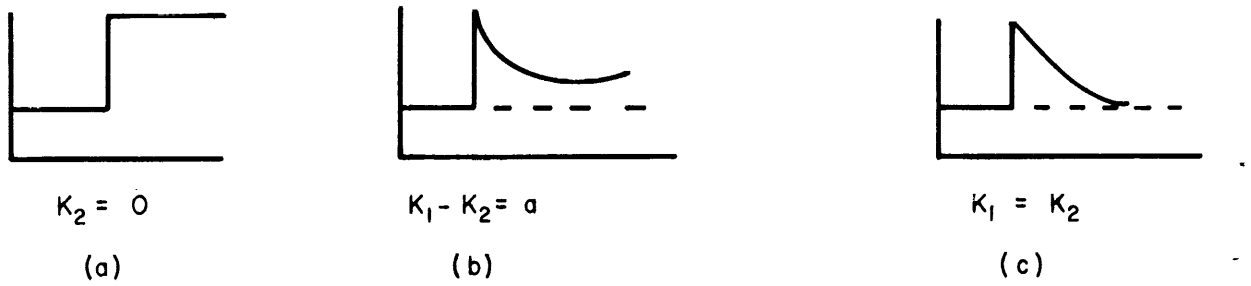

FIGURE D1.—*Overall responses to a step acceleration for various values of* K_1 *and* K_2 *in different fibers.*

used directly for body control as in the case of eye movements. The problem of body control, as we see it, is for the physiological computer to select from storage the proper program of movement as rapidly as possible. Velocity signal would be too slow for this purpose, as it requires an integration of acceleration. The overall otolith signal, on the other hand, gives a very fast signal corresponding nearly to jerk or rate of change of acceleration. These higher derivatives of the controlling function would not be of significant value to a conventional linear closed-loop servo.

The analysis by Drs. Young and Meiry seems to confirm the suggestion made in our papers that the overall otolith signal is utilized to control involuntary eye movements to add vestibular to visual signals and thereby provide a signal which includes information both about body position and its higher derivatives. Our formulation, however, does not account for the lack of symmetry of the response for clockwise and counterclockwise rotation, and I am interested in discussing with Dr. Young how their model may account for it, if it does.

Session VI: TESTS OF CANAL FUNCTION

Chairman: **GEORGE CRAMPTON**
Edgewood Arsenal

N68-29153

Tests of Canal Function With Special Reference to Central Vestibular Pathways

N. G. HENRIKSSON, A. LUNDGREN, LITA TIBBLING, A. NILSSON, AND A. ANDERSON

University of Lund, Sweden

SUMMARY

In a rotating spacecraft the complex vestibular stimulations will probably involve separate parts of the vestibular system quite differently. For this reason methods for differentiated examination of the vestibular systems are advocated and techniques for examination of some different parts or controlling mechanisms of the vestibular reflex arc are described.

INTRODUCTION

Life on board a rotating spacecraft will probably involve more bizarre stimuli to the vestibular apparatus and its central connections than to any other sensory system. It can be assumed that certain parts or certain mechanisms of the vestibular system will be especially sensitive to these complex stimuli. An important goal, therefore, must be as selective as possible an evaluation of the various parts and pathways and of the various working and controlling mechanisms of the vestibular system. The aim of this paper is to show to what extent adequate stimuli and proper evaluation of responses will make such differentiated examinations possible.

Different kinds of caloric or rotatory stimuli which cause variations in frequency of impulses in the vestibular nerve are frequently used in testing the vestibular system. These variations are conveyed through different parts of the brain to different response organs. Somatic responses, like nystagmus, deviation of the eyes (ref. 1), and vestibulospinal effects (ref. 2), as well as perceptual phenomena, like sensation (ref. 3), are brought about in this way. Under special conditions, perceptual phenomena can also be studied as oculogyral illusions (ref. 4) or as deviations of a retinal afterimage (ref. 5). The repetition of the stimuli (refs. 6–8) as well as the variation of alertness of the test subject (ref. 9) may contribute possibilities for studying the central control of vestibular impulses.

Thus a variety of vestibular responses can be obtained, responses that do not always primarily give information concerning the condition of the peripheral organ but rather informs us as to the way in which the vestibular stimuli have been propagated to different response organs and have been interpreted or controlled. Such a conception of the vestibular system with some of its central projections and controlling mechanisms is presented in figure 1. For a differentiated examination of these levels, a suitable stimulation in combination with adequate evaluation of the responses will be needed. The main principles for vestibular stimulations, together with some somatic and perceptual responses, are diagrammatically presented in figure 2.

For details regarding vestibular stimulations, the reader is referred to papers dealing with such problems (refs. 10–13). However, the main principles involved in evaluating responses to vestibular stimulation are discussed.

EVALUATION OF VESTIBULAR RESPONSES

Recording of Somatic Responses

Eye Movements

Different nystagmus qualities.—Nystagmus reactions constitute significant vestibular re-

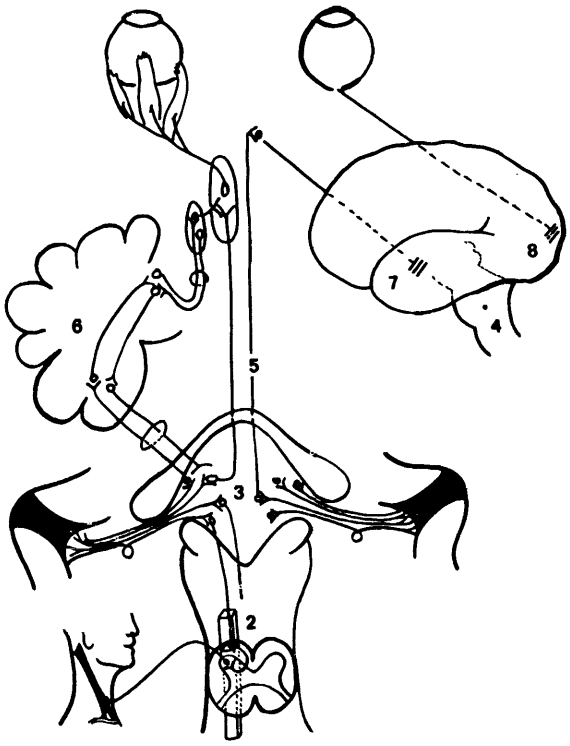

FIGURE 1.—*The different anatomic levels of the vestibular reflex arc and the anticipated locations of its control mechanisms.* (1) *Peripheral sensitivity;* (2) *vestibulospinal connections;* (3) *vestibular nuclei (anticipated main location of central vestibular imbalance);* (4) *the reticular formation which controls alertness and thus the nystagmus pattern;* (5) *the longitudinal fasciculus—probable location of lesions causing dysrhythmia;* (6) *cerebellum containing vestibular habituation mechanisms;* (7) *cortical projection of vestibular sensation; and* (8) *anticipated location of the perception of the oculogyral illusion.*

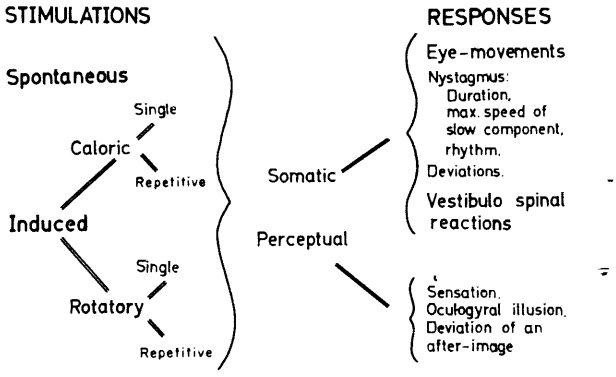

FIGURE 2.—*Vestibular stimulations and responses.*

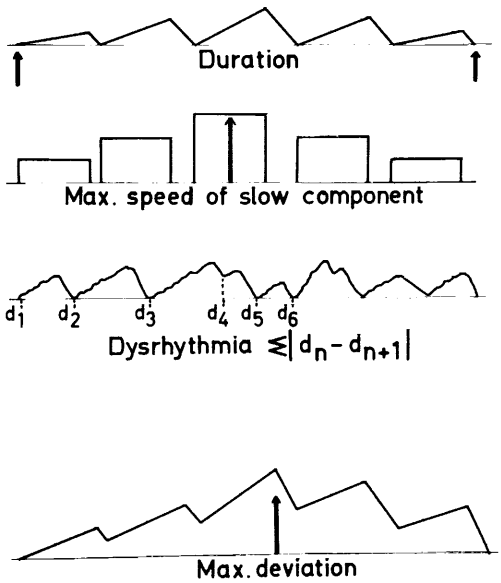

FIGURE 3.—*Four different and uncorrelated parameters in the caloric nystagmus reaction.*

sponses and, therefore, should always be recorded, preferably by some electro-oculographic method. Electrical arrangements make it possible to analyze nystagmus patterns according to the following, fairly uncorrelated parameters (fig. 3):

(1) The duration of the reactions (ref. 14).

(2) The maximum angular velocity of the eyes in the direction of the slow component (time constant = 0.03 sec) (ref. 15).

(3) The rhythm of the nystagmus beats (ref. 16).

Deviation of the eyes.—The deviation of the eyes (time constant = ∞) is independent of the presence or absence of nystagmus, but in spite of this can be a further expression of a caloric (ref. 1) or a rotatory (Henriksson et al., in preparation, 1967) stimulation.

It must be considered advantageous to record movements of the eyes in the vertical as well as in the horizontal direction. This makes recording of vertical nystagmus also possible and provides control over eye closure which, for evaluation of nystagmus responses, frequently is crucially important (ref. 17).

Vestibulospinal Reactions

In caloric as well as in the rotatory tests, it is always possible to record vestibulospinal response simultaneously with nystagmus reactions.

Two cushions behind right and left occiput are used in the caloric test; the differential pressure in these two cushions will express quantitatively the effect of the vestibulospinal reflexes (ref. 8). In the rotatory test a potentiometer arrangement on the head will make possible a recording of the turning of the head and thereby also provide information about vestibulospinal reflexes (fig. 4) (Henriksson et al., in preparation, 1967).

Reported Perceptual Vestibular Responses

(1) The sensation cannot be objectively recorded, but a report by the patient according to the scheme of Lidvall (ref. 18) can be very informative in routine work.

(2) Presentation of an afterimage to a test subject will make possible reports of another perceptual phenomenon, the position of an afterimage (ref. 5). Deviation of this afterimage is frequently caused by vestibular imbalance and can be objectively controlled by simultaneously recording deviation of the eyes in the same direction (ref. 17).

(3) By presenting a single visible object, such as a tiny light spot without a reference frame, an apparent movement of this object is effected; this phenomenon is often referred to as the oculogyral illusion (ref. 4). Study of the duration of the oculogyral illusion (OGI) can contribute adequate information about central vestibular connections on the conscious level (Alf Nilsson and N. G. Henriksson, "The Oculogyral Illusion and Its Relation to the Spiral Aftereffect in Repeated Trials," 1967(a), in press).

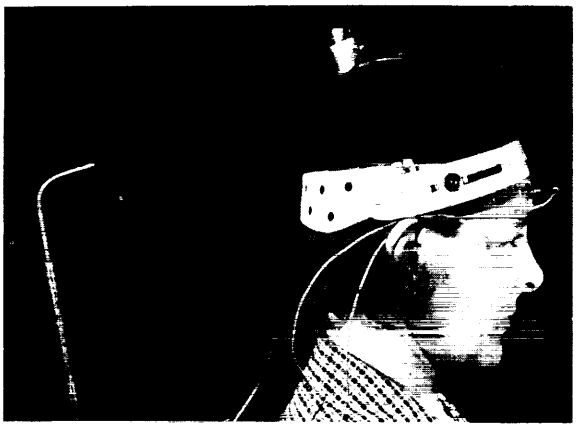

FIGURE 4.—*A technique for recording of the position of the head in rotatory experiments.*

Response to any vestibular stimulation can thus be evaluated by any of the above techniques. It is possible in many cases to use a combination of the techniques for evaluation; in other cases, the various techniques will conflict with each other in such a way that any combination will be impossible. For example, the oculogyral illusion and deviation of the eyes in the direction of the slow component upon presentation of an afterimage cannot be studied along with the nystagmus pattern because visual impulses will abolish or heavily interfere with the nystagmus movements. Therefore, a correct selection of perceptual or somatic responses from the different combinations of stimulations and responses has to be made for each scientific or clinical purpose.

Conclusive evidence of the location of a lesion or of a definite anatomical basis for divergent or pathological findings in some individuals is always difficult to show. Sometimes a certain test pattern might indicate or even prove the precise location of a disorder within the brain while other test results would give little indication of such a location. For as clear a presentation as possible, various vestibular phenomena have been ascribed somewhat hypothetically to different levels of the vestibular reflex arc or sometimes ascribed also to certain anatomical structures. A few such "levels" are presented, together with their related vestibular characteristics.

LABYRINTHINE SENSITIVITY

In clinical work it is frequently important to prove differences in reactivity between the right and left ear (ref. 19). This constitutes the main task of the otoneurologist upon examination of a patient with Ménière's disease or one with neurinoma. Then it is essential to know if any such difference exists between the two labyrinths, and it is also important in the examination of a space crew applicant, at least as long as we do not know how men with an asymmetric labyrinthine disorder may react in a rotating space station.

Rotation stimulates both labyrinths simultaneously. Even after total loss of one labyrinth, the rotatory responses, however, might be nor-

mal; therefore, such rotation tests cannot be used to compare the sensitivity between the right and left labyrinth.

Caloric stimulation which can be made separately in one ear at a time can, with proper evaluation of the responses, furnish information on differences in sensitivity between the two labyrinths. It must be pointed out, however, that the duration of nystagmus reactions during caloric stimulation is not a proper expression of the sensitivity of the labyrinths. This is based both on experimental findings and on clinical experience. Thus, in nystagmus reactions provoked by repeated experiments with increasing degrees of caloric stimuli (irrigations with 35°, 33°, 31°, and 29° C), the speed of the slow component will increase by about 300 percent, corresponding to the increase of the stimuli. The duration of these reactions will, however, increase only by some 30 to 40 percent (ref. 10). The variations in intensity of the stimuli are thus clearly reflected by values for the maximum speed of the slow component, but only vaguely by the durations. In clinical work a decrease in labyrinthine sensitivity is correspondingly reflected by a decrease in the maximum speed of the slow component, but not by the durations which might be quite equal on both sides.

VESTIBULAR TONUS DIFFERENCE

A peripheral as well as a central disorder may cause a difference in vestibular tonus. If a peripheral lesion is responsible, however, in most cases this is frequently revealed also by a decrease in peripheral sensitivity, as was just mentioned. If no such decrease can be found, therefore, the vestibular imbalance must be attributed to central disorders which frequently can be ascribed to disorders of the vestibular nuclei (ref. 19). Independent of whether this imbalance is the result of peripheral or central disorders, however, the imbalance in itself is revealed by a number of somatic as well as by perceptual phenomena. Some of these will be discussed in this paper.

Certainly a difference in duration of nystagmus after rotatory or caloric stimulation might indicate the presence of such an imbalance. Since a rebound effect (post-post-nystagmus) after both kinds of stimulations will make determination of the durations difficult, we will have to rely upon spontaneous phenomena for the diagnosis of small vestibular tonus differences.

Vestibular influence on the eyes is constantly interfered with by three extravestibular eye-controlling factors: (1) the retinal fixation, (2) the voluntary and (3) the eye-centering mechanisms. In darkness the retinal fixation mechanism and some of the voluntary impulses are excluded. In this way the eyes are controlled by vestibular influence and the eye-centering mechanism.

When a vestibular tonus difference is present, a conflict between the deviation of the eyes caused by the vestibular stimulus and the eye-centering mechanism will cause a nystagmus movement. Thus the first sign of a minor tonus difference can be revealed only in darkness, by proving the existence of a spontaneous nystagmus. This, of course, has to be done by some nystagmographic technique. A caloric preponderance in light, and finally a spontaneous nystagmus in light (ref. 19), will also be found with increasing vestibular imbalance.

With introduction of a retinal afterimage (AI) which the test subject can perceive in darkness, the retinal fixation mechanism is also excluded. Thus, when a vestibular imbalance tends to move the AI and the eyes, the voluntary eye movements with inhibition of the eye-centering mechanism will direct the gaze toward the deviating AI. In this way the vestibular system can control the position of the eyes without any negative interference with the other gaze-controlling systems.

Normal persons not exposed to vestibular stimulations will generally perceive this afterimage as quite steady in front of them. In a few normals, however, this afterimage spontaneously deviates toward the right, almost never toward the left. Upon careful study of electro-oculographic records taken in darkness on such individuals, a minute spontaneous nystagmus which is always directed toward the left frequently will be found. This finding is related to previous findings by Jongkees and Philipszoon (ref. 13), Lundberg (ref. 20), and Bergstedt (ref. 21), who all found a prevalence for a preponderance of nystagmus toward the left. When a pathological nystagmus is present, however,

no matter whether it results from some central or peripheral disorder, the afterimage and the eyes always turn in the direction of the slow phase (fig. 5).

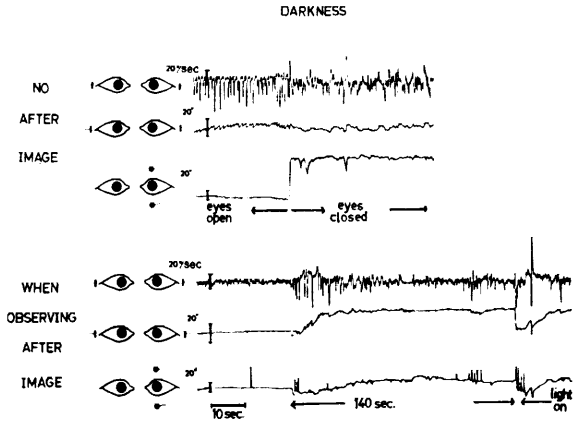

FIGURE 5.—*A pathological spontaneous nystagmus at observation of an afterimage changes into a deviation of the eyes in the direction of the slow component.*

DEVIATION OF THE EYES AND WAKEFULNESS

It is striking how well normals even with strong caloric stimulations are capable of keeping their eyes in the midposition. Any decrease in alertness will, however, cause the eyes to deviate during the nystagmus beats in the direction of the slow phase. With increasing sleepiness this deviation will increase, and the nystagmus will gradually change into a tonic conjugate deviation (ref. 1). The eye-centering mechanism thus seems very dependent upon the level of consciousness.

Position of the eyes during caloric nystagmus will thus provide information about the alertness of the patient and, thereby, also about the reticular formation of the brain stem. At the same time it will also give information on the reactivity of the vestibular reflex arc. This implies that a deviation in the direction of the slow component in nystagmus reflects impaired control of wakefulness (fig. 6). Such a finding in nonmedicated patients should be related to afflictions of the brain stem. This is supported also by the fact that such deviations are frequently found to be combined with dysrhythmias. Deviations in the direction of the slow component

FIGURE 6.—*The caloric nystagmus pattern changes with sleepiness—the eyes deviate during a series of nystagmus beats in the direction of the slow component and return to midposition with a fast movement of large amplitude, giving the impression of two kinds of nystagmus beats, interfering with each other.*

seen in some caloric reactions must therefore be considered as expressions of an impaired control of wakefulness.

In this connection it must also be pointed out that deviation of the eyes during a rotatory test does not take place in a similar manner, but is seen as a constant phenomenon both in the normal state of wakefulness and in sleepiness. It seems to take place, however, always in the direction of the fast component (fig. 7). This

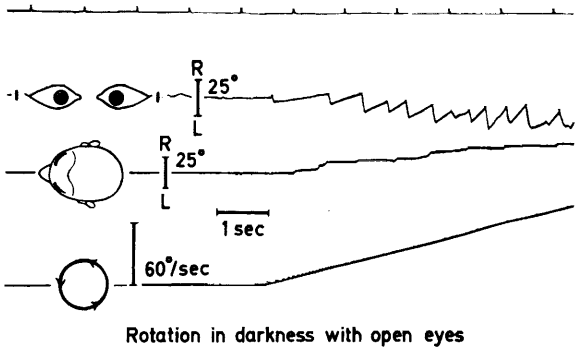

FIGURE 7.—*Recording of eye movements in a rotation with constant angular acceleration. Upper tracing records the position of the eyes (time constant = ∞); the middle tracing shows the position of the head; the bottom tracing the angular velocity of the rotating device. Note the deviation of the eyes in the direction of the fast component.*

intriguing difference between findings with the caloric and the rotatory tests is now being investigated by the authors.

VESTIBULOSPINAL PATHWAYS

Introduction of the laterotorsion test in routine examinations has proved very useful (ref. 17). When some pathological process in the upper part of the brain stem has abolished the nystagmus reaction, the presence of vestibulospinal reflexes might indicate normal peripheral re-

activity. Interesting also is the pattern we have found so frequently in patients with encephalitis; that is, intense nystagmus reactions combined with very low vestibulospinal reactions (ref. 22). Furthermore, inconsistent or absurd vestibulospinal reflexes might indicate pathology of the brain stem.

During rotation, the vestibulospinal reflex is less consistent than in caloric examinations and thus seems to be of less value. Here the lack of relevant data about any possible relationship between the position of the eyes and the position of the head in rotations is quite obvious.

CENTRAL VESTIBULO-OCULAR PATHWAYS

Induced nystagmus in healthy subjects is rather regular and in electro-oculography (EOG) shows a consistent sawtooth pattern in which each sawtooth complex is very similar to the one preceding and the one following. In patients with ischemic conditions of the brain stem, this pattern becomes quite disintegrated. The normal smooth deviation of the eyes in the nystagmus beats in direction of the slow component is replaced by irregular, uneven eye movements in this direction. The sharp and determined borderline between the slow and the fast phases becomes more rounded, which might even give a slight impression of an undulating congenital nystagmus. Furthermore, nystagmus beats of long duration are followed by those of short duration, and there is also a corresponding variation in the speed of the slow and the fast components (fig. 8).

When such dysrhythmic reactions are present, they always seem to originate in both ears and never in one ear exclusively. Further, the dysrhythmias never appear in disorders due to a peripheral lesion which should rule out a peripheral site as the source of the condition. Since dysrhythmias are infrequently seen in combination with spontaneous nystagmus, the vestibular nuclei can also be excluded as the probable location of the pathophysiological process causing the phenomena.

For these reasons dysrhythmias cannot be regarded as reflecting either a peripheral or central unilateral vestibular disorder. They

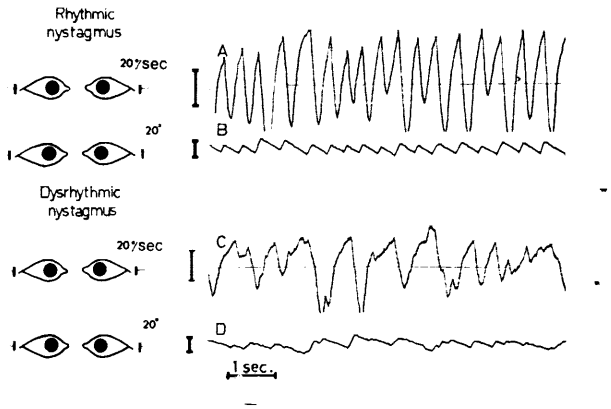

FIGURE 8.—*Rhythmic and dysrhythmic nystagmus patterns. Of the two pairs of recordings, the top ones show the velocity of the eyes (time constant = 0.03 sec), the bottom ones the position of the eyes (time constant = ∞). The upper two recordings are achieved from a normal subject and the recordings below from a subject with a dysrhythmic pattern due to ischemia of the brain stem.*

should be looked upon rather as expressions of disintegration of the common vestibular pathways; that is, the medial longitudinal fasciculus. Dysrhythmias seen in patients after a moderate intake of barbiturates and those occurring with simple repetition of the stimuli favor the assumption that they arise in a central location.

An objective quantification of the degree of the dysrhythmia is extremely difficult as it involves changes of many qualities of nystagmus. The difference in the duration of the speed of the slow component as well as that of the fast component in consecutive nystagmus beats could, however, be used for such a quantification since these differences can be integrated and measured by electrical methods (fig. 9).

With few exceptions (refs. 16 and 23–25) dysrhythmias seem to have been overlooked by most workers in the vestibular field. As they do not reflect peripheral lesions, the otologists have not shown much interest in them. Rather few neurologists seem to appreciate the information they may contribute. It is absurd, however, to regard the caloric reaction as normal because the nystagmus reactions provoked from both sides are of equal durations and may also be equal in maximum speed of the slow component when these reactions are combined with a pronounced dysrhythmia. An analysis of the nystagmus with respect to the presence of such

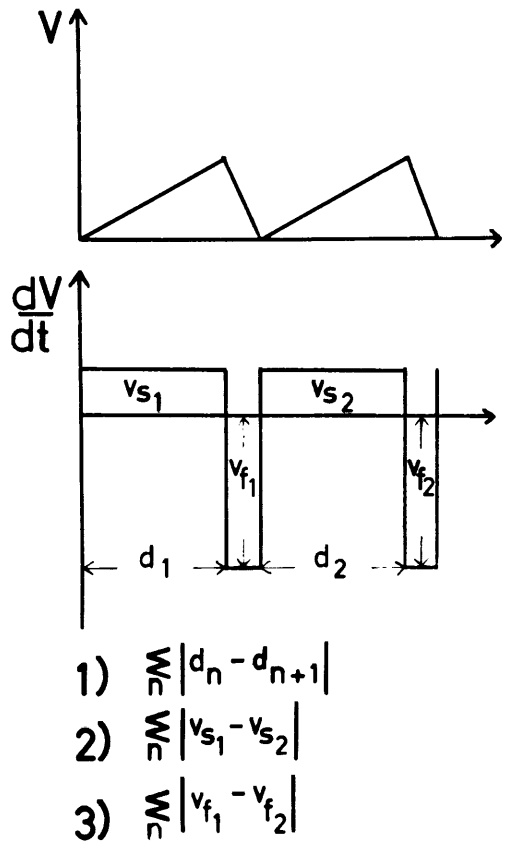

FIGURE 9.—*Principles for objective evaluation of dysrhythmia.*

patterns perhaps should also be included in the vestibular examination of applicants for a space journey.

HABITUATION OF VESTIBULAR RESPONSES

The ability to acquire vestibular habituation as well as the ability to retain it must be determined for a complete evaluation of the different vestibular functions. This cannot be defined, however, by determining habituation of only one of the vestibular parameters, since each habituates differently. Thus, a peripheral vestibular preparation of a frog will show no habituation at all (ref. 26). On the other hand, after 12 repeated caloric stimulations the nystagmus durations will show a minor degree of habituation, the speed of slow component as well as the laterotorsion will show a moderate decay, while the sensation of turning, caused by the repeated

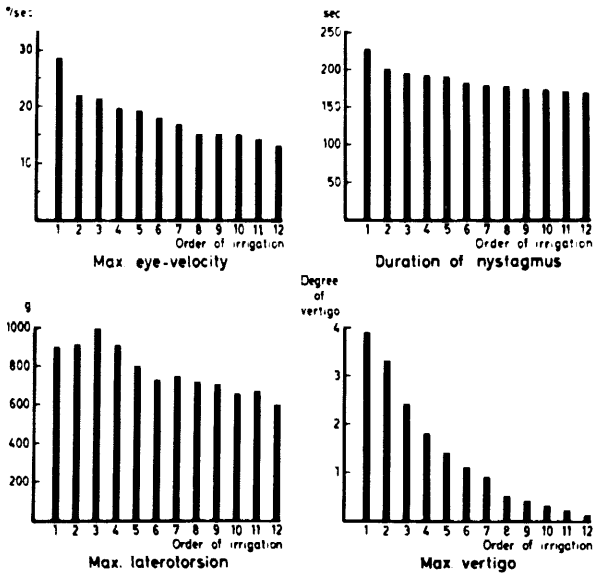

FIGURE 10.—*Habituation of four vestibular phenomena. Diagrammatic representation of maximum eye velocity, duration of nystagmus maximum laterotorsion and maximum vertigo following repeated calorizations. Mean values from 15 normals, all irrigated 12 consecutive times in darkness for 40 seconds with water of 30° C in the right ear. (From ref. 3.)*

stimulations, will be quite abolished at the end of the series (fig. 10) (ref. 3).

When duration of the oculogyral illusion at repeated rotations was studied in some individuals, divergent in their personality, even an increase in response with repetition of the stimuli was found (Alf Nilsson and N. G. Henriksson, "Adaptive Patterns in the Oculogyral Illusion and Their Relations to the Serial Colour-Word Test," 1967(b), in press). These experiments thus prove quite a different kind of habituation at different levels of the vestibular reflex arc.

VESTIBULAR RESPONSE AND PERSONALITY

Hallpike et al. (ref. 27) and Angyal and Blackman (ref. 28) have been able to correlate the durations of caloric responses with personality. Hallpike et al. found long-lasting nystagmus reactions in patients with a tendency toward anxiety neurosis, while Angyal and Blackman found short caloric reactions among patients with schizophrenia. Lidvall (ref. 29) failed to

prove any correlation between neurotic anxiety and habituation of caloric responses.

Quite recently we compared the duration of the oculogyral illusion (OGI) with the duration of the spiral aftereffect (SAE) and were able to prove a high correlation ($r_s = 0.73$) between these two phenomena (fig. 11) (Nilsson and Henriksson,

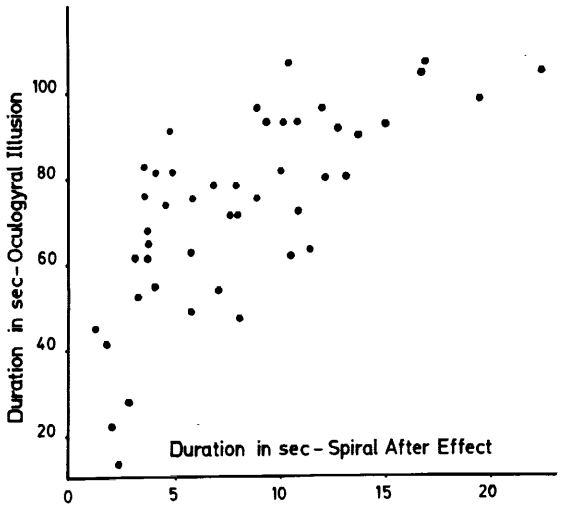

FIGURE 11.—*The duration of the oculogyral illusion* ($OGI_I + OGI_{II}$) *as a function of the duration of spiral aftereffect* (SAE) *in the same individuals* ($r_s = 0.73$).

1967(a), in press). Thus, these quite different sensory systems seem to have a controlling factor in common.

As the SAE had previously and successfully been used for studies of personality, an effort was made to correlate personality objectively evaluated by the color-word test (CWT) with the habituation of the OGI (Nilsson and Henriksson, 1967(b), in press). In this connection a few words should be said about the color-word test. The test subjects are exposed to a chart with printed words in which the word "blue" appears in green, red, or yellow; the word "red," in blue, green, or yellow; and so on. In the test the subject has to name the printed hue, but to ignore the printed word. The variations in time for reading a color-word chart have been found to reveal important information about the personality of the subject (ref. 30).

The initial duration of the OGI was studied along with the degree of habituation of the duration in repeated rotations. Some individuals showed a high and some a low initial duration. In both these groups, individuals were found who showed a positive regression (increase of duration with repetition of the stimuli) and also negative regression (decrease of duration with repetition of the stimuli). Each of these four groups seemed to reveal specific patterns when tested with the CWT, indicating that this specific vestibular test also may contribute information about personality (fig. 12).

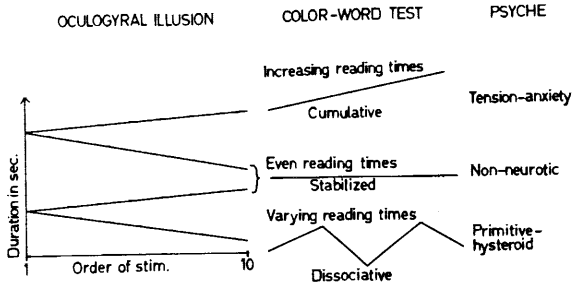

FIGURE 12.—*The duration of oculogyral illusion* (OGI_{I+II}). *The pattern of the color-word test and its relation to personality.*

Any one specific test cannot be said to provide information covering the whole vestibular system with its large variety of working and controlling mechanisms. The time has passed when we had to rely upon differences in durations of postrotatory or caloric nystagmus for judging the labyrinth and its central connections. A differentiated analysis of each part or level of the vestibular pathways must be made. The results from the various tests or different kinds of analyses can then be put together, furnishing an integrated vestibular profile. This profile may then be the basis for judging individuals from a clinical point of view or may form the basis for evaluation of the vestibular system in relation to space travel.

It might seem a truism to point out that, in our future life as well as in a spacecraft, we are completely restricted to the limits set by our biological systems. For the vestibular apparatus and its central connections, this limit seems not only to vary between different individuals but also to be, to a large extent, subject to change by training or habituation. A full knowledge of the vestibular patterns, including also the feasible

range of habituation, might raise the biological limits of the vestibular system enough to make possible long-lasting residence in a rotating spacecraft.

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DISCUSSION

STEER: On the habituation series that you ran, did you run all the temperatures in one direction?

HENRIKSSON: Right.

STEER: Then did the subject at a later time recover from this habituation? The other part of the same question is: If you initially started with a hot then a cold water stimulus, then ran a sequence of hot, and at the end of the long sequence a cold, was there habituation with the cold stimulus also? In other words, does the envelope of the response decrease?

HENRIKSSON: It is very difficult to control the retention of habituation. This is due partly to the fact that each control also introduces a stimulation. To answer the second question, we irrigated the right ear of cats 10 times with cold water, 20° C, and obtained nystagmus toward the left, diminishing with the order of irrigation. We then obtained no or very little nystagmus when after that we irrigated the opposite or left ear with water of 48° C. When we applied water of 48° C in the right ear, however, we got a brisk normal response, directed toward the right. So, habituation of nystagmus is direction specific.

BENSON: I would like to make a comment on your correlation between the duration of the oculogyral illusion and the duration of the spiral aftereffect. My colleague, Reason, and I have confirmed this observation but have also extended it to include other situations where the subject had to report the disappearance of an exponentially decaying signal. We found that there was a correlation not only between the duration of the spiral effect, the duration of the postrotatory sensation, these two test situations being equivalent to yours, but also with duration of an aural signal which decayed exponentially into a background of white noise, and with the duration for which a light could be discriminated which decayed in brightness against a background of constant illumination. So, I would agree with your observation, but not with your interpretation. We feel these correlations express a more general feature of the way in which the individual deals with neural signals or perhaps the way in which he makes a judgment in an ambiguous judgment situation.

The other point of interest here is that we have found that the individuals who had long aftereffects were also those who seemed to have an increased susceptibility to motion sickness. Perhaps they do not have such well-developed adaptive mechanisms within their central nervous systems.

TOROK: I enjoyed all that you have said, Dr. Henriksson, because it is clear and easy to understand. Why do you term the optokinetic nystagmus a "perivestibular" sign or phenomenon? Basically, except for appearance, there is nothing in common between the vestibular and optokinetic nystagmus. The neurophysiological mechanism, the cause, and the significance of the two are all different. To term the optokinetic eye motion as *perivestibular* might be misleading. It is rather a *nonvestibular* sign.

HENRIKSSON: I think the question you raise is an important one. The optokinetic eye movements, although closely correlated to vestibular impulses, are not quite uncorrelated. An intense vestibular stimulation will also change the optokinetic pattern, while moderate gaze nystag-significance of the two are all different. To term the optokinetic eye motion as *perivestibular* might be misleading. It is Therefore, the result of the optokinetic test is of great interest to the clinician interested in the vestibular system. This is why I suggest the term "perivestibular" as it indicates an indirect, but no direct connection with the eye-vestibular system.

MELVILL JONES: It is delightful to see how nicely one can use an afterimage in a relatively simple clinical test. Can you guess at the kind of physiological information which goes to perception to give you that afterimage shift? In particular, does it derive from efferent signals going out to the oculomotor muscles or from muscle and other afferents coming back from the orbit? The second point I would like to make refers to the tendency you mention for a d.c. shift to occur in the direction of the quick phase of nystagmus. What sort of functional connotation do you attach to this shift?

HENRIKSSON: At present we are trying in different ways to find out why the eyes in a rotatory test deviate in the direction of the fast phase, while in the caloric test they seem to stay in the midline, or in pathological cases, deviate in the direction of the slow phase. At present our guess is that this difference should be related to spinovestibular impulses; this guess is not, however, supported by any substantial experimental finding, at least not until now.

As to the deviation of the eyes when the test subject is observing an afterimage: this deviation must be a direct expression of the vestibular control which directs the eyes and the afterimage without any inhibiting interference with other control mechanisms. In all cases in which there is a vestibular asymmetry, causing a spontaneous pathological nystagmus in a certain direction, you will invariably find this deviation of the eyes and of the afterimage in the opposite direction, that is in the direction of the slow phase. In the normal, vestibular asymmetry, the one causing deviation of the afterimage toward the right, has been connected with left or right handedness. No evidence of such a relation has been found, however. This vestibular asymmetry might also be related to the way in which we read from the left toward the right; there are, however, other ways.

CRAMPTON: What percentage of the population shows a detectable spontaneous nystagmus?

HENRIKSSON: I would guess 20 percent or so.

JONGKEES: There are quite a lot of people who have spontaneous nystagmus in one or two positions. When you want to call it spontaneous nystagmus, spontaneous nystagmus in any position, then the number is not so large, but in one or the other position, some spontaneous nystagmus is quite common. I agree, about 20 percent.

N68-29154

Effects of Linear Acceleration on Vestibular Nystagmus[1]

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SUMMARY

The notion that human vestibular perception of rotation is uniquely attributable to the semicircular canal models, and perception of linear acceleration attributable only to the otoliths, is clearly an oversimplification. The range of relevant experimental data on the subject of interactions between the two sets of sensors is reviewed in an attempt to produce some preliminary testable models of this interaction.

This paper summarizes the results of this analysis. The major portion deals with the influence of linear acceleration on vestibular nystagmus and postulates a simple model based on otolith contribution. Subjective orientation on the basis of canal and otolith outputs is also treated briefly.

A tentative model used to tie together the variety of data on vestibular cross-coupling between angular and linear accelerations is shown in figure 1. It was based on the following assumptions:

(1) Lateral displacement of the otolith, corresponding to a shear component of specific force, produces an additive component of nystagmus with the slow phase in the direction of the otolith displacement (compensatory) and with sensitivity of the order of 10° per second per g. We will call this linear acceleration sensitive component "L-nystagmus."

(2) The resulting eye-movement nystagmus is determined by the vector addition of the semicircular canal and otolith contributions.

(3) The semicircular canal contribution may be influenced by linear forces either through distention of the canal or by utricular inhibition.

(4) A jerk receptor is an important feature of the otolith response.

The information upon which this model was developed came from a variety of sources and represented a number of different types of investigations. Since the data were primarily of the input-output variety (acceleration in, nystagmus out), the basis for assigning functions to the otoliths is relatively weak.

Vestibular nystagmus has characteristically been attributed to the stimulation of the semicircular canals and explained teleologically in terms of the requirement for maintaining a "stable platform" of the eyes in space despite motion of the head. Most attempts to elicit vestibular nystagmus by stimulation of only the linear acceleration sensors have met with equivocal results in the past. McCabe (ref. 1) reported vertical eye movement with occasional nystagmic response in cats, chinchillas, and humans subjected to vertical oscillations, and Jongkees and Philipszoon (ref. 2) found horizontal eye movements on lateral translation of rabbits. Young and Kilpatrick, and Young, Meiry, and Graybiel (unpublished) have observed highly irregular but definitely present patterns of horizontal nystagmus in humans during lateral horizontal oscillations of large magnitudes. It would appear that the lack of control over mental alertness or the direction of gaze accounted for much of this variability.

In a set of controlled experiments using periodic linear acceleration stimuli in the horizontal plane, Niven et al. (ref. 3) found consistent

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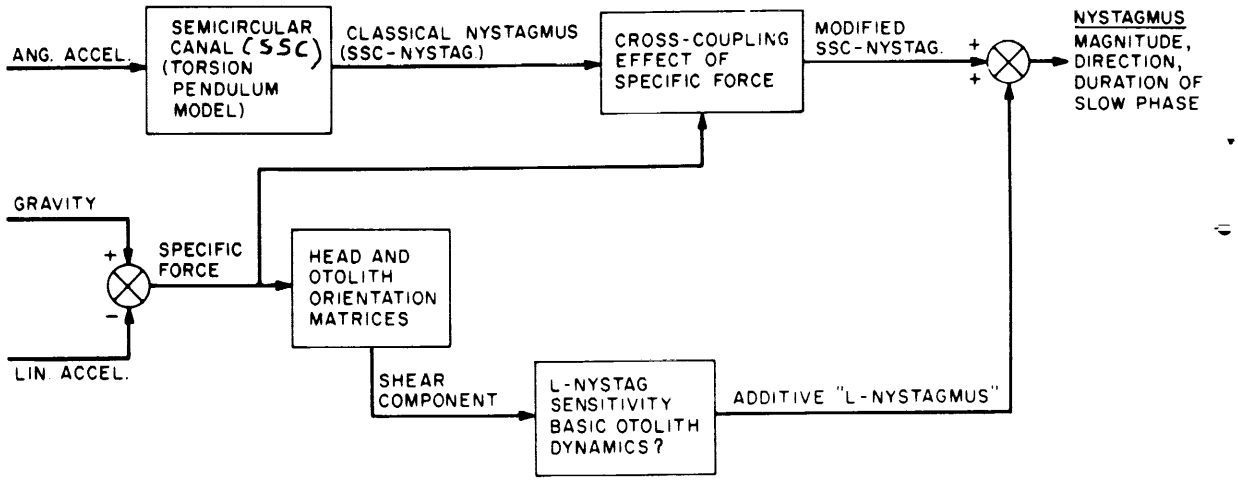

FIGURE 1.—*Preliminary structure of model of influence of linear acceleration on nystagmus.*

horizontal nystagmus. They never observed vertical nystagmus even when the subject was oscillated along his longitudinal axis. Magnitude of the peak slow-component velocity was measured, and the phase shift of the compensatory slow-phase eye movement behind the sinusoidal acceleration stimulus was also recorded, at stimulus frequencies of 0.2, 0.4, and 0.8 cps. The phase lags, increasing from 26° to 38° over these three frequencies, were close to, although consistently lower than, the phase lags of our basic otolith model. The magnitude of the peak slow-phase velocity at each of these frequencies remained nearly constant, approximately 9.3°/sec for a constant 18.6-ft/sec^2 peak acceleration. This yields a constant sensitivity of L-nystagmus of approximately 16°/sec/g, in this frequency range.

Having established an additive L-nystagmus contribution, perhaps of the otolith, we are now led to consider the inhibitory part of the cross-coupling. Working with rabbits, Owada and Okubo (ref. 4) found that increasing the pressure on the utricle tended to suppress the nystagmus response to caloric stimulation. They found that a stimulus which pressed on the saccule, increasing the compressive force on the macula, decreased the nystagmus to the ipsilateral side and increased the nystagmus to the contralateral side. On the basis of simple acceleration inputs, this apparently additive component could not be differentiated from the effect of a lateral shear on the utricular otolith. Additional evidence for the inhibitory effect of otolith compression was given by Milojevic (ref. 5), who experimented with caloric nystagmus on cats placed in a variety of positions with respect to gravity. It is known that the caloric nystagmus depends upon the magnitude and orientation of the head with respect to the g-vector, calculated simply on the basis of the current theory; however, Milojevic's investigation showed that even when caloric tests are performed at an angle which is not optimal for lateral semicircular canal stimulation, there is a significant increase in the duration of postcaloric nystagmus. This angle placed the frontal-occipital axis at 135°, such that the utricular otolith was "hanging" maximally from the hair cells. Thus the occurrence of tension rather than compression in the hairs supporting the utricular otolith appears to enhance nystagmus, at least in the cat. It is interesting to note that subjective perception of orientation with respect to the vertical in humans becomes exceedingly poor when they are tilted more than 90° from the vertical. At these angles, with no compressive force on the otoliths, the gravity receptor orientation signals are "weak." Consequently, they are less able to indicate "no rotation" in the perceptual conflict with the semicircular canal "apparent rotation" output which results from caloric stimulation. This notion is consistent with the idea of inhibition of the semicircular canal outputs by compressive

forces on the utricular otolith. It must be emphasized, however, that an equally good case can be made for the effects of linear acceleration on vestibular nystagmus by the mechanism of distortion of the flexible semicircular canal and resultant cupula displacement. Steer has pursued this theory and we plan to test this hypothesis at MIT in early 1967.[2]

The simple model for otolith contribution to nystagmus may be tested by reference to two recent experiments of a very similar nature performed by Benson and Bodin (ref. 6) and by Correia and Guedry (ref. 7). Subjects were rotated about a horizontal longitudinal axis at various rotation rates, and nystagmus was measured. Long after the normal semicircular-canal-stimulated nystagmus would have died out in rotation about a vertical axis, eye movement continued for this "barbecue-spit" experiment. At the highest rotation rate tested (30 rpm, by Correia and Guedry), a reversing nystagmus was seen to appear; that is, the direction of slow-phase angular velocity changed cyclically during each revolution of the body. The magnitude of eye velocity as a function of angular orientation with respect to the vertical is shown in figure 2 (from Benson and Bodin). Notice that 0° represents nose upward, 180° nose downward. Not only does the relation change with angular velocity but all the curves are skewed to the left. Assuming that there exists an average nystagmus velocity which is not affected by the cyclic variations (perhaps attributable to the flexibility of the canals), the cyclic modifications can be attributed to L-nystagmus. When the nose is up or down (0° or 180°), no lateral specific force component acts on the otoliths, and neglecting any dynamic lags, no additive L-nystagmus should be present. In the 90° orientation, however, with right ear down, the specific force is to the subject's right, equivalent to an acceleration component to his left, which would be expected to produce a slow-phase L-nystagmus right, subtracting from the average nystagmus.

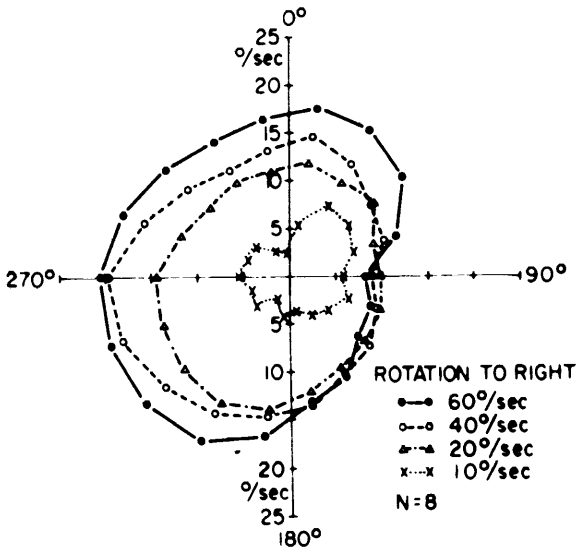

FIGURE 2.—*Plot in polar coordinates of slow-phase velocity of nystagmus against body position. 0° = nose upward. 180° = nose downward. (From ref. 6.)*

At 270° the left ear is down, leading to an L-nystagmus left which adds to the already existing component. This is in accordance with the general features of the data. By taking half the difference between the 90° and 270° magnitudes, the L-nystagmus is established for that frequency. Consider the Benson and Bodin data for rotation at 60°/sec (0.167 cps). At 270°, with L-nystagmus adding to the steady state, the slow-phase velocity is 21°/sec. At 90°, with L-nystagmus subtracting from the steady state, the slow-phase magnitude is 8°/sec. The calculated L-nystagmus contribution consequently is a peak of 6.5°/sec, and assuming that the full 1 g acted in the shear plane of the otolith, the L-nystagmus sensitivity at this frequency is 6.5°/sec/g. Similar calculation at 40°/sec (0.11 cps) yields sensitivity of 5°/sec/g, whereas at 20°/sec (0.055 cps) the sensitivity is down to 2°/sec/g.

Correia and Guedry (ref. 7), performing the same type of experiment at Pensacola, presented data which lead to a calculation of L-nystagmus at 0.167 cps of 7°/sec/g for clockwise rotation and 8°/sec/g for counterclockwise rotation, in close agreement to the Benson and Bodin data. If one assumes the dynamic lag between shear acceleration and L-nystagmus which was found in the

[2] Postsymposium note: The experiments do support the flexible canal explanation. See R. Steer, "The Influence of Angular and Linear Acceleration and Thermal Stimulation on the Human Semicircular Canal," Sc. D. thesis, MIT, Sept. 1967.

pure linear oscillation experiments of Niven et al., the maximum L-nystagmus points should be taken (for 0.16 cps) at 24° after the acceleration peaks, or 114° and 294°, respectively. When this is done, the calculated L-nystagmus becomes 4°/sec/g for clockwise rotation and 4.5°/sec/g for counterclockwise rotation. Since these contributions are clearly not the peak ones, the 90° to 270° comparison only is considered hereafter.

The other experiment described by Correia and Guedry (ref. 7) was at 30 rpm, where reversing nystagmus occurred. This effect may be accounted for by a larger L-nystagmus contribution at this higher frequency, the calculated sensitivity being 14°/sec/g and 14.5°/sec/g for clockwise and counterclockwise rotations, respectively. This sensitivity is in good agreement with the sensitivity to pure linear acceleration in this same frequency range, referred to above. A plot of calculated L-nystagmus sensitivity versus log frequency for the two barbecue-spit experiments and the sinusoidal-horizontal acceleration is shown in figure 3. Notice that

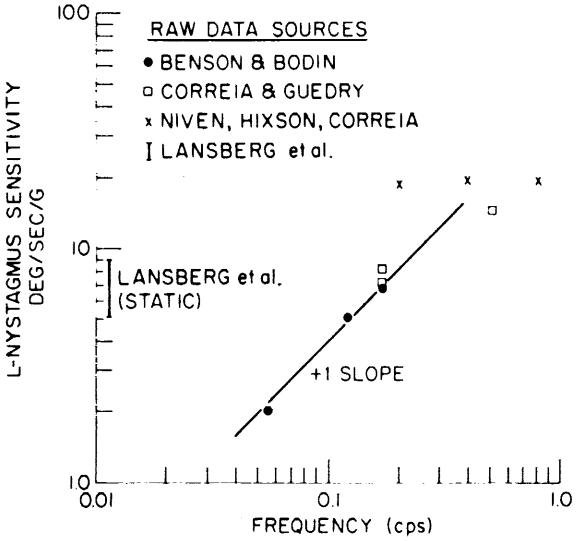

FIGURE 3.—*Composite frequency response, L-nystagmus sensitivity.*

the data fall close to a + 1 slope (amplitude ratio proportional to frequency) with break frequency in the vicinity of 0.5 cps. We have not yet been able to correlate this feature with any response data to support a dynamic model on the basis of them. The barbecue-spit experiments described above involved a sinusoidal linear acceleration stimulus and a constant angular velocity stimulus which would normally give no prolonged vestibular nystagmus.

Important tests of a different type were carried out by Lansberg et al. (ref. 8) on a centrifuge, in which the semicircular canal stimulation was a conventional protocol to evoke vestibular nystagmus (acceleration, constant velocity, deceleration to a stop), and the effect of resultant linear (centripetal) acceleration in different orientations was studied. The contributions of the otolith system to resulting nystagmus could be determined by comparing two tests, in which the planes of the semicircular canals remained unchanged relative to the plane of rotation, but the orientation of the resultant specific force relative to the otoliths was changed. The body orientations in the experiments are shown in figure 4. Consider, for example, the vestibular nystagmus resulting from rotations in body positions D and D_1, the data for which are shown in figure 5. The direction of the arrows indicates the direction of the fast phase, and their height above the x-axis is the slow-phase velocity magnitude. Counterclockwise rotation for both positions stimulates the semicircular canals to yield compensatory nystagmus (slow phase right and

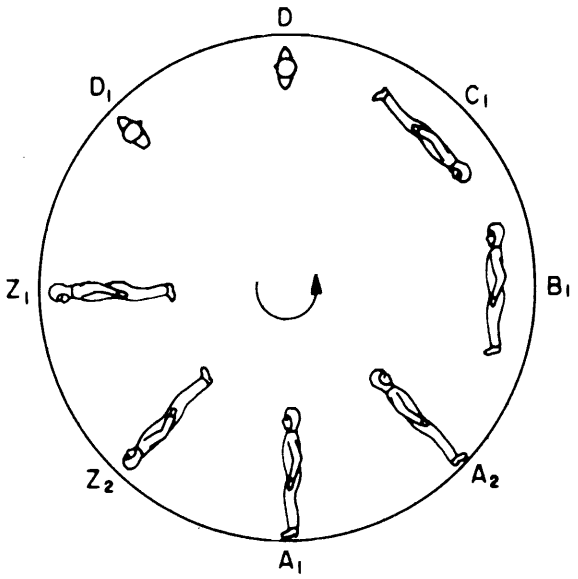

FIGURE 4.—*Body orientation.* (*From ref. 8.*)

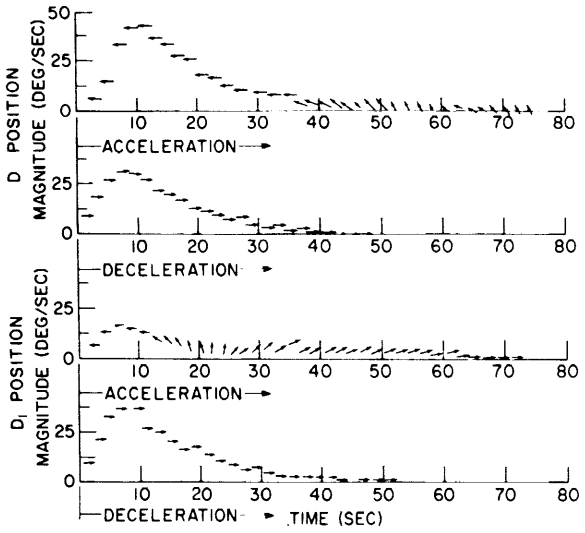

FIGURE 5.—*Vectorial presentation of nystagmus. (From ref. 8.)*

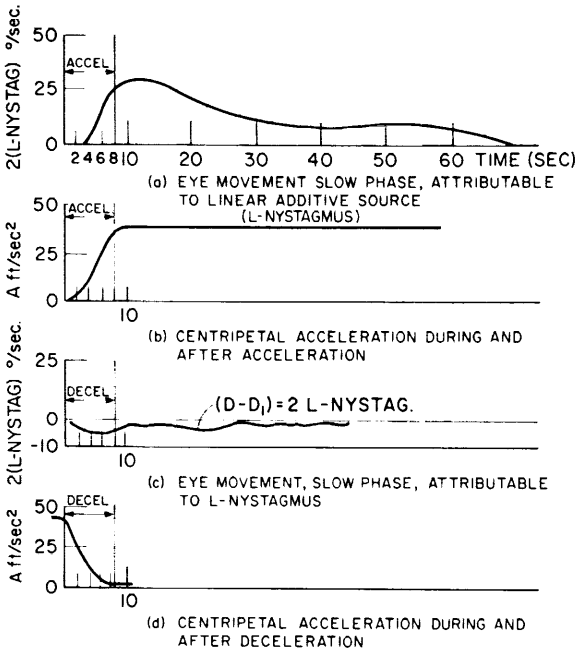

FIGURE 6.—*Calculated L-nystagmus from Lansberg et al. (ref. 8) tests with* D *and* D_1 *body positions.*

fast phase left), with the magnitude decreasing exponentially during the constant velocity turning. Consider, however, the linear acceleration acting on the otoliths during body positions D and D_1 of figure 4. In position D, during the constant velocity phase, the centripetal acceleration acts to the subject's left, causing a presumed L-nystagmus with slow phase right, which adds to the semicircular canal nystagmus. During the constant velocity turning in position D_1, however, the centripetal acceleration acts to the subject's right, causing L-nystagmus of slow phase left, which subtracts from the semicircular canal nystagmus. Inspection of figure 5 shows that indeed the acceleration and constant velocity phases of D show nystagmus which is increased in magnitude and velocity over the normal pattern, whereas in position D_1 the initial nystagmus is low, decreases in magnitude, and reverses direction.

By assuming that the difference in response magnitudes between D and D_1 during the constant velocity portion is attributable solely to L-nystagmus, yet another estimate of L-nystagmus sensitivity can be made. Figure 6(*a*) is a graph of the difference between nystagmus from test D and D_1 during the acceleration and constant-velocity phases; figure 6(*b*) shows the lateral centripetal acceleration which is presumably responsible for the L-nystagmus. Notice that $(D-D_1)$ which should be equal to twice the L-nystagmus contribution, rises sharply with the increase in centripetal acceleration, and then decreases slowly, with a time constant of the order of 5 to 10 sec during the constant centripetal acceleration phase. This transient behavior is again indicative of a component of the L-nystagmus response sensitive to rate of change of acceleration, and is reminiscent of the "habituation" seen in otolith nerve recordings and in sensation of tilt. It is a transient response similar in character to that predicted by our revised otolith model (in a preceding paper by Laurence R. Young and Jacob L. Meiry). When the L-nystagmus contribution is subtracted from the D response, and added to D_1, the resulting transients are similar to a normal (no linear acceleration) nystagmus response to this rotary input.

To determine the static sensitivity, consider the 10-sec period following acceleration, in which $(D-D_1)$ is relatively constant at 26°/sec. The centripetal acceleration at that time of 43 ft/sec² yields an L-nystagmus sensitivity of 9.7°/sec/g. This sensitivity is of the same order as the determinations from the three other sets of experimental data mentioned above. Referring now to the differences between D and D_1 for the

deceleration and no rotation parts of the experiment, it is seen in figure 6(*c*) and 6(*d*) that the calculated L-nystagmus is approximately zero during the prolonged period of zero centripetal acceleration. The negative calculated L-nystagmus during the deceleration phase may be attributable to the jerk receptors noted above. However, no linear model will suffice, since the responses in figure 6(*a*) and 6(*c*), starting with identical initial conditions on the output and opposite inputs, do not yield opposite transients.

An alternate explanation for the differences seen during the acceleration and deceleration phases, which leaves intact the theory of L-nystagmus responding to lateral linear acceleration, involves the notion of semicircular canal nystagmus inhibition by compressive forces on the otolith. During acceleration in position D, the compressive forces on the utricular otolith are reduced, which enhances the semicircular canal nystagmus. During acceleration facing backward, position D_1, the otolith is pressed against the macula, thereby inhibiting the semicircular canal nystagmus. Just the opposite effect holds during deceleration. The inhibition theory predicts, at least qualitatively, the positive difference in nystagmus response $(D - D_1)$ during acceleration and the negative difference during deceleration. Still another possible mechanism for explaining these transients is the hypothesis of a unidirectional rate sensitivity element, common to many biological subsystems. If the otolith or L-nystagmus mechanism were far more sensitive to an increase in lateral acceleration than to a decrease toward zero of lateral acceleration, the transient responses of the type shown in figure 6 could be explained. Since no other direct evidence for this theory is known at present, it is not being actively pursued.

Comparisons of the Lansberg data for other body positions were analyzed in a manner similar to the $D - D_1$ comparison, keeping in mind Lansberg's caution on interpretation of these latter data because of subject differences. In comparing A_1 and A_2 acceleration and constant velocity, for example, the centripetal acceleration has the same compressive component on the otolith in each case and should have the same direction of additive L-nystagmus, slow phase down. This is in the same direction as the conventional semicircular-canal-stimulated nystagmus for A_2 but in the opposite direction for A_1, which indeed shows a direction reversal. The difference between A_1 and A_2, shown in figure 7,

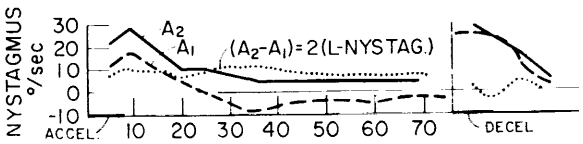

FIGURE 7.—*Calculated L-nystagmus from Lansberg et al. tests with* A_2 *and* A_1 *body positions.*

is a relatively constant 10°/sec nystagmus magnitude, which yields an L-nystagmus sensitivity to vertical acceleration of 4°/sec/g. This is a lower sensitivity than the horizontal-lateral acceleration sensitivity, which may be explained by realizing that only part of the acceleration is a shear component. When the calculation is performed relating the L-nystagmus to the shear component of g-force, assuming the utricular otolith plane elevated by 30° from the horizontal, the resulting sensitivity is 8°/sec/g, in closer agreement with the horizontal L-nystagmus sensitivity figures.

Finally, in comparing orientations B_1 and C_1, the L-nystagmus adds to the semicircular canal nystagmus in C_1 and subtracts from it in B_1, yielding a very slowly decaying magnitude difference between the two, as shown in figure 8.

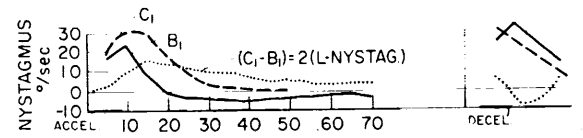

FIGURE 8.—*Calculated L-nystagmus from Lansberg et al. tests with* C_1 *and* B_1 *body positions.*

The calculated L-nystagmus sensitivity (vertical nystagmus) for this case is 4°/sec/g, considering only the g-component parallel to the otolith plane. These findings are not consistent with the inability of Niven et al. to find evidence of vertical nystagmus in response to linear periodic motion stimulation.

In conclusion, evidence from a wide variety of sources is used to support a preliminary model of the effects of linear acceleration on vestibular nystagmus. The evidence for an additive com-

ponent depending upon the direction and magnitude of the shear force on the utricular otolith is relatively strong, with sensitivity in the range 5° to 18°/sec/g. The evidence for modification of the semicircular canal nystagmus output by the compression of the otolith or distortion of the canal rests on considerably weaker ground. Data relevant to the dynamic response of L-nystagmus come from the barbecue-spit nystagmus experiments, our treatment of the Lansberg experiments, linear oscillation experiments, and our otolith model based on subjective orientation. We do not yet feel sufficient confidence in any one model to tie together all this evidence on the dynamic aspects, although work is continuing in this direction.

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DISCUSSION

VAN BUSKIRK: Could you explain to us what you mean by specific force and tell us why you have chosen this in your models as the stimulus for the otoliths rather than a linear acceleration vector which would include the contribution of gravitational action as well as all of the accelerations which occur as a result of movements relative to an inertial reference frame?

YOUNG: The principle of equivalence in the general theory of relativity states that gravitational mass and inertial mass are equivalent, or that it is impossible to distinguish directly between gravitational and nonfield forces. The resultant gravitational-inertial force on any mass (such as the otolith) is the vector sum of the weight (mg) in the direction of the vertical and the inertial reaction force (ma) in the direction opposite the linear acceleration of the mass with respect to inertial space. The resultant force is $m(\overline{g}-\overline{a})$, and the specific force $(\overline{g}-\overline{a})$ is the resultant force per unit mass. This unit is widely used in the inertial guidance field as it represents the "stimulus" which is measured by linear accelerometers and seems appropriate for consideration as the single otolith stimulation.

JONGKEES: I should like to ask some questions, not in the field of the model but in the field of what is behind it. There is one thing which I do not quite understand. You said you have to wait about 30 seconds before you can use your data; but when you use a rotating device, such as was shown earlier in the meeting, I am afraid there will be no blood left in the brain. This anemia of the brain will greatly influence the whole situation. In the second place, you talk about L-nystagmus which would add to the original canalicular nystagmus. Is it not the old Alexander law, as old as 1906, that when you want to enhance a nystagmus, you ask the patient to look in the direction of the quick phase, and when you want to prevent it, you have him look in the direction of the slow phase? Also, is there any place in your theory or model for the nystagmus you provoke by placing an animal on its side or asking a man to look sideways and only moving him in a complete linear accelerated movement?

YOUNG: I had hoped to ask you some questions about the basic information that goes into the modeling. I will take your questions in order. You misinterpreted what I said about waiting sufficient time for the counterrolling data. I was referring to the static counterrolling tests, which were just one of the series that Kellogg reported to us. To make a meaningful static test, you would have to move to, say, the 25° position and wait there better than a half a minute before taking the picture. With the dynamic counterrolling test in which you are continually rotating, surely you cannot wait or it would not be a dynamic counterrotating test.

JONGKEES: Are you not afraid you will introduce mistakes by measuring too soon?

YOUNG: You must measure in the dynamic counterrolling test as the man is spinning. You must measure simultane-

ously the eye torsional angle and the angle with respect to gravity.

JONGKEES: You would have to wait until the canalicular effects have passed?

YOUNG: That is another point entirely. As far as waiting until the canalicular effects have died out, yes. My impression is that they do wait several cycles until taking any data.

JONGKEES: But you have to wait for about 30 seconds in the vertical canals?

YOUNG: Yes. I do not know how long Captain Kellogg actually does wait.

KELLOGG: About five to six cycles.

YOUNG: So the minimum time you would ever wait would be 20 seconds. The second question Dr. Jongkees asked was about L-nystagmus and the direction of gaze. The L-nystagmus, as I postulated, is related solely to the direction of linear acceleration. My impression is that the experiments that were done here at Pensacola control the direction of gaze on the linear tract experiments when eliciting the nystagmus to pure linear acceleration. Is that correct, Dr. Guedry?

GUEDRY: This was an experiment by Niven, Hixson, and Correia. Dr. Correia was actually a subject in the experiment, so I had better let him answer that particular question.

CORREIA: An attempt was made to fix dead ahead during all of the experimental trials. Each subject was instructed to fix dead ahead, but, of course, this is not saying that it was achieved.

JONGKEES: I am afraid you cannot fix straight ahead.

YOUNG: Without a fixation point?

JONGKEES: When you undergo the influence of the otolithic reflexes, your eyes will move when you are in the dark. But you were in the dark, I think, or had you a light to look at?

CORREIA: No, we were in the dark.

JONGKEES: Then that is the whole examination on the parallel swing?

CORREIA: That is correct. But does not your point and Alexander's law pertain to an ongoing response to angular acceleration in which the magnitude of the response is modulated by the direction of the gaze?

JONGKEES: Yes.

CORREIA: In this particular experiment we were attempting to demonstrate whether pure linear acceleration could generate a systematic nystagmus which reversed in direction and was related to the stimulus regardless of its origin.

JONGKEES: Yes. Of course, that is the same as the parallel swing experiment the results of which we published some five years ago. I think it is also the same nystagmus you find on a quickly moved cart. Therefore, I do not quite understand why you say it is an influence on canalicular nystagmus. In my opinion, there is no reason to say this has something to do with a combination of the two. When you get this information on the parallel swing, it is possible, I think, to explain it completely by otolithic stimulation.

YOUNG: I fully agree with that. My schema had indicated, if you recall, a lower pathway (the L-nystagmus path) for pure otolithic stimulation. The upper path was pure canal. Then there was a cross-feed path showing possible inhibition or enhancement of the canalicular nystagmus by the otolith output.

JONGKEES: So you think you can have the path to the nystagmus both via the otoliths and via the canals and they may influence each other?

YOUNG: Yes. I am glad you added the "may influence each other." Of course, it is my opinion that that is where the questionable portion is.

CORREIA: In showing the Benson-Bodin data, you were talking about L-nystagmus and canal nystagmus, and I am trying to clarify this. Are you assuming that during constant velocity rotation about a horizontal axis you have a canal input?

YOUNG: The cause of the steady-state bias remains a puzzle. All the current theories that are worked out to any extent would expect those plots to be symmetric and not biased to one side. We have hopes that this question may be answered by Steer in his thesis at our laboratory. I was just talking about the nystagmus modulation from 90° to 270°.

CORREIA: How does your model handle the reversing nystagmus at 30 rpm that you get about the horizontal axis?

YOUNG: That came out very nicely just by the vector sum. At 30 rpm the semicircular canal nystagmus was down in amplitude. The L-nystagmus sensitivity was up in amplitude. As you remember, that curve was increasing rapidly with frequency. It reached a point where the L-nystagmus was greater than the semicircular canal nystagmus; consequently, for those portions of the cycle where you were subtracting L-nystagmus from semicircular canal nystagmus, you would get a reversal.

BENSON: I am now confused. Though first I must commend you for fitting our data to a straight line; that impresses me very much. However, I must also admit that it does not really help me to understand the mechanism by which the sustained perrotational nystagmus is produced, for, as a physiologist, this is what I am trying to understand. I wonder about the benefit of constructing mathematical models of systems that we do not adequately understand physiologically; but that is another subject.

Let me get one point straight. Concerning the sustained nystagmus you see during horizontal axis rotation, are you saying there is a canal component there or not?

YOUNG: I said we do not yet have an explanation for the sustained nystagmus.

BENSON: You put into your equation a component which you attribute to canal activity?

YOUNG: Yes, but that is a puzzle to me at present.

BENSON: Fair enough. I now understand that. The other point is the effect of otolithic or gravireceptor information on postrotational nystagmus. In your model this interaction is represented by a multiplier. We showed at the last meeting that when gravireceptor information was not in accord with an inappropriate semicircular canal signal, the suppression of nystagmus which occurred was not of a multiplicative or a subtractive character, but was one in which the time constant of decay was changed. Is this taken care of in your model too?

YOUNG: Dr. Benson's question gets at something which is clearly not handled by a simple deterministic model. We

have illustrated the way that the more complex relationships that we get into when there is conflict between canal and otolith output must be handled by an entirely different type of mechanism. The illustration shows that you can categorize the various combinations of canal and otolith output to give the sensation that would appear when these exist concurrently. The simple schema I showed did not take your point into account. Cataloged in the illustration are some of the partially explained and yet-to-be explained combinations of canal outputs and otolith outputs. For example, if you have an oscillating component of specific force sensed by the otoliths and various possibilities for what the canal is receiving at any time, you may feel either a parallel swing or barbecue spit, parallel swing and tilt, or the Ferris wheel sensation.

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Some Methodological Considerations in Caloric Tests of Vestibular Function

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SUMMARY

The widely used Fitzgerald-Hallpike caloric test of vestibular function is examined in detail. Improvements in the physical aspects of the test procedure are suggested. Experimental analyses of some variables which might affect the test response indicate that results are influenced by a considerable number of usually uncontrolled or poorly controlled factors.

INTRODUCTION

The effect of caloric stimulation on the vestibular system was noted over 100 years ago by Brown-Sequard (ref. 1) and was examined experimentally as early as 1876 by Bornhardt (ref. 2). However, it was not until 1906 that Bárány (ref. 3) first pointed out the clinical significance of this effect when used as a method of assessing vestibular function. Bárány also provided the first theoretical formulation of the origin of the reaction and described the results of aural stimulation with both cool and warm stimuli.

Although one of the most widely used clinical means of examining the integrity of the vestibular system, as well as a frequently employed experimental approach to assessing various aspects of vestibular function, caloric test methodology has varied considerably through the years, and varies considerably even today. In 1911 Brünings (ref. 4) published what is apparently the first account of a quantitative method for the caloric reaction. He devised an otocalorimeter to measure water volume and rate of flow as well as an otogoniometer to measure the angles for various test positions of the head. Since that time, a variety of methods of inducing caloric vestibular reactions has been advanced. These methods encompass a wide range of differences concerning temperature of the stimulus, duration of irrigation, water volume, rate of flow, position of the patient or subject, method of evaluating responses and, in short, almost every conceivable variable in the test procedure.

In 1942 Fitzgerald and Hallpike (ref. 5) described what is probably the best known caloric test methodology. Their procedure was designed to meet three requirements: (1) The test should be easy to apply and comfortable for the subject; (2) results should be reliable and valid measures of sensitivity; (3) the test should have the capability of revealing directional preponderance (ref. 6). Since the Fitzgerald-Hallpike technique is so widely known, and since many of the caloric test variations are simply modifications of this approach, the method will be examined in detail and some experimental evaluations of the elements of the test undertaken.

THE FITZGERALD-HALLPIKE CALORIC TEST

In following the Fitzgerald-Hallpike approach, the subject or patient reclines on an examining table with his head elevated 30°. (See fig. 1.) A water bath containing tap water at 30° or 44° C provides the source for cool or warm irrigations. Irrigation periods are prescribed for a duration of 40 seconds, with a recommended flow of at least 250 milliliters of water into the external

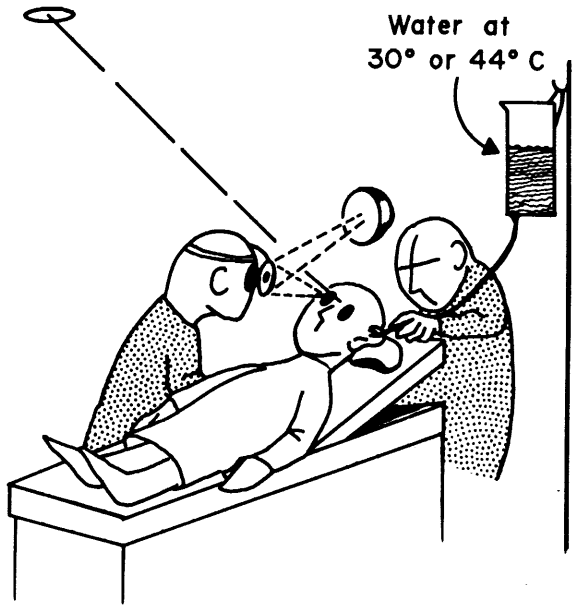

FIGURE 1.—*Illustration of the original procedure recommended in the Fitzgerald-Hallpike technique (adapted from fig. 2 in ref. 5).*

auditory meatus. The return flow of water from the ear is usually collected in an emesis can or other suitable container by the same individual who administers the stimulus. A second examiner visually observes and times the eye-movement response of the subject who fixates on a mark placed on the ceiling of the room. Two general modifications of this technique involve: (1) the use of Frenzel glasses, and (2) electronystagmography (ENG). Frenzel glasses do away with visual fixation and magnify the eyeballs, thereby making observation of the eye movements easier. Electronystagmography permits the recording (corneoretinal potential method) of ocular nystagmus, usually (in clinical settings) from behind closed eyes or in a "semidarkened" room with eyes open.

Some Physical Improvements

A number of physical improvements of the Fitzgerald-Hallpike technique are now possible. Water temperature can be kept constant by the use of highly controlled constant-temperature regulators, thereby assuring uniformity of the stimulus. Duration of the stimulus can be set on a timer, and by means of solenoids, delivery of the stimulus can be accomplished, and its duration regulated, simply by depressing a switch. Since water in the tubes will differ in temperature from water in the bath, draining of the irrigation tube is required. This process can be largely eliminated by using a closed-loop system whereby the water is circulated from the bath, through tubing and back to the bath, or by employing other types of circulation procedures. Considerable simplification of electrode use can be effected by attaching a box to the examining table and plugging leads from the subject into this nearby relay station. Of considerable aid is a device which provides a comfortable headrest for the subject, elevates his head to the proper position for caloric testing, and in addition, serves as a catch basin for the return flow of water from the ear. (See fig. 2.) If a drain and tubing are located at the rear of the device, a

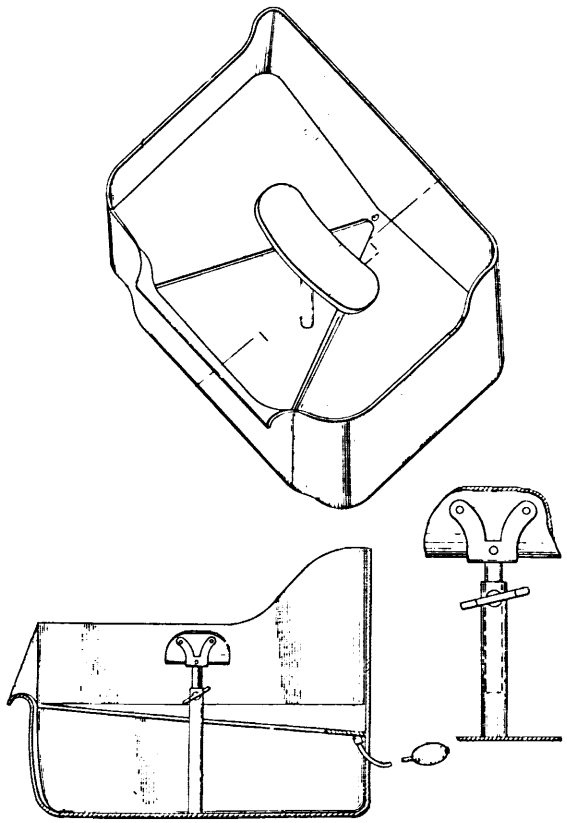

FIGURE 2.—*Illustration of the caloric irrigation receptacle. The device serves as a head elevator, headrest, and catch basin for the return flow of water from the ear. Three views are presented.*

receptacle may be placed under the table to collect the water. In this fashion, a large number of irrigations may be performed with a minimum of technical difficulty. (See fig. 3.)

Some Factors Affecting the Caloric Test Response

As a result of some findings relating arousal to rotation-induced nystagmic output (ref. 7), an evaluation of the subject's state of alertness on the caloric response was undertaken. Specifically, the nystagmus occasioned by angular acceleration was shown to be markedly influenced as a consequence of simple instructions which were labeled "mental arithmetic" and "reverie" and which appeared to influence states of arousal (ref. 7). The reverie condition resulted in significantly less nystagmus than the active mental arithmetic state. To assess the influence of this alertness variable on caloric responses, 16 subjects were given irrigations according to the Fitzgerald-Hallpike technique, with one exception: Instead of fixating on a ceiling marker, the subjects fixated on a marker suspended 30.5 centimeters above them (ref. 8). In total darkness (electronystagmography) and in illumination (where nystagmus was timed and rated by an experimenter who was unaware of the set of instructions given the subject), mental arithmetic tasks produced significantly more nystagmus and higher ratings than did reverie instructions. (See fig. 4.) Moreover, when an additional trial in illumination was administered with ceiling fixation (1.63 meters) and a mental arithmetic task, consistently shorter durations and lower ratings were obtained than in the case

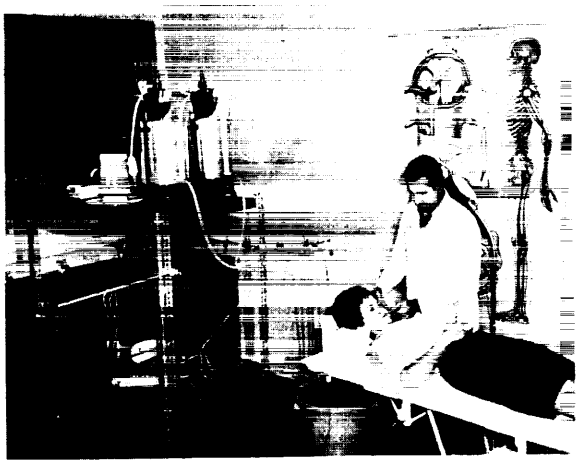

FIGURE 3.—*Depiction of a caloric irrigation test situation.*

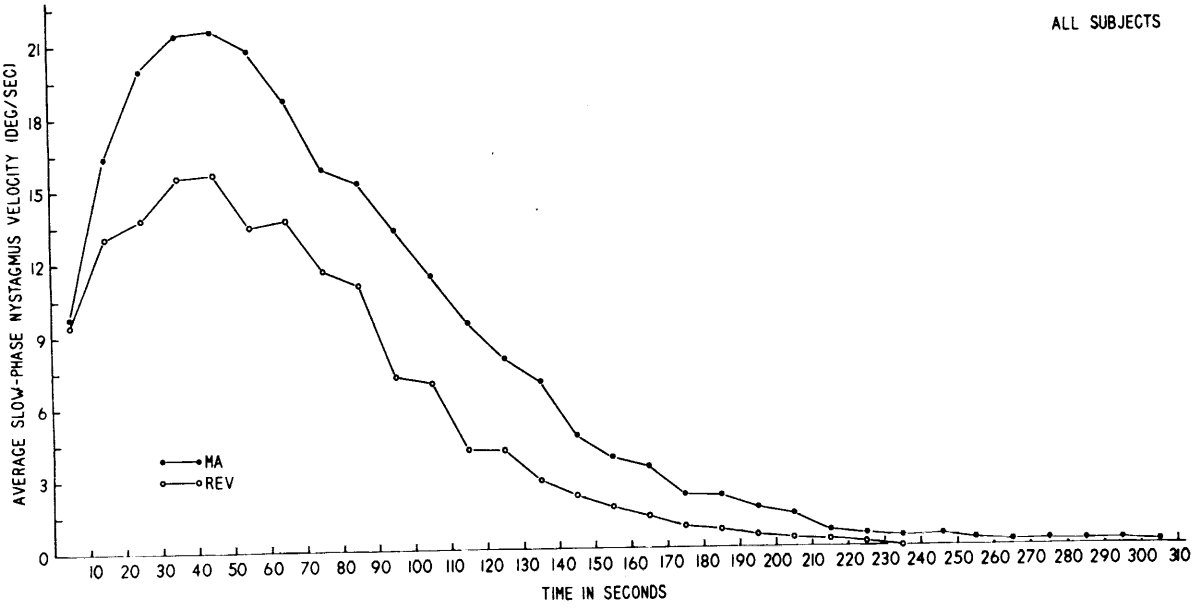

FIGURE 4.—*Slow-phase nystagmus plots showing the influence of mental arithmetic* (MA) *and reverie* (REV) *instructions on responses to caloric irrigations. Data were obtained from subjects tested in total darkness with their eyes open. (Reprinted from ref. 8 with permission.)*

of either mental arithmetic or reverie with near fixation. (See fig. 5.) In fact, two subjects were observed as having no detectable nystagmus during ceiling fixation. (A similar observation during pilot studies with two subjects had determined this design by emphasizing the importance of near-fixation. Incidentally, Bárány is reported to have used his finger as a fixation point for his patients.)

In ENG work, it should be pointed out, the greatest amplitude of nystagmic response, insofar as recording is concerned, is obtained with eyes open in total darkness; next best is a condition where the eyes are closed lightly; while least effective is an "eyes open" condition in an illuminated environment (nystagmus is frequently not recordable under the latter condition, even at fairly high amplifier gain settings, although the eye movements may be directly observable). A comparison of "eyes open" and "eyes closed" tracings obtained in total darkness can be found elsewhere (ref. 9).

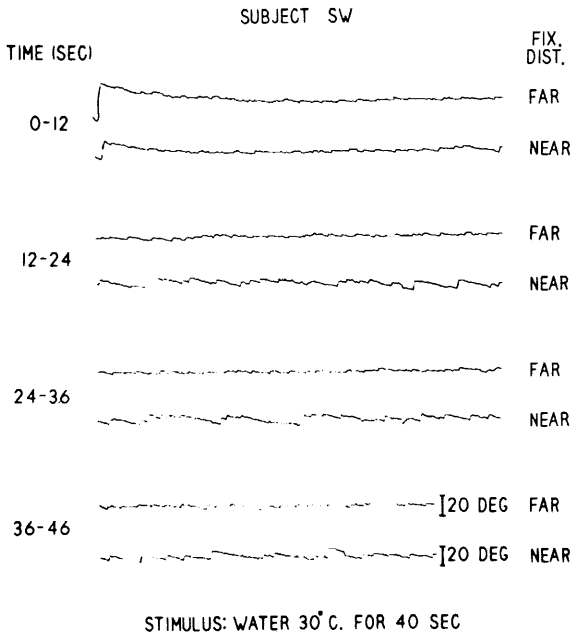

FIGURE 5.—*ENG tracings obtained from a subject while performing mental arithmetic in an illuminated room. The "near" record was obtained with a fixation distance of 30.5 cm (nystagmus rating by the observer was 2.0 on a four-point scale). The "far" record was obtained with ceiling fixation (1.63-m distance) and was rated 1.5. Zero time indicates moment of stimulus termination. (Reprinted from ref. 8 with permission.)*

Thus nystagmus is markedly influenced by the mental state of the subject, by near versus far fixation, by whether eyes are open or closed in the dark, and by the presence of visual-fixation objects.

Several studies have reported significant and marked reductions in duration and in slow-phase velocity of eye movement as a result of as few as four repeated caloric stimulations (refs. 10–12). Following Wendt's (ref. 13) notions regarding alertness and the findings noted above relating relaxed (reverie) and alert (mental arithmetic) states to nystagmic output, two groups of 10 subjects each were exposed to a series of 40 irrigations spread over 4 days. In all cases, these stimuli comprised 30°-C irrigations for 30 seconds. For one group all 40 trials were in total darkness (during which subjects performed varied mental tasks); for the other group, active visual fixation on ceiling markers was employed. On the day before, on the day after, and also 1 month after the 40 "habituation" trials, a series of irrigations both unilateral and bilateral and using both 30°- and 44°-C stimuli was administered in total darkness according to a modified counterbalanced design. During these pretests and posttests, subjects did mental arithmetic. Results showed no effects of the 40 trials on duration of response for either group (ref. 14). However, for the "darkness" group there was a statistically significant increase in the number of posttest eye movements and no change in the amount of slow-phase eye displacement, whereas the "fixation" group showed a different effect; that is, no change in frequency and a significant drop in slow-phase activity. Both groups showed a directionally specific reduction in the subjective reactions produced by calorization. (See table 1.)

Thus, over the course of just a few trials, no significant change in the caloric nystagmic response need be expected in alert subjects. However, with many stimuli a modification (not necessarily a response decline) of the nystagmic reaction may occur, with some changes apparently dependent upon the presence or absence of opportunities for visual fixation. Similar conclusions have been noted with respect to angular acceleration (refs. 15 and 16).

In seeking a convenient means of varying caloric stimulus intensity for a study on the

TABLE 1.—*Summary of Changes in Nystagmus Data and in Subjective Responses From 2 Groups of Subjects After Exposure to 40 Unilateral Caloric Irrigations*

[Values are expressed in percentages of the pretest response. Each group comprised 10 subjects. Post-2 tests were conducted 1 month after Post-1 tests with no intervening stimulation]

Direction	Dark group		Visual fixation group	
	Post-1	Post-2	Post-1	Post-2
Slow-phase nystagmus:				
Practiced	+1	−2	−23	−24
Unpracticed	+1	0	−11	−25
Number of nystagmus beats:				
Practiced	+30	+22	+7	−3
Unpracticed	+25	+24	+8	0
Duration of nystagmus:				
Practiced	+7	+4	0	−9
Unpracticed	0	0	−5	−12
Intensity of sensation:				
Practiced	−43	−28	−53	−24
Unpracticed	+19	+23	−14	+1

effects of repeated bilateral caloric irrigations of the cat, preliminary work indicated that, with temperature held constant, variations in the duration of irrigation seemed to affect considerably the vigor of the cat's nystagmic response (ref. 17). This brought into question a prevalent notion, usually based on duration data, that rate of flow, volume of water and, within some practical limits, duration of irrigation have little or no effect on human nystagmus. To examine these views, eight human subjects were tested in total darkness with ENG techniques using irrigation rates of 3 cc/sec for 25 and for 40 seconds and 15 cc/sec administered for 25 and 40 seconds, counterbalancing the order of stimulus presentation. Stimuli were all 30° C. Results showed no statistically significant differences in duration, frequency, or slow-phase output of nystagmus among the four stimulus durations for unilateral irrigations. (See fig. 6.) However, the longer durations of stimulation tended to produce greater peaks of slow-phase output—an effect that was also evident for the differences between rates administered for the same duration.

A new group of subjects was tested using bilateral stimuli (30° and 44° C administered simultaneously to the two ears). Stimuli were 3 cc/sec for 15 and 25 seconds and 15 cc/sec for those same two durations. Clear and statistically significant differences were obtained among the stimulus conditions for slow-phase and frequency measures of nystagmus. (See fig. 7.) Duration of response was not affected.

Thus, within the limits defined here, the interrelated aspects of flow rate, duration of stimulus, and volume of water appear to have marked influences on certain aspects of responses to bilateral stimulation and insignificant effects on the unilateral caloric test response. Duration of the nystagmic reaction, however, does not appear to be influenced by manipulation of these variables.

Temperature of the irrigation stimulus is a critical factor. Jongkees (ref. 18) and Aschan (ref. 19) have presented data evaluating the effects of water temperature on the caloric response. Within certain limits, very small differences in temperature result in substantial differences in the nystagmic reaction. Based upon their long experience in the field of caloric testing, both Jongkees (ref. 18) and Aschan et al. (ref. 20) recommend that cold stimuli should be 30° C and warm stimuli should be 44° C. (Aschan (ref. 19) has expressed the view that 45° C is required to produce a warm stimulus equivalent in deviation from body temperature to the 30°-C cool stimulus. Aschan uses a body temperature of 37.5° C as the base, whereas most other investigators cite the normal body temperature as 37° C.) Thus, the same values proposed in the Fitzgerald-Hallpike technique are recommended by these investigators. However, in employing electronystagmography, both Jongkees and his colleagues (refs. 18 and 21) and Aschan and his colleagues (refs. 19 and 20) noted that a stimulus duration of 30 seconds is sufficient to elicit a vigorous response.

The use of stimuli more divergent from body temperature than 30° or 44° C is considered unnecessary and liable to induce vertigo and/or sickness in subjects. Unless carefully administered (e.g., as in ref. 22), ice water is an unnecessarily strong stimulus for ordinary testing

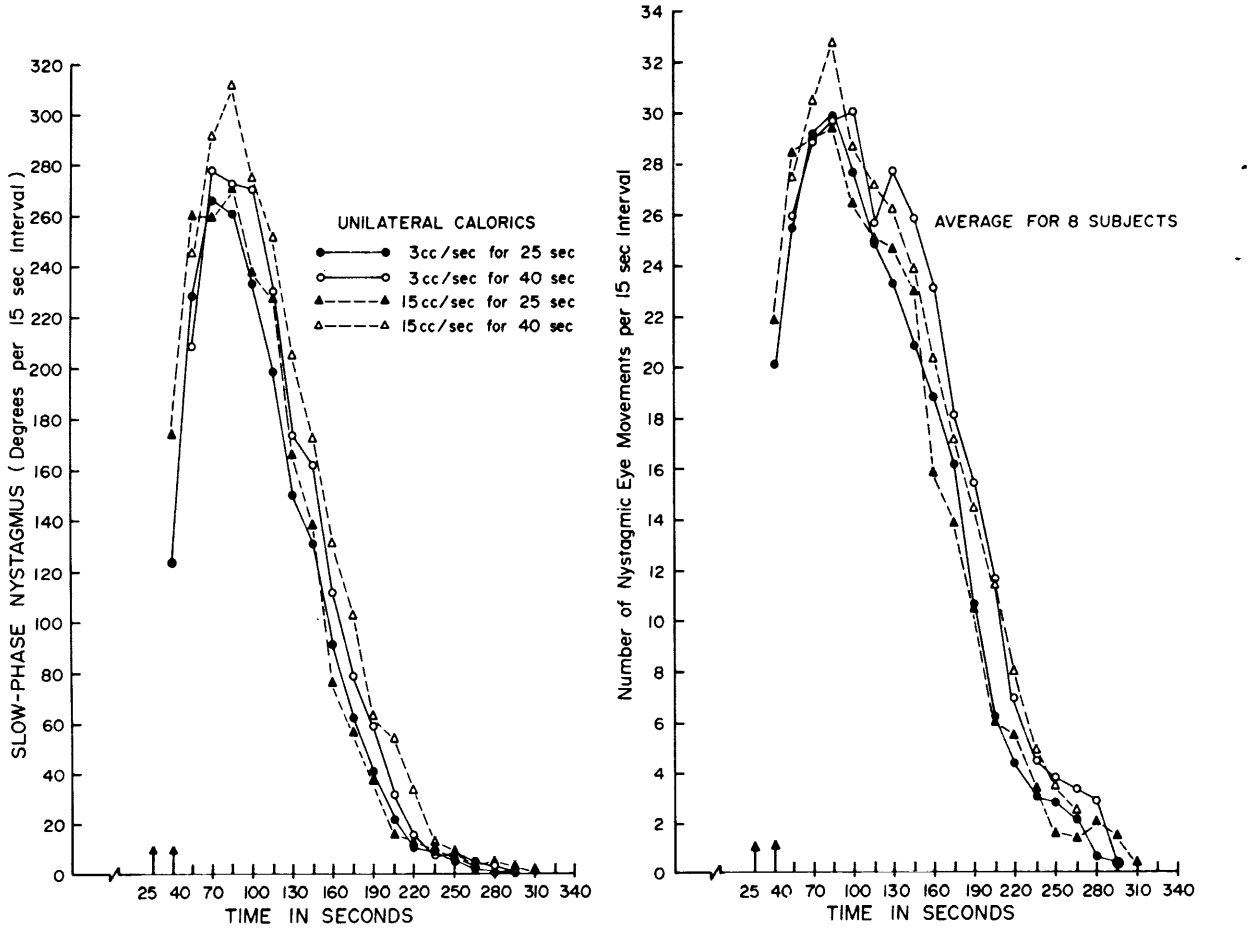

FIGURE 6.—*Slow-phase and frequency responses from eight subjects to four unilateral caloric stimuli (30°) with different rate durations. There were no statistically significant differences among the conditions.*

and can produce the undesirable side effects noted previously.

Related to the question of stimulus temperature is the problem of the time required for the temperature in the ear to return to normal after irrigation. Jongkees (ref. 18) reported an interval of 5 to 6 minutes as sufficient between two tests when water temperature does not differ by more than 10° from that of the body. Fitzgerald and Hallpike (ref. 5) cited 5 minutes as an appropriate intertrial recovery period. Cawthorne and Cobb (ref. 23) have reported measurements which indicate that the temperature within the lateral canal usually does not return to normal within 10 minutes after a 30°- or 44°-C irrigation. Loss or gain of temperature after 10 minutes was too slow to justify further observations. However, most of the temperature return occurred within 6 minutes.

Another point is of some interest. In electronystagmography, electrodes are routinely placed near the outer canthi of the eyes, and recordings are the result of the combined movements of the two eyes. Nagle (ref. 22) has indicated dissatisfaction with this approach on the basis of clinical observations. When both eyes were recorded separately but simultaneously (using the stimulating technique of 1 cc of ice water held in the ear for 40 seconds), Nagle noted that a clear difference in the response from each eye was consistently obtained (fig. 8). Specifically, the eye on the side of the irrigation yielded a stronger nystagmus. The effect did not appear under all stimulus conditions. However, an

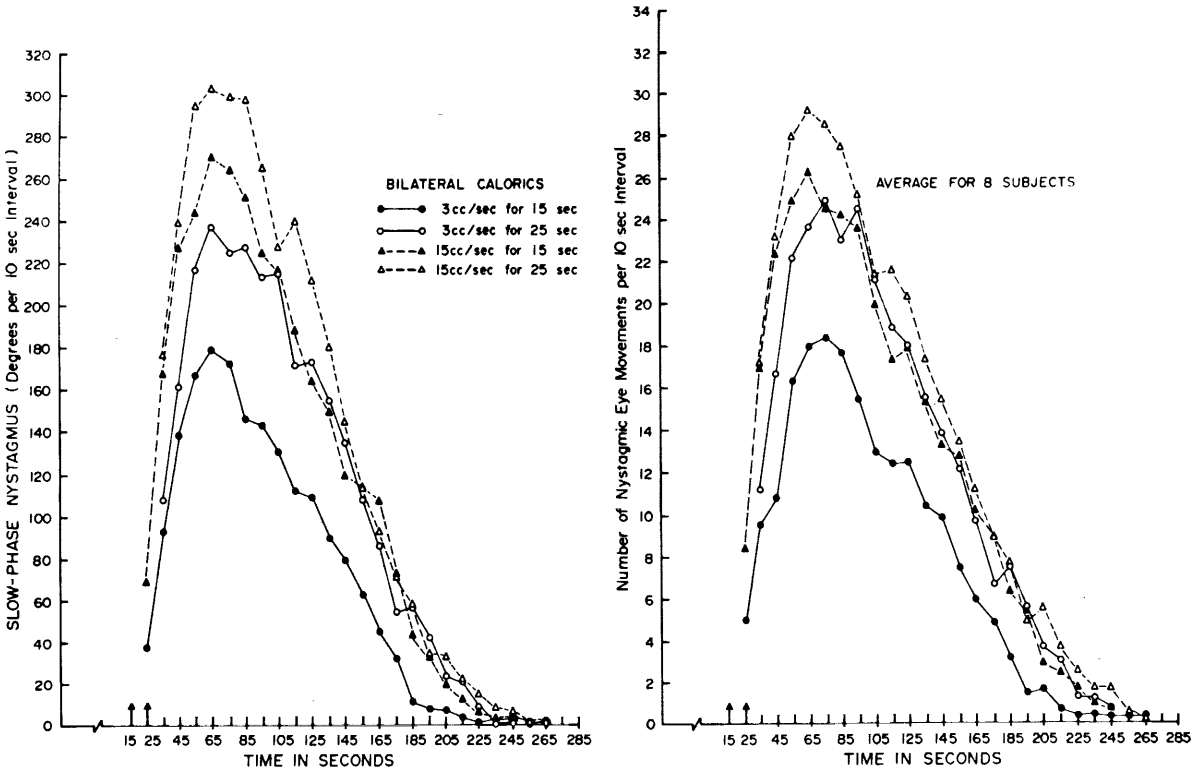

FIGURE 7.—*Slow-phase and frequency responses from eight subjects to four bilateral caloric stimuli (30° and 44° C administered simultaneously) with different rate durations. Statistically significant differences in slow-phase output and nystagmus frequency were obtained among the conditions. Duration of response was not significantly affected.*

interesting nystagmic response could be obtained from some subjects if both ears were simultaneously irrigated with a few cubic centimeters of ice water; viz, the eyes moved in opposed directions (fast phases toward the nose).

OVERVIEW

In the foregoing discussion, a description and evaluation of elements of caloric vestibular tests were undertaken with specific reference to the Fitzgerald-Hallpike technique. Other techniques are also used. Some of these have been devised to detect thresholds of nystagmus (e.g., Kobrak's method), while others appear to be used primarily because they are quick and convenient methods of providing all-or-none indications of vestibular function (refs. 6 and 24).

In summarizing this report, it would seem that there still exist gaps in information concerning the significance of various factors. These gaps and the lack of standardized equipment from one

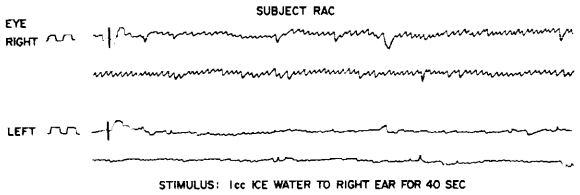

FIGURE 8.—*Separate but simultaneous recordings from both eyes of a subject given 1 cc of ice water in the right ear. The water was kept in the auditory canal for 40 seconds. Under these test conditions, the eye on the irrigated side shows a markedly stronger nystagmus. (Reprinted from ref. 22 with permission.)*

clinical situation to another make the recommendation of a single set of calorization procedures impracticable. The Fitzgerald-Hallpike approach has many excellent features (especially the mild stimulus temperatures recommended: 30° and 44° C) but, as originally described, can certainly be improved. Probably, however, more than one "standard" procedure is required to

satisfy the diversity of test situations and to stay in keeping with the notions that the test should be valid and reliable as well as comfortable for the patient and easy to administer. For example, when electronystagmography is employed, recording should be done in total darkness (eyes open) or, less preferably, with eyes lightly closed in an illuminated or "semidarkened" environment. Under these conditions, stimulation periods can be as short as 25 seconds. But, if ENG equipment is not available, Frenzel glasses appear desirable. If visual fixation is permitted (near-fixation is recommended), it may be necessary to use a 40-second irrigation. Finally, if there is no fine control of mild stimulus temperatures, Nagle's test procedure (ref. 22) appears satisfactory. Further work seems necessary to determine the optimum sets of factors for the several diverse situations in which caloric testing may be conducted.

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DISCUSSION

TANG: One thing I would like to mention concerns your trying to keep the subject alert by giving him mental arithmetic. I would suggest that if an electroencephalograph is used as a monitor, you can get a better idea whether he is in an alert state, especially in the dark with eyes open, because if he is not alert, alpha waves will appear on the EEG. When he is alert, asynchronous, almost low-amplitude asynchronous waves will be seen. We have tested this in subjects performing mental arithmetic during EEG recording. Prior to start of the mental task, alpha waves were seen in the EEG of male subjects, but with mental arithmetic these waves were replaced by asynchronous ones. Female subjects responded differently, however. When they were requested to do mental arithmetic during EEG recording, they either did not respond or gave the wrong answer, and the alpha waves continued on the tracing. In other words, mental arithmetic had no effect on the EEG of females.

Is the nystagmic reaction from each eye as you presented it synchronous or is each at a different rate?

COLLINS: At least in one of our tracings the right-eye movements tend to be a little sloppier than those of the left eye. They are pretty close but might not be exact.

With respect to the comments about EEG and about sex differences, a couple of points ought to be mentioned. Different tasks produce different results with respect to males and females. Some tasks are more conducive to holding the attention of males than others are, and I am sure the same holds true for females. We did some work with the EEG. We found that even with the mental tasks and even with the sensory stimulation of angular acceleration, you get alpha waves, with a good alpha subject, running right through the stimulus regardless; and that the eye-movement response tended to be a better indication of the subject's state of alertness than did the EEG.

KHALIL: Would you please give me an idea about the range of temperature change which is necessary to induce nystagmus on an average individual, the range of temperature change in the endolymph?

COLLINS: As far as getting nystagmus is concerned, this is going to depend upon what the subject is doing. If he is visually fixating, it is going to take more of a stimulus than it would in the dark for nystagmus to be recorded or observed. So with visual fixation, subjects can overcome some of the eye movements. The weaker the stimulus, the more readily the eye movement can be suppressed, simply by fixating visually. In total darkness with eyes open, you would elicit a recordable response with a weaker stimulus than would be required in an illuminated environment.

JONGKEES: One-tenth-of-a-degree range of temperature change in the dark will produce a response.

Eye-Mark Recording as a Vestibular Test Related to the Oculomotor Reflex[1]

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SUMMARY

Eye movements are essential for tracking an object in the visual field and stabilizing its image on the fovea. Therefore, for analysis of eye movements under this consideration, they should be observed in respect to the object in the visual field. For this purpose, a kind of "eye-mark recorder" which produces satisfactory results was introduced into the field of vestibular study.

The principal feature of this device is that the light reflected by means of a half mirror placed in front of the eye and an image of the visual scene taken by a lens fixed between the eyes are superimposed and transmitted to a 16-mm movie camera.

Optokinetic nystagmus was analyzed to illustrate the use of the device in this field of study. The exact relationship between eye movement and moving objects in the visual field is revealed, and several different patterns which would serve as clues to vestibular function information are distinguished.

INTRODUCTION

To analyze vestibular function in human subjects, investigations of eye movement have been widely carried out by various methods. These methods are based on two different frames of reference: (1) Observation of eye movement with respect to the head, and (2) with respect to the object in the visual field. With regard to the first reference frame, the techniques of electronystagmography, photoelectronystagmography, television, and so on have been used in investigating vestibular function. With regard to the second, an eye-mark recorder that has produced satisfactory results has been introduced in this field of study. By this method, the spot where the subject is looking and objects in the visual field are simultaneously recorded on one frame. These evaluations also provide a valuable clue to information regarding the labyrinth, since eye movements from the viewpoint of oculomotor physiology are considered to be responsible for enabling the eyes to fixate an object in the visual field.

The main aim of this paper is to demonstrate the outstanding value of this device and to illustrate its use in the field of vestibular research.

RECORDING OF EYE MOVEMENT

Eye movements are observed principally by three methods: mechanical, optical, and electrical. The mechanical method was introduced by Berlin (ref. 1) in 1891. He attached a small ivory cup with a bristle to the anesthetized cornea and registered eye movement by the bristle. Buys (ref. 2) reported another method in 1909 in which a small rubber ball filled with air was attached to an upper lid. Changes in pressure of the ball due to the movement of the lid corresponded to movement of the eye and were registered; this method is called pneumonystagmography. The optical method is divided into two types. One consists of taking pictures of the eyeball itself; another is that of registering reflected light from the cornea. The former type of observation was carried out initially by Von

[1] This work was carried out in part by cooperation with the vestibular research group in Kyoto University.

Judd, McAllister, and Steele (ref. 3), who took a motion picture of a white point which was attached to the cornea. The second-type observation was developed by Dodge (ref. 4). He placed a small lamp in front of the cornea and took a picture of the reflected light which followed eye movement. In 1951 Torok et al. (ref. 5) caught the reflected light by photocell and registered the eye movement; this technique is known as photoelectric nystagmography. Schott (ref. 6) developed the electrical method whereby eye movement is electrically recorded by the difference of the electrical potential between the cornea and the retina. This is the electronystagmographic technique.

In the beginning of the present century, various methods were used in the field of vestibular study to measure eye movement. Since electronystagmography was introduced, however, almost all studies have been carried out by this method (refs. 7–9). This technique was selected for the following reasons: (1) Eye movement could be recorded while the eyes were closed, and (2) eye movement other than the rhythmic movement called nystagmus could be avoided.

It has also been necessary in psychological studies to observe eye movement to determine the role vision plays in perceiving the environment. The electrical method was not used in every case; the optical method was used chiefly. The reasons for this may be as follows: (1) Observation of eye position as well as eye movement was necessary. Generally speaking, observation of eye position is difficult by electronystagmography; a d.c.-type amplifier was used by some researchers to alleviate this problem. (2) Observation of eye movement while the eyes were closed was frequently unnecessary, but there was a demand to observe eye movement in relation to the object in the visual field while eyes were open (ref. 10). In other words, it was necessary to know where the subject was looking. For this purpose, projection of the record of eye movement either onto a reference grid for transfer to the original scene or onto a facsimile of the original picture was used, but this is a troublesome procedure. The development of television, however, made it easy to superimpose two pictures on one television screen, and at the same time made it possible to observe where the subject was looking during the actual visual searching. J. Mackworth and N. Mackworth in 1958 (ref. 11) succeeded in projecting the spot where the subject was looking and the image of the objects in the visual field onto a television screen.

At the present time, eye mark is registered optically or electrically, and the eye mark and the image of the object in visual field are superimposed on movie films (optically) or on a television screen (electrically). The following are types of eye-mark recorders: (1) With Mackworth and Mackworth's device, the corneal reflection of a light following the movement of the eye appears on a television monitor screen as a bright spot, and the scene at which the subject is looking is displayed on the same television monitor. (2) Shackel's device (ref. 12) projects eye movement in both vertical and horizontal direction as a spot on an oscilloscope screen by applying electronystagmography. The object in the visual field is recorded by a television camera mounted on the head of the subject. The spot and the image of the visual field are superimposed on a television monitor screen by a mixer. (3) With the device of Mackworth and Thomas (refs. 13 and 14), the eye mark via a prism placed in front of eye and the image of the visual scene given by a lens fixed on the top of the head are transmitted to a 8-mm movie camera which is mounted on a helmet. (4) The device shown in figure 1 and called the NAC eye-mark recorder was developed through the cooperation of NAC's staff and the vestibular research group of Kyoto University, Japan. It has proven to be adequate for vestibular studies. A description of the device and of some advantages in using it follows.

DESCRIPTION OF NAC EYE-MARK RECORDER

Principal elements of the eye-mark recorder are shown in figure 2. A beam of light is projected onto the cornea from a spot lamp, which is fixed at the outer margin of the subject's eye. The reflected light from the cornea is further reflected upward by a half mirror which is placed in front of the eyes. A lens fixed above the half mirror makes a small image of the filament

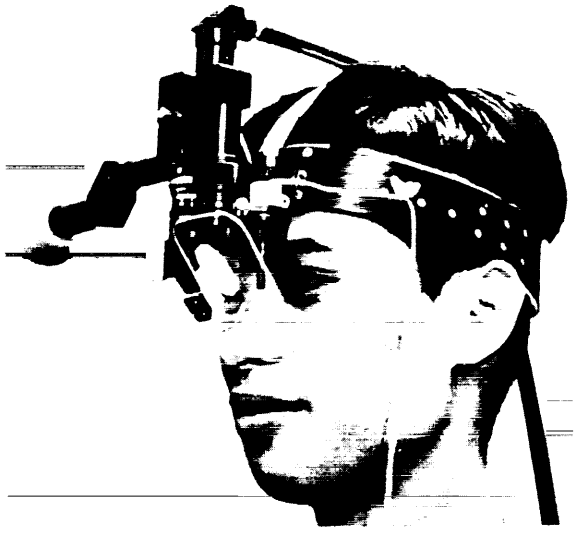

FIGURE 1.—*NAC eye-mark recorder.*

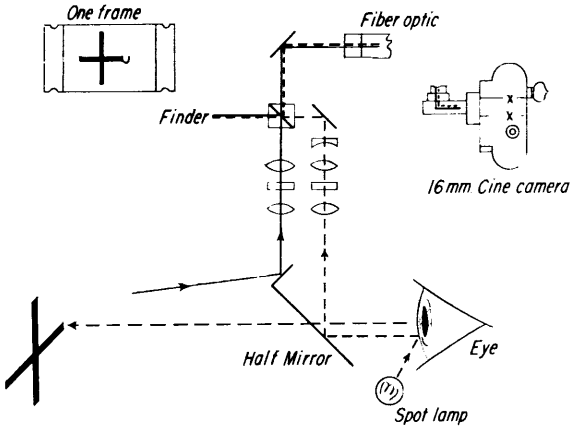

FIGURE 2.—*Principal construction of the eye-mark recorder.*

of the lamp. This small image is called the eye mark and indicates the spot at which the subject looks. The eye mark and objects in the visual field are recorded by a 16-mm movie camera through an optical fiber.

The limits of the visual field recorded by this equipment are 22.7° in the vertical direction and 31.4° in the horizontal direction. Head movements of the subject are determined by measuring the movement of the frame of the film in relation to a fixed object in the visual field. Eye movements with respect to the orbit are also determined by measuring the movements of the eye mark in relation to the frame of the film. Eye movement in relation to the object in the visual field can be determined directly by measuring the movement of eye mark in relation to the object on the film.

In studying the equilibrium function of human subjects, observations should be carried out accurately under natural conditions. The following merits of this device make the equipment satisfactory for fulfilling such requirements:

(1) Binocular viewing made possible.—Corneal reflected light, which indicates eye movement, is transmitted into the eye lens by the reflection of the half mirror placed in front of the eye so that natural binocular viewing is possible while the subject is being studied.

(2) Light in weight.—The optical system which should be fixed to the head of the subject is approximately 1.5 pounds in weight. As a result, the free movements of the subject are not disturbed by weight of the equipment.

(3) Small binocular parallax.—The lens which gives an image of the object in the visual field is placed between the eyes, so that the picture taken by the lens and the scene viewed by the eye produce as small a binocular parallax as possible.

(4) Available for 16-mm motion picture.—The device was originally designed for a 16-mm motion picture camera so that fine analysis is possible.

(5) Available for high-speed photography.—High-speed photography over 30 frames/second is available; it is impossible by television camera.

(6) Available for simultaneous recording of another phenomenon.—The device is also designed to be able to register an acceleration registrogram on the same film.

(7) Eye movements on either side may be observed without changing the lens.—With this equipment movement of either eye can be observed by changing the position of the lens. Sufficient data can be obtained in most patients by observing the movement of only one eye, since movements of both eyes coincide; but in other patients it is necessary to observe the movement of both eyes separately. This device permits such observation.

(8) Simultaneous observation by two examiners is possible.—One finder attached to the camera and one finder attached to the optical system

make possible simultaneous observation by two examiners.

ILLUSTRATIVE USE

The present study, which was undertaken to analyze the vestibular mechanism with this device, illustrates its use in the observation of optokinetic nystagmus, which has a close relationship to the function of the vestibular system.

In this demonstration an optical cylinder was rotated in front of the subject; that is, the subject was required to look at lines which moved from one side of the visual field to the opposite side. The speed of the movement of lines was increased at a certain rate. Previously, the induced optokinetic nystagmus had been registered and analyzed by means of electronystagmography. Different results were obtained from normal subjects as compared to those from patients with dizziness with regard to the speed of the slow phase, number of beats, and so on. Eye movement provoked by optokinetic stimuli is considered a combination of pursuit movement and return movement. But, from glancing at the registrogram (ENG), it is difficult to know how closely the eyes are following each moving object in the visual field, because the ENG shows only the relationship between the position of the eyeball and the orbit.

Figures 3 and 4 show some consecutive frames taken by the eye-mark recorder in this experiment. This film was taken at 24 frames per second. By looking at these figures, we can easily understand the correlation between the eye movement [white spot] and the objects [white lines] in the visual field. When the objects moved slowly, the eyes followed each object perfectly (fig. 3); but when the objects moved more rapidly, the eyes were unable to follow this movement (fig. 4), although nystagmus was induced in both cases. Further observations gave us more detailed information. In figures 5 and 6 several consecutive frames are placed vertically in a row. Each frame was simplified so that only the position of an eye mark and the vertical lines remained. The number which appears on the left side indicates the number of the first frames of each group; the consecutive numbers are deleted. This number also indicates the period of time which passed after the cylinder began rotating. For example, the number 7–13 indicates that the corresponding frame was taken $7^{13}/_{24}$ seconds after the optical cylinder began moving. The group of frames which begins with no. 7–13 shows typical optokinetic nystagmus. The eye mark moves to the left side and is fixed on the line which moves to the left side. On the frame 7–17, the eye mark slides a little. Next frame, 7–18, shows the rapid phase of nystagmus. On the next frame, 7–19, the eye mark catches the following line exactly. Then the eye mark moves to the left again, fixing on the line. The groups of consecutive frames in figure 5 were taken when the line moved slowly. In this case, the velocity of the eye-mark movement coincides with the movement of the line; that is, the eye mark moves to the left side fixing on the line which moves to the left side. However, some varied patterns are created when the eye mark jumps from one line to the following line. In consecutive frames starting from no. 2–02, the eye mark stops before reaching the next line as shown in frame 2–11. Then the eye mark moves to the left side with the same velocity as that of the line (2–11—2–13). Next, the eye mark moves to the right in order to catch the consecutive line. This type of pattern

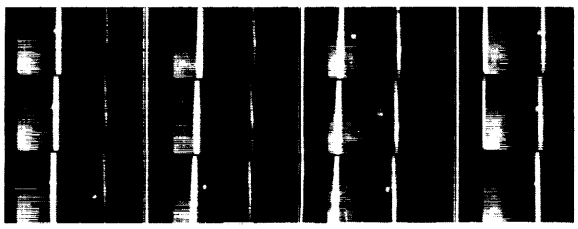

FIGURE 3.—*Consecutive frames of optokinetic nystagmus taken by the eye-mark recorder during slow rotation of optical cylinder.*

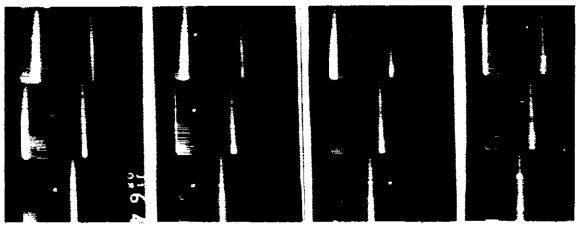

FIGURE 4.—*Consecutive frames of optokinetic nystagmus taken by the eye-mark recorder during rapid rotation of optical cylinder.*

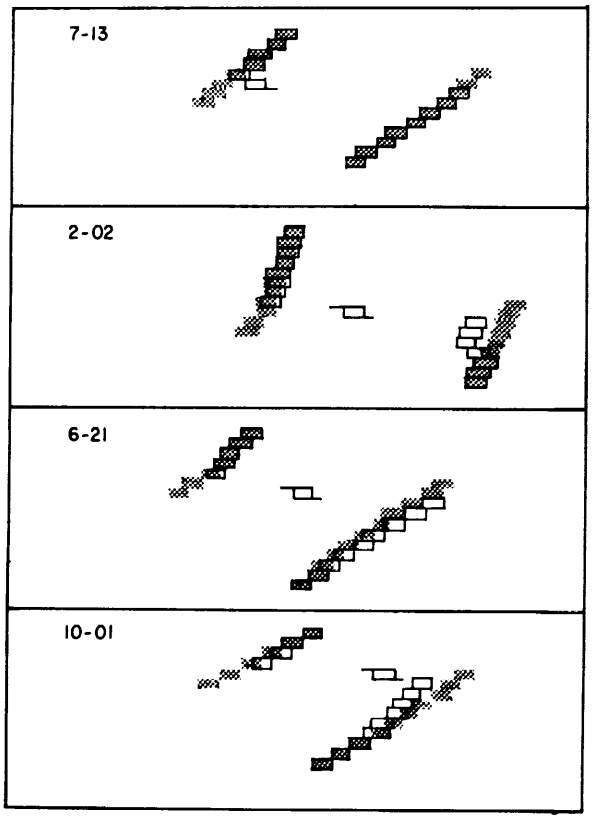

FIGURE 5.—*Simplified schema of consecutive frames of optokinetic nystagmus. The white square indicates the eye mark and the shaded square indicates the vertical line.*

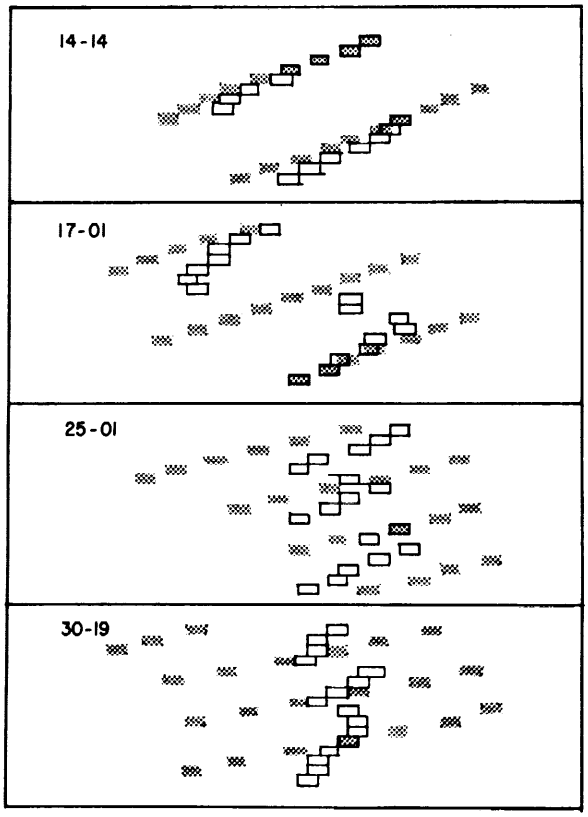

FIGURE 6.—*Simplified schema of consecutive frames of optokinetic nystagmus.*

is frequently observed when the line moves very slowly. In this case, the number of beats of nystagmus is greater than the number of lines which pass in front of the eyes. In the group of consecutive frames starting from 6–21, the eye mark jumps over the consecutive line (7–3) and then gradually returns to it. In the group of consecutive frames starting from no. 10–01, the eye mark waits for the consecutive line to appear (10–6—10–8), then catches it gradually. The degree of the overjumping or waiting is small. The groups of consecutive frames in figure 6 are those taken when the lines moved rapidly. In this case, the velocity of movement of the eye mark is slower than that of line movement. In the group of consecutive frames beginning with 14–14, the eye mark caught the line at the beginning, but gradually dropped behind the line. When the lines move rapidly, sometimes the eye mark misses the following line (17–8—17–9). In this case, the number of beats of nystagmus is less than that of the lines which pass in front of the eyes. The degree of overjumping (25–7) or waiting (17–10) becomes greater. Sometimes, a slow phase of nystagmus appears which is completely independent of the line. When the lines move more rapidly, the eye mark moves slightly and reacts to the line when the line meets the eye mark as shown in the group of consecutive frames starting from 30–19.

From this observation, several different patterns are distinguished which would be clues to vestibular information. A number of patients and normals will be studied with this method and the findings reported.

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DISCUSSION

VALENTINUZZI: In order to enlarge the technical possibilities in this field, I would suggest another procedure; that is, the measurement of the electrical impedance variation. Recently I visited Baylor University where the impedance variation has been used to follow other physiological events. The measurement of the impedance variation of the eye has been tried by Geddes in the horse, with good results. He published a paper in 1965 (The Southwestern Veterinarian, vol. 19, no. 1). Also, he considers this technique to record eye movement in his book on bioelectronics which will be published (Geddes, L. A.; and Baker, L. E.: "Principles of Applied Biomedical Instrumentation," John Wiley & Sons, 1967). I tried this technique in the cat at Baylor University, and it seems that it works. Dr. Fernández and I have in mind the possibility of using this procedure. Of course, it has to be systematically investigated and standardized. It simplifies the problem of electrodes, since it is sufficient to introduce into the skin two thin wires or needles which are connected to the impedance meter and through it to the recording system.

ORPIN: Can you get enough light falling on the cornea to produce a photographic image?

KITAHARA: The intensity of the light is reduced by optical fiber by 50 percent. Nevertheless, high-speed photography of about 200 frames per second may be possible.

ORPIN: Is it an unpleasant optical stimulation on the cornea?

KITAHARA: Projection of such light to the cornea is not desirable, but it has been my experience that it was not disturbing to the subjects.

ORPIN: Also have you done any infrared studies using infrared illumination on the eye?

KITAHARA: No. An application of an infrared ray should be good if the technical problem can be solved.

CRAMPTON: In this case the source of light for the spotlight was a tungsten filament, was it not?

KITAHARA: A small tungsten of 6 watts, 6 volts. I have had no experience with another light source.

Physical Properties of the Labyrinthine Fluids and Quantification of the Phenomenon of Caloric Stimulation

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SUMMARY

The physical properties of endolymph and perilymph (viscosity, density, thermal coefficient of viscosity, and coefficient of thermal expansion) which are pertinent to the quantification of the dynamic behavior of the human vestibular sensors have been evaluated. Descriptions and error analyses of the instruments used for the measurements are presented.

The phenomenon of caloric stimulation of the semicircular canals is described quantitatively, and a dynamic model is presented. To support the proposed model, the human's response to caloric stimulation is compared to his response to angular acceleration stimulation.

INTRODUCTION

The properties of density, coefficient of thermal expansion, viscosity, and thermal coefficient of viscosity have been measured for human endolymph and perilymph and cat endolymph, and are presented in table 1. Descriptions of the instruments used for these measurements are given in the following sections.

The human and cat endolymph and perilymph samples were obtained through the cooperation of the staff at the Massachusetts Eye and Ear Infirmary, and in particular with the assistance of Dr. Herbert Silverstein.

APPARATUS

Microviscometer Design

Lack of adequate instrumentation for very small fluid samples, of the order of 1 microliter, necessitated the design and construction of a microviscometer. The microviscometer built at the Man-Vehicle Control Laboratory was designed using the principle of Flowers' rolling-ball viscometer. Flowers used a sphere in a closed tube of fluid lying on an inclined plane, and showed that the viscosity of a fluid measured by this technique is given, to a first-order approximation by the following formula:

TABLE 1.—*Physical Properties of Labyrinthine Fluids at 35° C*

	Human endolymph	Human perilymph	Cat perilymph	Measurement accuracies, percent	H_2O
Specific gravity	1.00	1.00	1.00	±2	1.00
Coefficient of expansion	4.4×10^{-4}/°C	4.4×10^{-4}/°C	4.4×10^{-4}/°C	±5	4.0×10^{-4}/°C
Viscosity, centipoise	0.852	0.802	0.780	±2	0.7225
Specific viscosity	1.18	1.11	1.08		
Temperature coefficient of viscosity	−2.4%/°C	−2.3%/°C	−2.5%/°C	±10	−2.0%/°C

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$$\mu = \frac{K}{v}(\rho_B - \rho_F) = At(\rho_B - \rho_F) \qquad (1)$$

where

ρ_B = density of sphere
ρ_F = density of fluid
v = terminal velocity of sphere in fluid
t = time for ball to travel a fixed distance
K, A = gain constants of the instrument

Using the analysis of Hershey, we showed that the relative error obtained by ignoring initial acceleration to terminal velocity, for fluids with a viscosity near that of water, is of the order of 0.2 percent for an instrument of the dimensions used. To improve further the accuracy of the measurement of the terminal velocity of the rolling ball, in our viscometer the velocity is measured over a 1-centimeter distance at the end of the tube, long after terminal velocity has been reached. One further source of error arises from the variation of the gain "constant" of the instrument, A, with temperature. This variation is taken into account by careful calibration of the instrument with fluids of known viscosities at several temperatures.

Description of the Microviscometer

The basic velocity (or time) measurement unit is an epoxy block with two prefocused miniature lamps which form two 0.020-inch-diameter light beams, and two high-speed photodiodes to measure the time of travel of a 0.010-inch-diameter tungsten carbide sphere in a miniature pipet. A modified 5-microliter pipet (0.016 inch inside diameter) containing the sample is mounted in such a manner that each light beam is broken by the rolling sphere, and the time interval between the interruptions as registered by the outputs of the photodiodes is recorded by an external electronic counter. As shown in fig-

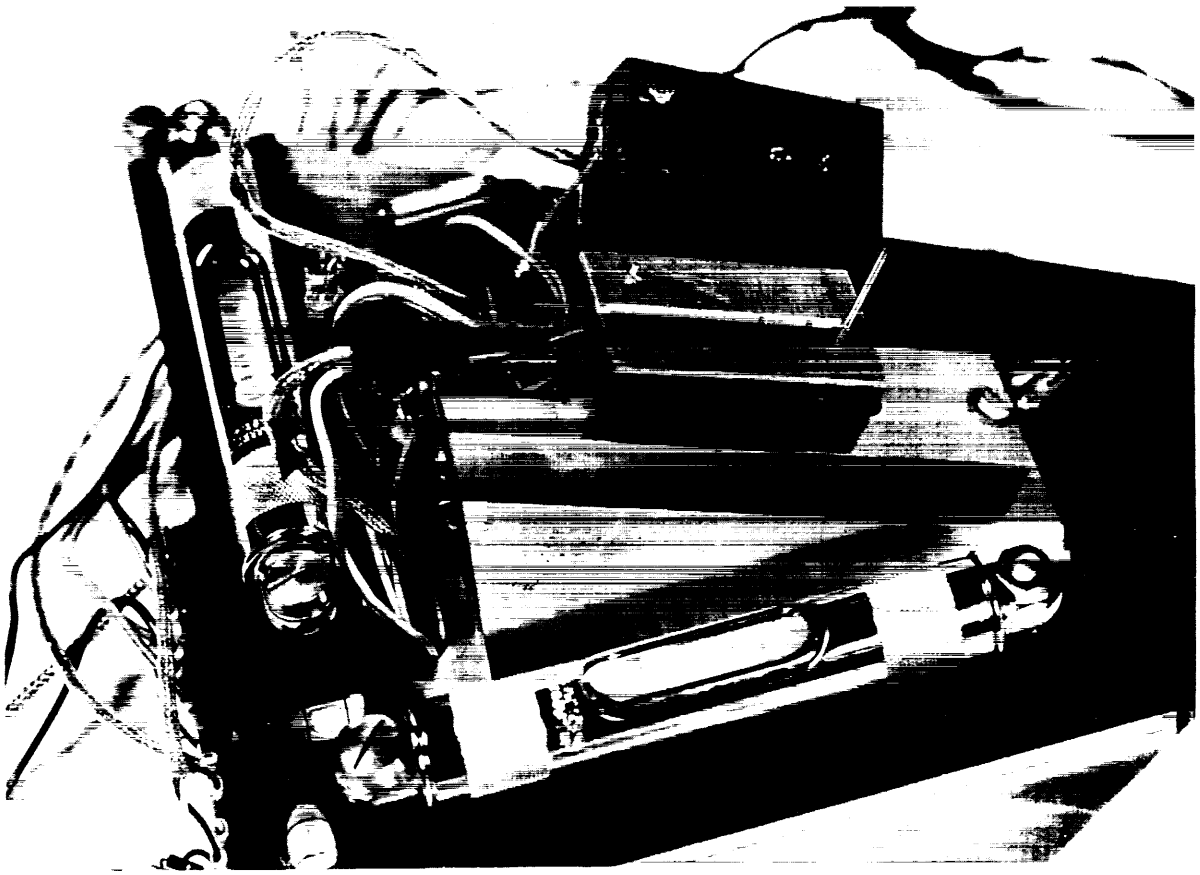

FIGURE 1.—*Closeup view of microviscometer.*

ure 1, an electrically grounded aluminum shield is sandwiched between the sections of the epoxy block and serves both as an electrostatic shield for the rolling sphere and as a temperature regulator for the sample. The temperature of the aluminum shield, and thus of the sample, is regulated to an accuracy of $\pm 0.1°$ C through power resistors mounted in both halves of the block and a sensitive calibrated thermistor attached to the underside of the shield plate.

The velocity measurement unit is mounted on a hinged inclined plane at an angle of 20° from its base and is provided with an external cable to tilt the platform to return the ball to the beginning of the tube. The inclined plane is mounted on a 10-inch triangular plate which is provided with two levels and two adjustable legs for leveling. The entire apparatus is confined by an aluminum-covered Plexiglas case which improves temperature stability, and provides a Faraday cage for the elimination of electromagnetic pickup. The entire measurement setup is shown in figure 2.

liter hypodermic syringe, custom equipped with a 0.008-inch outside-diameter needle, is used to transfer the samples. A four-step (alcohol, acetone, ether, air) cleaning process is used on the tubes and syringe before loading a new sample. After loading a sample it is necessary to centrifuge it to separate the oil droplets from the sample. The oil in the open end of the tube provides a barrier which the sphere cannot penetrate because of its high surface-tension forces. A brass cap with an attached surgical steel wire is inserted into the tube to limit the travel of the ball for large samples.

The sample with its ball and cap is demagnetized to eliminate any magnetic attractive forces between the ball (which was inserted into the tube with magnetized tweezers) and the travel-limiting steel wire. The sample is then inserted in the V-groove in the microviscometer and allowed 15 minutes to reach the proper temperature. The syringe, capillary tube end cap, and a section of a calibrated tube with a sphere enclosed are shown in figure 3.

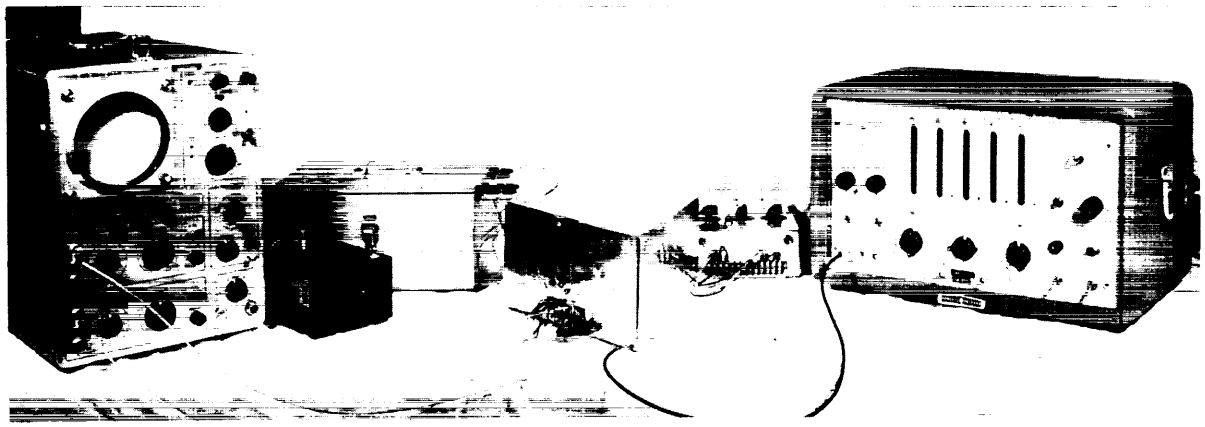

FIGURE 2.—*Viscosity test setup.*

METHODS

Sample-Handling Technique

Because of the volatility and small quantity of endolymph and perilymph, extreme care must be exercised in transferring the samples into the calibrated pipets. In the most successful technique to date, mineral oil is used as a seal for the open end of the capillary tube, and a 10-micro-

Calibration of Microviscometer

The capillary tubes to be calibrated are cleaned, sealed at one end with an alcohol burner, then fitted with a clean sphere. They are then filled with distilled water, centrifuged to eliminate bubbles, and fitted with caps. A "standard" tube is sealed at both ends and used as a "calibration reference." The capped tubes are then run in the viscometer at the desired

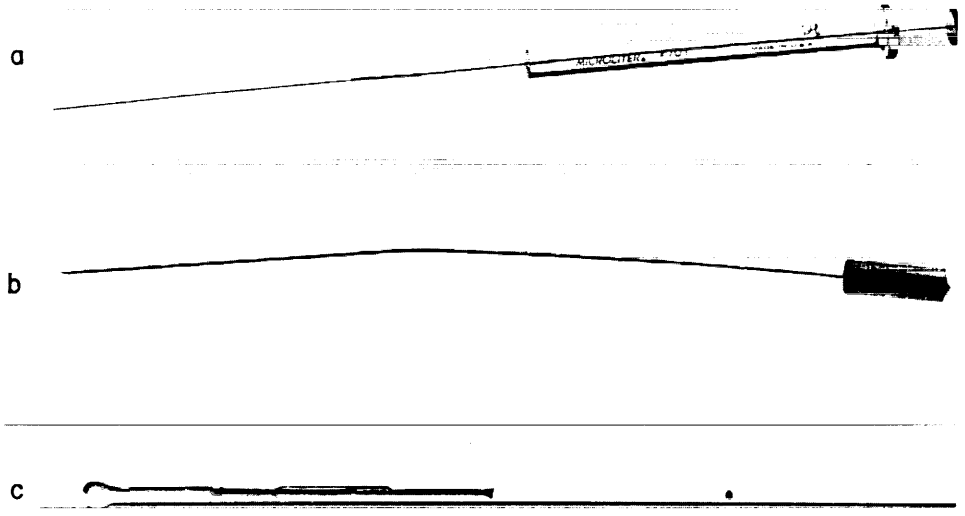

FIGURE 3.—(a) *Modified syringe for sample transfer;* (b) *calibrated-tube cap; and* (c) *calibrated tube (0.030-inch outside diameter, 0.016-inch inside diameter) with sphere.*

temperature, and at least 30 measurements are made to determine the "gain constant" of the tube-ball assembly. It was found that for a clean tube the standard deviation of the 30 measurements was approximately 0.2 percent.

In calibrating the tube in this manner we are actually evaluating

$$A=\frac{\mu_{H_2O}}{t_0(\rho_B-\rho_{H_2O})}$$

Rewriting equation (1) using the above value of A,

$$\frac{\mu}{\mu_{H_2O}}=\frac{t}{t_0(\rho_B-\rho_{H_2O})}(\rho_B-\rho_{H_2O}+\rho_{H_2O}-\rho_F)$$
$$=\frac{t}{t_0}\left(1+\frac{\rho_{H_2O}-\rho_F}{\rho_B-\rho_{H_2O}}\right)$$

Since the specific gravity of tungsten carbide is 13.0 ± 0.1, a difference of 2 percent in density between water and the fluid measured contributes less than 0.2 percent to the measured value of μ.

For each of the samples measured, the transit times for 30 repeated measurements showed a standard deviation of from 0.2 to 0.4 percent. Also, to an accuracy of ±2 percent the densities of the fluids were indistinguishable from that of water at 35° C. Thus, after combining the randomness in the measurement of t and t_0, and the possible density error (3σ) of ±2 percent, the overall accuracy of the instrument is ±2 percent.

FINDINGS

Density Measurement of Labyrinthine Fluids

By weighing a calibrated micropipet when empty, filled with water, and filled with cat or human endolymph or perilymph, it was found, as just stated, that to an accuracy of ±2 percent, their densities were the same as water. Since this accuracy was sufficient for accurate computation of their viscosities, the more accurate "density gradient column" technique was not used. These results, although not so precise, are consistent with the findings of Money et al. who reported the specific gravity of pigeon endolymph and perilymph to be 1.0033 and 1.0022, respectively (ref. 1).

Thermal Coefficient of Expansion

For calculation of the torque on the endolymph resulting from caloric stimulation, it is necessary to know the change in density of endolymph resulting from variations in temperature. For this purpose it is convenient to recall that

$$\frac{\partial v}{v\partial T}=-\frac{\partial \rho}{\rho\partial T}$$

where

v = volume
ρ = density
T = temperature

The coefficient of expansion ($\partial v/v\partial T$) was obtained by measuring the change in length of a 0.500-inch column of fluid in a glass capillary, using a microscope equipped with a micrometer adjustable with a resolution of 0.05×10^{-3} in. By measuring the change in length for a 10° C change in temperature and accounting for the expansion of the glass pipet, the coefficient of expansion of cat and human endolymph and perilymph was found to be 4.4×10^{-4}/°C ± 5 percent.

Newtonian Behavior of Human Endolymph

By operation of the microviscometer at two different angles of inclination (20° and 35°), it was found that the viscosity did not vary appreciably, even though the terminal velocities of the rolling sphere were nearly doubled. The viscosity was also measured after sitting for 1 day, and again after 1 week; within the 2-percent accuracy limitation of the instrument, no measurable change in viscosity was noted. Thus it appears that endolymph is not a shear-thinning fluid nor does its viscosity change with "sitting time." Further, chemical analysis of endolymph shows a low protein content that is typical of Newtonian fluids.

QUANTIFICATION OF HUMAN RESPONSE TO CALORIC STIMULATION

The phenomenon of caloric stimulation of the semicircular canal system has become a powerful diagnostic tool since the original qualitative proposals of Bárány in 1906 (ref. 2). The works of many subsequent investigators have produced overwhelming evidence in favor of Bárány's convection current theory.

In this paper the results of previous investigators are viewed in the light of control system analysis, and a dynamic model based on physical principles is proposed. This model can predict cupula deflections caused by application of a caloric stimulus to the external auditory meatus, and, to the extent that the human's subjective and nystagmus responses are related to cupular displacements, they too can be predicted.

The Existence of a Thermal Gradient Across the Lateral Semicircular Canal

From a purely physical viewpoint, a thermal gradient can be developed across the lateral semicircular canal since the ampullar section is close to the external auditory canal, and its opposite side is close to the brain which is thermally regulated by blood flow.

Indeed the works of Dohlman (ref. 3), Schmaltz (ref. 4), and Cawthorne and Cobb (ref. 5) have clearly shown the existence of a time-dependent temperature gradient across the lateral canal resulting from irrigation of the external auditory meatus with water above or below body temperature. The measurements of Cawthorne and Cobb are particularly amenable to interpretation in the context of a control theory description of caloric stimulation.

For a linear system the weighting function $w(t)$ can be computed from the time history of the output associated with a transient input to the system. This can be effected by implementation of the equation

$$g(t) = \int_0^t w(t-\tau)f(\tau)\, d\tau \qquad (2)$$

The system transfer function is given by

$$W(s) = Lw(t) = \int_0^\infty w(t)e^{-st}\, dt \qquad (3)$$

where

$g(t)$ = output of system
$f(t)$ = input to system
$w(t)$ = weighting function (response to a unit impulse)

In practice, it is often possible only to approximate $w(t)$ because one is often required to make use of a discrete set of data whose accuracy is not perfect, and whose sample interval is not necessarily uniform. Further, there rarely exists a "linear" system in the real world, and one is often forced to make a "best linear approximation."

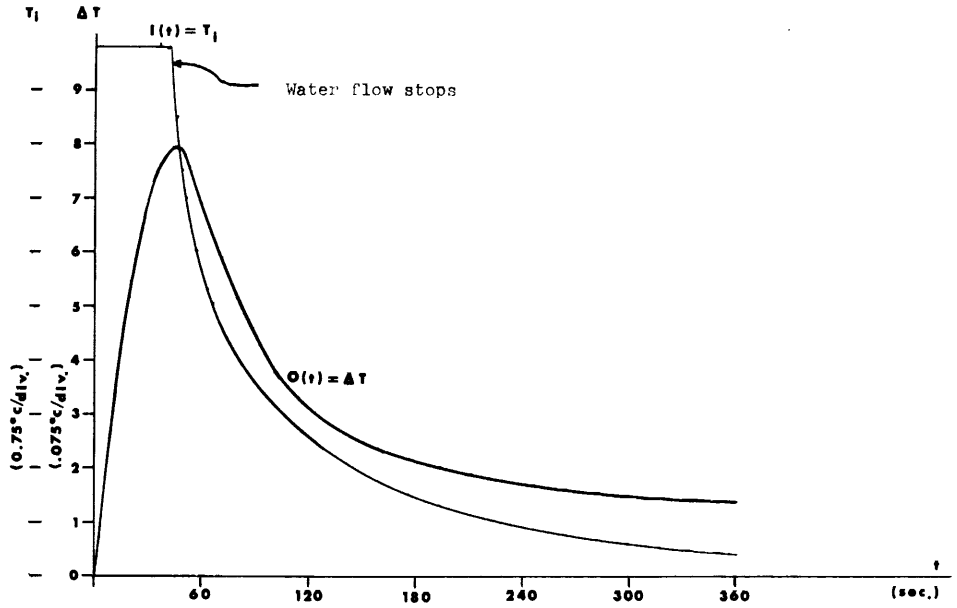

FIGURE 4.—*Time history of temperature difference across the lateral semicircular canal* (ΔT) *in response to caloric irrigation in the external auditory canal. The temperature at the tympanic membrane* T_i *is also plotted as a function of time. (Data from ref. 5.)*

For a finite set of n uniformly spaced data points at intervals k, equation (2) can be written in discrete form:

$$g(n)=\sum_{k=0}^{n} w(n-k)f(k) \tag{2a}$$

from which

$$w(n)=\frac{1}{F(0)}\left[g(n)-\sum_{k=0}^{n-1} w(k)f(n-k)\right] \tag{4}$$

Figure 4 shows the data of Cawthorne and Cobb (ref. 5) on the time history of temperature gradient across the lateral semicircular canal. Application of equation (4) to the data of figure 4 yields the thermal system weighting function for the perilymph, bone, and labyrinth structure. It can be approximated by a first-order lag of the form:

$$W_T(s)=\frac{\Delta T_i}{T_i}(s)=\frac{K}{\tau s+1} \tag{5}$$

where

T_i=temperature at the tympanic membrane (above body temperature)

ΔT=temperature difference across the lateral semicircular canal

τ=thermal-lag-time constant

K=system gain

From a minimum squared error fit of the data of figure 4, the values of the coefficients are:

$$\tau=25 \text{ sec}$$
$$K=0.1$$

Figure 5 presents both the measured temperature gradient and the gradient as computed from the analog model. The agreement is very good during the first 120 seconds, especially in view of the fact that the thermal system is a distributed parameter system which cannot be described by a simple first-order differential equation. It was found by Cawthorne and Cobb (ref. 5) that some subjects showed considerable differences in the peak amplitude of the thermal gradient; however, the form of the response remained the same. This indicates that the time constant τ should be relatively invariant, whereas K varies from individual to individual.

Torque Induced on a Ring of Fluid in a Uniform Temperature Gradient Field

When a ring of fluid in a gravity field is placed in a uniform temperature gradient field, a torque

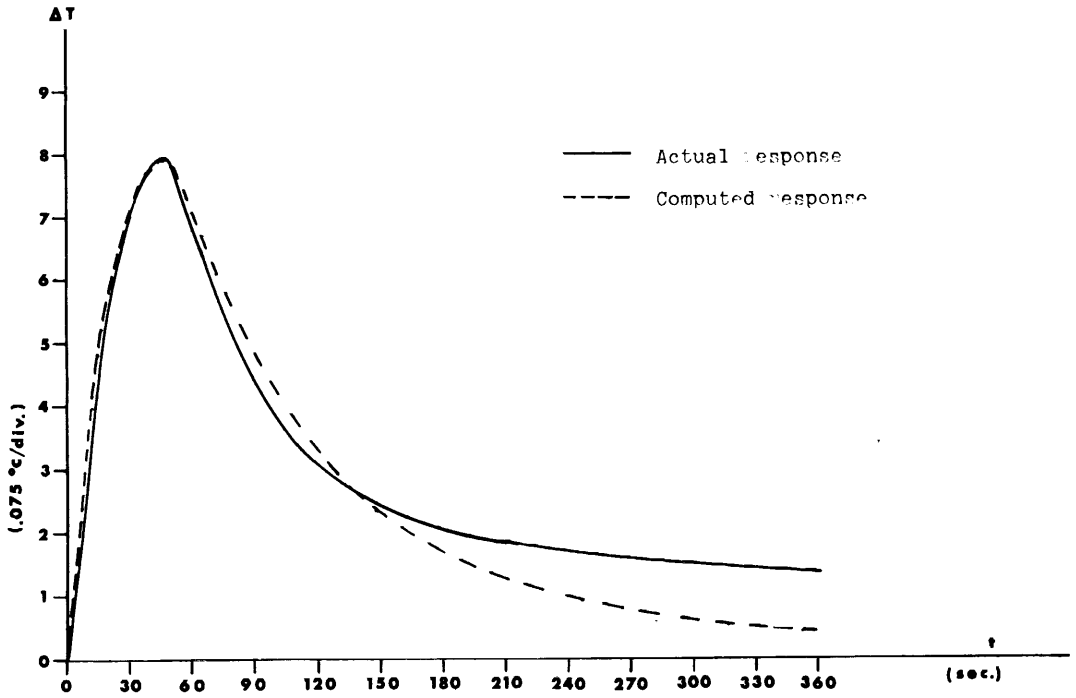

FIGURE 5.—*Measured and calculated temperature differences* (ΔT) *across lateral semicircular canal for stimulus applied in figure 4.*

is exerted on it, which will accelerate the fluid if it is unrestrained. The computed torque is

$$M = -\frac{\pi^2 r^2 R^2 g}{2} \cdot \frac{\partial \rho}{\partial T} \cdot \Delta T_t \cdot \cos \phi$$

where

r = radius of cross section of canal
R = radius of canal
$\frac{\partial \rho}{\partial T}$ = change in density of fluid with temperature
g = gravitational acceleration
T_t = temperature difference across canal
ϕ = angle between the plane of the canal and the direction of g
M = torque exerted on fluid

Using the dimensions of the human semicircular canals and the coefficient of expansion of endolymph

$$R = 0.3 \text{ cm}$$
$$r = 0.015 \text{ cm}$$
$$\frac{\partial \rho}{\partial T} = -4.4 \times 10^{-4}/°\text{C}$$

the torque on the endolymph of the human lateral semicircular canal is

$$M \approx 4.0 \times 10^{-8} g \cos \phi \cdot \Delta T_t \text{ (dyne-cm)} \quad (6)$$

For a static "thin" ring of fluid, or a ring of inviscid fluid:

$$I = 2\pi^2 r^2 R^3 \rho$$

Thus the angular acceleration which will produce an equivalent torque is

$$\alpha = \frac{M}{I} = \frac{1}{4R}\left(\frac{\partial \rho}{\rho \partial T}\right) g \Delta T_t \cos \phi \quad (7)$$

For the human lateral semicircular canal:

$$= 20 \Delta T_t \cos \phi \text{ (deg/sec}^2\text{)}$$

The "static" ring of fluid approximation is valid for measurements of thresholds of perception, because of the extremely small flow of endolymph during this level of excitation. Thus,

knowing the thresholds of perception of angular acceleration, it is possible to estimate the thresholds of caloric stimulation.

From the data of Meiry and others, it has been well established that the threshold of perception of angular acceleration, α_{min}, in the plane of the lateral canal is about 0.15 deg/sec^2 for most subjects (ref. 6). The threshold caloric stimulation should therefore be

$$T_{min}=\frac{\alpha_{min}}{20K\cos\phi}$$

For subjects whose $K=0.1$

$$T_{min}=\frac{\alpha_{min}}{2(0.866)}=0.1^\circ\text{ C}$$

For subjects whose $K=0.02$

$$T_{min}=0.5^\circ\text{ C}$$

These results compare well with the measurements of McLeod and Meek (ref. 7), who found that nearly 50 percent of their subjects exhibited a nystagmus response to a 40-second irrigation with water at 0.2° C above or below normal body temperature and 75 percent responded to differences of 0.5° C. However, it appears that because of the long thermal lag, longer irrigation times could possibly have shown the thresholds to be lower.

If it is assumed that the dynamic properties of the semicircular canal are those of the torsion pendulum and the inertia of the fluid ring is therefore constant, then the overall system transfer function from temperature input to cupular displacement can be written

$$\frac{\theta_c(s)}{T_i(s)}=\frac{20K/\tau_1\cos\phi}{(s+1/\tau_1)(s+1/\tau_2)(s+1/\tau_3)} \qquad (8)$$

The time history of the motion of the cupula for a step input of caloric stimulation of amplitude T_i can be obtained from the solution of the equation:

$$\theta_c(t)=AT_i\int^{-1}\frac{1}{s\left(s+\frac{1}{\tau_1}\right)\left(s+\frac{1}{\tau_2}\right)\left(s+\frac{1}{\tau_3}\right)} \qquad (9)$$

where

$\theta_c(t)$ = time history of cupular displacement due to a step input of caloric irrigation

$\tau_1=25$ sec = thermal-lag coefficient

$\tau_2=10$ sec = long time constant of lateral canal

$\tau_3=0.1$ sec = short time constant of lateral canal

A = system gain constant

T_i = temperature at tympanic membrane (above normal body temperature)

After expansion of equation (9) and performing the inverse Laplace transformation:

$$\theta_c(t)=A\tau_1\tau_2\tau_3T_i\left[1-\frac{1^2e^{-t/\tau_1}}{(\tau_1-\tau_2)(\tau_1-\tau_3)}\right.$$

$$\left.-\frac{2^2e^{-t/\tau_2}}{(\tau_2-\tau_1)(\tau_2-\tau_3)}-\frac{3^2e^{-t/\tau_3}}{(\tau_2-\tau_3)(\tau_1-\tau_3)}\right], \qquad (10)$$

$$\theta_c(t)=Af(t)T_i$$

Figure 6 shows the function $f(t)$ as computed from equation (10) for a unit step input of T_i for the time interval 0 to 75 seconds.

It should now be possible to show, analogous to the "Muelder Product," that the latency time to the onset of caloric nystagmus follows the relationship

$$f(t_l)T_i=C=\text{constant}$$

In figure 7, the predicted "Caloric Latency Product" $f(t_l)T_i$ is calculated for several values of C.

To this end, a sequence of experiments is currently being conducted to measure the latency time to the onset of vestibular nystagmus following the start of caloric irrigation at various temperatures.

Dependence of Caloric Response on Linear Acceleration

It is apparent from equation (6) that the torque induced on the "ring" of endolymph is proportional to g. This has been shown to be true by the works of Bergstedt (ref. 8). More recently, zero-g flights by Kellogg and Graybiel (ref. 9) have shown that even ice-water-induced nystagmus can be completely suppressed in a zero-g

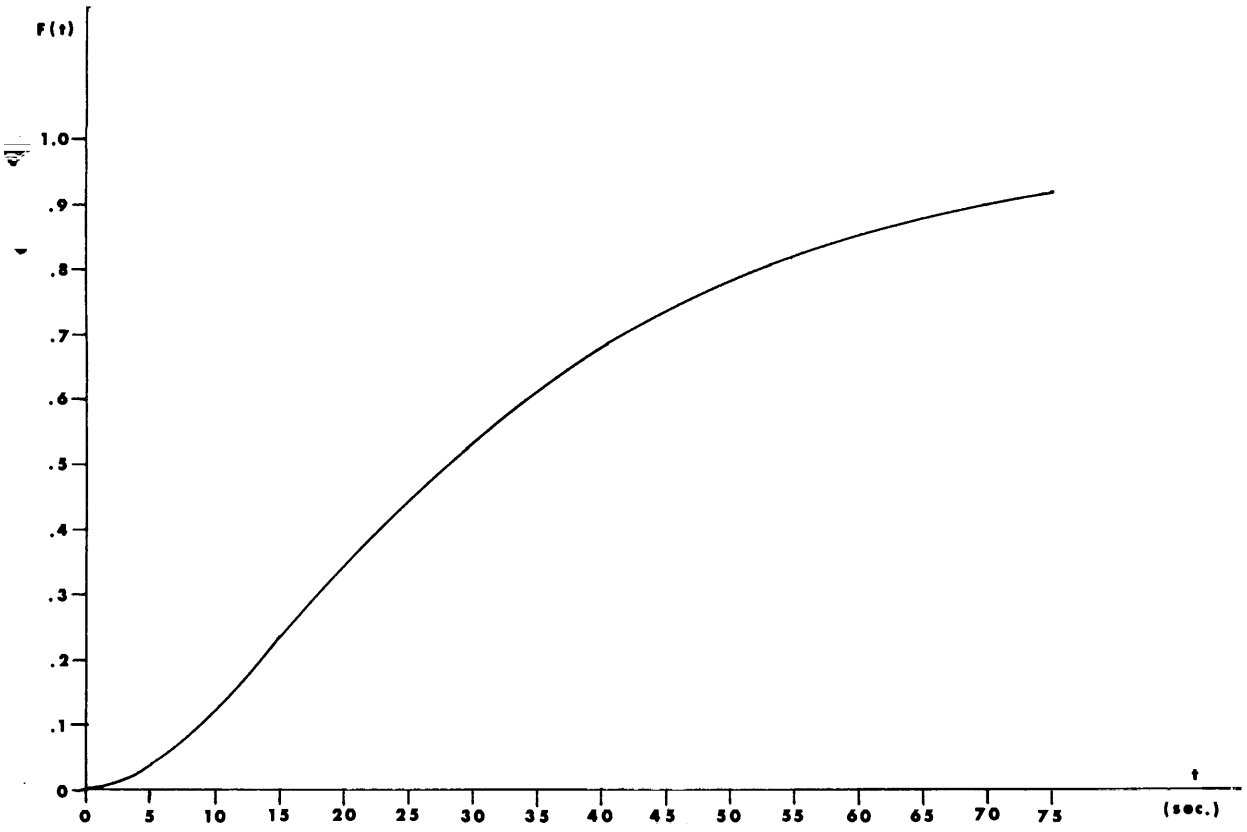

FIGURE 6.—*Plot of* f(t) *versus* t.

parabolic flight. If the caloric stimulus is the controlling factor of the nystagmus for this type of zero-*g* testing, then from equation (6) it is possible to predict the "*g* threshold" when an ice-water stimulus is used. If threshold caloric temperature is 0.36° C for 1 *g*, then for 36° C stimulus, from (6), the threshold torque should be exerted at 0.01 *g*. Since the thermal gradient is well established during the zero-*g* portion of the flight, the nystagmus reaction should be induced as soon as the threshold value of *g* is reached, and should not be hampered by the long thermal lag. We eagerly await the outcome of the "*g*-threshold" tests that are scheduled for 1967.

SYSTEM TRANSFER FUNCTION FOR CUPULAR DISPLACEMENT DUE TO CALORIC IRRIGATION

In figure 8 is shown a block diagram which illustrates the overall transfer function of the thermal inertia, convection gain, and lateral canal dynamics system.

In figure 9 is presented the normalized value of the time history of cupula displacement as calculated by the convolution of the overall system weighting function and three different temperature inputs at the tympanic membrane. Curve (1) is the calculated value of cupular displacement for a step input of temperature which lasts for greater than 5 minutes. Curve (2) uses the input at the tympanic membrane as measured by Cawthorne and Cobb and presented in figure 4, and curve (3) uses a step input of 40-second duration instantaneously followed by irrigation at body temperature to discharge the thermal capacity.

Since the data of Cawthorne and Cobb show the continued existence of a temperature gradient for as long as 6 minutes after irrigation, it is reasonable to assume that the anesthetic used on these subjects suppressed vasodilatation and resulted in a marked increase in the duration of

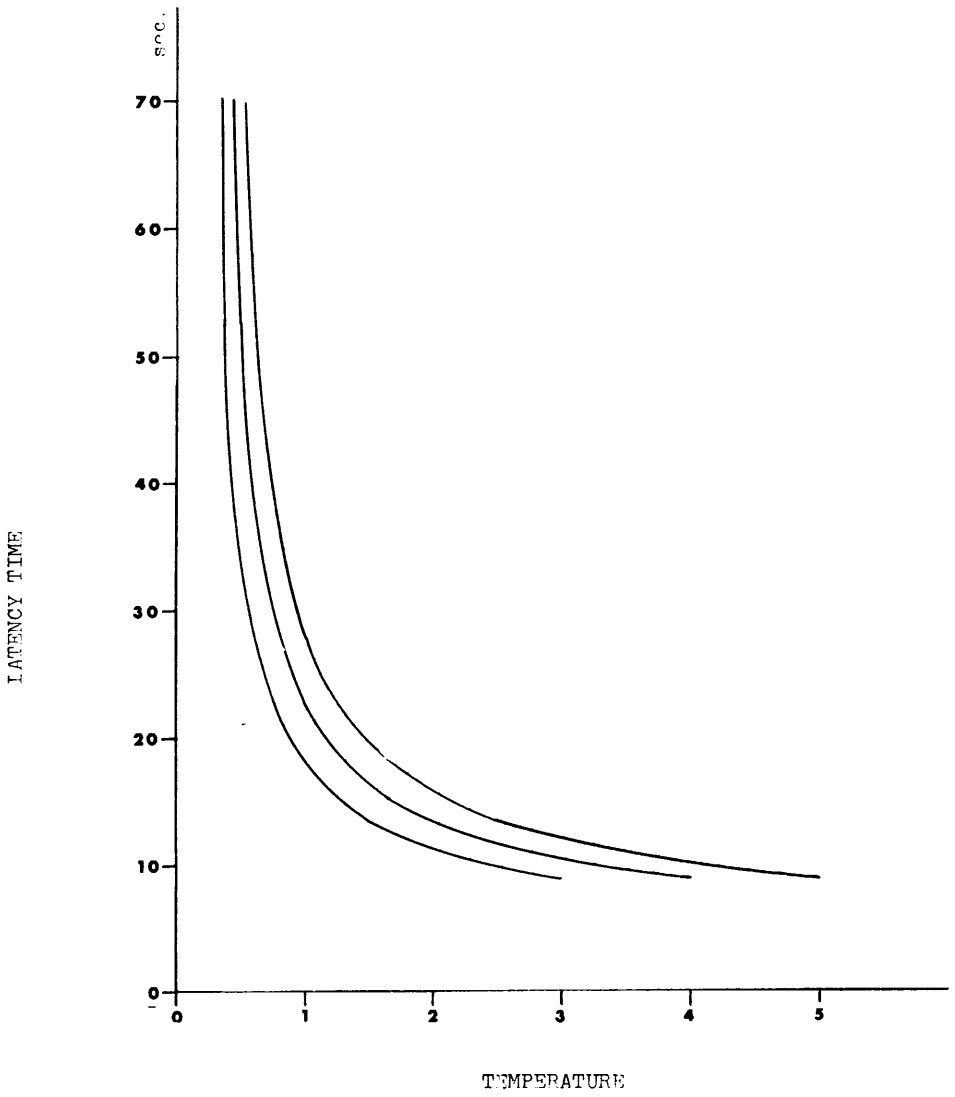

FIGURE 7.—*Plot of* $T_1 f(t) = C$ *for several values of* C.

the temperature gradient across the lateral semicircular canal, and at the tympanic membrane.

Thus, for a normal subject, in the absence of an anesthetic, the actual cupular displacement for a 40-second irrigation should lie between curves (2) and (3) in figure 9.

The time histories of cupular displacement as shown in curves (2) and (3) in figure 9 correlate well with the slow-phase nystagmus data of Henriksson and others in that the maximum amplitude of slow-phase velocity of caloric vestibular nystagmus occurs after about 50 seconds, and the typical duration of nystagmus is of the order of 2 to 3 minutes (ref. 10). However, according to figure 9, the duration of nystagmus should be a stronger function of time than is observed in practice.

Further modeling must take into account the effect of vasodilatation, which acts in the direction to add or subtract heat by increased or decreased blood flow. This will tend to decrease the duration of the temperature gradient across the lateral canal, and will therefore reduce the effect of the amplitude of the stimulus on the duration of caloric nystagmus. It can also account for the reversal of nystagmus that is occasionally

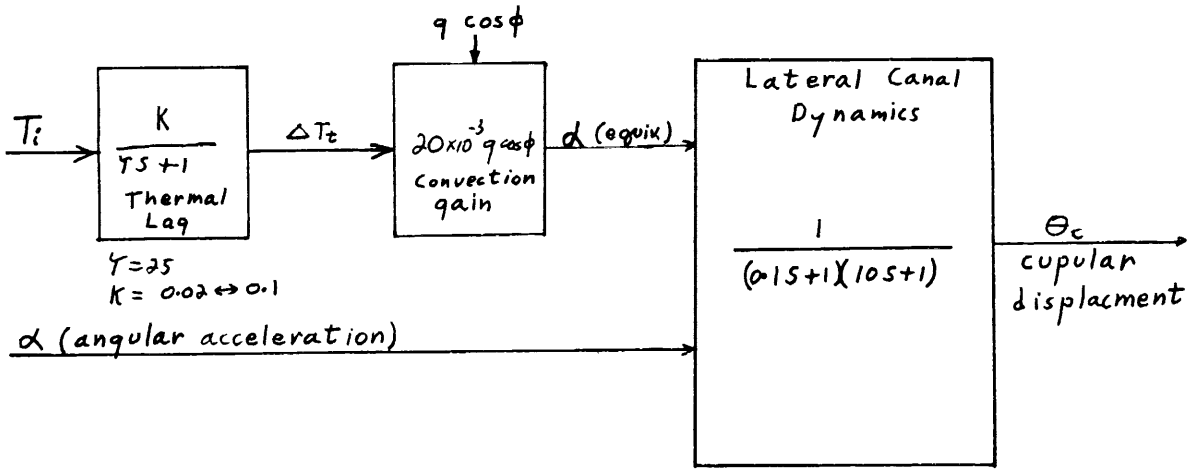

FIGURE 8.—*Block diagram for caloric stimulation.*

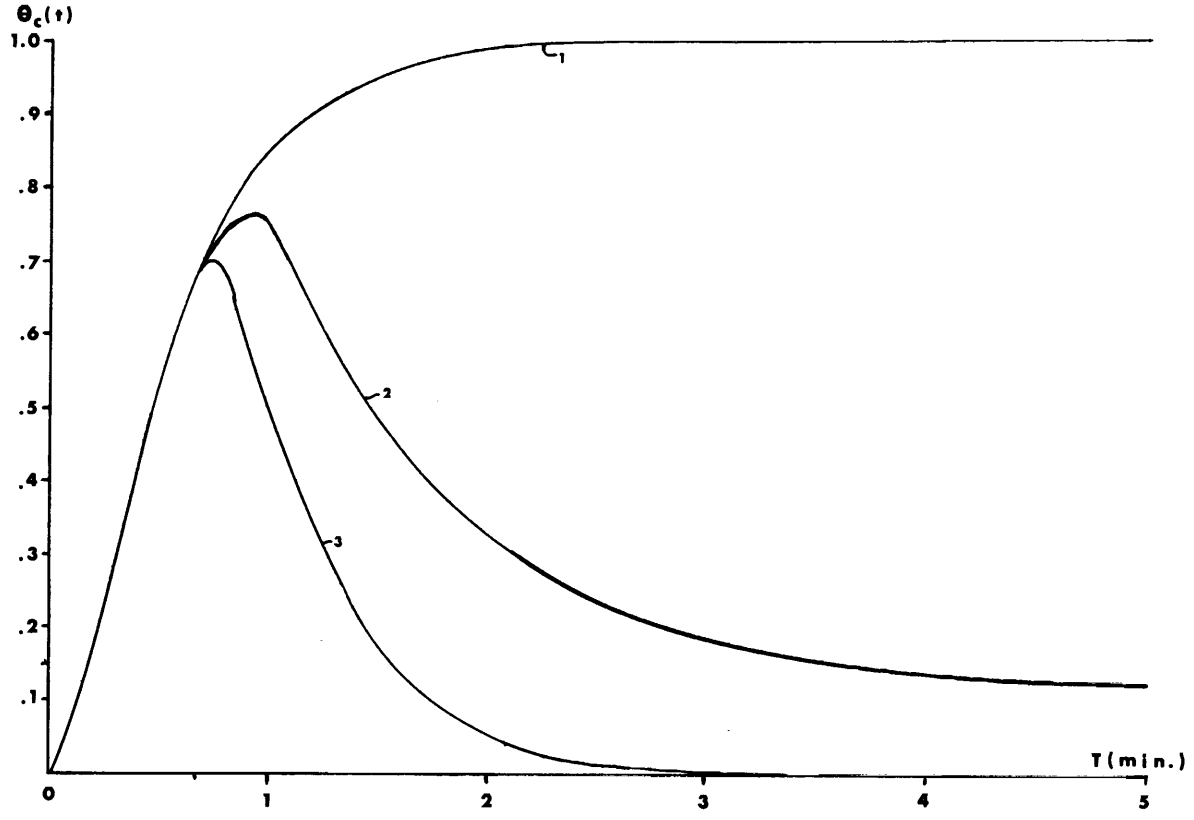

FIGURE 9.—*Calculated cupular displacements for various caloric stimulations.*

observed after the normal caloric nystagmus has stopped. However, at this time there are not sufficient data available in the literature to make any quantitative evaluations of this effect.

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Postrotational Sensation and Nystagmus as Indicants of Semicircular Canal Function

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SUMMARY

In man, measures of the time constant of decay of the vestibular response, following angular impulses in yaw, were found to differ according to whether postrotational sensations or nystagmus were studied. On the average, the time constant derived from the sensation cupulogram was about half that of the decay of nystagmus slow-phase velocity, which itself decayed more than twice as rapidly as subjective angular velocity.

The disparity of the subjective measures was attributed to: (1) an "adaptive" alteration in sensory threshold with the magnitude of the impulse; and (2) a power law relationship between subjective velocity and the physical stimulus.

It was concluded that nystagmus slow-phase velocity is the most stable indicator of the afferent signal from the ampullary receptors, though transduction in the vestibulo-ocular pathway can be modified by signals from other somesthetic receptors and the behavioral state of the subject.

INTRODUCTION

Over the last 50 years the vestibular sensory system has been of interest to the medical practitioner concerned with the health and safety of aircrew (refs. 1 and 2). Initially it was thought that control of the aircraft was primarily dependent upon the pilot's having an adequate *sense of equilibrium;* so, tests of vestibular function formed an important part of the medical assessment of flying personnel. Despite the demonstration (refs. 1, 3, and 4) that spatial orientation in flight could only be maintained by visual cues, it was not until blind flying became common practice that the role of the vestibular receptors in the cause of disorientation and loss of aircraft control was generally accepted (refs. 5 to 7). Although there is now a considerable body of knowledge about the etiology of disorientation in aerospace flight, little is known about the relationship between vestibular function and susceptibility to disorientation (ref. 8).

The experimental work reported in this paper began as an investigation of vestibular function in aircrew who came under medical care because of spatial disorientation in flight, which was soon extended to include aircrew with other perceptual disturbances in flight and airsickness. As this clinical investigation progressed, the inadequacy of some aspects of the theoretical concepts, upon which the rotational tests were based, became apparent. Further studies on the relationship between subjective and objective indicators of semicircular canal function in response to impulsive stimuli were initiated. It is the results of these inquiries, rather than the clinical significance of specific tests, that are reported in this paper.

Tests of Semicircular Canal Function

In normal man the ampullary receptors of the semicircular canals may be stimulated in different ways; namely, by angular acceleration, by thermal stimuli, and by electric currents. As the physiological function of the receptors is to signal angular motion, rotational tests have prima facie validity; though it must be acknowledged that the caloric test, as refined by Fitzgerald and Hallpike (ref. 9), is of greater clinical value than

rotational tests. However, our particular interest lay in determining how the vestibular sensory system of aircrew transduces the motion stimuli of flight, rather than in localizing pathological lesions. Accordingly, it was decided to confine the test procedures to rotational stimuli. Galvanic stimulation of vestibular receptors lacks specificity and has a limited application in the clinic or research laboratory.

Many types of rotational tests have been employed (ref. 10), and it would be beyond the scope of this paper to discuss them critically. When it is desired to establish the stimulus-response relationship for rotational stimuli, rather than to demonstrate simply directional preponderance, the technique of cupulometria, or cupulometry as it has come to be called, as developed by Van Egmond, Groen, and Jongkees (ref. 11) has much to commend it. The test entails the measurement of the duration of the sensation of turning, or the nystagmic response, evoked by a stopping stimulus. Several turntable velocities are used, so that the aftereffects evoked by a range of angular impulses may be determined and a stimulus-response graph plotted (figs. 1 to 3). If the impulse is plotted on a logarithmic scale,

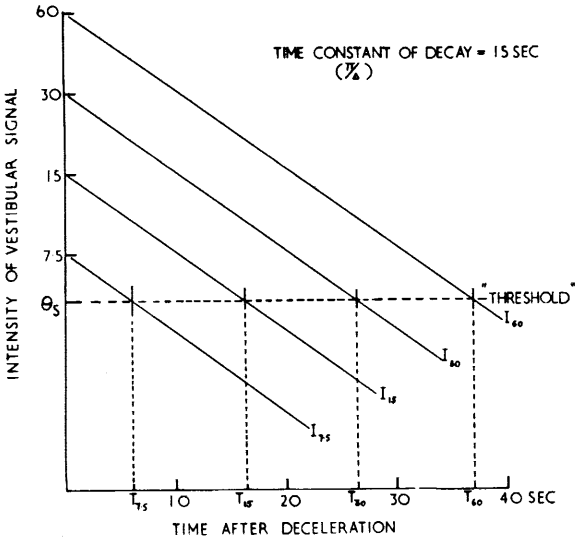

FIGURE 1.—*Theoretical magnitude and time course of cupular deflection produced by four angular impulses* ($I_{7.5}-I_{60}$). *Cupular deflection is represented by an arbitrary logarithmic ordinate scale. When the deflection is less than "threshold" intensity* (θ_s), *the aftersensation disappears at times* $T_{7.5}-T_{60}$.

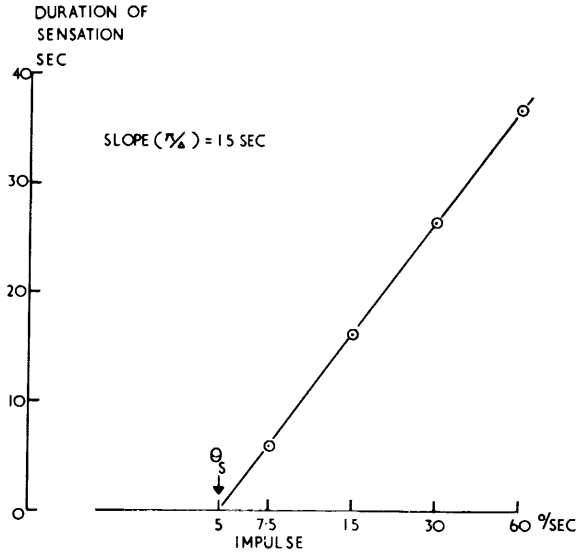

FIGURE 2.—*Theoretical cupulogram obtained by plotting the duration of the aftereffect* ($T_{7.5}-T_{60}$) *against log intensity of the angular impulse. The intercept of the line with the abscissa corresponds to threshold, and the slope of the line is the same as the time constant of decay of the cupula, shown in figure 1.*

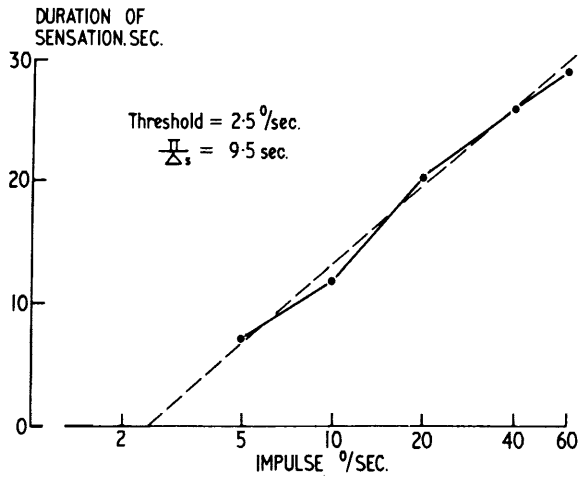

FIGURE 3.—*A yaw axis sensation cupulogram. Each point is the mean duration of the aftersensations evoked by two impulses (clockwise and anticlockwise). A measure of threshold is obtained from the intercept of the line, drawn through the points, with the abscissa. The time constant of decay* (π/Δ_s) *is the change in the duration of the sensation brought about by an increment of impulse* (I) *from* I_1 *to* eI_1.

the relationship between the duration of the aftereffect and impulse approximates a straight line. This intercepts the abscissa at an impulse intensity which is a measure of threshold,

and the gradient of the line is related directly to the rate of restoration of the cupula from the deflected to the neutral position. It should be noted that the delineation of threshold and time constant of cupular restoration from the cupulogram depends upon the assumption that (1) peak cupular deflection is proportional to the magnitude of the impulse, (2) the rate of decay is constant and independent of the magnitude of impulse, and (3) threshold is constant and independent of the magnitude of the impulse.

In the cupulometric test, two aftereffects are usually studied, one subjective—the duration of the illusory sensation of turning—and the other objective—the duration of the nystagmic response.

Determination of the point in time at which nystagmus disappears is not without its difficulties and introduces a subjective assessment, on the part of the experimenter, which destroys the purely objective nature of the test. Furthermore, alteration of the subject's behavioral state can modify considerably the quality and duration of the nystagmic response, particularly at the low impulse intensities employed (refs. 12 to 15). For these reasons it was decided to measure the decay of slow-phase velocity of the nystagmus evoked by the largest impulse used in the cupulometric test. Although the measurement of slow-phase velocity is a tedious procedure, it was considered that this separate measure of the rate of decay of the vestibular signal would be of value, and would minimize variation of the response consequent on alteration in the level of behavioral arousal.

METHODS

Apparatus

A turntable driven by an electric servomotor was used in all the experiments. Velocity was controlled to an accuracy of $\pm 0.5°$/sec. The turntable was stopped in a reproducible manner by an electropneumatic brake which in conjunction with the reverse torque of the drive motor gave a deceleration of approximately 150°/sec^2. For stimuli in the yaw axis, the subject sat on the turntable with his head supported in a vertical position, close to the axis of rotation. Alternatively, the effect of stimuli in roll could be assessed when the subject lay in a supine position on the turntable with his center of gravity close to the axis of rotation. He was surrounded by a lighttight canopy and was instructed to keep his eyes closed. Aftersensations were timed to 0.2 sec with a stopwatch and were measured from the instant the brakes were applied to the time at which the subject indicated that the sensation of turning had disappeared.

Lateral eye movements were recorded by the usual electro-oculographic technique; silver/silver chloride suction-cup electrodes, a d.c. amplifier (frequency response 0 to 60 cps), and a photographic galvanometer recorder were employed. The determination of slow-phase velocity of postrotational nystagmus from the galvanometer records was facilitated by the use of a specially developed trace reader (ref. 16).

Conduct of Experiment

Following the application of electrodes and installation of the subject on the turntable, he was told of the nature of the experiment and instructed to press a key when the sensation of turning, evoked by the sudden stopping of rotation, had disappeared. It was usually not necessary to supplement these "weak" (ref. 15) instructions, but if, after the first stopping stimulus, the aftersensations were very long (i.e., over 60 sec), the subject was asked if he had experienced difficulties in judging the disappearance of the sensation. Those who replied in the affirmative were advised to signal as soon as they became uncertain about the presence of the primary postrotational sensation.

Each test stimulus was a velocity step produced by stopping the turntable from a constant angular velocity. The turntable was accelerated at 1°/sec^2 from rest to the desired speed which was held constant for 60 sec before the brakes were applied. Turntable speeds of 60°, 40°, 20°, 10°, and 5°/sec were employed with rotation in the clockwise direction being alternated with rotation in the anticlockwise direction. Stimuli were presented in the order shown above rather than in an irregular sequence employed by Van Egmond, Groen, Hulk, and Jongkees (refs. 11 and 17). It is acknowledged that the order in which stimuli are presented can influence the

duration of aftersensations (ref. 18); but where it is desirable to determine the cupulogram of an individual without making the test too protracted, it was considered that the presentation of stimuli of descending magnitude (ref. 19) made the subject's task easier and helped to reduce the variability of the duration of the reported aftersensations.

Analysis of Records

Sensation cupulograms were plotted in the manner shown in figure 3, except that there were two points at each impulse intensity which corresponded to the duration of the aftersensations produced by clockwise and anticlockwise rotation. A straight line was drawn by eye through the points. The intercept of the line with the abscissa and the slope of the line were determined in order to obtain values for threshold (in deg/sec) and slope (in sec), respectively. The terminology introduced by Van Egmond, Groen, and Jongkees (refs. 11 and 20) is employed in this paper; hence π/Δ represents the time constant of restoration of the cupula from its deflected to neutral position. (π is the viscous damping consequent to endolymph flow and Δ the intrinsic restoring couple of the cupula.) Suffixes s or n indicate that the time constant was obtained from sensation or nystagmus measures, respectively.

In routine investigations the decay of the post-rotational nystagmic response was determined only for the two 60°/sec impulses. The angular velocity of the slow-phase component of each nystagmic beat, occurring in the 30 sec following the stopping of the turntable, was measured, and the value was plotted on a logarithmic ordinate scale against time; a straight line was drawn by eye through the points. The intercept of the line with the ordinate at $t=0$ provided a measure of peak angular velocity (ω_{t_0}), and the time constant of decay (π/Δ_n) was determined from the gradient of the line.

RESULTS

The Sensation Cupulogram

The distribution of the values of threshold and slope of the yaw axis sensation cupulogram of 142 subjects is shown in figures 4 and 5. Whereas slope values were found to have an approximately normal distribution, the extrapolated thresholds had a skewed distribution toward the low end of the range. The distribution of threshold measures was improved by a logarithmic transform, but, as is apparent in figure 4, this skewed the distribution in the opposite direction. Slope and threshold values were similar to those reported by Hulk and Jongkees (ref. 17), but on the average they were somewhat lower than the mean values of 8.6 sec and 4.6°/sec, respectively, calculated from the data on 320 normal subjects examined by Aschan et al. (ref. 19).

The sensation cupulograms in the roll axis, obtained from a smaller group of subjects ($N=78$), gave comparable distributions of slope and threshold values (figs. 6 and 7) to those found in the yaw axis. Thresholds were found not to differ significantly between the two stimulation axes, but the slope was lower ($p=0.001$) in roll than in yaw. The reason for the more rapid decay of aftersensations and nystagmus (refs. 21 and 22) following rotation in roll are imperfectly understood. It may be that the dynamic re-

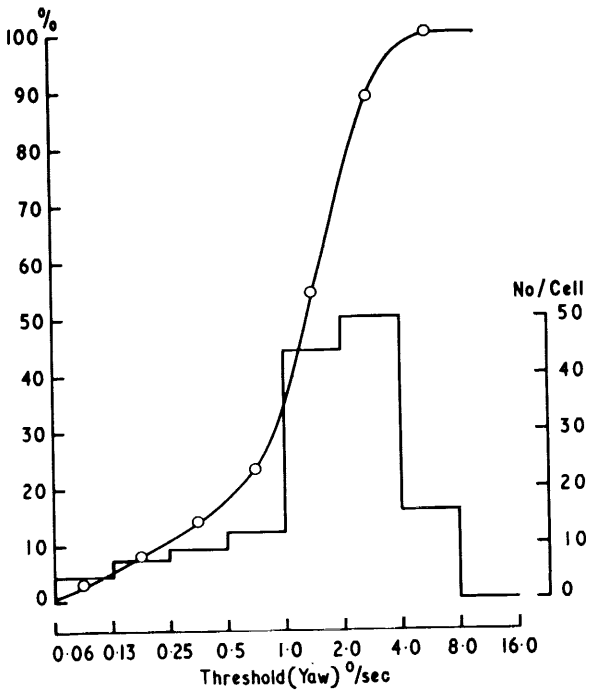

FIGURE 4.—*Distribution of extrapolated thresholds from yaw axis sensation cupulograms of 142 subjects. Histogram cells are scaled logarithmically.*

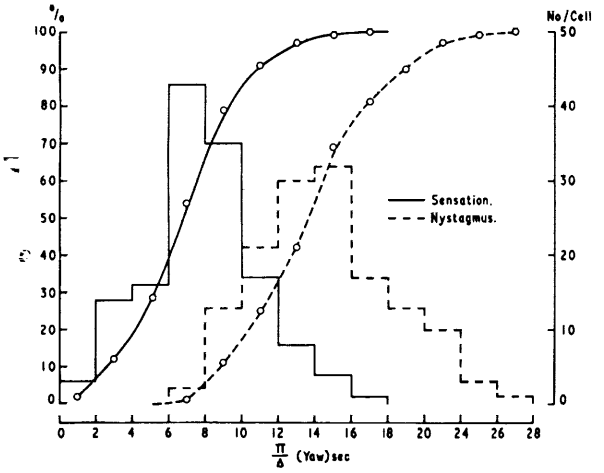

FIGURE 5.—*Distribution of yaw axis sensation cupulogram slopes (π/Δ_s) and time constants of decay of postrotational nystagmus (π/Δ_n) in 142 subjects.*

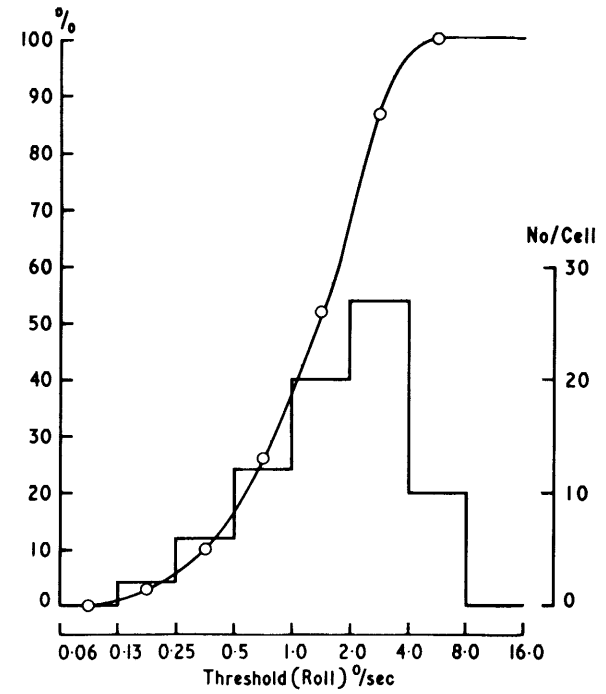

FIGURE 6.—*Distribution of extrapolated thresholds from roll axis sensation cupulograms of 78 subjects. Histogram cells are scaled logarithmically.*

sponse of vertical canals differs from that of the lateral canals, or it may represent the suppression of the vertical canal response when the rotational stimulus in roll is not coupled with a synergistic change in the direction of the gravity vector (ref. 22). With normal head movements in roll there is stimulation of both canals and otoliths, but on the turntable there is insignificant stimulation of gravireceptors.

Nystagmus Decay

Distribution of the time constant of decay π/Δ_n of the nystagmic response elicited by the 60°/sec impulses is shown in figure 5). This measure, like π/Δ_s, was found to be normally distributed, but had a median value of 14.0 sec in contrast to π/Δ_s which had a median value of 6.8 sec. Very few subjects had a sensation cupulogram slope greater than that of the nystagmus time constant, and, on the average, π/Δ_n was twice as large as π/Δ_s (fig. 8).

The time constant of decay of postrotational nystagmus found in the present series was in accord with earlier observations (refs. 20, 23, and 24). Furthermore, a value of 14 sec for this direct measure of nystagmus decay is very close to the mean slope of the nystagmus cupulogram reported by Hulk and Jongkees (ref. 17) and Aschan et al. (ref. 19); thus, irrespective of whether the time constant of decay of nystagmus is followed directly, or is determined by the

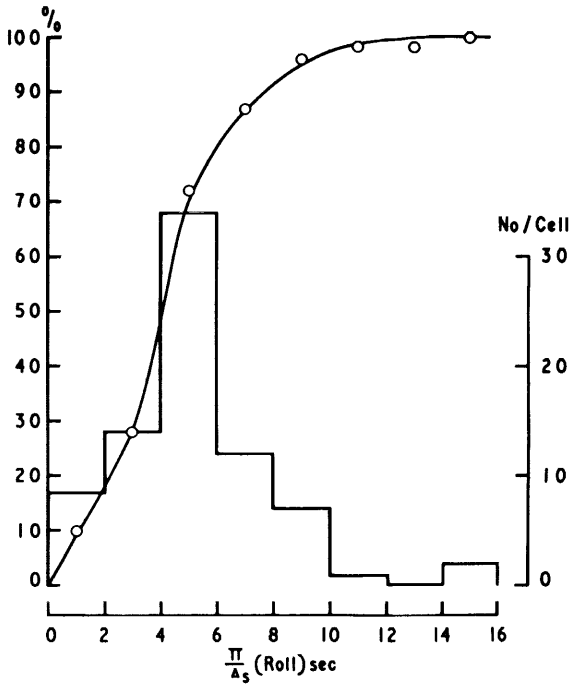

FIGURE 7.—*Distribution of slopes (π/Δ_s) of roll axis sensation cupulograms of 78 subjects.*

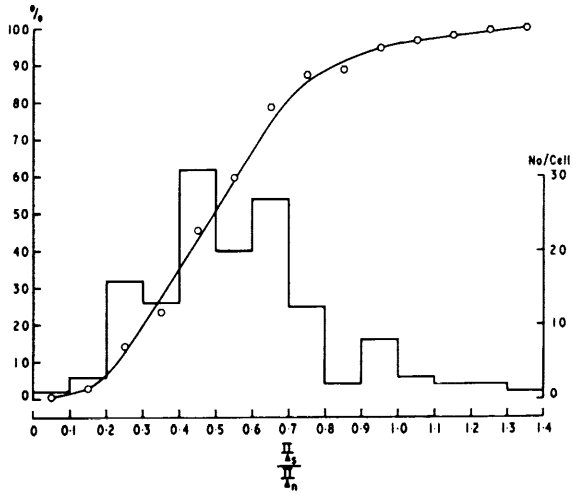

FIGURE 8.—*Distribution of the ratios of sensation cupulogram slope* (π/Δ_s) *to nystagmus time constant* (π/Δ_n) *in 142 subjects. Yaw axis responses.*

measurement of the duration of the nystagmic response at different impulse intensities, a similar value for the time constant is obtained. But why should this be consistently larger than the slope (π/Δ_s) of the sensation cupulogram? Groen (refs. 25 to 27) proposed that this difference in slope values was due to the greater "adaptation" of the neural system which subserves the sensation of turning than that which mediates the nystagmic response. Similarly, Stahle (ref. 24) has argued, following Lorente de Nó (ref. 28), that nystagmus slow-phase velocity follows more closely the signal from the ampullary receptors than does sensation, which is more susceptible to "cerebral influences."

One interpretation of Groen's adaptation hypothesis is that the aftersensation of turning does, in fact, decay more rapidly than the nystagmic response; though the sensation-cupulogram time constant could also be reduced if the sensory threshold (that is, the intensity of the afferent signal when the subject reports the disappearance of the sensation) varied in an adaptive manner with the magnitude of the impulse. In addition, a nonlinear relation of intensity, or of the rate of decay of sensation, to impulse can also be adduced as hypothetical mechanisms.

In an attempt to explore and if possible reject some of these hypotheses, a more detailed examination of the relation of aftersensations to nystagmus was carried out.

Relation of Postrotational Nystagmus to Impulse Intensity

During the course of performing the cupulometric test, as described earlier, it was rare to find subjects from whom a well-defined horizontal nystagmus, suitable for quantitative analysis, could be recorded at all impulse intensities. However, seven subjects were discovered in whom it was possible to measure the slow-phase velocity of postrotational nystagmus at all five impulse intensities (e.g., fig. 9). For each subject the results for clockwise and anticlockwise rotation at each impulse intensity were combined, and the mean eye velocity determined for each second of the 30 sec after stopping. These values were used to determine the mean decay curves for the seven subjects (fig. 10). Although this experiment was performed on a criterion group, the mean sensation cupulogram was found to have slope and threshold values of 9.0 sec and 2.5°/sec which were close to the median values of the larger unselected population. Likewise, a π/Δ_n of 15.5 sec for the 60°/sec impulses supported the opinion that the behavior of this group differed only in quality of the nystagmic response rather than in the manner in which ampullary signals were transduced within the central nervous system. Figure 11 is in accord with the theoretical behavior of the ampullary receptors following impulsive stimulation, for the rate of decay was similar at all impulse intensities (π/Δ_n values did not differ significantly from one another), and the initial slow-phase velocity (ω_{t_0}) was proportional to the impulse intensity (I). The mean factor relating ω_{t_0} to I was 0.62, a value which is in agreement with the observations of Stahle (ref. 24) and Henriksson (ref. 29).

As the times at which the subject reported the disappearance of aftersensations were known, it was possible by combination of nystagmus and sensation data to express the intensity of the afferent vestibular signal, at threshold, as an eye velocity (ω_{t_0}). It was found that the "threshold" determined in this manner was not constant, but increased with impulse intensity. The relationship between ω_{t_0} and I happened to fit a power law function with an exponent of 0.33, but there

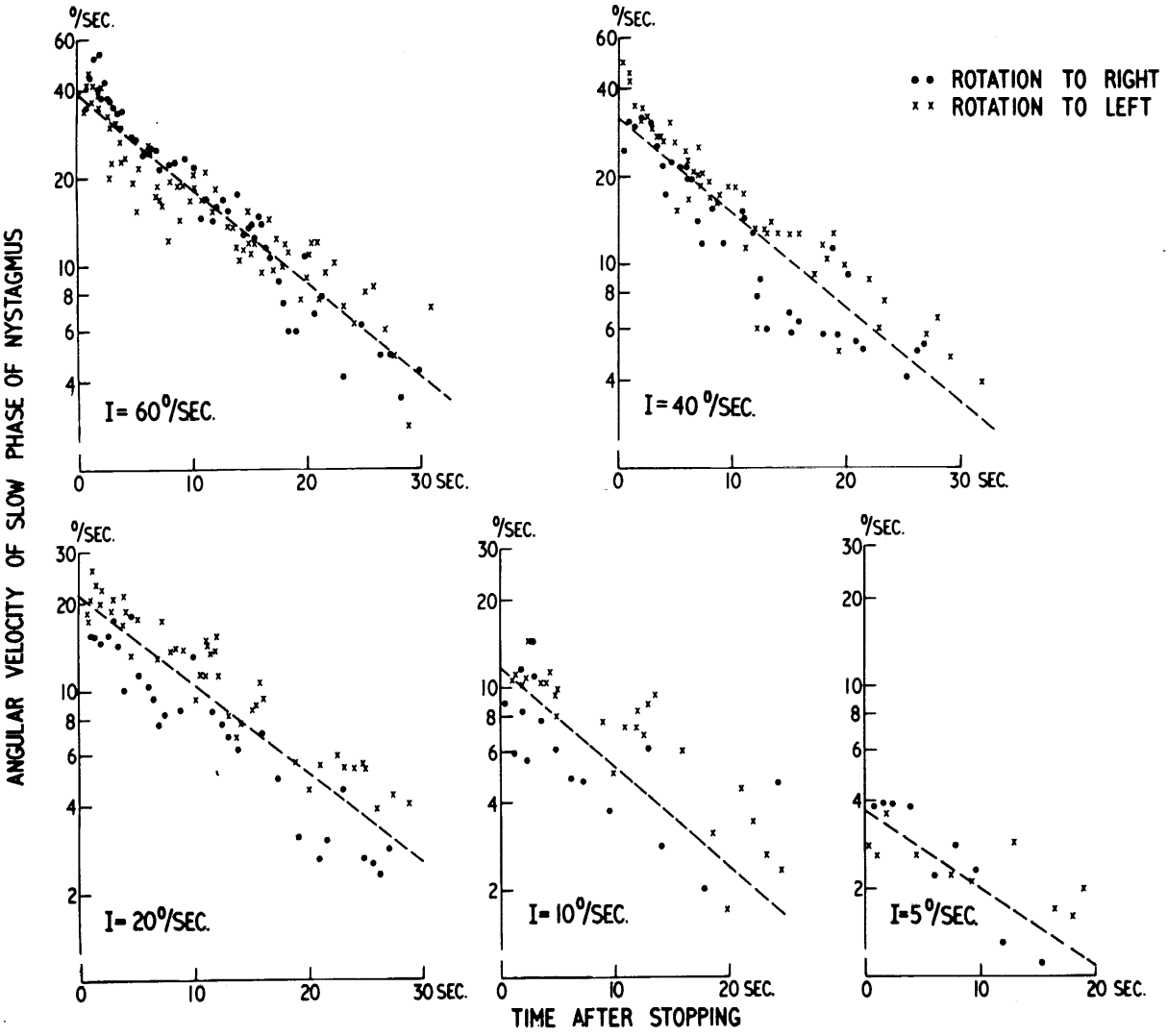

FIGURE 9.—*Relationship of postrotational nystagmus to the magnitude of the impulse* (I). *Each point represents the angular velocity of the slow-phase component of a nystagmic beat, which is plotted on a logarithmic ordinate scale against the time after stopping the turntable. Results are from one subject who experienced rotation to the right and to the left, at five turntable speeds.*

is no theoretical justification of which I am aware for this particular association between the two variables. However, the fact that "threshold" was not constant, but changed in an adaptive manner with the magnitude of the afferent signal, provides an explanation for the observed differences in the values of π/Δ obtained by subjective and objective techniques. Individuals who have a low $\pi/\Delta_s : \pi/\Delta_n$ ratio have a considerable shift in "threshold" with impulse; conversely, those who have a slope ratio close to unity have a relatively constant "threshold." By the same token, the parity of the nystagmus decay time constants, obtained by measurement of slow-phase velocity and by nystagmus cupulometry, is a manifestation of the relative constancy of the eye velocity which an observer, timing the duration of the nystagmus, calls the end of the response.

Decay of Subjective Velocity

The demonstration of an adaptive shift of threshold intensity is one explanation of the disparity of subjective and objective indicants of the postrotational response. However, it is

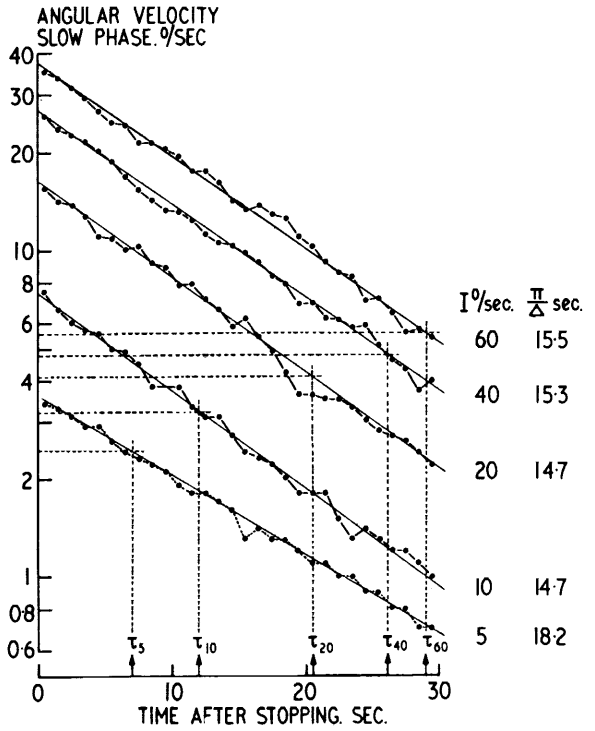

FIGURE 10.—*Mean decay of nystagmus slow-phase velocity of seven subjects who each experienced impulsive stimuli (as in fig. 9). Arrows on abscissa* ($\tau_5 - \tau_{60}$) *indicate mean duration of the aftersensation.*

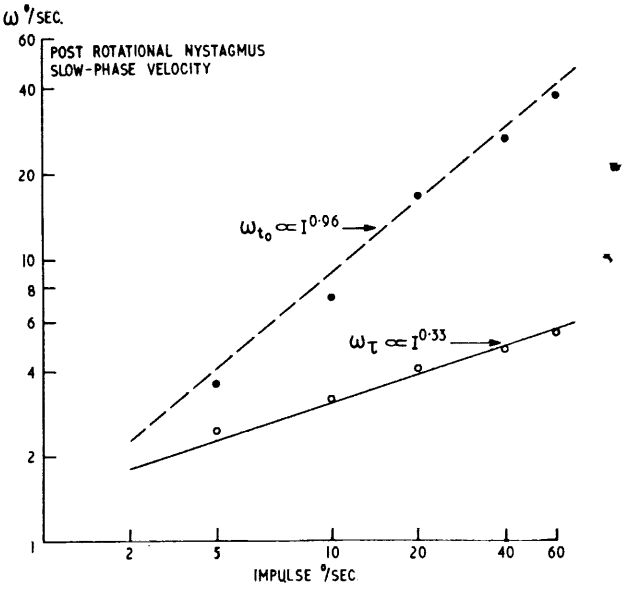

FIGURE 11.—*Relation of nystagmus slow phase velocity at* $t = 0 (\omega_{t_0})$ *and at the time the aftersensation disappeared* (ω_τ) *to the magnitude of the impulse. Values obtained from figure 10. Note logarithmic scales.*

not necessarily correct, for the sensation of turning may have a more rapid decay than the nystagmic response. Indeed, the demonstration of a considerable reduction in the rate of decay of nystagmus and sensations by competing gravireceptor signals (refs. 30 and 31) draws attention to the facility with which neural circuits can modify the time course of the response engendered by signals from the ampullary receptors.

A measure of the apparent velocity of the turning may be obtained by asking the subject to report the times at which he felt he had passed through a fixed angle (refs. 20, 25, and 32 to 34). In graphs shown in reference 20, the time constant of decay was 10 sec, and the peak subjective angular velocity corresponded with the magnitude of the impulse, but there was no indication that these values were representative of the population studied. In order to rectify these deficiencies, an experiment was carried out on eight subjects who experienced a rapid acceleration to a constant velocity which was maintained for 2 minutes before the turntable was stopped. They were asked to press a key every time they felt they had moved through an arc of 90° and to continue at this task until the sensation of turning disappeared; the endpoint was to be signaled by a double key press and verbal statement. Four turntable speeds were employed, namely, 80°, 40°, 20°, and 10°/sec with anticlockwise and clockwise rotation; the stimuli were presented according to a balanced design (8 × 8 Latin square).

The time between key presses was measured and the subjective angular velocity calculated. Individual graphs of log subjective angular velocity against time after acceleration and deceleration at each impulse intensity were plotted. From these graphs a mean subjective velocity for each 5-sec period was calculated in which the results for the two directions of rotation for all eight subjects were combined (fig. 12 (*a*) and (*b*)). The mean duration of the aftersensations was also determined and plotted in the form of a sensation cupulogram (fig. 13).

It was found that the time constants of decay were similar at the four impulse intensities, though the mean values were high, being 42.5 sec

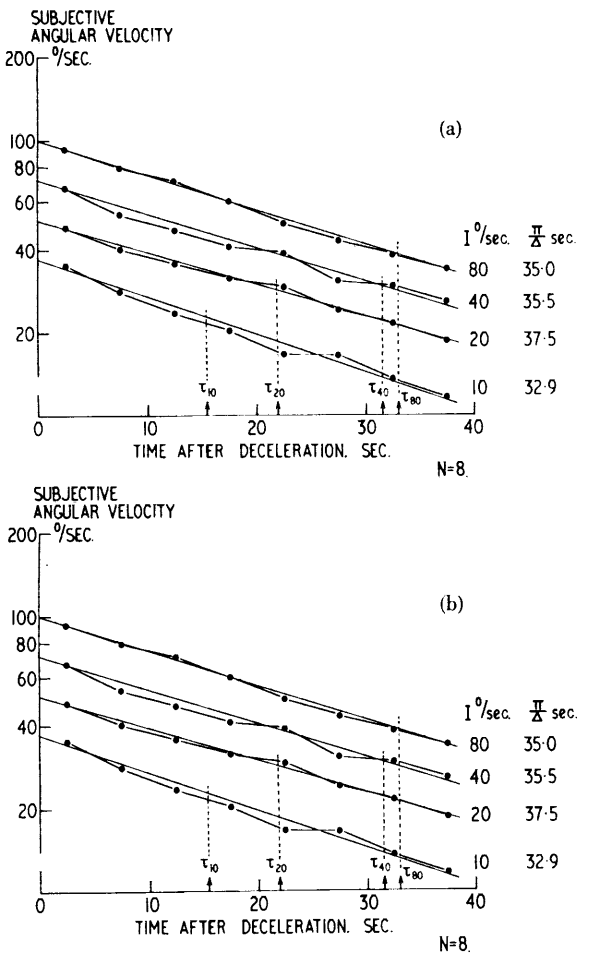

FIGURE 12.—*Decay of subjective angular velocity following impulsive stimulation.* (a) *The subjects were accelerated rapidly at* t = 0 *from rest to a constant speed, and reported the times at which they felt they had moved through an arc of 90°.* (b) *After 2 min the turntable was stopped and the sensory judgments repeated. Mean results of eight subjects who each experienced rotation to the right and to the left. Arrows on abscissae indicate the times at which the sensations of turning disappeared at each impulse intensity* ($\tau_{10} - \tau_{60}$).

following acceleration, and 35.2 sec following deceleration of the turntable. Coupled with these unexpectedly long time constants was the considerable overestimation of angular velocity, particularly at the low impulse intensities. For example, the 10°/sec impulse produced a peak subjective velocity some three times greater than that of the physical stimulus.

Despite these apparently bizarre results, the mean sensation cupulograms, obtained under

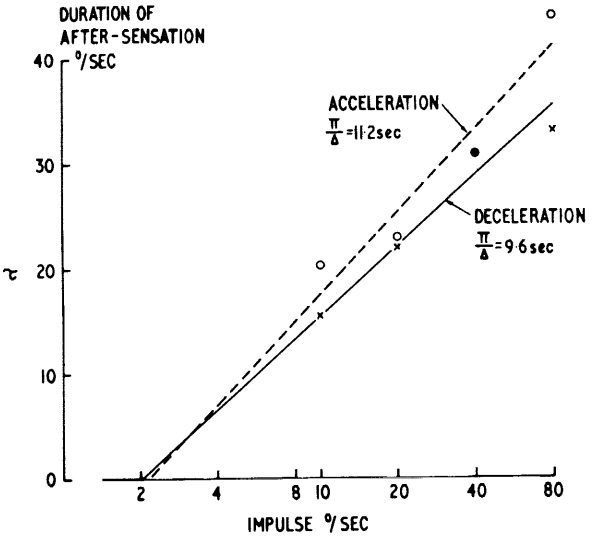

FIGURE 13.—*Sensation cupulograms obtained from figure 12*(a) *and* (b). *Open circles and crosses are the mean durations of the sensation of turning for the starting and stopping impulses, respectively.*

somewhat different stimulus and task conditions from those of the normal cupulometric test, had threshold and slope values which were within the normal range. From the cupulometric data and the subjective angular velocity plots, it was possible to determine the intensity of the sensation at the times the aftersensations were reported to have disappeared. Here, as with the expression of threshold as a nystagmus slow-phase velocity, there was a considerable alteration of threshold according to the intensity of the angular impulse. Thus, irrespective of whether nystagmus or sensation itself is used as an index of the signal from the ampullary receptors, it would appear that the intensity of the afferent signal, at the time at which the subject says that the sensation of turning has disappeared, is not constant. Threshold would appear to change in an adaptive manner so that it is lower when the preceding neural signal is weak than when it is strong.

More detailed examination of the extrapolated peak subjective angular velocity at the different impulse intensities, obtained in the same way as nystagmus ω_{t_0}, demonstrated a good linear relationship on a log/log plot (fig. 14). It would thus appear that the sensation of turning evoked by an angular impulse follows, in common with many other sensory modalities (ref. 35), a power law

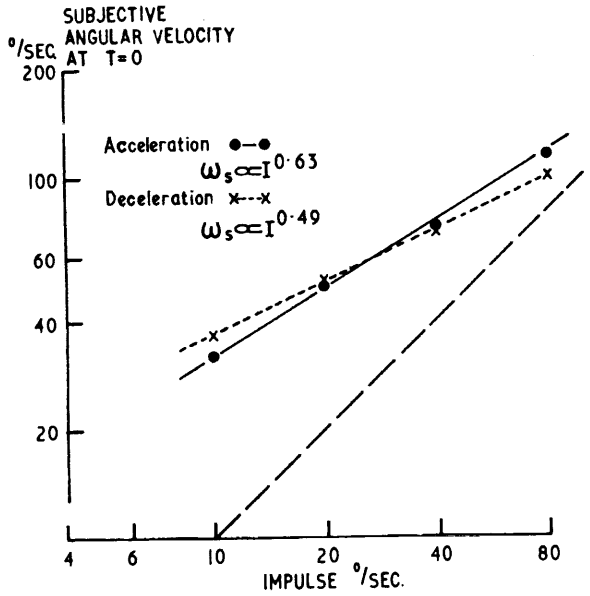

FIGURE 14.—*Subjective angular velocity at* t = 0 *related to magnitude of impulse. Mean values, obtained from figure 12*(a) *and* (b). *If the subjective response was proportional to the physical stimulus, the points would lie on, or parallel to, the interrupted line which has an exponent of 1.0. Note overestimation of the lower impulses and power-function relationship.*

function. The exponent was higher for the starting than for stopping impulses, but this difference was small when contrasted with the exponent of 1.0 reported by Brown (ref. 36). The disparity of the observations is considerable, yet is probably to be explained by differences in experimental techniques, for Brown used prolonged angular accelerations as test stimuli and subjective magnitude estimates. However, when impulsive stimuli were used and the subject reported apparent displacement, as in the experiment here reported, a nonlinear relationship between sensation and the physical stimulus was demonstrated. This observation has been confirmed by Reason (ref. 37) who, in a group of 20 subjects, found a power function exponent of 0.48 and a time constant of decay of 38.2 sec.

The presence of a power-function relationship between sensation and impulse can be invoked to explain the prolonged decay of subjective angular velocity, for the results depicted in figure 14 may be expressed as

$$\log S_{max} = m \log I + A \qquad (1)$$

where

S_{max} = subjective angular velocity at $t = 0$
m = gradient of the line
I = magnitude of the impulse
A = constant

Since the maximum deflection θ_{max} of the cupula produced by an angular impulse is proportional to I (eq. IV of ref. 20), then

$$\log S_{max} = m \log \theta_{max} + B \qquad (2)$$

where B = constant.

Since the time constant of decay of the subjective angular velocity did not change with I (fig. 12(*b*)), the initial relationship between S_{max} and I was maintained during the postrotational period. Accordingly, the specific conditions associated with equation (2) may be generalized so that

$$\log S = m \log \theta + B$$

or

$$\log \theta = \frac{\log S - B}{m} \qquad (3)$$

Following an impulse (I) the time course of the return of the deflected cupula to its neutral position is described by

$$\theta = cIe^{-kt} \qquad (4)$$

where c is a constant and

$$\log \theta = \log cI - kt$$

Substituting from equation (3)

$$\frac{\log S - B}{m} = \log cI - kt \qquad (5)$$

and

$$\log S = m \log cI + B - mkt$$

Thus an ampullary signal which decays with a time constant of $1/k$ should engender a sensation of turning which decays with a time constant of $1/mk$.

The power function exponent m for the postrotational response was approximately 0.5 (fig. 14); so, the time constant of the subjective velocity decay should be about twice as long as that of the afferent signal. As the mean subjective time constant was 35 sec, these calculations suggest that the afferent signal should have a time constant of 17.5 sec. This value is slightly greater than the average time constant of decay of the postrotational nystagmic response, but is sufficiently close to support the suggestion that the nonlinearity exhibited by the sensation of turning is responsible for the prolonged decay of the subjective response when assessed in this manner.

DISCUSSION

These studies of the sensation of turning and the concomitant nystagmus evoked by an angular impulse reinforce the already well-established opinion (refs. 24, 26, and 38) that the subjective response is a more capricious indicator of the behavior of the ampullary receptors than is nystagmus.

Investigations of the sensation of turning engendered by an angular acceleration require, in general, the subject to perform a task which may be difficult or unnatural. In the cupulometric test he has to judge the disappearance of a slowly decaying and at times ambiguous sensation, while subjective velocity measurements require the retention of the concept of a prescribed angle (ref. 38) and the perceptual integration of a signal from the end organ which relates primarily to angular velocity. It is accordingly not surprising that measures obtained by such subjective techniques can be readily modified by other sensory stimuli as well as by the behavioral state of the individual.

Yet despite the differing nature of the subject's task, measures of aftersensation duration and subjective velocity, both indicated that the sensory threshold varied according to the intensity and duration of the preceding signal. This is but one manifestation of adaptation within the vestibular sensory system which is responsible for the departure of the sensory response (ref. 38) from that predicted by the second-order differential equation (ref. 20) which describes the behavior of the canal-cupula-endolymph system.

An adequate description of the transduction of the ampullary signal to a sensation of turning must of necessity be complex, for in addition to the adaptive changes in threshold it must take into account the effect of a conditioning stimulus on the magnitude and duration of the sensation evoked by a test stimulus (ref. 18), the influence of the time course and intensity of the stimulus (ref. 39), and the depression (habituation) of the sensory response with iteration of the test stimulus (ref. 38). For those who are about to write down the transfer function, let them not forget the effect of alteration of arousal, of the intensity and significance of other sensory signals, and of instructions to the subject. The list is not complete, but perhaps the nature of the challenge is delineated.

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