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## VOLUME II: ECOLOGICAL AND PHYSIOLOGICAL BASES OF SPACE BIOLOGY AND MEDICINE

## PART III: EFFECT ON THE ORGANISM OF DYNAMIC FLIGHT FACTORS

## Chapter 1. Principles of Gravitational Biology[1]

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The study of gravity has been of special importance in the development of physical science. Its study in Aristotelian times marked the beginning of Physics -- and later enquiries into the behavior of gravity by Gaileo and Newton in the 17th century provided the foundation of modern physical science (Taylor, 1941).

The appreciation of the biological effects of gravitation developed much later. The first recognized overt effect of gravity on organisms was the geotropism of plants. Thomas Knight (1806) built a small water-driven centrifuge and placed germinating bean seeds about its perimeter. At accelerations of 1, 3.5 and 10 G the plants grew parallel to the field, rather than to gravity. He concluded that the ambient acceleration field was the orienting influence on plants. Somewhat later, Piorry (1826) examined the influence of Earth-gravity on the circulation of blood. He used the patient's response to a supine and upright posture to differentiate between apoplexy and syncope -- which was rather important since the contemporary treatment for apoplexy was bloodletting.

Animal experimentation on gravitational effects was first carried out by Salathe. Initially (1876), he investigated the relationship of posture -- head up or down -- upon cerebral volume, and heart and respiratory frequencies in dogs and infants. He found that rabbits held in a vertical position died after 15 minutes to 2 hours from a progressive failure of circulation and respiration. Subsequently (1877) he adapted a device that his teacher Marey had used for serial photography of bird wing-beating for the centrifugation of small animals. He developed instrumentation for measuring cardio-respiratory phenomena on the operating centrifuge, and found that the effects of orthostatic-hypotension could be reproduced with centrifugal forces. About the same time (1879), Tsiolkovskiy constructed a centrifuge and studied the acceleration tolerance of insects (200 G) and chicks (5 G) -- to determine the permissible operational characteristics of rockets for space travel (Rozenblyum, 1967).

Definitive scientific study of the physiological effects of acute acceleration began about 1917 when Garsaux of France studied circulatory changes in centrifuged dogs (Armstrong and Heim, 1938). "Grey-out" and "black-out," were reported by pilots during airplane races in turns about pylons (Bauer, 1926; Poppen and Drinker, 1951). Interest in centrifugal forces developed rapidly, and within a decade several large diameter human centrifuges were constructed (Gauer and Zuidema, 1961). Animal experimentation also was renewed to investigate the physiology and pathology of extreme acceleration conditions (Britton et al., 1946; Miura, 1942, etc.).

Aviation-oriented interest in acceleration is largely restricted to short-term phenomena, with exposures of no more than a few minutes' duration. Interest in the longer-term, chronic, exposure to centrifugation -- simulating an increase in gravity -- developed later in anticipation of space exploration. In 1951, Haber and Gerathewohl discussed the potential problems of prolonged space flight, and various ways that it might be simulated and studied. In 1953, Matthews reported the results of up to a year's exposure of rats of fields of

3 G and 6 G. Subsequently, chronic acceleration programs developed in the United States and elsewhere to study the effect of simulated changes in gravity -- but at the present time these number fewer than a dozen. Exposures of animals to weightlessness in Earth-orbit began in 1957 with the launching of the dog Laika in Sputnik 2 (Gerd and Gurovskiy, 1962).

So, Gravitational Biology has existed as an experimental science only since the 1950's. Obviously, the constancy of gravity, and our inability to alter it for significant periods on Earth were impediments to its earlier study. Were gravity as variable as the other common environmental factors, it would be quite well understood. For physical systems, brief periods of weightlessness obtained in free fall were sufficient for useful study. However, in biological systems, much longer exposure periods are required to elicit important changes.

## PHYSICAL PRINCIPLES

### Gravitational and inertial forces:

From the laws of fall were derived Newton's Laws of Motion, which relate force and displacement of unrestrained objects. The second of these laws is particularly important to gravitational biology, since it mutually defines forces and acceleration:

$$F \propto ma \quad \ldots\ldots\ldots\ldots\ldots (1)$$

The behavior of the accelerative force, gravitation, is described by Newton's Law of Universal Gravitation. This law proposes and quantifies the mutual gravitational attraction existing between all bodies of matter -- the force being proportional to the product of masses, ($m_1$ and $m_2$) and inversely related to the square of the distance (d) separating them:

$$F \propto \frac{m_1 m_2}{d^2}; \text{ or } F = G\ \frac{m_1 m_2}{d^2} \quad \ldots\ldots\ldots (2)$$

The relationship between the mass indicated by Newton's laws of motion (inertial mass -- m in equation 1), and by his Universal Law of Gravitation (gravitational mass -- m in equation 2) was dealt with by Einstein in 1911 as the "principle of equivalence" (Rosser, 1964; Witten, 1962). He concluded that these masses were equal for a given body and that the effects of accelerative forces were equivalent, irrespective of their physical bases. This principle was tested experimentally by Eötvös in 1922 and found valid to one part in $10^8$, and subsequently Dicke (1960) confirmed it to one part in $10^{11}$. This concept is particularly important to Gravitational Biology since it justifies comparisons between experimental observations on the effects of forces developed by motion (centrifugation) and those developed by gravitation.

Weight and mass:

Mass is a fundamental property of matter which also is defined by Newton's Law of Motion -- as expressed in the absolute system of units:

$$m = \frac{F}{a} \ldots\ldots\ldots\ldots\ldots (3)$$

So mass (m) is recognized behaviorally -- by the force (F) required to impart a unit of acceleration (a). Weight, however, is a phenomenon which develops in objects restrained from movement in an acceleration field.

The distinction between weight and mass is the fundamental physical principle for Gravitational Biology. Since these entities are frequently measured in the same units (lbs, gms, etc.) and also are essentially numerically equal in Earthly situations, there is little popular recognition of the distinction. Even in scientific situations, weight and mass are only rarely differentiated.[3]

The gravitational system (generally used by engineers) is particularly useful to biologists, and is generally applied in a modified form:

$$\frac{W}{M} = \frac{a}{g} = G \ldots\ldots\ldots\ldots\ldots (4)$$

Either of these ratios can be used to evaluate the dynamic properties of a particular environment -- that aspect which tends to make things move, or, if restrained, exhibit weight. The ratio $\frac{a}{g}$ has been called "gravitationally normalized acceleration," GNA (Dixon and Patterson, 1953), presenting a force as multiples of the Earth's gravitational constant. The weight-to-mass ratio, numerically equal to a/g, is the operational principle of accelerometers -- devices, resembling a spring balance, commonly used to measure accelerative forces. Either ratio is expressed as the dimensionless G ("g" being reserved for Earth's gravitational constant).

Weightlessness:

A condition of critical importance to Gravitational Biology is "weightlessness" -- in which objects with demonstrable mass lack a detectable weight.[4/] From the physicist point of view (W = ma), a body could be weightless only in the absence of accelerative force -- which, by the Law of Universal Gravitation, is theoretically impossible. "Free-fall," denoting unrestrained movement under the influence of the ambient forces, has been offered by physicists as an inoffensive alternative to "weightlessness" for objects in Earth orbit. However, this nomenclature has limitations, and does not cover all of the situations which many biologists wish to describe as "weightless."

Weightlessness was first encountered, briefly, in diving aircraft during World War I (Ferry, 1918), and with greater duration in WW II in aircraft (Von Diringshofen, 1952). In 1950, the Habers' proposed a flight maneuver (a "Keplerian arc") which would prolong the period of weightlessness -- and using high performance aircraft, to as long as 45 seconds (Roman et al., 1962). After World War II, experiments were initiated with rocket launched capsules which could accomodate small animals (Henry et al., 1952). With these, the weightlessness commencing at rocket burn-out, could be extended for many minutes. This weightlessness was truly the result of a free-fall -- which was only partially the case for the aircraft-produced weightlessness. Also, about the same time experiments were undertaken on the effects of buoyant immersion (Goff et al., 1956) which statically produced a condition of weightlessness that could be maintained for many days.

Thus, over the past two decades the biological effects of several conditions that are interrelated by a weightlessness aspect have come under scientific investigations. With the anticipation of manned space flight the significance of these biological effects, and the tempo of the research, have become greatly enhanced. It is obviously conducive to progress to adopt a generic term "weightlessness" to cover these varied conditions without demonstrable weight, and their effects. In this usage, "weight" and "weightless" are dealt with phenomenologically -- without reference to the component physical factors. Such latitude in definition has been recommended by NASA (Allen, 1965) which provides two criteria for "weightlessness:"

1. A condition in which no acceleration, whether gravity or other force, can be detected by an observer within the system in question; or
2. A condition in which gravitational and other external forces acting on a body produce no stress, either internal or external, in the body.

## Size and scale effects:

An important consideration in Gravitational Biology is the magnitude of organism, since systems (both physical and biological) of different size have many different properties. This was first recognized by Galileo (1638) and the Galilean concept of "Similitude" has been paraphrased more recently by Thompson (1917): "Man can not build a house, nor nature construct an animal beyond a certain size without altering the design or materials."

Strength and load relationship have important similitude considerations. Load (weight) is not an important consideration in small organisms. However, as the body size of an animal enlarges, the load will increase proportional to the cube of some dimension -- but the strength of the load-bearing structures will increase only in proportion to their cross-sectional area (i.e., the square of some dimension). Thus, if mice were scaled-up proportionately to elephant size, the body mass would increase to a much greater extent than the strength of the leg bones, and at some point they would fail and fracture spontaneously. The solution, of course, is the one suggested by Galileo, and as animals increase in body size, there is a relative increase in skeletal size (Thompson, 1917):

| Animal | Body mass | Skeleton % body mass |
|---|---|---|
| mouse, wren | 20-30 gms | 8% |
| dog, goose | 5 kg | 13-14% |
| man | 75 kg | 17-18% |

Thompson recognized that these differences are due to gravitational influence, since marine mammals have a lesser skeletal size and approximately the same relative skeletal proportions are found in porpoises and whales.[5/]

A very important consideration of size-related biological phenomena is that a minimum impediment from gravity will obtain below some size limit. The concept that the influence of gravity ceases to be important in small small systems (organisms) was proposed by Crookes (1896-97), Thompson (1917), and J.B.S. Haldane (1928).

### Scale limits of gravitational effects:

Although gravitation is a quite pervasive and constant phenomenon, it provides only a very weak field. For example, the gravitational attraction between two protons is only $10^{-36}$ as great as the electrostatic repulsion (Cook, 1960). In conditions compatible with animal life, Earth gravity is so much weaker than thermal energies or intermolecular forces that no influence is considered at the physical level of organization -- atoms and molecules (Salisbury, 1969).[6] Some phenomena which appear to result from gravitational effects at the molecular level may have other explanations.[7] Pickels (1950) concluded that gravity is a directly effective sedimenting force only for objects that are at least so large as erythrocytes.

Pollard (1965) examined the theoretical bases for anticipating effects of mechanical forces, in the order of Earth gravity, at the cellular scale. For bacterial cells of $1\mu$ dimensions, he found the influence of gravity on the statistical distribution of large molecules was insignificant. For larger cells, with relatively larger and denser organelles, the situation was quite different. In a mammalian tissue cell, $10\mu$ diameter, the influence of gravity on the distribution of mitochondria was potentially quite significant. However, when he compared the displacing effect of gravity with the convective streaming induced by metabolic activity (local density variation resulting from uptake of adjacent molecules), Pollard concluded that lack of gravity would not significantly affect the statistical distribution even of organelles.

Pollard also considered the effect of hydrostatic stress upon membranes, and the effect on their permeability, of anticipated degrees of distortion. At the tissue cell level, 10μ, no effect from gravity-induced hydrostatic pressures was anticipated. However, in an organism, the hydrostatic effect of a 1 meter column, transmitted to the membrane of the bottom cell would produce enough mechanical stress to theoretically affect its permeability to large molecules.

Others have considered the minimum size organism which is directly affected by gravity. Thompson (1917) divided organisms into three size categories with respect to their susceptibility to physical forces: large animals, such as man, that are affected primarily by gravity; smaller organisms, such as insects, that are more affected by such forces as surface tension; and micro-organisms, that are principally affected by viscosity, Brownian movement, etc. Haldane (1928) considered that hazards of gravity, such as entailed in falling, were limited to organisms larger than mice.

Went (1968) has provided a particularly interesting analysis of the influence of size (scale) on the susceptibility of objects to various categories of forces. He proposes a critical dimension appears to be in the order of 1 mm. At a lesser scale, forces of molecular origin have a dominant effect -- and at a greater scale, gravity and mass related phenomena dominate (Fig. 1). Since macro- and micro-systems have different mechanics, Went proposed a formal distinction

Fig 1

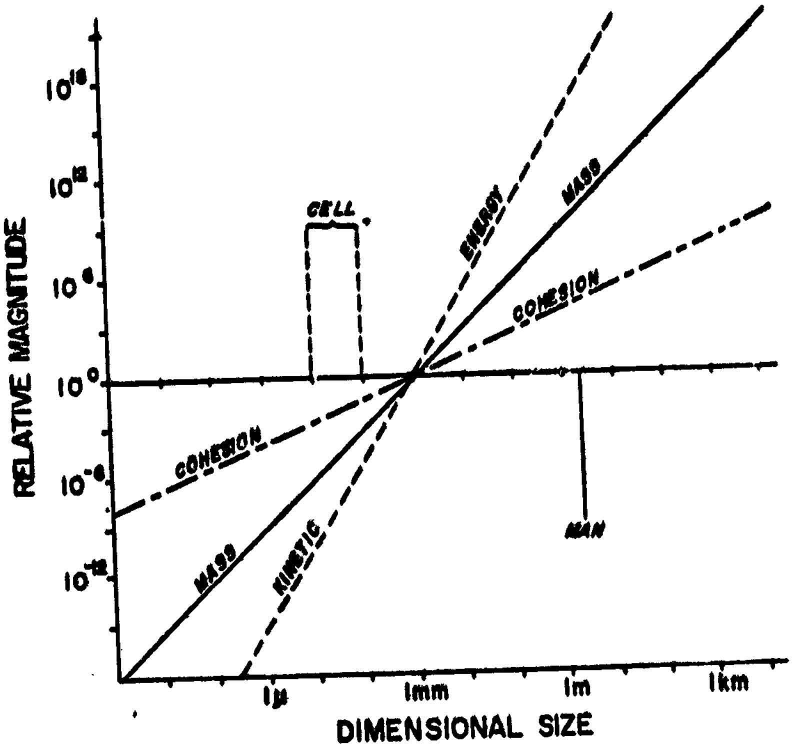

Figure 1: Size and Susceptibility to Various Forces.

The relative importance of (1) cohesion between surfaces, (2) mass (weight), and (3) kinetic energy upon the behavior of a system is compared with linear dimension. Both cohesion and kinetic energy values are only approximate, based on average roughness of surface and on average velocities of masses of various sizes (Went, 1968).

between them:

"Newtonian World" consisting of macro-systems in which mass and acceleration phenomena largely determine behavior.

"Gibbsian World" (honoring the American physical chemist Josiah Gibbs, 1839-1903), consisting of micro-systems which are largely regulated by forces of molecular origin. Systems of this category would be recognized by their greater behavioral modification with changes in temperature.

Of course, some rather important exceptions to Went's Rule are readily apparent. For example, the geotropism in woody plants must originate at the level of the cell, and in the growing point soon after cell division. Otherwise, the rigid cellulose walls would prevent the orienting response. However, in higher animals, acceleration fields appear to become effective at the gross (organ) level. Isolated (cultured) animal cells show little or no response to acceleration, up to fields of 200 G (Hartley, 1961; Edwards, 1963). But in intact homeothermic animals, effects are noted in relatively weak fields (2-7 G) and the severity of effect of the increased acceleration is proportional to body size. Cells are quite similar among such animals, despite a wide variation in body size (Driesch's law of constant cell volume), and diversity -- which would account for differential acceleration susceptibility, is first seen at the organ level. It appears that even weak forces can become effective if their influence is "amplified" through action on a large mass. For example, the Moon's gravitational force at the Earth's surface is approximately 2 x $10^{-6}$ G. But when this small force is applied through the volume of the seas, high energetic tides result. Similar situations, though on a much smaller scale, may be encountered in animals with moderate changes in the acceleration fields. For example, a field of 1 G acting on the whole organism may produce forces on the antigravity muscles that are 1000-fold its direct effect on those tissues. In this way the effects of acceleration upon a relatively large structure may become focussed upon a relatively small part, and elicit a specific response -- such as the release of a humoral agent or a neural stimulus.

Gravity as a biogenic factor:

The development of terrestrial organisms -- both phylogenically and ontogenically -- involves an increasing susceptibility to gravity. Life originated at no greater than cellular dimensions in an aquatic environment -- consequently it may be assumed that gravity had little direct effect on the origin of life.[8/] Some animals became terrestrial at a relatively small size, after an intermediate step of increased density and "bottom-dwelling" -- which induced adjustments necessary for life on a solid substratum (Gray, 1968). Subsequently, there was a general tendency for these species to develop slowly to larger size ("Copes Law"). In becoming terrestrial and increasing in size, such animals had to adapt and conform to the greater requirements imposed by gravity-induced loads. It is perhaps significant in this regard, that the largest terrestrial animals became extinct. However, among current terrestrial animals, life span does not appear to be regulated by gravitational susceptibility -- on the contrary, it tends to be proportional to body size (Heilbrunn, 1952). Those terrestrial animals which returned to an aquatic existence, the marine mammals, were able to continue development without gravitational interference (Smith and Pace, 1972), and among them are the largest animals which ever lived -- the blue whales.

# GRAVITY ORIENTATION

Gravity is a vector, with direction as well as magnitude, and it is the principal orienting agent in the Earthly environment. All but the most primitive organisms are gravity responsive -- either morphogenetically, posturally or in locomotion. This, of course, requires that gravity be perceived.

## Statocysts:

The prototype organ for gravity perception is the crustacean statocyst. This organ was identified by Kreidel (1893) as being gravity responsive, with the well known experiments in which iron replaced sand as the granular content of the organ. In this condition, orienting responses were obtained with a magnetic field, rather than gravity -- to which the normally sand-filled organ responded. The transduction of the gravity stimulus is by sensory hairs which line the statocyst cavity. The structural and functional aspects of this response has been discussed by Schöne (1971).

Similar gravity responsive organs are encountered in many other invertebrates (Horridge, 1971; Vinnikov, 1970; Vinnikov et al., 1970). Insects have somewhat different mechanoreceptors that respond to gravity -- neck proprioceptors in dragon flies (Mittelstaedt, 1950) and hair plates in bees (Lindauer and Nedel, 1959). Gravity perception and orientation in insects have been reviewed recently by Wilson (1971), Markl (1971) and Wendler (1971).

## Otolithic organs of vertebrates:

Vertebrates have developed somewhat more elaborate gravity-sensing organs than the invertebrate statocyst -- but the functional principles appear quite similar. These are associated with the labyrinthine mechanism of the ear region which also sense motion. The anatomy and physiology of these organs have been summarized by Lowenstein (1971).

Among vertebrates, the otolithic organs appear to be much less dominant in determining orientation -- are well integrated with ocular and proprioceptive inputs (Huertas and Graybiel, 1966; Graybiel 1965, 1968, 1969; Roberts 1967; Parin and Yemel'yanov, 1968; Razumeyev and Shipov, 1969).

### Gravity reception in plants:

Plants rather uniformly exhibit a complex geotropism, with stems responding negatively, roots, positively and root hairs being ageotropic. The early centrifuge experiments by Knight (1806) established that this orientation was in response to the ambient acceleration field. However, plants lack a demonstrable acceleration responsive organ comparable to the animal statocyst so the mechanism for the geotropism was not obvious. Haberlandt (1900) and Nemec (1900) reported that the sedimentation of cytoplasmic starch granules in a plant's cells was closely related to its geotropism and they proposed that these granules (amyloplasts) were the gravity susceptible statoliths that initiated the geotropic response. Subsequently a variety of exceptions were noted and there was a substantial discussion regarding the "Starch Statolith Problem" that has been reviewed by Larsen (1971).

Very little is known regarding the nature of the transduction of the gravity stimulus in plants -- i.e., the intermediate processes that are initiated by statolith sedimentation. A variety of concepts have been proposed and these have been summarized by Audus (1971) and by Merkis (1965). However, the geotropic response (the appropriate bending of the plant) is necessarily the result of differential growth between the upper and lower halves of the displaced plant tissue. This appears to be the result of an unequal distribution of plant growth promoting substances -- and the rather numerous observations supporting this conclusion have been reviewed by Wilkins (1971).

Particularly interesting results have been obtained with mutant tomato plants, which are naturally ageotropic (Stringham, 1966; Soressi and Cravedi, 1967; and Zobel, 1968). The factors responsible for this condition are inherited by simple Mendelian ratios. Geotropism can be restored in these plants, however, by several treatments (prolonged darkness, ethylene, supra-optimal auxin concentrations, etc.) -- indicating the importance of physiological processes in geotropism (Zobel, 1972). Continued study of these unusual materials should greatly enhance understanding of geotropism.

Some rather interesting variations in the geotropic response are encountered in acceleration fields artifically increased by centrifugation. There appears to be a time-intensity summation in the rate of response and field intensity (the "Reciprocity Rule," Rutten-Pekelharing, 1910) -- although this is subject to some limitations that have been discussed by Gray and Edwards (1971). This implicates the transport rate of growth promoting substances as determining the kinetics of geotropic responses. However, with a normal orientation, an increased field strength has very little effect upon growth rate -- and in fields greater than 100 G, growth is diminished (Gray and Edwards, 1971). Since transport of growth promoting substances should be enhanced in stronger acceleration fields, the results of centrifugation studies with plants in a normal and abnormal orientations are paradoxical.

Clinostat studies:

Since particulate ("statolith") sedimentation would be a time-requiring process, as indicated by Stokes law, a continual re-orientation of a plant with respect to gravity prevents its completion. At an appropriate rate, such treatment eliminates the orienting influence of gravity.[9] The responses of plants to clinostat scalarization of gravity have been reviewed by Gordon and Shen-Miller (1971). Generally they support the geotropic theory -- there is a reduction in auxin transport, and a proportional decrease in growth rate. The threshold for a geotropic response has been examined by Shen-Miller et al., (1968) and it appears to be 0.005 G, substantially less than the 0.012 G threshold required for otolithic stimulation in animals (Walsh, 1957).

## CHRONIC ACCELERATION

Chronic acceleration describes the exposure of organisms to an increased field for periods of sufficient duration to permit physiological adaptation. Consequently, animals so treated attain a new steady state, and exhibit a rather uniform physiology indefinitely -- i.e., "chronically." During the preceding period involving biological stress and physiological adaptation their physiology will be quite labile.[10]

Animal centrifuges:

For technical reasons, chronic acceleration necessarily involves centrifugation. Linear acceleration can be maintained for only brief periods -- a linearly accelerating object developing a 2.5 G field would attain an Earth-orbital velocity in about 8 minutes. Several animal centrifuges suitable for protracted operation have been reported: Kelly et al., (1960); Walters et al., (1960); Luther (1964); Canonica (1966); Cooke and Bancroft (1966); and Duling (1967a). Laboratory centrifuges also have been adapted for the prolonged treatment of avian eggs (Besch et al., 1965a,b), cultured cells (Hartley, 1961) and microorganisms (Wunder, 1955; Montgomery et al., 1963).

Centrifugation necessarily involves turning as well as the development of an acceleration field. Since turning has separate biological effects, its participation in the results must be determined. A convenient method is to carry rotated controls -- animals housed around the axis of rotation of the centrifuge, which share the rotatory stimulus but not the acceleration field of the chronically accelerated animals. Such rotated controls would also serve as vibration controls.

Alternatively, chronically accelerated labyrinthectomized animals, insensitive to rotatory stimulii, can be compared with intact animals to determine rotatory-induced effects (Wunder et al., 1966). The influence of rotation has been examined for rather slow processes (growth, feed intake, etc.), and no separate effect has been detected. This apparently does not result from a habituation to the turning, since chronically accelerated animals retain a labyrinthine sensitivity -- even with repeated cupulometric testing (Winget et al., 1962). A major factor in the apparent lack of rotatory stimulation in centrifuging animals may be the provision of "one degree of freedom" (Dixon and Patterson, 1953). This mounting of the centrifuge cage permits it to orient in response to gravity as well as the centrifugal force, so that only the resultant force, perpendicular to the cage floor, is perceived.

Generally the operation of animal centrifuges is not continuous, but is interrupted daily for observation and tending to the experimental animals. The influence of repeated intermittant centrifugation, varying from 10 minutes to 23.8 hours per day, was investigated by Burton (1970). In many respects there is a time-intensity summation for the intermittant treatment, so exposure of animals to a given field 98% of the time would induce physiological changes equivalent to continual exposure to a field of 98% the intensity. Consequently the daily interruptions in acceleration are not considered significant to the results.

## Acceleration stress and adaptation

Animals readily tolerate exposure to low intensity acceleration fields (eg., generally between 1-1.5 G, Smith and Burton, 1971). No biological changes are obvious from such minimal treatment -- it being accomodated by homeostatic mechanisms. With more intense fields, biological stress is induced which is recognized as a frank sickness. In the domestic fowl, two well defined acceleration sickness syndromes were identified (Burton and Smith, 1965), one of which was reversible, and the other became progressively more severe, and was uniformly fatal. Removal from the acceleration field generally resulted in a prompt (<24 hours) recovery indicating that processes capable of rapid change were responsible. Postmortem examinations indicated no limiting organic lesions, either grossly or microscopically, in acceleration sickness. So the pathogenic changes are sub-microscopic and perhaps metabolic, as indicated by their ready reversibility. Acceleration stress involves an adreno-cortical response which is ameliorated with physiological adaptation. A convenient measure of this involvement is by the transient lymphopenia — Fig. 2 (Burton et al., 1967b) -- which is highly correlated with the animal's degree of physical dibilitation (Burton ~~et al.~~ and Smith, 1968).

Fig 2

There are limits in the intensity of the acceleration field to which animals can become physiologically adapted. This acceleration tolerance limit is inversely related to size. Dorsophila larvae can survive several days' exposure to 2-3,000 G (Wunder, 1955). Mature diptera can tolerate fields of 20 G (Sarota and Shimazu, 1959). Larger insects, such as grasshoppers, can survive in fields of 9 G (Eberly et al., 1963). Among small homeotherms, the estimated acceleration tolerance is less, but still size related:

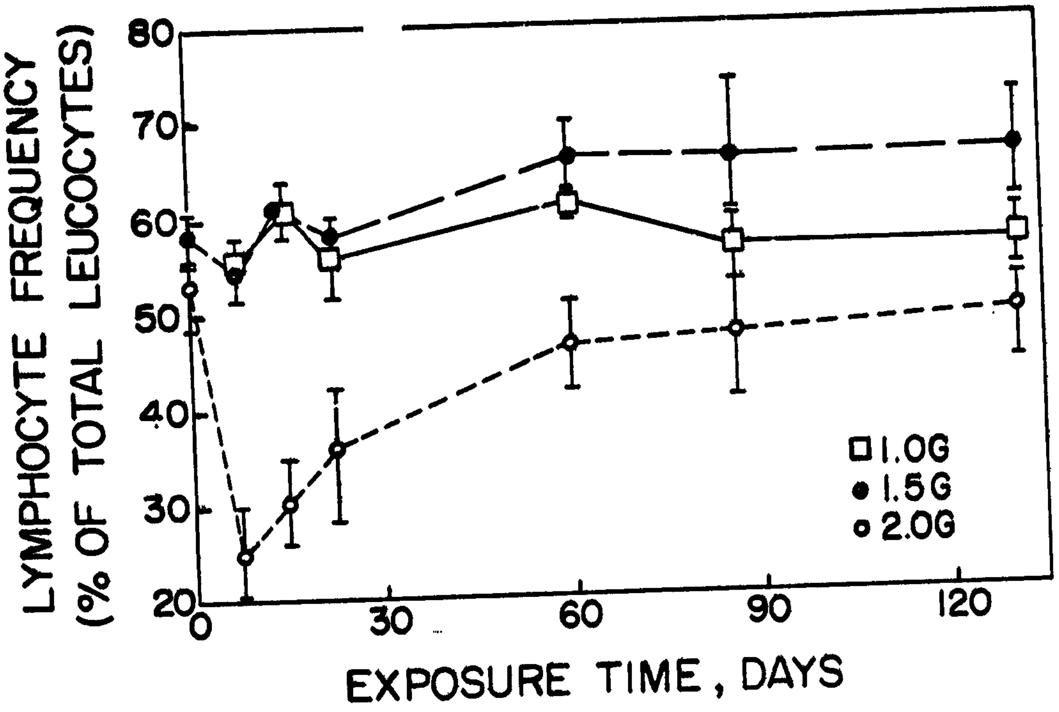

Figure 2. Relative Lymphocyte Frequencies In Adult Male Chickens Exposed to Increased Acceleration Fields.

Fields of 2 G intensity induce a cycle of stress and adaptation, whereas a 1.5 G field is compensated homeostatically. The points on the curves are mean values ± standard errors (Burton, et al., 1967b).

| Species | Approximate Mass (grams) | Estimated Chronic Acceleration Tolerance |
|---|---|---|
| Mice | 30 | 7 G (Wunder, 1962) |
| Rats | 200 | 5 G (Oyama and Platt, 1965) |
| Chickens | 1800 | 3 G (Burton and Smith, 1965) |

Tolerance limits also are affected by posture -- with bipeds surviving in more intense fields than for quadrupeds. There also may be an interaction between size and posture in regard to acceleration tolerance, but this cannot be evaluated at this time. The evolutionary aspects of the development of an upright posture in man, and its physiological basis and consequences with respect to gravity have been reviewed by Hellebrandt and Franseen (1943), Keith (1923), and Katsitadze (1968).

Acceleration tolerance also is affected by age, with young adults (shortly after skeletal maturity) being most capable of physiological adaptation to intense acceleration fields. Sex also is a factor, with females being more tolerant to acceleration.11/

Physiological adaptation to chronic acceleration is not necessarily permanent. Individuals which have adapted to acceleration may at later times develop acceleration sickness and die.12/ The acceleration sickness developing in previously adapted individuals appears to be quite similar if not identical to that developing in susceptible individuals early in the treatment.

An important aspect of physiological adaptation to chronic acceleration is the rather great heritability for its capacity. This has been reported only for the fowl (Smith and Kelly, 1961), but presumably the principle is general. After five generations of selection for acceleration tolerance (survival) a strain was developed that suffered only 10% as great a mortality as encountered in unselected stock with equivalent treatment.[13] The "selection progress" (improvement per generation) was quite rapid in the development of the acceleration-selected line. Because of the directness of the sequence: metabolic processes -- enzyme -- gene, geneticists associate a metabolic basis with processes that exhibit a great heritability (Wagner and Mitchell, 1955). So tolerance of chronic acceleration appears to have a metabolic basis -- as does the susceptibility to acceleration sickness (indicated by the lack of limiting organic lesions).

## Growth and Development

The influence of gravity upon development in amphibian eggs has a long history of investigation. Pflüger observed that these ova oriented spontaneously so that the axis between the animal and vegital poles remained parallel to the field of gravity. He also observed (1883) that the first division was parallel to the field of gravity even in eggs restrained to abnormal orientation -- and concluded that gravity was a determining factor in embryogenesis. Roux (1884), however, found that such eggs developed normally upon clinostats -- which scalarized gravity -- and concluded that gravity was unimportant to embryogenesis. This led to a spirited debate of almost two decades duration between Roux (1884, 1887, 1897 and 1900) and Schultze (1894, 1897, 1899 and 1900) regarding the role of gravity in early development. More recent experiments (Penners and Shliep, 1928a,b; Pasteels, 1938, 1939) indicate that the participation of gravity in these experiments was indirect -- the immediate basis being a turbulent re-arrangement of yolk and cytoplasm as a result of their different densities. The development of amphibian embryos is not particularly sensitive to acceleration (Hertwig, 1897), being normal up to 4.1 G, but becoming completely suppressed at 9.2 G. This was also examined by Konopacka (1908) who concluded that acceleration fields interfered with development by limiting the distribution of cytoplasmic materials during cell division.

Other ova are much more tolerant of acceleration. Sea urchin eggs (Harvey, 1933) and Ascaris eggs (Beams and King, 1937) continue to develop at 5000 G, although there is a substantial stratification of cytoplasmic materials. Grasshopper eggs (Bodine and Boell, 1935) continued to develop in fields of 20,000 G -- although there was a decreased respiration above 1000 G. So prenatal development does not appear to be necessarily susceptible to acceleration fields -- or gravity.

Post-hatching growth has been examined in Drosophila (Wunder, 1955; Wunder et al., 1959a,b; Moressi et al., 1961), a viviparous fly, <u>Sarcophaga perigrina</u> (Saruta and Shimizu, 1959) and grasshoppers (Eberly et al., 1963). In all cases there is a repression of growth rate which is proportional to field strength.

Early post-natal growth also has been examined in homeotherms -- mice (Briney and Wunder, 1960; Wunder et al., 1960; Oyama and Platt, 1967); hamsters (Briney and Wunder, 1962); rats (Oyama and Platt, 1965, 1967), and chicks (Smith et al., 1959). Ordinarily such growth is geometric (Brody, 1945):

$$M = Mo\ e^{kt} \quad \ldots\ldots\ldots\ldots\ldots (5)$$

Where: M is the body mass at time t;

Mo is the birth mass (ie., M when t = 0); and,

k is the proportionality coefficient.

When animals are born and raised on the centrifuge, these kinetics apply (Oyama and Platt, 1967). However, in most cases, young animals have been introduced to chronic acceleration at a later age, and the initial change is a marked reduction in body mass. A major factor is a marked but transient decrease in feed intake -- which may be the result of an increased secretion of FMS -- "fat mobilizing substance" (Nir et al., 1969). After a period of some days or weeks, feed intake increases, and growth rate resumes. Oyama and Platt (1965) analyzed this resumed growth in rats in terms of the early growth kinetics (equation 5), finding a rectilinear reduction in the growth rate (k) with increasing field intensity (G):

$$k \times 100 = 2.45 - 0.086\ G \qquad (6)$$

Later growth kinetics (comprising about two-thirds of the growing period) tend to be hyperbolic, with growth decreasing geometrically towards a mature body mass (Brody, 1945):

$$M = A - Be^{-kt} \qquad (7)$$

Where: M is the body mass at time t;

A is the mature body mass -- an asymptote which M approaches exponentially;

B is an arbitrary (integration) constant; and

-k is the proportionality coefficient.

The responsiveness of late growth kinetics to a change in acceleration field strength is quite rapid -- and conforms immediately to the kinetics appropriate to the second field (figure 3). Fig 3

The late growth coefficient (-k in equation 7; with "t" in days) is affected by acceleration (G) -- but differently among the species examined:

Chickens (Smith and Burton, 1967): $-k \times 100 = -0.85 -0.24\ G$..(8a)

Rats (Oyama and Platt, 1965, 1967): $-k \times 100 = -3.20 +0.24\ G$..(8b)

Mature body mass (A, equation 7) is decreased rectilinearly with increasing acceleration:

$$A = Ao - b\ G \ldots\ldots\ldots\ldots\ldots (9)$$

Where: A is the body mass on a field of G intensity, and is $\overset{A}{W_o}$ where G = 0; and,

-b is the proportionality coefficient.

The degree of this acceleration-repression of mature body mass is proportional to body size (Table 1). Table 1 From this summary, it appears that a 1 G change in acceleration field -- and perhaps Earth gravity -- would have no particular effect in animals of less than 20 grams body mass.

It also is important that this lesser body mass of chronically accelerated animals is regulated. Male chickens subjected to a 3-day fast while exposed to 1.5 to 2.0 G may lose 200 to 300 grams body mass; however, upon re-alimentation, they recover the lost body substance as quickly as the gravity controls (Smith and Burton, 1967). This clearly indicates that the acceleration-repression of body mass is not the result of any limitation in synthetic capacity, nor from a restriction in feed intake. Instead, it is a physiological phenomenon which is closely regulated. This was interpreted as indicating that the greater acceleration field merely resets the end-point which is effective

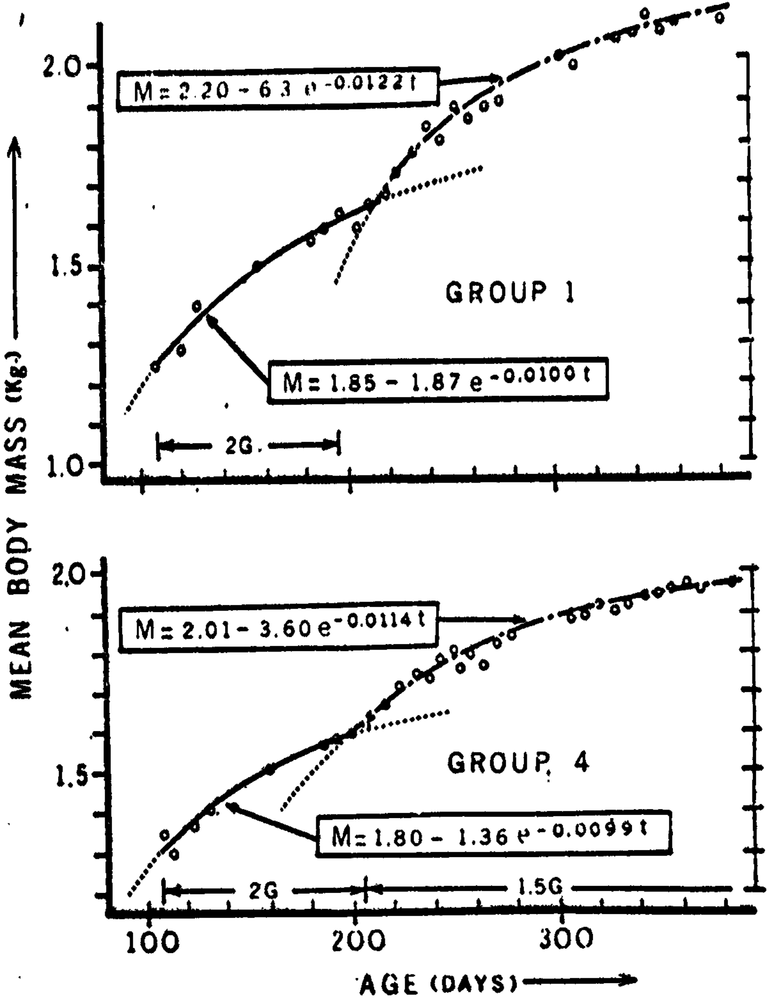

Figure 3. Growth Kinetics of Chickens With A Change In The Ambient Acceleration Field.

Mean body masses are indicated, before and after a reduction in the acceleration field -- for birds which survived to the end of centrifugation (516 days of age). Standard errors for Group 1 varies from 0.05 around 100 days of age, to 0.12 around 350 days; for Groups 4, 0.04, and 0.08 respectively (Smith and Burton, 1967).

**TABLE 1. Acceleration Fields And Mature Body Mass**

$A_o$ is the potential mature size indicated in equation 9, and $-b$ is the decrement induced by a 1 G field. "I" [ = $(\frac{-b}{A_o})$X 100], is the "inhibitory effect" (% size reduction) of Earth gravity.

|  | Species | $A_o$ | $-b$ | I [= $\frac{-b}{A_o}$ X 100] | References |
|---|---|---|---|---|---|
| ♀ | Mice | 38.5 gm | - 0.33 | - 0.9% | Oyama and Platt, 1967 |
| ♂ | Mice | 40.5 gm | - 0.33 | - 0.8% | Oyama and Platt, 1967 |
| ♀ | Rats | 307. gm | -17. | - 5.5% | Oyama and Platt, 1965 |
| ♂ | Polish Rabbits | 1.76 kg | - 0.33 | -18.6% | Unpublished |
| ♂ | NZ Rabbits | 4.70 kg | - 0.66 | -14.0% | Unpublished |
| ♂ | Coturnix Quail | 128. gm | - 6.1 | - 4.8% | Unpublished |
| ♂ | Leghorn Chicken | 2.29 kg | - 0.23 | -11.5% | Smith and Burton, 1967 |
| ♂ | Leghorn Chicken | 2.13 kg | - 0.17 | - 8.0% | Smith, Burton and Kelly, 1971 |
| ♂ | Arbor-Acre Chicken | 5.50 kg | - 0.77 | -14.0% | Unpublished |

in the feedback regulation of mature body size, with the specific processes functioning unchanged.

**Visceral growth:**

The growth of organs, as a function of body size, generally conforms to exponential kinetics (Brody, 1945):

$$y = ax^b \quad \ldots\ldots\ldots\ldots\ldots \quad (10)$$

Where: y is the size of an organ or part;

x is the size of the entire organism;

b is the proportionality coefficient; and,

a is the positioning constant, the value of y when x = 1.

Calculations fitting data to this equation generally involve a linear regression of the logarithmic transforms. Within a species, the relationships for differential growth of organs are quite diverse.[14/] Since acceleration systematically affects body size, estimation of its effect on organ growth by comparison to body size (e.g., as percent body mass) is suitable only for organs that are isogonic with body mass (such as blood volume) where the proportionality constant "b" is characteristically unity. Application of this simplified procedure to other organs may lead to spurious conclusions. Miller and Weil (1963) have provided a good discussion of the absurdities obtained when exponential relationships are treated arithmetically. However, in analyzing such data, a variety of procedures may be employed to avoid these difficulties.

Oyama and Platt (1965) evaluated the influence of chronic acceleration upon organ growth by comparisons between experimental animals and size controls -- younger animals of equivalent body mass. A similar procedure would involve controls fed so as to maintain the same body mass as the accelerated animals (Smith and Kelly, 1963). Another way to avoid errors induced by scale effects, is to compare organ sizes within the same animal.[15] However, the most satisfactory procedure is to carry rather numerous controls, sacrificing them and measuring organ sizes over an appropriate range of body sizes. With regressions, the somatic relationship ($y = ax^b$) can be established.

Studies of organ growth have been reported by Briney and Wunder (1962) for hamsters, Oyama and Platt (1965) for rats, and Smith and Kelly (1963) for chickens. In general, there is little systematic effect of chronic acceleration upon visceral size except for an enlargement of the liver.

Skeletal growth:

The skeleton, as the principal load-bearing system of terrestrial animals, might be anticipated to be quite susceptible to the weight-to-mass changes encountered in chronic acceleration. The responsiveness of bone structure to mechanical forces is one of the classics of biomechanics -- "Wolff's Law" [Wolff, 1892, discussed by Ham (1965); Thompson (1917)]. Changes in functional demand (load) also lead to gross changes in bone structure and also increasing bone density (Melnik, 1968). Over a century ago, Sedillot (cited by Thompson, 1917) found that removal of a tibial segment (a principal load-bearing bone) from the leg of a puppy, led to a 5 to 6 fold over-growth of the paired fibula, which attained the usual tibial diameter. The stimulating influence of moderate mechanical load, at Earth gravity, on growing bone has been demonstrated by Tulloh and Romberg (1963) in sheep, and by Denilova and Sviridov in dogs (1953)[16] Conversely, removal of mechanical forces by immobilization leads to a decrease in bone mass ("disuse atrophy"), largely by an increase in porosity (Ham, 1965).

*In vitro* studies with embryonic bone indicates that bone and bone forming tissues also respond to mechanical stresses. Glucksman (1942) observed that the application of mechanical forces to periosteum and perichondrium led to the disappearance of collagen, and enhanced the formation of cartliage. Differentiated cartilage, however, responded to tension or compression with disintegration of hyaline matrix and its replacement with fibrillar tissue, enhancing ossification.

Growth of bones has been examined in several terrestrial species during chronic acceleration. Wunder et al., (1960) found a relative, but not absolute, increase in femur growth in female mice at 4 G. Bone shape also changed, the diaphyseal cross section tending to become circular in centrifuged animals. Briney and Wunder (1962) observed no change in femur mass in female hamsters exposed to 4 and 5 G for 4 weeks. Femur length, however, was both relatively (significantly) and absolutely larger than in gravity controls. No significant change in diaphyseal cross section was observed. Oyama and Platt (1965) studied female rats exposed to fields of 2.5, 3.5, or 4.7 G for periods up to one year. Femur size was increased 10 to 18% after 4.5 months -- but not related systematically to field strength. After one year, the effect was much less -- a field of 3.5 G reducing femur size about 6%, and 4.7 G increasing it 8%. This indicates that the maximum acceleration effect is obtained early in the treatment -- which is reasonable in view of the more rapid skeletal maturation, as compared to soft tissues.

Smith and Kelly (1963) reported changes in skeletal growth in developing chickens exposed to a field of 1.5 - 3 G for 75 days. It appeared that the non-load-bearing humerus in growing chickens was more responsive to acceleration that was the load-bearing femur -- and generally the bones tend to become "stubbier," the width increasing more than the length. Other observations on birds which were skeletally mature at the onset of chronic acceleration did not reveal any skeletal differences even with a year or more of treatment. So, acceleration is effective in altering bone characteristics principally during skeletal development.[17/]

The influence of 4 and 5 G fields upon embryonic chick bone growth has been examined by Redden (1970). This treatment leads to a more rapid dimensional growth (length and width) for the first 17 days of development -- but later is markedly depressed so that at hatch the accelerated embryos have smaller bones. This effect is rather uniformly evident among several bones of the appendicular skeleton (figure 4). Fig. 4 The proportionality of the degree of response to field strength indicates that the changes are acceleration-induced.

In the period of enhanced bone growth, the effect is more pronounced on length than on width -- so the result is the opposite of the "stubbier" bones encountered with post-natal acceleration. However, in the embryonic environment, the soft tissues are buoyant, and exert a tension, rather than a compression on the bones.[18/] So the mechanical forces on the bones as well as the growth response may be

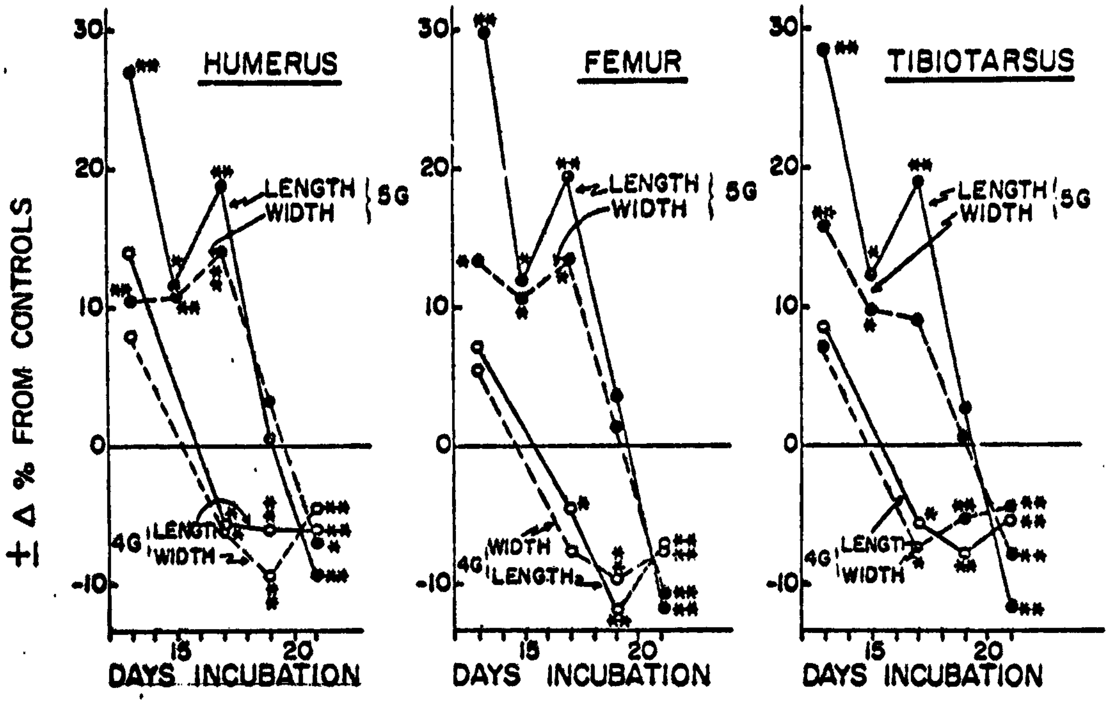

Figure 4. Influence Of Chronic Acceleration Upon Chick Embryo Bone Growth.

The characteristics of bones of centrifuged embryos are compared with those of static controls (after Redden, 1970). Random probability *, <0.05; **, <0.01

those anticipated with a reduction, rather than an increased acceleration field.

Several explanations have been offered to account for the acceleration-induced skeletal changes. Wunder et al., (1960) and Briney and Wunder (1962) have considered these effects in terms of Wolff's Law -- the greater load leading to a compensatory bone growth. However, in bipeds, greater response of the non-load-bearing humerus, as compared to the load-bearing femur (a situation not shared by quadrupeds) indicates that it is not a simple local response, but represents a "whole animal" regulation.

Muscle growth:

Muscle is specifically involved in postural maintenance in terrestrial organisms, and in the performance of mechanical work. Since these functions are largely antigravity in nature, muscular growth, like skeletal growth, may be expected to be especially responsive to changes in the ambient acceleration field. However, muscle tissue is much more plastic than bone. Even after the attainment of mature body size, muscle readily responds to an increased functional load with hypertrophy -- a form of compensatory growth.[19/]

The first chronic acceleration experiments (Matthews, 1953) were undertaken to determine the effect of loading upon muscle function. Small animals (rats) were selected to minimize circulation (hydrostatic pressure) effects and to emphasize the muscular response. After a year at 3 G, the centrifuged animals exhibited a marked decerebrate extensor tonus.

Briney and Wunder (1962) found significant increases in relative sizes of heart, diaphragm, and gastrocnemius in female hamsters exposed to fields of 4 and 5 G for 4 weeks. However, Bird et al., (1963) did not report significant relative size changes of these muscles in mice exposed to fields of 4 G for a period of 8 weeks. Canonica (1966) also observed a relative increase in gastrocnemius muscle mass in hamsters after 4 weeks at 4 G. Oyama and Zeitman (1967) found increases in relative gastrocnemius size in rats after 3 months and a year's exposure of rats to fields of 3 to 4.7 G -- but these were not statistically significant.

Burton et al., (1967a) examined the differential effects of chronic acceleration upon antagonistic skeletal muscles -- which avoids complications from scale effects. A hip flexor (m. sartorius) and hip extensor (m. adductor) were selected since they are normally of comparable size, and the latter is a principal postural muscle. The differential muscle response, Figure 5, indicates that hypertrophy is a result of increased loading induced by chronic acceleration -- but, unlike bone changes, the effect is quite local and selective. Paired muscles tend to establish a rather specific mass ratio that is gravity-dependent -- but the responsiveness is slow.

Fig. 5

Canonica (1966) studied the contractile properties, <u>in situ</u> at Earth gravity, of gastrocnemius muscles of hamsters that had been exposed to a 4 G field for 4 weeks. He found a transient increase in strength of tetanic contraction -- +21.6% at one week, and +36.6% at 4 weeks of treatment, and equivalent to controls at later times. The fatigue resistance to tentanizing stimuli was greater at all times for previously centrifuged animals.

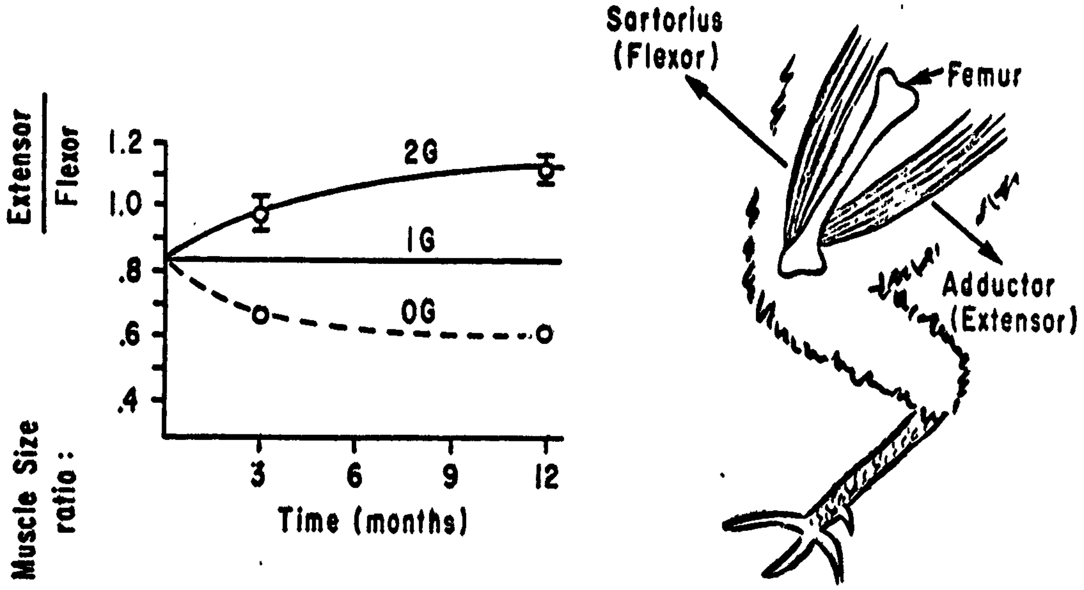

Figure 5. Effect Of Duration Of Acceleration Upon Extensor: Flexor Muscle Ratios.

Rates of change (t in months) is the mass-ratios of adductor (E) and sartorius (F) muscles have the kinetics:

$$\overline{E}:\overline{F}_{(2\ G)} = 1.17 - 0.33e^{-0.16t}$$

$$\overline{E}:\overline{F}_{(0\ G)} = 0.62 + 0.22e^{-0.49t}$$

Data for "0 G" represents intercept values from observations at several fields at the exposure times indicated (after Burton et al., 1967a).

## Hematology

Vascular columns of blood are susceptible to acceleration proportionately to their length and orientation with respect to the field. Hemodynamic properties of the circulation are monitored by a variety of baroreceptors, and regulated by reflex mechanisms. The cellular phase of the blood is an important, though disputed determinant of flow-resistance, which also affects the hemodynamic properties of the circulation. The cellular content of blood is regulated by a variety of humoral agents. The fluid phase of the blood, the plasma, is important to the distribution of body water -- largely the result of the plasma protein concentrations and hemodynamic pressures, which determine the partition of extra-cellular water. Consequently, hematologic changes may be anticipated with chronic exposure to an altered acceleration field.

Erythrocytes:

In rats exposed to fields of 2.5, 3.5 or 4.7 G for 5 months, Oyama and Platt (1965) found a reduction in erythrocyte numbers that was approximately linear to field strength (G):

$$\text{RBC's per mm}^3 \text{ blood} = (8.4 - 0.227\ G) \times 10^6 \quad . \ . \ . \ . \ . \ (11)$$

Similar reductions in circulating red cell numbers were reported by Duling (1967a) in mature male rats exposed to 3.2 G for 4 weeks, and by Vrabiescu and Enachescu (1969) in rats exposed to 4.5 or 6.5 G for 11 days. The latter also examined rats at 1 G on a restricted feed intake (equivalent to the 6.5 G animals). Since the hematology of these animals was the same as ad lib fed controls, inanition was eliminated as a factor. They also examined the erythropoietic marrow, finding decreased rates of cell proliferation and cell maturation. The mitotic index (MI) of the hematopoietic marrow was closely correlated ($p<0.01$) to the ambient acceleration field (G):

$$MI = 3.36 - 0.27\ G \quad \ldots\ldots\ldots\ldots (12)$$

Burton and Smith (1969) found that chickens, which are much larger than rats, respond to 3 G fields with an increase in erythrocyte frequency (RBC, cells per $mm^3$). This polycythemia is hyperbolically related to field strength (G):

$$RBC = 4.08\ (1 - e^{-2.09\ (G - 0.08)}) \quad \ldots\ldots\ldots (13)$$

This erythropoietic response in larger animals is difficult to rationalize in terms of current concepts -- that the fundamental stimulus for erythropoiesis is hypoxia (Grant and Root, 1952). It is possible that interference with pulmonary circulation may limit the animal's oxygen exchange capacity -- or that interference with cerebral circulation, or other locality, may lead to a focal hypoxia that triggers the erythropoietic stimulus. However, in this event, different kinetics would be anticipated.[20/]

Burton and Smith (1969) considered the likelihood that hydrostatic pressure in the region of the kidney might influence erythropoiesis. Humoral agents produced in the kidney, appear to be necessary stimulators of erythropoiesis (Bishop and Surgenor, 1964; Schalm, 1965) -- however, the mechanisms regulating the formation or release of erythropoietin are not completely known. The kidney, however, does respond to hemodynamic pressures with the release of other humoral agents, Angiotension and Renin, and it is possible that a similar mechanism may apply to erythropoietin. In this regard, it is significant that hypoxic situations also induce a hemodynamic response. For reasons of posture and body size, very little hydrostatic pressure would be produced by centrifugation in the renal region of rats -- but a significant effect would occur in chickens, which could account for the differential polycythemic response of rats and chickens to chronic acceleration.

Korzhuyev (1963) has suggested that erythropoietic function is a primary factor in gravity toleration -- the quantity of hemopoietic bone marrow being closely related to the degree of terrestrial adaptation, as indicated by body size and activity. He also found a lesser quantity of erythropoietic marrow in marine mammals, about 2% of the body mass in Black Sea Dolphins and in Caspian Seals (1968a,b).

Plasma volume:

Duling (1967a) found a sharp drop in absolute plasma volume (-13%) in rats after one week at 3.2 G, which was partially recovered after 4 weeks' exposure (-4.5%). However, there was an increase in relative plasma volume (cc/100 gm body mass): +5% at one week, and +18% at 4 weeks.

Plasma volumes also have been measured in chickens by Burton and Smith (1969) during chronic acceleration in fields of 1 to 3 G. Relative plasma volume (PV, ml/kg body mass) was found to be exponentially related to acceleration field intensity (G):

$$PV = 2.94\, e^{0.160\, G} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (14)$$

In the chronically accelerated animal there is a tendency for the blood volume to be displaced towards the lower portions of the body. As a consequence, atrial filling also is limited, inhibiting the Henry-Gauer reflex (reviewed by Gauer and Henry, 1963), which ordinarily blocks the secretion of anti-diuretic hormone (ADH). As a result, fluid retention continues, and plasma volume increases until a new steady state is attained. With an increased plasma volume, the normal activity of blood volume regulating mechanisms is re-established.[21]

Plasma Proteins:

Oyama and Zeitman (1967) found that rats at 3.5 and 4.7 G responded with decreases in plasma protein concentration. After one year at 4.7 G, the reduction was 10%, and statistically significant ($p<0.01$) from gravity controls.

However, chronically accelerated chickens (1 to 3 G) have elevated plasma protein levels (Burton and Smith, 1969), and the plasma protein concentration (PP, gms %) is consistently and rectilinearly related to the acceleration intensity (G):

$$PP = 4.0 + 0.61\,G \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (15)$$

The increase in plasma protein concentration with chronic acceleration is an appropriate compensation to increased hydrostatic pressures in maintaining capillary water exchange, as indicated by the Starling hypothesis. The nature of the relationship indicates that plasma proteins are regulated proportionately to increased hydrostatic pressures. No mechanism for the regulation of plasma protein levels is readily apparent in the literature. However, if intra-vascular pressures are involved, the regulatory mechanism would perhaps be located on the venous side of the circulation, since increased plasma proteins are characteristic with hypertension.

Chronic acceleration also differentially affects the serum proteins (Burton and Smith, 1969), reducing the A:G ratio -47% ($p<0.01$) at 3 G. The gamma globulin content was closely related to the individual status with respect to stress or adaptation, as indicated by its correlation with relative lymphocyte frequency.

## Body Composition

The chemical composition of organs or organisms can be quite informative in evaluating physiological status or in interpreting the metabolic influence of various environmental conditions. A variety of methods, both direct and indirect, have been employed in estimating body composition (Brozek and Henschel, 1961), and recent reviews are available summarizing the influence of various biological environmental conditions upon body composition (Brozek, 1963; National Academy of Science, 1968).

### Lipid:

The most frequently observed change in body composition of chronically accelerated animals is a visually obvious decrease in depot fat. This has been reported in mice (Wunder, 1962; Keil, 1969); rats (Casey, 1965; Oyama and Platt, 1965; Feller et al., 1965b; Steel, 1962); hamsters (Briney and Wunder, 1960; Canonica, 1966); and chickens (Smith and Kelly, 1963; Burton and Smith, 1965; Evans, 1968). Consistent with these observations is an increase in body fat in humans subjected to 9-days bed rest (Bernauer and Adams, 1968), which greatly reduces gravity-imposed energetic requirements. Although caloric intake was reduced 29%, chronically recumbent individuals accumulated about 100 grams fat per day.

The proximate composition of the dressed carcass of chickens, which approximates the edible portion, has been measured (Smith and Kelly, 1963; Smith and Burton, unpublished). The relative influence of acceleration upon carcass fat content, $F_G$ (the fat content ratio: experimental/control), is exponentially related to acceleration field strength (G), Figure 6:

$$F_G = 2.24\ e^{-0.79G}\ [r = -0.992;\ p<0.01]\ .\ .\ .\ .\ .\ .\ (16)$$

Similar reduction of fat content, $F_{\%}$ (% of body mass) in the chicken (less feathers) has been reported (Evans and Smith, 1968), as arithmetically related to field intensity (G):

$$F_{\%} = 31.5 - 8.5\ G\ [r = -0.83;\ p<0.05].\ .\ .\ .\ .\ .\ (17)$$

Most observations on acceleration-induced changes in body composition report the virtual absence of discrete fat deposits in animals exposed to rather intense fields. Particularly affected is the prominent abdominal fat pad which is amenable to quantitative dissection. Generally, the size of the abdominal fat pad (AFP:gms) is closely related to the carcass fat content ($F_c$; % of body mass) -- for example, in chickens:

$$AFP = 0.036\ F_c^{\ 2.1}\ .\ .\ .\ .\ .\ .\ .\ .\ .\ .\ .\ (18)$$

The relationship between AFP and body fat is not greatly affected by chronic acceleration. However, in chickens the relative size of this depot decreases exponentially with increasing field strength (G):

$$AFP_{(\%\ carcass)} = 11.5\ e^{-1.73\ G}.\ .\ .\ .\ .\ .\ .\ .\ (19a)$$

A similar acceleration-induced reduction of the abdominal fat pad also occurs in rats (Oyama and Zeitman, 1967):

$$AFP_{(\%\ body)} = 10.2\ e^{-0.924\ G}.\ .\ .\ .\ .\ .\ .\ .\ (19b)$$

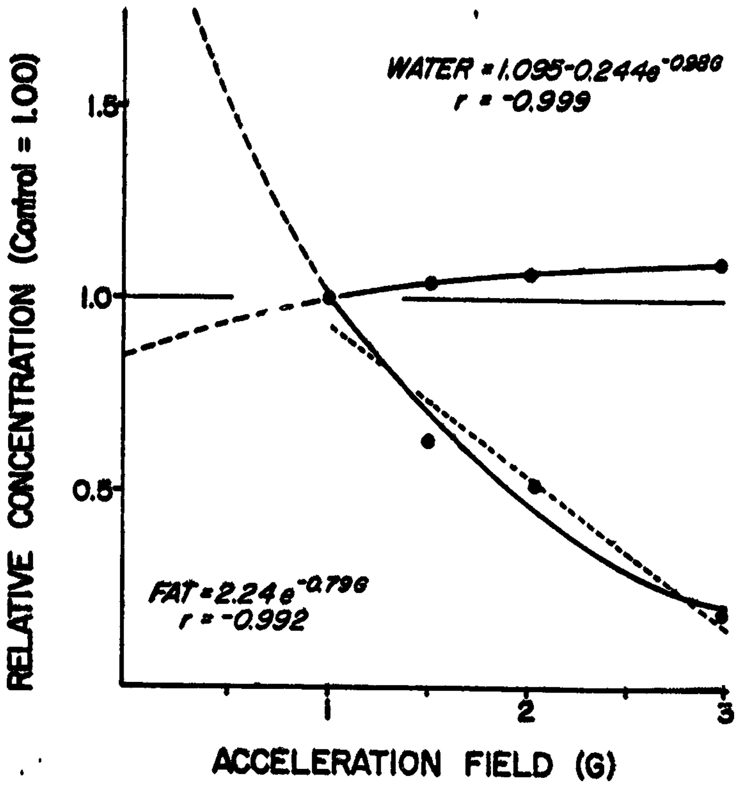

Figure 6. Influence Of Chronic Acceleration Upon The Relative Fat And Water Contents Of The Dressed Chicken Carcass.

The dotted line in the lower-right quadrant indicates the fat content treated as having zero-order kinetics (Smith and Kelly, 1963; Smith and Burton, unpublished).

The greater exponential loss of depot-fat in chickens (about double that for rats) is consistent with the generally encountered size relationship of acceleration effects -- larger animals being more severely affected. At the limit of chronic acceleration tolerance (3 G for chickens and 5 G for rats) the loss of body fat is approximately equal for the two species.

The selective effect of acceleration upon depot fat is similar to the findings in a human syndrome, lipodystrophy (Chalmers, 1965; Senior, 1965). Patients with this disease uniformly show: An enhanced musculature; enlarged liver; and virtual absence of depot fat -- changes generally characteristic of chronically accelerated animals. The etiology of lipodystrophy involves an over-secretion of a hormone -- the fat mobilizing substance, "FMS." FMS release also accompanies fasting, low carbohydrate intake, or low temperature exposure (Beaton et al., 1964 a,b, 1965; Beaton and Stevenson, 1966; Chalmers et al., 1958, 1960; Stevenson et al., 1964; and Weil and Stettin, 1947). It is a polypetide (M.W., about 5,000) produced in the pituitary in mammals, and hypothalamus in birds (Nir et al., 1969). In normal animals it increases circulating free fatty acids, increases plasma glucose and decreases circulating triglycerides and nonsaponifiable lipids. One FMS fraction depresses feed intake, and another enhances circulating FFA.

Evans (unpublished) found FMS activity in aqueous extracts of excreta of chronically accelerated chickens, and not in the excreta of gravity-controls. On the basis of chemical behavior (extraction and inactivation) the acceleration-induced FMS activity has a similar basis as that found in lipodystrophic or fasting humans. So, the mechanism of fat loss accompanying chronic acceleration may result from a stimulus of the pituitary or the hypothalamic region of the brain, resulting in the production of FMS. Since the reduction in body fat is proportional to field strength, it appears that increments of acceleration produce approximately equal increments of FMS production. Since any mechanical effect on this region of the brain would be proportional to field strength, it appears that the acceleration-related stimulus for FMS production may be mechanical and direct.

Water:

From the classical concept for regulation of tissue water, a balance between hydrostatic and osmotic pressures (the Starling Hypothesis), increases in tissue hydration might be anticipated as a result of increases in the ambient acceleration field. Measurements of water content of tissues and organisms exposed to chronic acceleration are few. Generally, an increased hydration is indicated -- however, the observations are not entirely consistent.

In chickens the relative carcass water , (the water content ratio: experimental/control) increases hyperbolically with increasing acceleration field strength (G) -- Figure 6.

$$W_G = 1.095 - 0.244\, e^{-0.98 \cdot G} \quad . \; . \; . \; . \; . \; . \; . \; . \; (20)$$

Inverse changes in hydration and fat content are anticipated even at normal gravity because of the lesser water content of adipose tissue (Pace and Rathbun, 1945). Regression constants[21] derived for various acceleration fields indicate that tissues of chronically accelerated individuals have a greater hydration which is unrelated to changes in fat content. Increase in tissue hydration is consistent with the greater relative plasma volumes.

## Metabolism

Chronic acceleration increases the weight-to-mass ratio such that an exposed animal of 1 kg body mass may weigh 2 or 3 kg. Since weight rather than mass is the principal determinant of mechanical work, chronically accelerated animals expend more energy for equivalent tonus, locomotion, etc., and this increases their metabolic requirements.

### Feed intake maintenance requirement:

The immediate response to acceleration is a marked decrease in feed intake and growth. At later times, increased *ad libitum* feed intake rates have been reported for rats (Steel, 1960, 1962; Oyama and Platt, 1964, 1965; and Casey et al., 1967) and for chickens (Smith and Kelly, 1963; Smith et al., 1971). Wunder (1961) measured growth rates of pair-fed mice at normal gravity and at acceleration fields up to 5 G, noting a lesser growth in the centrifuging animals -- indicating an increased metabolism.

Maintenance feed requirements[23] at several acceleration field intensities have been reported for chickens (Smith et al., 1971). Maintenance requirements increase with field strength to a maximum between 2 - 2.5 G, then decline toward limit of acceleration tolerance (3 G) -- Figure 7. In the extreme fields metabolic requirements may become less through decreased mobility, lesser mechanical work and a lower body fat.[24]

Fig. 9

Up to 2.5 G, the maintenance requirements may be rectilinearly related to field strength:

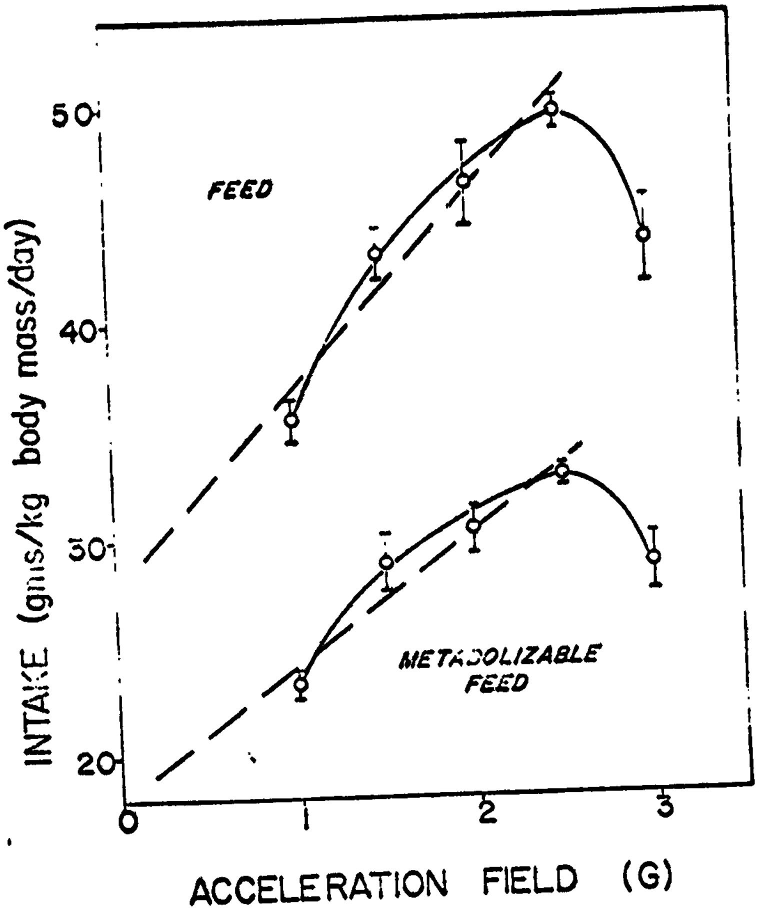

**Figure 7.** Influence Of The Ambient Acceleration Field Upon The Maintenance Requirements Of Chickens (Smith et al., 1971).

$$F_G = F_M + k\,G \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (21)$$

Where: $F_G$ is the maintenance feed intake rate (gms feed/kg body mass/day) in an acceleration field of G strength;

$F_M$ is the feed intake rate which is mass determined (where $G = 0$); and

k is the proportionality constant.

Regressions of the maintenance feed requirements (equation 21) upon field strengths indicate:

Maintenance feed: $F_G = 26.6 + 9.6\ G$

Maintenance metabolizable feed: $F_G = 17.3 + 6.5\ G$

So about 27% of the maintenance requirement of chickens is determined by Earth gravity -- 16 kcal/kg mass/G/day. As a physically determined requirement, this should apply generally, irrespective of body size. In animals of 75 kg mass, gravity would require 1200 kcal per day. Since their metabolic rates are 2500 - 3000 kcal/day, the gravity component is 40 - 50% of the metabolic energy. This is in good agreement with the energetic requirement for normal ambulation of young men at normal gravity (Bernauer and Adams, 1968). Kleiber (1969), utilizing pre~~viously~~liminarily reported results with chickens (Smith and Burton, 1968) estimated the influence of gravity upon the energetic requirements of larger animals on the basis of isokinetic behavior. He concluded that 40% of the energy metabolism of 70 kg animals would be gravity determined under natural conditions.

Intermediate metabolism:

Changes in the metabolic pattern also have been reported at the intermediate level. Feller et al., (1965a,b) studied the metabolism of labeled acetate by liver slices, in vitro, of rats previously exposed for a year to acceleration fields up to 4.7 G. Liver lipid concentrations decreased (-18%) at 4.7 G, but not at 3.6 G, and the incorporation of acetate into nonsaponifiable lipid increased (Figure 8). This differential incorporation of the tracer also is proportional to the changes in concentrations of saponifiable and nonsaponifiable lipids in the tissue. Acceleration differentially affected the fate of the two acetate-carbon atoms. At normal gravity, C-1 and C-2 were equally incorporated into fat, but at 4.7 G, 42% more of the C-2 followed this pathway. Acceleration had less effect upon the appearance of acetate-carbon atoms in free fatty acids, or in $CO_2$.

Fig. 8

The activities of enzymes involved in lipid and carbohydrate metabolism were examined by Evans et al., (1969; Evans and Bodu, 1970) in muscle and liver tissue -- with changes encountered only in the liver. Glucose-6-phosphatase, a key enzyme of gluconeogenesis, is approximally doubled in activity (+90%) at low fields (1.75 G) but this decreased as field strength increased (to +42% at 2.5 G). Malic and Citrate cleavage enzymes, important to lipid synthesis, behaved similarly to Glucose-6-phosphatase, increasing at low field strengths, and then decreasing, until at 3 G their activity was less than in the gravity controls.

The changes in enzyme activities observed under various acceleration fields are apparently correspondent with changes observed in energy metabolism. It remains to be determined if the changes are specific to acceleration, or are regulated by the animal's metabolic status.

Alpha-glycerol phosphate dehydrogenase undergoes changes unlike the other enzymes examined. In the birds, which tolerate 3 G asympto-

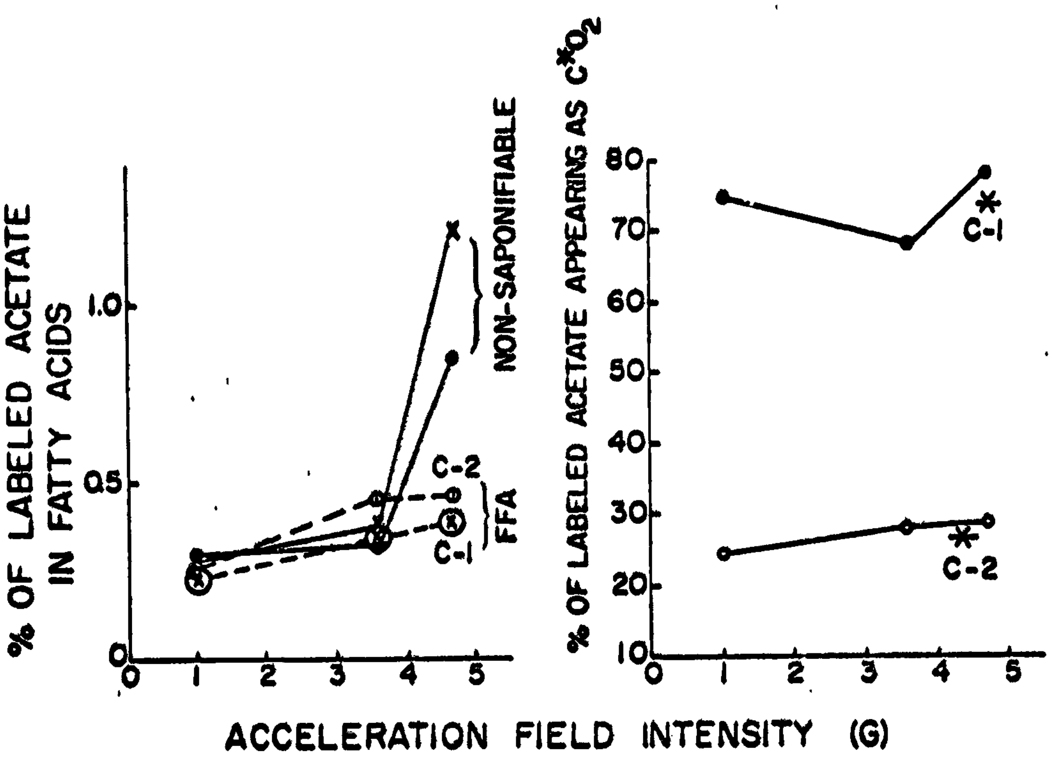

Figure 8. Fatty Acid Content And Metabolism Of Acetate By Liver Tissue From Rats Previously Accelerated For Approximately A Year.

Acetate labeled in the C-1 or C-2 position was used in separate experiments (after Feller et al., 1965 a and b).

matically, its activity increases greatly -- to more than double the control level -- but returns to normal values after a cycle of stress and adaptation. Since the fatty acid-forming enzymes (Malic and Citrate cleavage) have a low activity in asymptomatic birds, it was considered unlikely that its function was towards triglyceride synthesis. It may serve to recover glycerol for gluconeogenesis for energy utilization.

Evans concluded that during chronic acceleration fat becomes mobilized, and less of it is synthesized -- and this becomes most pronounced in those individuals that become stressed. With physiological adaptation, changes appear to permit the bird to return to a normal lipid utilization and synthesis, but with an increased carbohydrate utilization. However, even after adaptation, the body fat pool is not restored.

The influence of fields of 2.76 or 4.15 G for periods up to 3 months upon the carbohydrate metabolism of the isolated rat diaphragm has been reported by Daligcon and Oyama (1970). Diaphragm tissue incubated with uniformly labeled glucose at 1 G indicated that glucose uptake was increased 31% and its oxidation 101% by the previous chronic acceleration. No influence of the treatment was observed upon glycogen deposition. Chronic acceleration also increased the sensitivity of diaphragm to insulin, its influence on glucose uptake in the centrifuged animals being double that in their controls.

Thermoregulation:

Oyama et al., (1968, 1971) found that rats exhibited a depression of deep body temperature upon exposure to acceleration, and proportional in degree to field strength. The duration of this hypothermia (3-4 days) closely paralleled the acceleration-induced anorexia. With a repeated exposure, a lesser hypothermia was elicited -- and acceleration adapted animals maintained their body temperature. With larger animals (rabbits and dogs), they found (1969) no influence of chronic acceleration upon deep body temperature. Whether this represents a species difference in thermoregulatory function, or is merely a similitude related differential cooling is unclear at this time.

## Systemic Responses

Perhaps the most fruitful investigations of chronic acceleration effects will be those dealing with functional properties of organ systems. Since these are subject to regulating mechanisms which generally have rather rapid response times, their examination will require that observations be made on the operating centrifuge. However, remoteness factors become quite important to such observation -- and advanced instrumentation procedures must be employed, similar to those required for physiological research in orbiting satellites. For these reasons, most of the currently active chronic acceleration research programs have been oriented towards less rapidly responsive phenomena which can be studied adequately with observations "before and after" treatment. Such procedures are quite suitable to evaluations of pathology, anatomic change, growth, feed intake, etc. Some physiological measurements have been made on chronically accelerated animals after their return to normal gravity -- however, these are difficult to rationalize in terms of the centrifuging animal.

Circulation:

Duling (1967a, b) examined some aspects of circulatory function, at Earth-gravity, in anaesthetized rats, previously subjected to a 3.2 G field for 4 weeks.

Femoral venous pressure decreased about 10% and femoral arterial pressure increased 15% -- only the latter was statistically significant. Pressure-flow relationships in the posterior portion of the rats were measured by cannulating the abdominal aorta below the renal artery. These indicated a 20% decrease in basal resistance (result of vascular geometry and blood viscosity) but the myogenic resistance was doubled.

Measurements of resistance at various blood pressures (obtained by acetylcholine and epinephrine administration) indicated a 2 or 3 fold increase in the functional properties of baroreflexes. Hemodynamic responses to a brief hypoxia indicated a repression of the chemoreflexes.

Renal function:

Bengele (1969a,b) and Bengele and Wunder (1969) observed a transient (3 day) decrease in water intake, which was followed by an increased water intake and excretion which were quantitatively similar at 1.7 and 3 G. In The period of polyuria, plasma ADH decreased while [illegible] no change in daily solute excretion was observed.

Wunder et al., (1970) reported a more complex influence of chronic acceleration upon urinary excretion in mice. No effect was noted during 3 - 24 days at 2 G -- but at 4 G there was a marked polyuria.

## RESPONSE OF ANIMALS TO A DECREASED ACCELERATION FIELD

Observations of previously centrifuged animals upon return to Earth-gravity have been a rather routine part of chronic acceleration research. From these, it appears that the physiological responses to a reduction in the ambient acceleration field are not mirror images of those accompanying a quantitatively equivalent increase in the field. In no instance has a condition of stress been reported to accompany a decrease acceleration. On the contrary, animals suffering from chronic acceleration sickness, which may have been slowly induced, recover rapidly at Earth-gravity (Burton and Smith, 1965) There also do not appear to be any residual effects in animals at normal gravity from a previous adaptation to chronic acceleration.[25]

### Postural changes:

After chronic centrifugation, animals exhibit modification of posture under normal gravity. De-accelerated chickens generally assume a forward tilting of the body into a "duck-like" stance (Smith ~~et al.~~ and Kelly, 1959). In some animals, de-acceleration was accompanied by transient disorientation of high heritability. Ataxia, opisthotonus and somersaulting were observed during post-centrifugation (Smith ~~et al.~~ and Kelly, 1959; Burton and Smith, 1965). That such abnormal behavior is induced by the reduction of the acceleration field rather than by the tangential de~~-ac~~celeration, is indicated by its ready reversal upon re-centrifugation. Otherwise such postural difficulties persist for perhaps 12 hours at Earth-gravity. Lack of labyrinthine involvement in these debilities is indicated by the evident absence of nystagmus ; but neither could one be elicited by rotatory stimulation (Winget et al., 1962). The characteristically inverted position of the head suggested that an abnormal otolithic response, with a sensation of inversion, might be responsible. A similar phenomenon, an "inversion illusion" has been reported in humans during brief weightlessness (Graybiel and Kellogg, 1967) -- and a similar explanation offered.

Work capacity:

The functional significance of mass ratios of paired antagonistic muscles was examined to determine if muscle groups adjusted to a particular acceleration field could perform well or efficiently in a different field.[26] Animals adapted to 1.75 or 2.5 G were exercised to exhaustion, at weekly intervals, on a treadmill at normal gravity (Burton and Smith, 1967), being returned to the centrifuge after each exercise test. Some learning or adjustments appear necessary to exercise in a reduced-gravity environment. However, with some experience, the animals from hyperdynamic environments greatly out-performed Earth-gravity controls (Figure ~~8~~ 9). It appears that extensor (antigravity) muscle size, which generally is proportional to the acceleration field of residence, is the ultimate determinant of exercise capacity. Fig. 9

Growth:

The growth repression that commonly accompanies chronic acceleration is rapidly reversed with a reduction in the acceleration field strength, and growth deficits tend to be restored.[27] As indicated in Figure 3, the growth kinetics appropriate to the ambient field are assumed within a week. Even after a stable mature size has been reached in chronically accelerated animals, appropriate growth is

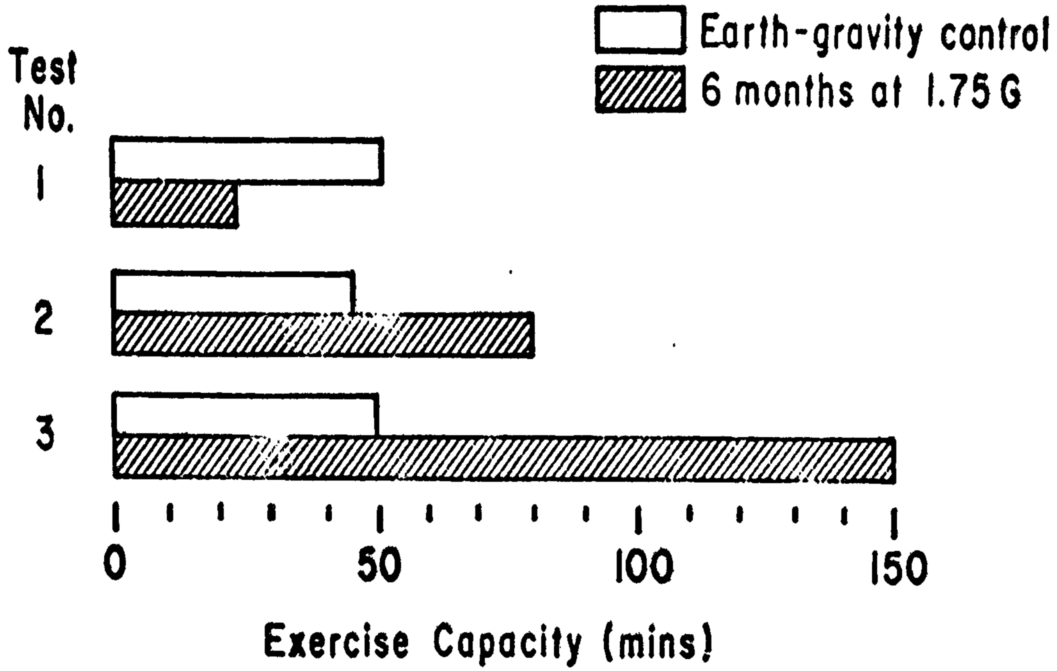

Figure 9. Exercise Capacity Of Chronically Accelerated Animals At Earth-Gravity.

Running time to exhaustion on a level treadmill operating at 130 feet/minute is shown. Test were taken at weekly intervals, with accelerated animals remaining on the centrifuge between tests (after Burton and Smith, 1967).

resumed when returned to Earth-gravity. For chickens (2 kg mass) about 60 days is required for the change in body size when the acceleration field is lowered from 2 G to 1 G (and about 30 days, from 1.5 G to 1 G). In all likelihood, scale effects apply to readjustments in body mass composition -- and perhaps to physiological phenomena generally -- following a reduction in the ambient acceleration field. Information necessary to scale effects upon such changes is not currently available.[28]

Physiological de-adaptation:

De-acceleration studies indicate that decreasing the ambient acceleration field changes both anatomic and physiological properties of animals -- but only to a level appropriate to the new field intensity. For some factors (eg., body size) the transition will be slow. However, processes that are subject to precise physiological regulation, such as hemodynamic functions, will change rather rapidly.[29] The general reversibility of environmentally induced changes indicates that (Brauer, 1965) as the animal becomes adjusted to the new field, it will lose the previously-acquired physiological adaptation to the more intense field. This concept is of particular importance to bioastronautics, since it implies that with protracted weightlessness astronauts will lose their tolerance of Earth-gravity, and must be reconditioned to it before return to Earth. Evidence of such gravity de-adaptation was found in the Cosmos 110 dogs (Libr. Congr. 1967; Parin et al., 1968). Pharmacological maintenance of the gravity-adapted state during space flight has been considered. The nature of anticipated changes with physiological de-adaptation and the potential usefulness of counteracting drugs have been reviewed recently by Parin et al., (1969).

Observations of the retention of acceleration-adaptation in centrifuged animals returned to Earth gravity (Smith and Burton, 1965; Burton, 1970) indicate that it is lost very slowly.[30]

# PHYSIOLOGY OF HYPER- AND HYPODYNAMIC FIELDS

The biological consequence of weight can be appreciated in several ways -- and from these, the response to alteration of gravity can be predicted. Such scientific speculations have a rather long history.[31] More recently the effect of gravity has been approached experimentally -- loading and unloading individuals and treating the induced changes as resulting from an alteration of gravity (Tulloh and Romberg, 1963; Margaria and Cavagna, 1964; Hewes and Spadey, 1964; and Wortz and Prescott, 1966). Similar effects (symmetrical loading) can be obtained by the technique of chronic acceleration -- which stimulates a change in gravity. Resolution of results of chronic acceleration experiments, involving several fields, can lead to a mathematical prediction of the effects of weightlessness (e.g. equations 11 through 17). Yuganov (1963) has proposed that the changes encountered during brief weightlessness (as provided by the parabolic maneuver) can be interpreted so as to predict the effects of chronic weightlessness. Although the nature of the environmental change is the same, the difference in duration would require assumptions on the nature of the response with continued exposure. This is in contrast with chronic acceleration, where the duration of treatment may be similar to that for chronic weightlessness (permitting physiological adaptation), but the nature of the environmental change is different.

Any indirect estimate of the biological effects of weightlessness must be considered as speculative -- and applied with caution. Although we may prefer to heed Crookes' (1896) admonishment: "... the prudent man shrinks from dogmatizing upon the egg until he has seen the chicken" -- the importance of avoiding surprises in bioastronautics may not permit that luxury.

## Continuity of acceleration phenomena:

Inherent in the analysis of multifield chronic acceleration data is the hypothesis that there is a continuous (or linear, in the mathematical sense) biological effect of acceleration fields from weightlessness (where, G = 0) to the tolerance limit. This concept, of course, is uncertain and will be resolved only by comparable (very long-term) orbital experimentation. However, at this time several factors tend to support the likelihood of the principle of continuity of biological effects of acceleration.

(1) Continuity of the physical phenomenon, and the dependent nature of biological responses.[31]

(2) Continuity of biological phenomena in short-term weightlessness.[33]

(3) General nature of biological regulation, which tend to be continuous.[34]

Some qualifications must be made to the concept of continuity of acceleration effects. Some processes may become saturated by very low fields (< 1 G), so they would appear to be acceleration insensitive in hyperdynamic environments. Other mechanisms (dependent upon asymmetric density distribution) may require some minimum field -- a threshold -- for orientation, and in lesser fields their acceleration responses would be completely unpredictable. For example, it has been found that a field of 0.05 G is required to orient hens' egg yolks (Sluka et al., 1966), which is about the same order as the threshold stimulus for the gravity sensing otolith.

Centrifuges and satellites:

The biological responses to chronic acceleration are of obvious importance in identifying phenomena which would be examined with orbital experiments -- ie., those things that are acceleration responsive. If the biologies of these two gravity states are unrelated, then chronic acceleration studies will be of no help in anticipating the biological effects of weightlessness. But in that event, the nature of such discontinuity, as a unique biological phenomenon, becomes important -- and deserving of further study for its own understanding.

However, if there is a general continuity of biological effects in fields above and below Earth-gravity, then chronic acceleration will provide a background of information, and perhaps principles, for the interpretation of satellite experiments. If all of the information of Gravitational Biology is limited to two points -- weightlessness and Earth Gravity -- no generalizations will be possible. Satellite experiments are equally important, and without them, Gravitational Biology will have no foundation. There also is a practical link between centrifuges and satellites. Since both techniques deal with artificial weight conditions, and impose remoteness factors on the experimenter, chronic acceleration research also would provide an excellent intermediate training function for space investigators.

The complemental nature of studies of chronic exposure to weightlessness or to increased acceleration fields with regard to understanding the biological effect of Earth-gravity also has been discussed by Gazenko and Gurjian (1965).

Human chronic acceleration:

Although chronic acceleration studies with small homoeotherms can contribute to the development of Gravitational Biology, there will be some limitations in their application to man. Satisfactory progress contributing to "Gravitational Medicine" will require chronic acceleration studies with humans.[35]

A particularly important aspect of such research would be determining the adaptational capacity rate of humans to chronic acceleration -- which would become quite applied in re-adapting deconditioned astronauts to Earth gravity. This could be accomplished by a series of experiments in which subjects became exposed to a particular accelerative force, but each at a different rate (Figure 10). As long as the accelerative force is low, there probably would not be much difference in response between the acceleration schedules. However, with greater forces, untoward changes would probably be seen with the greater rates of change. Consequently, a curve could be drawn for human adaptational capacity, as exemplified in Figure 10. This description may be oversimplified, since the onset of symptoms may be substantially later than the exposure which produced them. However, with interpretation, the data would permit some statement of adaptational capacity to hyperdynamic environments which otherwise would be lacking.

Fig. 10

Adaptational capacity rate between 1 G and 1.5 G should bear some relationship to that between weightlessness and normal gravity. The latter should not occur in a lesser time, nor at a lesser rate, which would allow a "ball-park" estimate of the optimum schedule for re-adapting deconditioned astronauts to Earth gravity. Of particular importance would be the observations where the adaptational capacity had been exceeded, which would furnish quite valuable "check points" for monitoring astronauts during any re-adaptation process.

The rate at which individuals lose physiological adaptation to an acceleration field also would be important. When related to gravity it would permit an estimate of the maximum duration of weightless exposure compatible with a direct return to Earth. Such information would be valuable to the planning of deep space probes. This could be studied with human subjects that had become adapted to an environment of 1.5 G -- perhaps after many months' or a year's exposure. Upon return to Earth-gravity their loss of tolerance to the hyperdynamic field would be estimated serially. In all likelihood, such loss of physiological adaptation would bear some relationship to the loss of tolerance to Earth gravity during protracted weightlessness -- it should not occur in a shorter time, nor at a lesser rate (Figure 11). This information should permit a "ball-park" estimate of the rate of de-adaptation to normal gravity, while weightless, and the duration of space probes compatible with a direct Earth return.

Fig. 11

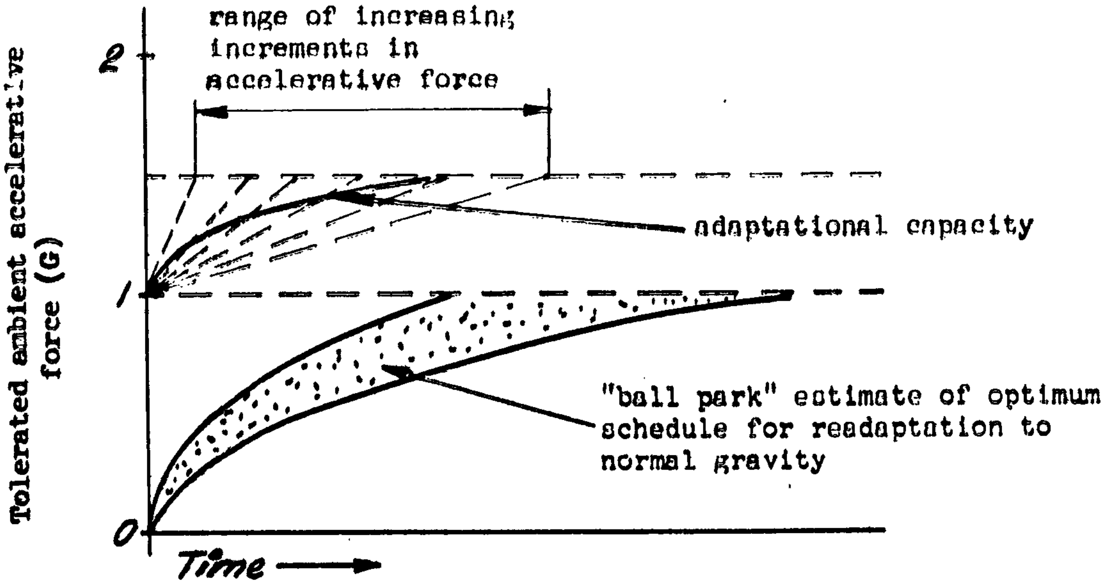

Figure 10. Schema of Adaptational Capacity to Accelerative Force

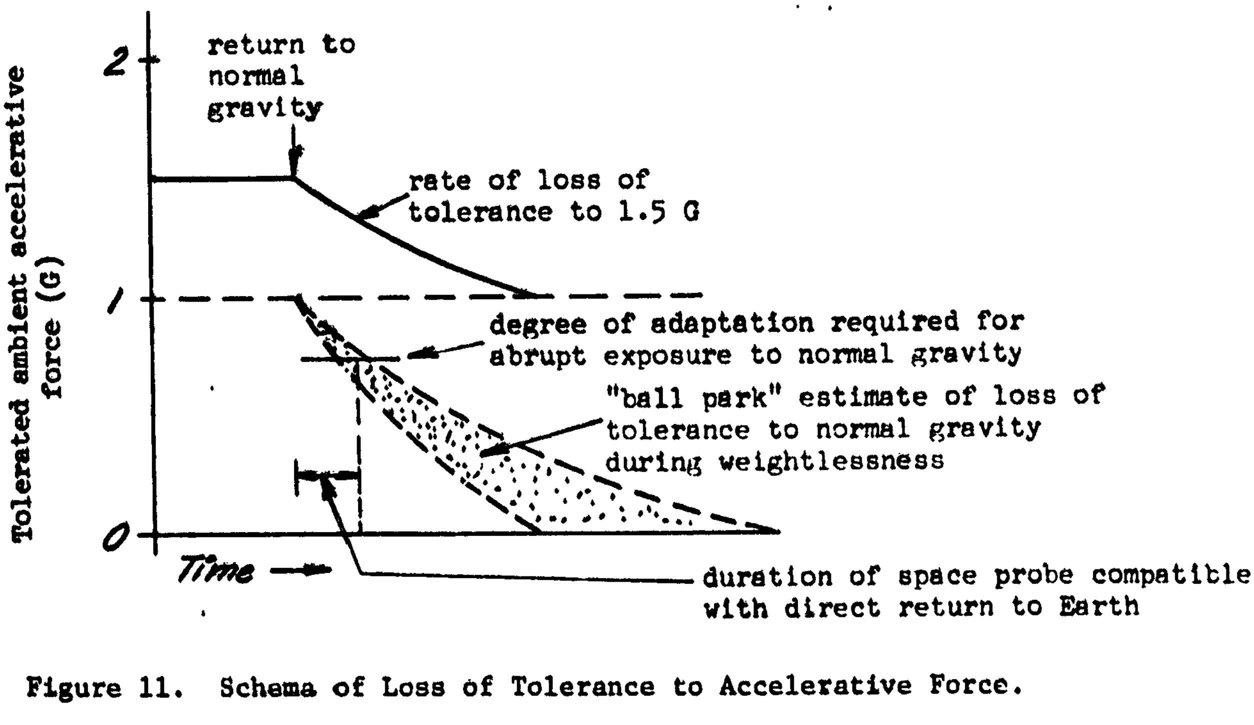

Figure 11. Schema of Loss of Tolerance to Accelerative Force.

# FOOTNOTES

1/ This chapter includes some unpublished observations and data from the Chronic Acceleration Research Unit, Department of Animal Physiology, University of California at Davis -- which is supported by a grant from the U. S. Aeronautics and Space Administration -- NGR 05-004-008.

2/ The author is pleased to acknowledge the benefit derived from the materials provided by the Russian compiler, Dr. L. R. Pal'mbakh -- and also the cooperation of the American contributors: Drs. R. R. Burton, T. Hoshizaki, Ann E. Kammer, C. F. Kelly and I. H. Wagman.

3/ For example, "weighing" with a balance is actually a determination of mass. The standards, commonly called "weights," function as mass units -- since they and the unknown object are affected equally by changes in the ambient accelerative force. However, the analogous operation with a spring scale is properly a weight determination -- since this device is equally affected by both variation in mass and in the acceleration field.

4/ The acceptance of the term "weightlessness" is determined by the concept of weight. Physicists conceive weight as merely another force -- abstractly, and without material connotations since in their treatment the units of weight and mass are different. Popularly, weight is considered rather specifically as a material descriptor. For example, "body weight" describes a quantity, indicated by the morning encounter with the bathroom scales -- without any reference to the ambient acceleration field, etc. Engineers appear to have intermediate concepts.

Although fully aware of the physical basis of weight, they consider it through the gravitational system in units as ordinarily equivalent to mass. Biologists do not appear to have considered the matter at all and hold more-or-less the popular concept. Scientifically, they use weight an index of relative material magnitude -- phenomenologically derived.

5/ Among terrestrial species, skeletal size increases proportionally to the 1.5 power of body weight (Keyser and Heusner, 1964). The kinetics of skeletal growth within species has been examined by Shmal'gavzen (1964).

6/ At the submicroscopic and microscopic levels of organizations, structures remain generally insensitive to forces in the order of Earth-gravity. For example, to selectively move the organelles in animal cells at significant rates requires fields in the order of 1000 G, and to separate large molecules (e.g., proteins) require fields in the order of 100,000 G (Davson, 1964). However, even in these very intense fields, particles less than 1μ are significantly affected by diffusion effects -- thermal phenomena. Even at 250,000 G, diffusion cannot be considered neglible until particle size are 0.05μ (Pickels, 1950).

7/ For example, Einsanian (1967) reported a change in electrochemical potential during free fall. In such systems, thermally-induced convections may be of substantial importance to the electromotive force produced. Consequently, the physical basis for the observed changes in electrochemical potential in brief weightlessness may be at a much greater than molecular scale.

Mel (1964) has reported a system ("Staflo") in which discreteness of moving columns of solutions is maintained by suitable density gradients. In this preparation, he has noted a selective movement of enzyme molecules along the field of gravity. Particle-medium interactions in such systems may lead to an "entrainment" of molecules, which would provide units of much larger dimensions that are readily susceptible to gravity. A similar entrainment, resulting in gross movement, has been observed in red blood cell suspensions under the influence of gravity (Burton et al., 1969).

8/ Of course, gravity was of critical importance in the ordering of the physical environment in which life originated. Without gravity there would be no seas or atmosphere, no thermal convection or other separation of materials of different density -- phenomena which were essential to the origin of life.

9/ In the clinostat literature, the effect is frequently called "gravity compensation" or "gravity nullification." Ordinarily, "compensation" describes the addition of one agent that acts equally and oppositely to another, offsetting the effect -- ie., a counterbalance. Nullification, implies the elimination, or "reduction to zero" of gravity -- which, of course, is not the case. So the application of these terms to clinostats does not seem appropriate.

Gravity is a vector quantity, posessing both direction and magnitude. In order to be effective in orienting a biological system, gravity must act for some minimum time -- the "presentation time." The clinostat merely changes the orientation, with respect to the acceleration field, at a greater rate than the presentation time -- functionally removing the orienting (directional) aspect of gravity. Effectively, the clinostat transforms gravity from a vector to a scalar quantity -- and the process is better described as "scalarization," than as "compensation" or as "nullification."

10/ In high altitude research these periods are distinguished by the terms "sojourners" and "residents." Sojourners have a limited, and variable exposure and, physiologically, may be at any state of reaction or adaptation to the environment. Residents, however, have had a very long exposure, and are assumed to be completely physiologically adapted to the environment.

11/ Females are generally more tolerant to other environmental stressors. Selye (1950) explains the greater adaptability of females on an endocrine basis: "...folliculoids tend to enhance and testiculoids repress adrenocortical function..." In laying hens, however, the mechanical properties of the functional (hypertrophied) oviduct are poor -- and in fields greater than 2 G they are quite susceptible to oviduct prolapsis, which is terminal.

12/ This "exhaustion" is quite similar in nature to "Monge's Disease" (Monge and Monge, 1966) -- the occurrence of high altitude sickness in Andean natives of pre-Colombian stock. Such individuals must go to lower elevations or die -- since they are no longer capable of physiological adaptation to altitude.

13/ The important factor in developing the acceleration-tolerant line is selection rather than treatment. Also, the mechanism is merely an increase in the gene frequency for processes that permit physiological adaptation, rather than the mutational development of some new process. No qualitative distinctions became apparent between individuals of the acceleration-selected line and unselected stock -- acceleration-tolerant or susceptible individuals from either source behave quite similarly, if not identically, on the centrifuge. The obvious advantage is the greater survival of the acceleration-selected line -- so that more of them are available for experimentation after protracted centrifugation.

14/ The relationships between organ mass (kg) and body mass (M, kg) are generally parabolic. The equations cited indicated the differences between organs of a particular species and the lesser differences for a given organ between species of different size (Brody, 1945):

| | Rats | Chickens | Dogs | Horses |
|---|---|---|---|---|
| Blood = | $0.070\ M^{0.98}$ | $0.038\ M^{0.99}$ | $0.072\ M^{0.95}$ | - - |
| Brain = | $0.734\ M^{0.17}$ | $0.0034\ M^{0.39}$ | $0.044\ M^{0.25}$ | $0.141\ M^{0.24}$ |
| Heart = | $0.0029\ M^{0.80}$ | $0.0048\ M^{0.87}$ | $0.010\ M^{0.93}$ | $0.013\ M^{0.91}$ |
| Kidney = | $0.0065\ M^{0.82}$ | $0.0045\ M^{0.85}$ | $0.0115\ M^{0.70}$ | $0.0243\ M^{0.66}$ |
| Liver = | $0.280\ M^{0.68}$ | $0.0024\ M^{0.67}$ | $0.064\ M^{0.71}$ | $0.137\ M^{0.61}$ |
| Lung = | $0.0038\ M^{0.72}$ | $0.0049\ M^{0.87}$ | $0.0138\ M^{0.82}$ | $0.133\ M^{0.58}$ |

15/ A "standard organ" which matures early, and consequently is less affected by later imposed environmental influences is selected for this purpose. Brain and eye have been considered appropriate organs for such comparisons (Palsson, 1955). Casey (1965) presented organ size data for centrifuged and irradiated rats as ratios to brain mass.

16/ Tulloh and Romberg (1963) maintained weanling lambs on two levels of nutrition (high and low), and loaded some of the "low" level lambs with "rugs" that carried lead weights, deriving three groups:

HP: optimum nutrition, maximum growth rate;

LP: restricted intake, with a growth rate about half that of HP group; and,

LPW: similar to LP group, but mechanically loaded to 30-40% of their body mass.

By this procedure, there was little difference in body growth rates between LP and LPW groups, but the leg-loading of the LPW group was about 80% of the HP group. Compared to chronic acceleration, this would be equivalent to a field of 1.3 to 1.4 G.

Bone growth (metacarpal) was greatly altered by these treatments. Bone growth (mass) on the high plane of nutrition (HP) was much greater, almost double that of the low plane (LP). However, mechanical loading also increased growth (mass) -- the rate being midway between that for the HP and LP groups. Bone conformation also was affected, mechanical loading (LPW) and maximum growth (HP) inhibiting bone elongation -- but enhancing epiphyseal width. Consequently, the "length:width" ratio is greatly reduced, leading to "stubby" bones.

17/ Oyama and Zeitman (196~~8~~7) examined the influence of chronic acceleration upon the composition of rat bone (Ash, Ca, P, Mg and N), finding no consistent or significant effect. Fosse (1971) made histological studies of chronically accelerated mice bone, finding an increased bone density in females -- but not in males.

18/ Galileo (1638) noted the reversal in the loading of bones in terrestrial and aquatic animals. In terrestrial forms, the load of the soft tissues is borne by the bones -- whereas in aquatic forms it is the less-dense soft tissues that support the load of the denser bone.

19/ The selective growth of extensor muscles in early post-embryonic life has been described by Smith and Burton (1970) in chicks. A similar development in young humans, and its relation to development of an erect posture has been analyzed by Semenova (1958, 1967), Veselova (1954) and Tambiyeva (1968).

20/ The curve described by the equation 13 is sharply inflected -- the principal change occurring between 1 to 2 G and with little change between 2 and 3 G. Circulation impairment between 2 and 3 G would be at least as great as between 1 and 2 G. Also, the increases in cell numbers by centrifugation (+15%) are quite small as compared to the hypoxic response (+38% in chickens at 12,500 ft. elevation; Smith and Abbott, 1961).

21/ Water immersion is a particularly efficient stimulator of the Henry-Gauer reflex, causing marked diureses (Graveline and Jackson, 1962; Graveline and McCalley, 1963) and a corresponding reduction in plasma volume and severe tissue dehydration (Hunt, 1967; Pestov, 1968). Particularly interesting is the recent report of the lack of ADH in the blood of marine mammals (Ridgway, 1972).

22/ Comparisons of carcass fat and water content among individuals receiving similar treatments indicated a rectilinear relationship:

Water = a -b (fat)

Where: a represents the hydration (% water) of lean
tissue -- the "Pace Constant;" and,
a (100-b) is the approximate water content of
the adipose component.

23/ The feed energy required to maintain a constant body mass (with a fixed composition) approximates the energy metabolism (Brody, 1945; Kleiber, 1961). The procedure can be refined by measuring metabolizable feed intake (feed less excreta), which is simplified in birds due to their single phase excreta.

24/ Fat synthesis requires about 20% more energy than does the synthesis of lean body substance (Brody, 1945).

25/ For example, rats adapted to 3 G had the same radiosensitivity as controls, when simultaneously returned to Earth-gravity and subjected to whole-body X-irradiation (Casey et al., 1967). However, there was a strong interaction between simultaneous irradiation and centrifugation.

26/ These experiments were undertaken at the time of the Gemini flights when considerable difficulty was encountered with the performance of extra-vehicular activity.

27/ Superficially this resembles the well-known retention of the growth potential during periods of malnutrition -- which was first recognized as the "equifinality of growth" by Osborne and Mendel (1915). It appears that the greater acceleration field "resets" the standard towards which growth proceeds -- and with its removal, the "normal" growth standard is restored, and without apparent affect from the previous treatment.

28/ However, size relationships have been found in the rates at which excesses or deficits of body constituents are resolved (e.g., following fasting or forced-feeding) among rats, rabbits, dogs, and man (Adolph, 1943). Generally, the rate at which an imbalance is restored is proportional to the natural variability of that constituent -- and the later is generally inversely related to body size. Consequently, large animals tend to be "less plastic" than small ones -- and generally undergo physiological change at a slower rate. So, equivalent processes that require 2 months for completion in a 2 kg animal (eg., chicken) may require 6 months or longer in a 75 kg animal (eg., man).

29/ Matthews (1956, 1960) was able to utilize a free-fall of 4 ft. (producing 500 msec of weightlessness) to determine the effect of gravity loading upon stretch reflexes. He found that the ankle-jerk response disappeared after 140 msec weightlessness.

Longer periods of weightlessness have been obtained with parabolic flight in jet aircraft (Campbell, 1961; Hawkins, 1963). With such brief periods, the effect of removing gravity-load has been examined in hemodynamic parameters (Roman et al., 1962); maximal torque that can be exerted (Whitsett, 1964); the sensitivity of otolithic stimulation (Yuganov and Afanasyev, 1964); cupulometric function (Jackson and Sears, 1966); precision in motor skills (Chekirda, 1968); circulation time (Warren, 1967); respiratory dynamics (Foley and Tomaskefski, 1969); and orientation of blind goldfish (von Barmgarten et al., 1969).

30/ Mature chickens may require 60-90 days to become physiologically adapted to a 2 G field. If they are returned to Earth-gravity, then abruptly re-exposed periodically to 2 G for 24 hours, some index of their retained adaptation can be estimated from their lymphocytic response (in comparison with similarly treated, but previously unadapted controls). On this basis, previously 2 G adapted chickens retained about 70% of their physiological adaptation after 6 months' residence at Earth gravity.

31/ Galileo (1638) and Spencer (1863) considered the influence of buoyant immersion of aquatic animals in terms of weightlessness, and its effects on form and function. Sir Charles Bell (1827) also dwelt upon the influence of gravity upon man. Sir William Crookes, who was a spiritualist as well as a physicist, considered the influence of gravity, and its alterations upon human form and function (1896). Thompson (1917) compared the variations in form and function among animals of different size, noting systematic scale relationship which were interpreted in terms of gravity. Thompson also speculated upon the biological responses to a change in gravity.

32/ All investigations indicate that the independent variable in acceleration experiments is the acceleration field -- and the biological changes induced are purely dependent upon it. Earth-gravity is not a critical point (its value is not zero), and there is a continuity of the physical phenomenon from zero up to the limit of biological tolerance. Consequently, it is most logical to assume that there is a similar continuity of the dependent biological phenomena over the tolerable range of acceleration fields.

33/ There also is a relationship between the effects of short- and long-term exposure to chronic acceleration, the former inducing a biological stress to which the latter provides a physiological adaptation. The only experiments performed so far involving both weightlessness and hyperdynamic environments (up to 3 G), were carried out by Roman et al., (1962) using the parabolic maneuver in high-performance aircraft and human centrifuges, and with a 45 second test period. He examined hemodynamic parameters in humans and found no discontinuity between the weightless and supragravity conditions. This continuity of short-term effects tends to support the likelihood of a similar continuity between chronic acceleration and weightlessness effects.

34/ If there is no continuity of biological response between subgravity and supragravity conditions, this would be contrary to the general pattern of biological regulatory mechanisms. It would mean that there are different and discontinuous regulatory mechanisms for fields greater and lesser than Earth-gravity -- which would be biologically unique.

35/ For such experimentation, it would be desirable to develop fields of approximately 1.5 - 2 G, while limiting the rotation rates to 20 - 30° per second -- one which can be tolerated even on a planar basis (Guedry et al., 1964). To meet these requirements, a centrifuge would have a diameter of 300-600 ft. -- and could be provided by self propelled cars operating on a circular track.

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