PRACTICAL AND THEORETICAL IMPLICATIONS BASED ON LONG-TERM FOLLOW-UP OF MÉNIÈRE'S PATIENTS TREATED WITH STREPTOMYCIN SULFATE

Ashton Graybiel, Harold F. Schuknecht, Alfred R. Fregly, Earl F. Miller, II, and Michael E. McLeod

Bureau of Medicine and Surgery
Project MR005.13-6001
Subtask 1 Report No. 123

NASA Order No. R-93

Released by
Captain H. C. Hunley, MC USN
Commanding Officer

25 October 1965

* This study was sponsored by the Office of Advanced Research and Technology, National Aeronautics and Space Administration. It represents a cooperative effort between the U. S. Naval Aerospace Medical Institute and the Massachusetts General Hospital.

U. S. NAVAL AEROSPACE MEDICAL INSTITUTE
U. S. NAVAL AVIATION MEDICAL CENTER
PENSACOLA, FLORIDA
SUMMARY

THE PROBLEM

Four patients who had received streptomycin sulfate in the treatment of Ménière’s disease were evaluated in terms of the long-range effects of therapy and utilized as experimental subjects.

FINDINGS

None had experienced a return of symptoms over the entire follow-up period which ranged from 11 to 13 years. There was residual tinnitus, and deafness ascribable to the disease and ataxia ascribable to toxic effects of the drug as well as the disease.

In the three subjects who had one normal ear each, there was no effect of the streptomycin on the hearing in that ear but considerable suppression of semicircular canal function with some recovery.

In all of the five diseased ears there was a slight significant improvement in hearing (later lost in one) but great suppression of semicircular canal function with little recovery.

Otolith function, as measured by ocular counterrolling, was within the normal range in two subjects and greatly suppressed in two. Although tests were not carried out prior to therapy, it was believed that the suppression was due more to disease than the drug.

When exposed to bizarre stimulation of the semicircular canals in the SRR none were susceptible to canal (motion) sickness, but the three with unilateral disease perceived the Coriolis illusion. The findings utilizing a new ataxia test battery were similar to those obtained in persons with complete loss of vestibular function. Inasmuch as the greatly differing degrees of otolith function bore no relation to these test results, they were ascribed mainly to loss of canal function.

An attempt was made to interpret the findings in terms of the etiology of idiopathic Ménière’s disease, and the suggestion was put forth that it might represent a disturbance attributable to the secretory cells of the crista.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge the splendid cooperation of Mrs. CA and of Mr. AN, OC, and KI. We are also indebted to Dr. Vernon Bragg for the audiometry tests and to Dr. Makato Igarashi for suggestions based on a critical review of the manuscript.
INTRODUCTION

Eight patients who had been given streptomycin sulfate parenterally in the treatment of Ménière's disease by Schuknecht were re-examined and the findings reported in 1957 (1). These patients had been followed for periods varying between fourteen and fifty-two months after the drug was administered to the point of suppression of semicircular canal function with resulting ataxia. The noteworthy findings reported in 1957 (hereafter termed the first follow-up) were freedom from vertiginous attacks in all eight patients, significant improvement in auditory thresholds in four of the five with unilateral disease and in one of the three with bilateral. There was no loss of hearing in either the normal or diseased ears.

Four of these eight patients agreed to come to the Naval Aerospace Medical Institute in 1963 (second follow-up) for medical evaluation and to participate in experiments. Approximately two years later, a limited opportunity was taken (third follow-up) to inquire into the status of these subjects in connection with an experiment carried out in Cambridge, Massachusetts.

The present report deals with the follow-up studies of these four patients. The purpose was twofold: first to gather information on the effects of streptomycin sulfate in the treatment of Ménière's disease and, second, to identify those experimental subjects who have presumed preservation of otolith function but whose semicircular canal function is suppressed.

PROCEDURE

The functional status of the semicircular canals was determined during the second follow-up by means of the threshold caloric test (2) which was scored as the temperature of the thermal stimulus nearest to body temperature that caused a definite nystagmic response. The functional status of the otolith organs was measured by ocular counterrolling (3), and bodily equilibrium was assessed by utilizing a new ataxia test battery (4). Susceptibility to canal (motion) sickness was estimated in the Slow Rotation Room by means of the dial test (5,6). In the same Room were recorded the subjects' perceptions of two variants of the oculogyral illusion (7,8), one termed the Coriolis illusion, which have their genesis in the semicircular canals. During the experiment at Cambridge, threshold caloric and ataxia tests were given to three of the four patients.

Details regarding the method of administering the various tests, their scoring, and their significance are given in the next section of this report.
RESULTS

SCHUKNECHT'S FINDINGS

These are summarized in Table I; additional details concerning the audiometric and caloric tests will be presented under these headings. The symptomatology was severe in all cases and was typical of idiopathic Ménière's disease except in patient K1. His attacks had some of the features of migraine, namely, visual disturbance and headache which were followed by drowsiness.

Schuknecht administered streptomycin sulfate to the point of complete suppression of response to the caloric test in the diseased ear in those with only one ear affected, which also resulted in a greatly diminished response in the normal ear; in K1, with bilateral disease, there was complete suppression on the left and greatly reduced response on the right. Spontaneous nystagmus was noted with the beat directed away from the ear with the greater decrease in caloric response. Early symptoms precipitated by treatment were loss of appetite and nausea, in that order. None experienced an increase in tinnitus, a known precursor of loss of hearing, but all experienced an increase in ataxia which was the only permanent side effect of streptomycin therapy.

GENERAL STATUS DURING FOLLOW-UP PERIODS

In the interval between the first and second follow-up none of the patients had a recurrence of any symptoms characteristic of Ménière's disease (Table II). There was, however, persistence of slight deafness, ataxia, and tinnitus although none categorized these symptoms under "complaints." Two manifested mild cardiovascular abnormalities which, in all probability, were unrelated to Ménière's disease. At the time of the "third follow-up" all were in good health, and it was possible to carry out ataxia and threshold caloric tests on three.

TEST RESULTS

Hearing

The audiometric findings are summarized in Figures 1–4. The three subjects with unilateral disease did not manifest any significant changes in the normal ear although in CA there was a decrease in the auditory threshold of more than 10 db at low frequencies. Patient OC, who had registered a significant decrease in auditory threshold in the diseased ear at the time of the first follow-up, reverted to the pretreatment level while the other two, who had manifested insignificant changes on the first follow-up, registered striking decreases in threshold on the second. The subject with bilateral disease not only held the improvement in hearing indicated at the first follow-up but experienced a slight further improvement on the right.
Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Duration of symptoms</th>
<th>Discrimination (%)</th>
<th>Recruitment</th>
<th>Caloric responses before treatment</th>
<th>Streptomycin</th>
<th>Ataxia</th>
<th>Return to full work load (mos.)</th>
<th>Caloric response after treatment</th>
<th>Recurrence</th>
<th>Follow up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC</td>
<td>38</td>
<td>10 mo. 36</td>
<td>C* Decr. Norm.</td>
<td>22 1/2</td>
<td>7 1/2</td>
<td>++</td>
<td>2</td>
<td>Lost Gr.decr. No. 48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>39</td>
<td>12 yr. 34</td>
<td>C Decr. Norm.</td>
<td>54</td>
<td>26</td>
<td>++</td>
<td>4</td>
<td>Lost Gr.decr. No. 31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AN</td>
<td>48</td>
<td>1 yr. 6 mo. 70</td>
<td>C Decr. Norm.</td>
<td>28</td>
<td>14</td>
<td>+++</td>
<td>9**</td>
<td>Lost Gr.decr. No. 25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KI</td>
<td>32</td>
<td>5 yr. - R. 74 R</td>
<td>Decr. Decr.</td>
<td>45</td>
<td>24</td>
<td>+++</td>
<td>2 1/2</td>
<td>Gr. decr. Gr.decr. No. 35</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* C = Complete
** Psychoneurosis contributed to prolonged morbidity.
## Table II

### MEDICAL FINDINGS AT TIME OF SECOND FOLLOW-UP STUDY

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>SEX</th>
<th>PRESENT AGE</th>
<th>FOLLOW-UP (YEARS SINCE THERAPY)</th>
<th>INTERVAL HISTORY</th>
<th>VERTIGINOUS ATTACKS</th>
<th>FITNESS FOR HARD WORK *</th>
<th>SYMPTOMS</th>
<th>MOTION SICK SUSCEPTIBILITY</th>
<th>PRE- THERAPY OTOSCOPY</th>
<th>POST- THERAPY OTOSCOPY</th>
<th>WEBER</th>
<th>RETINOSCOPY EXAM.</th>
<th>HEART</th>
<th>ECG</th>
<th>VCG</th>
<th>Hgb. gm %</th>
<th>URINALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC</td>
<td>M</td>
<td>50</td>
<td>11 1/4</td>
<td>NONE</td>
<td>MOD.</td>
<td>Sl.tin. Sl.atx.</td>
<td>&lt;&lt;av.</td>
<td>NIL</td>
<td>NO ABN</td>
<td>L. ac&gt;bc</td>
<td>INC. LIGHT REFLEX</td>
<td>N 160/100</td>
<td>NONE</td>
<td>LVH ischemia</td>
<td>14.5</td>
<td>neg.</td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>F</td>
<td>49</td>
<td>9 3/4</td>
<td>NONE</td>
<td>GOOD</td>
<td>Sl.tin. Sl.atx.</td>
<td>&lt;&lt;av.</td>
<td>NIL</td>
<td>NO ABN</td>
<td>MID ac&gt;bc</td>
<td>NO ABN</td>
<td>N 125/80</td>
<td>sys.ejc M&amp;A I-II</td>
<td>NO ABN</td>
<td>11.5</td>
<td>neg.</td>
<td></td>
</tr>
<tr>
<td>AN</td>
<td>M</td>
<td>56</td>
<td>9 1/3</td>
<td>NONE</td>
<td>GOOD</td>
<td>Sl.tin. Sl.atx.</td>
<td>&lt;&lt;av.</td>
<td>NIL</td>
<td>NO ABN</td>
<td>MID ac&gt;bc</td>
<td>NO ABN</td>
<td>N 138/78</td>
<td>NONE</td>
<td>NO ABN</td>
<td>16</td>
<td>neg.</td>
<td></td>
</tr>
<tr>
<td>KI</td>
<td>M</td>
<td>42</td>
<td>9 4</td>
<td>NONE</td>
<td>GOOD</td>
<td>Sl.tin. Sl.atx.</td>
<td>NIL</td>
<td>NIL</td>
<td>NO ABN</td>
<td>MID ac&gt;bc</td>
<td>tort. A &amp; V. INC. LIGHT REFLEX</td>
<td>N 150/110</td>
<td>NONE</td>
<td>SL LVH</td>
<td>15</td>
<td>neg.</td>
<td></td>
</tr>
</tbody>
</table>

* Subject's estimate
Figure 1

Audiograms of Patient OC before and after Administration of Streptomycin Sulfate
Figure 2

Audiograms of Patient CA before and after Administration of Streptomycin Sulfate
Figure 3

Audiograms of Patient AN before and after Administration of Streptomycin Sulfate
Figure 4

Audiograms of Patient K1 before and after Administration of Streptomycin Sulfate
Comment. The absence of any measurable hearing loss in the normal ears indicates that streptomycin sulfate did not destroy any significant number of cochlear hair cells or indeed any related structural element essential to their function. This lack of toxicity was strongly emphasized by the fact that there was improvement in hearing on the diseased side. Thus, even the combined effect of disease, "injury," and drug "toxicity" was insufficient to result in loss of function; indeed, the effect of the drug was salutary. The time-course of the changes in auditory threshold in the diseased ears is of particular interest. In three instances there was a significant decrease and in one an increase in threshold between the first and second follow-up, a period ranging from two to four years. Important implications are 1) the injurious agent, although "active," must have been of an exceptionally mild character; 2) these effects, direct or indirect, must have taken place with almost incredible slowness; 3) the most likely location was in the peripheral organ where the basic integrity of many sensory receptors was maintained although function depressed; and 4) prolonged follow-up in these cases is essential to determine the evolutionary changes.

Semicircular Canals

The functional status of the semicircular canals based on the caloric test is shown in Table III. In the early tests, including the first follow-up, the procedure consisted essentially of measuring the duration of nystagmus following irrigation with water at 80°F or "ice water" contained in a syringe which had been cooled by contact with crushed ice. In subsequent "threshold" tests, the response to cold water was measured in terms of the highest irrigating temperature at which nystagmus was evoked. The temperature was measured at the exit nozzle. At the time of the second follow-up the lowest temperature used was 12°C, and at the third follow-up, 8°C.

Administration of the drug resulted in suppression of response which was greater in the diseased than normal ears with the exception of complete suppression on the normal side in OC. At the time of the first follow-up there was evidence of recovery of function in the normal ears which was striking in OC and only slight in the others. There was "good recovery" of function in only one of the five diseased ears. In the second and third follow-up examinations the only unexpected finding was the decrease in function on the normal side in OC. It was concluded that the cause of the decrease, occurring some time in the four to eleven years after therapy, was far more likely to be due to some incident other than Ménière's disease or to a delayed response to the drug.

Comment. Comparative data on squirrel monkeys are of interest. In one experiment (9) eight animals were given streptomycin sulfate to the point where there was no nystagmus response to ice water in ten ears, and the threshold response in the remaining six ears ranged from 19°C to 24°C. Over a period of six months or more there was recovery of response to the threshold levels prior to administration of the drug in all but four ears, and in these the threshold levels had risen to 30° to 32°C. Pathological studies revealed loss of hair cells in the sensory epithelium of the cristae in all animals, varying from very slight to severe.
<table>
<thead>
<tr>
<th>Subject</th>
<th>EAR</th>
<th>Before Therapy</th>
<th>Time Max Effect of Drug</th>
<th>First Follow-up</th>
<th>Second Follow-up</th>
<th>Third Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC</td>
<td>R(d)</td>
<td>80°F 30&quot;</td>
<td>ICE WATER NIL</td>
<td>48 1-W 83&quot;</td>
<td>1 1/4 30.6 th</td>
<td>13 + 31.3 th</td>
</tr>
<tr>
<td></td>
<td>L(n)</td>
<td>80° 120&quot;</td>
<td>I-W NIL</td>
<td>1-W 110&quot;</td>
<td>12.0 NIL</td>
<td>8.5 th</td>
</tr>
<tr>
<td>CA</td>
<td>R(d)</td>
<td>80° 60&quot;</td>
<td>I-W NIL</td>
<td>34 1-W NIL</td>
<td>9 3/4 12 NIL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L(n)</td>
<td>80° 85&quot;</td>
<td>I-W 80&quot;</td>
<td>1-W 90&quot;</td>
<td>25 th</td>
<td></td>
</tr>
<tr>
<td>AN</td>
<td>R(n)</td>
<td>80° 80&quot; 1-W 110&quot;</td>
<td>I-W 65&quot;</td>
<td>25 1-W 75&quot;</td>
<td>9 1/3 31.5 th</td>
<td>11 1/4 32.6 th</td>
</tr>
<tr>
<td></td>
<td>L(d)</td>
<td>80° 1-W NIL 40&quot;</td>
<td>I-W NIL</td>
<td>1-W NIL</td>
<td>12 NIL</td>
<td>8.2 th</td>
</tr>
<tr>
<td>KI</td>
<td>R(d)</td>
<td>80° 90&quot;</td>
<td>I-W 40&quot;</td>
<td>35 1-W 2&quot;</td>
<td>9 3/4 12^3 NIL</td>
<td>12 16.5 th</td>
</tr>
<tr>
<td></td>
<td>L(d)</td>
<td>80° 65&quot;</td>
<td>I-W NIL</td>
<td>1-W 60&quot;</td>
<td>12^3 NIL</td>
<td>17.0 th</td>
</tr>
</tbody>
</table>

1 = threshold response; typical normal temp. = 35 — 36.5°C  
2 = 3rd day of streptomycin treatment  
3 = severe pain despite codeine; irrigation shortened  
4 = limited to caloric and ataxia tests  
5 = irrigation for 3 minutes
It would seem that, in man, recovery of a normal threshold response is less likely than in the squirrel monkey, although more data on man are needed. In both animals and man it would appear that the very slow phase of the lowering of the threshold response must be the result of central compensation.

Otolith Organs

Under rigidly controlled test conditions it has been demonstrated not only that ocular counterrolling is a specific or nearly specific indicator of otolith function but also that test-retest reliability is good (10). The results may be expressed: 1) in absolute values, 2) as a counterrolling index (C-1) defined as one-half the maximum right and left ocular torsion, and 3) right-left asymmetry. The range of counterrolling index values for 100 normal subjects (11) at a tilt of 25° and 50° has been found to be 183-626, with a mean of 344 minutes of arc, and for ten subjects with bilateral vestibular defects (10), 21 to 126 with a mean of 68. Threefold right-left differences were sometimes observed. With rare exception, the roll at 50° tilt was greater than that at 25°, and in these exceptional cases the magnitude of the roll at 25° was notably great.

The results of this test, obtained at the time of the second follow-up, are plotted in Figure 5 where the shaded area indicates the normal range. Only CA (Index 127) shows abnormal right-left asymmetry; on leftward tilt the counterroll at 25° is greatly suppressed and at 50°, nil. The findings in OC (Index 305) were "normal," although they could represent a reduction in counterroll compared with that prior to his illness. The counterrolling values for AN (Index 235) fall within the normal range, but they are far below the mean. Counterrolling is clearly reduced below normal in KI, although there is good left-right asymmetry.

Comment. Inasmuch as counterrolling measurements were not obtained prior to streptomycin therapy, one can only speculate as to the relative etiological significance of the disease process and drug therapy in causing the reduction in otolith function. Based on a very small experience, we can state that the counterrolling index is significantly below normal in subjects manifesting loss of hearing and suppression of canal function confined to one side. This suggests that in OC, and probably AN, there is bilateral function of the maculae and that any reduction in function is far more likely to have been due to the disease injury rather than drug toxicity. The large reduction in counterrolling can be explained for KI on the basis of bilateral disease. The great reduction in CA might be explained either on the basis of complete destruction of the maculae on the diseased side due to disease or unusual susceptibility to the toxic effect of streptomycin combined with disease injury.

In the squirrel monkey experiment referred to above (9) only three of the eight animals that received large doses of streptomycin showed pathological changes in the maculae. In each instance it was very slight; the macula of the saccule was affected in three and in one of these the utricle also was affected. The same predilection for the
Figure 5

Ocular Counterrolling Response to Body Tilt Measured in Patients OC, CA, AN, and KI During Second Follow-Up Study (Mean Values) and in 100 Normal Subjects (Mean Values ±1 S. D)
A semicircular canals has been demonstrated when streptomycin was administered to cats (12, 13) but not in guinea pigs (14) where the receptors in the crista and utricle were equally affected. Insofar as the results on animals might be extrapolated to man, it would tend to minimize the etiological role of streptomycin in causing a suppression of otolith end organ function.

**Ataxia Test**

The subjects performed all tests (4) in the following sequence: 1) Classical Romberg Test, consisting of standing with eyes closed, arms at sides, and feet together on the floor for a period of sixty seconds; 2) Sharpened Romberg Test (SR), consisting of standing on the floor with eyes closed for sixty seconds in the stringent body position of body erect or nearly erect, arms folded against chest, feet in heel-to-toe position and tandemly aligned; 3) Test Battery (Short Version), also performed in the stringent body position, consisting of walking with eyes open (Walk H/T Test) on a \( \frac{3}{4} \) wide rail, standing with eyes open (Stand E/O Test) on the \( \frac{3}{4} \) wide rail, and standing with eyes closed (Stand E/C Test) on a 2\( \frac{1}{4} \) wide rail; 4) standing on one leg for thirty seconds with eyes closed and arms folded against chest (SOLEC). The best three out of five trials constituted the scoring of the Test Battery (Short Version), and weighted scores were used for the SR and SOLEC tests. Maximum scores available were as follows: Classical Romberg: 60 seconds; SR: 240 (60 x 4) seconds; Walk H/T: 15 (steps); Stand E/O and Stand E/C tests: 180 (seconds); SOLEC: 150 seconds (30 seconds x 5 trials). The tests were repeated on several daily occasions to determine the extent of improved performance with practice.

Results from all four patients tested during the second follow-up and three of the four tested in 1965 are summarized in Tables IV and V.

**Classical Romberg Test:** All four subjects obtained perfect scores; i.e., they stood on the floor for a period of sixty seconds with eyes closed.

**Walk H/T Test:** Three of the subjects scored within the average normal range, but only one of these three (AN) improved appreciably with practice (133%). The fourth subject, KI, initially scored at the 2nd percentile, but he improved considerably with practice (225%) that his improved score fell within the high average range (82nd percentile).

**Stand E/O Test:** None of the subjects' initial scores fell within the average range. All four subjects improved sufficiently with practice to produce scores within the average range, although such improvements were not always maintained. Subject KI, who scored poorest initially among the subjects, showed improvement with practice at a level consistent with the improvement levels shown by the other three subjects.
### Table IV
SERIAL ATAXIA TEST SCORES IN FOUR STREPTOMYCIN TREATED PATIENTS AT TIME OF SECOND AND THIRD FOLLOW-UP

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>FOLLOWUP PERIOD</th>
<th>TEST SESSIONS</th>
<th>WALK HEEL/TOE</th>
<th>STAND EYES OPEN</th>
<th>STAND EYES CLOSED</th>
<th>SHARPENED ROMBERG</th>
<th>SOLEC** RIGHT</th>
<th>SOLEC LEFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC</td>
<td></td>
<td></td>
<td>Score Percentile</td>
<td>Score Percentile</td>
<td>Score Percentile</td>
<td>Score Percentile</td>
<td>Score Percentile</td>
<td>Score Percentile</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>12</td>
<td>70th</td>
<td>7</td>
<td>5th</td>
<td>8</td>
<td>1st</td>
<td>11</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>5</td>
<td>7th</td>
<td>12</td>
<td>30th</td>
<td>10</td>
<td>1st</td>
<td>12</td>
</tr>
<tr>
<td>II</td>
<td>3</td>
<td>9</td>
<td>40th</td>
<td>10</td>
<td>20th</td>
<td>11</td>
<td>1st</td>
<td>26</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>6</td>
<td>17th</td>
<td>6</td>
<td>4th</td>
<td>8</td>
<td>1st</td>
<td>18</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>5</td>
<td>13th</td>
<td>9</td>
<td>17th</td>
<td>8</td>
<td>1st</td>
<td>12</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>8</td>
<td>35th</td>
<td>9</td>
<td>17th</td>
<td>6</td>
<td>15</td>
<td>1st</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>11</td>
<td>74th</td>
<td>9</td>
<td>17th</td>
<td>9</td>
<td>21</td>
<td>1st</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>13</td>
<td>87th</td>
<td>10</td>
<td>35th</td>
<td>7</td>
<td>1st</td>
<td>17</td>
</tr>
</tbody>
</table>

Max Improvement 8 per cent 71 per cent 38 per cent 136 per cent 50 per cent 73 per cent

<table>
<thead>
<tr>
<th>CA</th>
<th></th>
<th></th>
<th>Score Percentile</th>
<th>Score Percentile</th>
<th>Score Percentile</th>
<th>Score Percentile</th>
<th>Score Percentile</th>
<th>Score Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>1</td>
<td>13</td>
<td>90th</td>
<td>8</td>
<td>10th</td>
<td>11</td>
<td>10th</td>
<td>6</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>8</td>
<td>30th</td>
<td>13</td>
<td>35th</td>
<td>12</td>
<td>15th</td>
<td>16</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>8</td>
<td>30th</td>
<td>9</td>
<td>15th</td>
<td>8</td>
<td>2nd</td>
<td>7</td>
</tr>
</tbody>
</table>

Max Improvement 0 per cent 63 per cent 9 per cent 167 per cent 0 per cent

<table>
<thead>
<tr>
<th>AN</th>
<th></th>
<th></th>
<th>Score Percentile</th>
<th>Score Percentile</th>
<th>Score Percentile</th>
<th>Score Percentile</th>
<th>Score Percentile</th>
<th>Score Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>1</td>
<td>3</td>
<td>18th</td>
<td>6</td>
<td>7th</td>
<td>6</td>
<td>1st</td>
<td>9</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>4</td>
<td>20th</td>
<td>9</td>
<td>30th</td>
<td>7</td>
<td>1st</td>
<td>14</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>4</td>
<td>20th</td>
<td>6</td>
<td>7th</td>
<td>5</td>
<td>1st</td>
<td>8</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>6</td>
<td>17th</td>
<td>13</td>
<td>65th</td>
<td>7</td>
<td>1st</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>7</td>
<td>26th</td>
<td>9</td>
<td>17th</td>
<td>6</td>
<td>1st</td>
<td>10</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>6</td>
<td>17th</td>
<td>13</td>
<td>65th</td>
<td>8</td>
<td>1st</td>
<td>9</td>
</tr>
</tbody>
</table>

Max Improvement 133 per cent 117 per cent 33 per cent 56 per cent 31 per cent 91 per cent

<table>
<thead>
<tr>
<th>KI</th>
<th></th>
<th></th>
<th>Score Percentile</th>
<th>Score Percentile</th>
<th>Score Percentile</th>
<th>Score Percentile</th>
<th>Score Percentile</th>
<th>Score Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>1</td>
<td>4</td>
<td>2nd</td>
<td>8</td>
<td>1st</td>
<td>10</td>
<td>1st</td>
<td>12</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>6</td>
<td>5th</td>
<td>6</td>
<td>1st</td>
<td>12</td>
<td>1st</td>
<td>13</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>7</td>
<td>7th</td>
<td>14</td>
<td>13th</td>
<td>9</td>
<td>1st</td>
<td>10</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>4</td>
<td>2nd</td>
<td>7</td>
<td>5th</td>
<td>7</td>
<td>1st</td>
<td>12</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>7</td>
<td>22nd</td>
<td>9</td>
<td>12th</td>
<td>9</td>
<td>1st</td>
<td>12</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>10</td>
<td>48th</td>
<td>14</td>
<td>43rd</td>
<td>7</td>
<td>1st</td>
<td>13</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>13</td>
<td>82nd</td>
<td>12</td>
<td>31st</td>
<td>7</td>
<td>1st</td>
<td>15</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>13</td>
<td>82nd</td>
<td>13</td>
<td>36th</td>
<td>13</td>
<td>10th</td>
<td>9</td>
</tr>
</tbody>
</table>

Max Improvement 225 per cent 75 per cent 30 per cent 42 per cent 27 per cent 14 per cent

II Indicates Second Follow-up, 1963
III Indicates Third Follow-up, 1965

* This Subject's Period II Percentiles are based on a succeeding normative age group to which he advanced since Period I.
** SOLEC—Stand one leg eyes closed
Table V

<table>
<thead>
<tr>
<th>TEST</th>
<th>MEAN NORMALS</th>
<th>MEAN MÉNIÈRE'S</th>
<th>DIFF</th>
<th>U</th>
<th>P</th>
<th>DIFF</th>
<th>U</th>
<th>P</th>
<th>DIFF</th>
<th>U</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walk H/T</td>
<td>10.5</td>
<td>8.0</td>
<td>2.5</td>
<td>7</td>
<td>0.02</td>
<td>0.2</td>
<td>0</td>
<td>0.02</td>
<td>0.2</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Stand E/O</td>
<td>24.8</td>
<td>7.3</td>
<td>17.5</td>
<td>0</td>
<td>0.02</td>
<td>0.2</td>
<td>0</td>
<td>0.02</td>
<td>0.2</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Stand E/C</td>
<td>65.8</td>
<td>8.8</td>
<td>57.0</td>
<td>0</td>
<td>0.02</td>
<td>0.2</td>
<td>0</td>
<td>0.02</td>
<td>0.2</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>SR</td>
<td>143.5</td>
<td>9.5</td>
<td>134.0</td>
<td>0</td>
<td>0.02</td>
<td>0.2</td>
<td>0</td>
<td>0.02</td>
<td>0.2</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>SOLEC</td>
<td>64.5</td>
<td>11.8</td>
<td>52.7</td>
<td>0</td>
<td>0.02</td>
<td>0.2</td>
<td>0</td>
<td>0.02</td>
<td>0.2</td>
<td>0</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Mean postural equilibrium (ataxia) test performance differences between a group of Ménière's treated individuals and a group of age-matched, randomly sampled normals.
Stand E/C Test: Initially, three of the subjects scored at the 1st percentile, and
despite 30 to 38 per cent improvement with practice, their scores remained at the 1st
percentile. The fourth subject, CA, initially scored at the 10th percentile, and although
a gain of 9 per cent improvement was shown, the improvement was not maintained.

Sharpened Romberg Test: Consistent with findings on the Stand E/C Test, initially
the same three subjects scored at the 1st percentile, and despite the very marked im-
provements ranging from 42 to 136 per cent their scores remained at the 1st percentile
level. Subject CA initially scored at the 9th percentile, and while an improvement of
167 per cent was realized, this improvement was not maintained.

SOLEC Test: All four subjects initially scored at between the 1st and 4th per-
centile. One subject (CA) failed to improve with practice; the three remaining subjects
improved 14 to 91 per cent with practice, but nevertheless the corresponding percentile
levels either did not change (subject KI) or improved only very slightly (subjects AN
and OC).

Although the subjects all made poor scores, there were intragroup differences. The
over-all rank order was CA best, KI worst, with the others falling between. With refer-
ence to the residual vestibular functions, it would appear that there was no correlation
as far as otolith function is concerned. Although there was a clear difference between
KI with severe bilateral suppressed function of the canals and the remaining three sub-
jects with greater residual function on one side, other factors may have accounted for
the difference. In all likelihood, there was nothing to choose between caloric threshold
levels (one ear) of 25° to 31.5° C, all representing severe depression in terms of
ataxia.

Comment. These four individuals as a group, in comparison with a group of age-
matched individuals randomly sampled from a normal population, performed poorer on
all of the postural equilibrium (ataxia) tests (Table V), and on all of the tests except
Walk H/T the mean performance differences were statistically significant (P .02 by U
test). The performance of KI was similar to that of subjects with bilateral suppression of
both canal and otolith function (15) and that of the remaining three was only slightly
better.

Habituation as Indicated by the Oculogyral Illusion

This illusion has been defined (7) as an apparent movement of objects in the visual
field resulting from stimulation of the semicircular canals by angular acceleration and
has been shown to be related to involuntary eye movements (16). One characteristic
type of this illusion is perceived when a person, rotating about one axis, tilts his head
about a second axis. This simultaneous rotation of the head about two axes constitutes
an effective but bizarre stimulus to the semicircular canals, involving not only the
oculogyral illusion but also symptoms characteristic of motion sickness as well.
This illusion has been used as an indicator in previous experiments carried out in the Slow Rotation Room (SRR). This room rotates counterclockwise and if a subject, fixating a luminous target in the dark while rotating at constant velocity, tilts his head toward the left shoulder, the target will appear to rise. It was learned early on that subjects habituated to this illusion (17), and experiments were devised to study the nature and characteristics of this adaptation. The investigation was conducted in the rotating room and required that an otherwise immobile subject tilt his head in a systematic manner over a period of hours until the illusion was greatly reduced or extinguished. When this was done it was found that, after cessation of rotation, the same head movement would still evoke an illusion but in the opposite direction; tilting the head to the right evoked no response (Figure 6). These findings indicated that habituation involved a compensatory response, and the fact that it was elicited after cessation of rotation indicated it was also a conditioned response. Inasmuch as nausea and other side effects restricted the number of head movements in a given period of time using normal subjects, the opportunity was taken to repeat the experiment using the Ménière's subjects who were insusceptible to the nausea syndrome.

The object was to determine if habituation would occur in a matter of minutes. The subjects, seated in the dark, fixated, at a distance of about 8 feet, a 6-inch cube illuminated within and dimly outlined by a series of small holes along the edges as perceived in the dark; with cube slightly canted, the "height" was $5\frac{1}{2}$ inches. Estimates of apparent movement were made in terms of units equal to the height of the box. Estimates were made before, during rotation at 10 RPM, and after cessation of rotation moving the head toward the shoulder. The practice movements during rotation were experimenter-paced at the rate of 12 full movements every minute. They were continued until the illusion was extinguished or negligible in amount.

The results for three subjects are summarized in Table VI; KI did not perceive the illusion. The results are clear in showing habituation to the illusion within periods ranging from about three to twenty-five minutes and involving 38 to 250 head movements. The number of movements is in line with the results of previous experiments (17) although individual variance is too great to draw further comparisons. There was some indication that habituation extended beyond the first experimental day as shown by decreasing illusory effects on successive days. It would appear that the findings in AN demonstrated that habituation was in the nature of a compensatory and conditioned response. It was not clearly evident for the other two subjects. This is not out of line with previous findings (17) which demonstrate individual variance.

Comment. One additional observation deserves mention. Prior to carrying out the experiment just described the subjects were exposed to angular accelerations in the plane of the horizontal pair of canals by causing the SRR to accelerate to 10 RPM in about eight seconds, and, after a period of at least two minutes at constant velocity, to decelerate in about five seconds. Not only were the illusory responses greatly reduced in comparison with the normal, but two of the three did not regularly perceive the oculogyral illusion in the horizontal plane. It came as a surprise therefore that they perceived
**Table VI**

**ALTERATION IN PERCEPTION OF THE OCULOGRYRAL ILLUSION AS THE RESULT OF TILTING HEAD TO LEFT SHOULDER ABOUT ONCE EVERY 5 SECONDS WHILE ROTATING COUNTER CLOCKWISE AT 10 RPM IN THE SLOW ROTATING ROOM**

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>EXPERIMENTAL DAY</th>
<th>SRR STATIONARY</th>
<th>10 RPM</th>
<th>Shortly after Cessation of Rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Head Left</td>
<td>Head Right</td>
<td>Prior to Stop</td>
</tr>
<tr>
<td>OC</td>
<td>1</td>
<td>Sl. Rot.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>NIL</td>
<td>1</td>
<td>1/2 1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Sl. Rot.</td>
<td>2 1/3 1</td>
<td>2/3 1</td>
</tr>
<tr>
<td>CA</td>
<td>1</td>
<td>Sl. Rot.</td>
<td>2</td>
<td>1 1 1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Sl. Rot.</td>
<td>1 1/2 1</td>
<td>2 1</td>
</tr>
<tr>
<td>AN</td>
<td>1</td>
<td>NIL</td>
<td>3 1 2 1</td>
<td>2 1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>NIL</td>
<td>1/2 1/2 1</td>
<td>1/2 1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>NIL to 1/2 1</td>
<td>1 1 1/2 1</td>
<td>150 (12 min)</td>
</tr>
</tbody>
</table>

*Distance in terms of width (5 1/2") of target  **Error in pacing
COMPARATIVE MAGNITUDE AND DIRECTION OF THE CORIOLIS ILLUSION ASSOCIATED WITH SINGLE HEAD MOVEMENTS BEFORE, DURING AND AFTER PROLONGED ROTATION AT 5.4 RPM. TESTS CARRIED OUT AT 7.5 RPM.
the oculogyral illusion as readily as normal subjects when the head was rotated simultane-ously about two axes. There are two possible explanations for the difference: first, that the horizontal canal may have been more severely damaged than the vertical canals, and second, that only one (horizontal) canal was involved when the angular accelerations were in that plane but that more than one canal was involved in the Coriolis type of acceleration. The possibility of differentially testing the canals by this method is suggested.

Susceptibility to Motion Sickness

Even prior to streptomycin therapy the subjects had not experienced much motion sickness although none had been exposed to very stressful force environments. Following therapy, there not only was no history of motion sickness but also none experienced the nausea syndrome in the SRR while carrying out the dial test (5,6) or as a result of habituation to the oculogyral illusion. The dial test involved an experimenter-paced task in which the subject was required to set five different dials so placed around a seat that it involved maximum rotations of the head out of the plane of the room's rotation. One hundred such settings while the subjects were rotating at 10 RPM did not produce any characteristic symptoms of motion sickness which persons with normal vestibular organs would, in all likelihood, have experienced. This insusceptibility to canal (motion) sickness was in line with previous findings, indicating that even slight suppression of canal function prevented the nausea syndrome.

DISCUSSION

The effects of streptomycin therapy in these patients must have significance in terms of the etiology of "idiopathic" Ménière's disease. The salient emergent facts were abolition of acute attacks associated with suppression of semicircular canal function and followed by lowering of the auditory threshold in all of the diseased ears. Information concerning the "attacks" was based mainly on the subjective symptomatology, hence, furnished only a gross indicator of disease injury and drug toxicity; the caloric and audiometric test findings, however, provided information often below the level of subjective awareness. The former indicated severe depression of canal function in all diseased ears shortly after administration of the drug with little or no recovery save in one instance. Changes in audiometric threshold, however, occurred over a period of several years and, in one instance, initial "improvement" was lost. Although tests of otolith function were not carried out until many years after therapy, there was indirect evidence that the drug caused little or no macular suppression save possibly in one subject.

Theoretically, the therapeutic activity of streptomycin might have been due to its antibiotic effect on microorganisms or by virtue of its toxic effects on structural elements of the auricular sensory systems. In the absence of any information implicating a microorganism in idiopathic Ménière's disease, even a "cure" resulting from the exhibition of an antibiotic is insufficient proof of an infectious agent although it imposes a requirement to rule it out.
Regarding the second possibility, there was evidence of toxic destruction involving the canalicular system in the diseased ears. By extrapolating from relevant investigations on animals, we can say that the sensory epithelium over the cristae, especially the hair cells themselves, are most vulnerable. Indeed, this predilection raises the possibility that "drug ablation" prevented symptoms simply by reducing the sensory input. While this might account for vertigo, it does not account for tinnitus and deafness which also characterize the typical attack. With regard to the cochlea the evidence clearly indicated that streptomycin did not cause toxic destruction of sensory receptor units but, rather, had a salutary effect. It is difficult to imagine how destruction of sensory elements in the cristae, presumably taking place over a short period, could account for changes in auditory threshold occurring over a period of many years. The only explanation for these changes which comes to mind is variation in fluid pressure in the cochlea. This raises the question whether the major therapeutic effect of streptomycin is not concerned with restoration of normal fluid dynamics in the vestibular labyrinth and cochlea. Westfall and Hawkins (13) offered the suggestion, based on pathological studies in the cat, that streptomycin is concentrated in the endolymph through the activities of the secretory cells in the crista. The toxic effects on secretory cells rather than on the hair cells of the crista might account for the major therapeutic action. This conclusion would be in line with the evidence (18-20) that idiopathic Ménière's disease is due to "hydrops" of the labyrinth.

The use of these patients as "naturally occurring human subjects" deserves brief comment. If it is assumed that OC and AN had "adequate" otolith function, then the absence of the nausea syndrome in the Slow Rotation Room suggests that suppression of canal function was responsible, a conclusion supported by findings on squirrel monkeys (9). The degree of suppression which was adequate to prevent symptoms, and, quite possibly more than adequate, was severe loss of canal function in one ear and partial loss in the other. Moreover, it keeps alive the possibility that drugs of the streptomycin series still hold promise in the treatment of motion sickness. At least loss of hearing is not a contraindication to their use if the present findings hold true for all subjects or patients tested.

If the same reasoning is applied in the case of ataxia, then these degrees of suppression of canal function are almost equivalent to total suppression insofar as maintenance of postural equilibrium is concerned. In short, a slight increase in caloric threshold levels, in terms of the total range (0° to 36° C), is responsible for almost total loss of this function. The rapid habituation to the bizarre stimulation of the semicircular canals as indicated by the oculogyral illusion is of theoretical and practical importance. If frequent head movements can be tolerated in the absence of the nausea syndrome, then the time required for habituation to a rotating environment may be greatly shortened.
REFERENCES


**ABSTRACT**

Four patients who had received streptomycin sulfate in the treatment of Ménière's disease were evaluated in terms of the long-range effects of therapy and utilized as experimental subjects. The findings are reported in terms of a lack of return of their symptoms, and the effect of the drug on hearing, the semicircular canals, otolith organs, ataxia, and the Coriolis oculogyral illusion. An attempt was made to interpret the findings in terms of the etiology of idiopathic Ménière's disease, and the suggestion is made that it might represent a disturbance attributable to the secretory cells of the crista.
**INSTRUCTIONS**

1. **ORIGINATING ACTIVITY:** Enter the name and address of the contractor, subcontractor, grantee, Department of Defense activity or other organization (corporate author) issuing the report.

2a. **REPORT SECURITY CLASSIFICATION:** Enter the overall security classification of the report. Indicate whether "Restricted Data" is included. Marking is to be in accordance with appropriate security regulations.

2b. **GROUP:** Automatic downgrading is specified in DoD Directive 5200.10 and Armed Forces Industrial Manual. Enter the group number. Also, when applicable, show that optional markings have been used for Group 3 and Group 4 as authorized.

3. **REPORT TITLE:** Enter the complete report title in all capital letters. Titles in all cases should be unclassified. If a meaningful title cannot be selected without classification, show the title classification in all capitals in parenthesis immediately following the title.

4. **DESCRIPTIVE NOTES:** If appropriate, enter the type of report, e.g., interim, progress, summary, annual, or final. Give the inclusive dates when a specific reporting period is covered.

5. **AUTHOR(S):** Enter the name(s) of author(s) as shown on or in the report. Enter last name, first name, middle initial. If military, show rank and branch of service. The name of the principal author is an absolute minimum requirement.

6. **REPORT DATE:** Enter the date of the report as day, month, year; or month, year. If more than one date appears on the report, use date of publication.

7a. **TOTAL NUMBER OF PAGES:** The total page count should follow normal pagination procedures, i.e., enter the number of pages containing information.

7b. **NUMBER OF REFERENCES:** Enter the total number of references cited in the report.

8a. **CONTRACT OR GRANT NUMBER:** If appropriate, enter the applicable number of the contract or grant under which the report was written.

8b. **PROJECT NUMBER:** Enter the appropriate military department identification, such as project number, subcontract number, project number, task number, etc.

9a. **ORIGINATOR'S REPORT NUMBER(S):** Enter the official report number by which the document will be identified and controlled by the originating activity. This number must be unique to this report.

9b. **OTHER REPORT NUMBER(S):** If the report has been assigned any other report numbers (either by the originator or by the sponsor), also enter this number(s).

10. **AVAILABILITY/LIMITATION NOTICES:** Enter any limitations on further dissemination of the report, other than those imposed by security classification, using standard statements such as:

   1. "Qualified requesters may obtain copies of this report from DDC."
   2. "Foreign announcement and dissemination of this report by DDC is not authorized."
   3. "U. S. Government agencies may obtain copies of this report directly from DDC. Other qualified DDC users shall request through "
   4. "U. S. military agencies may obtain copies of this report directly from DDC. Other qualified users shall request through "
   5. "All distribution of this report is controlled. Qualified DDC users shall request through "

If the report has been furnished to the Office of Technical Services, Department of Commerce, for sale to the public, indicate this fact and enter the price, if known.

11. **SUPPLEMENTARY NOTES:** Use for additional explanatory notes.

12. **SPONSORING MILITARY ACTIVITY:** Enter the name of the departmental project office or laboratory sponsoring (paying for) the research and development. Include address.

13. **ABSTRACT:** Enter an abstract giving a brief and factual summary of the document. If the report is classified, indicate the classification of the report. If additional space is required, a continuation sheet shall be attached.

   It is highly desirable that the abstract of classified reports be unclassified. Each paragraph of the abstract shall end with an indication of the military security classification of the information in the paragraph, represented as (TS). (S). (C) or (U).

   There is no limitation on the length of the abstract. However, the suggested length is from 150 to 225 words.

14. **KEY WORDS:** Key words are technically meaningful terms or short phrases that characterize a report and may be used as index entries for cataloging the report. Key words must be selected so that no security classification is required. Identifiers, such as equipment model designation, trade name, military project code name, geographic location, may be used as key words but will be followed by an indication of technical context. The assignment of links, roles, and weights is optional.