EYE AND OTOLITHS

A. COLENBRANDER

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A CENTRIFUGE STUDY ON THE OCULAR RESPONSE TO OTOLITH STIMULATION

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE RIJKSUNIVERSITEIT TE UTRECHT OP GEZAG VAN DE RECTOR MAGNIFICUS, PROF. DR. H. FREUDENTHAL, VOLGENS BESLUIT VAN DE SENAAT DER UNIVERSITEIT IN HET OPENBAAR TE VERDEDIGEN OP DINSDAG 7 JULI 1964 TE 16.15 UUR

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From the

Koninklijk Nederlands Gasthuis voor Ooglijders,
F. C. Dondersstraat 65, Utrecht, the Netherlands,

and the

Stichting Nationaal Luchtvaart-Geneeskundig Centrum,
(National Aeromedical Centre), Soesterberg, the Netherlands

MET MIJN VROUW,
AAN MIJN VADER

VOORWOORD.

Het gereedkomen van een proefschrift noopt tot omzien. Daarbij blijkt alras aan hoevelen de promovendus dank verschuldigd is omdat zonder hun directe of zijdelingse steun de vrucht van zijn academische studie niet tot rijping zou zijn gekomen.

In de eerste plaats noem ik mijn vader, die de kiem van mijn wetenschappelijke belangstelling heeft gelegd en opgekweekt, door steeds weer te tonen hoe een wetenschappelijk probleem kan schuilen ook in het schijnbaar vanzelfsprekende.

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Zo rolle dan deze vrucht de wereld in, in de hoop dat hij vruchtbare kiemen bevatte.

SAMENVATTING.

Het evenwichtsorgaan bestaat uit twee stelsels, dat der halfcirkelvormige kanalen en dat der otolithen. Tegenover de gedetailleerde kennis van de wijze waarop het eerstgenoemde deel op draaiingen reageert, staat een veel onvolkomener kennis van het otolith-systeem. Elk binnenoor bevat twee verschillend geplaatste otolithen, een in de sacculus en een in de utriculus. De otolithen bestaan uit een kalkhoudende massa en rusten op een onderlaag van zintuigcellen die van fijne tastharen zijn voorzien. Daar de otolithen zwaarder zijn dan de omgevende vloeistof oefent hun gewicht een kracht op de haarcellen uit, die ons in kan lichten over de stand van het hoofd ten opzichte van de zwaartekracht.

Oudere theorieën meenden dat de haarcellen geprikkeld worden als de otolith er op drukt (Quix) of er aan hangt (Magnus). In de laatste decenniën zijn door dierproeven steeds meer argumenten bijeengebracht die het aannemelijk maken dat de prikkeling ontstaat als de zwaarte van de schuin geplaatste otolith de zintuigharen doet afbuigen. Bovendien kent men aan de sacculus otolith weinig invloed meer toe en meent men dat alleen een naar buiten gerichte schuifkracht effectief is. Rekening houdend met deze factoren en met de positie van de utriculus otolithen die ongeveer 7,5° naar buiten hellen, verwacht men een verband tussen de otolithprikkel en de hoofdstand zoals weergegeven door de dunne lijn in fig. 11.

Teneinde de geldigheid van deze op dierproeven gebaseerde theorie ook voor de mens te toetsen, is het nodig een effect van de otolithprikkeling te registreren, dat niet van andere factoren afhankelijk is, en waarvan de grootte in een getal uitdrukbaar is. De tegenrolling van de oogbollen in de oogkassen die optreedt wanneer het hoofd naar een schouder geneigd wordt en die niet willekeurig beïnvloed kan worden, lijkt hiervoor bijzonder geschikt. Toch is het nooit gelukt de gevonden tegenrolling op eenvoudige wijze uit de (verwachte) otolithprikkel te verklaren. De oorzaak

hiervan moet gezocht worden in de invloed die de houding van romp en nek op de tegenrolling heeft.

In onze proefreeksen werden de waarnemingen verricht in een grote centrifuge. Het bleek dat de door de centrifugaalkracht toegenomen zwaarte van hoofd en romp geen invloed heeft op de door de houding van romp en nek veroorzaakte tegenrolling. De toenemende zwaarte van de otolithen echter betekent wel een toenemende prikkel voor de haarcellen; daarbij bleek het hierdoor veroorzaakte deel van de tegenrolling naar evenredigheid toe te nemen. Het verschil tussen de bij tweemaal de normale zwaarte gemeten tegenrolling en de tegenrolling onder normale omstandigheden is dus wel als een zuiver otolitheffect te beschouwen. De dikke lijnen in fig. 11 geven de uit 3600 oogrollingsmetingen op één proefpersoon afgeleide grenzen weer waarbinnen het effect van de otolithprikkel gelegen moet zijn. De overeenstemming met de theoretische curve is evident.

Ook over de andere factoren die tegenrolling veroorzaken werden enkele proeven gedaan; deze maken het aannemelijk dat ook in een toestand van gewichtloosheid nog enige tegenrolling zal optreden.

Ons onderzoek had bovendien betrekking op de subjectieve localisatie. Daartoe werd bij elke oogrollings-bepaling een bepaling van de subjectieve localisatie (subjectief waterpas en subjectieve loodlijn) verricht. Bij elke actieve beweging van hoofd of ogen verplaatst zich het beeld van de buitenwereld over ons netvlies; toch zien wij de buitenwereld stilstaan. De *compensatie* die optreedt voor deze *retinale* beeldverschuiving hebben wij *retinale compensatie* genoemd. Bij passieve oogbewegingen treedt géén retinale compensatie op, zoals blijkt uit de schijnbeweging van de buitenwereld die men ziet als men het oog met de vinger wat opzij drukt.

Als men het hoofd opzij neigt treedt er geen schijnbeweging van de buitenwereld op. De beschreven tegenrolling compenseert slechts een gering deel van de hoofdhelling, daarnaast moet dus ook een retinale compensatie van de hoofdhelling optreden. Dankzij de gepaarde bepalingen van tegenrolling en retinale compensatie was het ons, door een eenvoudige variantie-analyse, mogelijk aan te tonen dat deze retinale compensatie geheel onafhankelijk van de tegenrolling tot stand komt. De reflectoire tegenrolling gedraagt zich dus ten opzichte van de retinale compensatie als een passieve oogbeweging.

Analyse van de tegenrolling leerde dat deze gestuurd wordt door de otolithprikkel èn door andere factoren. De retinale compensatie echter bleek gestuurd te worden door de otolithprikkel òf door andere factoren. Bij kleine hoofdhellingen domineert de otolithprikkel en leidt toenemende zwaarte in de centrifuge tot een te grote retinale compensatie; bij grotere hoofdhellingen daarentegen domineren de andere factoren en heeft de toenemende zwaarte geen invloed meer. Bovendien bleek steeds een belangrijke invloed te bestaan van de tevoren ingenomen hoofdstand.

Onze proeven konden dus een eenvoudig, lineair verband aantonen tussen de otolithprikkel en een deel van de tegenrolling; daardoor was het ons mogelijk de geldigheid voor de mens te bewijzen van de op dierproeven gebaseerde werkingshypothese betreffende het otolith-orgaan.

Bovendien bleek dat tegenrolling en retinale compensatie twee compensatiemechanismen van de subjectieve localisatie zijn, die op verschillende wijze gereguleerd worden en onderling onafhankelijk zijn. Bij een studie van de subjectieve localisatie moeten deze beide mechanismen dan ook afzonderlijk beoordeeld worden.

CONTENTS.

INTRODUCTION.

Some dates.

This study deals with the relation between stimulation of the labyrinth and counterrolling of the eye. Elaborate surveys have been given in the literature. We will mention but briefly the most important investigations relevant to our subject.

Rolling of the eyes to compensate for movements of the head was first described by John Hunter (1786); Donders at first (1846) denied its existence and was still quoted for this in the second edition (1896) of the Handbuch der Physiologischen Optik by H. von Helmholtz (1867), long after the day that M. E. Mulder, working under Donders, described and firmly established the phenomenon in his doctoral thesis (Utrecht, 1874).

Later the main controversy turned on the extent of the rolling, the enormous differences between some authors being undoubtedly due to variations in experimental set-up and method of measurement.

Breuer (1874), Crum Brown (1874) and Mach (1875) were the first to suggest a different function for the different parts of the vestibular organ: otolith organ and semicircular canals. In the search for a reliable indicator of the otolith-stimulus Bárány (1906), then working under Politzer, was the first to measure counterrolling of the eyes on a large number of patients.

Of the later studies on man those of Grahe's pupils Opfer (1933) (on normals) and Gollas (1936) (on patients) should be mentioned and experiments of M. H. Fischer (1927, 1930) (mostly on himself). Recently data on the topic were published by Miller (1962).

Theories on the otolith function.

Breuer suggested a sliding movement of the otolith on its macula as the adequate stimulus for the otolith organ. This results in a sinusoidal relation between the stimulus and tilt of the head. That the curve of the counterrolling plotted as a function of head tilt resembles a sine curve does not seem to have impressed many people much. Breuer's theory was soon discarded when the displacement of the otoliths could not be readily proved.

Two rival theories were established, each having its most vehement protagonist at the Utrecht university: namely Magnus (1924) who based his theory of the otolith pulling on the macula largely on his studies of postural reflexes, and Quix (1924) proclaiming the otolithic pressure as the active force, largely on clinical evidence.

The fact that the counterrolling does not vary proportionally to the otolithic pressure cannot be used as an argument against Quix's theory, because it would be possible to conceive of a central nervous mechanism that releases some tendency to counterrolling as the pressure decreases. Other data, however, should have made Quix more suspicious as to the correctness of his theory. On several occasions he stated that the accuracy with which a subject is able to judge his position is highest when the pressure of the otoliths is maximal. ('Je mehr Otolithen in Druck sind und je grösser dieser Druck ist um so mehr Angaben für eine richtige Schätzung und eine um so bessere Schätzung wird sich ergeben') (1929). This statement is correct, but to conclude from it to the pressure theory is in contradiction to the general law of Weber-Fechner, which states that the sensitivity of any organ is inversely proportional to the load. When the pressure is maximal the shearing force is minimal, Breuer's theory is therefore in agreement with Weber-Fechner's law.

Direct experimental evidence.

Only comparatively recently has more experimental evidence accumulated.

Versteegh (1927) succeeded in separately destroying the saccular macula; animals with such a lesion exhibit normal postural reflexes, whereas even minor lesions to the utricular macula cause marked abnormalities.

More refined techniques allowed the non-destructive manipulation of the labyrinth.

Ulrich (1935) manipulated the pike's otoliths and demonstrated reactions to sliding in all directions except towards the medial side.

De Vries (1950) was able to demonstrate that under natural conditions the displacement measured 0,1 to 0,2 mm only.

Löwenstein (1949) and his co-workers recorded action potentials from single fibres of the utricular nerve of the ray. They found a 'frequency modulated' signal that was proportional to the shearing force of the otolith along the sensory epithelium of the macula.

These data show that the similarity between the sensory cells of the maculae with their otoliths on the one hand, and those of the cristae ampullarum with their cupulae on the other, is not only an anatomical one, but is also functional. The deformation of the hairs that project from the sensory cells to connect these to the otolith or the cupula is the adequate stimulus in either instance.

Indirect evidence.

A vast difference still remains between the response of a single nerve fibre of a dissected ray, and the reactions of a normal human being.

Halfway between these extremes come the animal experiments of Von Holst (1950). Von Holst made his experiments on fishes that have a strong tendency to swim upstream. By regulating the flow of the water he could keep them in front of his measuring devise, stabilizing them along their longitudinal axis, yet leaving them completely free to turn around this axis. The fishes will then assume a position of equilibrium that is a compromise between the tendency to turn their belly towards the centre of gravity and the tendency to turn their back towards what might be called the 'centre of illumination'. The first tendency could be shown to depend upon the functioning of the otoliths, the second one to depend upon the functioning of the eyes. The position of equilibrium is plotted as a function of the angle of incidence of the light, the angle of incidence of the apparent gravitational force (the whole apparatus being placed on a centrifuge) and the magnitude of this force. Evaluation of the resulting relations yields a set of cogent conclusions on the function of the otolith organ:

1) the shearing force of the otolith is the adequate stimulus for the macula;
2) the signal provided by each macula is directly proportional to this stimulus;
3) the measure of the tendency towards gravitational orientation is directly proportional to the sum of the signals from the individual maculae.

Theoretical considerations.

What are the essential points in the arrangement of Von Holst? His studies are based on the assumption that it is the function of the semicircular canals to respond to the angular acceleration occurring with a *change of position*, and that it is the function of the otolith organ to respond to *position*. If the otolith organ is to be tested on this assumption it follows that the stimulus should be a static one, and that the animal's response chosen to be recorded should not involve dynamic reactions. Many of the positional reflexes, which were so extensively studied by the school of Magnus, clearly aim at the correction of a change of position. The stable position of equilibrium assumed by the fishes of Von Holst is more appropriate to serve as an indicator of the position dependent characteristics of the otolith organ.

The normal static stimulus for the otolith organ is the gravitational force. Of this force only one parameter *(direction)* can be varied; to vary the other parameter *(magnitude)* the gravitational force must be combined with another linearly accelerating force. The only one of such forces that can be kept constant over any desired period of time is the centrifugal force; the use of a centrifuge thus is another essential element of the experiment. The resultant force from the gravitational force and the centrifugal force may be called apparent gravitational force; it acts on the otoliths essentially as a single force, because it is even theoretically impossible for any measuring instrument to distinguish inertial forces from gravitational ones.

In this text the notation G will be used to denote the apparent gravitational force. Its unit magnitude, the gravitational force of the earth, will be indicated by 1g.

Our experiments.

The lucid reasoning behind Von Holst's experiments and the cogency of the mathematical evaluation, made us consider the feasibility of corresponding experiments on man.

The response best suited for this purpose seemed to be the counterrolling of the eye, which can be quantitatively recorded, which is generally accepted to be largely due to otolith stimulation and which is one of the very few reactions in man which cannot be influenced voluntarily.

Most investigators today would not seriously object to our hypothesis: that the conclusions made by Von Holst are applicable to the human otolith organ too. Most of the counterrolling measurements reported in the literature are in qualitative agreement with this hypothesis.

Recently, however, Miller (1962) found that a sine curve, as theoretically required, could not be fitted to the data from a large series of ocular torsion measurements. Miller introduces a cosine square function to fit in with his data; however good the mathematical fit may be, this function lacks physiological evidence and does not bring us nearer to the solution of the problem.

The human centrifuge provides us with the means to obtain from man the amount of extra information that could previously be obtained in animal experiments only. Miller used modern apparatus, but as he applied the gravitational stimulus only, his experiments were not essentially different from those that could be made a century ago. We therefore felt that an attempt should be made at a quantitative evaluation of counterrolling data gathered from the human centrifuge. We were not the first to measure counterrolling on the human centrifuge. Woellner and Graybiel (1959) did so before, and their results are in good agreement with the hypothesis that the otolith organ is stimulated by the shearing force of the otolith. They did not, however, use the magnitude of the apparent gravitational force as a variable independent of its direction, and their results are not numerous enough to allow a complete quantitative analysis.

Subjective localisation.

Moreover, we decided to extend the scope of our experiments by including into our series measurements of the subjective visual localisation in the frontal plane.

Since the classical description of Aubert (1861) it has been known that the subjective horizontal, if determined in the absence of visual directional cues, shows typical deviations that depend upon the position of the head. The phenomenon is known as the Aubert phenomenon; Graybiel (1952) coined the term oculogravic illusion when he studied the effect under centrifuge conditions.

Two questions seemed to us to be of interest. First, whether the reflex ocular torsion has any effect on the subjective localisation. Secondly, whether a quantitative explanation of the effect could be given by using the data on the otolith signal, which could be expected to be obtained from the evaluation of the data on ocular torsion.

To the first question the following remarks should be added. The fact is well established that the subjective localisation is not altered by a change of position of the eye as long as the new position has been voluntarily assumed. If the new position is the result of a passive movement or of the failure of an active movement, the subjective localisation is altered correspondingly. Eye positions caused by reflex movements such as ocular torsion, might be comparable either to actively assumed eye positions or to passively induced ones. Similar controversy exists on reflex movements of the eye, patients suffering from nystagmus seldom complain of corresponding changes of the subjective localisation, yet the vestibular nystagmus has often been put forward to account for the visual illusions occurring on a turning chair.

A comparative study of ocular torsion and subjective localisation has been made by many investigators. The data used, however, were always provided by separate experiments. In order to obtain the most accurate information possible on this subject, we have considered it to be essential to measure ocular torsion and subjective localisation throughout on the same centrifuge runs. These combined measurements and the use of the centrifuge are the novel elements in our approach to this part of the problem.

ARRANGEMENT OF THE EXPERIMENTS.

Position of the subject.

If the influence of the otolith organ is to be studied, then not only should the proper stimulus be used, but also the influence of other receptors that could possibly supply information about our spatial position should be minimized.

Visual spatial cues can easily be eliminated, the elimination of tactile cues is possible to a limited extent only. Yet tactile cues can be very important. Fischer (1930) described a labyrinthine-defective subject whose settings of the subjective vertical were more accurate than those of normals, because he was guided exclusively by the weight of the ruler used for these settings and was not 'hindered' by labyrinthine information.

Jongkees and Groen (1950) described a girl who could adequately indicate a small change in the direction of the apparent gravitational force on a centrifuge; she had lost the function of both inner ears, but only an accurate quantitative analysis of her reactions made it clear that the accuracy of her indications fell far short of normal and that she derived her information not from some residual otolith function but from asymmetrical tactile stimuli.

The position of the subject's head must necessarily be varied to expose the otolith organ to differently directed stimulation. It is optional whether to achieve this through bending of the neck (simple head tilt) or through tilt of the body without changing the position of the head relative to the body (body tilt). The above mentioned case suggests that asymmetrical stimulation of body receptors might make a quantitative evaluation of the otolith stimulus very difficult. We therefore chose for head tilt. This choice gave no difficulties with the Soesterberg centrifuge as the gondola with the chair in it is hinged from its top, so that it will adjust itself to the direction of the apparent gravitational force. This force thus remains parallel to the subject's spine, whatever its magnitude.

By making this choice we introduced the problem of the neck reflexes and whether they are influenced by an increase of G. Fischer (1927) used weights to pull the head to one side, and he demonstrated that an increased load on the neck muscles had no influence on the counterrolling. We did not repeat his experiments, but obtained indirect evidence to support his findings from our tilt table experiments.

Fischer did find an influence of the position of the neck, however. This influence therefore must be due to position receptors of the neck that react independently from the tension receptors.

We concluded that the increased weight of the head would not cause a counterrolling reaction, but that the position of the neck might do so. The influence of the position receptors of the neck can be subjected to separate experiments, however; whereas this is not very well possible for the influence of asymmetrical stimulation of the ill-defined complex of other receptors (skin, joints and internal organs).

Methods of measurement.

Many methods have been devised for measuring ocular torsion. They can be divided in two groups: subjective methods where the subject is asked to indicate the spatial position of an after-image or of his blind spot, and objective methods where an observer measures the position of some landmarks of the eye, either artificial ones (markings, sutures, egg-membrane) or natural ones (iris, conjunctival vessels, the optic disc seen through a calibrated Thorner's ophthalmoscope, or the axis of corneal astigmatism). The most refined example of the last group is Miller's (1962) technique, using enlarged colour-slides of the iris.

For our purpose photographic methods would be very costly and would record the counterrolling of one eye only, the presence of an extra observer in the gondola would present serious difficulties, and observation of the eye on a TV monitor did not seem accurate enough. The after-image method is reliable and accurate, but limits the time available for each set of measurements. We therefore preferred recording the position of the blind spot; this method is somewhat less accurate, but offered the following advantages:

1) series of measurements of any length can be made;
2) measurements can be made on both eyes, thus possible differences between the eyes can be detected;

3) on the same measuring device the subjective localisation can be measured, thus eliminating from a comparison of ocular torsion and subjective localisation possible errors due to misalignment of two measuring devices and a degree of uncertainty due to a longer lapse of time between the two measurements.

The subjective localisation is usually determined by adjusting a line-shaped object to what is called the subjective horizontal or the subjective vertical. We prefer to speak of plumb-line instead of vertical, as the plumb-line is directly related to the apparent gravitational force at the point of measurement. The terms horizontal and vertical should be used to refer to the direction of the horizon rather than to the structure of the gondola.

In our first trial runs, when we used a drawn line to be set to the subjective plumb-line, a certain ambiguity was noticed: at larger angles of head tilt there was a tendency to forget the plumb-line criterion and to set the line more parallel to the median plane of the head. To suppress this rivalry between egocentric and gravicentric localisation the line was replaced by a drawing of a typical Amsterdam canal with a row of 17th century facades with their dominant perpendicular lines. The drawing gives a frontal view without perspective. With the use of this drawing the ambiguity in criterion was no longer noticed. Moreover, we considered that the use of both horizontal and vertical cues projected on a large retinal area bears more resemblance to the physiological conditions of visual localisation. The use of the picture also enforces a level criterion upon the observer, if the picture is not set correctly to the subjective plumb-line the water of the canal makes the definite impression to be flowing to one side.

Number of subjects.

As we did not aim at finding new phenomena, but rather at giving a quantitative analysis of a phenomenon which is well known qualitatively, we decided not to use many subjects, but to do many measurements on one subject. Approximately 15.500 measurements were made by the author himself; of these 7.200 belong to the main series. These will be dealt with at length, the results of the 8.300 measurements in earlier series will be mentioned only in so far as they contain any additional information. By one other subject 580 measurements were made, the results of which are in agreement with those found by the author, as did the results of a total of 570 measurements on 13 other subjects.

Some subjects from the last group were pilots of the air force, they happily participated. All other subjects experienced more or less unpleasant feelings on the centrifuge. The author found that the accuracy of his own measurements increased considerably when the centrifuge runs became more of a routine. At first a head tilt of 45° at 2g could not be endured, later it was possible to make measurements with no more than average variance even at 60° head tilt.

Apparatus.

The centrifuge used in these experiments is the human centrifuge of the National Aeromedical Centre (N.L.G.C.) at Soesterberg, the Netherlands. The gondola of this centrifuge is suspended at 2.60 m from the axis and is free to swing out as the centrifuge moves, it will thus always adjust itself to the apparent gravitational force. In the gondola a chair is mounted to which the subject is fastened by seatbelts, the subject is facing forward with the axis to his left. The subject's head is fixed by a dental impression which can be adjusted to the positions desired at 15° intervals.

In front of the subject a revolving disc of approximately 80 cm diameter is mounted with its axis at eye level approximately 80 cm in front of the eyes. The subject wears a mask with diaphragms for each eye which can be so adjusted that each visual field is completely occluded except for the central part in which the disc revolves. In this way any visual spatial cues from the structure of the gondola are withheld from the subject.

The disc is black, on it is mounted the drawing mentioned above and two white spots at positions such that they can be made to just disappear within the subject's blind spot. If the disc is rotated one of them will appear at the upper or lower border of the blind spot. For measuring the position of the blind spot a small fixation mark is provided in the axis round which the disc rotates; when determining the subjective plumb-line the fixation is left free. During observations with one eye the other eye is voluntarily closed.

Running from left to right in front of the subject there is an endless wire by means of which the subject may move the disc, care has thus been taken to prevent the subject from reproducing his settings by means of tactile cues.

The other side of the disc has been calibrated. By means of a closed TV circuit this calibration is reproduced at the control desk. There an observer reads and records the settings. Subject and

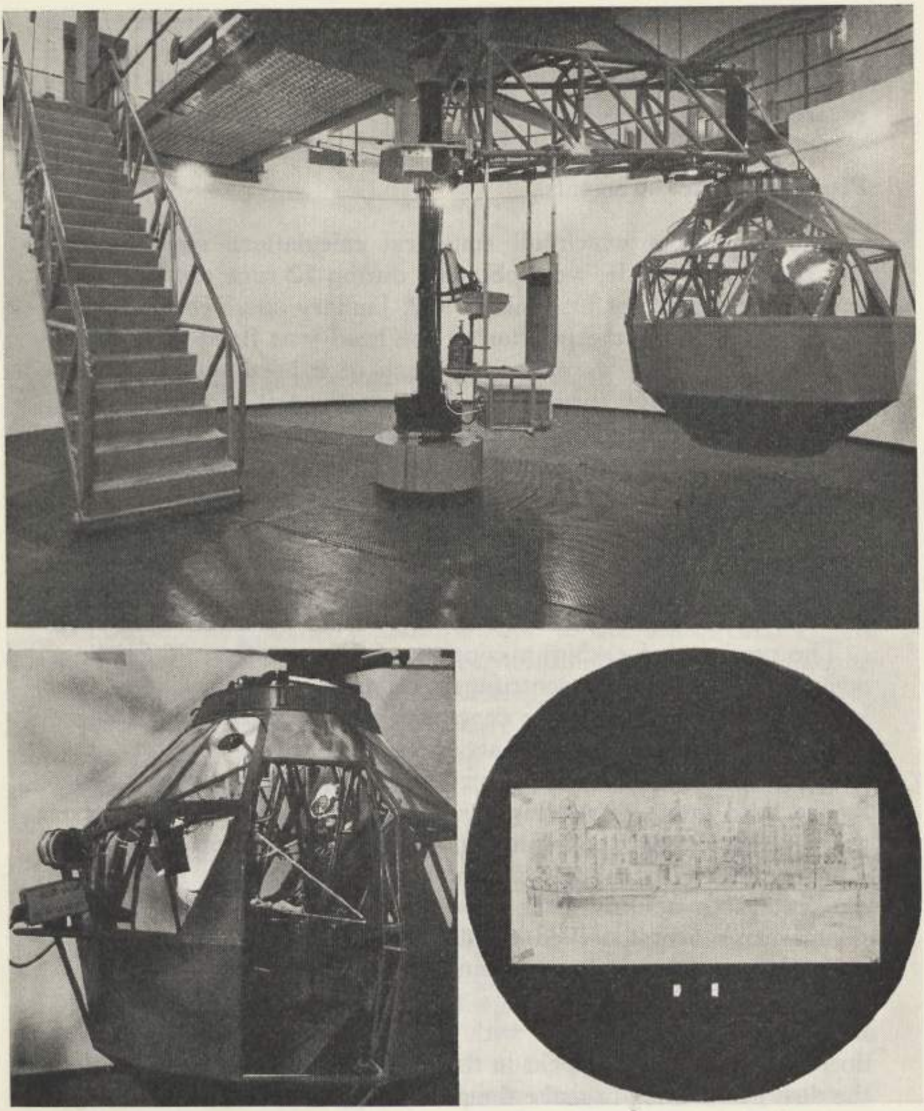


Fig. 1. APPARATUS. The staircase is hoisted out of the centrifuge pit when the centrifuge is used. In the gondola the subject is seen, wearing his mask and biting the dental impression, the fixing mechanism of which is not well visible. The subject holds the endless wire by which he can move the disc, which is shown separately. At the left (front) of the gondola is the TV camera viewing the other, white side of the disc; the calibration on this side of the disc is invisible in the reproduction.

observer can speak to each other by means of an intercom, which is normally used only by the subject to tell the observer when to take the readings, never is any information given to the subject regarding the correctness of his settings.

Program of measurements.

The data from which all statistical calculations mentioned in this thesis were made, were obtained during 72 runs on the centrifuge in the months of December 1962, January and February 1963.

During each run the position of the head was fixed by a dental impression. 8 Runs were made at each of 9 head positions, indicated by H = —60° (head tilted 60° to the left shoulder), H = —45°, H = —30°, H = —15°, H = 0° (head up), H = +15°, H = +30°, H = +45°, H = +60° (head tilted 60° to the right shoulder).

On one day up to 4 or 5 runs could be made, between the runs the head position was changed by 15° steps, either increasing or decreasing the angle of tilt, or by 30° steps moving from left to right or vice versa. No irregular sequences of head positions were used.

The program of each run consists of 5 parts: first 20 readings were taken while the centrifuge remained stationary, this part is indicated by $1g_1$; next the centrifuge was accelerated to a speed at which the resultant force acting on the head was 1,5g, again 20 readings were taken, indicated by $1{,}5g_1$; after acceleration to 2g the third group of readings, indicated 2g, was taken; thereupon the centrifuge was decelerated for a second group of readings at 1,5g (indication $1{,}5g_2$) and finally stopped for the last 20 readings (indication $1g_2$). Only after the end of the complete run was the dental impression loosened to allow the head to be moved to a different position for the next run.

For each set of 20 readings the following sequence of 4 settings was repeated 5 times: with the left eye closed the two white dots were made to disappear in the blind spot of the right eye, then the disc was rotated to make the picture appear level; next the right eye was closed, the white dots were made to disappear in the left eye's blind spot, and the picture was set again to make a level impression upon the left eye.

During each run thus 5 × 20 = 100 readings were taken, and for each head position (8 runs) 8 × 100 = 800 readings, making a total of 9 × 800 = 7.200 readings for the full series (9 head positions).

EVALUATION OF THE OTOLITH EFFECT FROM THE COUNTERROLLING DATA.

Adaptation.

Mulder (1874) noted that after a rapid change of position of the head a considerable counterrolling of the eye occurs. Within 1 or 2 seconds the counterrolling decreases to a level on which it will remain. Mulder found his own counterrolling unchanged even after 45 minutes. This phenomenon has been confirmed by many authors.

We cannot answer the question what the effect will be of a rapid change of G, since we always changed G very slowly in order to keep the angular acceleration stimuli to the semicircular canals subliminal. That the residual counterrolling remains unchanged was proved by us for series of settings up to 4 times the length of our usual series. On this evidence we decided to pool each set of 5 measurements. The following calculations were made on the averages of these sets of 5.

Differences between the torsion of the left eye and of the right eye.

To find out whether it would be possible to demonstrate any differences in the reactions of the left eye and the right one the following calculations were made. For each part of each run the difference of the values obtained for each eye was calculated; for each group of 8 values from runs at the same head position the average difference was calculated and the standard deviation of the group. These average differences are graphically represented in fig. 2. For a group of 8 the $\pm\ \sigma$ limits of the group represent the $P = 0{,}03$ probability limits of the mean.

From these curves it is clear that neither the head position nor a change of G causes any difference in reaction between the right eye and the left one. The average value of the difference in position ($12{,}25°$) is due to the physiological angle between the line through the point of fixation and the centre of the blind spot of

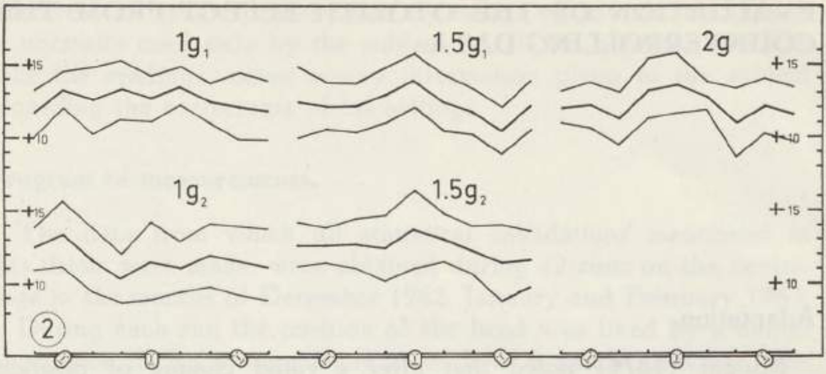


Fig. 2. OCULAR TORSION, differences of the corresponding values obtained from each eye.

the left eye and the corresponding line for the right eye.

If there is only a random difference (at least with respect to the parameters under investigation: head tilt and magnitude of G) between the values obtained from the two eyes, we may consider them to be independent estimates of the same ocular torsion. For all further calculations therefore the average of both values will be used; physiologically it indicates the bisector of the angle mentioned above.

Differences between the values at $1g_1$ and $1g_2$ and those at $1{,}5g_1$ and $1{,}5g_2$.

Similar calculations were made to investigate the differences between the values at $1g_1$ and $1g_2$ and those at $1{,}5g_1$ and $1{,}5g_2$. The results are similarly represented in fig. 3.

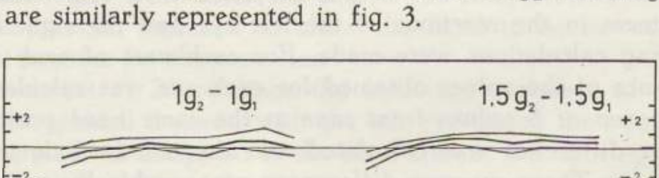


Fig. 3. OCULAR TORSION, differences of the corresponding values obtained at the beginning and at the end of each run.

Following the same line of reasoning as above we further pooled all values at 1g and also all values at 1,5g.

For each of the 72 runs these manipulations leave us with only

3 values instead of the original number of 50 readings. The variance between the runs (in groups of 8) is reduced from an average of 1,78 ($1g_1$) to 3,00 (2g) to an average of 0,95 (1g) to 2,18 (2g).

Representation of the data.

The reduced data are graphically represented in fig. 4.

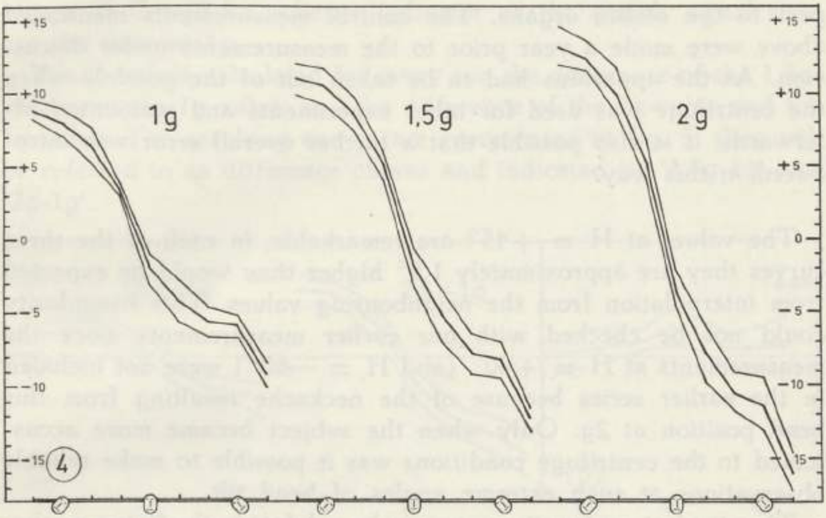


Fig. 4. COUNTERROLLING, the curves obtained at 1g, at 1,5g and at 2g.

The 1g-curve is seen to have the well known S-shape; the increase in counterrolling produced by a 15° increase in head tilt decreases as the head tilt increases. The curves for 1,5g and 2g have the same general shape, but are definitely steeper, and reach values of counterrolling that are never reached at 1g.

Considering the overall shape of the curves, each curve appears to be symmetrical not around $H = 0°$, but rather around $H = —7{,}5°$. Part at least of this lack of symmetry can be explained.

In an earlier part of this study measurements were carried out which made it clear that the gondola does not adjust itself exactly to the apparent gravitational force. Because of mechanical imperfections there is a 2° difference between the position of the gondola and the direction of the apparent gravitational force at the position of the head.

It was also found that the head positions as measured from a line through the outer canthi of the eyes fall short approximately

3° of the indications at the dental impression. The figures are based on the indications on the dental impression. The above mentioned errors cause the apparent gravitational force to be perpendicular to the line through the outer canthi at $H = -5°$, instead of at $H = 0°$.

A further 2,5° difference could be due to the fact that the line through the outer canthi is not necessarily symmetrical with respect to the otolith organs. The control measurements mentioned above were made a year prior to the measurements under discussion. As the apparatus had to be taken out of the gondola when the centrifuge was used for other experiments and remounted afterwards, it is also possible that a further overall error was introduced in this way.

The values at $H = +45°$ are remarkable, in each of the three curves they are approximately 1,5° higher than would be expected from interpolation from the neighbouring values. This irregularity could not be checked with our earlier measurements since the measurements at $H = +60°$ (and $H = -60°$) were not included in the earlier series because of the neckache resulting from this head position at 2g. Only when the subject became more accustomed to the centrifuge conditions was it possible to make reliable observations at such extreme angles of head tilt.

The simplest explanation seems to be a defect in the fixing mechanism of the dental impression, either at $H = +45°$ or at $H = +60°$. Such a defect was not found in the control measurements mentioned above, but may have been introduced later. If the actual head positions were either $H = +46,5°$ or $H = +57°$ the irregularity would be explainable. That the irregularity is hardly apparent in the difference curves '1,5g-1g' and '2g-1g' favours this explanation.

Elimination of non-otolith effects.

Since the eyes cannot be rotated through any angle, the question is justified whether the flattening of the counterrolling curves at larger angles of head tilt is due to mechanical limitations. The fact that the 2g-curve bends only at counterrolling values that are never reached by the 1g-curve, makes it clear that the shape of the curves is not dependent upon the motor mechanism effecting the ocular torsion. The fact that all curves do bend at the same head tilt values confirms our hypothesis that the shape of the curves must be the expression of certain characteristics of the receptor system governing the ocular torsion.

It has been noted already that Fischer concluded from his experiments that the part of the counterrolling that is due to neck reflexes is not influenced by the tension of the neck muscles. If this is true an increase of G will not influence the neck reflexes and therefore the *increase* of the counterrolling caused by an *increase* of G will be a better indicator of the otolith signal than are the data at 1g.

We therefore calculated for every run the difference of the 1,5g-value and the 1g-value, and the difference of the 2g-value and the 1g-value. The resulting curves are represented in fig. 5, they will be referred to as difference curves and indicated by '1,5g-1g' and '2g-1g'.

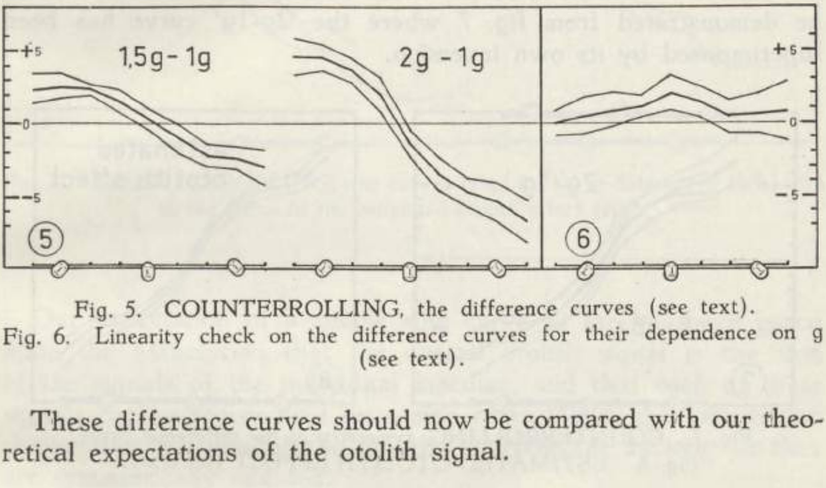


Fig. 5. COUNTERROLLING, the difference curves (see text).
Fig. 6. Linearity check on the difference curves for their dependence on g (see text).

These difference curves should now be compared with our theoretical expectations of the otolith signal.

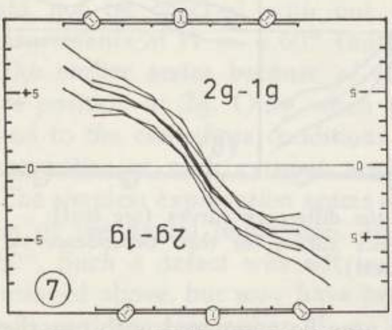
Dependence on the magnitude of G.

The shearing force of the otolith is directly proportional to the magnitude of G. If our hypothesis is correct we must expect all '2g-1g' values to be twice as large as the corresponding '1,5g-1g' values. To test this hypothesis we calculated for every run the difference between the expected '2g-1g' value (twice '1,5g-1g') and the value that was actually found. The results of these calculations are represented in fig. 6. This way of calculating doubles the effect of any deviation occurring in the 1g-values or in the 1,5g-values, yet an average difference of only 0,87° results. This amount is always positive, but hardly exceeds its standard error; if it is significant it means that less dextro-torsion (i.e. more counterrolling with head tilt to the left, less counterrolling with head tilt to the right) is found at 2g than would be expected.

We must conclude that as far as the dependence on the magnitude of G is concerned, the congruence between our data and the theoretical expectation is as satisfactory as could reasonably be expected for biological data.

Dependence on the angle of head tilt.

The theoretical curve that depicts the dependence of the otolith signal on the angle of head tilt, is necessarily symmetrical; it is no use checking it to the asymmetrical irregularities of our data. Our data curves are largely symmetrical (provided that the centre of symmetry is taken at $H = -7{,}5^{\circ}$ as mentioned before) as can be demonstrated from fig. 7 where the '2g-1g' curve has been superimposed by its own inversion.



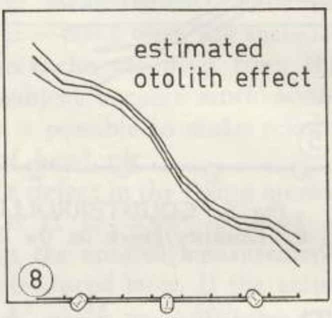


Fig. 7. COUNTERROLLING, symmetry of the difference curve.
Fig. 8. ESTIMATED OTOLITH EFFECT (see text).

Calculating the average of the curves given in fig. 7 we obtain a symmetrical curve, which is represented in fig. 8. The probability limits of this curve have been narrowed as it is based on 16 values for each head position (except the extremes) instead of 8. The probability limits given in this case are the $P = 0{,}05$ limits of the mean. This curve represents the *best estimate of the otolith effect* that can be obtained from our data.

The theoretical curve.

Fig. 9 (in which the data curves are indicated by their probability limits only) clearly demonstrates that the approximation given by a simple sine curve is much better for the latter curve than it is for the 1g-curve. Yet the fact remains that the fit is not complete, we have to compromise between a sine curve that fits in with the extreme values and a sine curve that fits in with the slope of the central part of the data curve. Can this fit be further improved?

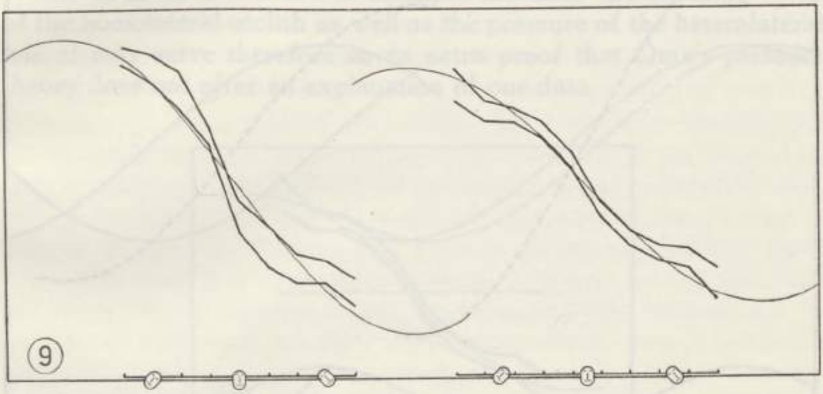


Fig. 9. COUNTERROLLING, sine curves fitted to the 1g-data curve (left) and to the curve of the estimated otolith effect (right).

Our expectation of a simple sine curve so far has been based upon the assumption that the overall otolith signal is the sum of the signals of the individual maculae, and that each of these signals can be represented by a sine curve. With this assumption the relative position of the otoliths is irrelevant as long as they are symmetrically situated.

Animal experiments (Ulrich, Löwenstein) have given good reasons, however, to suppose that each macula reacts to a laterally directed shearing force of the otolith only.

If a shearing force directed medially has no effect the resulting signal must be represented by what might be called a rectified sine. With this assumption it is important to take into consideration the relative position of the different maculae. The effect on the sum of the signals is demonstrated in fig. 10 for the utricular maculae and for the saccular maculae. Quix (1933) gives values of 8° and 42° for the angle between the plane of the anterior parts of these maculae and the transversal plane of the head. For simplicity in the calculations we used the values 7,5° and 45°.

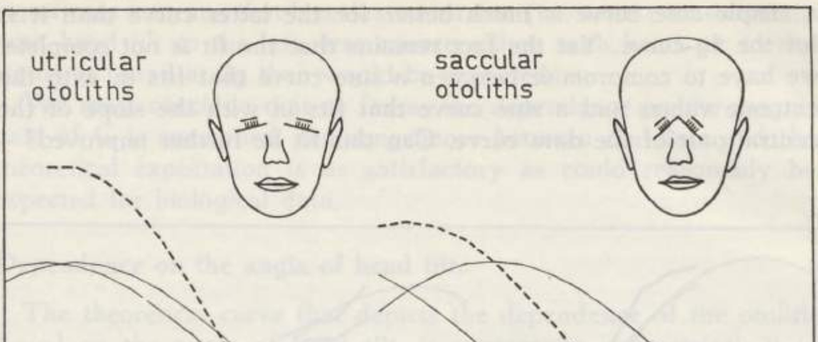


Fig. 10. OTOLITH SIGNAL, the predicted signal from each pair of maculae, on the assumption that the shearing force is active in both directions (upper curves) or in a lateral direction only (lower curves).

These curves represent the *best prediction of the otolith signal* that can be made on the basis of experimental evidence gathered from a wide diversity of sources, the validity of which we wanted to be tested in man.

Conclusions on the otolith signal.

Comparing the predicted curve of the otolith signal (fig. 10) with the deducted curve of the otolith effect (fig. 8), the congruence is seen to be excellent (fig. 11).

The excellence of this fit establishes the correctness of our assumptions.

The theoretical curve for the saccular maculae does not fit in with our data. Nor can the fit of the utricular curve be improved upon by adding to it a fraction of the saccular curve. It is generally believed today that the role of the saccular maculae is negligible; however suspicious one should be about such opinions, this one seems to be warranted by our data.

The saccular curve in our example indicates the shearing force of the homolateral otolith as well as the pressure of the heterolateral one, it may serve therefore as an extra proof that Quix's pressure theory does not offer an explanation of our data.

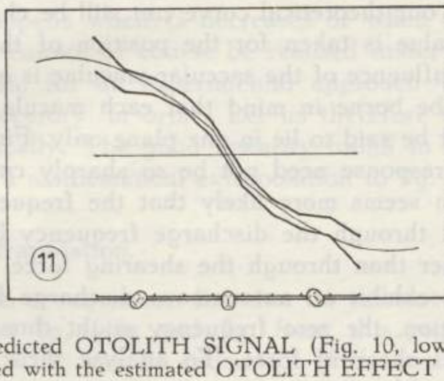


Fig. 11. The predicted OTOLITH SIGNAL (Fig. 10, lower lefthand curve) compared with the estimated OTOLITH EFFECT (Fig. 8).

Summarizing the evidence brought forward sofar we would formulate the following conclusions:

I the 'pressure theory' of otolith function is inadequate to explain our data;

II our data can be explained quantitatively by the following set of hypotheses:

1) the adequate stimulus for the otolith organ is the shearing force of the otolith along its macula, if this force is directed outward;
2) the signal generated by the utricular maculae is directly proportional to this force;
3) the overall otolith signal is the sum of the signals of both utricular maculae, provided that these signals are given opposite signs;
4) a change of this otolith signal causes a change of ocular torsion which is directly proportional to it.

Here it should be stressed again that our experiments dealt with static stimulation of the otolith organ. If some authors conclude from parallel swing experiments that the otolith organ reacts to a change-of-acceleration rather than to acceleration, this can be explained from the fact that by applying a stimulus which involves change-of-acceleration rather than acceleration, they probably studied other functional units of the otolith system.

Moreover, as our experiments were limited to the effects in the frontal plane, our conclusions are strictly valid in this plane only.

From our data we do not feel justified to draw any further conclusions concerning the otolith function.

The shape of our theoretical curve can still be changed in detail if a different value is taken for the position of the maculae and if more or less influence of the saccular maculae is assumed. Moreover, it should be borne in mind that each macula is curved and therefore cannot be said to lie in one plane only. Finally, the curve of the macular response need not be so sharply cut off as in our example; it even seems more likely that the frequency modulated signal is limited through the discharge frequency becoming practically zero rather than through the shearing force becoming zero. As the maculae exhibit an autonomous discharge frequency even without stimulation, the zero frequency might thus be reached at a slight inward shearing force. To analyse these possibilities is beyond the scope of our experiments.

EXTRAPOLATION TO 'ZERO g'.

So far we have dealt with an increase of G only; the question arises what happens when G decreases or when it becomes zero. This condition cannot of course be realised under laboratory conditions on earth, for an experimental approach we will have to wait for a laboratory 'in orbit'. Let us therefore tackle the question mathematically. The good linearity found in the range of 1g to 2g calls for a mathematical extrapolation to 0g.

Method of extrapolation.

For each run a regression line can be calculated to the ocular torsion data at 1g, 1.5g and 2g; from this regression line the ocular torsion at 0g can be estimated. If the method of the least squares is used to determine the regression line the following simple formula results:

$$\text{'0g'} = 2 \times \text{'1g'} - \text{'2g'}.$$

This formula was used to calculate from the combined data of both eyes, a 0g-value for each run.

Results.

The resulting 0g-curve is given in fig. 12.

If otolith stimulation is the only cause of counterrolling we would expect no counterrolling at zero g. It is seen that the counterrolling is definitely not zero.

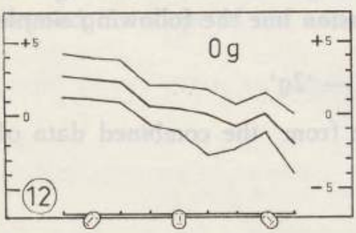
Discussion.

How can the counterrolling at 0g be accounted for? Could our calculations be at fault?

The ocular torsion data might be incorrect by systematically underestimating the counterrolling at 2g, the only way in which such a deviation could be caused would be if the dental impression gave way under the increased weight of the tilted head. Control runs were made to measure this effect, no measurable effect could be found.

The G data might be at fault. If the 2g level were really only 1,7g the 0g-curve would be flattened. We were not in a position to be able to measure the actual G force at the position of the head. The centrifuge is regulated on the readings of the velocity of rotation of the driving axis; from the number of r.p.m. the resultant G force was calculated. No possible sources of error could be thought of to explain such a large difference between the calculated and the real G force.

Finally, the supposed linearity might be incorrect. It is not unusual for physiological systems to give a linear response over a limited range, but to become saturated as the stimulus increases. In our case such saturation could only be expected at larger angles of head tilt, for the range of H = —15° to H = +15° (where the magnitude of the shearing force at 2g does not exceed the 1g-values for the range of H = —30° to H = +30°) good linearity should be expected. Yet here too the 0g-curve shows a marked slope.



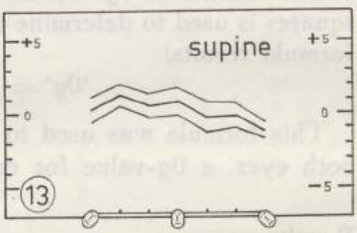


Fig. 12. COUNTERROLLING, extrapolated to 0g.

Fig. 13. COUNTERROLLING, in supine position.

Conclusions.

So we are led to the conclusion that the 0g-curve does indeed represent a physiological phenomenon. It looks obvious that it represents that part of the counterrolling which Fischer attributed to neck reflexes. Yet, we decided to do some further experiments to check this hypothesis.

EXPERIMENTS ON THE INFLUENCE OF NECK REFLEXES.

The gondola of the centrifuge of the N.L.G.C. is not large enough to allow experiments where the position of the head is constant while the position of the trunk is varied. The following experiments had to be made outside the centrifuge and could therefore be made at 1g only; they thus lack the essential extra information that can be obtained by varying the magnitude of G.

Experiments in supine position.

A series of measurements was made with the subject in supine position on a stretcher, the head's position was shifted towards the right shoulder and towards the left one and fixed by the same dental impression as used on the centrifuge. Ocular torsion readings were made on the same disc now mounted horizontally over the subject.

In this position it is expected that counterrolling due to neck reflexes will present itself, whereas the gravitational force will not cause any counterrolling.

From fig. 13 it is seen that counterrolling does indeed occur under these conditions and that it is slightly less than that under calculated 0g-conditions.

Tilt table experiments.

Another series of measurements was made on a tilt table. The subject lay down on his side with the head fixed in the $H = 0^\circ$ position, the stretcher with the subject could then be moved to a nearly vertical position or to a position that was 20° past the horizontal. For tilt to the right the subject was positioned on his right side, for tilt to the left on his left side; in a strictly vertical position the stretcher was not quite stable. The measurements are thus divided in two groups which are not linked up.

In these measurements the effect of the neck reflexes is expected to be negligible, but the otolith effect will be present, now supplemented by the influence, if any, of such receptors of the body as can supply positional information (proprioceptive information from muscles and joints, tactile information from the skin).

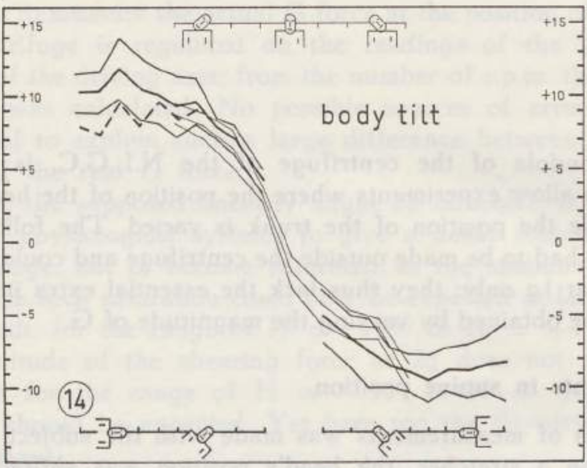


Fig. 14. COUNTERROLLING and body tilt (heavy lines). Also, counterrolling and head tilt at 1g (thin lines), and counterrolling and body tilt with little support of the head (broken line).

The results are given in fig. 14 to which the 1g-curve of the centrifuge data has been added. Also have been added the results of a trial series in which the head was supported by the dental impression only; as this gave rise to neckache in the nearly horizontal positions the space between head and stretcher was later filled with a stiff pillow.

Discussion.

The difference between the curves made with and without a pillow is probably without significance. If any conclusion is to be attached to it, it must be that Fischer was right in claiming that an increase of the tension of the muscles of the neck does not cause an increase of ocular torsion. In our case it is accompanied by a decrease of ocular torsion.

More important is the close approximation between the head tilt curve and the body tilt curve. Fischer made similar experiments, and found that body tilt produced less counterrolling than did head tilt, and that the difference was equal to the amount of counterrolling produced by bending of the neck only. In our data this difference evidently does not exist. We therefore favour the hypothesis that the amount of counterrolling that is not dependent upon the otolith organ, is dependent upon the impression one has formed about one's spatial position. This impression in turn is dependent upon all non-otolithical information available, whether it be from the receptors of the neck or from receptors of the body. Fischer had his subjects fixed in a well-padded wooden case; perhaps the uncommonly gentle support reduced the positional information from those receptors of the body that are usually stimulated in an oblique position, thus likewise reducing the resultant counterrolling.

Conclusions on the counterrolling of the eye.

We have seen that an important part of the counterrolling of the eye is dependent on and directly proportional to the otolith signal.

Our data further led us to conclude that the otolith signal does not explain all counterrolling. The remaining counterrolling is dependent upon the spatial position of the body and head. From our data it is not possible to identify more exactly the receptors involved.

The question what happens when these receptors are subjected to an increase of G, can be answered in the negative for the conditions of our centrifuge runs, in which the receptors of the body were stimulated symmetrically. It is highly improbable that the effect would be so exactly similar to the effect of the utricular maculae, not to spoil the fit of our curves. We cannot predict the effect of asymmetrical stimulation of these receptors as used in the experiments of Woellner and Graybiel.

More data on this point and on points concerning the interaction of the otolith organs from each side can be expected from centrifuge experiments on persons who have lost the function or part of the function of one or of both labyrinths. Such persons are rare, and rarer still is their willingness and ability to participate in the tiresome centrifuge experiments. We have not been lucky enough to meet such a person.

THE DATA ON THE SUBJECTIVE PLUMB-LINE.

Introduction.

We now proceed to an evaluation of the data obtained from our measurements of the subjective plumb-line. Our investigation of the counterrolling of the eye started with a well defined concept of the underlying mechanisms. The arrangement of our experiments and the treatment of our data could be based on this concept, thus creating the foundations for a quantitative analysis.

For the evaluation of the subjective localisation a similar concept is lacking. Consequently this section will be seen to yield conclusions of a qualitative nature only, some of which may be suited to form a basis for a future quantitative analysis.

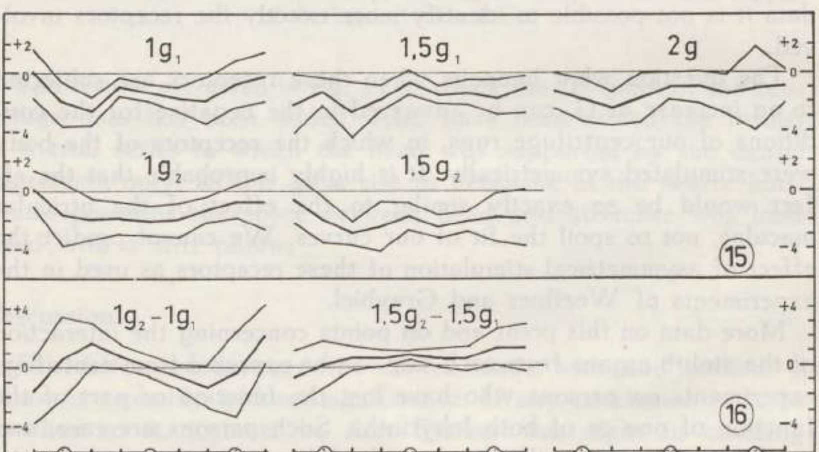


Fig. 15. SUBJECTIVE PLUMB-LINE, differences of the corresponding values obtained from each eye.

Fig. 16. SUBJECTIVE PLUMB-LINE, differences of the corresponding values obtained at the beginning and at the end of each run.

Differences between the data from the right eye and the left eye, between the data at $1g_1$ and $1g_2$ and between the data at $1{,}5g_1$ and $1{,}5g_2$.

The data on the subjective plumb-line were tested for differences between the right eye and the left one, and for differences between the first part of each run and the last one. The procedure was the same as that used on the ocular torsion data. The results are given in fig. 15 and 16.

There appears to be an average difference of 1,5° between the subjective plumb-line settings made with the right eye and those made with the left one; this value is in good accord with the 1° in-cyclophoria which the author exhibits on the synoptoscope.

We decided again to compile the readings into 3 values for each run.

Representation of the data.

The data for each of the 72 runs are given in fig. 17.

In this figure the individual values are indicated by a mark which also indicates the preceding head position. The spread is much larger than the spread among the ocular torsion data, but the larger part of this spread is seen to be due to a remaining influence of the head position of the preceding run, the random spread is more or less of the same order as that among the ocular torsion data.

This effect must be due to some process of adaptation; it appears in all parts of the run and is not influenced by a change of G, it could not be demonstrated to diminish during the time used for each run, for it is not appreciably less at $1g_2$ than at $1g_1$. Since it appears in the 2g-curve as well as in the 1g-curve it disappears in the difference curve. The mean of each group of 8 runs does not seem to be seriously disturbed by this effect, as we have taken care as much as possible to approach each head position from both sides. Yet our series seems not to be appropriate for an adequate evaluation of this effect; to this end a separate series of measurements will have to be planned.

The adequacy of the effect.

The deviations of the subjective plumb-line, as represented in fig. 17, are not very large; the largest deviations are $\pm$ 18° and

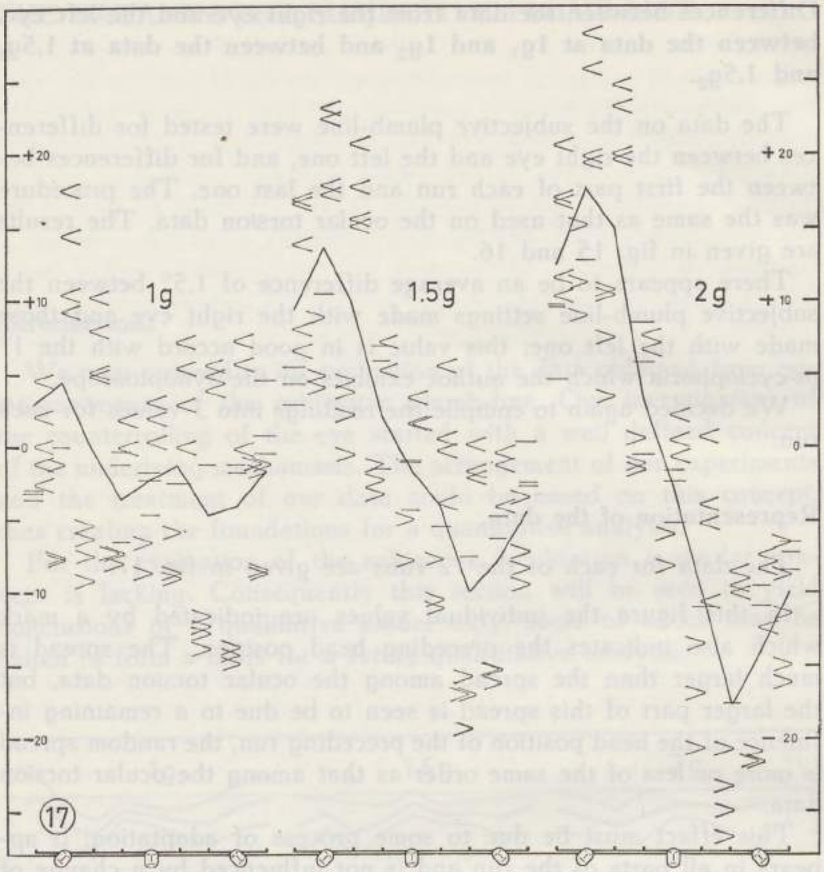


Fig. 17. SUBJECTIVE PLUMB-LINE, the data obtained at 1g, at 1,5g and at 2g. When the head position of the preceeding run was more towards the right (left) shoulder, the data are indicated < (>). Data obtained from the first run of any day are indicated —.

occur at 2g. These figures may serve to illustrate the idea behind our substituting the subjective plumb-line for the commonly used subjective vertical. At 2g the objective plumb-line in the gondola deviates 60° from the objective vertical, which is the direction of the axis of the centrifuge. Comparing the subjective vertical to the objective vertical, one should say that the least deviation found at 2g was 42°, the largest 78°; Graybiel in doing so called the effect oculogravic illusion. We prefer not to speak of an *illusion*, but of an *adequate mechanism* that adjusts the subjective plumb-line to the objective one by compensating for the angle of head tilt. At 1g this compensation is fairly accurate, at 2g the compensation is in excess of the angle of head tilt.

Retinal compensation.

The counterrolling reflex of the eyes is one way to bring about this compensation. In man (in contrast with some animals) the compensatory eye positions fall far short of the angle of head tilt to be compensated for. So man needs another mechanism to compensate for the remaining shift of the retinal image. We have coined the term *retinal compensation* for this mechanism, and have attached to it a value that at any moment *indicates which retinal meridian conveys the impression of the subjective plumb-line.*

The retinal compensation can be measured but indirectly; we have derived a retinal compensation value from each pair of two successive settings by subtracting the ocular torsion reading from the subjective plumb-line reading. We thus obtained 50 retinal compensation values for every single run, which can be reduced to 3 values (1g, 1,5g and 2g) for each run as was done for the ocular torsion and for the subjective plumb-line.

EVALUATION OF THE INTERACTION OF THE COMPENSATING MECHANISMS.

The function of the subjective localisation centre.

How does the retinal compensation originate? We would call the centre that determines the localisational value of every retinal element the subjective localisation centre.

Retinal compensation is the name we have given to the output of this centre, its input must consist of positional information from different sources. Visual psychology tells that the subjective localisation centre compensates for voluntarily assumed eye positions, but that it does not for passively induced ones. In other words, information about voluntarily assumed eye positions is part of its input, information about passively induced eye positions is not.

The first question to be answered in our case is whether information about reflex ocular torsion is a part of its input or whether it is not. If it is, we expect the centre to compensate a change of the ocular torsion by an opposite change of the retinal compensation, thus stabilizing the subjective plumb-line.

If the centre does not compensate for changes of the ocular torsion a change of the ocular torsion will result in a change of the subjective plumb-line, consequently a positive association is expected to be found between the ocular torsion values and the subjective plumb-line values. If the centre compensates its output for changes of the ocular torsion such an association between the ocular torsion values and the subjective plumb-line values is not likely to appear.

Between the ocular torsion values and the retinal compensation values a negative association exists due to the fact that we calculated the retinal compensation values by subtracting the ocular torsion values from the subjective plumb-line values. A positive association, however, may be expected from the fact that the otolith signal which dominantly determines the ocular torsion probably is also a part of the input of the subjective localisation centre. If this centre counterbalances a change of the ocular torsion by a change of the retinal compensation, a third association is introduced, which is negative. As a result we cannot predict the association to appear between the ocular torsion values and the retinal compensation values. If the subjective localisation centre does not take into account the ocular torsion, the last cause of negative association is lacking; we therefore have a better chance to find a positive association between the ocular torsion values and the retinal compensation values.

From these considerations it follows that the associations mentioned above may give us an indication as to the way in which the subjective localisation centre functions.

To determine whether an association exists we can calculate either the coefficient of correlation or the co-variance of the two quantities concerned. When two quantities are variable independently of each other the variance of their sum (difference) will be equal to the sum of their individual variances (variance is the squared standard deviation). When two quantities are associated their co-variance is half the amount by which the variance of their sum (difference) exceeds (falls short of) the sum of their individual variances. The co-variance is positive (negative) if the coefficient of correlation is positive (negative), i.e. if an increase of one quantity is accompanied by an increase (decrease) of the other one. So, for instance, if a positive correlation exists between the ocular torsion values and the subjective plumb-line values the variance of their differences (the retinal compensation values) must be less than the sum of their individual variances.

Variance between the measurements.

Applying this test to our data we calculated the variance within each set of five individual measurements for each quantity (ocular torsion, subjective plumb-line and retinal compensation) for each part ($1g_1$, $1{,}5g_1$, $2g$, $1{,}5g_2$ and $1g_2$) of each run (9 head positions, each 8 times) and for each eye.

To avoid an overcrowding of notations we have given in fig. 18 the average values of these variances, once grouped according to the head position and once grouped according to the part of the run.

No correlation appears to exist between the ocular torsion measurements and the subjective plumb-line measurements. Are we to

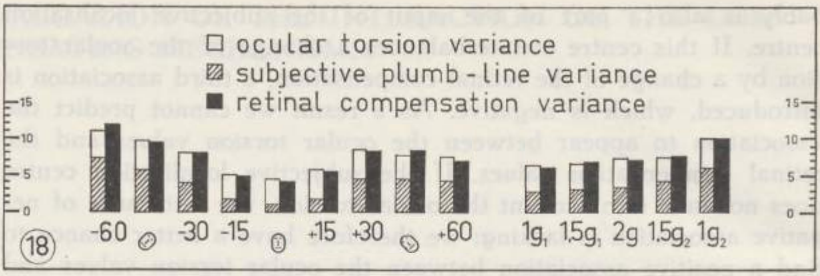


Fig. 18. AVERAGE VARIANCE, within the sets of 5 measurements.

conclude from this evidence that the subjective localisation centre does compensate for changes of the ocular torsion?

Before jumping at conclusions let us consider the question more closely. What are the possible sources of the variance among the ocular torsion readings? These readings could be:

1) exact measurements of an unstable ocular torsion;
2) inexact measurements of a stable torsion;
3) inexact measurements of an unstable torsion.

If the measurements are exact, the ocular torsion itself must be variable. That of its variance nothing is reflected in the variance of the subjective plumb-line settings must indicate one of two things: either the subjective localisation centre compensates for variations of the ocular torsion, and does so very exactly indeed, or the variations of the ocular torsion are so swift that they have no influence on the next setting. Such swift variations could well be due to rotary movements of fixation on the disc while it is moved to and fro prior to each setting.

Such movements of fixation would certainly affect the subjective plumb-line settings too. At $H = 0°$, however, the accuracy of the subjective plumb-line settings is much better than that of the ocular torsion settings. Movements of fixation could therefore at best explain a small part of the variance, but cannot account for the lack of co-variance.

If the variance of the ocular torsion settings is not due to variance of the ocular torsion itself, but to the inadequacy of our method for determining the ocular torsion, it is quite clear that the subjective plumb-line settings are not influenced by it. In this case no conclusions should be drawn with regard to the way in which the subjective localisation centre functions, because the variance has no bearing on the function of this centre.

Variance between the runs.

The comparison of the variances within each group of 5 individual measurements has not provided an answer to our question. Perhaps an evaluation of the variance between these groups will give us a better insight. All our data can be divided into sets of 8 runs, the runs of each set of 8 were made on different days, but were otherwise comparable.

Consequently we calculated the average of each set of 5 measurements and the variance between the runs for each set of 8 averages. Having done so for each quantity, for each part of the runs at each head position and for each eye, we again reduced our abundance of numbers, grouping them according to head position and according to the part of the run. The graphical representation of the average variances is given in fig. 19.

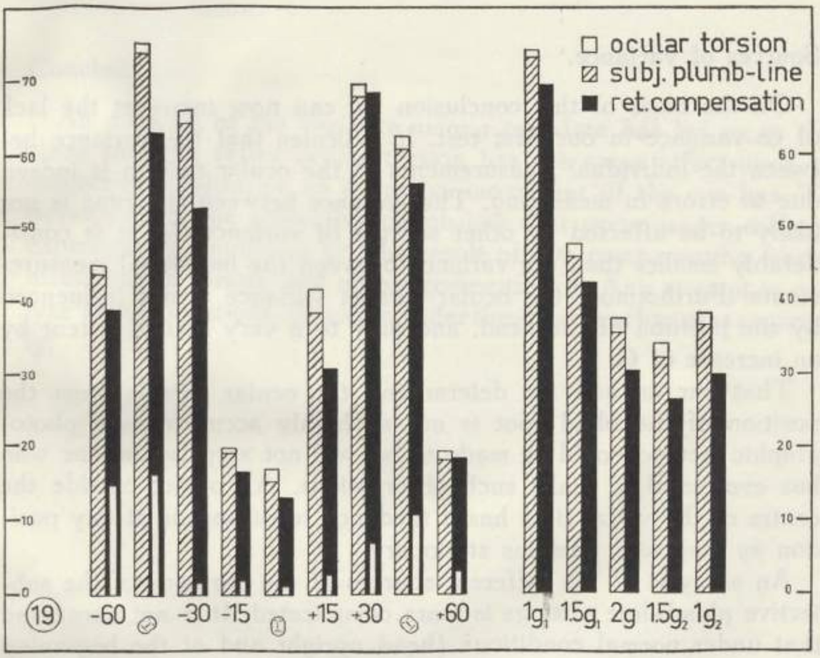


Fig. 19. AVERAGE VARIANCE, between the data from 8 corresponding runs. The small white column within the black column indicates the average variance of the difference values '2g-1g' of the retinal compensation.

From these values definite correlations become evident. The day-to-day variance of the retinal compensation is considerably smaller than that of the subjective plumb-line, thus establishing a positive correlation between the subjective plumb-line and the ocular torsion. Such a correlation was seen to be characteristic for a subjective localisation centre which does not take into account the existing amount of ocular torsion.

If the centre functions in this way we also expect to find a positive correlation between the ocular torsion and the retinal compensation; this expectation comes true also: in most instances the variance of the subjective plumb-line is seen to exceed the sum of the other two variances. This correlation indicates that the positional information which effects the ocular torsion has at the same time been used to regulate the retinal compensation; it does not mean that this information has been made use of in the same way, neither that a simple proportionality between ocular torsion and retinal compensation should exist.

Sources of variance.

On the basis of this conclusion we can now interpret the lack of co-variance in our first test. It indicates that the variance between the individual measurements of the ocular torsion is indeed due to errors in measuring. The variance between the runs is not likely to be affected by other sources of variance, for it is considerably smaller than the variance between the individual measurements. Furthermore the ocular torsion variance is not influenced by the position of the head, and only to a very limited extent by an increase of G.

That our method for determining the ocular torsion from the position of the blind spot is not so highly accurate as a photographic method could be made to be, will not surprise anyone who has ever tried to make such observations. An object outside the centre of the visual field has a tendency to disappear at any position as long as it remains stationary.

An analysis of the different sources of the variance of the subjective plumb-line settings is more complicated. It is not surprising that under normal conditions (head upright and at the beginning of each run) a great precision can be obtained in these settings in which a large part of the retina — including the macular region — is involved. Under these conditions the accuracy of the subjective plumb-line settings is higher than that of the ocular torsion settings. When the head is tilted the accuracy in the determination of the blind spot does not suffer; but the accuracy of the subjective plumb-line settings considerably deteriorates when more retinal compensation is required.

The adaptational mechanism that was described already causes the variance between the runs to be incomparably larger than the variance between the individual measurements. This effect makes it impossible to interpret the increase in the variance between the measurements occurring in going from $1g_1$ to $1g_2$, while the variance between the runs decreases in the same order.

No attempt has been made to give a complete analysis of the variance of our data, for we feel that little will be gained as long as the influence of the adaptational mechanism is not better known. For a better understanding of this mechanism a separate series of experiments is needed. The variance of the difference curve '2g-1g' of the retinal compensation is added in fig. 19 to indicate how much the variance can be reduced by the elimination of the adaptational factor.

Conclusions.

An analysis of the variance among our data has led us to conclude that the reflex ocular torsion has the same effect upon the subjective localisation as a passive movement of the eye has. The deviations of the subjective plumb-line that occur under different experimental conditions are the result of two compensating mechanisms: ocular torsion and retinal compensation. Any attempt to analyse these deviations should consider these two mechanisms separately.

EVALUATION OF THE DATA ON THE RETINAL COMPENSATION.

Representation of the data.

In determining the subjective plumb-line we determine the sum of two separate effects. One of these effects — the counterrolling of the eye — has been analysed, for a further analysis of the subjective localisation in the frontal plane we must now turn our attention to the retinal compensation.

The data on the retinal compensation have been represented in the usual way in fig. 20. Comparing this figure with other figures of this text one should note that the vertical scale has been reduced to 1/5 of that of the other figures.

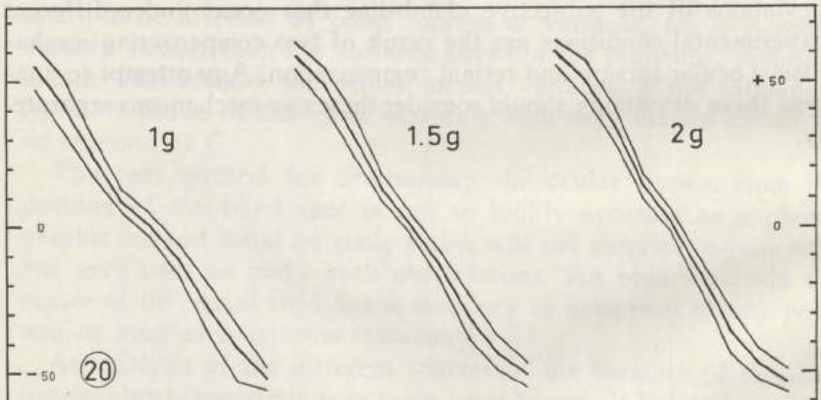


Fig. 20. RETINAL COMPENSATION, the curves obtained at 1g, at 1,5g and at 2g.

The general shape of all three curves greatly differs from that of the counterrolling curves, they all resemble a straight line rather than a sine curve.

Estimating the otolith effect.

The calculating of difference curves for '1,5g-1g' and for '2g-1g' served well to extract the otolith effect from our ocular torsion data. We decided to do the same calculating for our retinal compensation data. The result is given in fig. 21 together with the check for linearity in the dependence on the magnitude of G.

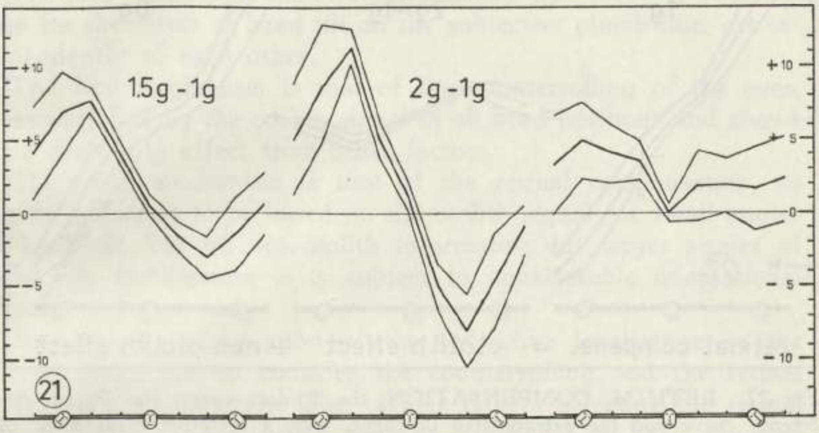


Fig. 21. RETINAL COMPENSATION, the difference curves and the linearity check for their dependence on g.

It is seen that in the range of H = —30° to H = +30° the retinal compensation is dependent upon the angle of head tilt and the magnitude of G in about the same way as was found for the ocular torsion. The relation is less exact as far as the magnitude of G is concerned.

When the angle of head tilt becomes larger than 30°, however, the effect of an increase of G rapidly diminishes and evidently tends to disappear. If we attribute the effect of an increase of G to the otolith system, this finding must indicate that the otolith system guides the retinal compensation in the region of the nearly normal head positions, but that with larger angles of head tilt its influence disappears.

Estimating the non-otolith effect.

To estimate the non-otolith effect from the ocular torsion data, we extrapolated to 0g conditions. In the case of the retinal compensation data we are, strictly speaking, not allowed to do so, because the linearity check did not indicate the degree of linearity found in the ocular torsion data. None the less we have ventured to extrapolate, the results are given in fig. 22.

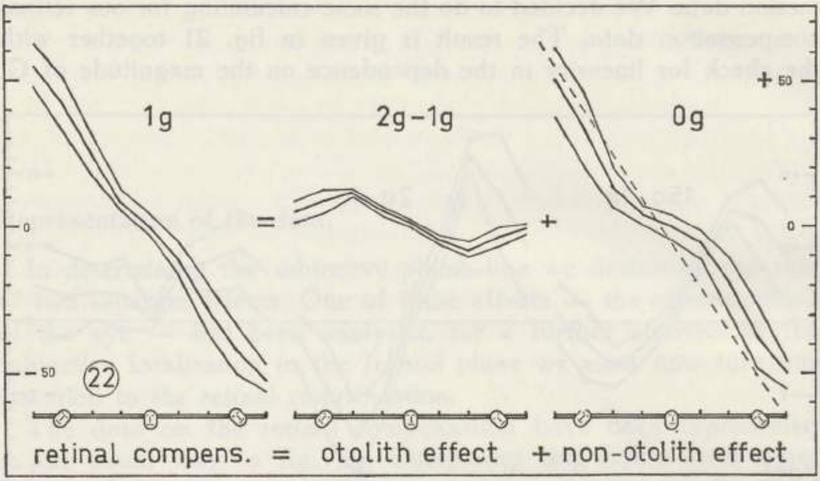


Fig. 22. RETINAL COMPENSATION, the 1g-data curve, the '2g-1g' difference curve and the extrapolated 0g-curve, with a tentative explanation of their meaning.

The curve is seen to be almost flat for the range of $H = -15°$ to $H = +15°$, outside this range it gets steeper to become almost parallel to the line which indicates full compensation for the angle of head tilt. If we attribute the 0g-curve to the effect of positional receptors other than the otoliths, it follows that in the region of the nearly normal head positions these receptors have hardly any influence on the retinal compensation.

When the angle of head tilt increases the influence of these receptors increases to the point where they cause full compensation for the angle of head tilt.

So the subjective localisation centre under all circumstances seems to work on the best positional information available. For small angles of head tilt the otolith signal is a very sensitive indicator, but for larger angles of head tilt it becomes less sensitive; at nearly horizontal positions of the head its sensitivity to small differences in position is expected to be almost nil. The sensitivity of the proprioceptive information from muscles and joints seems not to depend upon position; at larger angles of head tilt this source of information must surpass the otolith signal in sensitivity.

Final conclusions.

This study has quantitatively confirmed the validity of our hypotheses on the function of the otolith organ, which is excellently suited to indicate moderate deviations from the normal head positions, but whose sensitivity decreases as the angle of head tilt increases.

We also found that the two mechanisms, that serve to compensate for the effect of head tilt on the subjective plumb-line, act independently of each other.

The first mechanism is that of the counterrolling of the eyes, it is controlled by the otolith signal in all head positions and shows little disturbing effect from other factors.

The other mechanism is that of the retinal compensation, its regulation seems to be based on the otolith signal for small angles of head tilt, but on non-otolith information for larger angles of head tilt, furthermore it is subject to considerable adaptational effects.

Any future investigation of the subjective localisation in the frontal plane has to consider the counterrolling and the retinal compensation separately. The various factors affecting the retinal compensation ask for further analysis in which a tilt chair mounted on a human centrifuge will prove to be a powerful tool in distinguishing otolith effects from non-otolith effects.

SUMMARY.

The question how the otolith organ is made to react to the gravitational force has long been a controversial subject.

Recently the matter seems to have been decided in favour of the oldest theory, which stated that a sliding movement of the otoliths provides the adequate stimulus. Ample evidence has been provided by animal experiments, both directly through observation and manipulation of the otoliths, and indirectly through the study of freely moving fishes on a centrifuge (Von Holst). Quantitative evidence in man was still lacking.

Dynamic stimulation is not appropriate to test the static function of the otolith organ, the only adequate test stimulus is the apparent gravitational force (G) on the human centrifuge. The counterrolling of the eye may serve as an indication of the otolith signal if the effect of other receptors is eliminated; this can be done by relating the increase of counterrolling to the increase of G. In this way a simple linear proportionality could be demonstrated between the outward shearing force of the otoliths on the utricular maculae and the counterrolling response. Up to 60° of head tilt and up to 2g no departures from this simple rule were found.

The second part of this study deals with the subjective localisation in the frontal plane. It is argued why the direction which is determined should be called the subjective plumb-line rather than the subjective vertical. The term retinal compensation is introduced to indicate which retinal meridian conveys the impression of the subjective plumb-line.

From an analysis of the variance among the data it could be shown that the retinal compensation is not influenced by the ocular torsion. The effect of the counterrolling reflex on the subjective localisation is similar to that of a passively induced movement of the eye.

In a study of the subjective localisation in the frontal plane the effects of counterrolling and retinal compensation should therefore be taken into account separately.

In doing so and in applying the tests for otolith and non-otolith influence developed in the first part of our study we found that the retinal compensation — apart from an important influence of the preceding head position — seems to be based on the otolith signal for small angles of head tilt and on non-otolith information for larger angles of head tilt.

REFERENCES.

AUBERT, H. (1861) Eine scheinbare bedeutende Drehung von Objecten bei Neigung des Kopfes nach rechts oder links.
Virchows Arch., **20**, 381-393.

BÁRÁNY, R. (1906) Über die vom Ohrlabyrinth ausgelöste Gegenrollung der Augen bei Normalhörenden, Ohrenkranken und Taubstummen.
Arch.Ohr.-Nas.-KehlkHeilk., **68**, 1-30.

BREUER, J. (1874) Über die Funktion der Bogengänge des Ohrlabyrinthes.
Med. Jahrb. öst. Staates, **1874**.

COLENBRANDER, A. (1963) The influence of G-forces on the counterrolling of the eye.
Ophthalmologica, **146**, 309-313.

CRUM BROWN, A. (1874) On the sense of rotation and the anatomy and physiology of the semicircular canals of the internal ear.
J. Anat. Physiol., **8**, 327.

DONDERS, F. C. (1846) Physiologische en pathologische aanteekeningen van gemengden aard; IV. De bewegingen van het menschelijk oog.
Ned. Lancet, **1846-1847**, 104-138.
—(1846) Beitrag zur Lehre von den Bewegungen des menschlichen Auges.
Holländ. Beitr. anat. physiol. Wiss., **1**, 105-145, 384-454.
—(1875) Über das Gesetz der Lage der Netzhaut in Beziehung zu der Blickebene.
Graefes Arch. Ophthal., **21**, 125-130.

FISCHER, M. H. (1927) Messende Untersuchungen über die Gegenrollung der Augen und die Lokalisation des scheinbaren Vertikalen bei seitlicher Neigung.
I. Mitteilung, Neigungen bis zu 40°.
Graefes Arch. Ophthal., **118**, 633-680.
—(1930) II. Mitteilung, Untersuchungen an Normalen, Neigungen bis zu 360°.
Graefes Arch. Ophthal., **123**, 476-508.
—(1930) III. Mitteilung, Untersuchungen an einem Ertaubten mit Funktionsuntüchtigkeit beider Vestibularapparate und einem einseitig Labyrinthlosen.
Graefes Arch. Ophthal., **123**, 509-531.

GOLLAS, E. (1936) Untersuchungen der Raddrehung der Augen bei einseitigem Labyrinthausfall.
Arch.Ohr.-Nas.-KehlkHeilk., **140**, 340-354.

GRAYBIEL, A. (1952) Oculogravic illusion.
Arch. Ophthal., Chicago, **48**, 605-612.

HELMHOLTZ, H. VON (1867) *Handbuch der Physiologischen Optik*, Leipzig, 1867, p. 528.
2nd ed. Leipzig, 1896, p. 669; (this edition was revised by Von Helmholtz up to p. 640, after p. 640 by König).

HOLST, E. VON (1950) Die Tätigkeit des Statolithenapparats im Wirbeltierlabyrinth.
Naturwissenschaften, **37**, 265-272.
Die Arbeitsweise des Statolithenapparats bei Fischen.
Z. vergl. Physiol., **32**, 60-120.

HUNTER, J. (1786) The use of the oblique muscles, in *Observations on certain parts of the animal oeconomy*, London, 1786.
3rd ed. p. 274-276 (1837).

JONGKEES, L. B. W., GROEN, J. J. (1950) A quantitative analysis of the reactions of a person after loss of the function of both inner ears.
J. Laryng., **64**, 135-140.

LÖWENSTEIN, O., ROBERTS, T. D. M. (1949) The equilibrium function of the otolith organs of the thornback ray.
J. Physiol., London, **110**, 392-415.

MACH, E. (1875) *Grundlinien der Lehre von den Bewegungsempfindungen*, Leipzig, 1875.

MAGNUS, R. (1924) *Körperstellung*, Berlin, 1924.

MILLER, E. F. (1962) Counterrolling of the human eyes produced by head tilt with respect to gravity.
Acta oto-laryng., Stockh., **54**, 479-501.

MULDER, M. E. (1874) Over parallelle rolbewegingen der oogen.
Diss., Utrecht, 1874.
Über parallele Rollbewegungen der Augen.
Graefes Arch. Ophthal., **21**, 68-124.

OPFER, P. H. (1933) Untersuchungen über die Raddrehung der Augen beim Normalen, gemessen am Augenhintergrunde nach Grahe.
Arch.Ohr.-Nas.-KehlkHeilk., **136**, 298-313.

QUIX, F. H. (1924) Die Otolithenfunktion in der Otologie.
Z. Hals-Nas.-Ohrenheilk., **8**, 516-537.
— (1929) Experimente über die Funktion des Otolithenapparates.
Z. Hals-Nas.-Ohrenheilk., **23**, 68-96.
— (1933) Die Otolithentheorie der Seekrankheit.
Z. Hals-Nas.-Ohrenheilk., **32**, 279-299.

ULRICH, H. (1935) Die Funktion der Otolithen, geprüft durch direkte mechanische Beeinflussung des Utriculusotolithen am lebenden Hecht.
Pflügers Arch. ges. Physiol., **235**, 545-553.

VERSTEEGH, C. (1927) Ergebnisse partieller Labyrinth-extirpation bei Kaninchen.
Acta oto-laryng., Stockh., **11**, 393-408.

VRIES, H. DE (1950) The mechanics of the labyrinth otoliths.
Acta oto-laryng., Stockh., **38**, 262-273.

WOELLNER, R. C., GRAYBIEL, A. (1959) Counterrolling of the eyes and its dependence on the magnitude of gravitational or inertial force acting laterally on the body.
J. appl. Physiol., **14**, 632-634.

STELLINGEN

I

Een otolith-systeem, dat functioneert op de in dit proefschrift gestelde wijze, is in het bijzonder adaequaat om de houdingsreflexen te sturen. Bij gestrekte nek is het otolithsignaal steeds evenredig aan het koppel van krachten dat het lichaam uit de loodrechte stand drijft, ook als $G \neq 1g$ zoals bij een sprong.

II

Het otolith-systeem kan geen uitsluitsel geven over richting èn grootte van G. Onder normale statische omstandigheden is $G = 1g$, alleen met behulp van deze vooronderstelling kan het otolithsignaal dienen als informatiebron betreffende de richting van G.

III

Dat het otolith-systeem een onjuiste richtingsinformatie verschaft als $G \neq 1g$, maakt de centrale rol van dit systeem bij het ontstaan van zeeziekte verklaarbaar, met name voor de theorie die het ontstaan van bewegingsziekte verklaart uit tegenstrijdigheid van verschillende zintuigindrukken.

IV

Ter verklaring van de voorbijgaande sterke tegenrolling der ogen na snelle hoofdbewegingen denke men — behalve aan een effect van de halfcirkelvormige kanalen — aan het effect van een snel adapterend deel van het otolithsignaal.

V

Voor patienten die beademd worden via een trachea-canule die de luchtpijp geheel afsluit, is het niet kunnen spreken een zware extra belasting. Het is gewenst dat een techniek wordt uitgewerkt die hen het spreken mogelijk maakt op een kunstmatig langs de stembanden gevoerde luchtstroom.

VI

Mond-op-mond beademing is een noodmaatregel die bij zuigelingen noodlottige gevolgen kan hebben. Het tussenschakelen van een drukbegrenzend ventiel verdient aanbeveling.

VII

Vaccinatie van zuigelingen dient te geschieden door de arts die ook overigens met de praeventieve gezondheidszorg is belast.

VIII

De prognose van de juveniele hypertensie is door een oordeelkundig gebruik van de moderne hypotensiva sterk verbeterd.

IX

Het gebruik van chlooramphenicol in gevallen waarin ook andere middelen ter beschikking staan is af te wijzen.

X

Het als routine tellen van de kiemen bij een urineweginfectie is een voorbeeld van nodeloos ver doorgevoerde diagnostische perfectie.

XI

Bij de histologische beoordeling van het endometrium is kennis van door de patient gebruikte zwangerschapsverhinderende pharmaca van groot belang.

Charles (1964), *J. clin. Path.*, **17**, 205.

XII

Het stroma van een geslaagd corneatransplantaat wordt niet door gastheerweefsel vervangen.

Polack, e.a. (1964), *Amer. J. Ophthal.*, **57**, 67.

XIII

Het op gelijktijdigheid beoordelen van zintuigindrukken vindt plaats in de dominante hemisfeer; daardoor worden gelijke, gelijktijdig en symmetrisch toegediende stimuli als ongelijktijdig ervaren.

Efron (1963), *Brain*, **86**, 261.

XIV

De aandacht van de weggebruiker is niet onbeperkt. Aanwijzingen voor het verkeer dienen op het eerste gezicht begrijpelijk te zijn. Hiervan af te wijken, hetzij om een juridische hetzij om enigerlei andere reden, brengt de verkeersveiligheid in gevaar.

XV

Waar wij op de schilderijen van Geertgen tot Sint Jans en andere middeleeuwse meesters naast de Christus een dubbelganger van Hem zien, stelt deze Jacobus de Mindere voor.

XVI

De stelling 'Oeconomia politica non sine maximo damno a theologo practico negligi potest' heeft haar waarde ten volle behouden.

H. Roodhuyzen, diss. 1858.
Overgrootvader van de promovendus.

A. Colenbrander
7 juli 1964