THE EFFECTS OF ANTICONVULSIVE MEDICATION
ON VESTIBULAR FUNCTION
AN ELECTRONYSTAGMOGRAPHIC STUDY

by

Yoginder Nath Mehra, M.B.,B.S.(Panjab) F.R.C.S.(C)

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Department of Neurology and Neurosurgery,
Montreal Neurological Institute and
Vestibular Function Laboratory,
Royal Victoria Hospital.

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INTRODUCTION

This study was conducted during the years 1960-61 when I was appointed a Hosmer Teaching Fellow in the Department of Otolaryngology, McGill University, at the Royal Victoria Hospital, Montreal.

The original plan of this study was to evaluate the possible effect of some temporal lobe lesions upon vestibular function. It has been reported that a lesion of the temporal lobe may produce directional preponderance of nystagmus to the side of the lesion in response to caloric stimulation. (Fitzgerald and Hallpike 1942, and Carmichael, et al, 1954).

Patients with temporal lobe lesions were studied both during the pre-operative and post-operative periods. The alternate cold and hot caloric test, according to the technique of Fitzgerald and Hallpike (1942) was done and the resulting nystagmus was recorded electronically as an electronystagmogram.

Most of the subjects studied were "seizure patients" with lesions in the temporal lobe and they were on anticonvulsive medication, especially Dilantin and Phenobarbitone, both in the pre-operative and post-operative periods. In some cases pre-operative tests were done after medication had been discontinued for several days. All of the patients had anticonvulsive medication during the post-operative tests.

When the caloric induced nystagmus in these patients on anticonvulsive medication was compared with that of normal healthy controls, it was noticed that there was quite marked suppression of nystagmus in the case of the patients under treatment. This presented difficulties in calculation.

It is well known by the work of Bender (1946) etc. that barbiturates do affect nystagmus. Dilantin in higher doses is also known to produce spontaneous nystagmus and vertigo. This effect of Dilantin is thought to be due to toxic effects on the Central Nervous System. Hoffman (1958) has shown a lesion in the cerebellum of a patient with a history of Dilantin intoxication.

The overall suppression of nystagmus seen in the seizure patient on anticonvulsive medication was suspected to be an effect of the medication.

It seemed advisable that more should be known about the possible effects of anticonvulsive medication upon the vestibular apparatus before accurate information could be obtained about the relationship between the temporal lobe lesions and vestibular reactions.

The poverty of the literature on the effects of Dilantin on the caloric induced nystagmus was noted.

The project was thus modified to study the effect of medication. Patients who had been on long term medication, both during the time they were on medication and after they were taken off, were studied, and the results compared with those obtained from normal individuals.

Individuals with healthy ears and without obvious central nervous system disease were given clinical doses. The caloric tests were

done before and after this medication and the results studied.

This work was done at the Royal Victoria Hospital and the Montreal Neurological Institute, Montreal.

CHAPTER I

A. NYSTAGMUS

Nystagmus is a term of Greek derivation and it means to nod. It is applied to rapid oscillatory movements of the eye. Normally the eyes are moving to and fro; without this movement the eyes have a staring look (Crosby 1953). These fine movements are not perceptible either to the subject or to the observer, but they can be recorded on amplified records as in Electronystagmography. (See fig.1)

Movements of the eyes in clinical nystagmus are almost always conjugate, but may be more marked in one eye than in the other (Duke-Elder, 1954).

The direction of the nystagmus is described in terms of the quick phase. Rhythmic jerking movements - nystagmoid jerks - most pronounced at the extreme limits of the eye deviations are not uncommon in normal people under certain conditions, as in fatigue, and should be

TIME MARKER

10°

NORMAL RECORD
EYES CLOSED

Figure 1

distinguished from true nystagmus. On voluntary basis it is almost impossible to produce nystagmus.

Nystagmus may be congenital or acquired. Congenital or early infantile nystagmus occurs in congenitally deformed eyes where the infant is unable to fix either due to albinism or congenital or acquired opacities in the media. This is usually without any quick and slow components. Acquired nystagmus may occur spontaneously due to diseases of the midbrain, cerebellum and vestibular tracts, as well as of the semi-circular canals. It may also be induced experimentally.

Vestibular nystagmus is characterized by quick and slow components. It is usually of short duration, from a few moments to a few weeks, but may require magnification to detect it. The direction of this nystagmus is either horizontal or rotatory, rarely oblique. True vertical nystagmus is rarely seen in peripheral vestibular disease.

Periodic alternating nystagmus is also described. Kornhuber (1958-60) stresses the independence of this nystagmus from peripheral vestibular stimuli. He explains its dependence on central excitation and fatigue on the basis of a close connection between spontaneity of nystagmus and the reticular activating function.

Induced nystagmus is of several types.

(1) Optokinetic Nystagmus. The eyes follow a passing object (slow phase) and then jerk back in the opposite direction. It is also called Railway Nystagmus. The test consists of subjects looking at moving stripes or lights. Optokinetic nystagmus is affected by certain diseases of the cerebrum and its connection with the brainstem nuclei. Carmichael, et al. (1954), have used optokinetic nystagmus as a diagnostic test for lesions of the posterior part of the temporal lobe. Optokinetic nystagmus is not affected by destruction of the vestibular apparatus and its central connection, for example, in cases of ototoxicity from antibiotics like Streptomycin (Dix, et al, 1949).

(2) Auditory or Audiokinetic Nystagmus

has been described by Hennebert (1960).

When a moving auditory stimulus is given to the subject, the eyes naturally follow the source of sound. He recommends this as a test for malingerers.

(3) Olfactory Nystagmus has also been demonstrated in dogs by Van Deinse, et al. (1954).

(4) Positional Nystagmus. This is nystagmus which occurs when the position of the head is altered. To demonstrate it, the patient should be examined not only with head in the erect position, but also with head back in the supine position, with the head forward as in the prone position, with the head on each side, and with the head in the hanging position.

Nylen (1953) describes three types of Positional Nystagmus.

(a) Nystagmus which changes direction with change in head position (Nylen Type I).

(b) Direction-fixed Positional

Nystagmus which has the same direction with different positions of the head (Nylen Type II).

(c) Irregular Positional Nystagmus which may sometimes present Type I as above, sometimes as Type II, and sometimes changes its direction although the head position is the same (Nylen Transitory Type).

Frenzel and Seifert's classifications are similar to Nylen's although they include Type I and III in the same group.

Nylen (1950) mentions that when eliciting the Positional Nystagmus, change of position should take place very slowly, 90° in 5 seconds. He considers the presence of the positional nystagmus as indicative of disturbance in the vestibular system. He feels that the direction-changing, and the transitory positional nystagmus suggest a central lesion, whereas the direction-fixed nystagmus may appear in labyrinthine and retro-labyrinthine lesions.

Mechanisms of Positional Nystagmus:

Barany (1906-21) attributed positional nystagmus to pathology in the vestibular apparatus, possibly the otolith organs, but he left open the possibility of its arising in the Central Nervous System.

Nylen (1924) suggested that there was a probability that both the peripheral and central systems are capable of giving rise to positional nystagmus. Nylen (1950) made the statement that the pathogenesis of positional nystagmus can be explained on the assumption of pathologically altered tonus, either in the entire vestibular system or in parts of it.

de Kleyn and Versteegh (1930) described a positional nystagmus which followed alcohol poisoning in a rabbit, and disappeared after bilateral labyrinthectomy. It was present after removal of both sacculi. They concluded that it arises from the tonic part of the labyrinth. They were careful to point out however, that in no one case has nystagmus been shown to arise from stimulation of the otoliths in man.

Jongkees (1961), mentions that de Kleyn and Nieuwenhuyse (1927) could prove that changes in the lumen of the vertebral artery, provoked by rotation of the cervical vertebrae may give rise to a positional nystagmus in otherwise perfectly normal persons. He further states that it has never been proven that the position is essential. On the contrary it seems very probably that this phenomenon is a reaction caused by the movements required to obtain this position.

McNally (1956) states that utricular disease has not been proven to be the cause of positional nystagmus.

Citron and Hallpike (1956), and Cawthorne and Hallpike (1957) have studied a certain type of positional nystagmus which they describe as a benign paroxysmal type, found to be associated with lesions of the utricular macula.

Bergstedt (1961) in his studies of positional nystagmus in the human centrifuge, came to the conclusion that the otolith organs can reasonably be considered to be the primary release mechanism for positional nystagmus.

Fernandez, et al.(1959), by making lesions in the nodulus cerebelli, produced positional nystagmus which disappeared when the labyrinths were destroyed.

From the above discussion one would conclude that there is no agreement as to the site of lesion causing positional nystagmus. The labyrinth is necessary for the presence of positional nystagmus. There is equivocal evidence about the responsibility of the otoliths. The case is well expressed by Jongkees (1961) when he says that there may be a disturbance in the harmonic co-operation of the various parts of vestibular organs and the central connections which causes positional nystagmus.

(5) Caloric Nystagmus. The semi-circular canals can be stimulated by changes in temperature, a phenomenon commonly used for the testing of vestibular function. Either a warm or a cold stimulus can be used and methods vary widely. Hot or cold water and cold air are the more common stimuli used, the latter being useful when the ear drum is perforated.

The temperature of the normal human tympanic membrane at basal conditions as calculated by Jørgensen (1956) is 36.95°C with a mean variation of $\pm 0.065^{\circ}\text{C}$ for males and $36.99 \pm 0.065^{\circ}\text{C}$ for females. There was seen to be a decline of temperature from the age of five to eighty years.

The thermal variation of the bone and modification of the endolymph is essentially a physical phenomenon depending upon the temperature of the water, quantity of water, velocity of irrigation, area of tympanic surface on which the jet of water is directed, size and pneumatization of the bony bridge between the tympanum and the external wall of the lateral semicircular canal and the velocity of the blood stream. The temperature change is transmitted by bony tissue six times quicker than by air (Arslan 1955).

Dohlman (1925), and Cawthorne and Cobb (1954) recorded the magnitude and time course of temperature changes induced by caloric stimulation in the canal of the cadaver and

living beings respectively. Cawthorne and Cobb found that there was a temperature change of 0.8°C in the horizontal semicircular canal when the water in the external ear canal was 7°C above body temperature. When the stimulus was 7°C below body temperature, the mean fall within the semicircular canal was 0.67°C .

The reaction from the vertical canals is not usually as intense or as prolonged as is the reaction from the horizontal semicircular canal. McNally, et al. (1948), quote Dohlman's explanation that the heat conduction to the vertical canals is not as direct as it is to the horizontal canal. For this reason the best response is obtained from the horizontal canals, especially when they are perpendicular to the horizontal axis. This is taking advantage of gravity, for the convection currents produced in the endolymph by the temperature change are in a vertical plane.

Mechanism of Caloric Nystagmus:-

Jongkees (1948) (b) reviewed the literature on the mechanism of caloric stimulation. He agrees with Barany that convection current in the endolymph cause the stimulation. He also gives Bartel's view that the effect of temperature changes on the nerve endings directly causes vestibular stimulation. Kobrak (1919) felt that the stimulus caused changes of a vascular nature in the endorgan. The vessels in the periphery of the labyrinth are constricted by a cold stimulus. Consequently the central vessels react with dilation. Jongkees agrees with this view to some extent and also quotes Barrie's view that the caloric reaction is a reaction of the whole labyrinth, especially of the otolith's. Brunner, according to Jongkees, disagreed with this statement, and in his opinion the reaction of the caloric test must be central. The fact that strong stimuli have an effect on the subsequent caloric tests for as long as twenty minutes caused Woletz to consider the existance of a central effect.

Aschan (1955) carried out caloric tests by irrigating either one ear or both ears simultaneously, and came to the conclusion that a central nervous process is able to add to or subtract from the impulses released by peripheral vestibular stimulation. The secondary phases of nystagmus and the turning sensation, according to them, have a central origin.

(6) Rotational Nystagmus. Rotational nystagmus is an induced nystagmus and is used for clinical testing. As compared to the caloric induced nystagmus, the value of the rotational test is less because both labyrinths are stimulated at the same time. The caloric reaction is usually produced by stimulating one labyrinth at a time. The vertical canals can also be investigated by rotation. "In contrast however, to caloric stimuli, the physical forces engendered within the canals by rotational stimuli can be calculated with considerable precision." Cawthorne, et al.(1956).

The test in the simplest form may be carried out by placing a patient in a rotating or swivel chair which is turned ten quick turns in about twenty seconds. The patient's eyes should be closed during the test to exclude ocular nystagmus. (McNally and Stuart, 1953.) The head is so positioned that each set of parallel semicircular canals are stimulated separately. The stimulation of the labyrinth occurs with any change of acceleration, either during or at the beginning and at the end of turning. For practical purposes it is easier to examine the patient at the end of the turning (Post-rotatory) when the direction of nystagmus is reversed from what it was at the onset of the turning.

Van Egmond, et al. (1948), have objected to the above test often described the Barany Test on the grounds that it applies too severe a stimulus to the labyrinth, and that the stimulation is too complex. They state that the rapid rotation produces a build up of positive angular acceleration and that before

this can have its full effect upon the labyrinth the rotation is stopped suddenly with the introduction of an equally strong and oppositely directed negative angular acceleration. These authors have advocated the use of a slower rotation beginning at the subthreshold level of stimulation. The rate is slowly increased but never beyond 90 degrees per second per second. The duration value of the nystagmus and of the rotation sensation of the patient is charted on a graph for different speeds of rotation. This method is called Cupulometry, and the graph is called a Cupulogram. For a proper control of this test, electronically controlled rotational chairs are helpful. The subject's eyes are covered, or the test is done in the dark, and the nystagmus is recorded electrically. Otherwise, the subject is fitted with especially illuminated convex glasses by Frenzel. This obviates fixation of the eyes and facilitates the examination of the nystagmus.

(7) Fistula Sign. In cases of a fistula of the bony labyrinth with an intact membranous labyrinth, increased or decreased pressure in

the external auditory canal results in the presence of nystagmus during the change in pressure. This sign is of considerable diagnostic value. However, if the labyrinth is non reactive or destroyed, this sign will not be positive although clinically the fistula is present.

Nylen (1923) studied the mechanism of this sign and showed that the fistula symptoms still could be produced after elimination of the otolithic membranes by centrifugation of the animals, showing that the fistula test was essentially a reaction elicited in the semicircular canals.

Dohlman (1953) quotes Zwerguis as having presented persuasive evidence that the fistula test is a reaction of the ampullar cristae. Zwerguis also postulated that endolymph movements are necessary for eliciting the fistula symptoms and showed that the round window and oval windows play an important role in the test.

(8) Pseudofistula Symptoms. Nystagmus can be produced by compressing and by aspirating the air in the external ear canal even in cases in which there is no fistula in the labyrinth. It has been described in cases of congenital syphilis.

(9) Reaction of Tullio. Tullio, quoted by Pursiainen (1954) showed in his tests on pigeons that after an opening had been made in a bony semicircular canal, a loud sound could cause head movements accompanied with movements of the eyes, trunk and extremities. This so called Tullio Reaction is rare in man but has been reported.

(10) Galvanic Induced Nystagmus. Nystagmus can be induced by galvanic stimulation of the labyrinth. However, because positive results can be obtained by the current stimulating either the vestibular nerve or the central nuclei, the value of this as a clinical test is limited.

THE MECHANISM OF VESTIBULAR NYSTAGMUS:

Vestibular nystagmus is characterized by the presence of a quick and slow component.

The slow component is considered to be of peripheral vestibular origin. There are very divergent views on the locus of the quick component.

Spiegel and Price (1939) summarize two groups of theories to explain the origin of the quick component.

Group I - The cerebral theory which attributes the function to the parts of the Central Nervous System above the midbrain.

Group II - Theories assuming that the origin of the rhythm is in parts of the Vestibulo Ocular Reflex.

Group I:

The Cerebral Theory is based on the fact that nystagmus disappears or diminishes under deep anaesthesia or in deep sleep. This theory, however, is refuted on the ground that both slow and quick phase remain intact after extirpation

of the cerebral hemispheres. Spiegel and Price (1939), Duke-Elder (1949), Bauer and Leidler (1912), Magnus and de Kleyn (1923).

Group II - Theories in the Second Group are as follows:

(1) The Proprioceptor Theory - assumes that the rhythmic reaction is due to proprioceptive impulses from the ocular muscles. However, this theory can be refuted on the basis of failure of nystagmus induction when the proprioceptors have been paralysed by the injection of Procain Hydrochloride into ocular muscles. de Kleyn (1922).

(2) The Ocular Muscle Nuclei Theory. This theory supposes that the rhythm of the nystagmus can be controlled by the action of the oculomotor nuclei, in that the bilateral centres, for example, of the external rectus muscles, inhibit each other mutually through nerve cell processes crossing the midline. If this supposition is correct, the median longitudinal bundle of one side will be

sufficient to induce labyrinthine nystagmus in both eyes. This, however, according to Spiegel's experiment is not the case (Spiegel and Sommer 1944).

(3) The Labyrinthine Theory - seeks the origin of the rhythm in the labyrinth. This theory however, cannot explain Bechterew's compensatory nystagmus. If, after one labyrinth is ablated, and the post operative nystagmus has subsided, the other labyrinth is destroyed, a spontaneous nystagmus appears for some time.

(4) The Vestibular Nuclear Theory and

(5) The Reticular Substance Theory.

Most of the present day discussion about the location of the origin of quick component centre around these two theories.

Lorente de No (1933) proposed that the quick component is mediated through the reticular substance. He observed that after the long pathways (fasicula longitudinal posterior and tractus vestibulo mesencephalic connecting the primary vestibular nuclei with the motor nuclei) are cut, all labyrinthine reflexes of the

ocular muscles can still be elicited. After puncturing the reticular substance from the dorsal aspect of the pons, he found that the quick component of nystagmus was abolished, and only the tonic deviation of the eyes was present.

Lorente de No also came to the conclusion that the whole vestibular system is a physiological unit that finds itself in constant activity. According to its functional state the afferent impulses set up reflexes of determined patterns because they find open only a limited number of extremely numerous anatomic pathways. He put forward the theory of a closed self re-exciting chain of neurons.

Spiegel and Sommer (1944), however, object to this theory because they found that unilateral destruction of the reticular substance does not product nystagmus. Nystagmus should result from a disturbance of balance of impulses between the two sides as it does in lesions of vestibular nuclei, if Lorente de No's theory is to be accepted. Spiegel and Price (1939)

produced punctures of the reticular substance through the floor of the fourth ventricle as did Lorente de No. They, however, examined the animals at a time much later than the acute phase and found the changes noted by Lorente de No to be reversible to a great extent. They came to the conclusion that the reticular substance is not indispensable to the mechanism of nystagmus. This does not mean, however, that the reticular formation does not participate in the conduction of vestibular impulses to eye muscle nuclei.

With this background Spiegel and Sommer (1944) came to the conclusion that the rhythm is of central origin. Because the areas in the rhombencephalon, cerebrum, diencephalon, cerebellum, eye muscle nuclei, as well as the substantia reticularis rhombencephali are dispensable, they regard the vestibular nuclei as the site of origin, not only of the mechanism that innervates the slow component, but also of that which activates the quick component of the nystagmus.

Koike (1959) observed that eye speeds in the slow and in the quick phase are not independent of each other.

RHYTHM OF NYSTAGMUS:

Although the theories described above attempt to explain the slow and fast component of the nystagmus, the question of rhythm is not explained by these theories.

Bender (1955), in his study of the eye movements, supposes that there must be a mechanism which turns the eyes away (deviational) from the centre and which brings them back. He named this mechanism the Eye Centering System. He further states that nystagmus, which has a slow and a quick phase (horizontal, vertical and rotational) may be another clinical manifestation of the activity of an eye centering system. Experimental and pathological lesions in structures which mediate eye centering may result in the abolition of the quick component. The Eye Centering System is in equilibrium with the conjugate deviational system and these in turn are constantly influenced by visual, proprioceptive and somatosensory systems.

Bender gives the location of the system. Its efferent pathways are situated in the cerebrum and project down into the brain stem to the midbrain and pons. These pathways are situated in the paramedian zone in close proximity to the oculo-motor nuclei. The function mediated by these pathways is to coordinate the movements of the eyes. He quotes experimental evidence which demonstrates the effect of the cerebrum on eye deviation and feels that this eye centering mechanism exists. He also states that the quick component is but one manifestation of an eye centering system. Bender conceded that this theory of his will not solve all problems which may be encountered in the study of ocular movements.

LAWS FOR INTERPRETATION OF NYSTAGMUS:

For the proper interpretation of the characteristic of induced nystagmus, certain rules have resulted from the experiments of Flourens and Ewald.

Flourens, quoted by McNally and Stuart (1953), was the first to note that when the semicircular canal of a pigeon was stimulated or injured, the resulting head nystagmus, or eye nystagmus was in the plane of the injured canal.

Ewald (1892) noted from his experiments with a pneumatic hammer in the semicircular canals of pigeons that a movement of the endolymph directed towards the ampulla (ampullopetal flow) in the horizontal semicircular canal evoked a stronger reaction than a corresponding ampullofugal flow. He also observed that the conditions were reversed in the vertical canals.

From the experiments of Ewald, it has been generalized that when a semicircular canal is maximally stimulated, it elicits a quick phase of nystagmus to its own side.

Arellano (1938), from his studies, came to the conclusion that nystagmus due to rotation is always in a plane at right angles to the axis of rotation, irrespective of the position of the head, and that post rotational nystagmus is always in the opposite direction to the rotation.

The findings of Ewald have been generally accepted to explain the mechanism of canal stimulation.

From time to time experimental evidence has been produced to contradict these findings with regards to their applicability in human beings, and many authors have come forward with the opinion that these so-called Ewald's laws should be modified, especially with respect to the bidirectional maximal and minimal responses of a semicircular canal.

Fitzgerald and Hallpike (1942) carried out labyrinthine tests on humans by using alternate hot and cold caloric stimulation. Water at seven degrees above and seven degrees below the body temperature was presumed to be equal and opposite stimuli to the labyrinth. Calculating the response from the horizontal semicircular canal to the stimulus as the total duration from the onset of stimulation to the end of the nystagmus, they reported that in eighty per cent of their patients the reactions to cold caloric stimulation were slightly in

excess to that of the hot. If one accepts Ewald's laws, there is an ampullopetal current in the endolymph - a maximal stimulus of the horizontal semicircular canal when it is in a vertical plane (Patient's face to ceiling) if the stimulus is hot water. Because they found that hot gave a weaker reaction than did cold water, they came to the conclusion that Ewald's laws do not apply in the human being. However, one could object to their opinion on a technical basis. The cold and hot solutions, although equidistant by seven degrees from the normal body temperature, may not necessarily be equal and opposite stimuli. Secondly, more recent studies using electro-nystagmography have shown that total duration of nystagmus as a calculating factor is not a very accurate indication of the vestibular function.

Aschan (1955) found that although duration of nystagmus following warm water stimulation of the labyrinth is shorter, the maximum slow speed induced is the same as with cold water. He postulates

this to be due to the change in viscosity of the endolymph. There is decreased viscosity with hot irrigation as compared to that with cold irrigation. Thus, according to him, this could account for a quicker levelling out of temperature in the former case.

McNally, et al. (1948), carried out labyrinthine tests on humans by the alternate hot and cold caloric method as had been used by Cawthorne, et al. (1942), but in addition to examining the patients in the face-up position, they reversed the position of the semicircular canals by putting the patients face downwards. In this manner the ampullopetal force in the horizontal canal was produced by the cold water stimulation. They also measured the reaction from the onset of stimulation to the end of the nystagmus.

McNally, et al. observed that in the face-up position, cold was a more effective stimulus for the horizontal canal than was the hot in approximately sixty-five per cent of their cases.

This seemed to confirm the observation of Cawthorne, et al. contradicting the Ewald's Law. However, in the face-down position, they found that cold is still a more effective stimulus in approximately sixty-nine per cent of the series. In this position the endolymph flow in the horizontal canal due to cold is ampullopetal, and this finding confirmed Ewald's Laws.

McNally, et al. put forwards the theory that the increased effect of cold in both the face-up and face-down position may be due to the effect of gravity on the cupula. These authors also suggest that the hot and the cold caloric stimuli used in their study, as well as the stimuli used by Cawthorn et al. are not necessarily equal. They feel that the conclusions based upon these tests are not well enough founded to serve as a refutation of Ewald's Laws.

Van Egmond, et al. (1949), studied the cupulograms of a number of people with total or partial loss of function of one inner ear.

They came to the conclusion that Ewald's Laws are not clearly valid at all.

In a recent international symposium at Basel on problems in Otoneurology, the problem of applicability of Ewald's Laws was discussed.

Hallpike (1961), from his study and interpretation of the caloric tests of patients and of normal individuals, came to the opinion that within the normal working range of the semi-circular canal this inequality does not exist and that the canals responses then exhibit a directional equality. He is of the opinion that Ewald's second law needs to be repealed.

Dohlman (1961) states that the caloric reaction must be regarded as an acceptable method for producing cupula deflection giving a nystagmus response which enables us to compare the effects of utriculofugal and utriculopetal endolymph movement.

He also stresses the fact that in using the caloric reaction, the effect of stimulation of the receptors of the canals cannot be measured

by the duration of visible nystagmus strokes. Measuring the recorded speed of the slow nystagmus component is the means which he feels enables us to get as close to the answer as it is possible.

He believes that the ability of the peripheral sense organ in the crista to react both to utriculopetal and utriculofugal endolymph movements does exist. He considers that there is a difference in the different stages of development, from fish to mammals, in the ability of the vestibular nuclei and central connections to evaluate the modulations in resting frequency. All can respond to an increase in the action potential frequency from the cristae. Lower animals cannot respond to a decrease, birds only to a certain extent and man apparently equally well to an increase and decrease.

Ledoux (1961) concluded from his electrophysiological studies of the vestibular apparatus, that the validity of Ewald's laws is open to question.

Montandon (1961) studied this problem with precise clinical giratory examinations, with per-rotatory electronystagmography on several thousand subjects and confirmed the principle of a strongly predominant unidirectional excitation of the semicircular canals.

Groen (1961) concluded from his discussion that this law still holds also for the human labyrinth, with the general comment that in certain range of positive and negative stimuli, the size of which depending upon the species involved, there exists a constant sensitivity for stimuli in either direction. Beyond this range the original wording of unequal sensitivity still counts. He also gives a developmental reason for the difference of the horizontal and vertical canal reaction. He believes that the horizontal canal actually developed from the anterior vertical and still keeps the orientation of the sensory cells in the cristae as in the vertical. However, as both open in

the utricle near each other due to their rotation in the axis, ampullofugal movement in one axis is ampullopetal in the other.

Hood (1961) did rotational tests on normal subjects and patients with unilateral labyrinthectomy, and calculated the cupular deflection with and without adaptation. He came to the conclusion that there is essentially a bidirectional character to the canal mechanism which thus contravenes the principles upon which Ewald's Law is founded.

Stahle (1961), from his experience of routine clinical work, has concluded also that Ewald's Second Law is untrue, at least when the rotatory test is performed as in cupulometry. He also observed that patients with total unilateral loss of labyrinthine function have shown that the ampullar organ probably has bidirectional sensitivity, and that this is equal for ampullopetal and

ampullofugal streaming of endolymph.

Aschan (1961) also stated that in man ampullofugal and ampullopetal deviations produced by caloric or rotatory stimuli do not give any support to the validity of Ewald's Second Law.

Reviewing most of these authors, one gets the impression that Ewald's Second Law does not hold completely true for man.

DIRECTIONAL PREPONDERANCE OF NYSTAGMUS:

Bauer and Leidler in 1911 showed that after extirpation of one cerebral hemisphere in the rabbit, the post rotation nystagmus after turning to the normal side was much stronger than the nystagmus after turning to the operated side. Bauer and Laidler concluded that after extirpation of one cerebral hemisphere the ipsilateral labyrinth is more excitable than the contralateral.

Dussur de Barenne and de Kleyn (1923) repeated these experiments, extirpation of one cerebral hemisphere in the rabbit, and showed that after syringing the homolateral ear with hot water, and the contralateral ear with cold water, a much stronger nystagmus was produced then after syringing the homolateral ear with cold water and the contralateral with hot water. This they termed Nystagmusbereitschaft.

de Kleyn and Versteegh (1927) tested thirty-six patients suffering from cerebral disease with this technique and found eleven with Nystagmusbereitschaft.

Cawthorne, et al. (1942)(b), used the method of alternate hot and cold caloric stimulation and found this phenomenon of "nystagmusbereitschaft" which they called Directional Preponderance. It was present in twenty per cent of a series of fifty cases of Meniere's Disease. They concluded that it resulted from utricular disease.

Fitzgerald and Hallpike (1942) examined a series of patients with cerebral lesions and found that directional preponderance occurred

more often when the disease was present in the temporal lobe than when the disease occurred in other parts of the cerebral hemisphere. They believed that this effect of temporal lobe lesions was due to a disturbance of a controlling action normally exerted by the temporal lobes upon the reflex response of the lower vestibular centres.

Carmichael, et al.(1954), did further study of the directional preponderance of caloric nystagmus and optokinetic nystagmus, and from this study they concluded that the directional control of caloric and optokinetic nystagmus is normally exercised through independent nervous mechanisms situated respectively in the posterior parts of the temporal lobes and in the supramarginal and angular gyri.

Stahle (1956) said that it is difficult to decide whether or not directional preponderance is present. If the limits are set close together more cases will be taken to show directional preponderance. As different authors have chosen different criterion to consider the

presence or absence of directional preponderance, the results vary.

Jongkees (1948)(a) accepted this phenomenon as present when the value of nystagmus beating in one direction surpassed that beating in the other direction by twenty per cent or more. He found in his series of normal individuals a directional preponderance of seventeen per cent.

Hamersma (1957) found a directional preponderance of fifty-five per cent in his series using the same formula for calculation. He used the electronystagmographic method of calculation. Statistical analysis of the results in the same group revealed this directional preponderance to be insignificant.

Hallpike, et al. (1951) found no directional preponderance in normal persons. They used a standard deviation of fifteen seconds for their calculations by the statistical method.

Aschan (1956), using the same method of calculation, also did not find any apparent directional preponderance in his normal test group.

With this background it is safe to say that until now no standard mode of calculating direction of preponderance has been accepted, and it is difficult to study different authors' results. Thus it becomes difficult to attach clinical importance to the presence or absence of directional preponderance.

SUMMARY

In this section is included a review of the literature on Nystagmus.

Different types of spontaneous and induced nystagmus have been mentioned. Vestibular nystagmus has been described in more detail, and different modes of stimulation of each has been described.

The mechanism of Vestibular Nystagmus is discussed. The slow component is considered to be peripheral vestibular in origin, while

the quick component is ascribed to the vestibular nuclei, and the reticular substance.

Bender's view on the Rhythm of Nystagmus is included. Different laws for interpretation of Nystagmus are discussed. Directional Preponderance of Nystagmus has also been reviewed.

B. THE RECORDING OF NYSTAGMUS

I. METHODS OF RECORDING:

Nystagmus is the most reliable objective expression of the vestibular excitation (Torok 1953; Aschan, et al 1956; Hamersma 1957). This applies to the nystagmus which is either spontaneous or induced by various manoeuvres such as caloric or rotational stimuli.

Various methods have been used at different times to observe and record nystagmus. The classification that follows is based upon Duke-Elder (1942) who divided the different methods into two main groups for recording the ocular movements.

(A) Subjective Methods:

(1) The Method of "After Image".

If the formation of an after image is stimulated from an area of the retina it is projected into space, and since the image follows accurately every movement of the part of the retina which is responsible for its production,

its path forms a replica of movements of the eye which is of considerable accuracy. In the investigation of the vestibular apparatus, this method is used by some in the rotational tests of cupulometry.

(2) The Method of the "Blind Spot" by which the projection of the blind spot is observed.

(3) The comparison of corresponding images of the two eyes. This cannot well be used for investigation of nystagmus because usually in vestibular nystagmus there is conjugate movement of the two eyes.

(B) Objective Methods:

(1) Methods of Direct Observation.

Nystagmus may be observed directly, or the subject's eyes may be covered with special 20⁰D glasses which serve to obliterate the fixation of the subject. The nystagmus movements are magnified by the glasses and some of these, like Frenzel's Glasses, have built in illumination.

It is difficult to do accurate calculations from visual records. The method is not too accurate from a statistical point of view.

(2) Mechanical Recording Methods.

(a) Pneumatic capsules have been applied upon the eyelids to record the movements of the eyelids (Buys, 1909).

(b) Records by levers of the movements of a cup fitted upon the globe.

These two methods suffer from the fact that the records are very coarse and eyes cannot be opened and closed during the tests.

(c) Mirrors have been applied to the globes and photokymographic records have been made (Dohlman, 1925).

(3) Photographic Methods.

Direct cinematography of the eyes is a useful procedure for the recording of the eyes, especially rotatory nystagmus which cannot well be recorded by other methods.

However, the technique requires that the eyes be kept open, thus fixation of the eyes may occur, which in turn affects the duration and character of nystagmus.

Recently Aschan, et al. (1957)(b), have used infra red cinematography. Thus they can keep the subject's eyes covered with opaque glass without fixation and record photographically the eyeball movements.

These methods are still cumbersome for vestibular investigation.

(4) Electronic Methods.

(a) Photo-electric cell method:

In this method light is thrown over the eyes so that the bright spot is at the limbus. The image of this is picked up by a photo-electric cell which is fed through an amplifying and recording system. Torok, et al. (1951) and Sullivan, et al. (1958) have used this method for recording nystagmus.

(b) Electrical Recording -
Electronystagmography:

This method depends upon the utilization of the Corneo Retinal Potential for recording. The human eyeball acts as a bipole with the cornea electropositive and the retina electronegative.

The changes in the bipole are picked up by circumorbital electrodes which, after being fed through electronic amplifying and recording systems, gives a permanent record.

(i) Corneo Retinal Potential.

Du Bois-Reymond (1849) was the first to discover the corneo-retinal potential in the eye of the tench, a European fresh water fish.

Meyers (1929) used bitemporal electrodes on humans with a sensitive string galvanometer to record nystagmus. He believed that it was the action potential produced by contraction of the eye muscles that activated the galvanometer.

Jacobson (1930), using the same technique as Meyers, came to a similar conclusion.

Mowrer, et al.(1936), confirmed the presence of the action potential, but came to the opinion that it is not due to muscular contraction as the action currents from the intact contracted muscle does not summate as that seen in the eye. This effect, according to them, comes from the high metabolism of the retina and relatively low metabolism of the cornea. They gave variations of this of the order of 0.50 to 0.75 millivolts for the movement of the eyes from the median position to an extreme lateral or vertical position.

Marg (1951), gave a review of the literature on cornea-retinal potential, and discussed the subclassification of standing potential and illumination potential. According to Marg, Kohlrausch in 1931 described some of the features. He mentioned that in vertebrates the cornea is positive relative to the retina, and in the invertebrates this ratio is reversed.

The polarity of the standing potential is increased by light in the vertebrates. Kohlrausch also noticed the influence of ionic changes or mechanical insults on the standing potential. It appeared to Marg that the site of origin of corneo-retinal potential was the retina.

Fenn and Hursh (1937) found that potential varies from 0.2 to 0.8 millivolts and was seen to be constant for any one individual.

Noell (1952) studied the effect of medication upon the corneo-retinal potential. He found that anoxia produced a slow rise of the potential difference during the first three minutes of its action. The same happened when Iodoacetic acid was given. Hydrocyanic acid in sublethal doses was ineffective. However, Adenosene Triphosphate, when injected to the homolateral carotid artery, increased the potential difference suddenly. He theorized that the site of origin of the potential difference is the sensory element. The free end of the visual cell was thought to be negative with reference to its base in

the cephalod retina. Sodium iodate reduced the potential by chemical destruction of retina cells in the rabbit as shown by Philipszoon (1959).

(ii) Recording:

This corneo-retinal potential has been used for recording nystagmus, among others by Schott (1922), Meyers (1929), Perlman and Case (1939), Glorig, et al.(1950), Powsner and Lion (1950), Hertz and Riskaer (1953), Ruding, (1953), Mittermaer and Christian (1954), Van-Egmond and Tolk (1954), Montandon, et al. (1955), Henriksson (1956), Aschan, et al.(1956), Hamersma (1957), McLay, et al.(1958), Stahle (1959), Arnold, et al.(1959), and Hallpike, et al.(1960).

Mainly two types of machines, Electrocardiographs with a preamplifier, or Electroencephalographs have been used.

In the interpretation of the results of the deviation of the eyes, the advantage of having a DC amplifier is that one gets a true representation of the eye ball

movement. However, there are technical difficulties with this procedure, such as the needle drift during recording which is due to voltage fluctuation within the amplifier and at the electrodes. This interferes with proper recording. For this reason a capacity coupled alternating current amplifier with a time constant of 1.5 seconds to 10 seconds has been used which gives perfectly acceptable results. In order to calculate the slow speed, a DC amplifier or amplifier with a long time constant is required. In the present study a time constant of 4.5 seconds has been used.

Henriksson (1955) has applied an electronic derivation procedure by adding a clipping diode to the current for recording slow phase only.

Hallpike, et al. (1960), coupled the writing pen of one channel used for recording nystagmus to the other channel used for recording the deviation of the eyes to either side of the horizontal plane. This gave a superimposed record of nystagmus and deviation of the eyes.

The disadvantage of the electronystagmographic record based on the corneo-retinal potential is that purely rotatory nystagmus cannot be recorded.

(c) Arrangement of the Electrodes:

Meyers (1929), Perlman and Case (1939), Powsner and Lion (1950), Aschan, et al.(1956), Henriksson (1956), Stahle (1956), Hamersma (1957), Hallpike, et al.(1960) and others have also used bitemporal electrodes for recording horizontal nystagmus.

Miskolczy, et al.(1959), studied the different arrangement of electrodes around the orbit and came to the conclusion that the use of bitemporal electrodes has the advantage of a stronger recording effect as compared to the arrangement where in each eye the movement is recorded separately. They showed that the bitemporal lead produced a recording effect which was about 1.73 times greater than the unilateral arrangement. As a rule both eyes have associated movement. Advantage is taken from this arrangement of bitemporal leads in the present study.

II. METHOD OF CALORIC STIMULATION OF VESTIBULAR APPARATUS.

The caloric test is one of the most important features of the examination of the labyrinth! Stahle (1956). Its value over other methods of induced nystagmus is that each ear is tested separately. Jongkees (1948), Arslan (1955), Stahle (1956), and Aschan (1955), among others, give a good historical review of this modality of vestibular stimulation. Barany (1906) was the first to stress the clinical value of the reaction. His original technique was based on the temperature required to elicit nystagmus, and he used large quantities of water. This method is called mass irrigation.

Kobrak in 1918, according to Stahle, (1956) introduced the minimal irrigation technique. Initially only 5 ccs of water at different temperatures was used to establish the threshold level for nystagmus. Various modifications of this were introduced and nowadays, 3 ccs of ice cold water is quite commonly used.

Fitzgerald and Hallpike (1942) introduced the method of syringing with a large volume (250 ccs) of water 7° degrees above and below the body temperature for forty seconds in the supine position with the head flexed forwards 30 degrees.

McNally, et al. (1948) used the technique of Fitzgerald and Hallpike and measured the duration and latent period of the nystagmus.

Jongkees (1949) used a smaller amount of water, 50 to 100 ccs.

Aschan (1955) and Henriksson (1955) used the same technique but syringed for thirty and forty seconds respectively.

Stahle (1958) and Hamersma (1957) followed the same technique but they used thirty seconds as a stimulus time.

Preber (1958) followed the Fitzgerald and Hallpike routine.

Groen and Jongkees (1949) found no significant difference in the duration of nystagmus for 500, 50 and 5 ccs of water at

30° and 44°c. Jongkees (1949) however, found that 5 ccs irrigation could not be reproduced satisfactorily. He also observed that the velocity of irrigation has little influence. He also, along with Aschan (1955), and Henriksson (1956) believed that the temperature of the water was more important than the volume.

There has been some debate whether cold and hot syringing by this method should be considered equal stimuli. Fitzgerald and Hallpike (1942), McNally, et al. (1948), Hallpike, et al. (1951), Hamersma (1957), and others have shown that cold water produces nystagmus of longer duration than than produced by hot water. Jongkees (1948) claimed that this could be explained on the basis of a vasomotor effect. Aschan (1955), Henriksson (1956), and Aschan, et al. (1956), noticed that the mean maximum eye speed in the slow phase was the same after both cold and hot water. McNally, et al. (1948), had their doubts if this was equal stimulus. Jongkees (1949) gave the opinion that the time inbetween the tests need not be longer than six minutes.

In the present study ten minutes were allowed between each test.

III. INTERPRETATION OF RESULTS OF THE CALORIC STIMULATION.

Graphic recording of the induced nystagmus has certain advantages over direct observation. Jongkees (1949), and McNally and Stuart (1953), have pointed out the difficulty of determining the cessation of the nystagmus. Calculations of the speed of slow component of nystagmus, the latent period of onset, the total number of beats per reaction, and the total amplitude of the deviation of the eyeball can only be measured from a graphic record.

A. Duration of the Nystagmus:

An estimation of the duration of nystagmus as the chief measure of the vestibular sensitivity has been done since caloric tests became popular. Fitzgerald and Hallpike (1942), Jongkees (1948), McNally, et al. (1948), Aschan (1955), have all used this as an indicator.

According to Stahle (1956), Barany and Wittmaack seem to doubt that the duration of nystagmus reflects the entire course of caloric stimulation, and they stressed the importance of noting also amplitude, frequency and eye speed.

Cawthorne, et al.(1956) agreed that a serious quandary would arise if quantitative comparisons were needed between short nystagmic reactions of large amplitude and long reactions of small amplitude. However, these authors state that in practise in any individual, the larger response is usually associated with longer duration.

Aschan, et al.(1956) found that greater variations occurred with regards to the slow speed and total amplitude, as compared to the variation of total duration.

Henriksson (1956) made a comparison between the eye speed and the durations for normal ears, ears operated on with radical mastoidectomy, and cases with unilateral nerve deafness, and showed a great difference in eye speed, but about the same duration. He came to the opinion that the duration of nystagmus cannot be an adequate expression of the excitatory effect of caloric stimulation on the sensory epithelium in the labyrinth.

Pursiainen (1954) did caloric tests on patients before and after fenestration operation and noted that in the post operative tests duration of nystagmus was shorter in a considerable number of his cases.

Stahle (1956), from an electro-nystagmographic study of the caloric tests, concludes that an estimate of the duration of nystagmus alone as a measure of the sensitivity of the labyrinth cannot be considered adequate, and should be complemented by assessment of the other features of nystagmus. Hamersma (1957) also came to the same conclusion.

Many cases in the present study seemed to confirm the opinion of these authors. These cases show periods of absence of nystagmus during the reaction which Stahle (1956), and Riesco-MacClure and Stroud (1960) refer to as Dysrhythmia of Post Caloric Nystagmus. Such phenomena would be missed if only total duration was observed, and thus indicate an increased reaction despite the fact that the other components of the nystagmus are relatively less.

B. Latent Period of Onset of Nystagmus:

The time lag from the commencement of syringing to the appearance of the first beat of the nystagmus is considered as the latent period.

Kobrak (1912), Alexander and Brunner (1922), and Wodak (1952) have attached diagnostic importance to the latent period. McNally, et al. (1948) have suggested the use of the latent period along with the duration of the nystagmus. Dohlman (1925), Fischer and Wolfson (1943), Fitzgerald and Hallpike (1942), and Arslan (1955) have disregarded it as it depends on other factors also, for example, the structure of the temporal bone. Aschan, et al. (1956), mentions that the first few beats may not be properly recorded as the stimulus is still being used. This causes in some subjects a discomfort with possible squeezing of the eyelids, thus interfering with proper recording.

Jongkees (1953), according to Hamersma, is of the opinion that in the present knowledge of the latency, the latent period must be viewed with reserve.

Stahle (1956) concluded that pronounced asymmetry in the latent periods is reflected in other features of the nystagmus. He considered it as a complement to a complete examination of vestibular reactions.

C. Total Beats:

Calculation of the number of total beats in each reaction has been used by Frenzel (1925) and Arslan (1955) among others. Fischer (1928), however, felt that this shows great individual variation and it is not reproducible in successive tests. Stahle (1956-58) also showed that the number of beats is subject to greater variation than the duration, but reported that the number of beats, total amplitude and maximum intensity give largely similar results.

Hamersma (1957) mentions that the maximum speed of the slow phase of nystagmus, the total amplitude and the total number of beats represent the labyrinthine activity due to thermic stimulation, more accurately than the duration. From the electronystagmographic record it is easy to calculate the total number of beats per reaction.

D. Total Amplitude of Nystagmus:

This is calculated by adding all the fast components of the nystagmic beats in a graphic record. It is expressed as degrees of eyeball rotation.

Mittermaier and Christian (1954) regard the total amplitude as an important measure of the magnitude of the response.

Aschan, et al.(1956), and Henriksson (1956), and Hamersma (1957), have demonstrated that considerable variations in the number of beats, total amplitude, eye speed can exist although duration of nystagmus shows normal response.

E. Maximum Speed of the Slow Component:

Buys (1924-25), Dohlman (1925), and Lorente de No (1935), have shown the eye speed in the slow phase of nystagmus is a direct expression of cupular deviation and may therefore be taken as a measure of labyrinthine reaction. Van -Egmond and Tolk (1954), Aschan, et al.(1956), Henriksson (1956), and Hamersma (1957), have all shown the importance of calculation of slow speed of nystagmus.

Henriksson (1956) devised a derivation unit to record directly the slow speed, and he felt that the speed of the slow component and not the duration is the adequate expression of the sensitivity of the vestibular apparatus in caloric tests.

Koch, et al (1959), came to the conclusion that eye speed recording rather than duration is a much more certain way to reveal cases with impaired vestibular reactivity and is thus indispensable for the important differentiation between central and peripheral lesions.

Stahle (1956) gives the name of 'intensity' of the nystagmus to the total deviation of the eye during a chosen period, and considers this comparable to the eye speed in the slow phase.

SUMMARY:

Methods of recording of Nystagmus are reviewed in this section. The difficulties of the visual examination for the presence of the nystagmus are mentioned. Different methods for recording the eyeball movements have been described. The most commonly used method of recording is Electronystagmography which uses the corneo-retinal potential difference.

Nystagmus has been analysed from this record by considering the total duration of nystagmus, latent period of onset, total beats, total amplitude, and maximum slow speed. Most accurate information about the peripheral labyrinth is derived from the maximum slow speed, total amplitude and total beats estimation.

CHAPTER II

REVIEW OF PHARMACOLOGY

Different drugs have been known to affect vestibular function. The great impetus to the use of some of the anti-histamines for motion sickness was given by Gay and Carliner (1949) when they used Dramamine in subjects suffering from motion sickness. Since then other authors have tried similar preparations and have reported a beneficial clinical effect (Beaumont 1949, Palmer 1950, Chinn, et al. 1950, 1952, 1953, etc.). De Wit (1953) investigated during cupulometry the effect of dimenhydrinate and atropin on human subjects. He found that these preparations diminished the duration of the after reactions.

Riskaer and Permin (1954) could also, by the use of an antihistamine, suppress horizontal nystagmus in rabbits which had been induced by a unilateral injection of 0.1 mg/kg. DFP into the common carotid artery.

Gutner, et al. (1954), also showed that Cyclizine, another antihistaminic drug, caused a marked suppression of the labyrinthine excitability to caloric stimulation.

Aschan, et al. (1957)(a) investigated the effects of some of the antihistamines on positional alcohol nystagmus and found there was inhibition of positional gaze nystagmus. This effect to them seemed to be more closely related to their antiemetic effect and their effect on motion sickness than with their sedative effect.

Effects of Phenobarbitone:

Effects of the barbiturate group of drugs on the eye movements has been studied. Bender and O'Brien (1946) studied the eye movements in patients with lesions of peripheral vestibular apparatus, brain stem, or cerebrum by the use of injection of sodium penthotal in conjunction with rotational, optokinetic and caloric stimuli. They took care to prevent the patient falling asleep. They noticed that there appears a coarse nystagmus after the injection. The optokinetic nystagmus was abolished. They

concluded that nystagmus produced by barbiturates is not peripheral in origin, as it could be produced in subjects with paralysis of peripheral vestibular apparatus, but that it is probably central in the cerebral cortex and partly in the brain stem. The barbiturates, acting as a brain anaesthetic, also interfere with impulses going and coming from the vestibular nuclei.

Gutner, et al. (1951), studied the effect of Dramamine and other drugs including Secobarbital Sodium on the caloric induced nystagmus. They could not show any effect on the nystagmus by oral Secobarbital Sodium.

Bergman, et al. (1952) studied the effect of drugs on electrical recording of normal and abnormal eye movements. They noticed that intravenous injection of Amobarbital Sodium very soon produces a non descript disorganization of the nystagmogram baseline with random movements. As the dose is increased nystagmus of a jerky character appears producing a saw tooth wave. Again they observed disappearance of the optokinetic nystagmus as well as of any manifest spontaneous

nystagmus. They observed a similar effect with Mephensen (Tolserol) although it required higher doses of Mephensen to produce the effect.

Rinaldi and Ferrari (1951), administered Pentothol to rabbits setting up a state of pre-sleep. In almost all cases they noted a phenomenon which they thought was similar to that provoked by a symmetrical stimulation of the labyrinth, that is, lateral conjugate deviation of the eyes and nystagmus. However they observed that this phenomenon was completely independent of variations in the position of the head. The same recurred when the animal was awakening from sleep after the medication.

They could not postulate a basis for this phenomenon except that it might be an inhibition or a liberation of different degrees of sensibility of the Central Nervous System due to the drug.

Aschan, et al.(1956) observed positional nystagmus in patients who gave a history of Barbiturate ingestion.

Anderson, et al. (1958) used intravenous Amobarbital while doing caloric tests on normal individuals and in patients with neurological disease. They observed that most involuntary movements, including spontaneous nystagmus are altered by ingestion of the barbiturates and that nystagmus is abolished during the caloric tests.

Philipszoon (1959) studied the effect of Nembutal on the vestibular function in rabbits and human beings. In the rotation and parallel swing tests he found that the vestibular eye reflexes were suppressed by Nembutal only if very deep anaesthesia was reached.

Site of Action of Phenobarbital:

Goodman and Gillman (1956) gave the locus of action and mechanism of action of barbiturates as at all segments of the Central Nervous System, the cerebral cortex and the reticular activating system being the most sensitive.

According to Toman (1952) Phenobarbitone blocks the conduction in the peripheral nerves and is more effective than other preparations.

Krantz and Karr (1958), believe that the barbiturates act at the cerebral cortical level.

Gangloff and Monnier (1957) studied the action of anticonvulsant drugs by electrical stimulation of the cortex, diencephalon and rhinencephalon in the unaesthetized rabbit. They came to the conclusion that Phenobarbitone has definite action on the diencephalon "after discharge" and a somewhat slighter influence on the rhinencephalon.

Arduini and Arduini (1954) demonstrated that Pentobarbital both inhibited responses in the reticular formation evoked by peripheral stimuli, and blocked the EEG arousal response to stimulation of the reticular formation.

This view has been confirmed by Killam and Killam (1958) who also showed that the inhibitory effect of the reticular formation stimulation on responses in the auditory system was also blocked by Pentobarbital.

Bradley's (1958) observations with Pentobarbitone confirmed these findings of Arduini and Arduini. He also suggested that

barbiturates block conduction in the medial pathways at the brain stem level.

Effects of Diphenyl-hydantoin (Dilantin)
on Vestibular Function:

Since the introduction of Dilantin for the treatment of convulsive disorders in 1937 by Merritt and Putman, it has been very extensively used. In 1939 these authors described toxic symptoms following long term therapy. In the Central Nervous System ataxia and diplopia with nystagmus were among the symptoms. These symptoms disappeared on the withdrawal of the medication. Similar toxic symptoms have been reported by Blair, et al (1939), Feterman (1940), Goodman and Gillman (1956), Merritt (1958), Michaux, et al.(1959), Schwab and Murphy (1959-60) among others. An intensive search of the literature on Dilantin revealed only one reference on the study of the effects of clinically high doses of Dilantin on the Caloric tests for vestibular function.

Vettori (1956) studied two groups of five patients each, epileptics and non epileptics, to whom Diphenyl-hydantoin in high doses of 0.6 to 0.8 gm. were given. Caloric tests were carried out before and after medication. He found that in these cases with one exception, there appeared the phenomenon of hyper-reflectivity of the vestibular apparatus along with vertigo, asynergy, adiadokokinesia and dysmetria. He postulated that Diphenyl-hydantoin causes an irritation of the nuclei and pathways of the vestibular apparatus and of the cerebellum. He did not use any mechanical or electrical methods of recording nystagmus.

The mechanism of action of Diphenyl-hydantoin on the Nervous System has not been fully elucidated (Goodman and Gilman 1956). Diphenyl-hydantoin is closely related to the barbiturates being a derivative of Glycolyl urea instead of Malonyl urea (Goodman and Gilman).

Merritt and Putnam (1938) measured the capacity of this group of drugs to increase the threshold of the motor cortex in cats.

They found that the principle pharmacological response to Dilantin is a depression of the motor cortex.

Goodman, et al. (1946) found on close analysis of the phenomenon observed that Dilantin does not raise the threshold for minimal electroshock seizures in normal animals, nor does it prevent such convulsions. This was proven in a variety of laboratory animals by observing the occurrence of EEG seizure discharge, overt convulsion and postictal depression.

Woodbury (1955) showed that Dilantin elevates the electroshock threshold in rats by seventeen per cent. Gangloff and Monnier (1957), tested the action of anticonvulsive drugs during electrical stimulation of the cortex, diencephalon, and rhinencephalon in the unanaesthetized rabbit. They showed that Dilantin in doses of 100 to 150 mg. per kgm. of body weight, has a marked effect on the diencephalon.

Morrel, et al. (1959), using an artificially produced primary epileptogenic cortical focus in the rabbit studied the effects of Dilantin, Tridione and Phenobarbital on discharge frequency

of the primary focus and propagation. They came to the conclusion that the clinical anti-convulsive effect could be best correlated with a limitation of spread rather than with the suppression of the primary focus. They observed that transcortical propagation was effectively limited with Dilantin.

Effect on the Peripheral Nerve:

Toman (1952) found that when untreated frog sciatic nerve is stimulated excessively and repetitively, the threshold falls to about half and recovers over a period of a minute. Pretreatment with a number of anticonvulsant drugs can abolish these effects.

Morrel, et al. (1958) studied the effects of systemic Dilantin on the peripheral nerves in situ in the rabbit. They noticed that there is, among other findings, an increase of the threshold to electrical stimulation of the peripheral nerve or its nerve endings.

Iannone, et al.(1958) and Braham and Saia (1960) have used Diphenyl-hydantoin for trigeminal and other neuralgia with good results, on the basis that it reduces nerve excitability.

Morris, et al (1956) described two cases on Dilantin therapy which exhibited a transient hemiplegia which disappeared on withdrawal of the drug.

Hoffman (1958) described cerebellar lesions in a patient after parenteral Dilantin administration. Microscopic studies of the brain sections showed abnormalities in the basal ganglia, cerebellum, and to a lesser extent in the hippocampus. The most obvious changes were seen in the cerebellum where the Purkinje cells had virtually disappeared.

Manlapaz (1959) reported two cases of Dilantin intoxication in children in whom there was marked abducens nerve palsy in conjunction with cerebellar symptoms. He believed that with predominance of brain stem and cerebellar symptoms in Dilantin intoxication, there is most likely a difference in its quantitative accumulation in the different structures of the brain and it may have selective absorption.

Hoffman, et al.(1959) injected intravenously Dilantin in curarized cats maintained on artificial respiration and observed depressive effect on the myocardium when the dose was increased to prevent the epileptogenic discharge.

Schwab and Murphy (1959-60) have shown that patients will show ataxia and nystagmus even within thirty to forty minutes following the intravenous injection of Dilantin.

SUMMARY:

In this chapter the pharmacological actions of Phenobarbitone and Dilantin have been reviewed.

Phenobarbitone and other drugs of the barbiturate groups act at different levels of the Central Nervous System. The cerebral cortex and the reticular activating system are the more sensitive areas. The barbiturates have been shown to produce coarse spontaneous nystagmus and also abolish induced optokinetic nystagmus.

The mechanism of action of Dilantin on the Nervous System has not been fully elucidated. It is shown to elevate the electroshock threshold. Clinical anticonvulsive effect could be best correlated with a limitation of spread rather than with the suppression of the primary focus. Dilantin has also been shown to reduce the excitability of the peripheral nerve.

Dilantin in toxic doses produces spontaneous nystagmus and ataxia. However, not much has been written on the effect of Dilantin on vestibular function as it is administered in common clinical practise.

CHAPTER III

METHODS OF INVESTIGATION

A. SELECTION OF SUBJECTS:

(1) Normals:

Thirty-one young adults have been used as controls for the study of the normal response to caloric stimulation. In all of these the results of the otolaryngological examination were normal, including the audiograms. Twenty-nine of the subjects were female nursing students from the Royal Victoria Hospital School of Nursing. Their ages ranged between seventeen and eighteen and a half years. Two were male medical students from McGill University, their ages being twenty-two and twenty-eight years. None of these subjects had a history of oto-neurological disease. They had not taken medication routinely or in large amounts before or during the testing. The present test was their first vestibular function test.

(2) Subjects on Anticonvulsive Medication:

In this group are included twenty-two seizure patients who had a history of anti-convulsive medication - Phenobarbitone and

Dilantin (Diphenyl-hydantoin). This main group is further subdivided into two subgroups.

(a) Fifteen subjects were on Phenobarbitone and Dilantin at least at the time of one of the tests. Out of these, seven had two tests; one test was done during the time when the therapy was discontinued. They had the other test while on the medication. Included in this subgroup are nine males and six females. Their ages ranged from fifteen to fifty-four years. Ten had focal cerebral seizures - seven in the left temporal region, two in the right temporal and one bitemporal. The other five had centren- cephalic seizures.

(b) This subgroup comprises seven seizure patients who gave a history of long term medication but at the time of the vestibular test were off the medication from three to seven days. Three cases had the last medication three days, two - four days, one - five days, and the last case - seven days before the test. Two subjects also had Mysolin and one Mesantoin. There were five males and two females in this group, their ages ranging between twelve and

thirty-three years. The seizure activity was right temporal in four, one left frontal, one left occipital and one centrencephalic.

In this main group 2, none of the subjects showed either spontaneous nystagmus or any manifestation of Dilantin intoxication.

The usual dosage of Dilantin had been 100 mg. t.i.d., of Phenobarbitone it was 100 mg. h.s., of Mysolin 250 mg. q.i.d., and of Mesantoin 100 mg. t.i.d.

These subjects were chosen from the Montreal Neurological Institute from the services of Dr. T. Rasmussen and Dr. F. McNaughton.

(3) Subjects on Dilantin:

In this group are included seven subjects; five males and two females, their ages ranging from twenty-one to sixty-seven years. These served as control subjects on Dilantin therapy. They were carefully screened to exclude the possibility of their having any otoneurological symptoms or of having had any medication of a sedative nature. These were

comprised of the following subjects: One male suffered from Carcinoma of the lung, another from Carcinoma of the hypopharynx, another from Hodgkin's Disease, and one had a Nasal Polypectomy. The other three had non specific symptoms.

All of the seven subjects had one test before the start of Dilantin therapy; the other test was done at least a week after being on medication.

Six of this group had the complete alternate hot and cold caloric stimulation. One girl, who could not tolerate the warm water, had only the cold water test. None of these subjects showed any symptoms of toxicity and tolerated Dilantin well.

B. PROCEDURE:

The test was conducted in a quiet semi-darkened room. The subject was given a complete ear, nose and throat examination to exclude any wax in the ear canal or any perforation of the ear drum or fluid in the middle ear.

The subject was then laid on a couch with head flexed 30° forwards to bring the horizontal canals in a vertical plane. The subject's eyes were kept closed all the time except for examination of any gaze nystagmus or for calibration.

(1) Application of the Electrodes:

Five electrodes were applied on each subject. Two of these recorded movements of the eye in the horizontal direction, two in the vertical direction, and one was placed in the centre of the forehead as a ground.

(See fig. 2)

The electrodes used were silver discs of 1 cm. in diameter and 1.5 mm. in thickness. The horizontal electrodes were fixed on the face about 2 cm. away from the outer canthus of the eye. Any nearer to the eye would produce disturbing irritation to the patient with consequent screwing up of the eye.

Similar silver electrodes were used for the recording of vertical nystagmus, one on the forehead and the other one over the cheek, 1 cm. above and below the orbital margin,

ARRANGEMENT OF ELECTRODES

Figure 2

slightly medial to the pupil. This vertical record helped in differentiating blinks from true nystagmus.

Firstly the skin was cleaned to remove the excess grease from the skin. Ordinary ECG electrode jelly was used to make contact with the skin, and the electrodes were securely fixed with the help of ordinary adhesive tape. Sometimes, when an excess of jelly was used, or the patient sweated profusely, the electrodes would become loose. Since this effects the recording, especially with longer time constants, the test had to be repeated.

(2) Recording Equipment:

The electrodes were connected through tinsel covered wires to a four channel Grass Polygraph with type 5 P1 low level DC pre-amplifier with a pen writing oscillograph.

Initial attempts with DC recording were not very successful and AC recordings were done. However, as the built in maximum time constant of these preamplifiers for AC recording is 0.8 seconds, special capacitors

were inserted to give a time constant of 4.5 seconds.

For the Nystagmograph ordinary EEG paper was used, and the paper speed was set at 15 mm. per second. Two channels were used for recording nystagmus; one for the horizontal and the other vertical. With the subject well grounded, and the high frequency filter of the oscillograph amplifier set at 15 per second, a special wire cage over the subject to reduce the electromagnetic interferences produced by the mains and TV signals was not found necessary.

The preamplifier sensitivity was usually set at 0.05 mv. per cm. This setting however depended upon the calibration of the machine. If a 10^0 deviation of the eyes caused deflection of the needle more than 2 cm., a lesser sensitivity of 0.1 mv. per cm. was used.

An electronic timer was connected to one spare channel to mark the beginning and the end of the stimulus.

Following the usual routine, the polarity of the oscillograph recording the nystagmus was such that the eye deviation to the right produced a deflection in the upward direction, and the deviation to the left in the downward direction. Similarly, in the vertical channel, upward and downward movement of the eyes caused deflection of the needle upwards and downwards respectively.

(3) Calibration:

To alleviate the effect of light adaptation, the subject was kept in the room at least ten minutes before initial calibration was done. After the application of the electrodes to the face the eye movements were calibrated by asking the subject to look at the 'gonioscope' especially built for this purpose. There are flashing lights which, when used at the proper distance of 1.5 meters from the cornea, subtended an angle of 10° from the midline on both the right and the left side. Calibration was done at the start and the end of the test, both for the right and the left sides, at least six times in each direction. (See fig. 3)

Figure 3

There was seen to be no difference of the corneo-retinal potential during the test. For the reading of the records all four calibration values were added and the mean calculated.

(4) Observation of Spontaneous or Positional Nystagmus:

This was done following calibration. Spontaneous nystagmus is easy to record. Quick change from a sitting to a lying position with the head turned to one side was used to elicit positional nystagmus.

(5) Caloric Stimulation:

In the present study the original technique of Fitzgerald and Hallpike (1942) was followed. Cold water at 30°C and hot water at 44°C in the amount of 250 ccs for 40 seconds was the stimulus.

Two water baths (Haake Thermostat Model F) were used. One was set at 30°C and the other at 44°C. Water continuously circulated through the outlet and inlet rubber tubing. At the end a Y connection was used, and a small rubber tube connected to the third end of the Y tube. At the tip of the rubber tube was

fixed a nozzle of such a size that the amount of water ejected by the pump of the water bath was 250 ccs in 40 seconds. The thermo-regulator of the water-bath was set to insure that the water ejected at the nozzle tip was at the required temperature. This thermostatic control was frequently checked for accuracy. (See fig. 4) The body temperature of the subjects was not taken into account in regulating the thermostat as it would not have made much difference in the overall result of the four tests.

Caloric stimulation was done in the following order: right cold, left cold, right hot, and left hot. At least ten minutes were allowed between each stimulus. Any vegetative reaction in the subject was noted.

After the caloric testing, calibration was repeated. Face and ear canals were wiped dry, thus completing the procedure.

APPARATUS FOR CALORIC IRRIGATION

T. THERMOSTAT
H. HEATER
P. PUMP

Figure 4

C. METHODS OF ANALYSIS:

Each subject's reaction to caloric stimulation was determined by a careful analysis of the nystagmograph under the following headings.

(1) Duration of Nystagmus:

This was calculated from the beginning of the stimulus to the last of the nystagmus beats in the same direction. Any after-nystagmus in the reversed direction was not included.

(2) Latent Period of Onset of Nystagmus:

This was computed from the beginning of the stimulus to the onset of the first nystagmus beat.

(3) Total Beats per Reaction:

The number of nystagmus beats recorded on the graph during each reaction were calculated with the aid of a hand counter. All the beats with both the quick and slow components were included.

(4) Total Amplitude:

From the graphic record it was calculated by adding all the fast components. Such was achieved by tracing, over the individual

beats, a map measure. The total distance indicated on the map measure was converted into degrees of rotation by the use of the calibration.

(5) Maximum Speed of Slow Component:

In this study the maximum eye speed was calculated from the inclination of the slow phase over a period of at least 10 seconds during the height of the response. It is expressed as degrees per second. Care was taken to count only the nystagmus beats recorded on the base line. (See fig. 5)

D. ERRORS OF THE METHOD:

(1) Accurate reproduction of the slow phase of the nystagmus is best reproduced by DC recording. However, considering the difficulties encountered with this set-up, the next best method was used. AC recording with a long time constant of 4.5 seconds gave fairly accurate results. Direct recording of the slow speed can be done by using derivation units (Henriksson, 1956). In the present study, due to lack of the necessary electronic equipment,

Figure 5

Slow speed is calculated as y/x degrees per second with the help of the calibration.

this was not done. However, the slow speed was computed manually. This is a time consuming procedure, but the results compared well with those obtained by others.

(2) Miles (1940), studied the influence of illumination upon the corneo-retinal potential. He found a decrease of about 10 per cent after a dark adaptation of five minutes.

Aserinsky (1955) also found a similar effect of adaptation.

Henriksson (1955) and Aschan, et al, (1956), found the decrease to be negligible.

In the present study the subject was in the semi-darkened room for at least ten minutes before the calibration was conducted. No fall was seen during the test as revealed by calibration before and after.

(3) Extra movements, such as those of the eyelids, swallowing and talking were reflected in the record, more so in the vertical leads, which thus served to make more manifest the nystagmus in the horizontal leads.

(4) Subjects who were tired and sleepy, or apprehensive, showed far more rolling of the eyes which was recorded as a slow swinging round topped curve. However, this does not have the characteristics of vestibular nystagmus (slow and quick phase) and is not difficult to identify.

(5) Groen and Jongkees (1948) noticed that in man, when repeated rotational stimuli are given, the successive responses are diminished. This phenomenon has been called by Hallpike and Hood (1953) as Response Decline. Hood and Pfaltz (1954) observed this phenomenon in rabbits to repeated rotation tests of physiological range. They could not elicit this however on repeated caloric testing.

Philipszoon (1959), from an electronystagmographic study in the rabbits, did not notice any response decline in the maximum slow speed after repeated turning.

For the caloric tests in humans, Fitzgerald and Hallpike (1942) could not detect any response decline.

Similarly, Stahle (1956) found no response decline in duration, number of beats and total amplitude. He could not exclude the possibility of response decline in the intensity of nystagmus. He gave the opinion that this phenomenon can be discarded in clinical practise.

Hamersma (1957) could not elicit any response decline during the cold testing. There was, however, response decline during the hot irrigations, although an interval of thirty minutes was allowed between successive tests.

Henriksson, et al.(1961) did repetitive tests on the cat with caloric stimuli and recorded the nystagmus electronystagmographically. They noticed a decremental effect upon the nystagmus reaction, particularly with respect to the maximum eye speed. The response decline became increasingly apparent as the sequence of irrigation is repeated.

Lidvall (1961) did repeated monoaural caloric stimulation with water of constant temperature at intervals of ten minutes in twenty-five healthy subjects. He observed a progressive decline of the vertigo and nystagmus responses

as measured by mean values of the latency, duration and maximum intensity of the vertigo, duration of the nystagmus and total duration of the nystagmus beats. He did not observe any change in the latency. He felt that the results of his investigation indicate that both the vertigo and the nystagmus responses are centrally controlled.

(6) Fixation Affecting the Vestibular Nystagmus:

Aschan (1955), Aschan and Bergstedt (1955), Henriksson (1955), Hamersma (1957), have all noticed that fixation of the eyes on an object during the test has the effect of lessening the duration and other characters of the nystagmus.

Aschan, et al. (1956), showed that spontaneous nystagmus, observed with Frenzel glasses, becomes more prominent after the eyes are covered. They came to the conclusion that Frenzel glasses do not completely obliterate the fixation element and advised closing the eyes. In the present study the eyes were kept closed during the testing.

CHAPTER IV

RESULTS

ANALYSIS OF DATA AND DISCUSSION

The nystagmographic records from the caloric irrigation of the ears in the three groups of subjects have been analysed. The mean values (mean) and the standard deviation of the mean (SD) is given in each case.

Certain abbreviations have been used in the discussion.

- TT is Total Time of the duration of the nystagmus in seconds.
- LP is Latent Period. The interval between the start of the stimulus and onset of the nystagmus.
- TB is Total Number of Nystagmic Beats.
- TA is Total Amplitude in degrees of eyeball rotation.
- MSS is Maximum Slow Speed. It has been calculated by taking readings during the period of maximum caloric response.
- RC is Right Ear, Cold Water stimulation at 30°C
- LC is Left Ear, Cold Water stimulation at 30°C.
- RH is Right Ear, Hot Water stimulation at 44°C.
- LH is Left Ear, Hot Water stimulation at 44°C.

I. Normal Subjects:

Record of a typical caloric induced nystagmus with quick component to the left side in normal subjects is shown in fig.6.

In this group of thirty-one subjects the following results were obtained from the four irrigations of the ears.

TABLE I

		<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	Mean	187.0	177.8	160.9	176.6
	SD	34.7	24.0	24.8	28.1
<u>LP</u>	Mean	38.7	38.1	40.8	38.0
	SD	11.8	12.3	8.7	12.7
<u>TB</u>	Mean	180.3	168.4	173.3	201.9
	SD	57.0	62.4	68.4	77.4
<u>TA</u>	Mean	2063.	1919.	1875.	2149.
	SD	868.	947.	1077.	1023.
<u>MSS</u>	Mean	21.5	20.5	26.2	25.9
	SD	8.4	9.4	14.3	12.2

Figure 6

Stahle (1956), Aschan, et al. (1956) and Hamersma (1957) obtained slightly lesser responses in their normal studies. However, the irrigation of the ear used by them was 100 ccs of water for 30 seconds, while in the present study, the original technique of Fitzgerald and Hallpike, 250 ccs of water for 40 seconds, has been used.

Although the means for the total time of duration and the total beats are very similar, the standard deviation for the total beats is greater, revealing a greater variation in the total beats than in the total time. The standard deviation for the total amplitude and the maximum slow speed are of the same order as that of the total beats.

The difference between the mean value of two correlated samples in the same population is studied statistically by employing the 't' test (Ferguson 1959).

The following formula is used to obtain the 't' value.

$$t = \frac{\bar{D}}{\frac{SD}{\sqrt{n}}}$$

Where $\bar{D}$ is the difference between the means, and SD is an estimate of the variance of the sampling distribution of $\bar{D}$ using an unbiased estimate of the population variance.

The number of degrees of freedom used in evaluating 't' is one less than the number of pairs of observations, or (N-1); where N is the number of observations. In the study of the normal group of thirty-one subjects (N-1 = 30), to be statistically significant for the two-tailed test at 0.05 probability, the value of 't' should be more than 2.042.

For an individual reading the difference is considered significant if it is more than twice the standard deviation of the difference of the means. Two standard deviations on either side of the mean include ninety-five per cent of the normal population.

The normal group has been analysed under the following headings:

(A) Cold and Hot Sensitivity:

The mean values and standard deviation obtained from cold and hot irrigation for both the ears are given in Table II.

TABLE II

		<u>Cold</u> (RC + LC)	<u>Hot</u> (RH + LH)	<u>'t' value</u>
<u>TT</u>	Mean	364.8	337.0	4.60
	SD	49.0	41.6	
<u>LP</u>	Mean	76.8	78.8	0.53
	SD	19.5	20.9	
<u>TB</u>	Mean	343.3	378.4	2.14
	SD	98.8	139.0	
<u>TA</u>	Mean	3850.	3779.	0.46
	SD	1755.	1963.	
<u>MSS</u>	Mean	42.8	53.1	4.47
	SD	14.5	23.0	

Significant value of 't' for 0.05 probability = 2.042.

Discussion:

The total time of duration for cold water stimulation shows a significantly longer response than that for hot irrigation. This finding has been shown previously by Fitzgerald and Hallpike (1942), McNally, et al. (1948). Stahle (1956) and Aschan, et al. (1956) did not observe any difference between the durations following the two irrigations. Hamersma (1957) found a longer duration following cold water irrigation, but as he showed a response decline

following hot irrigation in his series, he believed that this difference could have been due to a response decline. Six subjects showed a significant difference in the individual readings, the reaction to the cold being more marked than to the hot.

The latent period gave a 't' value of 0.53 which is not significant.

The total beats with a 't' of 2.14 also show a significant difference. However, in this instance, the mean for hot is larger than that of the cold. Hamersma, who also studied the total beats did not notice any difference in his series. Two subjects in this study showed significant increased responses to the hot stimulation on the individual readings.

The total amplitude did not show any significant difference with a 't' value of 0.46.

The maximum slow speed gave a 't' value of 4.47 again showing a more marked response to hot than to the cold. There were four individual readings which were significantly

higher for the hot irrigation. Hamersma also noticed higher values for left hot.

A comparison of the results of cold and hot irrigation of the labyrinth shows a longer total time duration response to the cold stimulation. However, the total beats and maximum slow speed estimations show more reaction to the hot. It was also noted that most of the subjects had more marked subjective responses, for example, dizziness, with hot irrigation than with the cold irrigation. Thus an estimate of the total time of duration alone is not a good indication of vestibular reaction.

(B) Right and Left Ear Sensitivity
(Canal Paresis)

Sensitivity of the right and left ears has similarly been statistically analysed.

The mean values and the standard deviation of the responses from either ear are given in Table III.

TABLE III

		<u>Right</u>	<u>Left</u>	<u>'t' value</u>
		(RC + RH)	(LC + LH)	
<u>TT</u>	Mean	351.5	354.5	0.45
	SD	46.6	42.2	
<u>LP</u>	Mean	79.2	76.5	1.03
	SD	19.4	17.8	
<u>TB</u>	Mean	354.	370	1.2
	SD	39.9	120.2	
<u>TA</u>	Mean	3938.	4068.	0.92
	SD	1698.	1799.	
<u>MSS</u>	Mean	42.8	53.1	1.1
	SD	14.5	23.9	

Significant value of 't' for 0.05 probability = 2.042

Discussion:

None of the test subjects showed any significant canal paresis from the analysis of the means of the different indices. This should be expected from a normal healthy group. Hamersma reports similar findings.

(C) Directional Preponderance:

A left beating nystagmus is compared to a right beating nystagmus by using the caloric test readings from right cold and left hot on the one hand, and from left cold and right hot on the other respectively.

The mean value and the standard deviations are given in Table IV.

TABLE IV

		<u>Left Beating Nystagmus</u> (RC + LH)	<u>Right Beating Nystagmus</u> (LC + RH)	<u>'t' value</u>
<u>TT</u>	Mean	363.7	338.9	2.60
	SD	56.4	41.5	
<u>LP</u>	Mean	76.7	78.5	0.55
	SD	20.5	18.8	
<u>TB</u>	Mean	386.3	338.4	2.2
	SD	125.2	119.4	
<u>TA</u>	Mean	4212.	3794.	1.58
	SD	1781.	1952.	
<u>MSS</u>	Mean	48.5	46.7	0.27
	SD	16.5	23.6	

The significant value of 't' for 0.05 probability
= 2.042.

The total time of duration shows a directional preponderance to the left side. However, in two subjects only was this considered statistically significant.

When directional preponderance is calculated according to the method of Jongkees (1948) who considers the difference to be significant only if it is more than twenty per cent of the total, there was seen to be only one subject with left sided preponderance. Hallpike, et al. (1951), did not note any directional preponderance in their series of normal subjects. Hamersma found a directional preponderance in fifty-five per cent of his subjects when calculated with the percentage formula of Jongkees. However, when calculated statistically for symmetry of left and right sided nystagmus, he found this difference to be insignificant.

Aschan, et al. (1956) did not find any directional preponderance in normal individuals on statistical analysis.

The latent period did not show any significant difference of the means. However,

one subject showed directional preponderance to the right.

The difference of the means of the total beats gave a 't' value of 2.2 which indicates a trend towards the left. Two subjects again showed a directional preponderance to the left.

The total amplitude did not give a significant 't' value. Two subjects showed a directional preponderance to the left in the individual readings.

The maximum slow speed findings were similar to those for the total amplitude.

The difference of the means between left and right sided nystagmus suggests a directional preponderance to the left side in the total time and total beats but not in the other three indices. Two subjects out of thirty-one showed directional preponderance to the left side in the total time, total beats, total amplitude and maximum slow speed.

(D) Dysrhythmia of Post Caloric Nystagmus

This phenomenon is a periodic cessation of nystagmic beats from five to ten seconds as seen in the nystagmographs of caloric stimulation. (See fig.7) Aschan, et al. (1956) have seen this phenomenon in cases of suspected cerebral lesions, but encountered this rarely in peripheral vestibular lesions. They could, however, produce it in normal individuals by irrigating the opposite ear too soon after the first irrigation.

MacClure and Stroud (1960) observed this dysrhythmia in patients with tumours in the midline structure of the posterior fossa, and believe that it is produced by damage to the cerebello-vestibular inter-connection. They observed such a phenomenon in the normal individual if a secondary caloric nystagmus was superimposed on spontaneous eye swinging movement which may occur when the eyes are closed. They did not find it difficult to differentiate it from the true dysrhythmia as it disappeared on opening the eyes.

In the present study of the normals this dysrhythmia was noticed in eight subjects. In none of these were eye swinging movements seen. This dysrhythmia disappeared when the subject's attention was diverted or if the eyes were kept open.

10°

DYSRHYTHMIA OF POST CALORIC NYSTAGMUS

Figure 7

II. Subjects on Anticonvulsive Medication:

Record showing some of the characteristics of the caloric induced nystagmus in medicated subjects is shown in Fig.8.

This group of twenty-two seizure patients gave a history of long term anti-convulsive medication.

(A) Fifteen subjects had caloric tests at the time when they were on medication. The mean values and standard deviations are as follows:

TABLE V

		<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	Mean	133.2	138.0	130.8	149.9
	SD	46.5	52.0	48.5	55.7
<u>LP</u>	Mean	46.6	40.5	40.7	42.5
	SD	17.9	15.0	19.2	17.7
<u>TB</u>	Mean	100.4	123.8	123.6	135.8
	SD	69.9	74.4	86.9	87.4
<u>TA</u>	Mean	1117.	1293.	1234.	1410.
	SD	842.	1094.	978.	979.
<u>MSS</u>	Mean	23.4	22.9	30.3	25.9
	SD	9.0	9.9	14.8	10.9

**NYSTAGMUS TO LEFT
EFFECT OF MED.**

Figure 8

Figure 8 shows the effect of medication on caloric induced nystagmus. The amplitude is diminished and the frequency of beats is also lesser.

The standard deviation of the mean shows a more marked variation as compared to that of the normal. The difference between the means of this group and the normal was compared statistically with 't' values obtained by using the formula for significance of the difference between the two independent samples (Ferguson, 1959).

$$'t' = \frac{\text{difference between the means}}{\text{standard errors of the difference between the means}}$$

This ratio has a distribution of 't' with $(N_1 + N_2 - 2)$ degrees of freedom, where N_1 is the number in group 1, and N_2 is the number in group 2. In the present comparison the number of degrees of freedom is 44 $(31 + 15 - 2)$, and the value of 't' should be more than 2 to be significant.

't' value for the difference of the means is given in Table VI.

TABLE VI

	<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	5.10	4.38	3.56	2.64
<u>LP</u>	1.97	0.91	0.01	1.09
<u>TB</u>	4.13	2.41	2.37	2.84
<u>TA</u>	3.53	2.01	1.96	2.35
<u>MSS</u>	0.63	0.6	0.12	0.21

Significant value of 't' of 0.05 probability = 2.021.

Discussion:

This comparison reveals a significant diminution in the total time, total beats and total amplitude for the medicated subjects. The comparison of total amplitude for right hot shows a value of 1.96 which lies between probabilities of 0.10 and 0.05.

(B) Seven of the above fifteen subjects also had tests when they were off their medication for three to seven days.

Table VII shows reading without medication.

TABLE VII

		<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	Mean	147.4	159.7	129.7	152.8
	SD	85.6	67.2	56.5	68.1
<u>LP</u>	Mean	41.4	44.	46.2	43.4
	SD	18.6	18.9	19.8	20.8
<u>TB</u>	Mean	121.7	119.	119.8	123.7
	SD	77.3	73.9	102.5	82.8
<u>TA</u>	Mean	1598.1	1549.	1314.	1541.7
	SD	1200.5	1071.	1149.	1243.
<u>MSS</u>	Mean	28.3	34.0	31.8	29.0
	SD	16.3	18.9	14.8	15.6

Table VIII shows reading with medication.

TABLE VIII

		<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	Mean	118.3	106.9	109.1	122.8
	SD	52.2	51.0	57.5	58.7
<u>LP</u>	Mean	52.5	45.1	40.8	47.1
	SD	25.2	20.4	20.5	25.6
<u>TB</u>	Mean	60.3	57.	76.5	72.8
	SD	38.4	38.4	67.4	47.3
<u>TA</u>	Mean	627.2	544.4	532.1	925.1
	SD	507.	592.	874.	652.
<u>MSS</u>	Mean	23.8	20.0	28.3	24.4
	SD	10.6	9.2	13.4	11.5

The difference of the means when studied statistically gives the following 't' values for six degrees of freedom.

TABLE IX

<u>'t' values</u>	<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	2.98	3.38	1.27	1.76
<u>LP</u>	3.09	1.06	0.37	0.92
<u>TB</u>	2.61	1.76	1.12	1.98
<u>TA</u>	2.75	3.21	1.09	1.69
<u>MSS</u>	0.9	4.3	1.10	2.35

Significant value of 't' for 0.05 probability = 2.447

Discussion:

A striking feature is the significant difference between the means of total time for cold irrigation which is not seen for the hot stimulus. Latent period is significantly increased only in the right cold irrigation while on medication. Total beats are diminished only in the right cold irrigation under the effect of the

medication. Total amplitude shows a significant diminution while on medication in the cold irrigations. Maximum slow speed gives only one significant reading, the left cold being decreased under the effect of the medication.

To make a comparison between the normal subjects and patients with a history of long term medication, fourteen patients were selected from the main group and kept off medication for three to seven days.

The mean values and standard deviation are given in Table X.

TABLE X

		<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	Mean	148.4	165.0	143.4	160.4
	SD	52.1	50.4	45.9	30.4
<u>LP</u>	Mean	41.0	42.0	41.7	42.
	SD	13.6	13.3	14.1	15.0
<u>TB</u>	Mean	105.5	114.4	115.9	126.5
	SD	65.3	61.1	75.8	66.1
<u>TA</u>	Mean	1504.	1590.0	1411.7	1635.
	SD	1106	940.4	867.	990.
<u>MSS</u>	Mean	27.6	30.6	30.3	28.1
	SD	12.2	14.0	11.6	10.2

These means are compared to those of the normal control group to find out if their responses are normal when the medication is discontinued at least three days before. The 't' values are given in Table XI.

TABLE XI

't' values:

	<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	3.51	1.69	2.37	1.70
<u>LP</u>	0.43	1.4	0.26	1.03
<u>TB</u>	3.9	2.7	2.57	3.23
<u>TA</u>	1.88	1.08	1.42	1.60
<u>MSS</u>	2.19	2.96	0.93	0.44

Significant value of 't' for 0.05 probability = 2.01

Discussion:

The total time shows a diminished response in the previously medicated patients for the right ear irrigations. Left ear irrigations have lesser values with significance of 0.10 probability.

Latent period shows no difference between the means.

Total beats show diminished results in all the readings.

Total amplitude results are not significant.

Maximum slow speed shows more effect on the cold irrigations.

This comparison reveals that there exists an effect of medication three to seven days after it is discontinued.

III. This group of seven is comprised of subjects with non neuro-otological problems who acted as controls for the effect of Dilantin on Vestibular function. Only six of the seven had hot irrigation. The mean values and standard deviations before they were given Dilantin are as follows:

TABLE XII

		<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	Mean	173.1	188.1	162.6	174.
	SD	92.8	89.3	81.9	83.9
<u>LP</u>	Mean	38.3	40.9	40.5	45.3
	SD	18.6	18.2	22.6	22.2
<u>TB</u>	Mean	209.3	204.0	158.3	174.
	SD	110.	110.	110.5	83.3
<u>TA</u>	Mean	2378.9	2264.7	1481.	1848.
	SD	1420.	1223.	1114.	1113.
<u>MSS</u>	Mean	26.9	24.04	22.16	29.5
	SD	13.6	12.1	12.2	14.

The controls in this study should show no significant difference from the normal control before an assessment of the effect of Dilantin can be done. Such a comparison was performed and the 't' values calculated with probability at 0.05 for 36 degrees of freedom for the cold reaction, and 35 degrees of freedom for hot irrigation.

't' values of difference of the means of normal control subjects and the controls in this study are as follows:

TABLE XIII

	<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	0.82	0.85	0.15	0.21
<u>LP</u>	0.02	0.7	0.05	1.31
<u>TB</u>	1.08	1.3	0.49	0.84
<u>TA</u>	0.62	0.88	0.54	0.67
<u>MSS</u>	1.53	0.75	0.73	0.60

Significant value of 't' at 0.05 probability = 2.03

None of these 't' values show a significant difference of the means confirming that the controls in this study belong to the normal population.

The means and standard deviations in this group after they had been on Dilantin for at least a week are as follows:

TABLE XIV

		<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	Mean	168.5	152.8	139.3	112.
	SD	92.3	83.9	74.3	85.8
<u>LP</u>	Mean	44.3	43.1	39.1	40.6
	SD	19.7	21.1	20.7	20.3
<u>TB</u>	Mean	132.8	131.5	107.	112.
	SD	86.8	100.3	63.6	86.7
<u>TA</u>	Mean	1461.9	1341.4	1000.0	1375.0
	SD	1400.0	1141.0	834.0	1253.0
<u>MSS</u>	Mean	16.8	19.4	18.6	25.0
	SD	12.8	10.0	9.7	12.1

The mean value of the post Dilantin test when compared to the mean values of the pre-Dilantin test reveal the 't' value as follows:

TABLE XV

	<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	0.31	2.08	1.25	1.03
<u>LP</u>	1.42	1.13	0.71	1.65
<u>TB</u>	4.37	3.0	2.58	3.45
<u>TA</u>	6.23	2.84	1.89	1.66
<u>MSS</u>	2.17	1.45	1.26	1.18

As there are seven subjects for the cold irrigations and six subjects only for the hot irrigations the degrees of freedom in these two sets of figures is six and five respectively. Corresponding value for significance of 't' value are 2.44 and 2.57.

Discussion:

The total time, the latent period, and the maximum slow speed readings do not reveal any significant difference after the effect of medication.

The total beats show a significant diminution in all the readings.

The total amplitude has a significant decrease in the cold irrigation, however, hot irrigation shows a less significant change.

To observe how long the effect of Dilantin on the vestibular function persists, two subjects were studied after discontinuance of the medication. One subject had tests three days after and did not show any improvement in reaction. However, the other subject had the third test after twelve days following stoppage of Dilantin and showed a return of function.

To study any difference between subjects on Dilantin only and those on Phenobarbitone and Dilantin, statistical analysis of the means of seven subjects of each group at the time of medication was done.

This comparison revealed the following 't' values as shown in Table XVI.

TABLE XVI

	<u>RC</u>	<u>LC</u>	<u>RH</u>	<u>LH</u>
<u>TT</u>	2.05	1.96	1.42	0.62
<u>LP</u>	1.44	0.36	1.17	0.84
<u>TB</u>	2.56	1.55	1.55	2.67
<u>TA</u>	1.73	1.36	1.40	0.97
<u>MSS</u>	3.7	1.57	0.59	0.93

For twelve degrees of freedom for the cold irrigation, and eleven degrees of freedom for the hot irrigation, the significant value for 't' should be more than 2.179 and 2.20 respectively.

On this basis there are only two findings showing better responses with Dilantin than those with Phenobarbitone and Dilantin. Total beats in the right cold and maximum slow speed in the right cold show significant changes. Thus, little difference is revealed between Dilantin and Phenobarbitone plus Dilantin with regard to their effect on vestibular function.

CONCLUSIONS:

I. Normal Subjects.

(a) Out of the five indices used for the study of nystagmus, total time of duration alone is not enough. It should be judged along with the total beat, the total amplitude and the maximum slow speed. The latent period did not show much changes under different conditions. Slow speed is considered a true vestibular component.

(b) Relatively more variations from the mean are seen in the total beats and total amplitude than the other three indices.

(c) A comparison of results of cold and hot irrigations of the ears shows an increased total time of duration to the cold stimulation, whereas the reverse holds true for the subjective phenomenon as vertigo, vegetative reactions, the total beats and the maximum slow speed.

(d) Right and left ears showed no significant difference in their responses in any of the indices of the reaction.

(e) Directional preponderance. Although the duration of the left-sided nystagmus is seen to be more preponderant than the right-sided when the means are compared, there are only two subjects who showed a directional preponderance to the left.

The total amplitude and the maximum slow speed shows no difference of the means. However, two subjects (same as above) show directional preponderance individually. Two subjects out of thirty-one normal individuals can hardly be considered significant.

(f) Dysrhythmia of post caloric nystagmus is seen in twenty-five per cent of the present series. It is hard to accept the views of Aschan, et al (1956), and MacClure and Stroud (1960) that it is pathognomonic of disturbance of the higher centres as none of the subjects showed any sign of a neurological disorder. Some other explanation will have to be found for it.

II. Subjects on Anticonvulsive Medication.

(a) The mean values of response of the subjects while on Phenobarbitone and Dilantin, when compared with those of the normal subjects, reveals a significant diminution in the total time of duration, total beats and total amplitude.

(b) The comparison of results of the two tests with and without medication show only a significant difference of the means of the total time and total beats for cold irrigations.

(c) Subjects on long term anticonvulsive therapy were taken off the drugs three to seven days before the test. The results of these tests were compared with those of the normals. The effect of the drugs was shown to persist for such time. Maximum effect was seen on the total beats. The maximum slow speed showed more changes for the cold irrigation only. This comparatively greater effect on the cold irrigation than the hot cannot be explained.

III. Subjects on Dilantin.

The subjects in this group were shown to be derived from the normal population before being put on Dilantin. The tests after

one week of medication showed suppressive but reversible effect on the total beat and total amplitude of the induced nystagmus. One subject who had the test after three days of discontinuance of medication did not show any return of function, while another showed return in twelve days time.

LEVEL OF ACTION OF PHENOBARBITONE AND DILANTIN

Phenobarbitone and other barbiturates are said to act at different levels of the central nervous system. Also they have been shown to have a depressant effect on the conduction in the peripheral nerves. It is not difficult to comprehend that these drugs can thus depress the vestibular function in normal clinical doses. Intravenous barbiturates have been shown to abolish optokinetic nystagmus before the stage of anaesthesia is reached. (Bender and O'Brian, 1946).

Dilantin in toxic doses has been known to produce disturbance of balance and spontaneous nystagmus. It has been shown to lower the excitability of the peripheral nerve and raise the electroshock threshold. Transcortical propagation of impulses is inhibited by Dilantin.

The results of caloric tests in the subjects on long term anticonvulsive medications show that there is inhibition of the responses. Most affected are the total duration, total beats and total amplitude. The latent period of onset of nystagmus and maximum slow speed do not show related changes. The latent period of onset and maximum slow speed can be considered better indices of the excitability of the labyrinth. If these drugs inhibit the peripheral labyrinth or nerve conduction, then they would produce diminution of the maximum slow speed and probably an increase in the latent period. Such has not been seen in this study.

The rhythm of Nystagmus and the mechanism of vestibular nystagmus has been shown to be controlled in the regions of the vestibular nuclei and the reticular formation. Barbiturates

(Pentothal) has been observed to inhibit responses in the reticular formation which have been evoked by peripheral stimuli (Arduini and Arduini 1954). Such inhibition could explain the diminished responses as seen in the total time, total beats, and total amplitude. All these indices are probably dependent on the activity of the reticular formation-vestibular nuclei complex.

In this study of vestibular function following Dilantin medication for a week, it has been shown that there is a reversible depression of certain characters of the induced nystagmus, i.e. the total beats and total amplitude. Again there is no effect on the maximum slow speed and latent period. Thus one could say that this effect of Dilantin does not appear to be on the peripheral vestibular apparatus.

Gangloff and Monnier (1957) have shown that Dilantin has a marked anticonvulsive action during electrical stimulation of the diencephalon in the unanaesthetized rabbit. Manlapas (1959) has noted abducent nerve palsy in two children with Dilantin intoxication. Higher doses of Dilantin have also been shown to produce disturbances of

cerebello-vestibular complex. It is difficult to postulate how and at what site of the Central Nervous System this suppressive effect of Dilantin, on induced nystagmus, is brought about. It may have an inhibitory effect on the cerebello-vestibular complex, or on the diencephalon, or locally on the oculomotor or vestibular nuclei.

In the subjects on clinical doses of Dilantin, spontaneous or positional nystagmus was not observed in any case. The role of the diencephalon over the vestibular reflexes is not clear. Thus, one may be tempted to exclude the cerebellum and the diencephalon from the regions being responsible for this effect. This leaves the oculomotor and vestibular nuclei which would seem more plausible to be the region involved.

From this study the question arises as to whether this suppressive effect of Dilantin on the vestibular function could be utilized in controlling the condition of irritation of the labyrinth, as for example, in Meniere's Disease.

There is another possibility that Dilantin may also be helpful in subjects with disturbing tinnitus as one of their symptoms. It has already been proven useful in cases of cranial nerve neuralgias.

SUMMARY AND ABSTRACT

This project, originally planned to study the role of the temporal lobe in vestibular function, was modified when it was seen that subjects under study showed markedly suppressed responses to caloric induced nystagmus. It was noted that these seizure patients were on anti-convulsive medication. The possibility of this suppression being due to the medication was considered and therefore the present study was undertaken.

A review of the physiology of nystagmus, its different types, and its mechanism of production, have been given. Methods of recording nystagmus have been discussed. The advantages of utilizing corneo-retinal potential for electronystagmography have been mentioned. The pharmacology of Phenobarbitone and Dilantin with special reference to vestibular function has been reviewed.

The main study consisted of alternate cold and hot caloric tests.

For standardization of the technique, thirty-one normal subjects were studied. The nystagmus was recorded by electronystagmography and the record studied for the total time of duration, latent period of onset, total number of beats per reaction, total amplitude of eyeball movement and maximum slow speed.

Cold water irrigation resulted in a longer duration of nystagmus than the hot while the reverse effect occurred with total beats, total amplitude and maximum slow speed. There was seen to be no difference between right and left ear sensitivity. Only two out of thirty-one subjects showed directional preponderance of the nystagmus to the left.

Eight subjects showed Dysrhythmia of the post caloric nystagmus.

Twenty-two seizure patients with a long term history of Dilantin and Phenobarbitone medication had caloric tests using the same technique as with the normal group. Fifteen had medication on the day of the test. The results were compared with those of the normals and showed a significant diminution of responses

with respect to total time, total duration and total amplitude in the medicated patients. Seven subjects in this group of fifteen had one test while off the medication for three to seven days. Comparison of the two tests in these seven subjects showed diminution while on medication, the effect being more marked on the cold irrigation than on the hot.

Fourteen subjects who have been off medication for three to seven days were compared with the normals. This revealed that the effect of medication persists for this time.

Seven non neuro-otological subjects had two sets of tests before and after a week of Dilantin therapy. The tests before the medication when studied with the normal controls revealed them to be from a normal population. After a week of therapy with Dilantin it was shown that the responses for total beats and total amplitude were diminished.

As there is no effect either on the maximum slow speed or the latent period it is postulated that the depressive effect of these drugs is on the central pathways possibly on the reticular formation and vestibular nuclei complex.

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