THE EFFECT OF SOME DRUGS UPON THE LABYRINTH

A NYSTAGMOGRAPHICAL STUDY

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A NYSTAGMOGRAPHICAL STUDY
OF THE ACTION OF ANTI-MOTION SICKNESS DRUGS

ACADEMISCH PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE UNIVERSITEIT VAN AMSTERDAM, OP GEZAG VAN DE RECTOR MAGNIFICUS Dr. J. KOK, HOOGLERAAR IN DE FACULTEIT DER NATUURFILOSOFIE, IN HET OPENBAAR TE VERDEDIGEN IN DE AULA DER UNIVERSITEIT OP DONDERDAG 17 DECEMBER 1959 DES NAMIDDAGS OM 5 UUR

DOOR

ADRIAAN JACQUES PHILIPSZOON

geboren op St. Eustatius

Promotor: Prof. Dr. L. B. W. Jongkees

Aan mijn Ouders
Aan mijn Vrouw

Dit proefschrift werd bewerkt in de Keel-, Neus- en Oorheelkundige Kliniek van het Wilhelmina-Gasthuis te Amsterdam.

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CHAPTER I

INTRODUCTION AND REVIEW OF LITERATURE

The aim of our research was to investigate the effect of sea-sickness drugs on the vestibular organ.

Motion sickness is characterized as a clinical syndrome by dizziness, nausea, vomiting and a general feeling of indisposition. These symptoms may arise when people are in conveyances, constantly subject to many accelerations. Motion sickness occurs on ships, in aeroplanes, trains, autocars, lifts, etcetera. The sickness has already been known for many thousands of years. The ancient Egyptians already knew it when riding on their camels (FERRERI, 1957).

Changes in speed can be perceived by the vestibular organ, the eyes, and the proprioceptive system. It is generally assumed that sea-sickness is caused by overexcitation of the labyrinth (QUIX, 1923; DE WIT, 1953 and 1958). Other unpleasant stimuli, such as being in close spaces or an overfilled stomach may also have a cumulative effect at causing sea-sickness. Psychical factors, naturally, may also play an important role at sea-sickness becoming manifest.

We may, however, assume as reasonably certain that overstimulation of the vestibular organ is a necessary link in the genesis of motion sickness. Rather strong evidence for this view is the fact that people without inner ears are reported not to become sea-sick. In 1896 JAMES announced the refractoriness to sea-sickness of deaf-mutes. SJÖBERG (1931) reports that it is impossible to cause experimental sea-sickness in dogs whose labyrinths have been removed. SJÖBERG concludes also "Optical and kinaesthetic impulses will not be necessary for the symptoms of sea-sickness to appear, but these impulses together facilitate and promote the appearance of the symptoms from the vestibular apparatus which is capable of functioning."

DE WIT showed that people who are hypersensitive to sea-sickness have a steep cupulogram (see Chapter V) compared with persons who are little troubled by that affection. DE WIT also drew the attention to the fact that people with vestibular affections get sea-sick sooner than healthy people.

KRIJGER (1954) stated, also because of evidence obtained with cupulometry, that a sensitive labyrinth predisposes to air-sickness.

NIEUWENHUIJSEN (1958) found that there is a correlation between the number of motions of a ship per time unit and the percentage of sea-sick persons on board. According to QUIX excitation of the otoliths is more important in the genesis of sea-sickness than excitation of the semicircular canals.

MCNALLY and STUART (1942) gave a review of literature on the physiology of the labyrinth in relation to motion sickness, in which they stated

that linear accelerations are most important as a cause of motion sickness.

Thus starting from the standpoint that the vestibular organ is essential for sea-sickness, methods were sought to investigate the effect of drugs on vestibular reactions as a contribution to the elucidation of the mode of action of anti-motion sickness drugs. If a close parallelism between efficiency as an anti-motion sickness drug and potency as regards inhibition of vestibular reactions would be found, such a parallelism could eventually be used for the measurement of the potency of anti-sea-sickness drugs in the laboratory.

Until a short time ago the great difficulty was the objective registration of vestibular reactions. Electronystagmography, however, now enables us to register adequately eye movements by vestibular excitation, so that the objectivity of the results can be much better guaranteed.

With our investigations we have studied the eye movements which were caused by excitation of the vestibular organ, both with linear and with angular accelerations. We made use of the nystagmograph with which HAMERSMA (1957) worked. The methods are described in the next chapters.

NYSTAGMOGRAPHY

The first attempts to register eye movements were carried out with photography or mechanical means. We mention BERLIN, 1891; BUYS, 1909; OHM, 1914; STRUYCKEN, 1918, 1920; DOHLMAN, 1925, KUILMAN, 1931.

Later on electronystagmography was introduced with which by far the best results were obtained.

In the retina electric processes are always taking place, even in the dark, causing the retina to be charged negatively as against the cornea. Hence the eye is to be considered as a dipole, the electrical axis of which

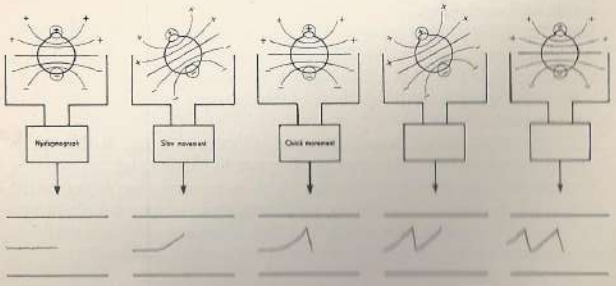


Fig. 1. Registration of nystagmus. The slow movement is directed towards the right and the quick movement towards the left.

coincides with the optical axis. Any movement of the eye gives a change of the field power in the region near the eye. With the nystagmograph the eye movements are registered via these changes in the field power (see fig. 1).

The existence of the above mentioned corneo-retinal potential difference was already described by DUBOIS-REYMOND in 1849.

Publications on electronystagmography appeared by SCHOTT, 1922; MEYERS, 1929; MOWRER, RUCH and MILLER, 1936; FENN and HURSCH, 1937; HOFFMAN, WELLMAN and CARMICHAEL, 1939; MILES, 1939; PERLMAN and CASE, 1944; GLORIG, SPRING and MAURO, 1950; MONTANDON and MONNIER, 1951; MITTERMAIER, EBEL, KÜBLER and BOESEL, 1952; HERTZ and RISKAER, 1953; RUDING, 1953; VAN EGMOND and TOLK, 1954, ASCHAN and BERGSTEDT, 1955; HENRIKSSON, 1955 and 1956; ASCHAN, BERGSTEDT and STAHLE, 1956; MAHONY, HARLAN and BICKFORD, 1957; HAMERSMA, 1957; STAHLE, 1958; ARNOLD, GIULIANI and STEPHENS, 1959.

REVIEW OF THE RESEARCH ON DRUGS AGAINST MOTION SICKNESS

The great progress in the field of the therapy against motion sickness occurred in 1947 when GAY and CARLINER treated a pregnant woman who suffered from urticaria with Dramamine (dimenhydrinate = diphenhydramine + chlortheophylline). This woman also happened to suffer very much from car-sickness. Not only did the patient recover from her urticaria, but also she quite unexpectedly was no longer troubled with car-sickness when she used the drug. This was the prelude to extensive investigation into the effect of antihistamines against motion sickness. In 1949 GAY and CARLINER, in their first publication on the effect of Dramamine on sea-sickness expressed their findings in dramatic terms: "In the troopship *General Ballou* (13.000 tons), 12 hours out of New York on November 27, 1948, the corridors of compartments were congested by sick men so ill that they were unable to reach the latrines. The men who reached these areas were unable to return to their compartments and remained stretched out in a semiconscious condition on the floors until more seaworthy individuals managed to drag them to the sick bay or back to their hammocks. The latrines became temporarily indescribably repulsive... On the previous trip of the *General Ballou* from Bremerhaven more than 100 intravenous injections of saline solution were required to relieve a number of dehydrated persons.

During the voyage which began on November 27 a series of tests were carried out with a drug known as "Dramamine" – compound of theophylline (with chlorine substituted for one hydrogen) with the substance well known as the antihistaminic agent "Benadryl" (= diphenhydramine). As soon as the ship left harbour a group of 134 men in one compartment of the ship were given 100 mg of the drug four times a day for two days; none of these developed nausea and vomiting in this time.

They were left then without treatment for 18 hours, and 41 by that time became sick. Dramamine was given again, and 40 regained their normal well-being within one hour of the first dose. These men were compared with a group of 123 men in another compartment who were given a placebo. Of these, 35 were sea-sick within 12 hours of leaving harbour. At the end of two days the sick men were given Dramamine and obtained complete relief within one hour of the first dose.

In addition to this experiment in prophylaxis another experiment was carried out in which men were treated after they became sick; they were in a third compartment of the ship. Out of 129 men 15 became sick after 12 hours at sea. These were given 100 mg doses of Dramamine every five hours, and all but one were completely relieved. The one was partially relieved. In a fourth compartment containing 99 men, 33 reported sick in 12 hours. They were given a placebo, which cured 19 whose complaints had been merely of nausea and dizziness. The placebo, however, did not relieve the remaining 14, who became steadily worse until they were given Dramamine, when all were cured. Further evidence of the curative value was obtained by treating 195 men who became sick out of 881 in other compartments. Of these there were only eight who were not relieved by taking 100 mg of the drug every five hours. The 187 men who were relieved were treated for two days, after which administration of the drug ceased; 44 of them then became sick again within 12 hours."

These first most spectaculair results of GAY and CARLINER were followed by many comments from authors, who tried diphenhydramine (= Benadryl) as anti-motion sickness drug.

BEAUMONT (1949) wrote enthousiastically after having applied Dramamine: "It is heartening to know that when one first sees a case of severe sea-sickness one can say with almost complete assurance, that the patient will vomit no more!".

PALMER (1950) compared the effect of Dramamine (Benadryl + chlortheophylline) with the effect of Benadryl alone and found that both had the same result.

CHINN, NOELL and SMITH (1950) compared the effect of hyoscine (= scopolamine) and diphenhydramine on motion sickness. They found that when hyoscine was used often disturbances of eye-sight or a dry mouth occurred.

FERMIN, VAN DEINSE and HAMMELBURG (1950) deepened our insight into the effect of diphenhydramine on the otolith reflexes of rabbits. They showed i.a. that the effects of unilateral extirpation of the labyrinth can be entirely compensated by administering diphenhydramine.

WINSTON, RUBIN, LEWIS and REIBERGER (1950) investigated the effect of 200 mg Dramamine, taken orally, on the excitability of the labyrinth by means of the rotation test of BÁRÁNY. With eleven normal subjects they could not ascertain any significant effect.

GUTNER, GOULD and BATTERMAN (1951) investigated whether dimenhydrinate and hyoscine had any effect on vestibular reactions. For this purpose they used a microcaloric test and the galvanic test in human beings. Dimenhydrinate clearly suppressed the vestibular activity, while hyoscine according to their observation heightened the sensitivity of the labyrinth.

GLASER and HERVEY (1951) made a comparative investigation on the prevention of sea-sickness with hyoscine, Benadryl and Phenergan. They found that all three drugs were active, hyoscine having a stronger effect than Benadryl and Phenergan. None of these drugs showed any unwanted side-effect.

KREJCI and BORNSCHEIN (1952) investigated in guinea pigs the influence of dimenhydrinate on the perrotatory nystagmus and otolith reflexes. They also found that hearing was not influenced by dimenhydrinate.

For the perrotatory nystagmus they used a rotating table with counterweight similar to the one we used in our rotatory test with rabbits. They also registered with electronystagmography; according to them dimenhydrinate suppressed the labyrinthine reflexes.

COJAZZI and PIVOTTI (1952), however, stated that Dramamine affected neither the peripheral vestibular apparatus nor the reflex arc of the nystagmus in any way; according to them Dramamine acted centrally on vegetative reactions.

PICHLER (1953) gives us the gratifying information that he saw very good clinical results with Dramamine on patients who were dizzy, suffering from the disease of Ménière and postoperative vertigo.

GUNS, GILLAIN and DOYEN (1953) found a striking effect of antihistamines on dizziness caused by the disease of Ménière, labyrinthine fistula and labyrinth-extirpation.

DE WIT (1953) investigated the effect of dimenhydrinate and atropine on subjects by means of cupulometry, the nystagmus being estimated by direct observation through the spectacles of FRENZEL. He found that Suprimal (the Dutch dimenhydrinate product) and atropine diminished the duration of after-reactions in the cupulogram. He also experimented with the parallelswing, measuring the fluctuations of the intra-ocular pressure due to the swinging of the parallelswing. The intra-ocular pressure was measured with the ophthalmodynamometer of BAILLART, as was done for the first time by HULK and HENKES (1949). The parallelswing is described in chapter IV. With the parallelswing the otoliths are stimulated. DE WIT saw no effect of Suprimal or atropine on the fluctuations of the intra-ocular pressure.

RISKAER and PERMIN (1954) caused a horizontal nystagmus in rabbits by a unilateral injection of 0.1 mg/kg D.F.P. (= Diisopropyl Fluoro Phosphonate) into the carotid artery. They succeeded in suppressing this nystagmus with diphenhydramine and Neptusan (also an antihistamine preparation).

GUTNER, GOULD and CRAVOGANER (1954) made a research with a micro-

caloric and a galvanic test in subjects and showed that another antihistaminic drug, cyclizine, gave a marked suppression of the labyrinthine excitability.

ARNER, DIAMANT and GOLDBERG (1954) gave ship's passengers dimenhydrinate and dimenhydrinate in combination with amphetamine. It appeared that the effect against sea-sickness was equal in both cases, whilst the people who had received amphetamine did not suffer from drowsiness.

GUTNER, GOULD and SWIFT HANLEY (1955) ascertained that another antihistamine drug, meclizine, also lowered the labyrinthine excitability; slightly less, however, than cyclizine and dimenhydrinate.

KREJCI and BORNSCHEIN (1955) administered 300 mg dimenhydrinate intravenously to eleven patients with spontaneous nystagmus. Seven of those patients had a vestibular nystagmus, the other four a nystagmus of central origin. Vestibular nystagmus disappeared under the influence of dimenhydrinate, this drug having no effect at all on a central nystagmus. The nystagmus was recorded by means of electronystagmography.

BARTALENA (1955) studied in 21 normal subjects the nystagmus provoked by the classical BÁRÁNY-test (ten revolutions in twenty seconds) and by the caloric test according to VEITS. He also found a marked suppression of the labyrinthine function by diphenhydramine.

SALERNO (1955) examined the effect of Largactil (chlorpromazine) on vestibular reactions. In rabbits having a nystagmus caused by destruction of one labyrinth, he found that the number of nystagmus-beats per minute decreased significantly. In 21 subjects he found that the rotatory nystagmus clearly decreased after they had been given Largactil.

CARBONARA and SALONNA (1956) found in guinea pigs a decrease of the vestibular activity when they administered Largactil. They investigated the number of beats of the postrotatory nystagmus.

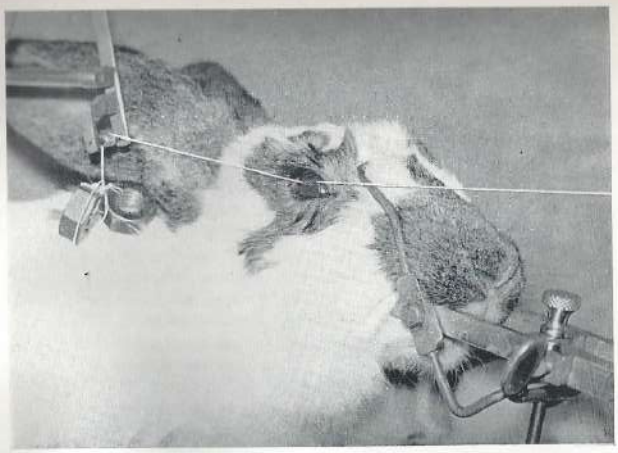
BERGSTRÖM and KOCH (1956) also found in cats and guinea pigs that chlorpromazine gave a decrease of the postrotatory nystagmus.

FELISATI (1956) described very good results in the treatment of giddiness with chlorpromazine in patients who had undergone a fenestration operation.

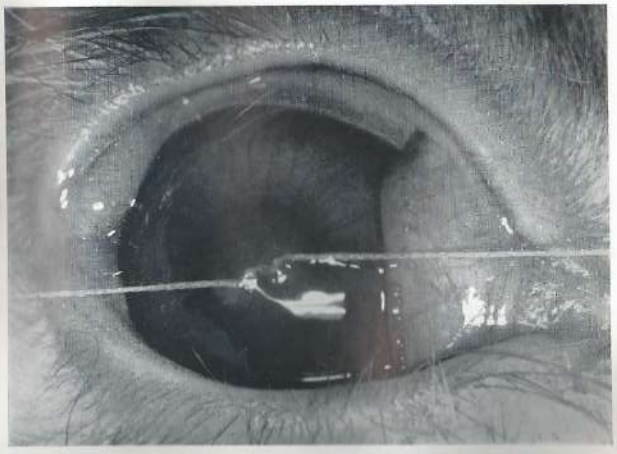
ASCHAN, BERGSTEDT and GOLDBERG (1957) investigated the effect of some antihistamines, chlorpromazine and amphetamine on the nystagmus provoked by the administration of alcohol. They actually found that antihistamines and chlorpromazine gave a marked suppression of the nystagmus, but they obtained no effect whatever when amphetamine was given. Amphetamine did not influence the antihistamine effect.

GLASER and MCCANCE (1959) made an extensive research in subjects rendered sea-sick by exposing them to an artificial wave dash in small rubber boats in a big tank. About one hour and a half before the machine was started the subjects received the drug. For an hour they were subjected to the artificial surge. They found that only 1 mg hyoscine had a marked preventive effect. Cyclizine (50 mg) had hardly

Photograph nr. 1.
Fixation of the electrodes in rabbits.



Photograph nr. 2.



Photograph nr. 3.
Measurement of the Corneo-Retinal Potential difference (C.R.P.) in rabbits.

any effect at all, whereas 25 mg meclizine and 8 mg perphenazine (a tranquillizer) had as much effect as a placebo.

Reviewing the results of the above publications, we must come to the conclusion that there is no consensus of opinion about the effect of antihistamines, hyoscine or atropine against motion sickness or on the excitability of the vestibular organ. About Largactil we always find in the publications data indicating that this drug lowers the vestibular excitability and gives relief to patients with dizziness.

In this connection we thought it interesting to collect, with the aid of electronystagmography, reliable evidence about the effect of drugs on the excitability of the vestibular organ. We decided to choose our compounds from several categories, including a classical compound like hyoscine (scopolamine), an antihistaminic drug reported to possess anti-motion sickness activity like Cinnarazine, the well known neuroleptic compound chlorpromazine, and a barbiturate.

CHAPTER II

MEASUREMENT OF THE CORNEO-RETINAL POTENTIAL DIFFERENCE (C.R.P.) IN RABBITS

For our investigations we used the same type of nystagmograph as HAMERSMA (1957). The system consists of a two-channel alternating current amplifier, from which the signal is led to a direct writing two-channel electrocardiograph (Elema Mingograf 24, Stockholm). A similar system was used by ASCHAN, BERGSTEDT and STAHLE (1956) and by HENRIKSSON (1955; 1956).

The principle of electronystagmography is based on the registration of the eye movements with the aid of the corneo-retinal potential difference (C.R.P.). In the region of the eyes electrodes are placed on the skin, which record changes in the field potential, caused by eye movements (see fig. 1, p. 12).

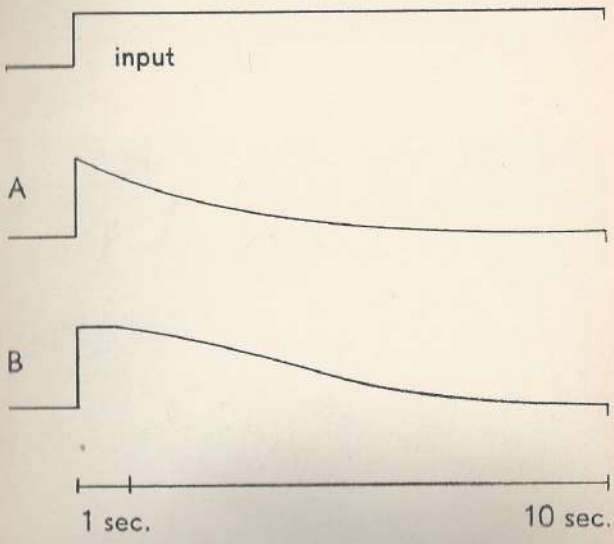


Fig. 2. A. Response characteristic of an amplifying system in which the response decreases immediately.
B. Response characteristic of our nystagmograph showing a constant level for 0.7 seconds.

To record the true position of the eye, a nystagmograph of the d.c. type should be used. This means that is has to respond also to the d.c. component in the signal. Instrumentally it is much simpler to construct an a.c. amplifier, which reacts essentially to variations in the input potential. Such an amplifier follows a sudden step in the input signal rather accurately, but the output signal immediately begins to drift back to the equilibrium value (see fig. 2A). By the use of a special coupling network between the stages of the amplifier, this response has been improved. After a sudden step in the input signal, the output remains for a short time (0.7 seconds) at its newly reached value, reaching the zero line in about 10 seconds (see fig. 2B). This expedient considerably improves the response to a square wave. On the other hand, the recovery time of the instrument is sufficiently short so as not to involve difficulties due to drift.

Fig. 3 shows the recording of the movement of a rabbit's eye, caused by pulling a thread that was sutured into the cornea (see below). The zero line is reached again in about 10 seconds. For a detailed description of the nystagmograph we refer to the above mentioned authors and to the publication of DE BOER, who designed our system.

As electrodes for rabbits we used three injection needles (nr. 20), which were isolated except for three millimeters from the point. One of the needles was used as earth or reference electrode, the two other serving to record changes in the field potential. The latter two were put in the skin on either side of one eye and fixed with collodion. The earth or reference electrode was put in the skin over the middle of the head (see photograph nr. 1).

Occasionally we saw small regular pulsations on the nystagmogram synchronous with nose movements of the rabbit.

It is conceivable that a drug influences nystagmogram-curves, not by changing the movements of the eye but simply by altering the electric

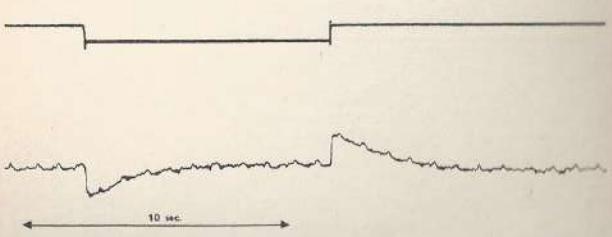


Fig. 3. Registration of two single passive eye movements in a rabbit. Here also we have a constant level for 0.7 seconds, while the zero line is slowly reached in 10 seconds.
A. Registration of the mechanical movement of the relais (see text).
B. Registration of the eye movement.

charge of the eye. If for instance a drug reduces the C.R.P. to zero, a straight line is to be expected, whether the eye moves or not. When this is taken into consideration it is clear, that we must exclude the possibility of an action of the drug via an effect on the C.R.P. and not on the movement of the eye, in every case where a drug modifies the nystagmogram. By always giving the same movement to the rabbit's eye and registering this movement, it ought to be possible, by measuring changes of the amplitude of the curve which may show on the registration paper, to draw conclusions about changes in the C.R.P. Thus, even if the absolute C.R.P. is not measured, changes in the electrical charge of the eye can indeed be found. In human subjects it is a much simpler matter to calibrate the amplitude of an eye movement. We place them at a given distance from a black board and make them look alternately at two white spots on that board. In this way the same eye movement can be reproduced at will. It goes without saying that this method is not practicable in animals. In that case we have to depend on passive eye movements in order to calibrate the excursions of the registration.

For this purpose the rabbit was fixed on a rabbit board, its head in a clamp. The electrodes were put in front of and behind the eye in such a way that a movement to the right gave an upward deviation on the registration paper and vice versa (see photograph nr. 1).

After the cornea had been made insensitive with pantocaïne 0.5 per cent a thread was sutured with two or three stitches in the cornea (see photograph nr. 2). One end of the thread was led via a small pulley to an electromagnetic relais, the other end was fastened to a small counter-

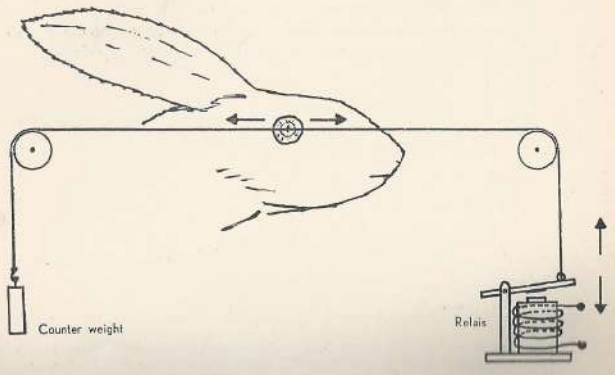


Fig. 4. Scheme showing the measurement and assessment of the corneo-retinal potential difference.

weight via another pulley (see fig. 4 and photograph nr. 3). Switching on of the current – that was given by an accumulator – caused the eye to be drawn forward. Switching off made the counterweight draw the eye back to its original position. In this way we could easily repeat the same movement of the eye. This movement was registered on the paper and directly checked by fixing to the lever of the relais a thread, that was connected via a pulley to another counterweight. The rotation of the latter pulley wheel was registered on the second channel of the recording system (the Mingograf). The position of the axle of the pulley was linearly converted into a voltage by a potentiometer that was electrically part of a Wheatstone bridge circuit.

Any change in the amplitude of the eye movement registered via the C.R.P., not accompanied by a simultaneous change in the curve of the direct registration, can only be due to a change in the C.R.P., as we always gave the same movement to the eye.

We also found, that only very slight spontaneous changes in the C.R.P. occur after a rabbit has been in the dark for half an hour or more. For this purpose we measured in ten rabbits the C.R.P. every five minutes for one hour and a half, starting immediately after they had been put in the dark. During the first half hour, and especially during the first fifteen minutes, the C.R.P. clearly decreased, to remain practically constant after the first half hour (see fig. 5).

On the strength of these experiments we began our rotation tests and parallelswing tests in rabbits half an hour after having put the rabbits in the dark. It is very improbable that a decrease of the amplitudes of the registered eye movements found in the experiments after these precautions would be due to a spontaneous decrease of the C.R.P.

Heck and Papst (1957) described a method to measure the C.R.P. in rabbits, which resembles ours. They cut the conjunctiva from the eyebulb and pulled the Mm. recti sup. and inf., thus fixing the eye in a vertical axis. This makes it possible to move the eye in the horizontal plane. For these complicated manipulations, complete anaesthesia is necessary, which is of course a disadvantage because this very much complicates the interpretation of drug effects. Another disadvantage of their method is that the manipulation of the eyemuscles interferes with the blood supply of the eyebulb, because the vessels which supply the eyebulb are situated in the eyemuscles (Polyak, 1957). This makes the C.R.P. less reliable. Noell (1952) described a method for the measurement of the C.R.P. in which the eyebulb and the eyemuscles are even more injured. Under local anaesthesia Noell cut the eyelids and retracted them from the cornea by means of threads while he severed the conjunctiva from its connection with the sclera. He also removed the bony and membranaceous roof of the orbit and dissected, in order to render the retrobulbar space freely accessible for an electrode, the loose tissue covering the superior ocular muscles. Noell prevented dehydration of the exposed tissues by a cover of cotton soaked in warm, liquid

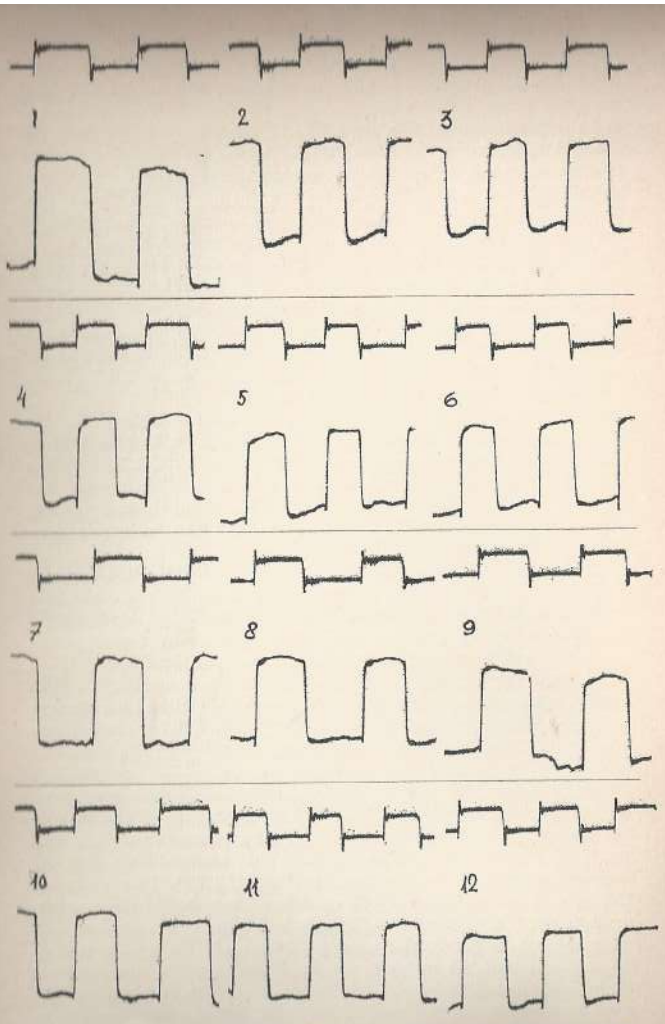
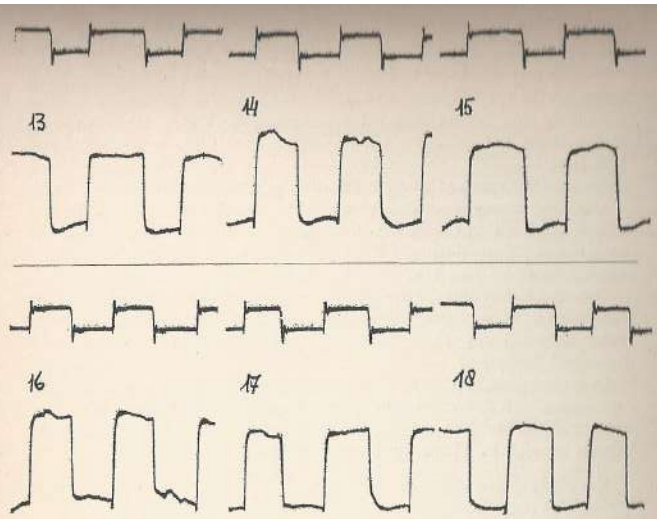


Fig. 5. The corneo-retinal potential difference in a rabbit, after it has been put in the dark, during one and a half hour, measured at intervals of 5 minutes. The upper line represents the movement of the relais, the lower line the movement of the eye.



paraffin. It is to be expected that in this set up the C.R.P. is quite vulnerable, much more than in our method, because the only injures we made to the eye were some sutures into the cornea.

In order to check our experimental arrangement we treated rabbits with sodium iodate ($NaIO_3$) and other rabbits with sodium azide (NaN_3). Sodium iodate reduces the C.R.P. by chemical destruction of the retina cells while sodium azide gives an enlargement of the C.R.P. (NOELL, 1952; HECK and PAPST, 1957). Using our method we got indeed a reduction of the C.R.P. by injection of 0.3 g $NaIO_3$ into a vein of the ear. We did not get a reduction of the C.R.P. to zero as NOELL (1952) and HECK and PAPST (1957), unless we gave huge doses which caused the animal to die. This is probably due to the fact, that the above mentioned authors used for the measurement of the C.R.P. methods in which the eyebulb and especially the eyemuscles are injured in such a way that little is needed to reduce the C.R.P. to zero. We easily succeeded to perform by an intraperitoneal injection of 20 mg NaN_3 the so called azide-effect (NOELL, 1952; HECK and PAPST, 1957) viz. an increase of the C.R.P.

The suppression caused by Cinnarazine and Nembutal of the nystagmus in the rotation test and the compensatory eye movements in the parallelswing-test (see Chapters III and IV) might conceivably be due to a disappearance of the C.R.P. Hence we investigated the effect of these drugs on the C.R.P.

The arrangement was as follows. After the rabbit had been fixed and prepared for the test, it was placed in the dark for half an hour, after which the test began. Every five minutes the C.R.P. was measured, twelve times in total. After the third time the drug was injected intraperitoneally.

Ten rabbits received 40 mg Cinnarazine per kg body weight, ten other rabbits got 60 mg Nembutal per kg. In none of those rabbits did the C.R.P. diminish measurably. We only observed slight fluctuations in the amplitude. These dosages always affected the vestibular eye reflexes (see Chapters III and IV).

Four rabbits received 8 mg Largactil per kg body weight, four other rabbits got 50 mg hyoscine per kg. No C.R.P. changes were observed when Largactil was given. A slight increase of the C.R.P. was caused by hyoscine.

In order to exclude an effect of pantocaïne 0.5 per cent on the C.R.P. we anaesthesised two rabbits completely with Nembutal. We then measured the effect of the instillation of pantocaïne 0.5 per cent in the eye on the C.R.P. There was no such effect.

For the reproduction of some curves we refer to the folding pages inserted at the end of this book.

CHAPTER III

ROTATION TESTS IN RABBITS

As already mentioned in the first chapter, we used electronystagmography for the registration of the eye movements provoked by stimulation of the labyrinth. One obvious advantage of nystagmography over the direct observation of eye movements – with or without Frenzel's spectacles – is the fact that it provides us with a curve of the eye movements which can serve as objective basis for discussions. Though the same curve may be interpreted in different ways, discussion can be expected to be more profitable if a concrete document is available rather than a verbal description of visual impressions. It is often difficult to judge with Frenzel's spectacles, whether an eye movement is a nystagmus or not. A nystagmus is a typical movement of the eye, characterized by a slow component and a rapid component in opposite direction. To judge whether this specific movement is really present may be very difficult, when both components differ only very little in speed. Frenzel's spectacles, one of the most important aids for the investigation of the labyrinth before nystagmography was introduced into the clinic, consist of two strongly positive glasses. Two small lamps are fixed on the inside of the frame on either side in order to illuminate the eyes of the test subject. Through the strong positive glasses and by the illumination the examiner can quite well observe the eye movements of a patient; the patient, however, cannot fix his gaze upon the objects around him. But difficulties remain e.g. in the case of a caloric test performed on a patient. When we observe nystagmus through Frenzel's spectacles, it is difficult to ascertain the duration of the nystagmus with a stopwatch, as often some nystagmus beats still occur after the stopwatch has been stopped. When we register a caloric nystagmus with the nystagmograph, there is a much slighter chance of overlooking subsequent nystagmus beats: we can keep the apparatus in action as long as we want. It has also been proved that the maximum speed of the slow phase of the nystagmus in the caloric test is a much more reliable criterion for the excitability of the labyrinth than the duration of the nystagmus (Van Egmond and Tolk, 1954; Henriksson, 1955 and 1956; Hamersma, 1957). Any reliable estimation of the maximum speed of the slow phase of the nystagmus with Frenzel's spectacles is out of the question. When using the caloric test in patients we often find that the two labyrinths differ little as regards the duration of the nystagmus, while the maximum speed of the slow phase of one labyrinth is a multiple of that of the other. This is often the case in patients whose other clinical data, such as e.g. the audiogram or symptoms of an acustical neurinoma make a great difference in excitability of the labyrinths highly probable.

The natural stimulus for the sense organs of the semicircular canals is an angular acceleration. When a human being or an animal is turned

round the endolymphe in the semicircular canals of the labyrinth is caused to flow by the inertia of the fluid along the wall of the canals. This flow is perceived by sense cells. The sense cells lie close together on one point (the crest) in the semicircular canal. From these sense cells long hairs emerge into the endolymphe. These hairs are bundled together by a jelly-like substance into the cupula. When in a semicircular canal fluid flow arises, its cupula will deviate in the direction of the flow. This deviation of the cupula is the stimulus for the sense cells. It is clear, that when someone turns round with a constant velocity, there is no flow of the endolymphe, as forces of inertia are not acting in that case. Only during an accelerated rotation there will be a flow of the endolymphe, causing the cupula to deviate. Besides the sensation of rotating in a direction opposite to the direction of the fluid flow, this deviation of the cupula provokes various reflexes. One of those reflexes is nystagmus. When there is a deviation of some cupulae, the sense cells transmit this stimulus via the nerve fibres to the central nervous system, which sends impulses to the eyemuscles, causing the eyes to deviate slowly in the direction of the endolymphe flow and in the plane of rotation. This slow eye movement is interrupted by a rapid movement in opposite direction. The rapid movement seems not to be caused directly by the endolymphe flow but by reflexes provoked by the change of position of the eye. A correlation between the magnitude of the angular acceleration and the rapid phase of the nystagmus has not been found, but there is a correlation indeed between the magnitude of the stimulus and the speed of the slow phase. The slow phase is called the vestibular and the rapid phase the central phase of nystagmus.

Nystagmus is a reflex, specifically a reaction following stimulation of a sense organ. The nervous impulses are led over the central nervous system and are not influenced by our will. If we want to investigate the effect of a drug on the excitability of the labyrinth, it is an advantage to do this with the aid of reflexes, as they are not or very little subject to the influence of suggestion. It is of the utmost importance for the objective value of the investigation that we are not merely dependent on the subjective opinion of the examined persons, whether the drugs are effective or not. A subject will sooner give an affirmative answer to a suggestive question than to a question asked in a neutral way. A sea-sick person will sooner start vomiting when he is in the centre of our attention, than when he does not get any attention at all. Thus the fact that a patient who takes sea-sickness drugs does not vomit is not in itself a reliable criterion. It may function as such if adequate statistical designs, such as a double blind procedure, are used. Another advantage of nystagmography over methods in which the eye movements are judged by direct observation lies in the fact that nystagmography offers fewer chances to self-suggestion of the investigator. For he can always let the curve be judged by other investigators and study it as many times as he likes and compare conclusions.

The problem to us was now how to provoke a constant rotatory nystagmus in rabbits. As in rabbits a small rotatory stimulus already provokes a distinct nystagmus, it was sufficient to cause a rotation over a small angle. For this purpose we put the rabbit on a rotating platform, which was turned by a weight over an angle of thirty degrees. As rotating platform we used a table with a circular top, easily about its axis supported by ball bearings. At the side of the platform a string was attached and a weight was fastened at the other end of the string. The string was tightened by the weight via a pulley (see fig. 6). This enabled

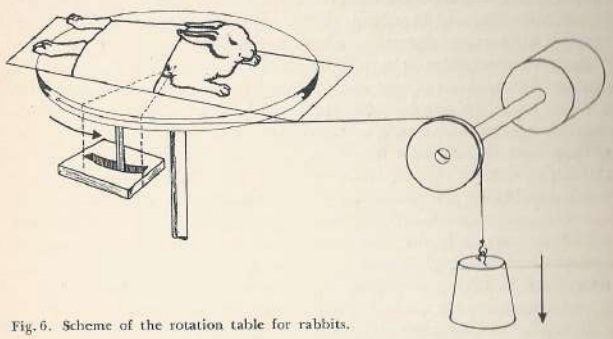


Fig. 6. Scheme of the rotation table for rabbits.

us to rotate the platform by dropping the weight freely. On the table a rectangular board was fixed on which a rabbit board was screwed. We arranged the table in such a way, that it was possible to rotate it always over an angle of thirty degrees. When we rotated the table, by dropping the weight, it was stopped by a clamp, which caught the side of the rectangular board. In this way we always gave the table the same rotation. In order to check whether the table indeed turned at the same speed over the same angle in every rotation, the axis of the pulley was connected with the axis of a linear potentiometer, in such a way that the two axes lay exactly end to end. The position of the pulley could be directly registered via the second channel of the Mingograf by means of the potentiometer, that was linked in a bridge of Wheatstone. The size of the pulley had to be chosen in such a way that, when the weight was dropped, the pulley did not turn more than 290°, the limit of movement of a potentiometer. The weight we used was 525 grams. Rotation over the angle of 30° was always performed within one second. The duration, however, varied, if very slightly, according to the weight of the rabbit. The rotation was not only checked by means of the potentiometer, but it could also be verified whether the nystagmo-

graph was not subject to irregularities during the experiment. Naturally, it is of great importance to know whether the stimulus for the labyrinth was always the same, because otherwise we should not have been justified in comparing with each other the nystagmus curves belonging to different rotations. In this way, indeed, we succeeded in always performing within narrow limits the same rotation, the external stimulus, therefore, was always identical. In order to be able to stimulate the semicircular canals always in the same way, it is also necessary to fix the rabbit and particularly its head. To this end the rabbit was fixed on the rabbit board with its legs; a towel was fastened round its body. The head was fixed in a rabbit's head clamp, so that it could be immobilized perfectly between the hasps of the clamp with a screw. Thus, when the table was rotated, the semicircular canals always received the same stimulus.

Each time we drop the weight an acceleration first occurs. The moment the table is caught in the clamp, it comes to a standstill with a deceleration. In our experiments, we always saw one or more nystagmus beats occur as a result of the acceleration; we also often saw one or two beats in opposite direction caused by the deceleration. After tightening the weight, we always waited at least thirty seconds before we dropped it lest the nystagmus should be influenced by the after-effects of previous movements. We placed the electrodes in front of the eye and behind it, because in these experiments the maximum amplitude of the nystagmus is to be registered in the horizontal plane. The electrodes were fixed in such a way that an eye movement to the right gave an upward deviation on the registration paper and vice versa.

In order to exclude possible light influence the rabbit was put in the dark during the test by screening it with card board and a lightproof photographic cloth. Changes in the quantity of light, such as sudden sun rays, may cause great changes in the corneo-retinal potential difference, which as a matter of fact affects the nystagmogram. We always began our experiments, after the rabbit had been in the dark for half an hour. After that time the potential of the eye is quite constant (see Chapter II). By keeping the rabbit in the dark during the experiment we also excluded the possibility of an opto-kinetic nystagmus.

RESULTS

1. *Calibration tests.*

The influence of adaptation and of normal saline solution on the nystagmus.

If we want to investigate the effect of drugs on the excitability of the labyrinth, we must first perform calibration tests as a background for pharmacological experiments. Our calibration tests with the rotation table were performed in twenty-five normal rabbits. The procedure was as follows.

After the rabbit had been in the dark for half an hour we started the

first rotation. The tightening did not agitate the animals much for after a few minutes most rabbits became very quiet and remained so during the whole course of the experiment.

We rotated each rabbit twelve times in succession, always at five minutes intervals. After the third rotation 10 ml normal saline solution was injected into the peritoneal cavity. In the experiments with drugs the same procedure was followed but after the third rotation an intraperitoneal injection of the examined drug was given.

All our twenty-five rabbits appeared to get nystagmus when they were turned on the rotation table over an angle of thirty degrees. Nystagmus always showed itself during all twelve rotations. To investigate whether the nystagmus was subject to adaptation or affected by the injection with saline solution, we studied the slow phase of the nystagmus that appeared at the beginning of the rotation, caused by the acceleration. In each experiment the series of twelve observations was divided into four groups of three subsequent observations, viz. group I, II, III and IV.

In each group we measured the average angle on the registration paper obtained as a result of the slow phase of the nystagmus. We called the average angle of group I: A; those of group II, III and IV were called B, thus we obtained three different values for B per experiment. The value for $C = B - A$ was now calculated expressed in percentages of A, i.e. per experiment 3 values for C. This is measure for the increase of the angle of the nystagmus. This value can also be used for the comparison of the results of different experiments.

Examples:

$$A = 53^\circ \text{ and } B = 57^\circ$$

$$\text{hence } C = \frac{57-53}{53} \times 100 = +8 \text{ per cent}$$

$$\text{or } A = 43^\circ \text{ and } B = 38^\circ$$

$$\text{hence } C = \frac{38-43}{43} \times 100 = -12 \text{ per cent.}$$

Consequently, with our twenty-five calibration tests, we obtained $3 \times 25 = 75$ values for C. The average value for C was + 1 per cent, from which we conclude that no adaptation occurs and that the injection of saline solution does not affect the rotation nystagmus in our experiments. In our experiments none of the 75 values for C exceeded $\pm$ 15 per cent. Hence, when a drug is investigated and a C value is found greater than + 20 per cent or smaller than −20 per cent we may assume that the drug has a significant effect.

Later on in our experiments with different drugs, it proved to be easy to cause the nystagmus to disappear completely. We then decided to take as criterion for the effectiveness of a drug the total disappearance of the nystagmus, because it is much easier to use this effect than to measure angles. Not only is the measurement of angles subject to considerable errors, it is also very time consuming.

In our experiments the maximum speed of the slow phase of the nystagmus did not decrease, contrary to the findings of HOOD and PFALTZ (1957), relating to the number of nystagmus beats occurring in rotation tests in rabbits. Neither did the number of nystagmus beats decline in our experiments. This difference in results is probably due to the fact that in our experiments the stimulus was much smaller than in those of HOOD and PFALTZ. In our experiments always one to five nystagmus beats occurred, whereas HOOD and PFALTZ regularly obtained series of ten to thirty nystagmus beats in their experiments.

2. *Cinnarazine.*

As an antihistamine we chose for our experiments Cinnarazine*).

Cinnarazine is akin to meclizine, which is said to have a strong effect against sea-sickness.

At a dosage level of 5 mg per kilogram body weight Cinnarazine did not influence nystagmus in one rabbit, 10 mg/kg completely suppressed it in one out of five animals, partly suppressing it in the other four, 20 mg/kg suppressed it completely in four and greatly inhibited it in one rabbit out of a series of five animals, whereas at a dosage of 40 mg/kg this compound completely suppressed nystagmus in nine and partly suppressed it in one rabbit out of a total of ten. Drowsiness was once observed at a dosage-level of 20 and once with 40 mg/kg. No other signs of disturbed behaviour were seen. The corneal and patellar reflexes were always present.

The result obtained with 40 mg/kg – disappearance of the nystagmus in nine out of ten cases – was compared with the result obtained in twenty-five controls, in which nystagmus never disappeared. According to the χ-square criterion the probability that Cinnarazine had no effect and that the outcome of our experiments was due to chance was smaller thans $1 : 2.10^5$. We did not consider it necessary to use the "double blind" technique (see Chapters V and VI) because the total disappearance of the nystagmus was not a doubtful criterion.

As Cinnarazine was dissolved in Solutio Petiti, we injected 10 ml of this liquid into two rabbits. No influence of this substance on the nystagmus was observed.

*) Cinnarazine = N-benzhydryl-N'-transcinnamylpiperazine, a new product of the N.V. Amsterdamsche Chininefabriek in Amsterdam.

3. *Largactil (Chlorpromazine).*

We injected 0.5, 1, 2, 3 and 4 mg per kilogram body weight Largactil intraperitoneally, using one rabbit at each dosage level. After 0.5 or 3 mg/kg the nystagmus did not change, while the rapid phase of the nystagmus disappeared in the three animals receiving the other dosages. The slow phases accumulated, so that a deviation of the eye to one side was apparent on the nystagmogram. The eye did not return to its original position. On the paper the curve returns slowly to the zero line. This is an artefact due to a property of our amplifying system (see Chapter II).

Two rabbits got 6 mg Largactil per kg. In one the rapid phase disappeared and the slow phase remained, whereas in the other animal both nystagmus phases remained present.

Ten rabbits got 8 mg/kg Largactil. In none of these animals the vestibular phase of the nystagmus was affected, in nine, however, the rapid phase disappeared, whilst in one rabbit both phases of the nystagmus remained present, although the rapid phase was inhibited.

Of the ten rabbits that got 8 mg per kilogram body weight Largactil, nine became soporous; the two rabbits that got 6 mg/kg were very drowsy, while those receiving a lower dose were apparently normal.

According to the χ-square criterion the probability that the disappearance of the rapid phase of the nystagmus was not due to the injection of Largactil was smaller than $1 : 2.10^5$.

4. *Hyoscine (scopolamine).*

The following hyoscine dosages per kilogram body weight were injected intraperitoneally: 0.5 mg, 1 mg, 2 mg, 4 mg, 10 mg, 20 mg, 40 mg, 80 mg, 250 mg and 500 mg. For each dosage two rabbits were taken. In seventeen animals the pupils were dilated and did not respond to light. Three rabbits that got 0.5, 2 and 4 mg/kg respectively failed to show this effect. After dosages above 4 mg/kg all animals were completely groggy. In neither of the twenty rabbits did the nystagmus disappear. To the contrary, with the higher dosages there was some indication that the amplitude of the nystagmus increased. Our findings suggest that the effect which hyoscine is reported to cause in sea-sickness, cannot be due to a suppression of the vestibular excitability.

5. *Nembutal.*

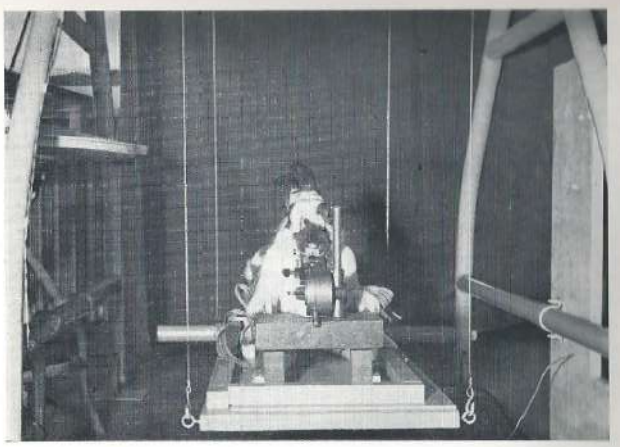
Besides drugs with an established reputation in the prevention of sea-sickness (antihistamic agents and drugs like hyoscine or atropine) or with a presumed suppressive effect on the labyrinth (Largactil), we thought it interesting to investigate also a drug, which depresses the central nervous system without displaying a marked specificity for structures like the labyrinth. We chose the barbiturate Nembutal.

Four rabbits got 10 mg/kg and six got 20 mg Nembutal per kilogram body weight intraperitoneally. In none of the rabbits that got 10 mg/kg were the righting reflexes abolished, although all animals were soporous and hardly reacted to painful stimuli. The slow nystagmus phase did not disappear in any of those rabbits, the rapid phase being suppressed, however, in two of them.

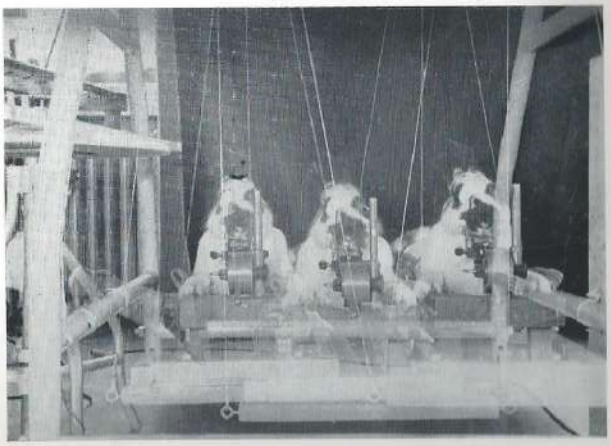
Of the six rabbits that got 20 mg per kilogram body weight, four became anaesthesized and lost their righting reflexes. In these four rabbits both phases of nystagmus disappeared. In the other two the slow phase remained present.

In one rabbit, that was in a deep narcosis, a spontaneous nystagmus arose. The animal did, however, not react to rotation.

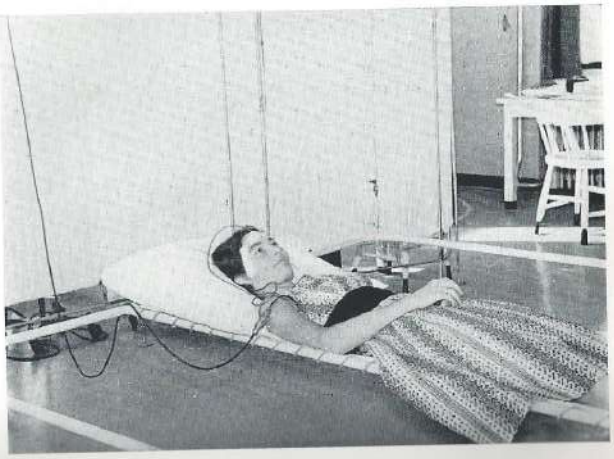
For the reproduction of some curves, see the end of this book.



Photograph nr. 4.



Photograph nr. 5.
Parallelswing for rabbits.



Photograph nr. 6.
Parallelswing for human beings.

CHAPTER IV

PARALLELSWING TESTS IN RABBITS

The natural stimulus for the otoliths is the linear acceleration.

The epithelium of the membranaceus covering of the otolith organs (utriculus and sacculus) consists in one place of sense organ cells, which are connected with fibres of the nervus vestibularis. These are the macula utriculi and the macula sacculi respectively. The two maculae utriculi lie almost horizontal with the front upwards (when the head is in the normal position), the maculae sacculi stand almost vertical with the front outwards. The sense organ cells of the maculae have hairs, held together by a jelly-like substance, on which are small crystals of carbonate of lime. This cohesive mass of lime forms the otolith. The specific gravity of the otolith is greater than that of the endolymphe. Linear accelerations cause a change in the size and direction of the pressure that is exerted by the otoliths on the hairs of the sense organ cells. This mechanical phenomenon serves as stimulus, which is transmitted to the central nervous system.

Although MACH (1875), who as a physicist mastered mechanics completely, and BREUER (1874; 1891), already in the past century set up the hypothesis, that the natural stimulus for the otoliths is the linear acceleration, this knowledge appears to have got lost for some generations. During that period a distinction was made between vestibular reactions induced by:

1. Dynamic stimuli:
   a) angular accelerations,
   b) linear accelerations caused by progressive movements.
2. Static stimuli caused by the force of gravitation.
3. Stimuli caused by the centrifugal force.

The reflexes caused by dynamic stimuli were attributed to movements, the static (also called tonic) reflexes were ascribed to a change of the position of the head with regard to the direction of the force of gravitation.

"The latter are reflexes (MAGNUS and DE KLEIJN) which last as long as a certain position of the head is maintained. The dynamic reflexes do not depend on position and are found solely when the head respectively the labyrinths are moved; they are always of short duration in comparison with the static reflexes."

Labyrinthology was led astray by this theory for a considerable time. Many investigations were devoted to these supposed different kinds of vestibular stimuli and reactions.

JONGKEES and GROEN (1946) were the first, since MACH and BREUER, who drew the attention to the fact that there is no fundamental dif-

ference between dynamic, static and centrifugal stimuli. The so-called difference between these stimuli is mere illusion and such a supposition is not in accordance with the laws of mechanics. All these stimuli are linear accelerations, which qualitatively are identical and which only differ quantitatively.

JONGKEES and GROEN (1946) exposed their views to us in the following terms:

"Let a well-known example of EINSTEIN make this clear. Suppose a person finds himself in a cage somewhere in our universe, beyond the gravitational range of influence of any celestial body. The cage is supposed to possess no acceleration relative to the average stellar matter. Then for him no gravity will exist. In this cage everything will float, the otoliths will not exert any pressure on the maculae. Now suppose we give to this cage an acceleration of 1,000 cm/sec². From this moment in a mechanical way everything is for the inhabitant of the cage as if he were back on earth. The objects will fall, the test person will stay on the floor (that is that wall of the cage which lies at the side from which the acceleration is pointed within the cage) and the otoliths will again press on their bottom layer. In this way EINSTEIN elucidates the meaning of his statement, that a body in the field of gravity of the earth finds itself in a field of acceleration of 1,000 cm/sec². It is absolutely the same for this body from a mechanical point of view to be either in the field of gravity of the earth or to be moved outside this field with a linear acceleration of the magnitude of the acceleration of gravity. The centrifugal force has just the same character. The action of an accelerated movement in which the acceleration is as great as the acceleration of the centrifugal force is mechanically identical with the action of this force.

No measuring instrument, however fine, can distinguish between a field of gravitation (i.e. a field of forces caused by gravity) or a field of forces caused by centrifugal force and a field of forces (of inertia) caused by an accelerated movement of the same magnitude and opposite direction. This is not the result of the practical inadequacy of the instruments, but of the essential identity of all three. In the same way it must be impossible for the measuring device in the human body, wherever this organ may be located, to distinguish between the action of gravity, of the centrifugal force, or of the force of inertia caused by a linear accelerated movement. Solely a distinction in a quantitative sense is possible, i.e. duration, magnitude and direction of the acting force.

In all those cases the stimulus for the sense organ is the linear acceleration. It is absolutely groundless and confusing to distinguish between different forms in which the linear acceleration shows itself.

A real mistake is made when one distinguishes between static and dynamic stimuli in the sense that the two could be perceived by different organs as qualitatively different influences. At most a quantitative difference is to be observed. Always the field of gravitation is present

and exerts its influence on all beings human and animal. This is exactly one of the difficulties in the research of the influence of linear accelerations on the sense of equilibrium.

It is impossible for that reason to examine this organ in the absence of the adequate stimulus, i.e. the acceleration of the force of gravitation. Such an experiment would be possible only during the free fall. This explains why the so-called static reflexes continue as long as the position of the head remains unaltered. In this case the field of acceleration does not change, therefore the stimulus remains the same both in magnitude and direction.

Those mechanical considerations force us to make the division of the labyrinth reflexes in another way than was usually done up till now. We may divide them as follows:

1) Reflexes and sensations caused by rotational accelerations.
2) Reflexes and sensations caused by linear accelerations (in gravity, centrifugal force and linear accelerated movements).

All reflexes and sensations in one group must be perceived by the same sense organ or organs."

Thus JONGKEES and GROEN.

Another example which illustrates that it is impossible for the vestibular organ to differentiate a linear acceleration caused by a movement from the linear acceleration caused by the force of gravity is the following. Unfortunately flying accidents sometimes happen, because the pilot thinks that he can fly solely with the aid of his sense organs, without using his measuring instruments. This is dangerous, because the pilot, when thinking that he is flying straight on, may not do so in reality. The direction in which he thinks he is flying is actually the direction of the resultant of the force of actual flying acceleration and of the force of gravitation. This has been the cause of many accidents.

Some authors (MAGNUS and DE KLEIJN, 1921; LORENTE DE NÒ, 1931; TER BRAAK, 1936) hold that both angular and linear accelerations can be perceived by the semicircular canals.

Findings of JONGKEES and GROEN (1946) deny that it is possible for the two stimuli (angular and linear accelerations) to be perceived by the same sense organ or organs. They found that the indication time (i.e. the time necessary for a stimulus to provoke the maximum reaction in an organ) and the time that a stimulated organ requires to quiet down again (to be ascertained from the after-reflexes and the after-sensation) is roughly three hundred times longer for an angular than for a linear acceleration.

On the strength of the above mentioned considerations we assume that angular accelerations are perceived by means of the cupulae and linear accelerations by the otoliths.

We were now confronted with the problem how we could subject rabbits and human beings in a simple way to linear accelerations and how we could best study reflexes caused by such a stimulus.

SJÖBERG wrote in 1931: "It is extremely probable that small reflex eye movements, invisible to the naked eye, occur in the case of rectilinearly accelerated vertical movements."

NELISSEN (1934) and RUYS (1945) described eye movements caused by linear accelerations in rabbits and guinea pigs.

JONGKEES and GROEN (1946) described compensatory eye movements in rabbits that were swung on a parallelswing. They observed these eye movements with the unaided eye. The parallelswing also enabled them to study sensations accompanying changes in position caused by linear accelerations.

For our investigations the parallelswing appeared a suitable instrument. Our aim was to develop a method which would enable us to register the eye movements with the aid of the nystagmograph and to study the effect of drugs on these eye movements.

The parallelswing is a very simple instrument, a stretcher or another bearing surface, which is hung on four cables of equal length fastened to its angles. The parallelswing can be swung in two directions, the bearing surface remaining horizontal during the swinging. The bearing surface remains horizontal because the junctures of the cables to the ceiling are perpendicular above the junctures to the bearing surface. The manner of swinging is shown by the photographs nrs. 4 and 5. If one uses this set-up, two kinds of linear accelerations, one in the horizontal plane and the other in the vertical plane arise, both with a sinus pattern. The vertical linear acceleration may be neglected because according to estimations of JONGKEES and GROEN (1946) it remains far below the minimum perceptible if the size of the swing and its cables are favorable. In the mid-position of the swing the horizontal acceleration is zero and the speed maximal. In the extreme positions the speed is zero and the acceleration or deceleration maximal. Velocity and acceleration differ 90 degrees in phase. As no angular acceleration arises the cupulae are not stimulated. For rabbits we made a parallelswing that could be deviated sideways by means of a thread. The rabbit was swung sideways. The swing moved in 22 seconds to and fro. The initial amplitude was 22 cm, the length of the cables was 112 cm, the maximum acceleration was 192 cm/sec^2, the maximum speed 65.3 cm/sec.

In our first trials we swung it along its longitudinal axis. We tried to register compensatory eye movements by placing the electrodes in front (rostrally) of and behind the eye (caudally). Not even with a very great excursion were eye movements observed on the registration paper. The most probable explanation seems that this particular way of moving the rabbit causes only rotatory eye movements, which was first observed by NELISSEN (1934), the eye rotating about its optical axis which coincides with the electrical axis. No changes in the field potential take place and our recording system does not register eye movements.

When we moved the rabbit sideways we did succeed in registering compensatory eye movements. The electrodes were then placed above

and below the eye, in such a way that an upward eye movement gave an upward deviation on the paper and vice versa.

From the above mentioned experiments it followed that the axis of compensatory eye movements is perpendicular to the direction of the movement and perpendicular to the direction of the force of gravitation.

Just like in the rotation tests the rabbit was bound on a rabbit board, its head being fixed in a rabbit clamp, and the experiments were carried out in the dark. As in the rotation test the mechanical movement was registered after it was translated into electrical terms by means of a potentiometer. The axle of the potentiometer was placed end to end with the turning point of one of the four cables and connected with the cable. In this way the movement of the parallelswing could be registered exactly, enabling us to check the initial amplitude to the swing. This potentiometer also checked the nystagmograph.

RESULTS

1. *Calibration tests.*

The influence of adaptation and of normal saline solution on the compensatory eye movements.

Calibration tests were carried out in twenty-five rabbits.

The procedure was as follows. After the rabbit had been fixed on the board and put in the dark, we waited for half an hour before we started with the first swinging. The rabbit was swung six times in total with intervals of a quarter of an hour. Immediately after the second swinging 10 ml normal saline solution was injected intraperitoneally. The curves of the compensatory eye movements provoked by these six swing tests were compared. In the experiments in which the effect of a drug on the eye movements was investigated, we followed exactly the same procedure, with the sole difference that in this case the drug was injected instead of the saline solution. The outcome of the drug experiments could thus be compared with the results of the calibration tests.

In the 25 calibration tests an important intra-individual variation of the amplitude of the eye movement became apparent. In neither of the control animals, however, did the compensatory eye movements disappear. The compensatory eye movements had the form of a sinus. As soon as the swing was set in motion, the recorded registering of the eye movements left its zero position. Our set-up did not enable us to measure the latent period.

On comparing the phase of the eye-sinus with that of the swing, we observed a phase difference, the average of which amounted to 64° for the twenty-five calibration tests. Within each series of six observations this difference in phase remained always about the same.

2. *Cinnarazine.*

To investigate the effect of Cinnarazine on the compensatory eye movements experiments were made in ten rabbits. These rabbits got 40 mg Cinnarazine per kilogram body weight.

In seven of these rabbits the eye movements disappeared completely; in the three remaining rabbits the eye movements diminished distinctly.

The result of these ten tests was compared with the result of the twenty-five calibration tests, in which the eye movements never disappeared entirely. These data were judged with the χ-square criterion.

The suppressive effect of Cinnarazine on the compensatory eye movements proved to be very significant. The probability that Cinnarazine had no effect and that the disappearance of the eye movements was due to mere chance was smaller than $3 : 10^5$.

Of these ten rabbits two became drowsy, while the other eight rabbits behaved normally after the test.

3. *Largactil.*

In ten rabbits that got 8 mg Largactil per kilogram body weight, we never saw the compensatory eye movements disappear.

All ten rabbits had compensatory eye movements during the entire swinging test. We tried to observe whether the difference in phase between the sinus of the eye movements and the sinus of the parallelswing was affected by the drug. This appeared not to be the case.

Of these ten rabbits eight became soporous, while the remaining two became drowsy.

4. *Hyoscine (scopolamine).*

The effect of hyoscine on the compensatory eye movements was investigated in ten rabbits. Two rabbits got 0.5 mg/kg, two 5 mg/kg, two 50 mg/kg and four 500 mg per kilogram body weight. In none of these rabbits we saw a decrease or a disappearance of the eye movements. After the test nine rabbits had wide and rigid pupils, whilst the pupils of the tenth rabbit, that had got 0.5 mg/kg, still responded to light. The two rabbits that had got 0.5 mg/kg and one of the rabbits that had got 5 mg/kg behaved normally after the experiment, the other animals were completely groggy.

5. *Nembutal.*

Three rabbits got 10 mg Nembutal per kilogram body weight. None of these three rabbits became anaesthesized, though they got very drowsy. In none of these rabbits the compensatory eye movements disappeared.

Three rabbits got 40 mg/kg. One of them got into a deep narcosis.

When it was laid on its back it did not turn into normal position. In this rabbit the eye movements were absent, while in the two other rabbits, that were merely soporous, the eye movements were still apparent.

In three rabbits, that had got 60 mg/kg, the eye movements disappeared completely. They were in a deep narcosis.

Just like in the rotation tests in rabbits, we found that the vestibular eye reflexes were only suppressed by Nembutal, if very deep anaesthesia had been reached.

Some curves have been reproduced at the end of this book.

CHAPTER V

ROTATION TESTS IN HUMAN BEINGS

CUPULOMETRY

Post-rotatory reactions, particularly the nystagmus, have been investigated in patients since BÁRÁNY (1907) introduced his rotation test.

When a person is placed in a rotation chair, and he is turned round with constant velocity, the deviation of the cupula provoked at the beginning of the rotation by the initial acceleration, will disappear completely. A state of equilibrium is reached, in which the subject has no turning sensations; neither are there any reflexes. When the movement is stopped, a deviation of the cupula arises, this time in the opposite direction and caused by the deceleration. The sensations and reactions both have a direction opposite to that during the acceleration phase. In the BÁRÁNY test the subject was turned ten times in twenty seconds, and then the movement was stopped abruptly. In this way the longest possible post-rotatory nystagmus was supposed to arise. Many objections may be raised against this method, which was used very much and which is still used. The most important objection is, indeed, that in this way no well-dosed stimulus can be given. The cupula, which deviates under the influence of the great initial acceleration, does not by any means return to its original position during the period of constant velocity which lasts less than twenty seconds. The abrupt stopping of the turning chair stimulates the cupula while it is still in a deviated position. It is clear that it is impossible to give an accurately dosed stimulus to the cupula in this way.

The method of VEITS (1931) may be considered a great improvement. The subject is set in motion so gradually that the cupulae are not stimulated as the stimulus remains subliminal. This very slow acceleration is maintained until a speed of 180°/sec. is reached. At this velocity the subject is rotated for a few minutes until the cupula is surely at its zero position. This may be concluded from the absence of nystagmus or sensations. Only then the turning is stopped. We can now be reasonably sure about the size of the stimulus for the cupula. The stimulus, however, is too strong to be called physiological. Quite to the contrary the probability that the subject will experience nausea is rather high and there is a real danger that a sick labyrinth will be damaged (VAN EGMOND and JONGKEES, 1948).

For our investigations in human subjects we used the rotation test of VAN EGMOND, GROEN and JONGKEES (1948), called cupulometry. Cupulometry is a rotation test in which small, harmless stimuli – physiological as regards their size – are given. In cupulometry we measure the duration of the post-rotatory nystagmus and of the after-sensation. The subject is sitting in a rotating chair with the head bent forward 30°. The horizontal semicircular canals are then situated in the plane of rotation. Under

these circumstances only the horizontal canals are stimulated. The subject is gradually set in rotation, until a constant velocity has been reached. After a short period the endolymphe in the semicircular canal does no longer flow. This can be checked by the absence of nystagmus beats on the registration paper of the nystagmograph. The chair is then stopped within one second. In this way it is possible to administer well-dosed stimuli to the cupula at different rotatory velocities. When we graph the duration of the post-rotatory nystagmus or the duration of the after-sensations in seconds as ordinate against the magnitude of the stopping impulse from a certain angular speed in degrees per square second as abscissa, the latter arranged on a logarithmic scale, we obtain a straight line. Such a graph is called a cupulogram (see fig. 9).

Encouraged by the result in animal experiments we investigated the effect of Cinnarazine on the excitability of the cupulae in ten human subjects, with the aid of cupulometry.

Whereas in animal experiments dosages high enough to suppress the nystagmus completely can be given, this cannot be done in humans. This deprives us of the all-or-nothing criterion which greatly facilitated the design of the animal experiments. In the case of humans we had to apply the "double blind" technique, in which neither the subject nor the observer knows whether in a certain case the drug or a placebo has been given. This is absolutely necessary, because the interpretation of nystagmograph curves leaves the possibility of false interpretations open, in contradistinction to the much simpler situation in the rabbit test. By doing our investigations in human subjects "double blind" we excluded any possibility of self-suggestion in the interpretation of the curves. Placebo and drug tablets are put in bottles labelled by someone, who does not participate in the experiment. The labelling of the bottles is in a code unknown to the experimenter. After the termination of the experiments, when all results have been calculated, the list is consulted to see when the subject had taken the drug and when the placebo.

The procedure in our investigation lasted a fortnight and was carried out as follows. The first cupulogram of each subject was always made on a Wednesday, the second one on the next Thursday, this time three hours after the subject had taken the drug or the placebo. One week later – also on Wednesday and Thursday – the same procedure was repeated, with the sole difference, that the subject who had taken the drug the first week, got the placebo the second week or vice versa. This could be done because the bottles were paired, one containing the drug and the other the placebo.

In our experiments the subjects were rotated both to the left and to the right with velocities of 20°/sec., 36°/sec. and 60°/sec. The subjects were rotated by man power, while the speed was checked with a stopwatch. The subject was sitting in a rotation chair, screened off with black curtains. The nystagmus was registered whilst the subject had his eyes closed.

Three stainless steel disks, 8 mm in diameter, 2 mm thick, with concave surfaces, were used as electrodes for human subjects. The cavities were filled up with electrode paste as used in electrocardiography. Two electrodes were fixed with plaster on the skin above the temples, about 2 cm removed from the lateral canthus. The third electrode, serving as ground electrode, was fixed in the middle of the forehead. The electrodes were fixed in such a way, that an eye movement to the left was registered on the paper as a downward deviation and vice versa. In this way only the horizontal eye movements are registered. If it is necessary to register vertical eye movements, the electrodes must be put above and below the eye. It is of course impossible to register a purely rotatory nystagmus, because in that case the eye rotates about its electrical axis. The axis of the dipole does not move with regard to the electrodes, in whatever places they may be fixed.

The head of the test subject was always bent forward over 30° during the investigation.

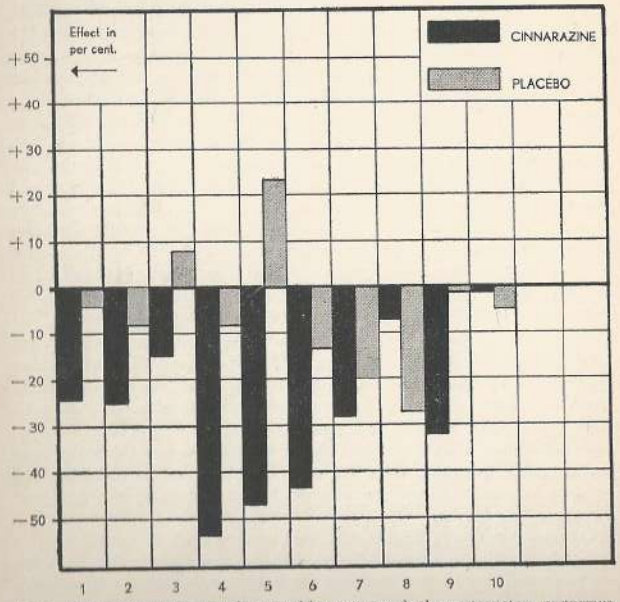


Fig. 7. Results of cupulograms in ten subjects as regards the post-rotatory nystagmus. The difference between the total duration of the nystagmus in the test, after the subject had taken Cinnarazine or the placebo, and the total duration of the blank test on the previous day is expressed in its percentage of the total duration of the blank test (see text).

We added the individual durations in seconds of the post-rotatory nystagmus of the six rotation tests (20°/sec., 36°/sec. and 60°/sec. to the left and to the right) we made per cupulogram. The same was done for the durations of the after-sensation. Thus we obtained for each cupulogram a value both for the post-rotatory nystagmus and for the post-rotatory sensation.

In order to be able to express the effect of the drug or of the placebo in a number, we expressed the difference between the values for the post-rotatory nystagmus and sensation obtained on Thursday and those on the preceding Wednesday, as percentages of the values found on Wednesday. In this way we got figures for the drug and the placebo effect administered for all subjects.

Our findings with 250 mg Cinnarazine or the placebo, both orally, are given in figs. 7 and 8. In fig. 9 four cupulograms are shown, obtained in one subject.

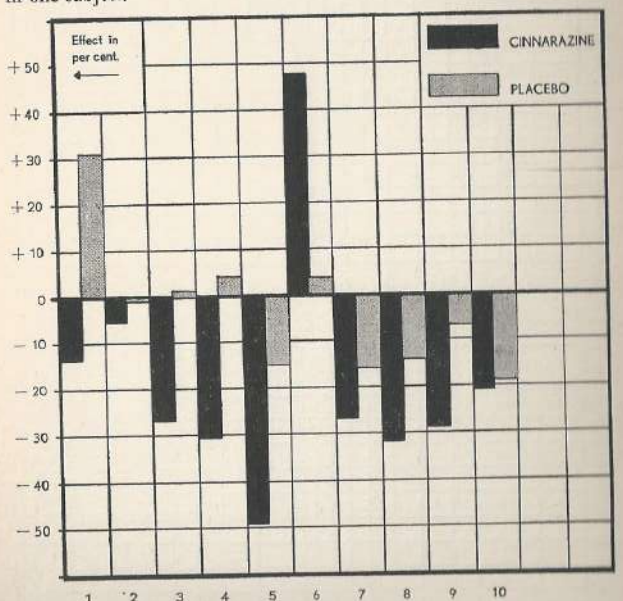
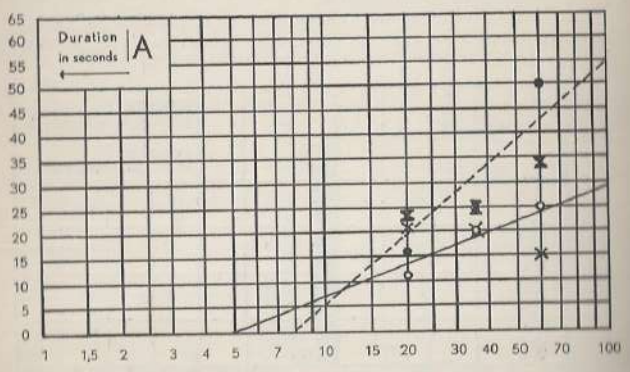


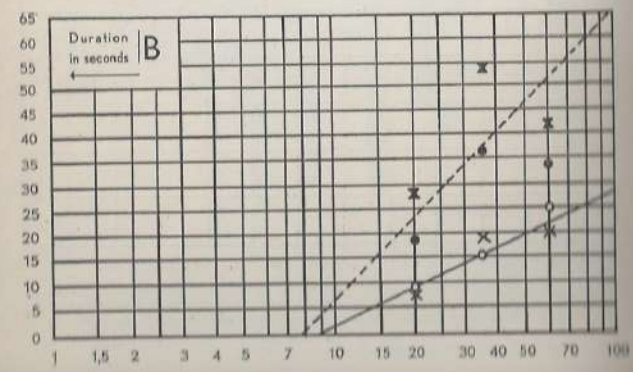
Fig. 8. Results of cupulograms in ten subjects as regards the post-rotatory sensation. The difference between the total duration of the sensation in the test, after the subject had taken Cinnarazine or the placebo, and the total duration of the blank test on the previous day is expressed in its percentage of the total duration of the blank test (see text).

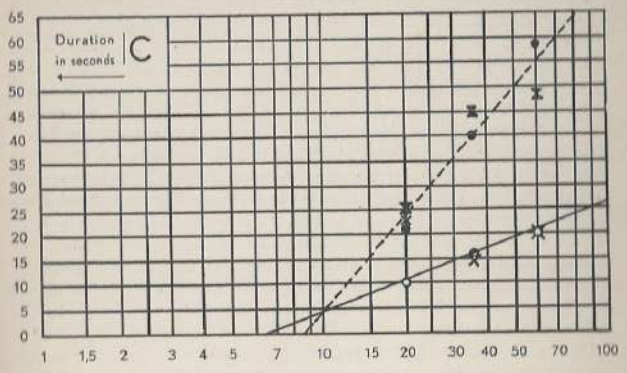
Inspection of these figures shows that Cinnarazine strongly suppresses vestibular excitability, but that also in the placebo series the vestibular reactions are slightly smaller after than before the "drug" has been given. This later difference is conceivably due to adaptation. The effect of Cinnarazine appeared to be highly significant, the probability according to WILCOXON's test being smaller than one per cent for the suppression of the nystagmus as well as for the disappearance of the sensation.

Before starting the experiments, we asked the subjects if they often suffered from motion sickness or not. We could confirm the findings of DE WIT (1953; 1958) and of KRIJGER (1954), namely that people with a steep cupulogram suffer more from motion sickness than people with a flat cupulogram.

For reproductions of some curves, see the end of this book.







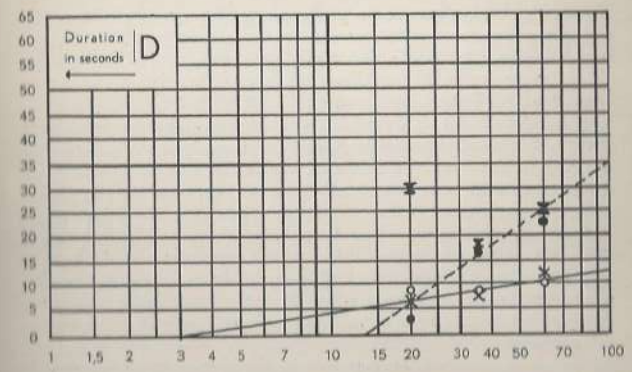


Fig. 9. Four cupulograms of the same subject. Acceleration in degrees/sec.²
A. Blank test B. After the placebo
C. Blank test D. After Cinnarazine

○ = Clock-wise sensation
× = Anti clock-wise sensation
● = Clock-wise nystagmus
⧗ = Anti clock-wise nystagmus

CHAPTER VI

PARALLELSWING TESTS IN HUMAN SUBJECTS

In the same way as already described for rabbits, the effect of a drug was studied in human subjects by means of the parallelswing.

We found that a parallelswing constructed from a normal sized stretcher hung on steel cables, was not sufficiently stable. When it was swung, torsion movements easily arose, as a result of which the movement of the swing became distorted. These disturbing movements provoked stimulation of the cupulae, causing frequent nystagmus beats. This complicated the interpretation of our results very much.

In our endeavours to construct a more stable parallelswing we had two alternatives. In the first place we could hang the parallelswing on steel bars instead of on steel cables, forcing the swinging via ball-bearings into one particular direction. We could also use a much larger bearing surface, which would give less chance of torsion. We chose the second alternative, its realization being much cheaper than that of the first one. In cases of lack of space, the first possibility might easily be the only possible solution.

Our bearing surface had a square frame of steel tubes, width 2 metres. In the middle of the frame two other tubes were welded, between which canvas was fixed, having the size of a normal stretcher (see photograph Nr. 6). The torsion movements of this swing were very slight indeed. In registering the compensatory eye movements no nystagmus was observed, hence this parallelswing satisfied our requirements. Just as with the parallelswing for rabbits the movements of this swing were also registered with a linear potentiometer.

In human beings as in rabbits the compensatory eye movements consist of a rotation round an axis of the eye, perpendicular to the direction of the force of gravitation. We found that compensatory eye movements could be registered when the subjects were lying or sitting, when they were swung in forward/backward direction. In subjects swung in this way, the electrodes had to be fixed above and below the eye. When the swing was moved sideways, eye movements could only be registered when the subject was lying on his back. It was not possible to register the eye movements when the subject was sitting and swung sideways, because then the axis of rotation coincided with the electrical axis of the eye.

For our experiments we preferred to swing the subject sideways in lying attitude. The electrodes were fixed in the same way as in the rotation test in the temporal regions. This was far easier than fixing the electrodes above and below the eye. In our experiments we gave the subject always the same initial amplitude, by starting from the same deviated position. This could be checked as in the test in rabbits with a linear potentiometer.

The head of the subject was fixed with a towel and with ties in order to eliminate as much as possible disturbing movements of the head relative to the underlayer.

In the parallelswing tests in human subjects we could calculate the amplitude of the eye movements that occurred during the swinging and we could express the eye rotation in degrees. This was not possible in the tests in rabbits. Before starting the test we calibrated the eye movements of the subjects in the following way. We placed the subject at a definite distance from a black board, on which two white dots had been painted. We asked the subject to look from one dot to the other to and fro. The distance between the two dots and the distance from the subject to the board was such that the subject, when looking from one dot to the other performed an eye rotation of 20°.

This movement was registered with the nystagmograph. The eye movements which occurred when the subject was swung on the parallelswing could now be expressed in degrees eye rotation. The total eye rotation during the first ten swingings was measured.

The initial amplitude of the swing was always 58 cm. The length of the cables was 338 cm. The maximum acceleration was 167 cm/sec^2. The maximum velocity was 98.6 cm/sec.

In twenty-eight subjects the same "double blind" procedure was followed as in the experiments with cupulometry. They got 250 mg Cinnarazine or placebo, orally.

To express the effect of Cinnarazine or of the placebo in a number, the difference between the value for the total eye rotation of blank tests and the value of tests performed on the next day was expressed in percentages of the value of the blank test. Our results are shown in fig. 10. We found that Cinnarazine gave more often a decrease of the eye movements than the placebo. The results, however, proved to be less pronounced than those of the cupulometry tests and those of the animal tests. According to the test of Wilcoxon it was not statistically significant. The probability that Cinnarazine had no effect and that the outcome of the experiments was due to chance was smaller than thirteen per cent. An explanation for the less satisfactory outcome of these experiments must be sought in the fact that the individual variation is considerable. The compensatory eye movements measured several times in one subject on different days vary considerably in size. Such a great spontaneous variability complicates the demonstration of a pharmacological effect. We tried to improve the design by shortening the interval between the observations. In nine subjects the two measurements – the blank and the drug (c.q. placebo) experiment – with an interval of only three hours did not markedly diminish the variability. The other possibility: augmentation of the number of the subjects did not look very attractive. According to a rough estimation, between 100 and 200 subjects might be needed for a statistically significant result. We did not feel that such a considerable extension of the experiments was justified, as the vesti-

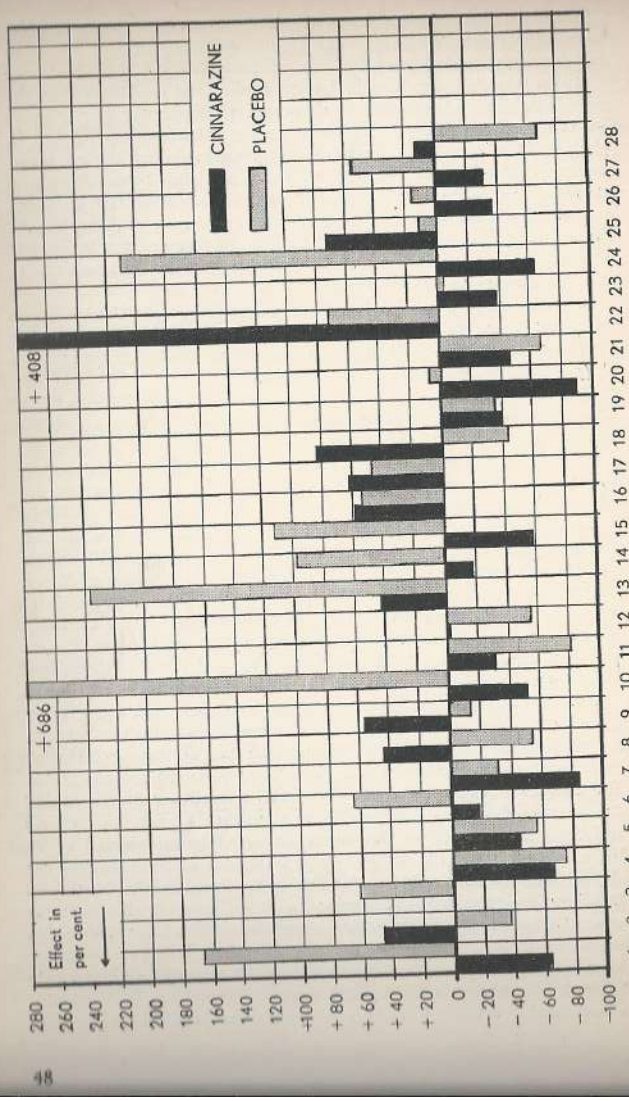


Fig. 10. Results of parallelswing tests in 28 subjects as regards the total amplitude of the eye movements during the first 10 excursions.
The difference between the total amplitude of the test, after the subject had taken Cinnarazine or the placebo, and the blank test on the previous day is ← expressed in its percentage of the total amplitude of the blank test.

bular effect of Cinnarazine had already been clearly shown in the other series of observations.

In the twenty-eight subject examined, the difference in phase between the sinus of the compensatory eye movements and the sinus of the parallelswing amounted to an average value of 52 degrees. We could not find any effect of Cinnarazine on this difference in phase.

As in the animal tests we failed to register a latent period for the eye movements. According to our apparatus—which is neither designed nor suitable for registration of the latent period—the eye begins to rotate immediately after the swing has been set in motion.

In the cupulometry tests and in the parallelswing tests in which fourty-seven human subjects had got 250 mg Cinnarazine and a placebo orally, twenty-four subjects became drowsy by Cinnarazine and two by the placebo. In view of the findings of ARNER, DIAMANT and GOLDBERG (1954) and of ASCHAN, BERGSTEDT and GOLDBERG (1957) we decided not to investigate whether there exists a correlation between the effects of Cinnarazine on the sensorium and on the vestibular excitability. The above mentioned authors found that amphetamine did neither change the effect of antihistamines against motion sickness nor the suppression by antihistamines of the nystagmus provoked with alcohol. On the other hand they observed that amphetamine counteracted the drowsiness caused by the antihistamines.

Reproductions of some curves are given at the end of this book.

CHAPTER VII

THE EFFECT OF CINNARAZINE IN PATIENTS WITH VERTIGO

We found a marked effect of Cinnarazine on the labyrinth not only in our experiments in normal human beings, but also in a number of patients with labyrinthine disturbances like spontaneous nystagmus and/or a difference in the caloric excitability of the two labyrinths.

Six patients suffering from vestibular vertigo, all with a spontaneous nystagmus, reacted very favourably to Cinnarazine, given in daily dosages from 15 to 75 mg (see fig. 11). They all obtained much relief from dizziness. The spontaneous nystagmus disappeared or got much less in intensity, and the differences between right and left to caloric stimulation diminished in all the six patients with peripheral disturbances of labyrinthine function.

Fig. 11. The disappearance of a vestibular spontaneous nystagmus after the administration of Cinnarazine.

On the other hand, we found no influence of the drug in patients who showed disturbances of extra-vestibular origin. Two patients who had a central spontaneous nystagmus did not react to the therapy with Cinnarazine. The same applies to three patients who complained about dizziness, but in whom it was impossible to find any objective vestibular or neurological symptom.

Though the number of patients is too small to draw definite conclusions, these findings are in excellent agreement with our view that Cinnarazine decreases the reactivity or sensitivity of the vestibular organ by a direct action.

DISCUSSION

We investigated the effect of several drugs, each typical for a pharmacological group, on the excitability of the labyrinth. We studied the antihistaminic Cinnarazine and the parasympathicolytic hyoscine (= scopolamine) as representatives of two favourite groups of anti-motion sickness drugs. Largactil was examined because in several publications a suppressive effect on the labyrinth was ascribed to this substance. We also included the barbiturate Nembutal, as a drug which can be expected to suppress the labyrinthine excitability as part of a general anaesthesia.

In our experiments we found that only the antihistamine Cinnarazine had a significant effect on eye reflexes caused by stimulation of the labyrinth, in human subjects as well as in rabbits. Both the reflexes caused by stimulation of the cupulae and the otoliths were suppressed.

Largactil did not cause an observable effect in rabbits on the vestibular phase of the nystagmus caused by rotation. We did find a distinct suppression and even a total disappearance of the central phase of the nystagmus by Largactil. The compensatory eye movements caused by stimulation of the otoliths with the parallelswing were not affected by Largactil. From our experiments we must draw the conclusion that Largactil does not affect the vestibular excitability, which is in contradiction with the findings of SALERNO (1955), CARBONARA and SALONNA (1956), BERGSTRÖM and KOCH (1956) and ASCHAN, BERGSTEDT and GOLDBERG (1957). This discrepancy may be due to the fact that the above mentioned investigators used criteria different from ours. They either paid attention to a decrease in number of nystagmus beats or they used as an end point the complete suppression of the nystagmus by Largactil. A deviation of the eyes to one side, which was not compensated by a rapid movement, escaped their attention.

Hyoscine (scopolamine) did not appear to suppress the vestibular excitability in any way. We were struck by the findings of GUTNER, GOULD and BATTERMAN (1951) who found an increase of the vestibular excitability by hyoscine because we also gained the impression that hyoscine increases the labyrinthine excitability instead of suppressing it. The effect against motion sickness ascribed to hyoscine can not, according to our experiments, be due to a suppression of the labyrinthine excitability.

Nembutal, indeed, as was to be expected, suppressed the vestibular excitability only as a partial effect of a deep anaesthesia.

SUMMARY

The aim of our investigations was to find methods to study the action of anti-motion sickness drugs.

Starting from the assumption, that overexcitation of the vestibular organ is essential for motion sickness, our object was to develop methods enabling us to investigate the effect of drugs on the labyrinth.

Arguments are given to sustain the above mentioned theory. In this connection we draw the attention to publications by JAMES (1896), QUIX (1923), SJÖBERG (1931), MCNALLY and STUART (1942), DE WIT (1953; 1958) and KRIJGER (1954).

Publications on drugs used for the prevention of motion sickness and on drugs having a suppressive effect on the labyrinthine excitability are discussed.

For the examination of the vestibular reflexes we used electronystagmography. The qualities of electronystagmagraphy as an outstanding aid in labyrinthology are discussed.

We developed a method for measuring the corneo-retinal potential difference in rabbits in order to be able to investigate the occurrence of spontaneous fluctuations of the corneo-retinal potential difference and the effect of drugs on the nystagmogram via an influence on the corneo-retinal potential difference. For this purpose we repeatedly gave the same passive movement to the rabbit's eye by drawing it to and fro with a thread sutured in the cornea. This movement was registered indirectly with the aid of the nystagmograph. Changes in the amplitude of the movement on the registration paper can only be due to changes in the corneo-retinal potential difference.

Theoretical reasons are given to consider the angular acceleration and the linear acceleration as specific stimuli for the semicircular canals and for the otoliths respectively. On account of these considerations methods were sought to administer appropriate stimuli to the labyrinth in rabbits and in human subjects.

For use in rabbits a rotating platform was constructed that was set in motion by a counter-weight. Both the nystagmus and the rotation of the platform were registered with the nystagmograph.

The linear acceleration was given to rabbits by swinging them sideways on a parallelswing (JONGKEES and GROEN, 1946). The compensatory eye movements, which occurred during the swinging, and the movements of the parallelswing were registered with the nystagmograph.

By means of cupulometry (VAN EGMOND, GROEN and JONGKEES, 1948) we studied post-rotatory nystagmus and after-sensation in human subjects. Nystagmus was registered with nystagmography.

Also for use in human subjects a method was developed to register with the nystagmograph the compensatory eye movements provoked by excitation of the otoliths with the parallelswing.

With the parallelswing compensatory eye movements are provoked, in which the eyes rotate around an axis, that proves to be perpendicular to the direction of the movement of the swing and perpendicular to the direction of the force of gravitation.

With the aid of the above mentioned methods the effect of drugs on the excitability of the labyrinth was investigated.

We examined drugs, representing different pharmacological groups.

Amongst the anti-motion sickness drugs commonly used we investigated the antihistaminic Cinnarazine and the parasympathicolytic agent hyoscine (scopolamine). Only Cinnarazine appeared to have a strongly significant suppressive effect on the labyrinth, in rabbits as well as in human subjects. Hyoscine failed to suppress the labyrinthine eye reflexes. On the contrary we had the impression that the excitability of the labyrinth was increased by hyoscine as GUTNER, GOULD and BATTERMAN (1951) indicated already.

We examined Largactil because a suppressive effect of Largactil on the labyrinth has been repeatedly reported in papers by SALERNO (1955), CARBONARA and SALONNA (1956), BERGSTRÖM and KOCH (1956) and ASCHAN, BERGSTEDT and GOLDBERG (1957). We found that Largactil only affected the central phase of the nystagmus and that it did neither influence the slow vestibular phase of the nystagmus nor the compensatory eye movements in the parallelswing tests.

Nembutal only inhibited the vestibular eye reflexes in dosage levels sufficient to cause a deep narcosis.

Of these drugs only hyoscine appeared to have a slight effect on the corneo-retinal potential difference, the others having no effect at all upon this potential difference. Therefore we are of the opinion that the alterations in the nystagmogram are not an expression of a change in the C.R.P. but of a changed vestibular function as a result of the instituted treatment.

Good results were seen of a treatment with Cinnarazine in patients suffering from vestibular vertigo.

SAMENVATTING

Het doel van ons onderzoek was het vinden van methoden om geneesmiddelen tegen zeeziekte te onderzoeken.

Uitgaande van de veronderstelling, dat bij het ontstaan van bewegingsziekte overprikkeling van het evenwichtsorgaan essentieel is, hadden wij ons ten doel gesteld methodieken te ontwikkelen, waarmee het mogelijk is de invloed van stoffen op het labyrint te onderzoeken.

Argumenten werden aangevoerd ter staving van bovengenoemde theorie. Gewezen werd in dit verband op publicaties van de hand van JAMES (1896), QUIX (1923), SJÖBERG (1931), MCNALLY en STUART (1942), DE WIT (1953; 1958) en KRIJGER (1954).

Als hulpmiddel voor de bestudering van vestibulaire reflexen werd de electronystagmografie gekozen. De kwaliteiten hiervan als eminent hulpmiddel voor de labyrintologie werden besproken.

Een overzicht werd gegeven van publicaties over stoffen die gebruikt worden voor de preventie van bewegingsziekte en stoffen die een remmende werking op de labyrintaire prikkelbaarheid bezitten.

Om de invloed van spontane schommelingen in de cornea-retina rustpotentiaal en de invloed van stoffen via een werking op de cornea-retina rustpotentiaal op het nystagmogram na te gaan, werd een opstelling gemaakt om bij konijnen veranderingen in de cornea-retina rustpotentiaal te meten. Hiervoor werd aan het konijneoog steeds dezelfde passieve beweging gegeven door het met een draadje, dat in de cornea was gehecht, heen en weer te trekken. Deze beweging werd met de nystagmograaf geregistreerd. Veranderingen in de uitslag van deze beweging betekenen veranderingen in de cornea-retina rustpotentiaal.

Theoretische beschouwingen werden gewijd aan de hoekversnelling en de lineaire versnelling als specifieke prikkels respectievelijk voor de halfcirkelvormige kanalen en voor de otolieten. Uit hoofde van deze beschouwingen werd gezocht naar methoden om bij konijnen en proefpersonen de labyrinten adequate prikkels te geven.

Voor konijnen werd een draaitafel geconstrueerd, die door een valgewicht in beweging werd gezet. Zowel de perrotatoire nystagmus als de draaibeweging werden met de nystagmograaf geregistreerd. De lineaire versnelling werd aan konijnen gegeven door deze op een parallelschommel zijdelings heen en weer te zwaaien (JONGKEES en GROEN, 1946). De compensatoire oogbewegingen die hierbij ontstonden en de bewegingen van de schommel werden met de nystagmograaf geregistreerd.

Door middel van cupulometrie (VAN EGMOND, GROEN en JONGKEES, 1948) werd bij proefpersonen de postrotatoire nystagmus en sensatie bij draaiprikkels bestudeerd. De nystagmus werd met nystagmografie geregistreerd.

Ook voor proefpersonen werd een methodiek ontwikkeld om de compensatoire oogbewegingen, die door prikkeling van de otolieten met de parallelschommel ontstaan, te registreren met de nystagmograaf.

Met de parallelschommel werden compensatoire oogbewegingen opgewekt waarbij de ogen om een as draaiden die loodrecht bleek te staan op de richting waarin de schommel werd gezwaaid en loodrecht op de richting van de zwaartekracht.

Aan de hand van bovenbeschreven methodieken werd de invloed van stoffen nagegaan op de prikkelbaarheid van het labyrint. Wij onderzochten stoffen die verschillende farmacologische groepen vertegenwoordigen. Van de tegen zeeziekte werkzame middelen onderzochten wij een antihistaminicum, Cinnarazine en een spasmolyticum, scopolamine. Van deze stoffen bleek Cinnarazine een sterk significant remmende werking op de prikkelbaarheid van het labyrint te hebben, zowel bij konijnen als bij proefpersonen. Scopolamine bleek op geen enkele wijze de labyrintaire oogreflexen te onderdrukken. Daarentegen hadden wij zelfs sterk de indruk dat de prikkelbaarheid van het labyrint onder invloed van scopolamine werd verhoogd zoals ook GUTNER, GOULD and BATTERMAN (1951) vonden.

Van Largactil werd de invloed op het evenwichtsorgaan nagegaan naar aanleiding van publicaties waarin over een remmende werking van Largactil op het vestibulum gesproken wordt door SALERNO (1955), CARBONARA en SALONNA (1956), BERGSTRÖM en KOCH (1956) en ASCHAN, BERGSTEDT en GOLDBERG (1957). Wij vonden dat Largactil slechts de centrale fase van de nystagmus beïnvloedde, terwijl deze stof geen invloed had op de langzame vestibulaire fase van de nystagmus en op de compensatoire oogbewegingen bij het parallelschommel-onderzoek.

Nembutal bleek pas in diepe narcose invloed te hebben op de vestibulaire oogreflexen.

Van deze stoffen bleek alleen scopolamine (hyoscine), zij het in geringe mate, de cornea-retina rustpotentiaal te beïnvloeden. De andere stoffen hadden in het geheel geen effect hierop. Gezien dit feit zijn wij van oordeel dat de veranderingen in het nystagmogram door sommige van bovengenoemde stoffen niet berusten op een invloed op de cornea-retina rustpotentiaal, maar op een veranderde vestibulaire functie.

Wij zagen goede resultaten van Cinnarazine bij patiënten die leden aan vestibulaire duizeligheid.

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ROTATION TESTS IN RABBITS

The upper line represents the movement of the table.
The lower line represents the eye movement.

1 sec.