J. H. BOS - ON VESTIBULAR NYSTAGMUS WITHOUT CAUSATIVE ENDOLYMPH DISPLACEMENT

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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 WISKUNDE EN NATUURWETENSCHAPPEN, IN HET OPENBAAR TE VERDEDIGEN IN DE AULA VAN DE UNIVERSITEIT (TIJDELIJK EVANGELISCH-LUTHERSE KERK, INGANG SINGEL 411) OP DONDERDAG 13 DECEMBER 1962, DES MIDDAGS TE 5 UUR

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PROMOTOR:
PROF. DR. L. B. W. JONGKEES

Aan mijn Ouders

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Bij de samenstelling van het manuscript stond Dr. E. de Boer mij steeds met raad en daad terzijde, mevrouw Patricia Havenaar-Marks corrigeerde de Engelse tekst, Dr. Em. Hammelburg verzorgde het résumé. Mevrouw A. J. L. Tichelman-Cahen en mejuffrouw Ied Boelen verrichtten het typewerk.

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CONTENTS

CHAPTER I

INTRODUCTION AND REVIEW OF LITERATURE

In an earlier series of experiments on rabbits performed in the Ear-, Nose- and Throat-Department of the Amsterdam University (PHILIPSZOON, 1959) it was shown that the effect of physiological stimulation of the labyrinth could be suppressed strongly by the action of antihistaminic drugs.
The effect of the stimulation was observed on the resulting eye movements. (The stimulation was evoked by moving the rabbit. Standardized accelerations, both angular and linear, were used).
The antihistaminic drug *cinnarizine* * was able to suppress the reactions following upon both kinds of stimulation. Though some arguments were brought forward which show a labyrinthine origin of these actions to be probable, the site or sites of interference of antihistaminic drugs is still uncertain.
The aim of our research now is to collect more knowledge on the site of interference of the antihistaminic drug cinnarizine on vestibular reactivity as measured in electronystagmography.

Nystagmography

The first attempts to record eye movements were carried out with photography (BERLIN, 1891; BUYS, 1909; DOHLMAN, 1925) and with mechanical devices (OHM, 1914; STRUYCKEN, 1918, 1920; KUILMAN, 1931).
With the introduction of electronystagmography more reliable results could be obtained. In 1849 DUBOIS-REYMOND described a corneo-retinal potential difference. In the retina electric processes are always taking place, in daylight as well as in darkness, causing the retina to be charged negatively with respect to the cornea. Hence the eye is to be considered as a dipole, the electrical axis of which coincides with the optical axis. Any movement of the eye causes the electrical field around the eye dipole to move with it. At any given place the electric potential

* Cinnarizine is N-benzhydryl-N'-transcinnamylpiperazine = Cinnipirine (a product of the N.V. Amsterdamsche Chininefabriek, Amsterdam), also known under various other names including Dimitronal, Mitronal, Midronal, Stutgin, Glanil, Marisan.

will change accordingly. Electronystagmography is the recording of eye movements by way of these changes of the electric potential.
Publications on electronystagmography appeared by SCOTT (1922); MEYERS (1929); PERLMAN (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, KUBLER and BOESEL (1952); HERTZ and RISKAER (1953); RUDING (1953); VAN EGMOND and TOLK (1954); ASCHAN and BERGSTEDT (1955); HENRIKSSON (1955, 1956); ASCHAN, BERGSTEDT and STAHLE (1956); MAHONY, HARLAN and BICKFORD (1957); HAMERSMA (1957); STAHLE (1958); ARNOLD, GIULIANI and STEPHENS (1959); PHILIPSZOON (1959); KÜRZINGER (1960); MAAS (1961); LIDVALL (1961).
In view of our research it is of the utmost importance to recall that PHILIPSZOON did not find a change in the corneo-retinal potential difference when cinnarizine was injected.

Review of the research on antihistaminics against vestibular excitability.

In 1947 GAY and CARLINER successfully treated a woman with Dramamine (= dimenhydrinate = diphenhydramine + chlortheophylline) for urticaria. The patient happened to notice, however, that she was no longer susceptible to carsickness as she used to be. This applied only as long as the drug was being used, the symptoms of nausea etc. recurred as soon as she stopped the medication. In 1949 a subsequent publication of GAY and CARLINER appeared on the effect of dimenhydrinate on seasickness.
They treated different groups of soldiers on the ship *General Ballou* with dimenhydrinate or placebo's. One group of 134 received 100 mg of the drug four times a day for the first two days of the journey. They were not seasick in that period; 18 hours after stopping the treatment 41 of them became seasick. A placebo was given to a control group of 123 people in the next compartment, 35 of them were seasick within 12 hours of leaving harbour. At the end of two days the sick men were given dimenhydrinate; they recovered within one hour after the first dose.
GAY and CARLINER did not only perform this prophylactic experiment, they also reported on an experiment with drug and placebo as a treatment, with similar spectacular results.
This first report on the influence of an antihistamine affecting seasickness was soon followed by many other enthusiastic publi-

cations: BEAUMONT (1949); PALMER (1950); CHINN, NOEL and SMITH (1950); GLASER and HERVEY (1951); ARNER, DIAMANT and GOLDBERG (1954). All of them reported excellent results with dimenhydrinate or with diphenhydramine on motion sickness.
It is generally assumed that motion sickness is caused by an overstimulation of the labyrinths by linear accelerations (QUIX, 1923; SJÖBERG, 1931; DE WIT, 1953, 1958). Therefore the effect of antihistaminic drugs had to be differentially investigated as regards the stimulation, specific for the different parts of the vestibular labyrinths, i.e. angular and linear accelerations. Many investigators examined the effect of dimenhydrinate and/or diphenhydramine on the per- or postrotatory nystagmus, only a few of them used electronystagmography.
Usually a marked suppressing effect of the antihistamine on the reaction to vestibular excitation was observed.
However, WINSTON, RUBIN, LEWIS and REHBERGER (1950) failed to find a significant effect after 200 mg dimenhydrinate per os, when employing the rotatory Bárány-test.
KREJCI and BORNSCHEIN (1952) investigated in guinea pigs the effect of dimenhydrinate on the perrotatory nystagmus, and recorded their results with electronystagmography. They found a suppressing effect on the labyrinthine reflexes, including otolith reflexes, e.g. „Labyrinthstellreflexe" of MAGNUS and DE KLEYN.
DE WIT (1953) ascertained the diminishing effect of dimenhydrinate on human vestibular reflexes. He observed the nystagmus in cupulometry with Frenzel's glasses.
MONNIER and LAUE (1953) investigated with electronystagmography the effect of four different antihistaminics on the perrotatory nystagmus in rabbits. They all had a depressing effect.
GUTNER, GOULD and CRAVOCANER (1954) used a micro-caloric method and proved that cyclizine, another antihistamine, is effective in decreasing labyrinthine excitability.
GUTNER, GOULD and SWIFT HANLEY (1955) also found meclizine to be effective in suppressing the reaction to microcaloric stimulation.
Using normal subjects BARTALENA (1955) studied the influence of dimenhydrinate on two kinds of nystagmus, first the one following the rotatory Bárány-test and second the one after the caloric test using Veits' method.
PHILIPSZOON (1959) investigated the effect of cinnarizine on the postrotatory nystagmus in rabbits. With electronystagmography he proved the suppressing influence of this antihistaminic drug on reactions to angular accelerations. In addition to this, the effect of

linear accelerations on the labyrinth examined on the parallel swing, appeared to be diminished as well.

After this survey of the literature it is clear that antihistaminic drugs affect the labyrinthine reflexes.
However, the site of action is completely unknown. Does the drug affect the labyrinth itself, the eighth nerve or any of the vestibular nuclei? It is not even exactly known how the vestibular stimulus proceeds from the peripheral organs to produce central activity and, ultimately, nystagmic eye movements.

In order to collect more knowledge about this problem, we investigated the influence of the antihistamine cinnarizine on types of nystagmus evoked without moving the endolymph in the semicircular canals.
Several forms of nystagmus provocation can be used for this purpose. As it was our goal to investigate cinnarizine's site of action in the vestibular system, we confined our experiments to those forms of nystagmus that have some bearing on the vestibular system.

CHAPTER II

NYSTAGMUS WITHOUT CAUSATIVE ENDOLYMPH DISPLACEMENT

Optokinetic nystagmus

An optokinetic nystagmus can be elicited by moving objects horizontally or vertically in front of the eyes. TER BRAAK discerns two forms of optokinetic nystagmus: a cortical form and a subcortical one. The one form is assumed to be cortical because it requires the subject's attention. There are few animal experiments on this type of optokinetic nystagmus.
In fact, the experiments of DE KLEYN with dogs, are the only we found. When he moved rabbits in front of a pointing dog, he obtained typical nystagmic head movements. It appeared to be of primary importance to use dogs that focussed on the moving rabbits. Lacking this obvious interest, no nystagmus movements of the head could be observed. VAN DEYNSE, JONGKEES and KLIJN (1954) repeated these experiments and found that this nystagmus was still present, even after blindfolding the dog. It disappeared only after closing its nostrils. They concluded that this so called cortical type of optokinetic nystagmus was not optokinetic but olfactory.
The subcortical type of optokinetic nystagmus needs no attention to manifest itself. BROERS and DE KLEYN reported in 1920 — experimenting on dogs about miner's nystagmus — that this type of nystagmus does not fuse with a labyrinthine one.
Ordinarily two different stimuli, leading to nystagmus of identical origin, evoke a single reaction combining both results. DE KLEYN found that these two nystagmus patterns, e.g. the miner's nystagmus and the caloric, brought together, resulted in eye movements in which both patterns were clearly recognizable. He concluded that the miner's nystagmus could be of a different origin, having no relation to the vestibular apparatus.
On account of these data, we did not include optokinetic nystagmus in our experiments, as it seems to be quite unconnected with reactions from the vestibular system.

Nystagmus following galvanic stimulation

PURKINJE (1820) found already that a galvanic current influences equilibrium. Since then several investigators have tried to find if and where the galvanic current affects the vestibular system. From the periphery onwards to the central parts of the vestibular system, several sites are explored and found to be of utmost importance in the mechanism of galvanic nystagmus.
After extirpation of the peripheral labyrinths the responses to galvanic stimulation persist. DOHLMAN (1929) advocated the ganglion of Scarpa in rabbits, but HUIZINGA (1931) was able to elicit reactions in absence of this ganglion in pigeons, by using a stronger current. LEDOUX (1948) found in frogs that the anode decreases spontaneous vestibular reactivity, whereas the kathode increases it. HENNEBERT (1950) prudently abstained from taking sides, he suggested that the site of action may be still more central. In short: the exact mode of action of the galvanic current is completely unknown.
Maybe that is the reason why galvanic stimulation has become less important among clinical vestibular tests since it can not localize a disorder.
GUTNER, GOULD and BATTERMAN (1951); KREJCI and BORNSCHEIN (1952); GUTNER, GOULD and CRAVOCRANER (1954); GUTNER, GOULD and SWIFT HANLEY (1955) published positive results of antihistaminic suppression on galvanic stimulation.

On the Nystagmogenic Centre of Lachmann, Bergmann and Monnier

In 1958 LACHMANN, BERGMANN and MONNIER described an entirely different method to induce nystagmus beats. They used the stereotactic method of MONNIER to insert electrodes in the brain, at a given place in the reticular formation. The laboratory animal, i.e. the rabbit, can be examined under local anaesthesia only, so that it is still possible to carry out pharmacological tests. They preferably placed the electrodes in the latero-dorsal region of the thalamus. Using frequencies of about 5-50 per second, they could induce deviations of both eyes and eventually nystagmus beats.
The direction of these beats was sometimes to the ipsilateral, and sometimes to the heterolateral side.
Circling movements and other signs of vestibular excitation were not induced in freely moving animals. A relation with the vestibular system was not mentioned in their paper. An exact localization of their 'Nystagmogenic Centre' was not described. We were given to

understand however that this subject is being studied now. (Private communication, MONNIER, 1961).

Nystagmus after unilateral labyrinthectomy and Bechterew nystagmus

Another interesting type of nystagmus is the one after unilateral labyrinthectomy. How does such a nystagmus originate? LEDOUX (1948) described a way to reach the nerve of one of the semicircular canals in the frog as LOWENSTEIN (1940) described in the ray.
They found a resting activity in the nerve, which diminished or increased according to the direction of the cupula deviation. One assumes that in equilibrium the resting potentials in the two statoacustical nerves are equal, so that the activities arriving at both groups of vestibular nuclei are of the same magnitude. GERNANDT and THULIN (1952) found that the vestibular nuclei only receive afferent impulses from the homolateral labyrinth.
When one labyrinth is extirpated, most or all of the impulses reaching the homolateral vestibular nuclei will be extinguished. The remaining labyrinth predominates, a nystagmus will appear beating to the unaffected side. After some time the loss will be compensated for, 'spontaneous' nystagmus will have disappeared. This compensation is thought to be due to an increase of activity of the vestibular nuclei on the deprived side; they seem to make up for the loss of supply. This line of thought becomes more acceptable if we take the Bechterew nystagmus into account.

The Bechterew nystagmus is the form appearing after extirpation of the second labyrinth at the end of the primary period of desequilibrium and is therefore certainly of central origin. This nystagmus beats into the direction of the first attacked ear, 'as if it were still there'.
In 1950, FERMIN, VAN DEINSE and HAMMELBURG investigated the effect of dimenhydrinate on the nystagmus that follows unilateral labyrinthectomy. The drug suppressed all reactions resulting from the extirpation.
A first question is: will the antihistamine cinnarizine act equally well upon the nystagmus after unilateral labyrinthectomy? A second question is: what is the mechanism of this effect?
There are two possibilities: either cinnarizine diminishes the spontaneous activity of the surviving peripheral organ, or the suppressing activity starts in or above the vestibular nuclei.
The latter probability would become more acceptable if it could be

proved that Bechterew nystagmus was also diminished after the administration of cinnarizine. Hence we will include both forms of nystagmus after extirpation into our program.

Nystagmus provoked by the use of chemicals

Another type of nystagmus provocation is effected by the use of chemicals.

The nystagmus appearing after ethyl-alcohol consumption is widely known as a typical positional nystagmus. (ROTHFELD, 1913; DE KLEYN and VERSTEEGH, 1930; TASCHEN, 1955; ASCHAN 1957; ASCHAN, BERGSTEDT and GOLDBERG, 1957).

This nystagmus has two consecutive reaction phases in man: the first appears some time after drinking the ethyl-alcohol, and is beating to the left when the subject is lying on his left side, and to the right when the subject is lying on his right side. The amount of alcohol imbibed influences the intensity, but not the duration of this nystagmus.

This first type of alcohol nystagmus lasts about three and a half hours. The positional nystagmus disappears for some ninety minutes after the first phase. Finally, coinciding with the hangover period, a positional nystagmus reappears of a completely reversed type: the nystagmus in the left lateral position now beats to the right and in the right lateral position to the left. Electronystagmographical recordings accompany the statements of ASCHAN e.a.

These findings in man are so very constant that TASCHEN recommended it as a simple way to test the degree of alcohol intoxication. As it is impossible (DE KLEYN and VERSTEEGH, 1930) to induce positional alcohol nystagmus in rabbits without labyrinths, we are inclined to consider this reaction to alcohol as of peripheral origin. ASCHAN e.a. investigated the effect of various antihistaminics on positional alcohol nystagmus type I. It appears that some were effective, whereas others were not. In view of these data we wanted to investigate the influence of cinnarizine on positional alcohol nystagmus.

A second form of chemically induced nystagmus is the nystagmus described in pethidine (= meperidine) intoxication. ANDERSEN, JEPSEN and KRISTIANSEN (1953) stated that administration of pethidine, to reach a certain degree of anaesthesia, always elicited several nystagmus beats before the desired effect was reached.

VAN DISHOECK in his experiments on the opto-gyral illusions in man, used pethidine as a central working agent and obtained clear vertical

illusions (private communication). The literature on this subject is not as extensive as it is on alcohol nystagmus, but we decided to include in our program experiments on pethidine intoxication as an example of chemically induced nystagmus.

Nystagmus evoked by irritation of the cervical nerve roots

In 1939 BIEMOND described three patients with the known complaints of an irritated plexus brachialis: hypaesthesia and paraesthesia of arm and hand, and pain when pressing Erb's point. At the same time these patients complained of vertigo. BIEMOND assumed one origin for both complaints, treated the irritated plexus, and obtained a joint disappearance of both affections.

So it seems that BIEMOND's notion was right: irritation of the plexus cervicalis may involve vestibular reactions. In 1961 another patient was described by BIEMOND, she was suffering from vertigo of an unknown cause. Some time after the onset of her complaints herpes zoster appeared on the skin region of C_{II} and C_{III}. Unwittingly this patient was a perfect example because she proved the exact anatomical localization of her illness.

In animal experiments on rabbits with DE KLEYN (1940) this author succeeded to elicit positional nystagmus by cutting the posterior root of the second, third or fourth cervical nerve. The positional nystagmus died out in a few minutes.

This positional nystagmus provoked by cutting C_{II} was not recorded but only observed with the naked eye. Nevertheless, when this nystagmus was recorded in 1961 by PHILIPSZOON with electronystagmography, the aforementioned observation was confirmed. Examination into the Marchi degeneration revealed that this could be traced along the homolateral posterior column. This degeneration merges into the nucleus of Burdach and the nucleus of Von Monakow and ultimately reaches the inferior vestibular nucleus.

A special feature in rabbits is that this inferior vestibular nucleus shows a gradual transition into the nucleus of Deiters, which is found more laterally.

This histological finding suggests that irritation of the cervical nerves is a way of stimulating the group of vestibular nuclei to induce nystagmus. Moreover, a secondary degeneration following labyrinthectomy appears to have stopped at the group of vestibular nuclei.

This may be due to impulses still coming up from the cervical nerves, keeping this central part of the nystagmus pathways in working condition.

In these experiments the considerable bleeding, which sometimes starts when one cuts the first cervical nerve roots, is a great drawback. PHILIPSZOON (1961) now cooperating with BIEMOND to record these nystagmus beats, proposed to stimulate the cervical plexus by rotating the rabbit's body along a longitudinal axis while immobilizing its head. This is a method of stimulation, as we found out later, which was previously described by BÁRÁNY in 1907 and sincethen completely forgotten.

BÁRÁNY and PHILIPSZOON eliminated all labyrinthine reflexes by fastening the rabbit's head in a clamp. The body of the animal was fixed on the rabbit board. This board can be moved in all directions, while the clamp is immobile. When twisting the neck around a vertical axis through the atlanto-occipital joint they observed that the eyes followed with a few rapid horizontal jerks in the same direction as the body was moved. When the body movements were stopped, the eye movements stopped as well. When the neck was twisted in a different way, e.g. along a longitudinal axis through the atlanto-occipital joint, the eyes still moved horizontally. However, when the animal's head was not in a normal horizontal position, BÁRÁNY observed that the eyes were moving in a different plane. In view of these two facts: the shortlasting reaction, and the varying of the movements in other head positions, BÁRÁNY was disinclined to speak of reflexes of the neck.

That they are short-lasting is in our opinion a matter of fatigue, they reoccur after a rest period. In our experiments we were not severely hampered by the exhaustion of reflexes. BÁRÁNY had to apply rather crude stimuli to induce reactions; the electronystagmography enabled us to use smaller stimuli and thus to postpone an exhaustion. By gentle stimulation PHILIPSZOON obtained typical compensatory eye movements; when applying more vigorous stimuli rapid jerks became superimposed. This result could be obtained equally well in rabbits without labyrinths. Since DE KLEYN and NIEUWENHUYSE in 1927 observed that vertigo complaints in cervical disorders could be ascribed to obstructed blood supply to one of the labyrinths, the vertebral artery was in the centre of interest. As obstruction of the vertebral artery is usually due to cervical arthrosis, the real reason in man remained obscure. Moreover in cervical arthrosis the cervical nerves are similarly mistreated.

MAGNUS and DE KLEYN described already in 1924 reflexes to neck stimulation, diminishing the rigidity of the limbs of decerebrate labyrinthectomized cats. The cutting of the first, second and third cervical nerve roots bilaterally abolished these neck reflexes. To

achieve the same results in rabbits, it was necessary to cut the fourth cervical nerve as well. They concluded that a centre for these reflexes could be sought somewhere between the entrance of the second and fourth cervical nerve.

MCCOUGH, DEERING and LING (1951) investigated on cats the receptors for neck reflexes. From work on labyrinthectomized decerebrate cats they concluded that the reflex impulses move to the ipsilateral vestibular system, and that the receptors lie in the atlanto-axial and the atlanto-occipital joints. These joints are innervated by C_I.

RYAN and COPE (1955, 1959) focussed attention on cervical vertigo and its treatment by a fixed collar for the neck.

MASPÉTIOL, CHARDIN and MILLARD (1954) and GRAY (1956) treated vertigo due to cervical irritations with procaine infiltrations in the pertinent areas.

KUILMAN (1959) discussed 154 cases with vertigo complaints attributed to the cervical syndrome. He regards perispondylitis as of greater importance in causing these complaints than the malformation of the spinal column itself.

COHEN (1961) experimenting on monkeys, found severe defects in balance, orientation and motorcoordination when he applied a local anaesthetic on the nerves C_I, C_{II}, C_{III}, C_{IV}. He checked the place of application in autopsy. In spite of several publications on the neurological basis underlying the vertigo complaints, namely irritations in the cervical plexus, credit is still given to the explanation via the compression of the vertebral artery (PFALTZ, 1958; SANDSTRÖM, 1962).

Concluding this survey of literature on neck reflexes we find a consensus of opinion on several points:

1. Neck reflexes leading to nystagmus can occur even without intact labyrinths. (MAGNUS and DE KLEYN, 1924; MCCOUGH, DEERING and LING, 1951; PHILIPSZOON, 1962).
2. The afferent pathway of the reflexes involves the first four cervical posterior nerve roots. (MAGNUS and DE KLEYN, 1924; BIEMOND 1939, 1940; MCCOUGH, DEERING and LING, 1951; COHEN, 1961).
3. The afferent way continues from the posterior roots of the cervical nerves, along the posterior columns, via the nucleus of Burdach and the nucleus of Von Monakow to the inferior vestibular nucleus. (BIEMOND, 1940).

We standardized the method of stimulating vestibular nuclei ad modum BÁRÁNY-PHILIPSZOON and investigated the influence of cinnarizine on the eye movements thus induced.

CHAPTER III

OWN EXPERIMENTS

On galvanic stimulation

In man it is possible to elicit nystagmus by a galvanic current of 2–3 mA, when the electrodes are placed on the two mastoids. The subjects sits quietly in a chair and does not feel any disturbance of equilibrium. It takes half a minute before the nystagmus beats appear, but they persist undiminished for more than six minutes, without signs of fatigue or decreasing. The recording does not show the classic type of nystagmus that we usually see on vestibular stimulation, i.e. a slow beat alternating with a fast one. The possibility of interference between galvanic current and our electrodes for electronystagmography is not easily excluded. So we decided to investigate whether a pure vestibular nystagmus does merge with a galvanic one.

Volunteers were stimulated galvanically to evoke nystagmus beats, while they were lying on a stretcher. As soon as the beats were clearly visible (using on an average currents of 2 mA) we started a caloric stimulation to induce a vestibular nystagmus in the same direction. Fortunately we had proved already that the nystagmus on galvanic stimulation lasts at least several minutes. The result of this experiment, as depicted by the nystagmograph, was really surprising (fig. 1). The nystagmograph showed that the two forms of nystagmus did not merge but that one nystagmus was superimposed on the pattern of the other. According to DE KLEYN this would mean that the galvanic nystagmus is not linked with the vestibular system. We repeated the experiments several times and in all ten persons we obtained similar results.

So the assumption seems justified that a galvanic stimulation to evoke nystagmus beats does not act via the vestibular system.

This may account for the various and controversial findings of different authors. They based their investigations on the assumption that the galvanic nystagmus is of vestibular nature. Even if the galvanic nystagmus is not vestibular, it is to be expected that animals need stronger stimuli after an operation than before to produce the same results.

We performed a galvanic test in ten rabbits. We placed the electrodes

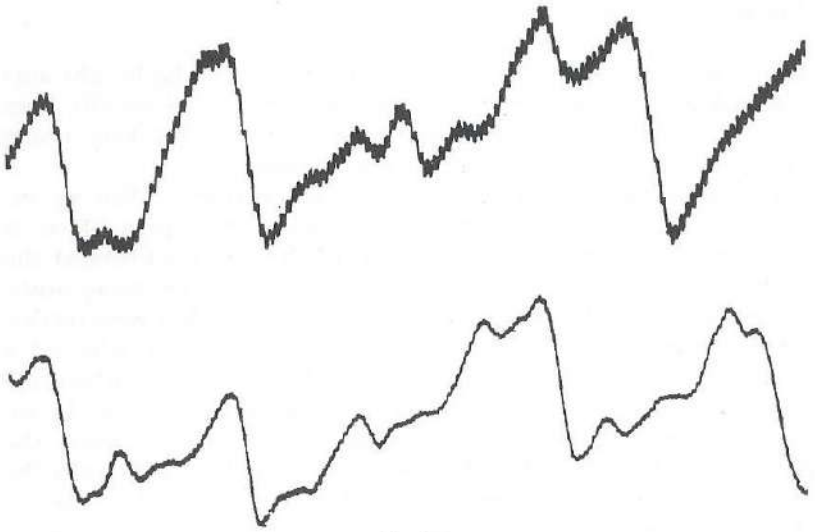


Fig. 1
Nystagmus resulting from simultaneous galvanic and caloric stimulation.
The big beats result from the caloric stimulation.
The small beats, superimposed on the slow phase of the caloric nystagmus, result from galvanic stimulation.

as deep as possible in both ears. Currents ranging from 1–20 mA were used to induce nystagmus beats. The results however were not very promising. In some of the animals no reaction was obtained at all, in others very evident nystagmus beats appeared.

With three rabbits which showed the nystagmus beats, the experiments were repeated after half an hour's rest. Though strictly the same conditions were observed no response was obtained. In view of these results we did not pursue this test on animals as the effects seemed to be irreproducible. Nonetheless, when a person, standing up, is subjected to galvanic stimulation, a very definite impression of displacement is felt in the direction of the anode, which suggests a direct action on the labyrinth itself, but it certainly does not prove a labyrinthine affection. These two impressions: one of the nystagmograph and one quite subjective, do not seem to agree with each other.

Without daring to express a final opinion about galvanic nystagmus, we think that the proof of its vestibular origin is not very sure, and therefore that conclusions from this kind of stimulation must be drawn with great care.

In our experiments we used ordinary rabbits as can be bought anywhere of medium age and weight. So our rabbits were usually from 7 to 12 months old and weighed from 1.5 to 2.5 kg. Very young rabbits were not used in view of their restlessness.

Before operating we gave a nembutal-ether narcosis. Then we extirpated the labyrinth ad modum DE KLEYN-VERSTEEGH. That is after an incision medial to the angle of the jaw we liberated the bulla by simply moving aside, not cutting away, the overlying tissue. We opened the bulla, first with chisel and hammer, but went further on with more delicate instruments, so that we finally achieved a good view of the middle ear, especially the promontory where the stapes indicates the site of the oval window. We proceeded by inserting a small hook into the round window and destroyed the promontory and the cochlea by pulling back the hook. Lesion of the stapedial artery results in an extensive, but short lasting bleeding.

After the removal of bony fragments the utricle and the utricular nerve are clearly visible. The view is, of course, greatly improved when we use an operation microscope.

In the position in which we operate the utricle is in the horizontal plane, its otoliths are hanging from the other side (the table side) of the limiting membrane, the nerve is directly visible. The membrane of the saccule is sometimes visible, but the saccular macula remains unseen. The saccule can be observed slightly above the utricle, the saccular macula is in the vertical plane, the otoliths of the saccular macula are the first structures to be reached.

In order to extirpate the labyrinth we attack the saccule first. By moving the hook a few times back and forth, we destroy its macula, then we proceed to the utricle and severe the limiting membrane, which is the membrane carrying the utricle. By the loss of endolymph, the whole pars superior is incapacitated. Naturally we finish the destruction mechanically, taking special care to include the maculae. Owing to the proportions of the rabbit's inner ear, the destruction of its labyrinths is mostly done in one movement, thus taking out saccule, utricle and canals in one action.

A direct proof of reaching the goal is found in the sudden reaction of all four legs as soon as we touch the vestibule. This reaction is very easily perceived even by a surgeon who is concentrating on the operation on the anaesthetized animal.

A second sign of success is a nystagmus movement of at least one of the eyes. As soon as the animal has sufficiently recovered from the

narcosis and its head is liberated from the clamp, it shows a violent turning along the longitudinal axis. A last sign of an effective operation is the position of the animal's head. When the rabbit is suspended in the air, the head is turned sideways, with the operated ear underneath. The final proof that such a labyrinthectomy has been complete is obtained when the animal some weeks later is submitted to an operation upon the other labyrinth. After destruction of its second labyrinth it no longer responds in the usual way to linear and angular accelerations.

We usually made recordings of the nystagmus on the second day after the operation. The body of the rabbit is then fixed on a rabbit board, its head in a special clamp, thus forming an immobile entity. The electrodes, to derive the potentials, are inserted subcutaneously; we use injection needles no. 12, insulated with plastic material, except for the tip that is bared for 3 mm. We place an electrode both above and below the eye; the third or reference electrode can be applied at any indifferent location: we put it on the nose. The electrodes are connected to the preamplifier and writing system in such a way that a movement to the right is recorded as an upward deflection. When the electrodes are placed above and under the eyes, a movement of the right eye to the under electrode and a movement of the left eye to the upper electrode are taken to be movements to the right. In order to attain a constant corneo-retinal potential the rabbit is put in the dark for half an hour. The necessity of this procedure was shown by PHILIPSZOON in 1959.

Movements of the eyes of the rabbit are now recorded when the animal is in a normal or prone position. Then we proceed to record the nystagmus – the animal is still fixed as described first – on its right side, then on its left side, in supine position, and finally standing upright with its head pointing upwards. After each change of position we have to wait about a minute before starting the recording, lest reactions to movements should interfere. Twenty minutes later we repeat the same tests. By twice recording the positional nystagmus we learn whether in a special situation amplitude and frequency actually remain constant. Proceeding in this way we happened to observe that the nystagmus following unilateral labyrinthectomy does not always beat into the presupposed direction.

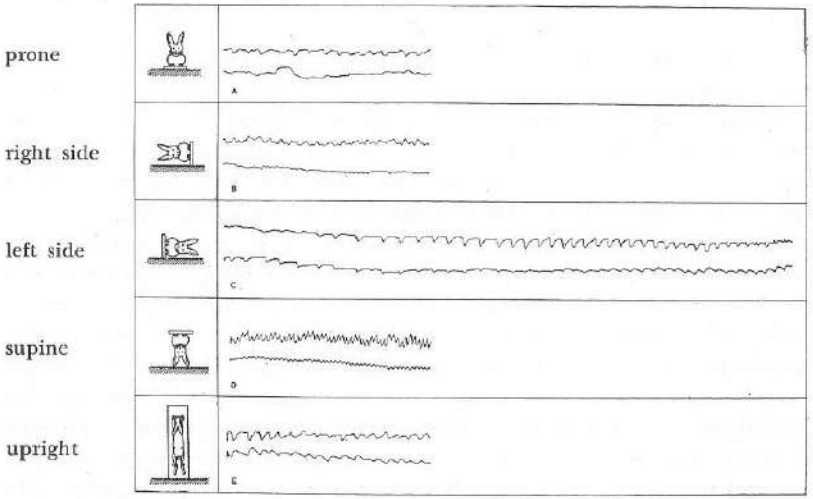
Nor are the two eyes found to be moving identically all the time as regards amplitude and direction.

Thirdly, positional influences on this type of nystagmus are very marked and variable.

a. *The direction of the nystagmus*

In this paper we only considered those cases in which movements of both eyes are recorded. We observed in ten animals three times a direction fixed type of nystagmus, all three were beating into the direction predicted by theory. Seven times a direction changing type of reaction was found.
We sometimes even recorded a change of the nystagmus in one eye, while the other eye maintained its original movement. This means that only in three out of ten experiments the nystagmus was as anticipated.
The situation that the one eye of the rabbit shows nystagmic movements whereas the other does not, has been explained as an artefact (Fig. 2). We will come back to this later.

Fig. 2
Labyrinthectomy left.



In prone position nystagmus in left eye alone.

In right side position only nystagmus in right eye.

In left side position nystagmus in both eyes, change of direction in the right eye.

In supine position, beats in opposite directions.

In upright position, beats in opposite directions.

b. *Positional influences*

In general we find the following: if the animal is in the supine position and when it is standing upright the eyes move slightly; when the animal lies on its non-operated side the eye movements are minimal or even absent; in the prone position and also when the operated side is down the reaction is maximal.

These findings in rabbits do not corroborate the generally accepted view (EWALD) which states that in man the nystagmus evoked by a peripheral lesion is in various positions always beating into the same direction.
This is opposed to the direction changing type which is thought to originate centrally. We do not presume that what happens in rabbits will happen identically in man, but it is evident that a contrast as mentioned above shows the need for a nystagmographical study on human subjects to reevaluate this notion on the vestibular organ.
The discovery of independent movements of both eyes makes it necessary now to discuss two matters at the basis of our methodology.
1. Does the relative position of the electrodes with respect to the eyes influence the amplitude of the recorded activities?
2. Does the electrical potential of the one eye affect the recording of movements of the other eye?
ad. 1. To study the influence the position of the electrodes has, the movements of the eyes should be made identical for all the tests. For this purpose we relied on the same principle as PHILIPSZOON (1959) when he proved that the corneo-retinal potential remained unaltered after an intraperitoneal injection of cinnarizine, and after application of pantocaine 1% on the cornea.
Accordingly we anaesthetized the cornea with pantocaine 1%, sutured with a few stitches a thread into the cornea and connected the thread on one side to an electromagnet and on the other side to a counter-weight. In this way we were able to cause a movement of the eye over a given distance.
Now we inserted the electrodes in the brim of the eyelids and recorded the forced movements of the eye. This was repeated a few times, each time inserting the electrodes more laterally to the eye, until a field of 1.5 cm was covered on both sides. From the recordings we can conclude that the place of insertion of the electrodes has no apparent influence (Fig. 3).
ad. 2. A similar procedure shed light on the interaction between the electrical potentials of the eyes. This time the position of the electrodes remained fixed. We recorded from both eyes each separa-

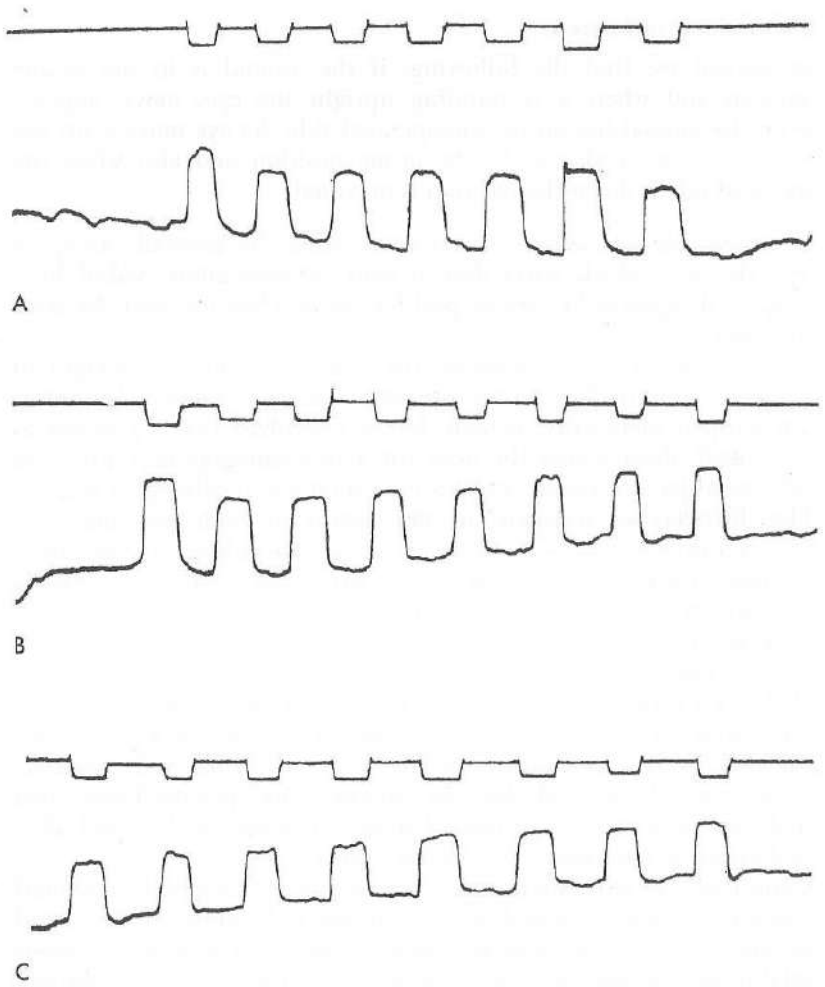


Fig. 3

Displacing the electrodes from the brim of the eye lids peripherally, over a distance of more than one cm., has no influence on the recording of the eye movements.

Upper tracing: the relay.
Lower tracing: recording of eye movements.

A. electrodes in the brim of the eye lids.

B. 1 cm peripherally.

C. 1,5 cm displaced.

The recording of the eye movements remains the same.

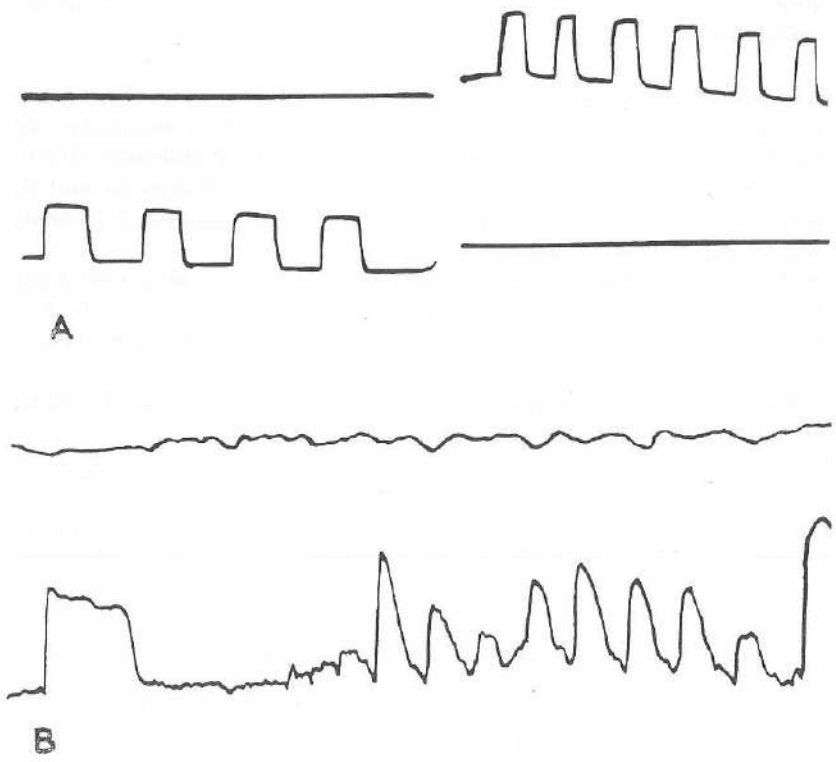


Fig. 4

Fig. A. Calibration of amplifying system.

Fig. B. A movement forced upon the right eye, does not influence the recording of movements of the left eye.

tely with a two-channel electronystagmograph and, during the recording, moved one eye with the aforementioned technique. Both channels were calibrated at the same level of sensitivity. The movements of the eye under coercion were duly recorded, it was also observed that the other eye remained stationary, registering no deviation of its electric potential (Fig. 4). On the strength of these experiments we may consider that the two recordings represent the actual movements of each of the eyes, which proves that both eyes can move independently, even in opposite directions, and that a nystagmus movement can be limited to one eye.

Results of the experiments concerning the effect of cinnarizine on the nystagmus after unilateral labyrinthectomy

Immediately after the second posture test as described above, on the nystagmus following labyrinthectomy on one side, cinnarizine (40 mg/kg bodyweight) was injected intraperitoneally. PHILIPSZOON (1959) was able with this dose to suppress reactions both to angular and to linear accelerations. Every twenty minutes the nystagmus, if present, was recorded in the 5 different positions (Fig. 5).
In eight rabbits we recorded the activities of both eyes after unilateral labyrinthectomy. A suppressing influence of cinnarizine on the eye movements was evident in seven of them; in one animal the nystagmus did not seem to be influenced.
Therefore we conclude that cinnarizine is able to influence this form of nystagmus.

The nystagmus of rabbit 527, two days after extirpation of the left labyrinth.

	10h		10h30		10h45	11h		11h20		11h45	
prone	R	L	–	–	cinna-	–	–	–	–	–	–
R.side	–	L	R	L	rizine	–	–	–	L	L	L
L.side	R	R	R	R		R	R	–	–	–	–
supine	–	L	–	L		–	–	–	L	–	L
upright	–	–	–	L		–	–	–	–	–	–

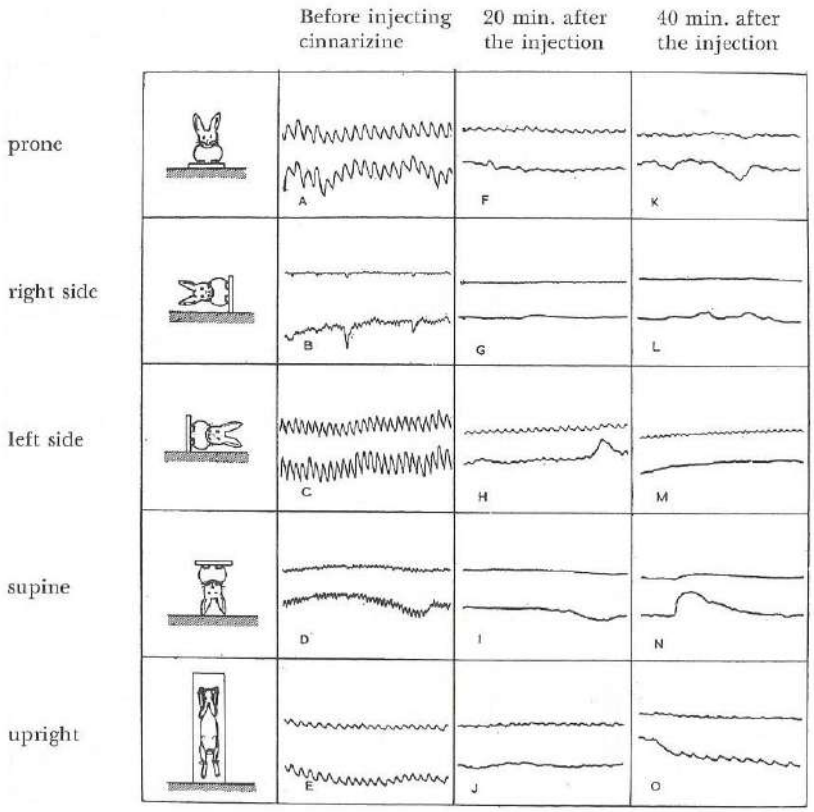
R = nystagmus movement to the right
L = nystagmus movement to the left
– = no nystagmus

Bechterew nystagmus

The origin of Bechterew nystagmus is, as we discussed already in the introduction, usually explained by a greater spontaneous activity in the group of vestibular nuclei on the side first operated upon. This is a very convincing idea, and it would explain the peculiar finding of nystagmus in a rabbit without labyrinths.
So far we have not been able to trace experimental evidence in the literature either supporting or denying this view.
When we investigate the influence of cinnarizine on Bechterew nystagmus, we might adhere to the hypothesis that this nystagmus is

Fig. 5

Labyrinthectomy left.

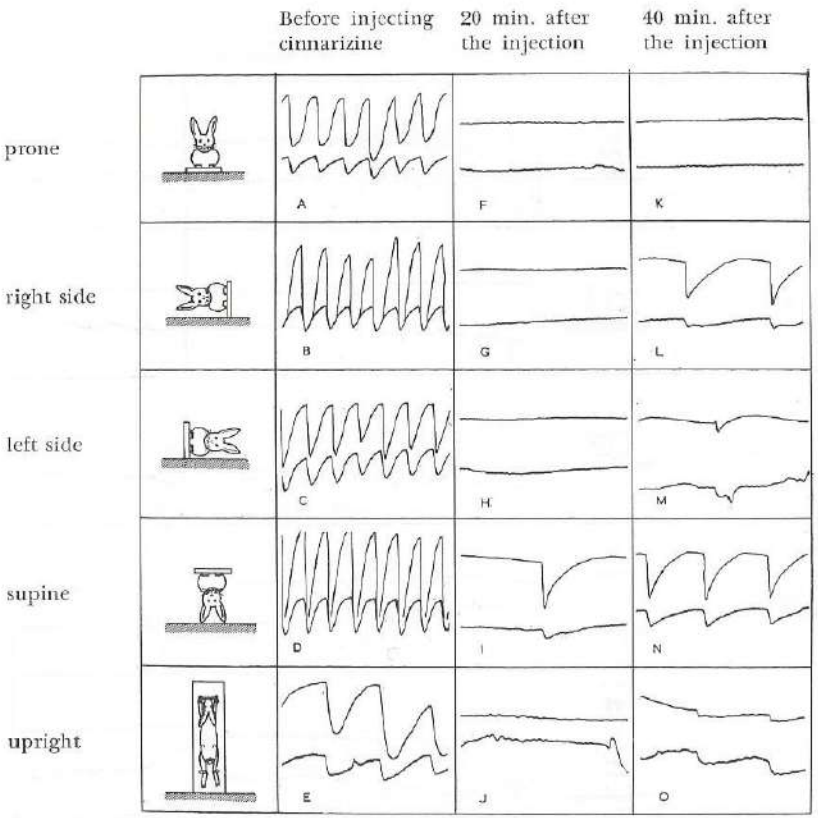


Upper tracing: movements of left eye.
Lower tracing: movements of right eye.
Note especially the evidence of positional influences.

the result of a desequilibrium in the vestibular nuclei and therefore of purely central origin.
We recorded this Bechterew nystagmus in eleven rabbits. The recording was performed within 36 hours, mostly within 24 hours, after the second operation. One of the major differences between the nystagmus following unilateral labyrinthectomy and the Bechterew nystagmus is the difference of their duration. The former may go on

Fig. 6

BECHTEREW nystagmus.



Upper tracing: movements of left eye.
Lower tracing: movements of right eye.

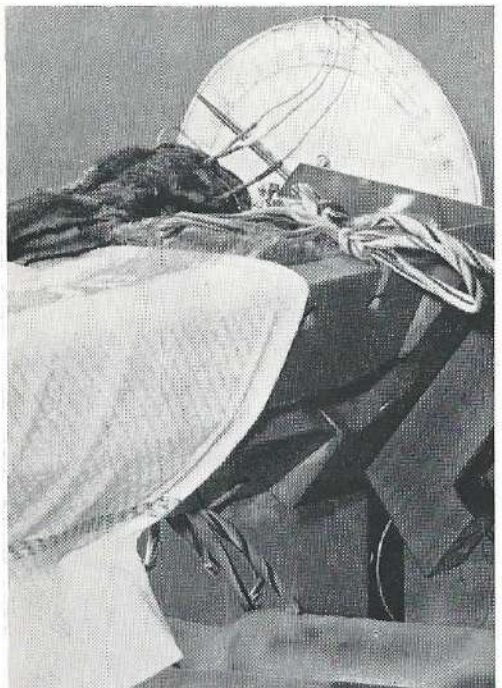
for many days, in some animals even for weeks, the latter extinguishes itself rapidly, sometimes Bechterew nystagmus has disappeared within 48 hours.

Some of the strange facts we discovered after the onesided extirpation are encountered again in the Bechterew nystagmus. In six of our experiments we found a direction fixed type of nystagmus, beating in the presupposed direction. But we also found here a direction changing type of nystagmus in the five others.

Fig. 11

TORSION OF THE NECK
in rabbits.

The head is immobilised, the body is moved to the left and to the right.



Summarizing our results we found that:

1. In Bechterew nystagmus the direction of the beats is not always according to theory.

2. In any given position the direction of the nystagmus as recorded, can gradually change in one eye, while the other eye goes on as before.

Results of our experiments about the influence of cinnarizine in the nystagmus according to Bechterew

After the first two blank tests, with twenty minutes intermission in the prone position, cinnarizine was injected intraperitoneally, again in a dosage of 40 mg/kg (fig. 6).
The action of this drug was investigated by recording the eye movements every twenty minutes. In eleven animals the effect of cinnarizine on the Bechterew nystagmus was tried. In ten rabbits the nystagmus was found to be diminished, at least for some time: one hour after injection of the drug the suppressing influence declined again. We got the impression that a higher dosage is required to abolish the reactions in a disorder of this type than is necessary in a peripheral affection. In one rabbit we failed to find unequivocal effect, the reactions were diminished as regards the amplitude only, the frequency was not affected.
On account of these experiments we are convinced that cinnarizine is able to diminish the nystagmus called Bechterew nystagmus. Therefore this drug must have a central depressing effect on the vestibular system.

The Bechterew nystagmus of rabbit 527, one day after extirpation of the right labyrinth.

	16h40			16h55	17h15		17h40		18h05	
prone	R	L	Cinna		–	–	–	–	–	–
R.side	R	L	rizine		–	L	–	–	–	–
L.side	R	L			–	–	L	–	R	L
supine	–	R			–	–	–	–	–	–
upright	–	–			–	L	–	–	–	L

R = nystagmus movement to the right
L = nystagmus movement to the left
– = no nystagmus

Nystagmus induced by chemicals viz. ethyl-alcohol and pethidine = meperidine

To study the influence of cinnarizine on nystagmus caused by chemical intoxication we performed experiments on various groups of rabbits. In these experiments we used the same kind of tame rabbits as in the previously described investigations.

We tested the nystagmus arising in alcohol and in pethidine intoxications. First we describe the results on the positional alcohol nystagmus.

Experiments on the first ten rabbits were performed in order to learn the normal behaviour of the eye movements in intoxicated animals. In the second group of eleven animals the influence of cinnarizine on this type of nystagmus is included.

The third group consisted of fifteen animals, deprived of their labyrinths, to study whether the inner ears are really indispensable for occurence of positional alcohol nystagmus.

The experiments started as usual with fixation of the rabbit; the electrodes were placed above and below the eye (cf. the situation after labyrinthectomy). Before ethyl-alcohol was given we examined the rabbit to make sure that it did not show a spontaneous positional nystagmus. Then a gastric tube was inserted and the alcohol administered through it. We want to draw special attention to the fact that the alcohol 96% was diluted 10 times before use, as we were afraid to damage the stomach's mucous membrane by pure alcohol.

De Kleyn and Versteegh observed positional alcohol nystagmus in rabbits when they applied 6 ml ethyl-alcohol 96%/kg bodyweight. Down to 4 ml/kg we constantly found a very clear nystagmus, if we gave 3 ml/kg the reaction to be investigated was not always found, so we investigated the nystagmus following a dose of 4 ml/kg.

The first group of 10 rabbits showed that alcohol nystagmus starts some thirty minutes after the application and goes on for at least two hours. This nystagmus was particularly evident in the two lateral positions and in the supine position. The velocity of the slow phase varied between 30 and 40 degrees per second in these positions. Prone or standing upright the animal showed eye movements to a minimal extent only.

Also in this chemically induced nystagmus we found that our observations did not always agree with current theory. The direction of alcohol nystagmus is supposed to be fixed, in such a way that in the right lateral position nystagmus beats to the right and in the

left lateral position to the left. We encountered however similar phenomena as we described previously in nystagmus after labyrinth extirpation on one side, and in Bechterew nystagmus. We noticed several direction changing types of nystagmus; nystagmus movements limited to one eye only, and even changes of direction in positional nystagmus in one eye, while the other eye did not alter its movements. (Fig. 7).

Fig. 7

ETHYL-ALCOHOL nystagmus.

Upper tracing: movements of left eye.
Lower tracing: movements of right eye.

Changing direction in positional alcohol nystagmus.

Aschan described the above mentioned form of positional alcohol nystagmus in man as PAN type I, as distinct from a PAN type II, that appears, coinciding with the hangover period. In this type II the direction is reversed, which implies that nystagmus in left lateral position now beats to the right, and in right lateral position to the left.

The moment of appearance of PAN type II is some 5½ hours after alcohol ingestion, in which period the blood alcohol level may or may not have reached the zero line. Therefore an alcohol nystagmus type II can be found even if alcohol is absent from the blood. In man antihistaminic drugs act favourably on this PAN type II.

Our results as regards the direction of positional alcohol nystagmus are ambiguous, so in our experiments a reversed type of nystagmus can hardly be recognized as such.

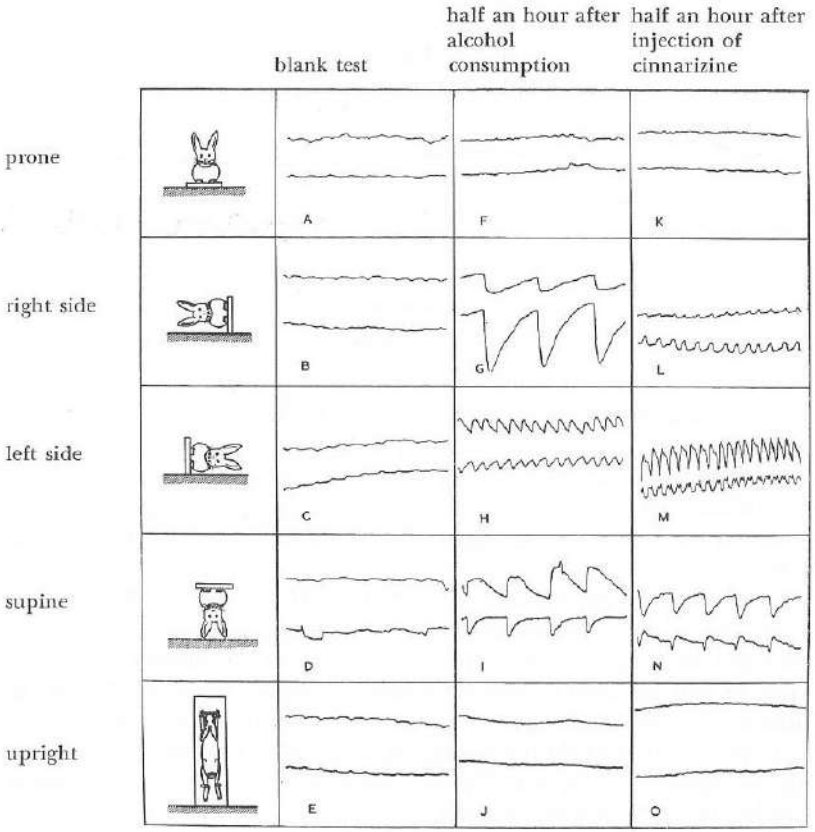
Lacking this characteristic we relied on the time element alone and recorded positional nystagmus in rabbits 6 hours after giving the alcohol. In ten rabbits we found no PAN type II. In two of them a nystagmus was found and suppressed temporarily by cinnarizine; in view of eight completely negative results, we consider the two positive nystagmus findings as a latent spontaneous nystagmus, appearing only in the discomfort following excessive alcohol consumption.

Aschan reported already in 1957 that a positional alcohol nystagmus

type II was not to be found in rabbits. In absence of nystagmus, cinnarizine's influence was not investigated.

Fig. 8

ETHYL-ALCOHOL nystagmus



Upper tracing: movements of left eye.
Lower tracing: movements of right eye.

Lying on the right side the nystagmus beats to the left.
Lying on the left side the nystagmus beats into opposite directions.
In the supine position the nystagmus beats have opposite directions.
Prone and standing upright the animal shows no nystagmus.

No influence of cinnarizine on the positional alcohol nystagmus is evident.

Results of the experiments concerning the influence of cinnarizine upon positional alcohol nystagmus

In eleven normal rabbits we tried to find whether cinnarizine 40 mg/kg has any effect on the PAN type I. We performed two posture tests to ensure the absence of a spontaneous positional nystagmus, before administering ethyl-alcohol in the above mentioned way. Thirty minutes after administering alcohol positional nystagmus was recorded. Following this (third) posture test, cinnarizine 40 mg/kg was injected in the abdominal cavity. Posture tests were repeated every twenty minutes during one hour. Cinnarizine is known to take effect within 15–20 minutes after administration, so a wide margin was observed to find results, even in case of a delayed action (Fig. 8). In none of the eleven tests a complete blocking effect was reached, not even a diminishing influence on the positional alcohol nystagmus could be detected. In all eleven animals the positional alcohol nystagmus appeared unaffected by cinnarizine. In three rabbits we investigated whether a correlation could be found between results of subsequent tests. In one of these animals the test was repeated after ten days, the direction of the nystagmus was found to differ. In the two other animals three successive tests were performed. Of the total of six tests only twice the directions in positional alcohol nystagmus were identical.

Ethyl-alcohol nystagmus in a rabbit.
No influence of cinnarizine.

	before		15h25		16h15		16h35		16h55		17h15	
			15h alc.				cinnarizine					
prone	–	–	–	–	–	L	–	–	–	–	–	–
R.side	–	–	–	–	L	L	L	L	L	R	L	L
L.side	–	–	–	–	R	L	L	L	R	R	R	R
supine	–	–	R	L	R	L	R	L	R	R	R	L
upright	–	–	–	–	–	–	–	–	–	–	–	–

R = nystagmus movement to the right
L = nystagmus movement to the left
– = no nystagmus

An equal amount of ethyl-alcohol was given to rabbits without labyrinths. These were checked to be free from positional nystagmus. We did not succeed in recording any nystagmus following the consumption of ethyl-alcohol in rabbits without labyrinths.

This finding is in complete accordance with data published by DE KLEYN and VERSTEEGH (1930).

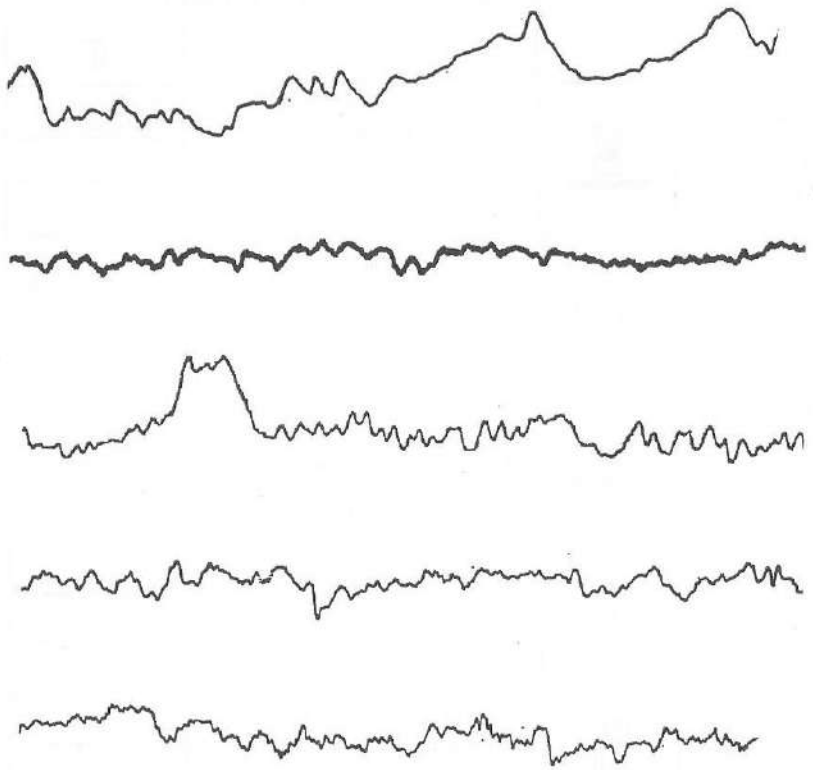
Nystagmus in pethidine = meperidine intoxication

ANDERSEN, JEPSEN and KRISTIANSEN report varying susceptibility to pethidine in man, but the average dosage that proved sufficient to evoke reactions (both nystagmical and anaesthetical) was 50 mg, applied intravenously.
Investigating the behaviour of rabbits in pethidine intoxication, we followed the same procedure as in our study of positional alcohol nystagmus. First the rabbit was fixed on the rabbit board, with its head in the clamp, then the electrodes were put in their proper places, in 50% of the experiments above and below the eye, in the other 50% in front of and behind the eye.

Results of the experiments on eye movements resulting from pethidine = meperidine intoxication

As soon as the rabbit was found to be free from spontaneous positional nystagmus, pethidine was injected into the abdominal cavity. We tried a full range of dosages from 10 mg/kg on, up to 100 mg/kg. In 34 rabbits we investigated the influence of 100 mg pethidine/kg bodyweight by recording the eye movements every twenty minutes for periods up to 2½ hours. It is to be noticed that we have given similar and even higher doses to the rabbits than those given in man to evoke nystagmus (ANDERSEN e.a.) or to induce vertical optical illusions (VAN DISHOECK).
In none of these 34 experiments a nystagmic type of eye movement could be recorded (Fig. 9). We did record, however, activities of the eyes, but these were incoordinated movements and had no visual resemblance to the wellknown rhythmic pattern of nystagmus. We emphasize this dissimilarity to nystagmus, because a suppressing influence of cinnarizine did appear.
When the animal was in a state of severe pethidine intoxication, not only eye movements could be found, but a spasmodic twitching of the whole body musculature was evident. On two occasions the animal even died after a period of frightful unrest. As we attributed this event to our medication we did not raise the dosage further. But even with the maximal dose of the drug we had sometimes to stop recording during a few minutes to avoid recording mainly artefacts. However, as soon as we applied the antihistamine cinnarizine, a

Fig. 9
Nystagmus? in PETHIDINE = MEPERIDINE intoxication.



Samples of eye movements in pethidine intoxication, only incoordinate eye movements are recorded, no trace of a nystagmus pattern.

drowsy calm came over the animal and both his eye and body muscles relaxed. This was visible in the recordings which became similar to those of a suppressed nystagmus. Even so, we did not find any trace of temporary nystagmus (Fig. 10).

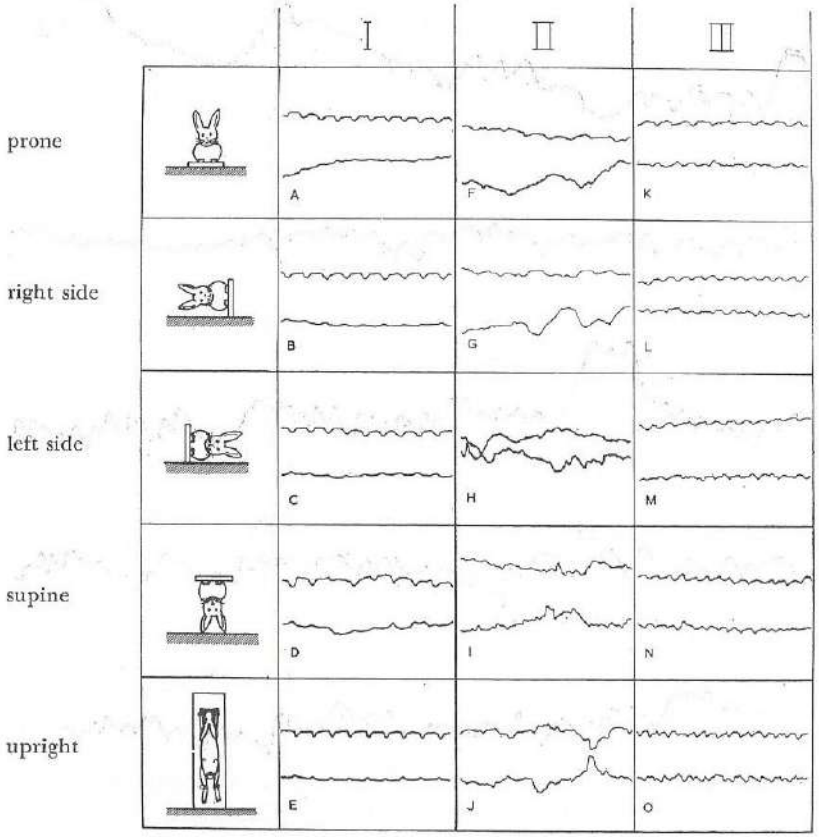
Reviewing our findings on the influence of cinnarizine in chemically induced nystagmus we summarize:

1. In rabbits a dose of 4 ml ethyl-alcohol 96%/kg bodyweight constantly evokes positional alcohol nystagmus.

2. The direction of positional alcohol nystagmus in rabbits does not obey known rules.

Fig. 10

INFLUENCE OF CINNARIZINE ON EYE MOVEMENTS IN PETHIDINE = MEPERIDINE INTOXICATION.



Upper tracing: movements of left eye.
Lower tracing: movements of right eye.

I = Blank test.
II = 30 minutes after injection of pethidine (= meperidine) 100 mg/kg.
III = 30 minutes after injection of cinnarizine 40mg/kg.

3. The inner ear is indispensable for the appearance of positional alcohol nystagmus.

4. Cinnarizine has no influence on this type of nystagmus of presumably peripheral origin.

5. We did not find nystagmus in rabbits intoxicated with pethidine (100 mg/kg) under the above mentioned experimental conditions.

6. Cinnarizine has a quieting effect on the spasmodic muscle twitching in pethidine intoxication.

Nystagmus evoked by irritation of the cervical nerves

MAGNUS and DE KLEYN (1924), as well as MCCOUGH, DEERING and LING (1951), investigated the occurrence of neck reflexes on decerebrate rabbits and cats, of which the labyrinths were previously destroyed. Evidence for the reflex action was found in a lessening of the decerebrate rigidity in the four limbs, which showed itself when the animal was lying on its back.

These investigators had to rely on such elaborate procedures as decerebrate rigidity before the neck reflexes could be ascertained. We, on the other hand, had an advantage of this era, an electronical recording equipment, i.e. electronystagmography, to record the induced nystagmus beats.

Starting point of our investigations was the occurrence of vertigo, originating from irritated cervical nerve roots. So we pursued BIEMOND's approach as published in 1939 and 1940. He described that cutting the cervical nerve roots of C_I, C_{II} and C_{III} induced a short-lasting positional nystagmus. PHILIPSZOON proposed to irritate the cervical nerves experimentally by applying a twisting force to the cervical vertebral column (Fig. 11). As we found out later, BÁRÁNY performed exactly the same series of experiments in 1907.

Though the approach differs from that of the above mentioned investigators, the main object was identical, i.e. to study the influence of neck reflexes on the vestibular system. We have the impression that the impulses, generated in the cervical nerves, follow, at least partially, the same 'nystagmus pathway' as the stimuli from labyrinthine origin.

From BIEMOND's experiments in 1940 it became evident that the inferior vestibular nucleus (lying next to the nucleus of Deiters) is involved when inducing the neck reflexes.

Since labyrinthine reactions proceed along the eighth nerve to the same group of vestibular nuclei, the common 'nystagmus pathway' apparently covers the area from vestibular nuclei to the nuclei of the eye muscles. That afferent pathways differ is clearly evident; the stimulus of the cervical roots follows the posterior columns, and the nuclei of Burdach and Von Monakow; the labyrinthine stimulus uses the vestibular nerve to gain the group of vestibular nuclei.

To check the independence of both forms of nystagmus provocation we examined the nystagmus evoked by torsion of the neck in rabbits

after destruction of the labyrinths. The eye reactions following neck torsion were found unhampered by the loss of labyrinths. On the other hand, we set out only to abolish the reaction to stimulation of the cervical nerves, while preserving the labyrinthine reflexes. Therefore we tried to intercept the afferent impulses, following torsion of the neck, in the posterior columns. An operation is likely to damage several structures, each of them might cause the suppression of the stimulus. So we decided to record the nystagmus again, immediately before the one intervention we thought to be decisive. Therefore we had to bare the spinal cord in the region of C_I.

After a median incision in the neck, immediately below the great window, we moved aside the structures overlying the vertebrae, which were mainly muscles. Then we performed a dorsal laminectomy on C_I and C_{II} so that the spinal cord became visible. At this moment reactions both to cervical torsion and to angular accelerations were recorded and checked to be normal.

As regards the means of intervention, one has to choose which course to follow: a simple section, or a reversible action.

We first tried to freeze the posterior columns to incapacitate their conduction faculties, but we did not succeed in suppressing the reactions under investigation. Secondly, the influence of locally applied procaine 4% was examined, again it appeared to be impossible to block the posterior columns without blocking the spinal cord completely, thus causing death by suffocation.

In only one rabbit we succeeded to stop the reactions to torsion of the neck by dissecting the entire posterior column. In this animal a nystagmus could still be elicited on the torsion swing, but not by torsion of the neck (Fig. 12).

In seven others we only succeeded in stopping the eye reaction to neck reflexes by completely severing the spinal column from the medulla oblongata (with the aid of artificial respiration the test animal can be kept alive). Half an hour later the experiment was repeated to show that the labyrinthine reactions were still present while it remained impossible to evoke nystagmus by torsion of the neck. In a ninth rabbit the reactions to irritation of the cervical nerves remained present, despite apparent spinal section. On autopsy a few fibres were found, connecting the two parts of the central nervous system, that we had tried to disconnect. In the other animals examination after death showed total section of the medulla.

In the instances where we were mistaken in the rabbit's anatomy and cut below C_I, the reactions to torsion of the neck were diminished but not abolished. Therefore we conclude that the impulses involved

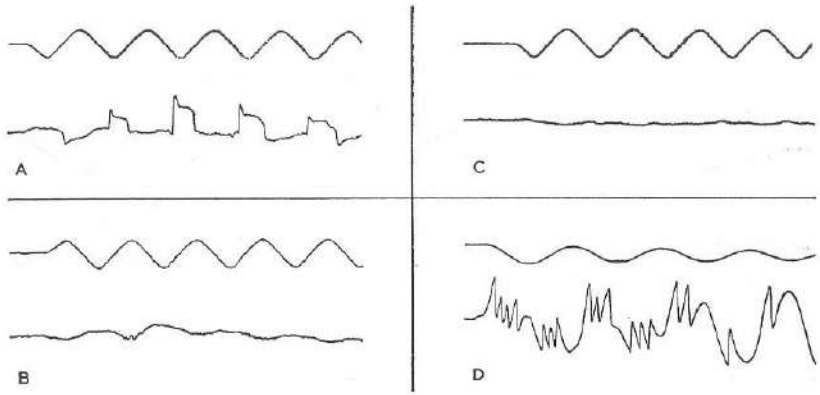


Fig. 12 Upper tracing: recording of swing movements.
Lower tracing: recording of eye movements.

NECK TORSION NYSTAGMUS.
Cutting of the spinal cord above C_I.

A. Before cutting very clear nystagmus movements.
B. After an incomplete cut slight compensatory eye movements are left.
C. No reaction on neck torsion after a complete cut above C_I.
D. Reaction on cupular stimulation remained normal.

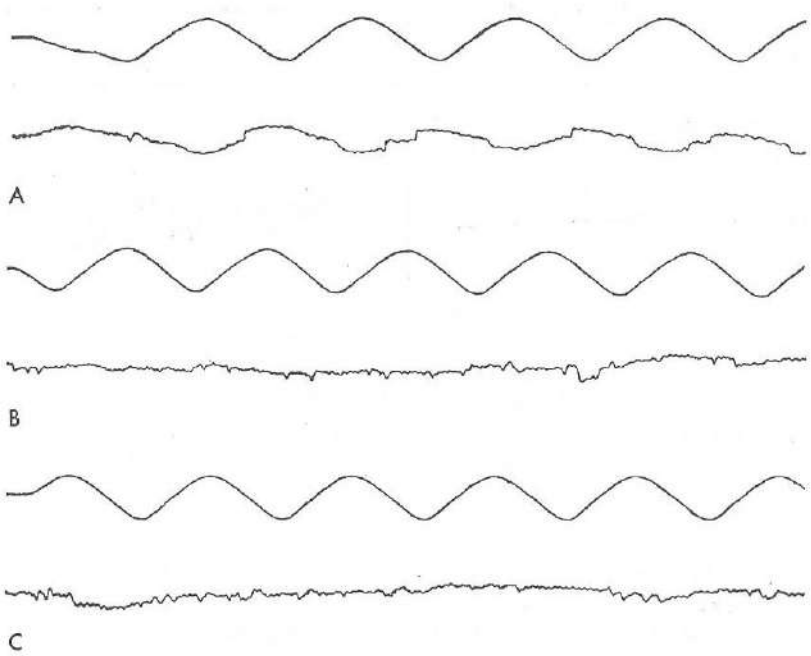
in cervical stimulation originate at the level of C_I and lower (C_I, C_{II}, C_{III}, C_{IV}).

This spinal section operation is usually accompanied by loss of blood and liquor cerebrospinalis. Our conclusions can thus be criticized; the disappearance of the neck torsion nystagmus may be attributed to shock, or more generally, to the weak condition of the rabbit. Although we admit that the animals, after the section, are not in good condition, the clear reactions to labyrinthine stimulation prove that at least the 'nystagmus pathways' are in perfect working condition.

A connection between labyrinthine nystagmus and the one after cervical stimulation can be demonstrated by evoking a cervical and a labyrinthine nystagmus at the same time. Nystagmus on torsion of the neck is then suppressed in one direction, yet augmented into the other.

In all the experiments on cervical nystagmus we rotated the body of the rabbit around a longitudinal axis, while keeping its head immobile, fixed in a clamp. Every rabbit's neck was twisted to the same degree and at the same rate. To investigate the effect of cinnarizine on this type of nystagmus we ultimately decided to use a torsion of 55° to the left and to the right, with a speed of 14

Fig. 13
NECK TORSION NYSTAGMUS in a rabbit.



Upper tracing: recording of swing movements.
Lower tracing: recording of eye movements.

Fig. A. Typical compensatory eye movements and nystagmus on torsion of the neck.

Fig. B. 20 minutes after an injection of cinnarizine, good suppression of the nystagmus.

Fig. C. 40 minutes after the injection of cinnarizine.

complete cycles per minute. Tests were performed during one minute.

An electrically controlled velodyne motor system served as source of power. Between torsion tests a rest period of twenty minutes was duly observed to ensure complete recovery from previous stimulation. As a matter of fact, in testing the animals at various degrees of torsion and velocity of the swing, we learned that the reflexes could be exhausted in a relatively short time. Hence the limited amount of cycles (14) and the long periods of rest. Thus a complete test consisted of five consecutive torsions, two before, three after the administration of the drug.

Results of the experiments concerning the influence of cinnarizine upon nystagmus evoked by irritation of cervical nerves

In a series of tests on 15 rabbits they all showed the eye movements due to neck torsion. Prior to the experiments we controlled to see that the eyes dit not show nystagmus when the animal was at a standstill. In most cases it was possible to diminish the reaction with cinnarizine in the dose of 40 mg/kg bodyweight (Fig. 13). However, it did not often happen that we procured a complete abolishment of the nystagmus, as depicted in Fig. 13. In some rabbits we could not see any effect at all. So we decided to resort to a blind procedure injecting the drug into rabbits of the one group, the solvens alone into the animals of the other, to study whether cinnarizine has a suppressing effect on these eye movements. We performed 31 tests to investigate the influence of cinnarizine on the neck reflexes and found in ten a positive result, in 21 cases a negative result. Five animals were used twice in this series of experiments, an intermission of at least two weeks, however, was duly observed, to diminish the possibility of interaction between the injected drugs.

Rearranging these data with respect to drug and placebo, we found 8 positive and 6 negative results for the drug, compared with 2 positive and 15 negative when injecting the placebo.

With Fisher's method (2 x 2 table) we investigated whether the possibility to find a diminished nystagmus, differed for both groups of laboratory animals examined.

At a 5% level of significance (two-sided) as is usual in medical statistics, we found that this probability indeed differs in both groups of animals. This indicates that cinnarizine can safely be assumed to affect the nystagmus due to neck torsion. *

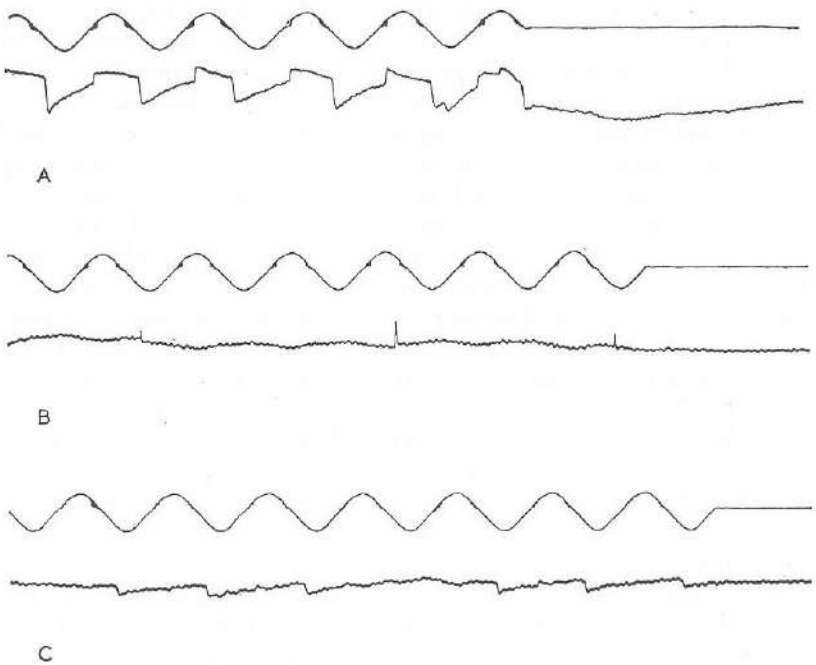
The neck reflexes evoke nystagmus movements even in rabbits without labyrinths.

We performed this test on 14 of them, and investigated the influence of cinnarizine upon the resulting eye movements. In this series we could not use the blind technique owing to the limited number of labyrinthectomized rabbits. Therefore the demand of acquiring quantitative results is not met. The test was carried out on 14 rabbits without inner ears. All of them showed reactions to torsion of the neck; in five of them a complete disappearance of nystagmus was acquired after the injection of cinnarizine (Fig. 14).

* We greatly appreciate the help of Dr. Chr. Rümke in this connection.

Fig. 14

NECK TORSION NYSTAGMUS in a rabbit without labyrinths.



Upper tracing: recording of swing movements.
Lower tracing: recording of eye movements.

Fig. A. Typical compensatory eye movements and nystagmus on torsion of the neck.

Fig. B. 20 minutes after an injection of cinnarizine, very good suppression of the nystagmus.

Fig. C. 40 minutes after the injection of cinnarizine, slight recurrence of nystagmus.

Rabbits without labyrinths show nystagmus beats on neck torsion. This finding could cause a change in views on the cervical syndrome. DE KLEYN and NIEUWENHUYSE (1927) mentioned in a terse publication the possibility that an impeded bloodsupply influences the function of inner ears. That the bloodflow through the vertebral artery was actually obstructed was suggested by test-results on autopsy.

The underlying idea was that an obstructed bloodsupply was able to influence labyrinthine function immediately. Sincethen a great deal of attention was drawn to the vertebral artery, to explain the

cervical syndrome, often without mentioning the possibility that neural irritations participate and influence the vestibular system. In most publications on the cervical syndrome the cause of the illness is sought in the obstructed vertebral artery, and medication is chosen accordingly. PFALTZ (1958) proposes to change the name cervical syndrome into vertebral syndrome, as he attributed major importance to an arterial obstruction causing this syndrome.

In our experiments however, we proved that a neural affection can cause the vertigo complaints in cervical syndrome. An irritation of the dorsal nerve roots of C_I, C_{II}, C_{III} and C_{IV} suffices to induce vestibular nystagmus as an objective proof of unbalance. The most important feature is that this lack of balance, recorded as nystagmus, can be evoked in absence of labyrinths. The impeded bloodsupply to the labyrinths is not even required to elucidate the vestibular affection, as the labyrinths do not necessarily play a part in the genesis of this disorder. In our opinion irritation of the dorsal nerve roots of C_I, C_{II}, C_{III} and C_{IV} gives a sufficient explanation of vertigo complaints accompanying cervical arthrosis. The connections of cervical nerves with the vestibular system are abundantly demonstrated. As a matter of fact this influence of cervical nerves on vestibular reactions is examined by several authors with different methods. The specific effect of cinnarizine on these nystagmus beats also shows that the vestibular system might be involved.

We do not absolutely deny that the obstructed bloodsupply has a role in the cervical syndrome; nevertheless we have the impression that irritated cervical nerves, with or without perispondylitis due to arthrotic vertebrae, can explain all symptoms of the cervical syndrome. Needless to say, on the above mentioned grounds we oppose PFALTZ's proposition to change the syndrome's name into vertebral syndrome.

In summarizing these data about the effect of cinnarizine on the neck torsion nystagmus, we are convinced that this dose of the drug has a positive, but not a complete suppressive effect on these reactions.

CHAPTER IV

CLINICAL ASPECTS OF NECK REFLEXES

A preceding chapter dealt with a similarity of reactions to labyrinthine stimulation and to neck torsion: both induce nystagmus movements of the eyes.
These reflexes of the neck are especially important in clinical vestibular diagnostics. They can be regarded from two different angles:
1. as confusing the results of vestibular function analysis.
2. as a means to stimulate the central part of the nystagmus pathways.

Ad 1. Performing the posture test it is a good habit to turn the patient as a whole into the various positions. Some investigators advocate electrically driven posture tables in order to exclude all extra reflexes due to labyrinthine or neck stimulation. In Amsterdam, patients are examined while lying on a stretcher; recordings are made when the patient rests quietly on the side under investigation. As we do not use posture tables or fixating collars, we wait one minute before being able to record a pure positional nystagmus. In still another method, positional nystagmus is investigated by only altering the position of the patient's head, leaving the body immoved. The advantage of this method is that it saves time and is easy to perform. It is, however, only reliable when negative results are found. All positive results require further testing.
DIX and HALLPIKE (1952) and CITRON and HALLPIKE (1956) described a 'benign paroxysmal positional nystagmus', they consider that this phenomenon proves disorder of the utricle, which is at that moment on the underneath side of the head. To elicit this nystagmus they move the patient's head and body backwards over an angle of 90°, in the same manoeuvre turning the head sideways over 45°, so that finally the patient is lying on his back on the examination table, the head is kept hanging off and turned aside. Observing or recording the resulting eye-movements, the benign paroxysmal positional nystagmus presents itself a few instances after these actions, augments to a certain maximum intensity and extinguishes again. These objective signs of vestibular affection are accompanied by a rising nausea and a general feeling of distress, which decreases simultaneously with the extinguishing nystagmus.

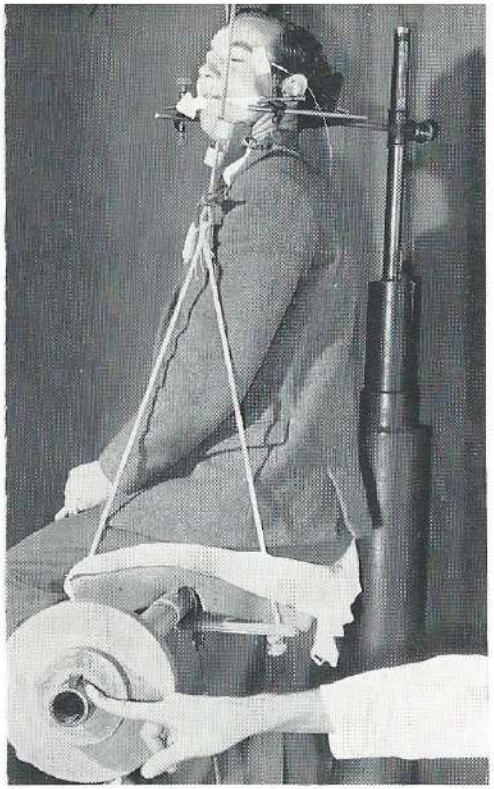
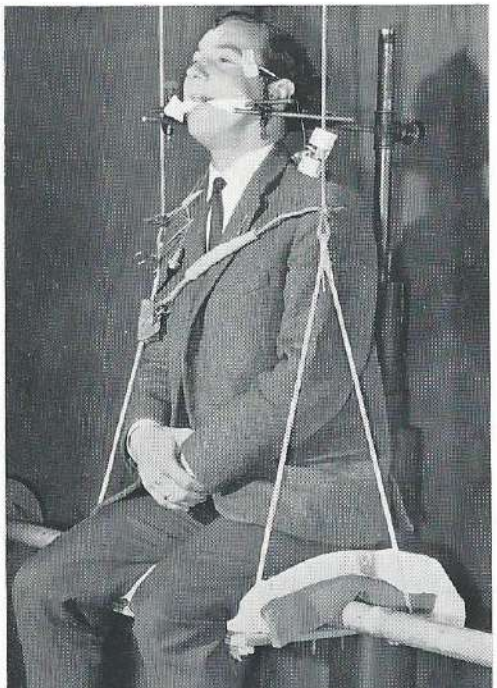
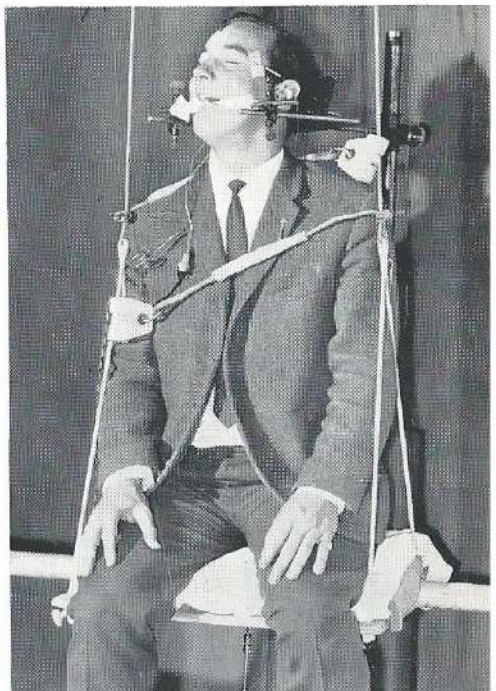


Fig. 16

Normal human subject on the torsion swing, the head is immobilised by a clamp on a floorstand.





We do not intend to reject a vestibular contribution to a genesis of this nystagmus type, but we want to draw attention to the fact that an identical procedure produces both 'benign paroxysmal positional nystagmus' and 'neck torsion nystagmus'. In both cases a tordating force is applied to the neck: in HALLPIKE's experiments an influence on the neck is added to one on the labyrinths, a resulting nystagmus can thus be attributed to both sources. That the nystagmus due to neck torsion stops even when the head is kept in the extreme position, is in complete accordance with our findings in experiments on animals.

In summarizing our evaluations on the benign paroxysmal positional nystagmus we are inclined to consider this form not as the result of one pure effect on the vestibular system, but as an answer to a very complicated stimulus, including accelerations – both linear and rotatory – and necktorsion.

Another interesting aspect of these irritations of cervical nerves in patients is the possibility of treatment. If the vertigo is attributed to an impeded bloodsupply – owing to arteriosclerotic bloodvessels and arthrotic vertebrae – there is not much choice of treatment other than vasodilatation. Such a dilatation is not easily attained in rigid bloodvessels. However, as we know now that in some patients irritation of the cervical nerve roots plays an important, if not a leading part in the genesis of vestibular disorder, it opens up other possibilities of treatment.

Firstly we want to draw attention to our results with cinnarizine in rabbits. On account of these data we expect that cinnarizine is able to suppress the symptoms of vertigo due to irritation of cervical nerve roots. Such a medication is bound to be purely symptomatic, whereas a more causal therapy should be considered as well.

KUILMAN (1959) applied ultra-sonic treatment to 154 of his patients and obtained very good results with this approach. All these patients belonged to the same age group, they were fifty years and older and they all had arthrotic cervical vertebrae.

In our routine vestibular tests on patients complaining of vertigo, we came across three young men, some thirty years of age, who had a positional nystagmus. This indicates in our opinion an organic cause for their complaints; the other tests on labyrinthine function were completely normal: a normal audiogram and equal reaction of both ears to caloric stimulation. The possibility of concussion of the brain could be eliminated. The cervical vertebral columns, however, showed signs of cervical arthrosis. These three men used to be very healthy sportsmen; they all happened to boast on their abilities as

judoka. Hence our attention was focused on this form of sport. We will refer to these three as group (a).
We next examined two other groups of judo enthusiasts, differing only as regards their period of training. These young men were between twenty and thirty years of age. In one group (b) of ten persons – training less than one year – no sign of spontaneous or positional nystagmus was found.
The other group (c) consisted of five men, all in intensive training for more than four years; they were all free from pathology in the

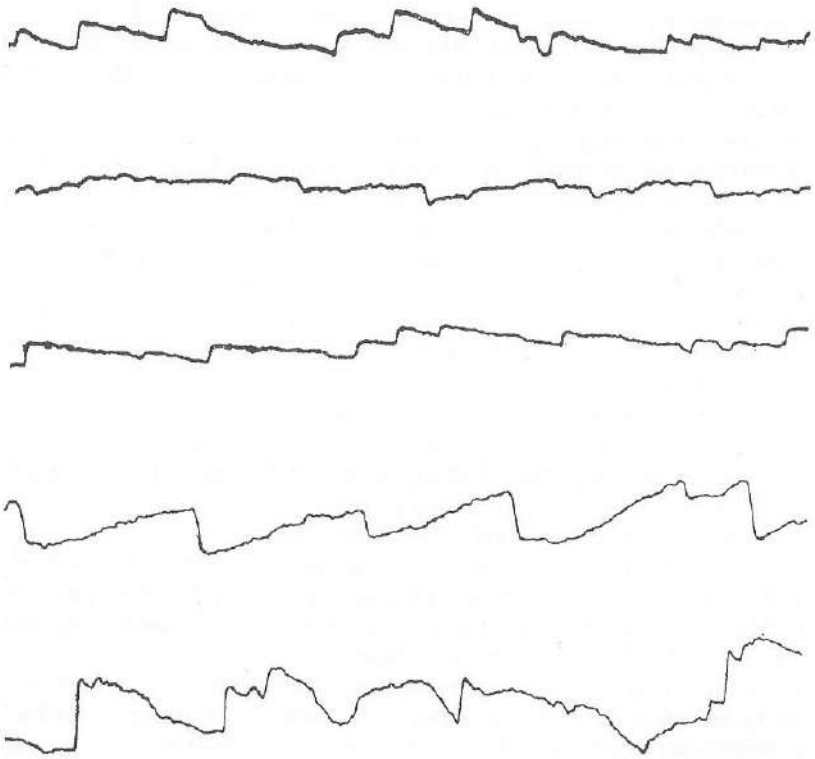


Fig. 15

JUDO.

Five judoka's without vertigo complaints, each training intensively during more than 4 years, showed a positional nystagmus.
We attribute this to irritation of cervical nerve roots.

domain of Ear, Nose and Throat and had had no concussion of the brain. All of them showed a spontaneous or positional nystagmus, but none complained of vertigo (Fig. 15).
One can imagine that in judo, where the neck is constantly active as if it were a fifth extremity, many factors are present which are likely to induce ultimately an irritation of cervical nerves. It is to be noted that in the aforementioned age groups the occurrence of arthrotic bloodvessels is so rare as not to impede our conclusions.
The cervical vertebral columns of these fifteen people did not show signs of cervical arthrosis. So a positive X-ray is not even needed to explain the origin of the nystagmus. Apparently it is simply caused by irritation.
The borderline between the groups (a) and (c) of judo addicts, one (a) with complaints and arthrosis, the other (c) without, separates in fact people in full training and people that stopped training. Whether the complaints formed the reason for the decision to abandon this sport, or that they originated at a later date, is not known. Our number of examined judoka's is too limited to show definitely whether cervical arthrosis develops earlier in judoka's than in other people; neither could we ascertain whether it arose during the training period or after stopping.
It is to be mentioned, however, that a positional nystagmus may well be due to irritation in the cervical nerve roots, and that it can be found notwithstanding an X-ray showing normal cervical vertebrae.
Ad 2. Some patients have two inexcitable labyrinths, due to various causes. But the patients have one feature in common: it is impossible to test their vestibular system. Therefore it is very hard to ascertain whether the lesion is limited to the labyrinths and the eighth nerve alone or that the whole vestibular system is affected.
Following the same principles as used in the rabbit tests we examined patients on the torsion swing. Thus the inexcitability of their horizontal semicircular canals was easily demonstrated.
Following this test, the patient's head was immobilized by a clamp attached to a floor stand; fixation was thus independent of the torsion swing (Fig. 16).
In normal human subjects this neck torsion technique made it possible to elicit nystagmus beats synchronously with movements of the torsion swing. The latter being recorded on the second channel of the Mingographe with the help of a potentiometer, coupled in a bridge of Wheatstone.
As we found out in animal experiments on neck torsion, stimuli

proceed from the cervical nerves to the inferior vestibular nucleus, thus evoking nystagmus beats, without passing through the labyrinths.

Three patients with inexcitable vestibular labyrinths were examined in this way.

A. acquired his vestibular inexcitability when the eighth nerve was bilaterally severed in fractures through both petrous bones after an accident. Repeatedly his faculties to react to linear accelerations on the parallel swing, or to angular accelerations on the torsion swing were examined, but the usual response did not appear. Twisting his neck in the way described above, we found that the pathways for nystagmus were functioning and able to produce nystagmic eye movements.

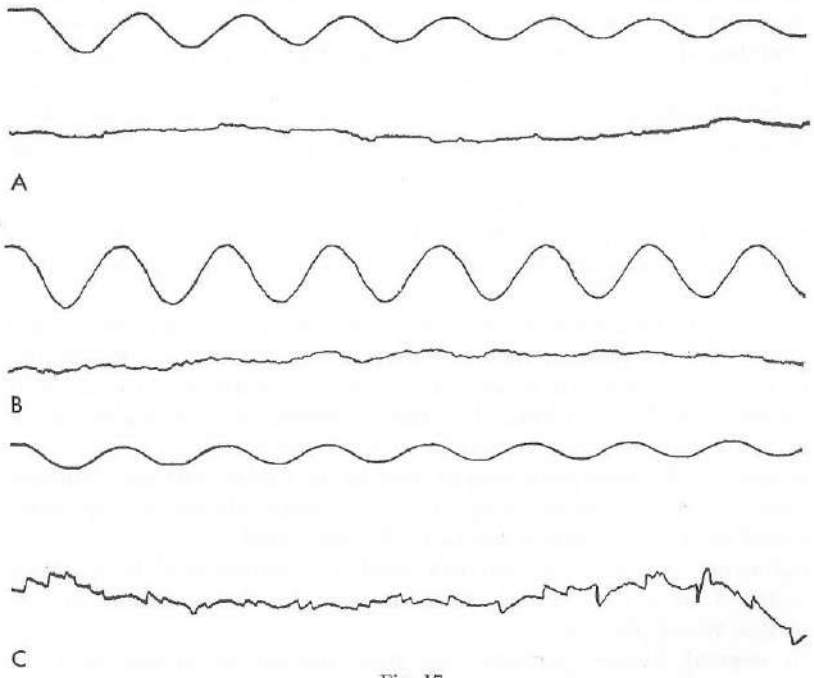


Fig. 17

Patient with two inexcitable labyrinths due to fractures in both petrous bones.

Fig. A. No reaction to cupular stimulation.

Fig. B. No reaction to macular stimulation.

Fig. C. A clear nystagmus on torsion of the neck.

The two other patients had received streptomycin treatment for tubercular meningitis. The inner ears of B. were completely invalidated, C. had retained her hearing faculties.

Neither patient reacted to angular accelerations when placed on the torsion swing, nor to linear accelerations on the parellel swing. In contrast to this, very clear nystagmus eye movements were obtained on torsion of the neck. This finding in both patients implies that vestibular nuclei have retained their ability to react normally to stimulation (Fig. 18).

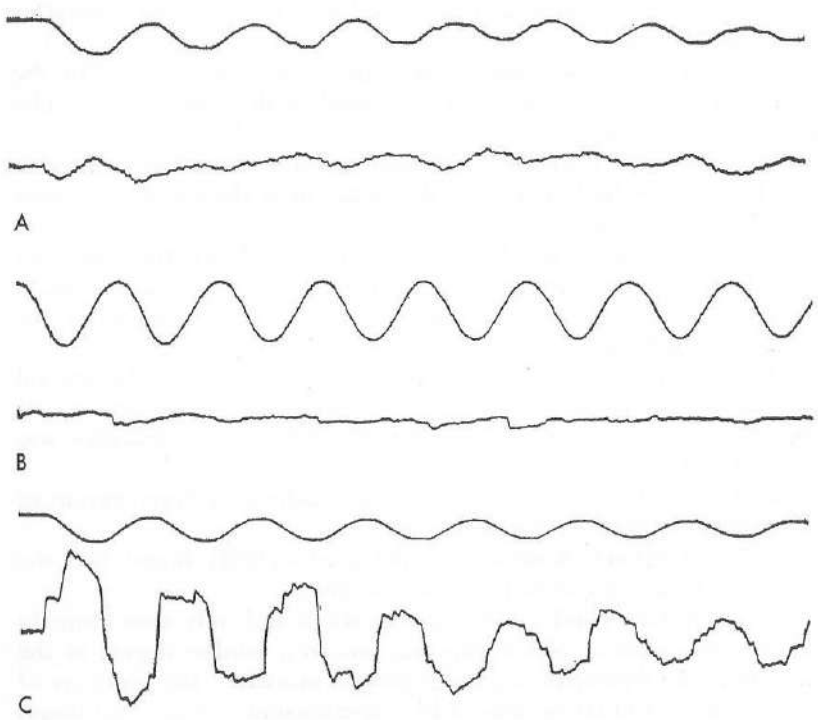


Fig. 18

Patient with two inexcitable labyrinths after streptomycin treatment.

Fig. A. No nystagmus on cupular stimulation.

Fig. B. No compensatory eye movements on macular stimulation. Only a spontaneous nystagmus to the left is evident.

Fig. C. Vehement nystagmic reactions in both directions on torsion of the neck, on top of compensatory eye movements.

In the literature some controversial evidence on this subject can be found. It is generally accepted that the vestibular labyrinth loses its function in prolonged streptomycin treatment. The effect of streptomycin on the central parts of the vestibular system is a much debated issue, as evident from the following synopsis.

MUSHET and MARTLAND (1946) did not find histological alterations in the central nervous system of dogs, intoxicated with streptomycin. The labyrinths were not investigated.

STEVENSON, ALVORD and CORREL (1947) described necrosis in the inferior vestibular nucleus of five patients and three dogs, after application of streptomycin.

FOWLER (1948) did not find histological alterations, either central or peripheral, in three men and four dogs.

RÜEDI, FURRER, ESCHER and LÜTHY (1948) describe changes in the vestibular nuclei of guinea pigs treated with streptomycin. The labyrinths were found intact.

WINSTON, LEWEY, PARENTEAU, MARDAN and CRAMER (1948), working on cats, localize the influence of streptomycin in the vestibular nuclei and the cerebellum.

FLOBERG, HAMBURGER and HEYDEN (1949) decided that the vestibular ganglion and the nucleus of Deiters were the site of the lesion produced by streptomycin on account of chemical changes in the cells of the centres.

CAUSSÉ (1949) experimented with mice; he considered the central nervous system to be intact. The only lesion he found was in the inner ears: the sensory epithelium of cupulae and maculae was degenerated.

BERG (1949) observed the same phenomena in cats, degeneration of sensory epithelium of cupulae and maculae.

CHRISTENSEN, HERTZ, RISKAER and VRA-JENSEN (1951) found that the neural pathways of guinea pigs were affected.

MANFORD MCGEE (1961), working on cats, found only alterations in the sensory elements of the cupulae, and to a smaller degree of the maculae. The neuropathologist OLSSEWSKI evaluated the histology of the central vestibular systems of his experimental animals and found no pathology.

All these studies are histological, only the staining techniques differed. Concluding this history of literature on streptomycin lesions we see that three authors, working on different laboratory animals, found comparable evidence: CAUSSÉ, BERG and MANFORD MCGEE saw degeneration of the sensory epithelium of cupulae and maculae, in the inner ears.

Our method is functional and can therefore not decide whether the pathways leading to nystagmus are anatomically intact, but it does show whether there is still the ability to react to stimuli.

In our patients normal labyrinthine stimulation was ineffective, whereas stimulating the vestibular nuclei with torsion of the neck procures nystagmic eye movements. This might prove that the central part of the nystagmus pathways remained intact, at least functionally.

SUMMARY

In this thesis we tried to investigate several forms of nystagmus provocation. Especially those forms where nystagmus is not induced by the natural stimulus of the vestibular system, namely: endolymph displacement in the semicircular canals and alteration of the pressure on the maculae (which were studied by PHILIPSZOON in this laboratory). Proceeding in this way we hoped to make some contribution to the understanding of this reflex. We also wanted to see how *cinnarizine* affected these forms of nystagmus, and to accumulate some material about the place where this drug influences the vestibular system.

Cinnarizine is a piperazine-compound with antihistamine activity. Antihistaminics as a group usually have a specific suppressing influence on the nystagmus following vestibular stimulation. This action has already been exhaustively investigated. In order to collect more knowledge about the site of action of the antihistamine cinnarizine in the vestibular system, we selected a few methods to evoke nystagmus without moving the cupulae. Among the various methods to provoke nystagmus we chose only those of which an influence on the vestibular system may be supposed to exist.

Some literature is given on the optokinetic and the galvanic nystagmus, nystagmus following unilateral labyrinthectomy, Bechterew nystagmus, nystagmus induced by chemicals, nystagmus evoked by torsion of the neck, and nystagmus induced through the 'Nystagmogenic Centre' of LACHMANN, BERGMANN and MONNIER.

The cortical and the subcortical type of optokinetic nystagmus are considered (TER BRAAK). Owing to findings in animal experiments of BROERS and DE KLEYN; VAN DEYNSE, JONGKEES and KLIJN, we did not include the optokinetic nystagmus in our program, its relation to the vestibular system not being sufficiently evident.

Several investigators have published controversial findings on the nature and origin of the galvanic nystagmus. Moreover the currents used vary. In man, currents ranging from 1–5 mA, are employed when the electrodes are fixed on the mastoids. On our volunteers 2 mA sufficed to induce nystagmus beats. Recordings did not show the classic type of nystagmus usually to be seen on vestibular stimulation, e.g. a slow beat alternating with a fast one. There is a possibility that stimulating currents interfere with the electric potentials around the eyes, and thus interfere with the recordings. Another possibility is that the galvanic nystagmus is not of vestibular nature. To elucidate the latter idea, we tried to provoke a caloric (= vestibular) nystagmus and a galvanic one at the same time. The recorded result suggests that galvanic nystagmus is not of vestibular nature as both nystagmus patterns could be recognized separately. So we did not include this type of nystagmus in our program.

The exact evaluation of the place and the function in the vestibular system of the 'Nystagmogenic Centre', as described by LACHMANN, BERGMANN and MONNIER, calls for a joint investigation with histologists. Only then can the effect of cinnarizine on stimulation of the 'Nystagmogenic Centre' be considered. This investigation is being prepared in Amsterdam.

Nystagmus following unilateral labyrinthectomy can be regarded as originating from a peripheral affection. Investigating this type of nystagmus in rabbits we observed that the direction of the nystagmus is not governed by such strict rules (Ewald) as we used to believe. According to current theory, the nystagmus following labyrinthectomy on one side, is always beating into the direction of the healthy ear. When performing the posture test with such animals, we observed this several times. But equally often we recorded other findings: e.g. nystagmus movements of one eye, while the other eye remained immobile, or was beating into the opposite direction. Even a change of nystagmus direction in one eye was observed sometimes, while the other eye did not change its pattern of movements.

Positional influences were very evident in this type of nystagmus, the eye movements were minimal when the animal lay on its non-operated side, or when its position was upright with the head pointing upwards. Cinnarizine was able to suppress this type of nystagmus.

Some time after the unilateral labyrinthectomy a central compensation mechanism manifests itself, suppressing the nystagmus. If we take away the second labyrinth after a compensation period, the nystagmus according to Bechterew appears.

In the Bechterew nystagmus of rabbits the same independance was encountered regarding the movements of both eyes, as we described in nystagmus following unilateral labyrinthectomy.

The eyes were sometimes moving in opposite directions, the direction of the nystagmus could change in one eye, while the other eye continued as before.

Apparently the eye movements in Bechterew nystagmus are not governed by the strict rules as yet generally accepted. Cinnarizine affected the Bechterew nystagmus and suppressed it.

As specimens of chemically induced nystagmus the reactions to ethylalcohol and to pethidine (= meperidine) were investigated.

Even with alcohol nystagmus, the same unpredictability of nystagmus direction was encountered; changes in the direction of the nystagmus, as well as different or opposite directions of the eyes were recorded. Since an intact inner ear is necessary for the manifestation of the alcohol nystagmus, some link with the vestibular system is supposed to exist. The reason why cinnarizine has no apparent influence on the positional alcohol nystagmus type I (nomenclature ASCHAN) is not yet known. A positional alcohol nystagmus type II, was not found in any of the ten rabbits we tested six to seven hours after the alcohol consumption. In two rabbits we did find a nystagmus, but the possibility of a latent spontaneous nystagmus could not be excluded.

Pethidine = meperidine nystagmus was not recorded in our experiments on rabbits. Dosages ranging from 10 mg/kg up to 100 mg/kg were given.

34 Experiments were performed, but only incoordinate eye movements were recorded.

The dosage of 100 mg/kg is very high, most of the rabbits showed involuntary twitching of all their body muscles. The quieting effect of cinnarizine (40 mg/kg) on these incoordinate muscle actions cannot be explained as a specific influence on the vestibular system, but may result from its general action.

Neck torsion nystagmus was the main object of our study. The torsion was performed by rotating the body of the rabbit over a given angle at a given speed against an immobilized head. In this way nystagmic eye movements can be provoked (PHILIPSZOON). Stimuli proceed via the dorsal roots of the first four cervical nerves into the homolateral columns to the nuclei of Burdach and Von Monakow. With the aid of Marchi degeneration, a few fibres could be traced, going up to the inferior vestibular nucleus, which, in rabbits, adjoins the nucleus of Deiters (BIEMOND).

Thus we arrived at the hypothesis that the cervical stimulus attains the vestibular system. The labyrinth is not included in this reflex. This idea could be ascertained experimentally when nystagmus eye movements, due to neck torsion, were effected in rabbits without labyrinths.

This finding may cast a shadow over the current explanation of the cervical syndrome. Some authors attribute symptoms to an impeded bloodsupply to the labyrinths owing to arteriosclerosis of the vertebral artery, and augmented still by obstruction through cervical arthrosis.

Irritation of cervical nerves also explains all symptoms of the cervical

syndrome, regardless of the condition of the inner ears.

This opinion is illustrated by an accidental finding in man. In a group of five judoka's (20–30 years of age) – training intensively over a period of more than four years – each showed a spontaneous or a positional nystagmus. They did not complain of vertigo and a possible concussion of the brain was excluded. In a control group of ten judoka's of the same age – training less than one year – no nystagmus was found. This nystagmus may be attributed to irritated cervical nerves. Rolling backwards over shoulders and neck, these people frequently irritate their cervical nerves creating in this way a place of lowered resistance. This finding in judoka's could imply that a spontaneous or a positional nystagmus does not prove necessarilly labyrinthine or central pathology.

This nystagmus due to irritation of cervical nerve roots is to be found in everybody. The cervical nerves are irritated by torsion of the neck. The patient is sitting on a torsion swing, his head immobilized in a clamp. Moving his body to the left and to the right we record nystagmus eye movements. The direction of these beats is alternating synchronously with the frequency of the torsion swing. These neck reflexes are so constantly and easily obtained that special care must be taken to prevent their appearance in vestibular function tests. Performing the posture test we bring the patient in the required position and wait a few moments before recording positional nystagmus, lest angular accelerations or cervical influences interfere.

The independance of vestibular and cervical nystagmus is indicated in another experiment.

Cutting the posterior columns above C_1 abolishes the nystagmus due to torsion of the neck. A labyrinthine nystagmus can still be induced after blocking the afferent pathways for the cervical stimulus.

The connections between labyrinthine nystagmus and the one after cervical stimulation can be demonstrated by evoking a cervical and a labyrinthine nystagmus at the same time. Nystagmus on torsion of the neck is then suppressed in one direction, yet augmented into the other.

DIX, CITRON and HALLPIKE elicit their 'benign paroxysmal positional nystagmus' by moving the body of a sitting patient backwards and turning the head sideways over an angle of 45°. Finally the patient is lying supine, his head is hanging free and turned sideways. A resulting nystagmus is attributed to a sick utricle, to wit the one on the underneath side of the head. A nystagmus due to irritation of cervical nerves can be obtained in a similar way, without labyrinth stimulation and also in absence of labyrinths. Therefore we are of

the opinion that in evaluating this symptom an influence of neck reflexes should be taken into account.
It may be possible that neck reflexes contribute positively in analysis of vestibular function. There is no decisive proof, but some arguments can be brought forward to show that the central pathways for vestibular and for cervical nystagmus may coincide. In patients with inexcitable labyrinths it is hard to ascertain whether the lesion is limited to the inner ears with the eighth nerve, or whether the group of vestibular nuclei and the pathways leading to vestibular nystagmus are affected.
When nystagmus on torsion of the neck is evoked in patients with inexcitable labyrinths we must consider the possibility that a vestibular lesion is limited to the peripheral part of the system. We performed this test on one patient with two broken petrous bones after an accident and obtained clear nystagmus beats, alternating synchronously with the swinging movements of his body. Two patients with inexcitable labyrinths after prolonged streptomycin treatment also reacted definitely to torsion of the neck, thus suggesting that the group of vestibular nuclei was able to react to stimulation.
Several authors found histological alterations in vestibular nuclei after prolonged streptomycin administration. Other investigators limited streptomycin's toxic effect to the sensory epithelium of the labyrinths. In view of our findings we are inclined to agree with the latter opinion.

Conclusions about the effect of cinnarizine on vestibular nystagmus. Its influence is evident on the nystagmus:

1. following labyrinthine stimulation.
2. following extirpation of one labyrinth.
3. according to Bechterew.
4. due to torsion of the neck.

These actions can be explained by supposing that cinnarizine's influence on the vestibular system is not merely peripheral as already proved, but that an effect at the level of vestibular nuclei, or higher still in the vestibular system, is apparent.
The lack of effect on alcohol nystagmus is up till now unexplained.

SAMENVATTING

In dit proefschrift hebben wij geprobeerd enige nieuwe vormen van nystagmus te onderzoeken, die niet door de natuurlijke prikkelwijze van dit vestibulaire systeem — d.i. door endolymphe verplaatsing in de cristae of drukverandering op de maculae (PHILIPSZOON bestudeerde dit onderwerp in dit laboratorium) — worden veroorzaakt. Op deze wijze hoopten wij enige gegevens te kunnen toevoegen aan de kennis van deze vestibulaire reflexuiting. Verder ging onze belangstelling uit naar de werking van een antihistaminicum, *cinnarizine*, op deze vormen van nystagmus, om zodoende gegevens te verzamelen over de plaats waar deze stof zou inwerken in het vestibulaire systeem. Op deze wijze is getracht de plaats waar het antihistaminicum cinnarizine in het vestibulaire systeem aangrijpt in een ompalende beweging te benaderen.
Cinnarizine is een antihistaminicum uit de piperazine reeks. De antihistaminica als groep tonen vaak een voortreffelijke onderdrukkende werking op de nystagmus, opgewekt door vestibulaire prikkels. Teneinde meer gegevens te verzamelen over de plaats waar dit antihistaminicum zijn werking uitoefent in het vestibulaire systeem, werd de invloed van dit middel onderzocht op nystagmusvormen, die niet door verplaatsen van endolymphe in de halfcirkelvormige kanalen, of door drukverandering op de maculae, worden geprovoceerd.
Zoals vanzelf spreekt kwamen enkele methoden om nystagmus te provoceren niet ter sprake in ons onderzoek, te weten de vormen, die geen duidelijke relatie hebben met het vestibulaire systeem.
Achtereenvolgens worden behandeld de optokinetische en de galvanische nystagmus, de nystagmus na labyrinthectomie aan een zijde, de Bechterew nystagmus, de chemische nystagmus, de nystagmus opgewekt door nektorsie, en de vorm verkregen door prikkeling van het „Nystagmogene Centrum" van LACHMANN, BERGMANN en MONNIER.
De beide types optokinetische nystagmus worden besproken: de corticale en de subcorticale vorm (TER BRAAK). Op grond van experimenten van BROERS en DE KLEYN; VAN DEYNSE, JONGKEES en KLIJN wordt van onderzoek van de optokinetische nystagmus afgezien, omdat in dierproeven geen relatie met het vestibulaire systeem kon worden aangetoond.
Aangaande de aard en de plaats van inwerking van de galvanische nystagmus bestaat een groot aantal tegenstrijdige gegevens van ver-

schillende auteurs. Ook de gebruikte stroomsterkte varieert. Bij mensen worden meestal stroomsterkten gebruikt van 1–5 mA, wanneer de electroden op beide mastoïden zijn gefixeerd. Bij onze proeven op vrijwilligers werd met 2 mA stroomsterkte gewoonlijk een nystagmusreactie geregistreerd. De curve toonde niet het fraaie resultaat dat wij van een vestibulaire reactie gewend zijn: de langzame fase direct en scherp omslaand in de snelle component van de nystagmusslag. Wij moeten rekening houden met de mogelijkheid dat de galvanische stroom de elektrische potentialen om het oog storend beïnvloedt. Een andere verklaring kan zijn dat de galvanische nystagmus niet van vestibulaire origine is. Daarom hebben wij geprobeerd de galvanische en de calorische nystagmus tegelijk op te wekken.

Het grafische resultaat doet ons veronderstellen dat de galvanische nystagmus geen vestibulaire oorsprong heeft, omdat beide uitingen onafhankelijk naast elkaar herkend konden worden. Daarom hebben wij ook de galvanische nystagmus niet verder in het onderzoek betrokken.

De nystagmus verkregen door prikkeling van het „Nystagmogene Centrum" van LACHMANN, BERGMANN en MONNIER is anatomisch noch functioneel exact bekend. Voor ons onderzoek betekent dit dat een gezamenlijke inspanning nodig is van histoloog, farmacoloog en fysioloog, teneinde de plaats van dit centrum in het evenwichtssysteem te bepalen. In een gemeenschappelijke studie zal dit onderzoek ter hand worden genomen.

Nystagmus na labyrinthectomie aan één zijde is een nystagmus tengevolge van een puur perifeer letsel. Bij proeven op konijnen is gebleken dat de richting van de op labyrinthectomie volgende nystagmus toch niet zo aan wetten (Ewald) is gebonden als tot nu toe wel werd gedacht. De ogen van konijnen bleken elk in een eigen richting te kunnen bewegen, zelfs precies tegen elkaar in. Ja, ook de eenmaal gevonden richting stond niet vast; wij hebben gezien dat soms het ene oog van richting veranderde, terwijl het andere zijn bewegingspatroon handhaafde. Positie invloeden zijn evenzeer duidelijk aantoonbaar.

Wanneer het proefdier op de niet-geopereerde kant ligt of rechtop staat, zijn de oogbewegingen minimaal, soms zelfs niet aantoonbaar; een perifere aandoening hoeft klaarblijkelijk niet altijd een even sterke reactie in alle standen te geven.

Enige tijd na de operatie treedt compensatie in voor de evenwichtsbezwaren; wanneer nu het tweede labyrint wordt weggenomen komt een nieuwe nystagmus tevoorschijn. De richting van deze tweede, Bechterew, nystagmus, is meestal alsof het eerst geopereerde oor nog

aanwezig was, dus in de richting van dit oor. Deze nystagmus is echter van oorsprong beslist niet perifeer. Ook bij deze vorm van nystagmus werd dezelfde onafhankelijkheid geconstateerd in de bewegingen van beide ogen, als hierboven reeds vermeld bij de operatie aan één zijde. Beide ogen kunnen tegen elkaar in bewegen, de richting kan in één oog veranderen, terwijl het andere oog dit niet hoeft te doen. Beide vormen van nystagmus konden geheel onderdrukt worden door cinnarizine 40 mg/kg. Klaarblijkelijk moeten wij voor cinnarizine toch een activiteit op het niveau van de vestibulaire kernen aannemen.

Als voorbeelden van chemische nystagmus werden de reacties op ethyl-alcohol en op pethidine onderzocht.

Bij alcoholnystagmus is het ontbreken van wetmatigheid in de richting van de nystagmus eveneens duidelijk aantoonbaar. Verandering van richting, ongelijke en ongelijknamige reacties van beide ogen zoals boven reeds beschreven, werden ook hier regelmatig gevonden. Een relatie met het vestibulaire apparaat wordt bewezen geacht door de onmogelijkheid bij labyrintloze konijnen alcoholnystagmus op te wekken.

Het merkwaardige feit doet zich evenwel voor dat cinnarizine geen merkbare invloed heeft op de alcoholnystagmus. Een verklaring hiervan kunnen wij nog niet geven. Een „positional alcohol nystagmus" type II, zoals door ASCHAN beschreven is bij de mens, kon bij onze konijnen zes tot zeven uur na het alcoholgebruik, niet vastgesteld worden.

Bij tien proeven werd slechts tweemaal een nystagmus gevonden, deze kunnen wij evenwel ook toeschrijven aan een latente spontane nystagmus.

Een pethidine-nystagmus hebben wij in onze dierproeven niet gevonden; in 34 experimenten konden wij geen typische nystagmus aantonen, slechts ongecoördineerde oogbewegingen werden geregistreerd. Bij de gebruikte dosering toonden trouwens alle spieren deze samentrekkingen. Hierop had cinnarizine wel een sederend effect.

Aan de nystagmus, die ontstaat bij torsie van de nek werd de meeste aandacht gegeven. Door draaiing van de romp t.o.v. de geïmmobiliseerde kop, kunnen bij konijnen nystagmus bewegingen worden opgewekt (methode PHILIPSZOON). De prikkels lopen via de dorsale wortels van de eerste vier cervicale zenuwen, en kunnen met behulp van Marchi degeneratie gevolgd worden in de banen van Goll en Burdach. Zij bereiken de kernen van Burdach en Von Monakow; enkele vezels gaan verder tot in de nucleus vestibularis inferior, die bij konijnen tegen de kern van Deiters aanligt (BIEMOND). In deze

opsomming is tegelijkertijd aangegeven waar het raakpunt ligt met het vestibulaire systeem, namelijk in de groep van vestibulaire kernen.
Het perifere labyrint speelt bij deze nystagmus door torsie van de nek derhalve geen rol. De waarheid van deze veronderstelling kan proefondervindelijk worden aangetoond: nystagmus door torsie van de nek kan worden opgewekt in konijnen zonder labyrinten. Dit zou een schaduw kunnen werpen op de theorie, die de geobstrueerde arteria vertebralis als hoofdoorzaak beschouwt voor de klachten van het cervicale syndroom.
Door plotseling verminderd bloedaanbod aan het labyrint zou de functie van dit binnenoor lijden, met vertigoklachten en eventueel doofheid als gevolg. Het blijkt echter dat de vertigoklachten geheel verklaard kunnen worden door prikkeling van de cervicale zenuwwortels, het binnenoor speelt hierbij in het geheel geen rol.
Fraai wordt zo'n verklaring door een toevallige vondst geïllustreerd. In een groep van jonge judoka's (20–30 jaar), die allen intensief en langer dan vier jaar trainden, werd bij ieder van hen een spontane nystagmus gevonden, zonder dat er evenwichtsklachten waren. Ook de mogelijkheid van hersenschudding kon bij hen worden uitgesloten. In een contrôlegroep van tien judoka's (eveneens 20–30 jaar), die korter dan één jaar trainden, werd niet eenmaal een spontane nystagmus gevonden. Wij zijn geneigd deze gevonden spontane nystagmus te verklaren door geïrriteerde cervicale zenuwen.
Deze irritatietoestand van hun cervicale zenuwen zou ontstaan door het actieve gebruik dat zij van hun nek plegen te maken, om, wegrollend over de rug, de schouders en de nek, weer op de been te komen. Aan deze bevindingen zou de stelling ontleend kunnen worden dat niet iedere spontane of positienystagmus hoeft te wijzen op labyrintair of centraal lijden.
Bij mensen is zo'n nystagmus door torsie van de nek precies eender op te wekken als bij onze proefdieren. Het hoofd wordt daartoe gefixeerd in een klem – eventueel compleet met bit – het lichaam kan door middel van een torsieschommel naar links en naar rechts bewogen worden.
Wij registreren dan met de electronystagmograaf duidelijk nystagmusbewegingen, waarbij de richting van de nystagmus omslaat, synchroon met de frequentie van de torsieschommel. Aangezien de nekreflexen zó makkelijk op te wekken zijn, moet hiermee terdege rekening worden gehouden bij de bepaling van de positienystagmus.
De onafhankelijkheid van de nektorsienystagmus van de labyrintaire vorm wordt ook aangeduid door het in dierproeven gevonden feit,

dat cupulaprikkeling nog in fraaie nystagmusslagen resulteert als na doorsnijding van de achterstrengen boven C_1 de nystagmus door torsie van de nek niet meer opgewekt kan worden.
Wat het samengaan van beide vormen van nystagmusprovocatie betreft, het is bij mensen gelukt de nystagmus door torsie van de nek duidelijk te beïnvloeden door middel van een calorische prikkeling. Wellicht zijn de banen, die beide soorten prikkels doorlopen vanaf de vestibulaire kernen, identiek.
Dix, Citron en Hallpike hebben de „benign paroxysmal positional nystagmus" beschreven, die volgens hen een aanwijzing zou zijn voor een zieke utriculus.
Deze nystagmus wordt opgewekt door de patient, die op een brancard zit, passief achterover te bewegen totdat hij ligt en zijn hoofd vrij van de brancard afhangt. Tijdens deze beweging omlaag wordt het hoofd ook nog 45° zijwaarts gedraaid.
Een positief resultaat wordt eerst na deze handelingen zichtbaar, de nystagmus neemt toe en sterft daarna weer uit, terwijl de patient in de beschreven houding blijft liggen.
Bij de beschreven manoeuvres wordt de nek van de patient getordeerd over 45°; dit is meer dan nodig is om een nystagmus door torsie van de nek op te wekken. Het verdwijnen van de nystagmus, terwijl het hoofd in de extreme stand wordt gehouden, wordt eveneens gezien bij de nektorsienystagmus zoals wij die opwekken. Een verschil met Hallpike's procedure is echter dat wij géén labyrintaire prikkel geven. Het bestaan van „benign paroxysmal positional nystagmus" achten wij derhalve geen aanwijzing voor het bestaan van een labyrintaire aandoening.
Op andere wijze kunnen de nekreflexen nog nuttig blijken te zijn. Bij patienten met onprikkelbare labyrinten is het bijzonder lastig na te gaan of de laesie beperkt is tot het labyrint met de achtste hersenzenuw, of dat het gehele vestibulaire systeem is uitgevallen. Wanneer alleen het perifere labyrint is aangedaan blijkt de nystagmus door torsie van de nek nog normaal opgewekt te kunnen worden. Wij kunnen niet bewijzen dat de weg van de vestibulaire prikkel identiek is met die van de cervicale prikkeling vanaf de vestibulaire kernen tot aan de kernen van de oogspieren. Er zijn wel enkele aanwijzingen dat beide prikkels tot gelijke effecten leiden. Zo kunnen bijv. een calorische en een cervicale prikkel hun resultaten superponeren.
Bij enkele patienten met onprikkelbare labyrinten hebben wij door torsie van de nek nystagmusbewegingen opgewekt. Hierdoor toonden wij aan dat de banen, die voor deze nystagmus nodig zijn, nog op een prikkel kunnen reageren. Eén patient had breuken in beide

rotsbenen, twee patienten hadden onprikkelbare labyrinten na een langdurige kuur met streptomycine. Alle drie reageerden zij op torsie van de nek met nystagmusslagen, die van richting wisselden synchroon met de bewegingen van de torsieschommel.
Het lijkt derhalve alsof het centrale deel van de nystagmusbanen, inclusief de vestibulaire kernen, nog functioneren. Dit resultaat is vooral bij streptomycinepatiënten interessant omdat sommige auteurs histologische afwijkingen in de vestibulaire kernen hebben aangetoond na een langdurige streptomycine behandeling. Dit in tegenstelling met anderen, die de aandoening van het evenwichtsapparaat in het labyrint zelf localiseerden.

Conclusies aangaande de werking van cinnarizine op het vestibulaire systeem.
Cinnarizine is in staat de nystagmus te beïnvloeden, die ontstaat:

1. door prikkeling van de labyrinten, zowel van de halfcirkelvormige kanalen als van de otolith organen.
2. na labyrintextirpatie aan één zijde.
3. in de situatie volgens Bechterew.
4. bij torsie van de nek.

Deze werkingen kunnen verklaard worden door aan te nemen dat cinnarizine niet uitsluitend perifeer inwerkt, zoals tot nu toe werd verondersteld, maar dat ook een centrale werking, in de groep van de vestibulaire kernen of nog hoger, bestaat.
Het gebrek aan effect op de alcoholnystagmus kunnen wij nog niet verklaren.

RÉSUMÉ

Dans ce thèse nous avons examiné quelques nouvelles méthodes pour provoquer un nystagmus vestibulaire, sans employer le stimulus naturel de ce système vestibulaire, c'est-à-dire ni le déplacement de l'endolymphe dans les canaux sémicirculaires, ni l'altération de la force de gravité sur les macules. (Ce sujet à été étudié par PHILIPSZOON, dans ce laboratoire). Par telles expériences nous avons essayé à ajouter quelques données à notre notion de ce réflexe.
En outre nous sommes intéressés à apprendre l'effet de l'antihistaminique *cinnarizine* sur ces réflexes pour reconnaître la localisation de l'effet de cette drogue dans le système vestibulaire.
La cinnarizine est un composé de pipérazine avec d'actions antihistaminiques. Certains antihistaminiques ont une influence supprimante au nystagmus vestibulaire. Nous avons examiné l'influence de la cinnarizine sur des formes de nystagmus provoquées sans déplacement de l'endolymphe. Il va sans dire que certaines méthodes à provoquer un nystagmus ne sont pas poursuivies ici, leur relation au système vestibulaire n'étant pas exactement connue.
Nous avons examiné les nystagmus optocinétiques et galvaniques, le nystagmus après labyrinthectomie unilatérale, le nystagmus selon Bechterew, le nystagmus chimique, le nystagmus par irritation des nerfs cervicaux, et celui par stimulation du „Centre Nystagmogène" de LACHMANN, BERGMANN et MONNIER.
Les deux formes de nystagmus optocinétique sont seulement mentionnées, notamment la forme corticale et souscorticale (TER BRAAK).
En vertu des expérimentations aux animaux de BROERS et DE KLEYN; VAN DEYNSE, JONGKEES et KLIJN, nous n'avons pas fait des expériences optocinétiques, puisque la relation avec le système vestibulaire n'est pas encore tracée.
Les différents auteurs ne sont pas d'accord sur la localisation du nystagmus galvanique, ni sur la meilleure méthode de stimulation galvanique. Quand les électrodes sont appliquées sur les deux mastoides de l'homme, un courant de 1–5 mA suffit pour évoquer une sensation de déplacement. Dans la plupart de nos expériences un courant de 2 mA suffisait pour le nystagmus galvanique. L'enregistrement par électronystagmographie ne montre pas le même type de nystagmus que le type vestibulaire classique,où la composante lente succède brusquement à la composante rapide.
Deux explications sont possibles:

1. le courant galvanique a une influence directe au potentiel électrique autour de l'oeil qu'on enregistre;
2. le nystagmus galvanique n'est pas d'origine vestibulaire. Stimulant à la fois galvaniquement et caloriquement nous avons obtenu un nystagmogramme remarquable. Les deux formes de nystagmus apparaissent indépendantes et se montrent clairement séparées dans le nystagmogramme. Il est donc possible que le nystagmus galvanique ne soit pas d'origine vestibulaire. Comme il n'est donc pas du tout certain que le nystagmus galvanique soit d'origine vestibulaire nous ne nous en sommes pas servis pour l'étude de l'influence de la cinnarizine sur l'appareil vestibulaire.

Le nystagmus suivant la stimulation du „Centre Nystagmogène" est connu comme phénomène, sa place et sa fonction dans le système vestibulaire sont encore mal définies. Une coopération entre l'histologiste, le pharmacologiste et le physiologiste serait nécessaire pour avoir une idée sur la place fonctionelle et anatomique du centre précité. Une étude commune sur ce sujet est en préparation dans le laboratoire à Amsterdam.

On peut considérer le nystagmus après labyrinthectomie unilatérale comme l'effet d'une lésion périphérique. La direction d'un tel nystagmus n'est pas toujours conforme à la théorie actuelle (Ewald). Les yeux du lapin peuvent agiter de manière indépendante, même en sens inverse. Il nous est même arrivé que dans quelques-uns de nos lapins la direction d'un nystagmus provoqué changeait dans un oeil sans changer dans l'autre. L'influence de la position est également très prononcée: en position verticale ou sur le côté non-opéré les mouvements oculaires sont minimes, parfois même absents. Il est donc clair que l'effet d'une lésion vestibulaire périphérique chez le lapin n'est pas nécessairement suivi par un nystagmus bien défini. Quelque temps après la labyrinthectomie unilatérale une compensation du déséquilibre s'impose, supprimant le nystagmus. Si on détruit l'autre labyrinthe après une période de compensation, le nystagmus de Bechterew, d'origine purement centrale, se manifeste. La même indépendance dans les mouvements des yeux a été trouvée dans le nystagmus selon Bechterew, comme dans le nystagmus après la labyrinthectomie unilatérale. Ces deux formes de nystagmus après extirpation (unilatérale ou bilatérale) sont supprimées par la cinnarizine (40 mg/kg). Apparemment on doit supposer une influence de ce drogue au niveau des noyaux vestibulaires.

Comme nystagmus chimique nous avons fait une recherche sur la réaction à l'ethylalcool et à la péthidine = méperidine. Le nystagmus alcoolique du lapin nous montre la même indépendance dans les

mouvements des yeux, que nous avons décrite ci-dessus.

Nous avons rencontré souvent un changement de direction du nystagmus, et des réactions variantes en direction ou en amplitude. L'impossibilité de provoquer un nystagmus alcoolique chez des lapins délabyrinthés des deux côtés, nous indique la relation du nystagmus alcoolique au système vestibulaire. Il est encore plus remarquable que l'antihistaminique cinnarizine n'ait aucune influence sur ce nystagmus, qui est supposé d'origine périphérique.

Le nystagmus de position type II (nomenclature ASCHAN) trouvé chez l'homme, six heures après l'administration de l'alcool, n'est pas retrouvé dans le lapin. En dix expériences nous avons trouvé deux fois un nystagmus de position. On peut attribuer ces cas également à un nystagmus spontané latent.

Dans nos expériences aux lapins nous n'avons pu démontrer aucun nystagmus après l'administration de péthidine (= méperidine). En 34 expériments un nystagmus typique ne se manifesta point. Nous avons enregistré des mouvements des yeux incoordinés et atypiques, combinés avec des contractions involontaires spasmodiques de toute la musculature corporelle. La cinnarizine a une influence calmante sur cette activité spasmodique.

Le nystagmus après irritation des nerfs cervicaux est le sujet principal de ce travail. En tordant le cou du lapin, à la tête immobilisée, on peut déclencher des mouvements nystagmiques des yeux (PHILIPSZOON). L'excitation monte des racines dorsales des quatres premiers nerfs cervicaux et atteigne les noyaux de Burdach et Von Monakow. On peut suivre la dégénérescence secondaire consécutive à la section de la racine postérieure de C_{II}; quelques fibres gagnent le noyau vestibulaire inférieur, joignant dans le lapin le noyau de Deiters (BIEMOND).

Cette énumération nous montre le point de tangence avec le système vestibulaire, c'est-à-dire le groupe des noyaux vestibulaires. Le labyrinthe n'est donc pas actif dans le mécanisme qui déclenche le nystagmus après irritation des nerfs cervicaux. Cette supposition est vérifiée dans l'expériment suivant: un nystagmus après torsion des vertèbres cervicales peut être démontré dans les lapins délabyrinthés des deux côtés. Cette constatation indique que l'obstruction de l'artère vertébrale n'est pas exclusiment à l'origine du syndrome cervical. On a cru longtemps qu'une réduction du flot de sang dans le labyrinthe, influença directement sa fonction, évoquant des vertiges et une surdité de perception. Apparemment les vertiges peuvent être expliqués par une irritation des racines postérieures des nerfs cervicaux; l'oreille interne n'y contribue rien.

Par hasard nous avons trouvé l'illustration de ce thèse. Dans un groupe de cinq judokas (agé de 20–30 ans), entraînant plus de quatre années, chaqun d'eux avait un nystagmus spontané sans aucune plainte de vertige. Nous avons pu exclure la possibilité d'une concussion du cerveau. Le groupe de contrôle consistait de dix judokas du même age (20–30 ans) qui étaient entraînés moins d'une année. Parmi eux aucun nystagmus spontané ou nystagmus de position a été trouvé. Ce nystagmus trouvé parmi les judokas entraînés ne peut pas être attribué à une dysfonction labyrinthaire, l'excitabilité des deux labyrinthes vestibulaires étant égale et l'audiogramme normal. Nous le considérons comme un nystagmus d'origine cervicale. L'irritation des nerfs cervicaux serait effectuée par la mode d'emploi du cou en judo; comme si le cou était une cinquième extrémité, spécialement désignée pour se lever de la position couchée. En outre il est évident qu'on ne peut pas attribuer tous les nystagmus trouvés à une pathologie labyrinthaire ou centrale.

Chez l'homme on peut évoquer un tel nystagmus par torsion du cou, comme chez les lapins. On immobilise la tête par un clamp, et arrive à la torsion du cou en rotant à droit et à gauche le corps du malade, qui est assis sur une balançoire de torsion. Nous enregistrons avec l'électronystagmographe les mouvements nystagmiques des yeux, alternant de direction synchrôniquement avec la fréquence du balançoire. Puisqu'il est tellement facile d'évoquer les réflexes du cou, on doit toujours tenir compte de cette possibilité quand on enregistre le nystagmus de position.

L'indépendance du nystagmus suivant la torsion du cou, de celui qui suit la stimulation labyrinthique, est démontrée dans une expérience dans laquelle les colonnes postérieures ont été sectionnées au-dessus de C_1. Le nystagmus après torsion du cou ne se manifeste plus, tandisque la réponse du stimulation labyrinthique reste normale.

Il y a bien une relation quelconque entre le nystagmus cervical et celui du labyrinthe. Evoquant en même temps un nystagmus cervical et un calorique (= vestibulaire) on constate que le nystagmus est augmenté dans la direction du calorique, diminué dans l'autre sens. Dix, Citron et Hallpike ont décrit le nystagmus de position „bénigne et paroxysmal", et le considèrent comme preuve d'une utricule malade. On évoque ce nystagmus de la façon suivante: le malade est assis sur une table d'examen normale. Le haut de son corps est bougé passivement en arrière en tournant la tête à droit ou à gauche sur 45°. Un résultat positif se manifeste après ces manoeuvres, quand le malade est couché sur le dos, le tête dépendant de la table et

tournée sur 45°. On voit un nystagmus, augmentant d'abord d'intensité et diminuant un peu plus tard.

Dans l'expériment le cou est tordu sur un angle de 45°, c'est plus que l'angle nécessaire pour trouver un nystagmus par la torsion du cou sans aucune stimulation labyrinthaire. La disparition du nystagmus quand la tête est tenue dans la position extrème, est trouvée également dans le nystagmus après torsion du cou. Nous ne croyons donc pas que ce nystagmus de position bénigne et paroxysmal fait preuve d'une pathologie labyrinthaire.

Dans un autre sens les réflexes du cou peuvent être utiles. Quand les patients ont des labyrinthes inexcitables, il est très difficile de décider si la lésion est limitée au labyrinthe avec le huitième nerf, ou bien si le système vestibulaire en totalité est détérioré. Si la partie périphérique est la seule abimée, le nystagmus après torsion du cou reste encore présent. Nous ne pouvons pas donner la preuve d'identicité des voies centrales vestibulaires et cervicales entre les noyaux vestibulaires et les noyaux des muscles des yeux.

Cependant il y a quelques indications que les deux stimulations différentes peuvent atteindre le même effet. Par exemple les résultats nystagmiques après stimulation cervicale et calorique apparaissent être superposés l'un à l'autre.

Dans quelques patients aux labyrinthes inexcitables, nous avons provoqué des mouvements nystagmiques par irritation des nerfs cervicaux, ce qui indique que les structures centrales peuvent répondre à leur stimulation normale.

Le premier patient avait son inexcitabilité à la suite des fractures dans les deux os pétreuses après un accident.

Deux autres malades avaient des labyrinthes inexcitables après traitement prolongé avec la streptomycine. Tous les trois réagissaient à la torsion du cou avec des mouvements nystagmiques des yeux, alternant de direction synchrône avec les mouvements du balançoire. Il est donc probable que la partie centrale de la voie nystagmique – y compris les noyaux vestibulaires – soit conservée. Surtout dans ces cas où l'inexcitabilité est attribuée à la streptomycine, ce résultat a de valeur spéciale. Quelques histologistes prétendent que le noxe de la streptomycine se situe dans les noyaux vestibulaires, tandisque d'autres localisent la lésion dans l'organe périphérique.

Conclusions sur l'effet de la cinnarizine au système vestibulaire.

Cinnarizine supprime le nystagmus après:

1. La stimulation des labyrinthes.

2. La labyrinthectomie unilatérale.
3. La situation de Bechterew.
4. L'irritation des nerfs cervicaux.

Cette activité peut être expliquée supposant que la cinnarizine n'a pas d'action exclusivement périphérique, comme on pensait jusqu'à présent, mais qu'il existe aussi une activité centrale, au niveau des noyaux vestibulaires, ou plus haut encore.
Nous ne pouvons pas encore expliquer le manque d'effet sur le nystagmus alcoolique.

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STELLINGEN

1. Galvanische labyrintprikkeling geeft geen inlichtingen over de toestand van het labyrint.

2. De hoge perinatale sterfte bij meervoudige zwangerschap is alleen te reduceren door herkenning vóór de dertigste week.

3. De gunstige werking van drop op het ulcus ventriculi moet worden toegeschreven aan het glycyrrhizinezuur (*Lancet,* (1962) *II,* 793).

4. De T.N.M.-indeling biedt ook voor de classificatie van het larynxcarcinoom, voordelen boven de thans gebruikte methoden. (*Surgery, Gynaecology and Obstetrics* (1961) *113,* 435).

5. De mate van analgesie, teweeggebracht door de zogenoemde witte ruis van niet schadelijke intensiteit, is te gering en te weinig constant om klinische betekenis te hebben. (*Anaesthesia* (1962) *87,* 17).

6. Het toedienen van dihydrostreptomycine, waar met streptomycine volstaan kan worden, is een kunstfout.

7. Wanneer de diagnose laesie van de meniscus wordt overwogen, dient de mogelijkheid van osteochondrosis patellae te worden uitgesloten.

8. Het fraaie effect, dat WILLIAMS en SPENCER bereikten bij patienten, toen zij de neurologische verschijnselen na reanimeren bestreden met koeling, kan niet worden toegeschreven aan invloed van de koeling op het hersenoedeem. (*Annals of Surgery* (1958) *148,* 462).

J. H. Bos, 13 december 1962.