EFFECTS ON CENTRAL NYSTAGMUS

W. J. OOSTERVELD

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THE INFLUENCE OF DRUGS AND THE INFLUENCE OF PERIPHERAL LABYRINTHINE STIMULI ON NYSTAGMUS PROVOKED BY ELECTRICAL STIMULATION OF THE MESO-DIENCEPHALIC NYSTAGMOGENIC CENTRE IN RABBITS

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

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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 19 DECEMBER 1963, DES MIDDAGS TE 4 UUR

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Aan mijn ouders
Aan mijn vrouw

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CONTENTS

Chapter I

Introduction

In 1876 a contralateral conjugate deviation of the eyes upon unilateral stimulation of the superior colliculus in monkeys was observed to our knowledge for the first time (Ferrier, 1876).

Nystagmus was noticed in a few cases by Ziehen (1890), Prus (1899) and Von Bechterew (1909) upon stimulation of the same tectal region. Blohmke (1929) carried out systematic investigations on this subject. He observed nystagmus regularly on stimulation of the midbrain reticular formation rostrolaterally to the nucleus ruber and medially to the lateral or medical geniculate body.

The recording and registration techniques were, however, of such a nature that the interpretation of the basic mechanisms underlying nystagmus were very difficult.

Several histological techniques have been described in the literature to show the pathways responsible for the elicitation and conduction of the nystagmus phenomenon.

De Kleyn (1920) stated that a galvanic nystagmus has no relation to the vestibular system.

Ohm (1922, 1936) assumed the vestibular nuclei to represent the junction of the pathways of vestibular and optokinetic nystagmus. From observations on fibre degeneration preparations Spiegel (1933) concluded that cortical impulses from the frontal and occipital lobes interact with labyrinthine nystagmus at the level of the vestibular nuclei.

Pompeiano and Walberg (1957) could not find terminal degeneration in the vestibular nuclei following lesions of the cerebral cortex or of the striate body.

Dix, Hallpike and Harrison (1949) claim that the fibres for optokinetic nystagmus in man run directly from the optic tract to the superior colliculi and do not reach the vestibular nuclei at all. Jung (1953) placed the site of interaction of optokinetic and vestibular nystagmus in the reticular formation. Brodal, Pompeiano and Walberg (1962) in their recently published book have given more information on the subject of fibres and pathways concerning vestibular nuclei.

A new approach to the above mentioned problems was presented by using stereotaxic apparatus and special stimulation and registration techniques.

MONNIER (1944) elicited deviation of both eyes and sometimes central nystagmus from definite areas in rhesus monkeys. On the basis of his experiments he suggested a central excitatory and inhibitory influence upon vestibular nystagmus. LACHMANN, BERGMANN and MONNIER (1957, 1958) and BERGMANN, LACHMANN, MONNIER and KRUPP (1959) recorded central nystagmus on stimulating a mesodiencephalic region in the rabbit's brain. LACHMANN, BERGMANN, WEINMAN and WELNER (1958) reported that sometimes the effects of central and labyrinthine stimulation simply superimpose by addition or subtraction, thus suggesting that their pathways meet at a common substrate in the mesencephalon. FELDMAN, WAGMAN and BENDER (1959, 1961) in recent studies on the activity of the vestibular nuclei in cats have obtained evidence of the influence of higher brain stem structures in these animals on the activity of the vestibular nuclei. They stimulated the midline thalamic nuclei, the hypothalamus and the midbrain reticular formation and studied the resultant electrical responses in the vestibular nuclei. While stimulation of the diencephalon was without effect, maximum responses in the vestibular nuclei were obtained upon stimulation of the midbrain in the region of the oculomotor nucleus, the medial longitudinal fasciculus and the medial reticular formation adjacent to these structures and below the central grey matter.

In this work "central nystagmus" means the nystagmus provoked by central stimulation. Central stimulation is defined as the unilateral electrical stimulation of a circumscribed area in the mesodiencephalon of the rabbit.

The reaction to electrical stimulation of the nystagmogenic centre starts with wide opening of the eyes, protrusion of the eyeballs and mydriasis. After a latency of three to thirty seconds a single slow movement of the eyeballs to the stimulated side is observed, followed by typical nystagmus, with the quick component towards the contralateral side. Intensity and frequency of this central nystagmus increase with time up to a maximum of about 3 jerks/sec. Optimal responses are usually obtained with a frequency of 30 impulses/sec. of 2 millisec. duration. When stimulation is stopped, nystagmic movements continue in the same direction as before for a period of three to twenty seconds (after-nystagmus). After half an hour, during which

the rabbit is stimulated every five minutes, the curve of the nystagmic response is levelled out and, each time stimulation takes place, the characteristic pattern of nystagmic response is reproduced. The central nystagmus shows latency and after-nystagmus, characteristic for labyrinthine – rotatory or caloric – stimulation and interacts with vestibular nystagmus by simple addition and subtraction of beat rates (LACHMANN, BERGMANN, WEINMAN and WELNER, 1958). In other words, they do not add their characteristic patterns together.

In a later report BERGMANN, LACHMANN and MONNIER (1960) state that transverse sections at various levels of the rabbit's brain stem have different effects both on vestibular nystagmus and centrally provoked nystagmus. When the vestibular component is abolished, the character of the response upon electrical stimulation changes. Latency and after-nystagmus disappear and the eye movements become so frequent (up to 5/sec.) as to allow no distinction between slow and rapid components. So the complete circuit for a normal central nystagmic response includes the vestibular nuclei.

MONTANDON and LIBOIS (1963) investigated the effects of experimental lesions of the nystagmogenic diencephalic area on rotatory vestibular nystagmus. They destroyed the area by electrocoagulation.

In our laboratory different forms of nystagmus were investigated. PHILIPSZOON (1959) investigated the action of different drugs on nystagmus provoked by stimulation of the vestibular apparatus. JONGKEES and PHILIPSZOON (1962) elicited nystagmus by linear accelerations. BOS (1962) studied nystagmus induced by chemicals and by irritation of the cervical nerve roots.

The purpose of this study was to investigate the influence of different drugs on central nystagmus. All these drugs were known for their action on the function of the vestibular apparatus or for their action in motion sickness.

Another part of the investigation was directed to the interaction of other forms of nystagmus on central nystagmus.

We observed the influence of the vestibular nystagmus, the optokinetic nystagmus and the nystagmus provoked by irritation of the cervical nerve roots.

Methods

For our investigations we used rabbits weighing about 2 kg each. The skin overlying the skull was anaesthetized with lidocaine (2 ml, 2%) and then incised along the midline. The skull was then freed from muscles. The periosteum was not destroyed. The stereotaxic socklet of Hess was adjusted in the way described by MONNIER and LAUE (1953) and LACHMANN, BERGMANN and MONNIER (1958). Holes were drilled in the skull and three isolated steel unipolar electrodes with a bare tip 1 mm long and 1.8 mm distant from each other were fixed in the socklet. The electrodes were introduced into the brain in the plan bD or bE (Charts I and II) according the designation of MONNIER and GANGLOFF (1961). Stimulation was applied by a Grass S 4 stimulator. The frequency of the stimuli was 30 impulses/sec. and the duration of each was 2 millisec. A resistor of 10.000 ohms was used in all experiments for adjustment of the stimulus parameters. The required amplitude of the stimulus, which remained constant during the experiments, lay between 0.5–6 volts.

We stimulated for a period of 1 minute, at intervals of 4 minutes (Fig. 1). The nystagmus was recorded by an Elema Minograph with Tektronics power supply type 127 with plug-in units type E as described by DE BOER (1962).

It was essential for the interpretation of the results to determine the site of the stimulating electrodes. The nystagmogenic centre was located accurately by LACHMANN, BERGMANN and MONNIER (1958), BERGMANN, LACHMANN, MONNIER and KRUPP (1959), and MONNIER and MONTANDON (1961). In the mesodiencephalon it extends from the rostral part of the reticular formation and its projections into the intralaminary system of the lateral thalamus to the mesencephalic reticular formation, medially to the lateral geniculate body. The most sensitive area is in the thalamic region (between the latero-dorsal and ventral nucleus, medial to the reticular nucleus and ventral to the superior colliculus). A little more caudally the most sensitive area is in the reticular midbrain formation, medial to the medial geniculate body and ventral to the superior colliculus.

In our experiments the place of stimulation electrodes was histologically * verified in five instances (Phot. B). We used the ferrocyanide technique for identifying loci of iron deposition, first described by HESS (1932) and later by ADRIAN and MORUZZI (1939).

* The histological examination was performed by Dr. J. P. Schadé and Mr. G. P. Rijskamp of the Nederlands Centraal Instituut voor Hersenonderzoek. (Director Prof. Dr. J. Ariëns Kappers).

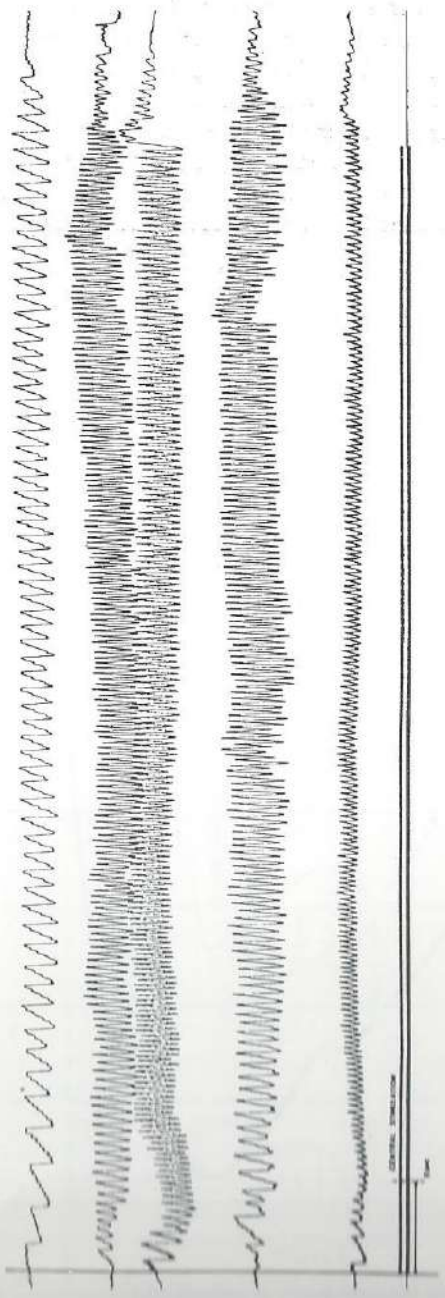


Fig. 1

Recording of eye movements of five rabbits during a sixty second central stimulation period. The lower tracing represents the stimulus.

After a successful experiment a current of 100 mA from the positive pole of a direct current generator was forced through the electrode for a period of five seconds. Following this 50 millilitres of a 1 : 1 mixture of 4% potassium ferrocyanide and 4% acetic acid was injected into each common carotid artery and the brain left in situ for half an hour. Frozen sections were then made and stained in the manner described by M. E. and A. B. Scheibel (1956). Sites of electrolysis at the tips of steel electrodes were recognized under light power as blue spots.

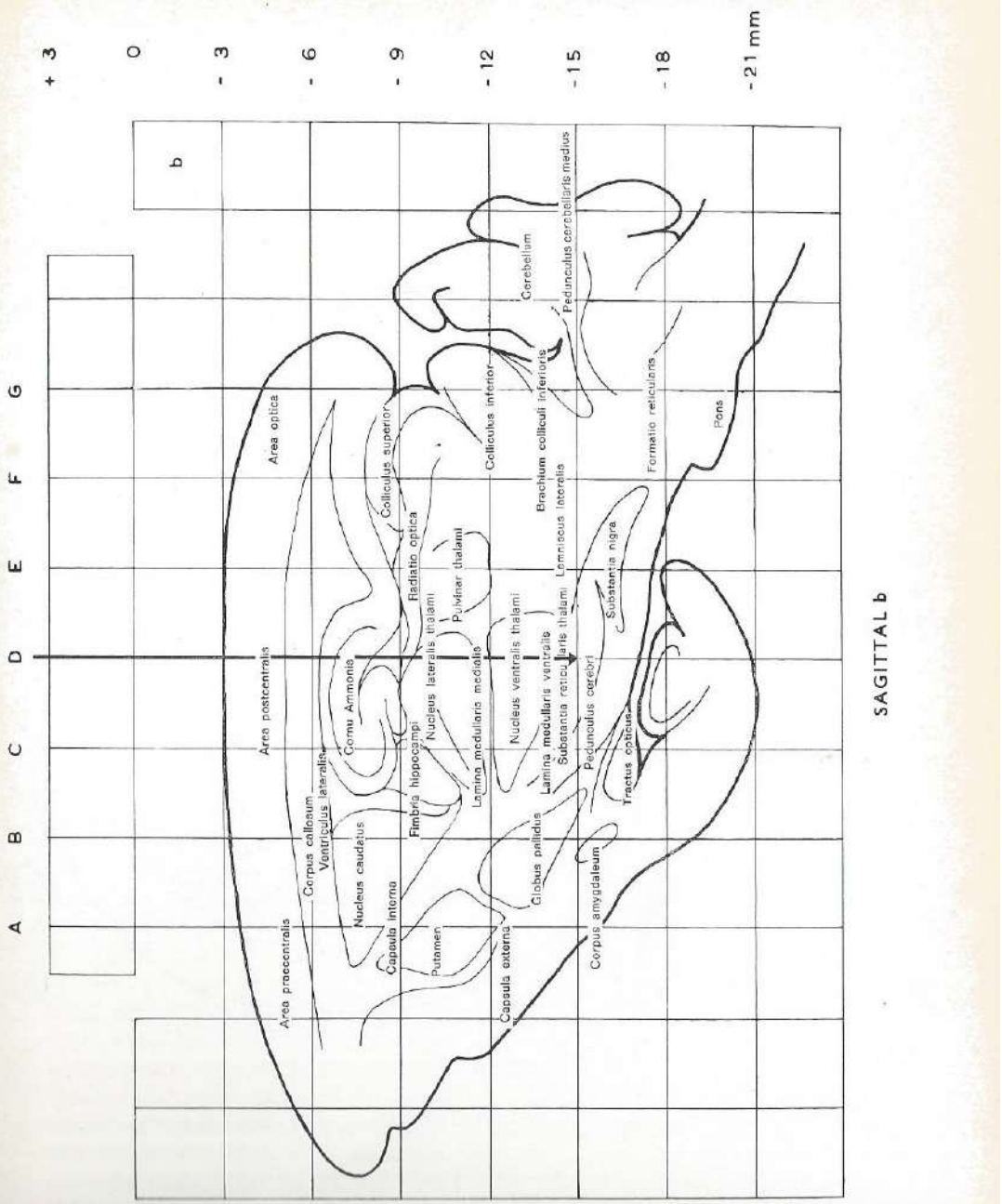


Chart 1

Localization of the stimulated centre.

Stimulation took place in the sagittal plane b in the perpendicular grid D on 15 mm from the lower surface (= 0 mm) of the socklet.

(from M. Monnier and H. Gangloff: Atlas for stereotaxic brain research on the conscious rabbit. Vol. I, Chart VI, Amsterdam, Elsevier, 1961). With kind per-

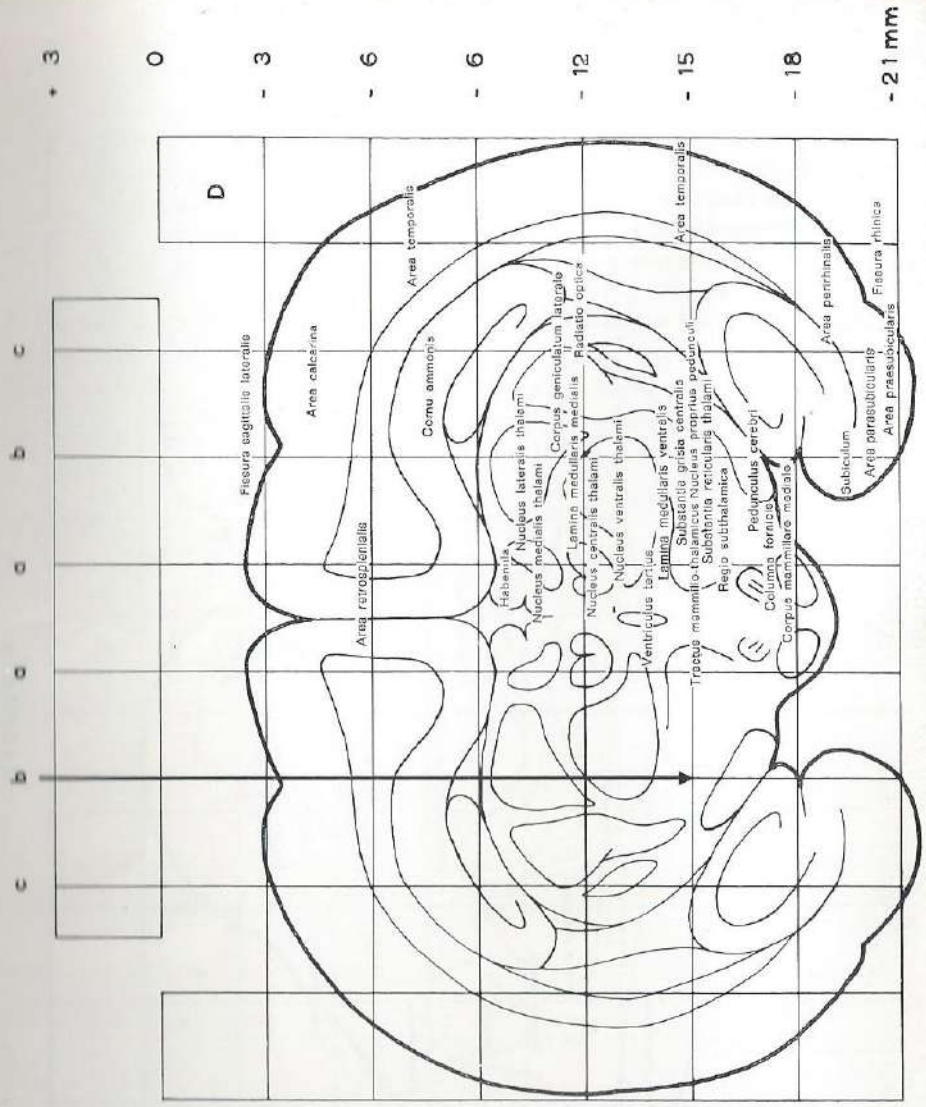


Chart II

Frontal section through the rabbit's brain.
(from M. Monnier and H. Gangloff: Atlas for stereotaxic brain research on the conscious rabbit. Vol. I, Chart XVI, Amsterdam, Elsevier, 1961). With kind permission of the publishers.

Chapter II

ON THE INFLUENCE OF DRUGS ON CENTRAL NYSTAGMUS

Introduction

Electrical stimulation of the nystagmogenic centre causes a central nystagmus. Repeated stimulation during a fixed period provokes a nystagmic pattern which can go unchanged for hours. After half an hour of intermittent stimulation the pattern of nystagmic response finds its definite form and does not change again for hours. This characteristic constancy makes it possible to examine the influence of varying circumstances.

The influence of certain drugs on central nystagmus has already been investigated. Such a study may give insight into the mode of action of drugs on central systems.

Bergmann, Gutman, Lachmann and Chaimovitz (1961) and Bergmann, Gutman and Chaimovitz (1962) investigated the action of chlorpromazine, phenothiazines and pentobarbitone. The results were found to be the following.

Small doses of chlorpromazine (0.25 mg/kg) cause an enhancement of the central nystagmus. Large doses (2.5 mg/kg) diminish the central nystagmus. This differential action of chlorpromazine is interpreted as a selective effect of small doses on the inhibitory components of the nystagmus circuit, which are distinguished from the excitatory elements by their electrophysiologic properties.

The effect of phenothiazines on central nystagmus depends on dosage. Small quantities (0.01 mg/kg) depress the response while doses above 0.1 mg/kg produce a biphasic reaction, i.e. enhancement for one or two hours followed by prolonged depression.

Similar gradation is observed with pentobarbitone. It was found that after doses of 5–10 mg/kg central nystagmus was enhanced. However, even fifteen to twenty minutes after injection of the drug a pronounced depression ensued, lasting for about an hour. Small doses (1–2 mg/kg) were often without any effect.

Different mechanisms are involved with these two types of drugs, as phenothiazines restore the nystagmus, suppressed by large doses of pentobarbitone, and vice versa.

The basis of the interpretation is the heterogeneity of nervous elements in the nystagmus circuit.

Methods

In order to evaluate the effect of a drug the number of beats during a sixty seconds stimulation, the number of after-beats and the latency time were measured.
The number of after-beats is an indicator of great value here as it will be shown to be the most sensitive one. In our experiments we generally made the stimulations at intervals of four minutes. After half an hour, during which the rabbit was stimulated every five minutes, the drug was administered.
Eight rabbits were used as controls; these did not receive any drug, and were stimulated every five minutes for five hours. The pattern of nystagmus response in these "controls" did not change.

CINNARIZINE

Introduction

Cinnarizine * (N-benzhydryl-N'-transcinnamylpiperazine) is an antihistaminic which was found to have a significant suppressive effect on the activity of the labyrinth both in rabbits and in human beings (Philipszoon, 1959, 1961, 1962; Bos, 1962). Consequently it might be expected to have an influence on nystagmus provoked by central stimulation.

Experiments

Cinnarizine, dissolved in solutio Petiti, was given to twenty-four rabbits in the following manner.
The twenty-four animals were divided into four groups, each group containing five normal rabbits and one labyrinthless rabbit. The first two groups received by intraperitoneal injection 20 mg/kg and 40 mg/kg of the drug, respectively. The remaining two groups received by intravenous injection 5 mg/kg and 10 mg/kg, respectively.
Solutio Petiti is a combination of pure alcohol, glycerin and water. We felt we should investigate it separately since there was a possibility of it having some influence on central nystagmus. If there was such an effect, the action of cinnarizine could not be measured. To check this we injected 10 millilitres of this liquid into four rabbits.

* Cinnarizine is the same as Cinnipirine (a product of the N.V. Amsterdamsche Chininefabriek, Amsterdam); it is also known under various other names including Dimitronal, Glanil, Lazeta, Marisan, Midronal, Mitronal, Sepan.

The nystagmus response was recorded continuously during a period of two to four and a half hours. In the reaction we observed two stages, each one hour long.

Results

Of the twenty normal rabbits sixteen did not show any reaction of central nystagmus to cinnarizine. Three rabbits showed a slight depression in the second stage after intraperitoneal application and one rabbit showed a depression in the first stage after intravenous injection of the drug. Of four rabbits submitted to bilateral labyrinthectomy not one showed a change of the nystagmic pattern after application of the drug.
Four more rabbits were treated with solutio Petiti only and did not show any effect.

Summary

The influence of the antihistaminic cinnarizine on centrally provoked nystagmus was investigated in twenty-four rabbits, four of which were totally labyrinthless. In twenty rabbits a depression was observed on four occasions, three of which were slight.
In the four totally labyrinthless rabbits no effect of the drug was proved.

CHLORCYCLIZINE HYDROCHLORIDE

Introduction

Chlorcyclizine hydrochloride, N-(p-chlorobenzhydryl)-N'-methyl-piperazine hydrochloride, has a significant influence on the function of the vestibular apparatus. It was originally introduced because of its antihistaminic activity, its potency in this regard being comparable to that of diphenhydramine.
Experimental studies in animals and men reveal it to be a relatively non-toxic compound. It has been successfully employed by Chinn, Noell and Smith (1950) in the prevention and treatment of motion sickness (seasickness, airsickness). Recently it has been examined by Spielman (1950), Gutner, Gould and Cracovaner (1954), Beauchamp (1956), Hough and Skouby (1957), and Wilhelm (1961) with regard to its action on vestibular function.

In galvanic and caloric tests it was shown that labyrinthine excitability decreased after the administration of chlorcyclizine hydrochloride. We decided to investigate the effect of chlorcyclizine hydrochloride on central nystagmus.

Experiments

Nine rabbits were used for this test. The drug dissolved in Ringer's solution was given intravenously in quantities of 5, 10 and 15 mg/kg to three groups of rabbits, respectively.

Results

Eight rabbits did not show any influence of chlorcyclizine hydrochloride on central nystagmus at all. In one rabbit only slight influence on the nystagmus response was found: after half an hour a depression was observed that lasted for about an hour. Then the response became normal again. This rabbit was one of the group that received 10 mg/kg of the drug.

Summary

Only one rabbit out of a group of nine showed a short-lasting depression after application of chlorcyclizine hydrochloride. There is no clear effect of chlorcyclizine hydrochloride on central nystagmus.

MECLIZINE

Introduction

Since chlorcyclizine hydrochloride did not have a clear influence on central nystagmus, we were interested in the influence of meclizine on central nystagmus. Meclizine, 1-(p-chlorobenzhydryl)-4-(m-methylbenzyl) piperazine, is a drug for a.o. the prevention and treatment of motion sickness of which good results have been described. (GOLDMAN, 1951; GUTNER, GOULD and BATTERMAN, 1951; WEIL, 1954; GUTNER, GOULD and SWIFT HANLEY, 1955 and MENGER, 1957).

Experiments

Meclizine hydrochloride was administered intravenously — dissolved in Ringer's solution — to two groups of six rabbits each in quantities of

MECLIZINE

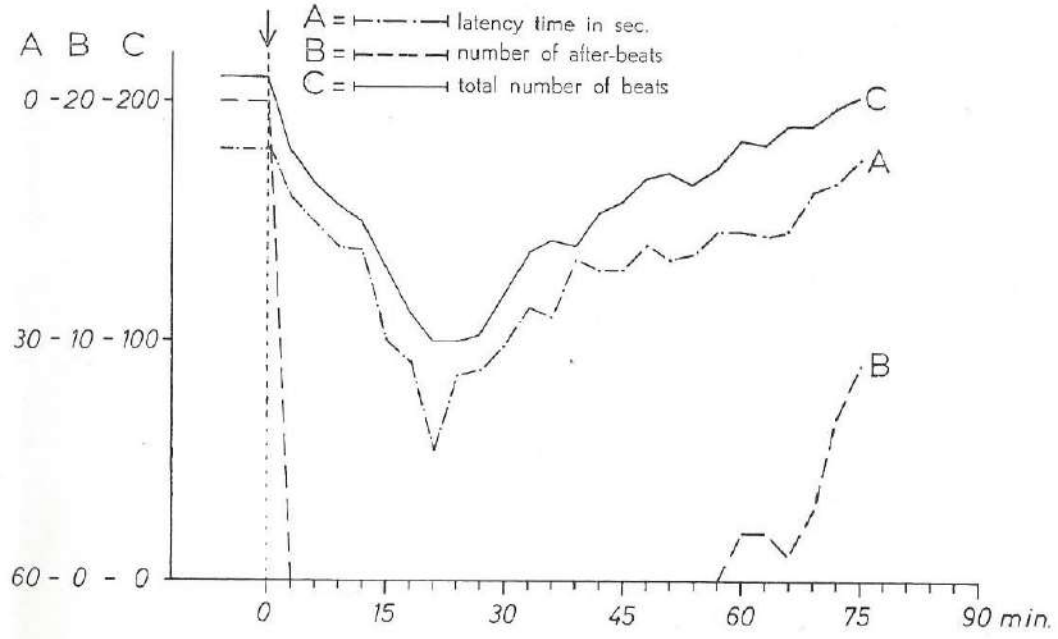


Fig. 2

The combined results of meclizine (5 mg/kg) on central nystagmus.

2 mg/kg and 5 mg/kg, respectively. Every three minutes the rabbits were stimulated for sixty seconds. We used the shorter intervals in view of the rapid action of the drug.

Results

In all rabbits the same effect of meclizine on central nystagmus was shown. Fifteen minutes after the application of the drug it became clear that a depression occurred. The latency time grew longer, the after-nystagmus disappeared and the total number of beats diminished.

The depression lasted for about ninety minutes and the normal nystagmic response came back within two hours (Fig. 2).

Summary

Meclizine has a clear depressive effect on central nystagmus. Depression of labyrinthine function (GUTNER, GOULD and BATTERMAN, 1951) and depression of the central nervous system both seem to be responsible for the effect against motion sickness.

NEMBUTAL

Introduction

The influence of barbiturates on central nystagmus has already been described by BERGMANN, GUTMAN and CHAIMOVITZ (1962). Since barbiturates often produce spontaneous nystagmus, it appeared that they might intensify the central nystagmus.

Experiments

Two groups of five rabbits each were used. Pentobarbitone (nembutal) was injected intraperitoneally in quantities of 2 mg/kg and 10 mg/kg, respectively.

Results

If small quantities were used an enhancement of the resulting nystagmus for fifteen minutes was followed by a depression which lasted for about an hour.
The higher dosage (10 mg/kg) produced an immediate and pronounced depression of the nystagmic response which lasted for more than two hours.

Summary

Barbiturates depress the central nystagmus and, according to PHILIPSZOON (1959), do not affect the vestibular apparatus proper.
As was to be expected, the central depressing activity of barbiturates is shown by the suppression of central nystagmus.

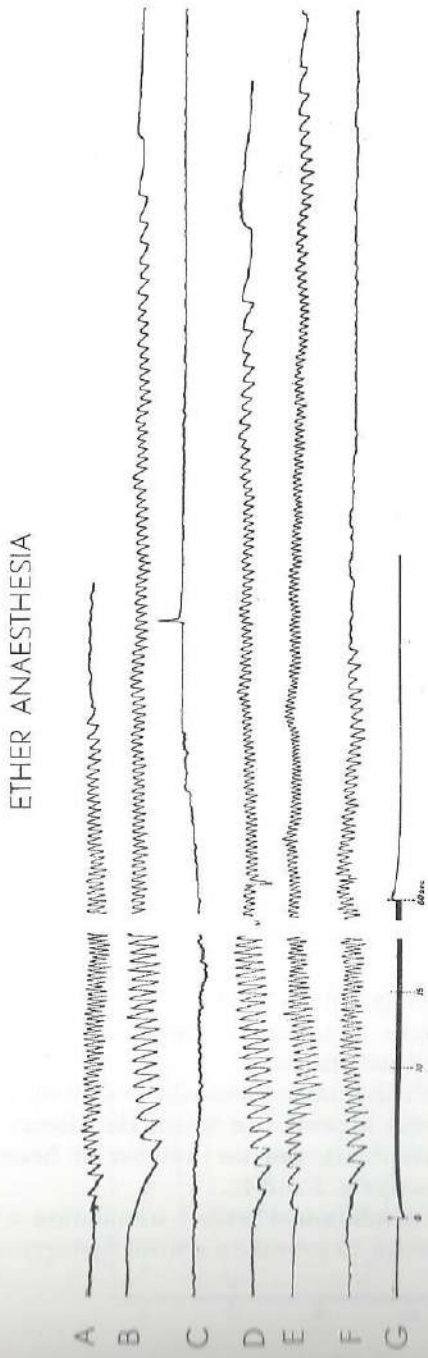


Fig. 3

The effect of ether anaesthesia on central nystagmus demonstrated with latency time and after-nystagmus.

A before ether administration
B after 3 minutes
C after 9 minutes
D after 23 minutes
E after 30 minutes
F after 60 minutes
G stimulus recording

ETHER

Introduction

LACHMANN, BERGMANN, WEINMAN and WELNER (1958) investigated the influence of the anaesthetic ether on a combined labyrinthine and central stimulation. They found that both responses were suppressed to the same degree under the influence of ether.
We investigated the influence of ether on normal central nystagmic response.

Experiments

For this experiment fifteen rabbits were used. Ether was administered by way of inhalation with air by means of a piece of cotton wool on which ether was dripped.
The investigation was carried out in two phases. During the first phase the ether was stopped immediately after the excitation stage. During the second phase it was stopped immediately after disappearance of the cornea reflex. Every three minutes a sixty seconds stimulation was given because of the rapid action of the anaesthetic.

Results

In our investigations all animals showed the same results.
We found that a very clear enhancement of the nystagmus response appeared immediately after the beginning of anaesthesia. The number of after-beats was the most sensitive measure of the effect of the anaesthetic.
After three minutes the response diminished, to disappear completely after ten minutes.
In the first phase of investigation in which anaesthesia was light, nystagmus and after-nystagmus diminished but did not disappear completely.
In the second phase of investigation in which anaesthesia was deep, nystagmus and after-nystagmus disappeared completely five to ten minutes after the beginning of anaesthesia.
Twenty to forty minutes after the start of anaesthesia in both phases a second stage of enhancement appeared in which the latency time was shorter than before anaesthesia and the number of beats and after-beats had largely increased (Fig. 3 and 4).
When the rabbit was given a subliminal central stimulation a light degree of anaesthesia was enough to provoke a central nystagmus.

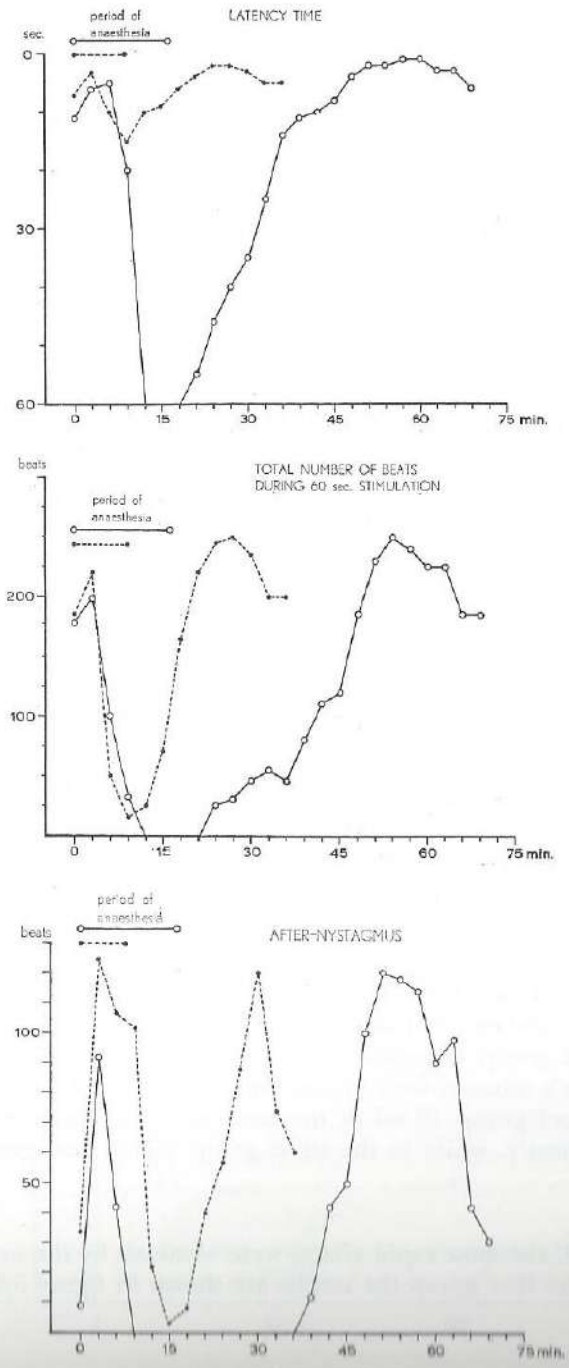


Fig. 4
Combined results of ether anaesthesia on central nystagmus.

Summary

Ether has a general excitatory influence in the beginning and at the end of anaesthesia. The same can be said of the effect of ether on central nystagmus.
In the intermediate stage of anaesthesia a depression of central nystagmus could be observed.

ALCOHOL

Introduction

Nystagmus as a sequel of alcohol intoxication was observed by Flourens (1826) in experiments in animals. It was also described as a clinical symptom in man by Joffroy and Servaux (1897). Bárány (1911) described experimental alcohol intoxication in healthy subjects during various vestibular tests. He is of the opinion that alcohol has a paralysing influence on the cerebellum. Rothfeld (1913) studied alcohol nystagmus in rabbits. De Kleyn and Versteegh (1930), Le Heux and De Kleyn (1937) and Goldberg and Störtebecker (1941) also investigated alcohol nystagmus in rabbits.
Recently positional alcohol nystagmus in men and rabbits was investigated by Aschan, Bergstedt and Stahle (1956) and Bergstedt (1961). Bos (1962) found that the drug cinnarizine, with a clear depressive action on all forms of vestibular nystagmus, did not have any effect on alcohol nystagmus.
So far investigations with alcohol intoxication have been performed in connection with labyrinthine function.
We decided to investigate the effect of alcohol intoxication on central nystagmus.

Experiments

Fifteen rabbits were used. The animals were divided into three groups according to the mode of administration of the alcohol.
In the first group 8 millilitres of a solution of 45% alcohol and 55% Ringer's solution were injected intravenously into each rabbit.
In the second group 10 ml of the same solution were administered intraperitoneally, while in the third group 15 ml were given orally.

Results

As expected, the most rapid effects were obtained by the intravenous route. Of the first group the results are shown in figure 5A.

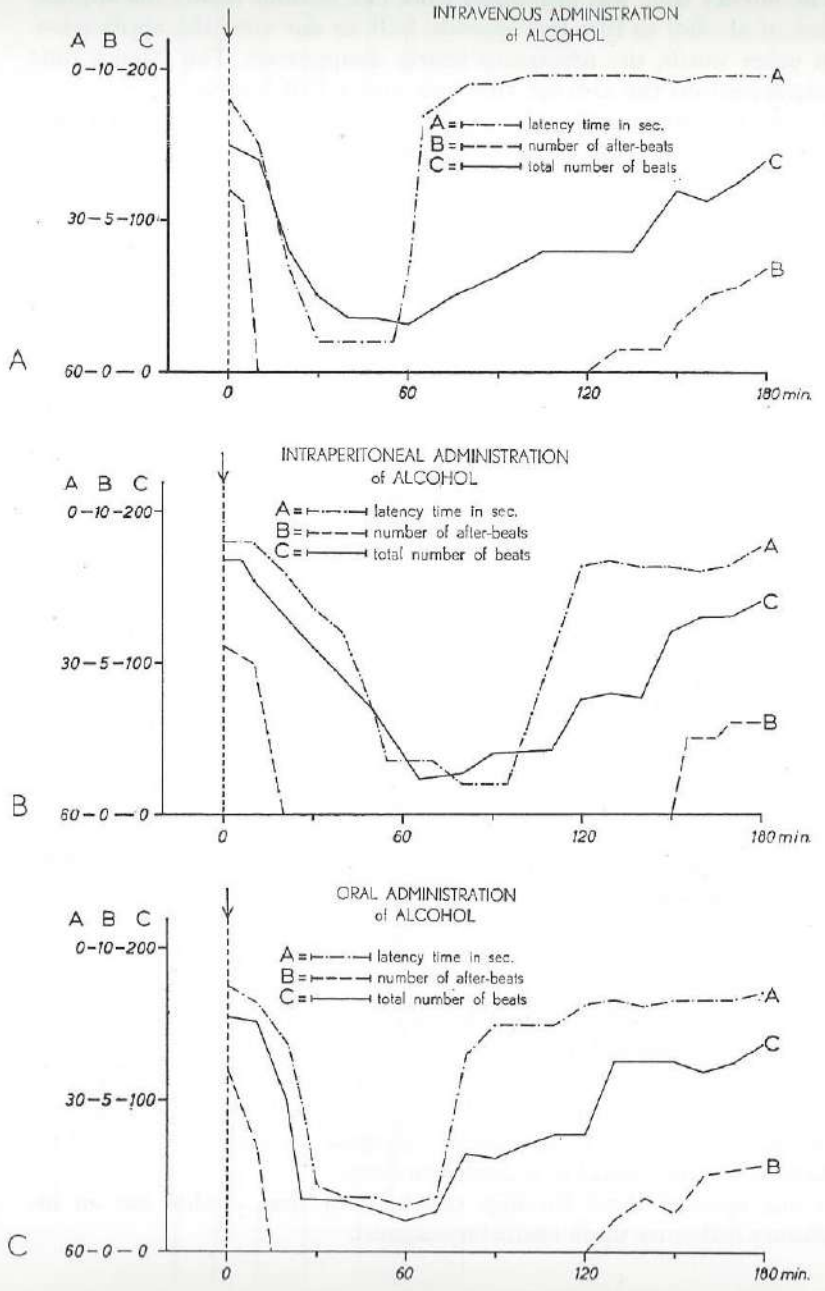


Fig. 5

The combined effect of alcohol on central nystagmus measured by latency time, after-nystagmus and total number of nystagmus beats during stimulation period.

The latency time was prolonged from five seconds before the application of alcohol to fifty-five seconds, half an our after the application. In other words, the nystagmus nearly disappeared. The latency time reappeared on the average after one and a half hours.
The total number of beats began to diminish ten minutes after giving the alcohol, to disappear nearly after thirty minutes and to recover after a period of three hours.
The after-nystagmus also disappeared ten minutes after the application of the drug and never reappeared completely within a period of three hours.
In the second group in which alcohol was administered intraperitoneally the results are recorded in figure 5B.
The latency time was prolonged from five seconds before giving the alcohol to fifty-five seconds after an hour. The latency time was almost normal after two hours.
The total number of beats began to diminish twenty minutes after the application, to disappear almost completely after an hour, and did not recover completely after three hours. After-nystagmus also disappeared twenty minutes after application and did not reappear completely within a period of three hours.
The results in the third group in which alcohol was administered orally, are tabulated in figure 5C and shown in figure 6. The latency time was prolonged from five seconds before the application of alcohol to fifty-five seconds after forty-five minutes. The latency time reappeared after approximately one and a half hours.
The total number of beats began to diminish fifteen minutes after the application to disappear almost after forty-five minutes, and did not recover completely within a period of two hours.
After-nystagmus also disappeared fifteen minutes after the application of the drug and did not reappear completely within a period of three hours.

Summary

In all our groups we could see that alcohol has a depressive influence on centrally provoked nystagmus.
In our investigations we found no enhancement of the nystagmic response at all. Every rabbit that was investigated in lateral positions showed a spontaneous positional nystagmus independent of the remainder of the central nystagmic response.
In our opinion these findings clearly show that alcohol has an inhibitory influence upon central nystagmus.

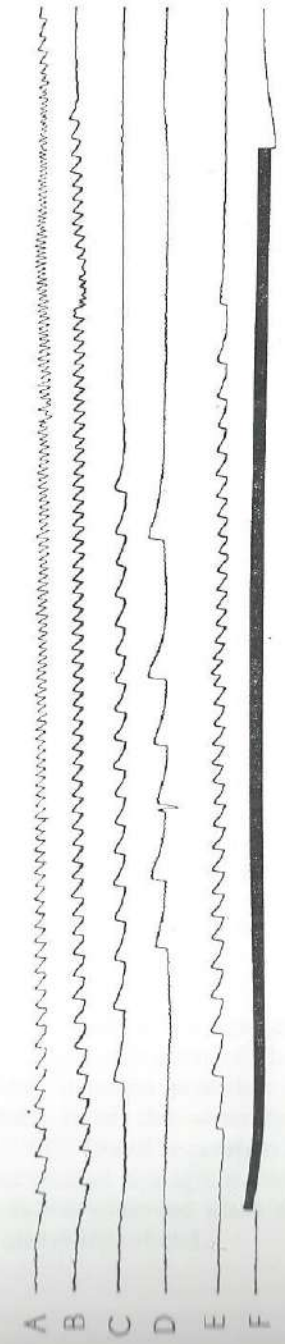


Fig. 6

The effect of alcohol (oral administration) on central nystagmus.
Nystagmus pattern: A before administration
B after 15 minutes
C after 30 minutes
D after 60 minutes
E after 120 minutes
F stimulus recording (sixty seconds)

HYOSCINE

Introduction

PHILIPSZOON (1959) did not find hyoscine to have any influence on eye movements of vestibular origin. He merely found an indication that the amplitude of nystagmus beats provoked by acceleration increased when large quantities were given.
We investigated the influence of the drug on central nystagmus.

Experiments

Twelve rabbits were used. Hyoscine (scopolamine) was given intraperitoneally in dosages of 50, 150 and 250 mg/kg.

Results

All rabbits showed the same results. The pupils dilated and did not respond to light. No influence at all on central nystagmus was observed.

Summary

The effect of hyoscine on motion sickness cannot be due to a suppression of the excitability of the peripheral labyrinthine function (PHILIPSZOON, 1959).
In our experiments we could not find evidence in favour of PHILIPSZOON's suggestion that hyoscine might have a favourable effect on motion sickness by its action on the central pathways.

CHAPTER III

ON THE INFLUENCE OF PERIPHERAL LABYRINTHINE STIMULI ON CENTRAL NYSTAGMUS

Introduction

LACHMANN, BERGMANN and MONNIER (1958), LACHMANN, BERGMANN, WEINMAN and WELNER (1958), BERGMANN, LACHMANN, MONNIER and KRUPP (1959), and BERGMANN, LACHMANN and MONNIER (1960) investigated certain aspects of the activity of the peripheral labyrinth on central nystagmus.
They found a simple form of cooperation of labyrinthine and central nystagmus by addition and subtraction. Since angular accelerations and linear accelerations are the stimuli proper for the semicircular canals and the otoliths, respectively, and since it has been proved in our laboratory (JONGKEES and PHILIPSZOON, 1962; PHILIPSZOON, 1962; and BOS, JONGKEES and PHILIPSZOON, 1963) that stimulation of the otoliths may also provoke nystagmus, we decided to test the effect of both modes of physiological labyrinthine stimulation upon central nystagmus.
In these series we examined the effect of the position of the rabbit upon central nystagmus using the torsion swing to cause angular accelerations and the parallel swing for linear accelerations.
Another aspect we looked into was the influence of caloric stimulation of the labyrinth on central nystagmus.

DIFFERENT POSITIONS

Introduction

Positional nystagmus is the nystagmus provoked in certain positions in relation to the direction of the force of gravity. BÁRÁNY (1921) suggested that it might probably originate from the otolith organs. NYLÉN (1952) is of the same opinion. GUTMAN, CHAIMOVITZ and BERGMANN (1963) found that when the rabbit's head was in the lateral position the central nystagmus response was enhanced. The greatest enhancement was observed when the head was tilted to the opposite side of the centre stimulated.

Experiments

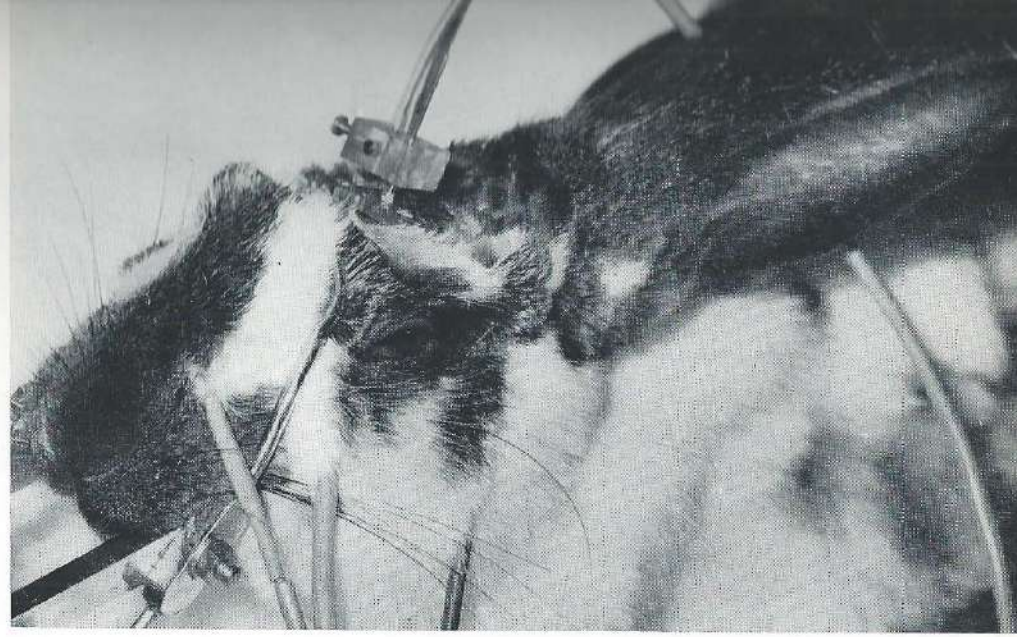
Twelve rabbits were used for this investigation. Central nystagmus was provoked in five different positions; prone, right lateral, left lateral, supine and vertical.
By way of control central stimulation in the prone position was given between any two position tests.

Results

The effect of the position of the rabbit on central nystagmus was clear. All rabbits showed a depression of the nystagmus response when lying in the supine position.
In all rabbits the vertical position changed the response to a higher frequency of nystagmus beats with a smaller amplitude. When lying in the lateral position six out of twelve rabbits showed a depression of nystagmus response. The deepest depression was observed when the rabbits were lying on the side of the nystagmogenic centre that was stimulated.
The other six rabbits showed a higher frequency and a smaller amplitude when they were lying on the side contralateral to that of the nystagmogenic centre stimulated and showed a depression of the response when lying on the ipsilateral side (Fig. 7).
One rabbit showed a spontaneous positional nystagmus in the left lateral position which was superposed on the central nystagmus pattern.

Summary

There is a clear effect of the position of the rabbit on central nystagmus.
The measure of this effect is different for each position.
Supine position depressed the nystagmus response while vertical position resulted in a higher frequency and a smaller amplitude.
In all rabbits a depression was observed in the lateral position on the side of the nystagmogenic area stimulated.
In some rabbits an enhancement, in other rabbits a slight depression was observed in the lateral position on the other side.



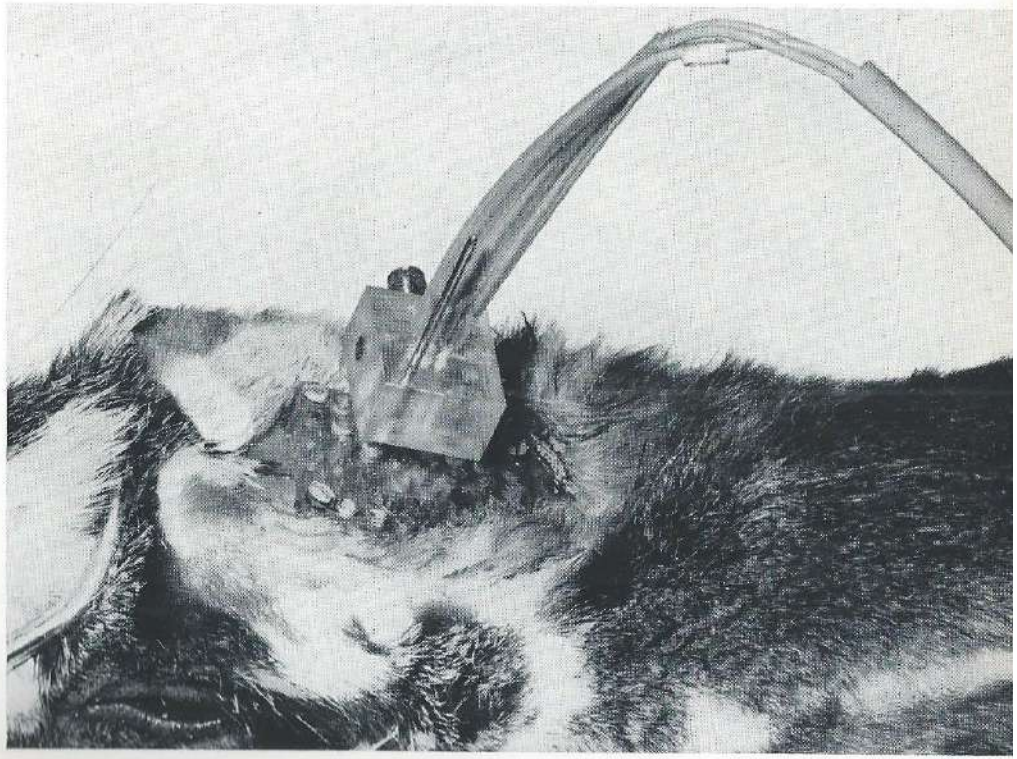


Photo A 1 + 2

The fixed rabbit's head with the stimulating and eye electrodes applied.

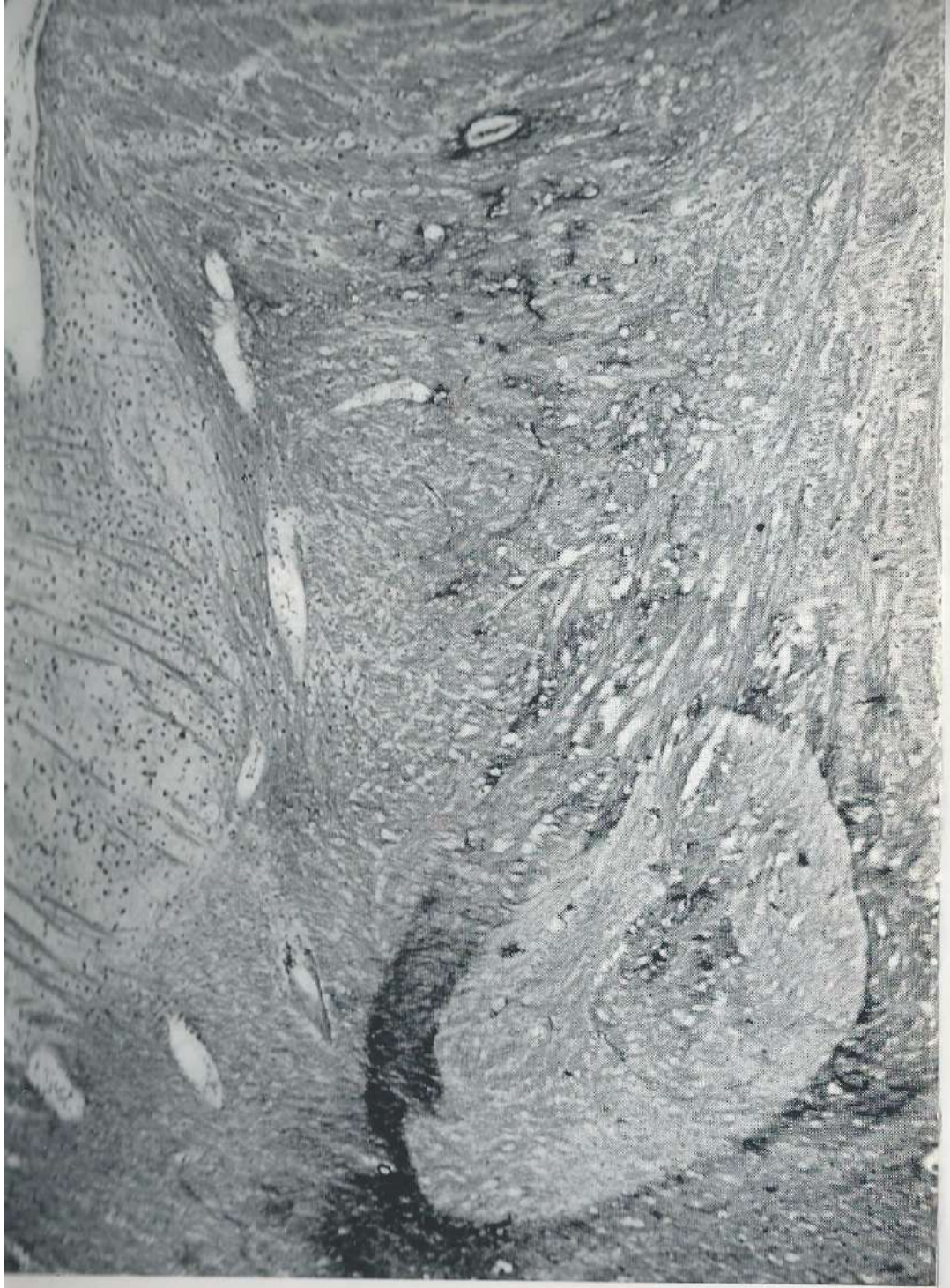


Photo B
Photo of the point of stimulation after coagulation.
Staining according to Bodian (protargol) after fixation according to Scheibel and Scheibel.

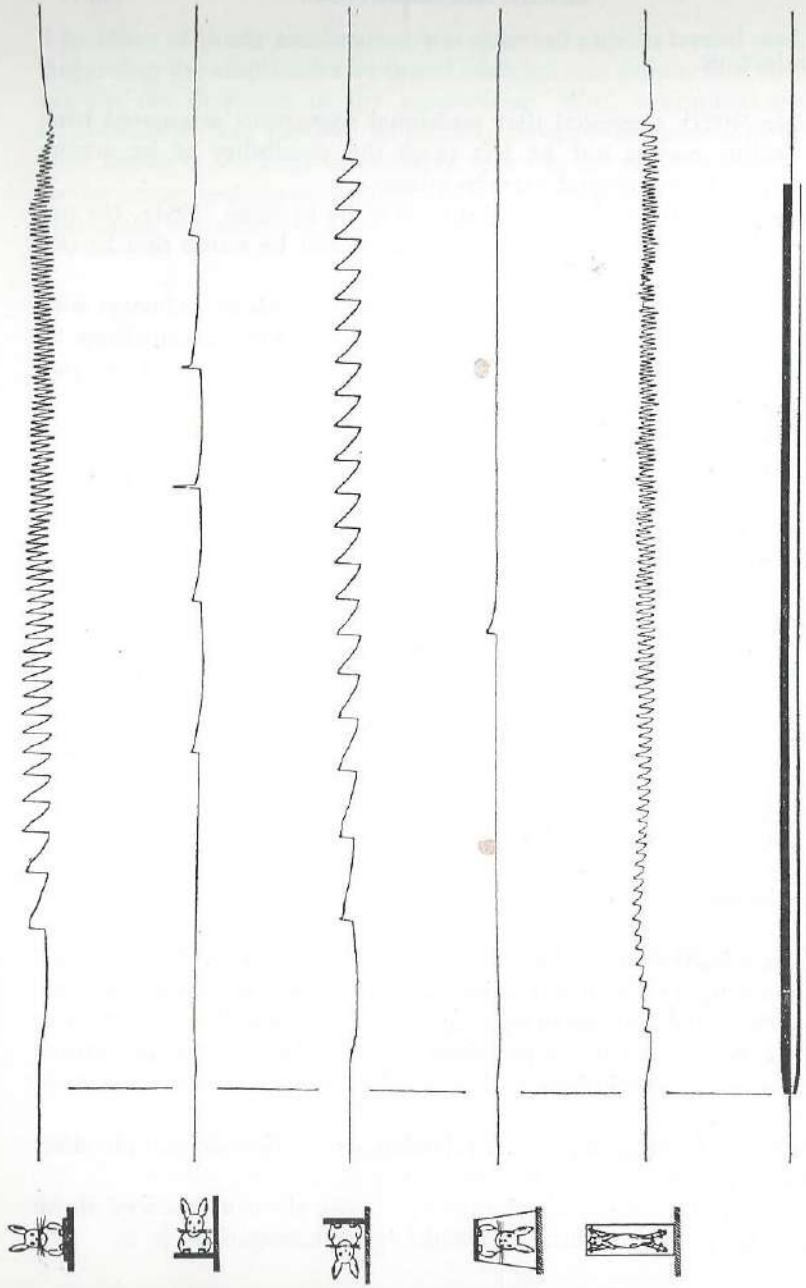


Fig. 7
The effect of different positions on central nystagmus. Lower tracing: recording of stimulus.

Introduction

BÁRÁNY (1921) suggested that positional nystagmus originated from the otolith organs but he left open the possibility of its arising exclusively in the central nervous system.
Linear accelerations in lifts were studied by SJÖBERG (1931). He was not able to record any definite nystagmus, but he stated that he saw reactions suggestive of it in several subjects.
BERGSTEDT (1961) could not elicit nystagmus in his experiments with linear accelerations on human subjects. In the human centrifuge he clearly demonstrated the influence of linear accelerations on pre-existent positional nystagmus.
In 1946 JONGKEES and GROEN described eye movements in human beings on the parallel swing. In our laboratory we succeeded in recording compensatory eye movements provoked by linear accelerations on the parallel swing (PHILIPSZOON, 1959; JONGKEES and PHILIPSZOON, 1960).
Nystagmus in rabbits on the parallel swing was described for the first time by JONGKEES and PHILIPSZOON (1961). In their investigations the rabbits were placed in the lateral position and the eye electrodes were fixed above and below the eye.
The results of the experiment showed that it is highly probable that the otoliths play an important part in the formation of this form of nystagmus. This conclusion was based on experiments with rabbits, with partial destruction of the labyrinths. (BOS, JONGKEES and PHILIPSZOON, 1963).

Experiments

Twelve rabbits were used for our test. For linear acceleration a parallel swing was used with an oscillation time of 3.7 sec. The maximum speed was 205 cm/sec and the maximum acceleration was 348 cm/sec^2. The rabbits were tested in all positions described in the chapter entitled "Positions". Supraliminal and subliminal central stimulation were used.
Two pairs of eye electrodes were fixed, one at horizontal and the other at vertical level.
Central nystagmus can also be recorded with electrodes placed above and below the eye, as there is a slight vertical component in it.

Results

The effect of linear acceleration was observed only in lateral position. Regarding the amplitudes we found addition and subtraction, depending on the direction of the acceleration. With subliminal central stimulation it was possible to provoke nystagmus when both effects were acting in the same direction in four out of twelve rabbits.
In the prone position no influence of the linear acceleration on central nystagmus was observed at all (Fig. 8).

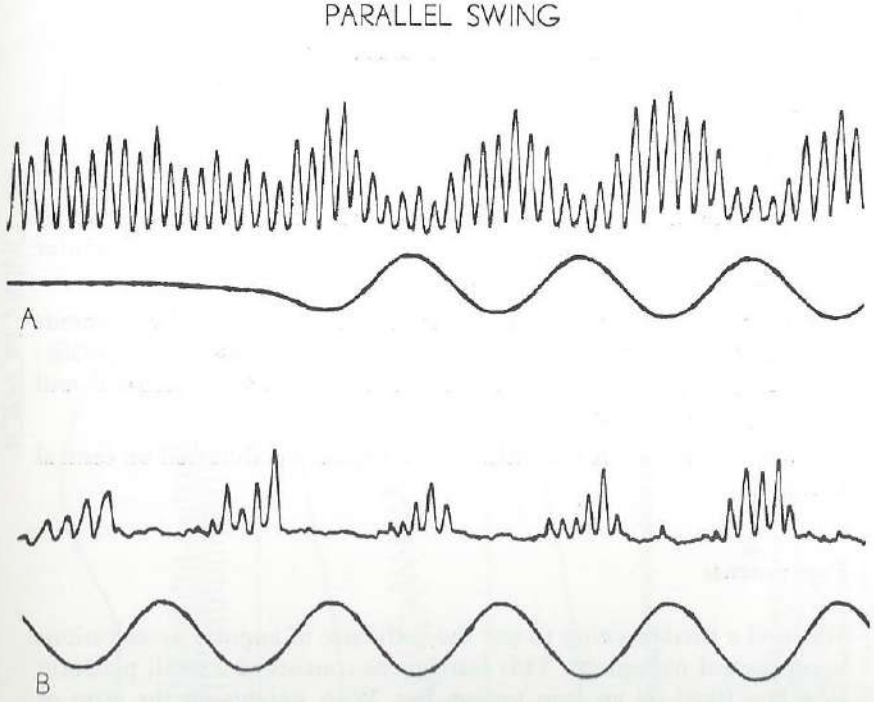


Fig. 8
The effect of linear acceleration on central nystagmus in a rabbit in lateral position.
A central nystagmus + linear acceleration
B subliminal central stimulation + linear acceleration
Upper tracing: recording of eye movements.
Lower tracing: recording of swing movements.

Summary

In prone, supine and vertical position no influence of linear accelerations, caused by the parallel swing, on central nystagmus could be demonstrated.

In the lateral position (which is the only situation causing nystagmus) a certain effect can be observed on central nystagmus, confirming the rule of addition and subtraction with regard to the amplitude.

ANGULAR ACCELERATIONS

Introduction

MACH (1875) and VAN EGMOND, GROEN and JONGKEES (1949) have already described alternating stimulation of the horizontal semicircular canals with the use of a torsion swing.

A torsion swing gives a damped sinusoidal movement. Experiments with this swing have also been described by HENNEBERT (1956); DE BOER, CARELS and PHILIPSZOON (1962); GREINER, CONRAUX and PICART (1963) and HARTOG (1963).

We were interested in the influence of angular acceleration on central nystagmus.

Experiments

We used a torsion swing to test the influence of angular accelerations upon central nystagmus. This instrument consists of a small platform in a box fixed on an iron torsion bar. With weights on the arms of variable length the time of swinging can be controlled. This instrument can swing over an angle of 180 degrees.

The periods we used were 10, 20 and 30 seconds. Under these circumstances the maximum speeds were 57, 28 and 19 degrees/sec, respectively, the maximum accelerations were 35, 9 and 4 degrees/sec^2, respectively. Twelve rabbits were tested.

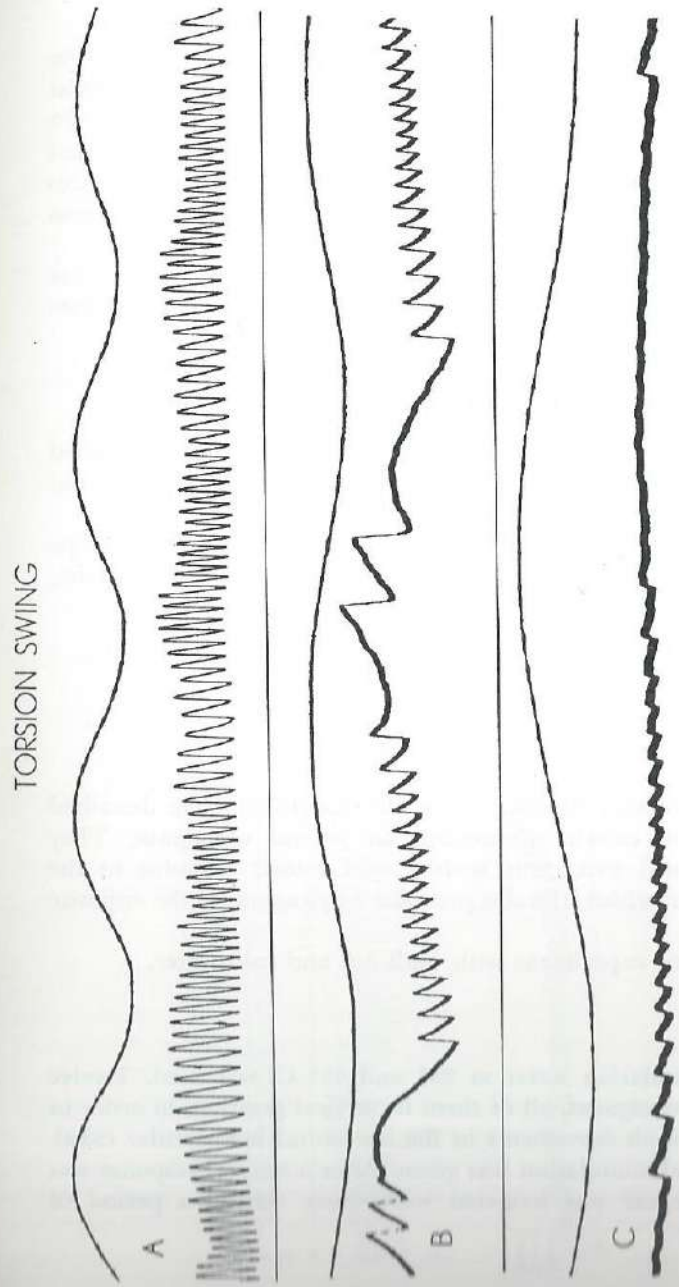


Fig. 9
The effect of angular acceleration on central nystagmus.
A central nystagmus + angular acceleration; oscillation period 10 seconds.
B subliminal central stimulation + angular acceleration; oscillation period 20 seconds.
C near-threshold central stimulation + angular acceleration; oscillation period 30 seconds.
Upper tracing: recording of swing movements.
Lower tracing: recording of eye movements.

Results

We found a complicated pattern of addition and subtraction of the frequency and amplitude of nystagmus when a normal central stimulation was given, together with the rotational stimulus. When we used subliminal central stimulation combined with subliminal acceleration this finding was confirmed. Under these circumstances it was possible to provoke nystagmus when the theoretical directions of both types of nystagmus coincided.
If the two were of opposite direction no nystagmus resulted. This was also the case when the two stimuli were near their threshold values (Fig. 9).

Summary

With regard to amplitude and frequency of nystagmus, combined angular acceleration and central stimulation resulted in a complicated addition and subtraction pattern.
A remarkable feature in the nystagmus pattern was that the envelope of the pattern is nearly flat on one (the lower) side, while modulating up and down on the other side.

CALORIC STIMULATION

Introduction

LACHMANN, BERGMANN, WEINMAN and WELNER (1958) have described the influence of caloric stimulation on central nystagmus. They suppressed central nystagmus with a cold caloric stimulus to the heterolateral ear, which stimulus provokes a nystagmus in the opposite direction.
We repeated this experiment with both hot and cold water.

Experiments

For caloric stimulation water at 25° and 45° C. was used. Twelve rabbits were investigated, all of them in vertical position, in order to provoke endolymph movements in the horizontal semicircular canal. At first a central stimulation was given. After a normal response was established one ear was irrigated with water during a period of twenty seconds.

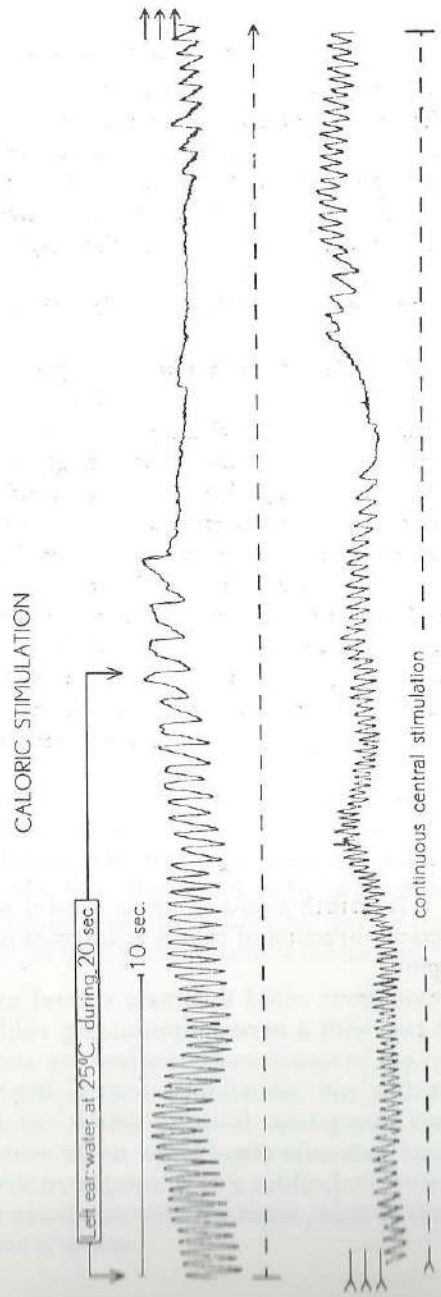


Fig. 10

The effect of caloric stimulation upon continuous central stimulation, observed when irrigating the left ear with water at 25 degrees C. during twenty seconds. Thirty-five seconds from the start of calorization caloric nystagmus is seen.
Seventy seconds from the start of calorization central nystagmus starts again.

Results

We could replace the central nystagmus by caloric nystagmus through stimulation with cold water in the contralateral ear. The reversal of direction took place after an interval of about ten seconds in which no nystagmus beats were recorded. Thirty-five seconds after the start of the irrigation caloric nystagmus was observed, which suppressed central nystagmus and lasted for about thirty seconds. Then suddenly this nystagmus stopped and within five seconds the original central nystagmus resumed.
All twelve rabbits showed the same results when irrigated with cold water.
In combination with central stimulation hot water irrigation gave the following results.
Ten seconds after the start of the central stimulation the ear at the side of the nystagmogenic centre stimulated was irrigated with hot water at 45° C. during twenty seconds. Thirty to forty seconds after the beginning of this irrigation caloric nystagmus was sometimes seen.
Six out of twelve rabbits reacted in this way. In three rabbits central nystagmus was only suppressed for thirty to forty seconds but no caloric nystagmus appeared. Three other rabbits did not show any reaction to irrigation with hot water at 45° C. (Fig. 10).
Thus only six rabbits reacted to hot water in the way the theory demands. Cold water at 25° C. probably is a stimulus of higher intensity than hot water at 45° C. for there is a greater departure from body temperature.

Summary

Caloric stimulation of a labyrinth could suppress central nystagmus completely if the theoretical direction of caloric nystagmus is opposite to that of central nystagmus.
In some cases caloric nystagmus could dominate central nystagmus. This was especially the case with a strong stimulus, e.g. cold water at 25° C.

CHAPTER IV

ON THE INFLUENCE OF OPTOKINETIC STIMULATION ON CENTRAL NYSTAGMUS

Introduction

Optokinetic nystagmus can be provoked by moving objects horizontally or vertically in front of the eyes.
The existence of a close relationship between optokinetic and vestibular nystagmus is clear (BÁRÁNY, 1921; VAN DEN BOORN, 1942; FISCHER and VEITS, 1928; MOWRER, 1935; HUIZINGA and VAN DER MEULEN, 1951; FUKUDA, HINOKI and TOKITA, 1957; and FUKUDA, 1959). We went into the problem of the influence of optokinetic stimulation upon centrally provoked nystagmus.

Experiments

Twelve rabbits were used in these experiments. Optokinetic nystagmus was produced by an apparatus almost identical to the one described by HUIZINGA and VAN DER MEULEN (1951) and FUKUDA (1959). A metal cylinder with a diameter of 90 cm and a height of 120 cm was used. Along the inner surface of the cylinder sixteen vertical black strips were placed on a white background. The black strips were 3 cm wide and separated by white strips of 15 cm width. The cylinder had a double floor, one moving with the cylinder and the other one smaller and stationary. On the fixed floor the rabbit sat comfortably with its body in a box, fixed, and only its head protruding. The interior of the cylinder was illuminated by diffuse light. The cylinder could be rotated in both directions by a motor which speed could be varied.

Results

In our tests we combined the rotation of the cylinder at various speeds with normal central stimulation. No influence of the optokinetic stimulus on normal central nystagmus could be observed. The combination of an optokinetic stimulus, strong enough to provoke optokinetic nystagmus, with a subliminal central stimulation provoked a central nystagmus with the rapid phase in the direction demanded by the central stimulus.

The direction of the optokinetic stimulus did not affect this direction at all.

We also investigated the combination of a near-threshold optokinetic stimulation with a near-threshold central stimulation. Each stimulation separately gave no more than one to four nystagmus beats during a period of sixty seconds stimulation. Both near-threshold stimulations simultaneously caused a clear nystagmus response. The direction of subliminal optokinetic stimulus proved to be unimportant since the direction of the provoked nystagmus was exclusively given by the type of the central stimulation. The frequency of the nystagmus response was much larger than the sum of the frequencies of the two single nystagmi separately (Fig. 11).

Summary

No influence of optokinetic stimulation was seen on normal central nystagmus. Subliminal optokinetic stimulation combined with subliminal central stimulation resulted in a central nystagmus with the rapid phase in the direction demanded by the central stimulus. The combination of a near-threshold optokinetic stimulation with a near-threshold central stimulation provoked a clear nystagmus response, again in the direction of the central stimulus. In this investigation the direction proper of the optokinetic stimulus was never of influence.

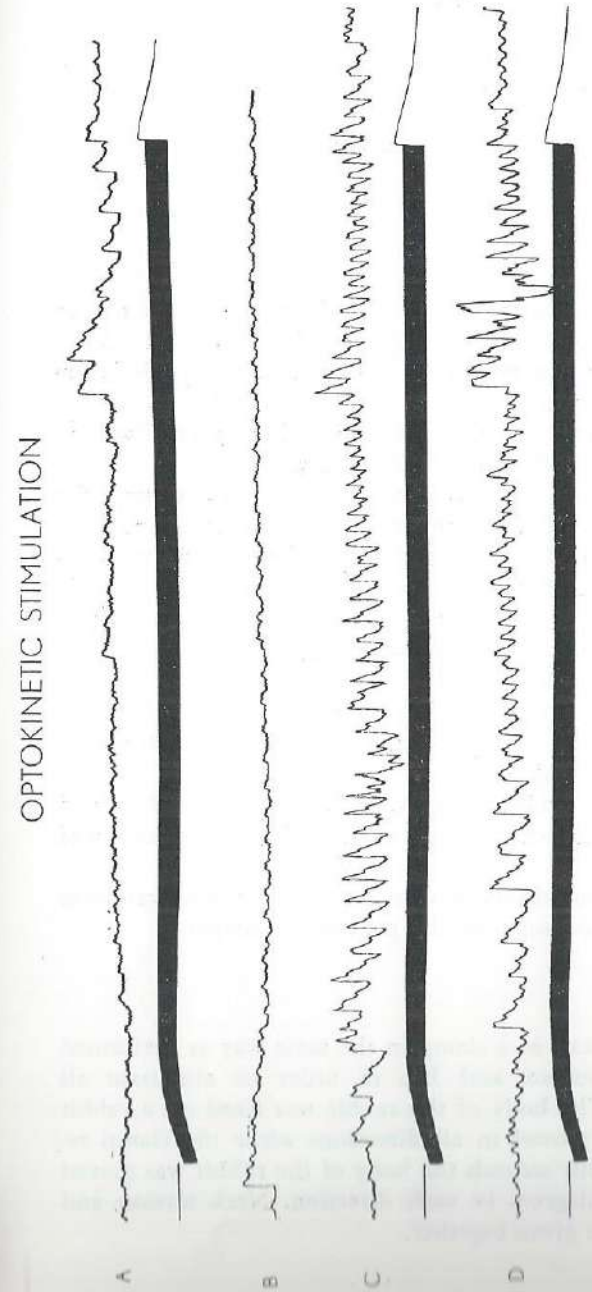


Fig. 11

The effect of subliminal optokinetic stimulation on subliminal central stimulation.

A subliminal central stimulation
B subliminal optokinetic stimulation
C combined subliminal stimulations (counter-clockwise)
D combined subliminal stimulations (clockwise)
Upper tracing: recording of eye movements.
Lower tracing: recording of stimulus (sixty seconds).

CHAPTER V

ON THE INFLUENCE OF IRRITATION OF THE CERVICAL NERVE ROOTS ON CENTRAL NYSTAGMUS

Introduction

In 1907 BÁRÁNY described a method to stimulate the cervical plexus by rotating a rabbit's body about a longitudinal axis while immobilizing its head. By fastening the rabbit's head in a clamp all labyrinthine reflexes were eliminated.
BIEMOND (1939, 1940, 1961) described patients suffering form vertigo presumably caused by irritation of the plexus cervicalis.
BIEMOND (1940) succeeded in provoking nystagmus by cutting the posterior roots of the second, third or fourth cervical nerves in rabbits.
PHILIPSZOON (1961) repeated this investigation and recorded the movements of the eyes electronystagmographically.
COHEN (1961) applied local anaesthetics to the nerves C_I, C_{II}, C_{III} and C_{IV} of monkeys and found defects in balance orientation and motor coordination as a result of this action.
MASPÉTIOL, CHARDIN and MILLARD (1954), RYAN and COPE (1955, 1959), GRAY (1956) and KUILMAN (1959) described vertigo in combination with cervical deviations in patients.
BOS (1962) found a positional nystagmus in judokas who had trained intensively for more than four years. He attributed this to irritation of the cervical nerve roots.
We were interested in the influence of nystagmus caused by irritation of the cervical nerve roots on centrally provoked nystagmus.

Experiments

We fixed the rabbit's head in a clamp in the same way as performed by BÁRÁNY and PHILIPSZOON and BOS in order to eliminate all labyrinthine reflexes. The body of the rabbit was fixed on a rabbit board which could be moved in all directions while the clamp remained immobile. In four seconds the body of the rabbit was moved over a distance of 90 degrees in each direction. Neck torsion and central stimulation were given together.

Results

We did not find any influence of neck torsion on central nystagmus. Neither addition nor subtraction was observed. If neck torsion was applied together with a subliminal central stimulation a central nystagmus pattern appeared. This pattern was not identical to the normal response to central stimulation.
It resembled the response to a low electrical stimulation, except that the latent phase remained short.
The investigation was done on twelve rabbits. All gave the same results (Fig. 12).

Summary

No influence of neck torsion on normal central nystagmus was observed. Neck torsion together with a subliminal central stimulation provoked a central nystagmus.
We could not explain the cause of the results described. It seemed that irritation of the cervical nerve roots, like optokinetic stimulation, made the nystagmogenic centre more sensitive to central stimulation.

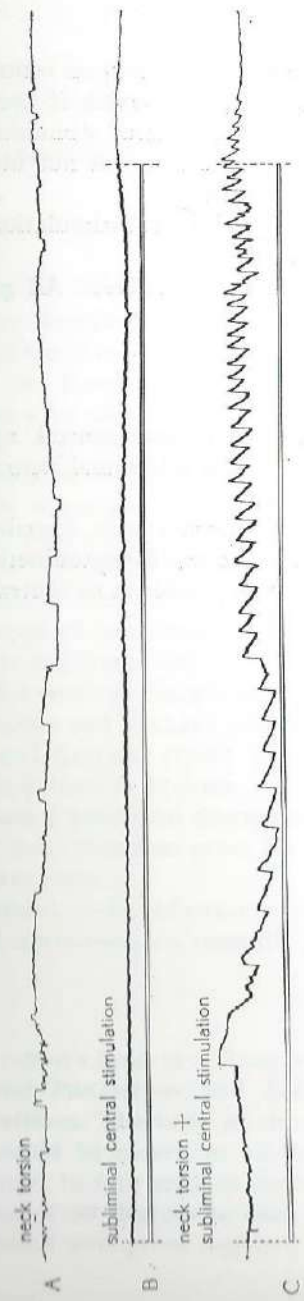


Fig. 12

The effect of neck torsion on subliminal central stimulation.
A nystagmus provoked by neck torsion
B subliminal central stimulation
C neck torsion combined with subliminal stimulation
Upper tracing: recording of eye movements.
Lower tracing: recording of stimulus.

SUMMARY AND CONCLUDING REMARKS

The investigation was concerned with the influences which can be exercized on nystagmus provoked by electrical stimulation of the mesodiencephalic nystagmogenic centre in rabbits.

The effect was examined of certain drugs, of the stimulation of the vestibular apparatus, of optokinetic stimulation and of the irritation of the cervical nerve roots.

The drugs *cinnarizine* and *chlorcyclizine* of which good results are known in the treatment of motion sickness, proved to be of no influence on centrally provoked nystagmus.

The drug *meclizine* – related to chlorcyclizine – proved to have a clear suppressive effect on central nystagmus.

The drug *hyoscine* – also effective in the prevention and the treatment of motion sickness – had no demonstrable effect on central nystagmus.

Ether and *alcohol* both suppressed central nystagmus. However, the suppression by ether anaesthesia was preceded and followed by a period of enhancement of central stimulation. This could possibly be explained by assuming that these drugs also influence other parts of the central nervous system.

The barbiturate *nembutal* when given in small quantities caused an enhancement of central nystagmus, but when given in large quantities it had a suppressive effect.

The influence of the vestibular apparatus on central nystagmus was examined by stimulating this organ together with the nystagmogenic centre.

By putting the rabbit in different positions in relation to the direction of the force of gravity the vestibular apparatus was stimulated by linear accelerations.

By rotating the animal it was subjected to angular accelerations.

We finally used caloric stimulation as well.

It was proved that many of these forms of stimulation of the vestibular apparatus could be of influence on centrally provoked nystagmus following the rule of addition and subtraction.

In this way central nystagmus appeared to be a useful indicator of a possible central component in the action of some drugs with a proved influence on central nystagmus, and also of some drugs without a proved action on vestibular nystagmus but effective in the treatment of motion sickness.

Subliminal optokinetic stimulation proved to be able to make the nystagmogenic centre more sensitive to electrical stimulation.

Irritation of the cervical nerve roots similarly had the effect of reduction of the stimulation for central nystagmus.

In both cases the direction of the resulting central nystagmus was solely determined by the electrical stimulation.

No effect of optokinetic or mechanical stimuli on the direction could be observed.

Since now a consistent pattern of action of drugs could be observed, further lines of research will be developed to elicit some of the basic mechanisms underlying the action of drugs on central nystagmus.

SAMENVATTING

Het onderzoek betreft de invloed die kan worden uitgeoefend op de nystagmus reactie opgewekt door electrische prikkeling van het in het mesodiencephalon gelegen nystagmogene centrum bij het konijn.

Nagegaan werden de invloeden van enige stoffen en geneesmiddelen, van prikkeling van het evenwichtsorgaan, van optokinetische prikkeling en van irritatie van de halszenuwplexus.

De geneesmiddelen *cinnarizine* en *chloorcyclizine,* die goed werkzaam zijn tegen bewegingsziekte, hebben geen invloed op de centraal opgewekte nystagmus.

Het aan chloorcyclizine verwante *meclizine* blijkt daarentegen een duidelijk onderdrukkende werking op de centrale nystagmus te hebben. Het effect op bewegingsziekte van meclizine behoeft dus niet alleen in het labyrint te worden gezocht.

Het eveneens bij bewegingsziekte werkzame *hyoscine* heeft geen aantoonbaar effect op de centrale nystagmus. Hyoscine heeft merkwaardigerwijs ook geen effect op de vestibulaire reacties.

Ether en *alcohol* onderdrukken beide de centrale nystagmus. De onderdrukking door ethernarcose wordt echter voorafgegaan en gevolgd door een periode van versterkte reactie op de centrale prikkeling. Mogelijk kan dit verklaard worden door een werking van deze stoffen op andere delen van het centraal zenuwstelsel.

Het barbituraat *nembutal* heeft in lage dosering een versterkende werking op de centrale nystagmus, in hogere dosering een onderdrukkend effect.

De invloed van het evenwichtsorgaan op de centrale nystagmus werd nagegaan door dit orgaan te prikkelen tegelijk met het stimuleren van het nystagmogene centrum.

De prikkeling geschiedde door het konijn in verschillende houdingen ten opzichte van de richting van de zwaartekracht te plaatsen, door rechtlijnige en hoekversnellingen aan te brengen en door calorisch te prikkelen.

De centraal opgewekte nystagmus blijkt door vele van deze vormen van labyrintprikkeling beïnvloed te kunnen worden en wel volgens optelling en aftrekking.

Omdat deze wisselwerking zo opmerkelijk was kwam de centrale nystagmus ons als een bruikbaar middel voor om een eventuele centrale component in de werking van enkele geneesmiddelen met een bewezen invloed op de vestibulaire nystagmus na te gaan, en omgekeerd.

De subliminale optokinetische prikkeling blijkt in staat te zijn het nystagmogene centrum gevoeliger te maken voor electrische stimulatie.

De irritatie van de halszenuwplexus heeft eveneens op de centrale stimulatie het effect van verlaging van de prikkeldrempel.

In beide gevallen wordt de richting van de nystagmus niet door de extra prikkel beïnvloed; deze blijft uitsluitend bepaald door de centrale electrische prikkel.

RÉSUMÉ

L'examen concerne l'influence qui peut être exercée sur la réaction du nystagmus provoquée par excitation électrique du centre nystagmogène situé dans le mesodiencephalon chez le lapin.

Nous avons examiné les influences de quelques matières et médicaments, de stimulation de l'organe de l'équilibre et de stimulation optocinétique et d'irritation des nerfs cervicaux.

Les médicaments *cinnarizine* et *chlorcyclizine,* très efficaces contre la maladie de mouvement, n'ont aucune influence au nystagmus provoqué centralement.

La *méclizine* associée à la chlorcyclizine se montre avoir un effet clairement supprimant au nystagmus central. Ce n'est donc pas exclusivement dans le labyrinthe que l'on doit chercher l'effet de méclizine sur la maladie de mouvement.

La *hyoscine,* également efficace contre la maladie de mouvement, n'a pas d'effet démontrable sur le nystagmus central.

L'éther ainsi que *l'alcool* suppriment le nystagmus central. Cependant la suppression par l'anésthesie au moyen d'éther est précédée et suivie d'une période de réaction plus intense sur la stimulation centrale. Il est possible que l'on puisse expliquer ce phénomène par un effet de ces médicaments sur différentes parties du système cérébro-spinal.

En petite dose le barbiturique *nembutal* a un effet fortifiant, en plus grande dose un effet supprimant au nystagmus central.

En stimulant à la fois l'organe de l'équilibre et le centre nystagmogène nous avons examiné l'influence de cet organe au nystagmus central. Par cette expérience nous avons pu constater un changement possible du nystagmus central. L'organe de l'équilibre fut stimulé en plaçant le lapin dans diverses positions par rapport à la direction de la force de gravité, par accélérations linéaires et angulaires et par excitation thermique. Il se trouve que par beaucoup de ces formes de stimulation des labyrinthes le nystagmus provoqué centralement peut être influencé suivant la règle d'addition et soustraction.

A cause du fait que cette interaction était si remarquable il nous semblait que le nystagmus central était un moyen praticable à examiner l'éventuelle composante centrale dans l'effet de quelques médicaments ayant une influence prouvée au nystagmus vestibulaire.

La stimulation optocinétique subliminale se trouve être à même de rendre plus sensible à l'excitation électrique le centre nystagmogène. L'irritation des nerfs cervicaux montre également l'effet de diminution du seuil d'irritation sur la stimulation centrale.

Dans les deux cas la direction du nystagmus n'est pas influencée par la stimulation supplémentaire; elle reste exclusivement définie par l'excitation électrique centrale.

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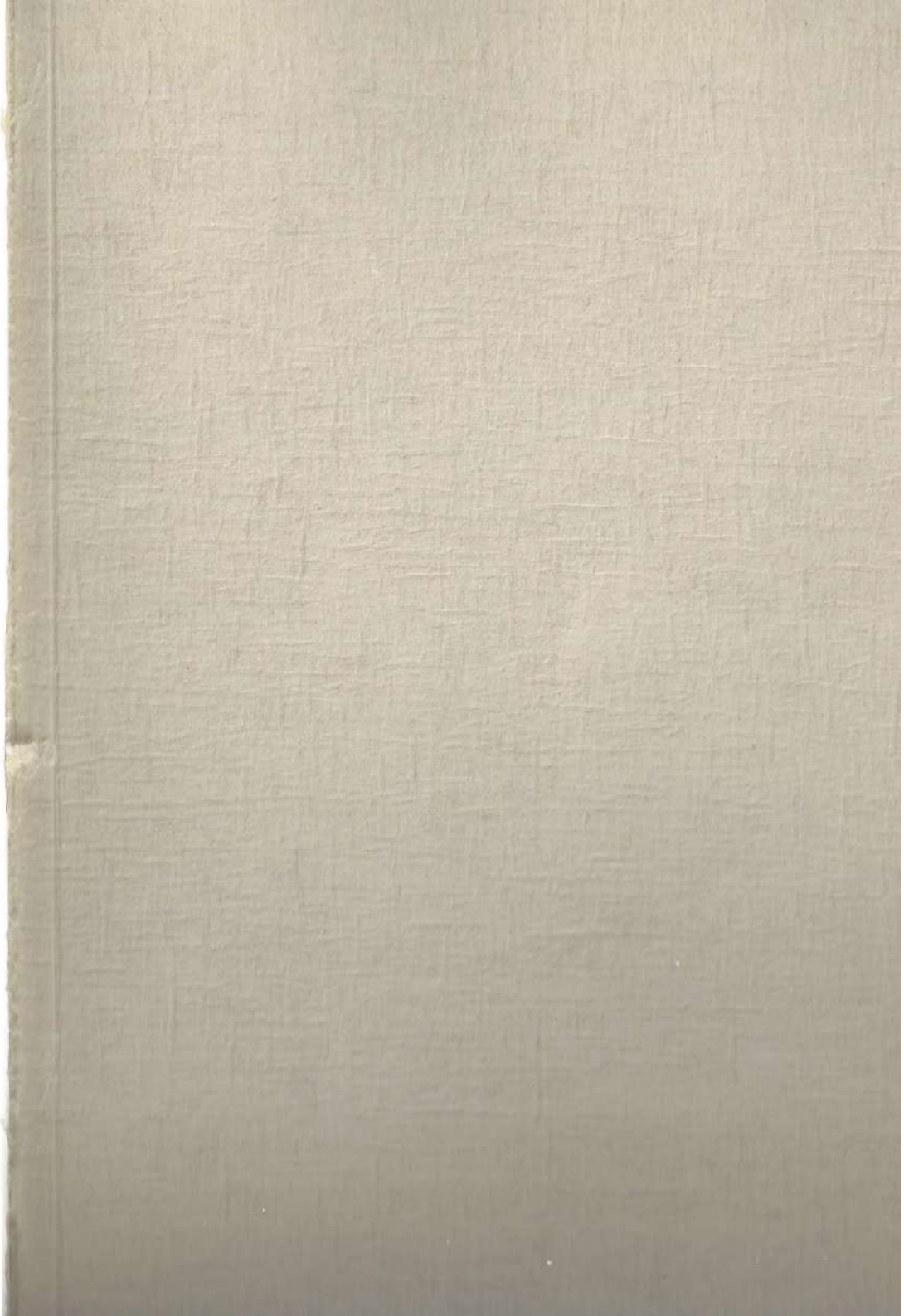
N.V. DRUKKERIJ VAN WIJK - OOSTZAAN



STELLINGEN

1

Aan alle nederlandse militairen had bij repatriëring uit voormalig Nederlands Nieuw Guinea een mijnwormkuur moeten worden gegeven.

2

De benaming „tropische kindergeneeskunde" suggereert het bestaan op medisch wetenschappelijk gebied van problemen die in werkelijkheid op sociaal economisch terrein gezocht moeten worden.

3

Het is waarschijnlijk dat de progressieve multifocale leuko-encephalopathie op een virusinfectie berust.

4

Het optreden van verschijnselen van een dialysedesequilibrium tijdens extra-corporale hemodialyse bij patiënten met acute nierinsufficiëntie is het gevolg van te late toepassing dezer behandeling of(en) een onjuiste samenstelling van de dialysevloeistof.

5

Het is onjuist de in de nieuwe literatuur met behulp van het elektronenmicroscopische onderzoek beschreven ruimte tussen het endotheel van de sinusoïden en de levercellen als de „ruimte van Disse" aan te duiden.

6

Bij acute koolmonoxydevergiftiging treedt een differentiële depolarisatie van neuronen op in het centrale zenuwstelsel, hetgeen de basis kan vormen voor een mogelijk latere degeneratie.

7

Inhibitoire en excitatoire synaptische potentialen ontwikkelen zich op verschillende tijdstippen tijdens de postnatale groei van de hersenschors bij het konijn.

8

Het substraat bij tonsillectomie bij personen ouder dan vijfendertig jaar dient pathologisch-anatomisch onderzocht te worden.

9

De maatschappelijke isolering van het overheidsapparaat, zoals in Nederland geschiedt door de concentratie in 's-Gravenhage, is nadelig voor een inventief overheidsbeleid.

10

In de ontwikkelingsplannen van de achtergebleven gebieden wordt de betekenis van de ontwikkeling van de landbouw voor de algehele economische ontplooiing veelal miskend.

W. J. Oosterveld

19 december 1963