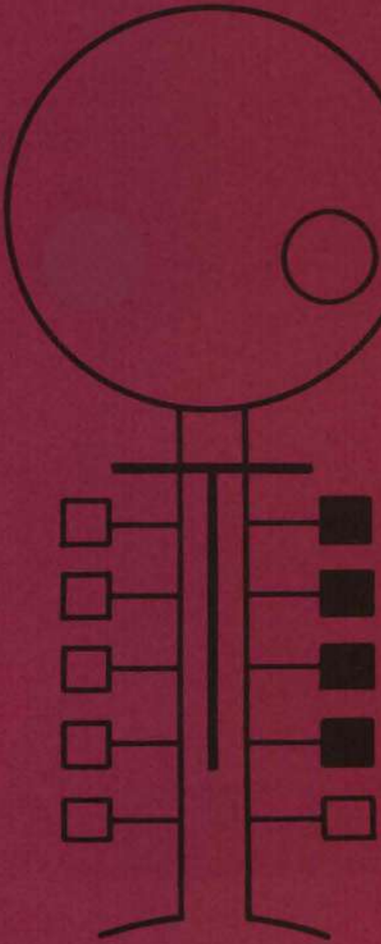
CERVICAL PROPRIOCEPTIVE NYSTAGMUS

ITS CENTRAL PATHWAYS



P.T.V.M. DE JONG

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ACADEMISCH PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
IN DE GENEESKUNDE AAN DE UNIVERSITEIT
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MAGNIFICUS DR. A. DE FROE, HOOGLERAAR IN
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door

Paulus Theodorus Vianney Maria de Jong

1973

Drukkerij Bevrijding Amsterdam

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

Aan Marij, Bouke en Ype

STELLINGEN

I

Het potentiaalverschil in rust tussen de voor- en achterzijde van het oog berust voornamelijk op niet in de retina gelegen factoren.

Electroenceph clin Neurophysiol 1965, 19, 291

II

Het is onjuist te stellen dat evenwichtsstoornissen na een nektrauma alleen dán op organische afwijkingen berusten wanneer nystagmus aanwezig is.

III

De betekenis van de varicocèle voor de mannelijke fertiliteit wordt nog steeds onvoldoende onderkend. Vindt men bij een keuring deze afwijking, dan dient men, zo een profylactische behandeling al niet geadviseerd wordt, de keurling van het bestaan van de afwijking en zijn mogelijke konsekwenties op de hoogte te brengen.

IV

Wanneer bij glaucoma simplex een verhoogde oogdruk tot aantoonbare afwijkingen heeft geleid, is in principe de indicatie tot operatieve drukverlaging aanwezig.

V

Om de waarheid beter te benaderen moeten de Dolle Mina's hun lijfspreuk wijzigen van 'Baas in eigen Buik' tot 'Baas in eigen Fuik'.

VI

Na een volledig uitgevoerd gezichtsveldonderzoek is het maken van een donkeradaptatiecurve als detectiemethode overbodig.

VII

In wetenschappelijke publicaties is het gebruik van pluralis majestatis of pluralis modestiae niet goed te keuren.

N Engl J Med 1971, 285, 1144

VIII

De mogelijke samenhang tussen het ontstaan van hepatocellulair carcinoom en het gebruik van androgene anabole steroiden maant tot groter voorzichtigheid bij het toedienen van deze stoffen, zeker wanneer dit op toch al dubieuze medische indicatie bij sportlieden plaats vindt.

Lancet 1972, II, 1273

IX

Het bestaan van de ziekte van Kugelberg en Welander sluit niet uit dat een deel der gevallen van spinale spieratrofie het gevolg is van slow-virus infecties.

X

Het willekeurig gebruik door de nieuwsmedia van academische titulatuur waarmee men tracht aan iemands woorden meer gewicht te geven, moet afgeschaft worden. Zo men het vermelden van iemands academische graad nodig vindt, dient de studierichting waarin deze behaald is erbij vermeld te worden.

XI

De door Akino, Ake en Arai geuitte suggestie dat lecithine in de long voornamelijk gevormd wordt door een transacylering tussen twee moleculen lysolecithine is zeer waarschijnlijk onjuist.

Biochim Biophys Acta 1971, 248, 274

XII

Eliminatie door middel van selectieve abortus van vrouwelijke individuen die zeker heterozygoot zijn voor een mutant X-chromosomaal recessief allel is medisch gezien toelaatbaar.

PTVM de Jong
Amsterdam, 8 februari 1973.

Dit proefschrift werd bewerkt in het fysiologisch laboratorium van de Keel- Neus- en Oorheelkundige Kliniek (hoofd Prof. Dr. L.B.W.Jongkees) van het Academisch Ziekenhuis van de Universiteit van Amsterdam (Wilhelmina Gasthuis).

VOORWOORD

Mijn vrouw wil ik bedanken voor het feit dat het aantal van haar opmerkingen hierover bijna omgekeerd evenredig was met de hoeveelheid tijd die ik aan haar en de kinderen ontnomen heb.

Voor de steun en hulp die ik van mijn ouders in de voorgaande jaren gekregen heb, ben ik hen erg dankbaar.

Naast de reeds vaak bezongen kwaliteiten van mijn promotor, Prof. Dr. L.B.W. Jongkees, zijn er mij twee in het bijzonder opgevallen: zijn kijk erop wanneer men een promovendus rustig zijn gang moet laten gaan en wanneer men hem aan moet sporen, en de gave om in de meest drukke tijden nog altijd ruimte te vinden voor het bespreken van experimenten en het snel en nauwgezet corrigeren van het op papier gestelde. Onder zijn leiding hoop ik deze serie proeven te mogen afronden.

Mijn broer Vianney, de hierna vaak aangehaalde J. de Jong, heeft mij in de K.N.O. kliniek geïntroduceerd, de proefopstelling besproken, de eerste operaties voorgedaan, mijn schrijven verbeterd en tenslotte vertaald. Als mijn dank de hoeveelheid tijd en aandacht die hij aan dit alles besteed heeft evenaart dan weet hij het beste hoe groot deze is.

Conservator van de goede sfeer op het fysiologisch laboratorium is de Heer W.D. van der Laarse die op de meeste problemen liggend tussen verstopte vloeistofstraalschrijvers en het superponeren van nystagmusslagen op een oogdeviatiecurve altijd raad wist.

Prof. Dr. P.E. Voorhoeve gaf vele nuttige aanwijzingen ter verbetering van de tekst en behoedde mij voor het schrijven van enkele onwaarheden.

Prof. Dr. Bernard Cohen kindly reviewed the manuscript and consented to referring to some of his articles, not yet published at that time.

Het hoofd van het fysiologisch laboratorium, Dr. W.J. Oosterveld, heeft regelmatig het manuscript in zijn verschillende stadia becommentarieerd.

Mr. D. Goodman wist, zelfs toen ik voor de zesde keer het Engels ter correctie aan hem voorlegde, zijn wanhoop nog te verbergen.

In de apotheek was de Heer P.E. Kamp menigmaal te vinden voor het oplossen van plotseling oprijzende problemen en met zijn zuiverheidsbepalingen van de adrenalineoplossingen wist hij in ieder geval één punt van onzekerheid weg te nemen.

Prof. Dr. J. Bethlem was zo vriendelijk de microscopische preparaten te laten vervaardigen en de cerebellectomiecoupes te bekijken.

De dames Ott, la Bastide en Coenen hebben tot op het laatste ogenblik nog fouten uit de drukproeven weten te halen nadat zij door het herhaaldelijk typen van het manuscript eigenlijk al lang woordblind hadden moeten zijn.

De Heren Bakker en de Ruyter waren altijd bereid door hen met zorg vervaardigde schemata en foto's te veranderen en bleven zelfs vriendelijk toen de veranderingen weer veranderd moesten worden.

De Heren Varenhorst en Zwaaf leerden mij de omgangsregels met konijnen en katten en pasten deze ook daarna in het laboratorium nog steeds voor mij toe.

Aan allen hier genoemd mijn hartelijke dank, evenals aan mijn collegae van de Koninklijke Marine welke mij het mogelijk maakten tijdens het vervullen van mijn dienstplicht aan mijn experimenten te werken.

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Chapter VI
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Chapter VII
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General introduction

The problem which is at the base of four series of experiments in this thesis is: which central pathways are involved in the production of nystagmus that is induced by blocking the cervical dorsal roots? The fifth series of experiments answers the question whether epinephrine injection at the site of the cervical posterior roots and the vertebral neurovascular bundles causes nystagmus. The structure of the thesis reflects my original plan to publish the results in five articles.

The second chapter has a short historical survey, and a summary of the results obtained by previous investigators of cervical nystagmus. Then some concepts and methods that are used in all subsequent parts of this thesis are introduced.

All subsequent chapters contain an introduction and paragraphs on materials and methods, results and discussion, and a conclusion.

The third chapter deals with cervical nystagmus elicited in rabbits after unilateral labyrinthectomy and the subsequent production of cervical nystagmus in the same animals after surgical interruption of posterior roots on one side of the neck.

In the fourth chapter the consequences of cerebellectomy for cervical nystagmus in the rabbit are discussed.

The fifth chapter contains a description of cervical nystagmus in the cat and a discussion of the significance of the posterior spinal columns for the occurence of this kind of nystagmus.

The sixth chapter describes experiments in cats similar to those performed on rabbits in chapter III. In addition after blocking of the remaining neck receptors by a local anesthetic ocular movements were studied after surgical destruction of one labyrinth, after unilateral deafferentation of the upper three cervical segments, and after complete mid-line splitting of the cord from the obex to the C4 segment.

The effects of epinephrine injections into the deep upper cervical tissues on extraocular movements in the cat and the rabbit are described in chapter VII.

Brief historical survey

An extensive review of the clinical and experimental literature on nystagmus caused by alterations in the spinal afferent information is given in the thesis of J. de Jong (1967) and the article of Biemond and J. de Jong (1969).

In 1939 Biemond described three patients who had symptoms of cervico-brachial neuritis or radiculitis and of vertigo and nystagmus as long as their heads were kept in a specific position. These clinical observations led to experiments in which the cervical dorsal roots on one side of the neck in rabbits were cut. These experimental results and a few more patients with vertigo as a symptom of cervical disease were described in three publications (Biemond, 1940a; 1940b; 1961).

J. de Jong (1967) confirmed Biemond's experimental results and demonstrated that cervical nystagmus arises by elimination of somatosensory afferent fibres. He emphasized the part played by afferents from the intervertebral joint receptors and from the deep neck ligaments. Briefly, his experiments were as follows:

When the deep paravertebral neck tissues were infiltrated with procaine in each of ten rabbits, positional nystagmus was produced. This did not happen after intragluteal injection of procaine in the same dosage. Injections of physiological saline into the neck did not cause nystagmus in eight out of ten rabbits.

In the remaining two animals a few nystagmus beats were recorded upon positional changes during the first five minutes that followed the injection.

Two rabbits were examined some weeks after unilateral deafferentation of the upper neck.

Administration of local anesthetic to either side of the neck caused positional nystagmus. However, after bilateral denervation of the afferent fibres of the segments C1 through C4, three rabbits with intact vertebral neurovascular bundles did not show nystagmus after infiltration of the cervical tissues with procaine. Local anesthesia of the neck in three animals caused positional nystagmus after bilateral destruction of the vertebral neurovascular bundles, while no nystagmus occurred after control injections into the gluteal musculature.

In order to identify the cervical receptors involved in the genesis of nystagmus, J. de Jong did four more series of experiments: in a series of five rabbits unilateral anesthesia of the skin and subcutis as well as surgical denervation of these tissues did not produce nystagmus. Positional nystagmus did occur, however, after detaching neck muscles from their insertion on the occiput and the arch of the vertebra C1. The nystagmus in the last experiment could have been produced by changes in information from either muscle afferents or joint and ligament receptors.

In a further series of experiments, therefore, the joint and deep ligament receptors were left intact while the nerves to all other neck tissues were cut. Subsequent unilateral section of the dorsal roots C1 and C2 produced transient positional nystagmus. After disappearance of this nystagmus, cutting of the posterior roots C1 and C2 on the opposite side was followed again by positional nystagmus.

Finally, he demonstrated that blocking of neck receptors did not elicit positional nystagmus in four rabbits that had been subjected to bilateral labyrinthectomy.

The conclusions drawn from these investigations were:

1. Injections of procaine into the neck bring about nystagmus by local action of the anesthetic.
2. Interruption of somatic afferent fibres is necessary and sufficient in order to produce neck nystagmus.
3. Elimination of signals from the deep ligaments and the intervertebral joints of the neck is the predominant cause of cervical nystagmus but a minor contribution of superficial ligament and muscle receptors cannot be excluded with certainty.
4. Procaine injections in the neck will only produce nystagmus in the presence of at least one functioning labyrinth.

On account of the third conclusion the term proprioceptive nystagmus is introduced. These investigations led to a number of hypotheses that, as far as they are relevant to the present study, will be discussed further on.

General materials, methods, and definitions

Rabbits of 1500 to 2000 g were used in the experiments of chapters III, IV en VII. Cats were used for the experiments described in chapters V, VI and VII, and weighed 2000 to 3500 g.

The animals were tied to a board in the prone position, with the head fixed in a clamp so that the naso-occipital axis was in the sagittal plane. Movements between head and body were made impossible by fixing the trunk to the board with bandages. The plane of occlusion of the jaws made an angle of about 40° with the horizontal, while the bitemporal axis was parallel to the horizontal plane. Ocular movements were studied in the prone and in both right and left lateral positions. Changes of position did not cause movements of the body with respect to the head.

Vertical and horizontal eye movements were recorded by electronystagmography (ENG) with the aid of subcutaneous needle electrodes. The nystagmograph, an AC-coupled amplifier with a time constant of 5 sec and a cut-off frequency of 15 cycles per second, was a ELEMA EM 81 recorder and preamplifier EMT 12 (Jongkees and Philipszoon, 1964). In rabbits the eyes were always observed while nystagmus was being recorded. Ocular movements of cats, however, had to be studied in a dark and relatively sound-proof room, as it was very difficult to distinguish on the ENG between spontaneous eye movements and nystagmus beats without these precautions.

Labyrinthectomies were performed after the technique of de Kleyn (1912). In rabbits neck receptors were blocked by injecting 1 to 4 ml of a 2 or 3 per cent solution of procaine hydrochloride (HCl) in the following way:

With the index finger of the left hand the cranial tip of the second cervical spinous process was localized and, at the level of this landmark, the needle was inserted dorso-ventrally until it touched the arch of the vertebra C1 about half a centimetre from the mid-line. If the needle tip was not in the lumen of a blood vessel, the procaine solution, pre-warmed to 37° C, was injected. Unless otherwise stated, by 'injections' or 'procaine injections' we mean injections of procaine HCl 2 per cent. The caudal end of the second cervical spinous process also served as a guide to deposit the local anesthetic in the direct vicinity of the arch C3. In the cat procaine was injected against the occipital bone instead of against the vertebral arch C1.

In the majority of animals procaine injections in the neck often did not lead to nystagmus; these 'unsuccessful' trials served as controls. For those few animals in which every injection resulted in nystagmus, intragluteal procaine injections, of an amount equal to the highest dose used in the neck, served as a control. In each trial procaine or epinephrine injections in the neck were always given unilaterally.

Positional changes were always accompanied by ocular movements and often also by a few nystagmus beats, both in intact animals and in animals that had been injected with procaine.

In most cases the nystagmus after blocking of neck receptors was a postural nystagmus. Occasionally, there was also nystagmus while the animal was in the prone position. In the initial period following a neck injection nystagmus was recorded in the prone position only on rare occasions. Some time later the eye movements would assume the characteristics of a positional nystagmus which, then, changed into a positioning nystagmus before disappearing altogether. A systematic description in terms of 'nystagmus', 'positional nystagmus', and 'positioning nystagmus' does not seem necessary here, since these terms have been explained extensively by Biemond and J. de Jong (1969). Therefore, the word nystagmus is used here without further specifications in most instances.

There was a time-lag of at least twenty-four hours between two subsequent injections in the same animal.

NECK NYSTAGMUS AND A CERVICAL EQUIVALENT OF BECHTEREW NYSTAGMUS IN RABBITS WITH ONE FUNCTIONING LABYRINTH

Introduction

It has been established that cervical positional nystagmus cannot be elicited in rabbits after denervation of the afferent fibres of the upper four cervical segments or following destruction of both labyrinths (Biemond and J. de Jong, 1969). Besides this a deliberate attempt by Magnus (1924) to produce rolling movements of the body about its longitudinal axis by labyrinthectomy after cutting the upper three pairs of cervical dorsal roots was unsuccessful.

This study was intended to provide further analysis of the interaction between labytinthine and neck-reflexes, with special emphasis on nystagmus. After recovery from the acute effects of the removal of one labyrinth, rabbits in the present study have been successively submitted to:

1. blocking of neck receptors with the aid of a local anesthetic
2. surgical deafferentation of one side of the neck
3. blocking of the remaining cervical receptors by local anesthesia

Materials and methods

On the rabbits described in chapter II a labyrinthectomy was performed following the technique of de Kleyn (1912). The nystagmus resulting from this operation disappeared in the course of eight to twelve weeks. Neck receptors were blocked with the aid of 1.5 to 4 ml of procaine 2 or 3 per cent.

In the beginning rabbits received 4 ml of a 3 per cent procaine HCl solution. Because this dosage was sometimes toxic, the amount was reduced to 1.5 to 2 ml of a 2 per cent solution in the subsequent experiments. Through experience this was found to be the most appropiate dosage.

Unilateral section of the dorsal roots C1 and C2 as well as of the nerves C 3 and C4 was performed under local anesthesia, via a mid-line approach. The first two cervical dorsal roots were cauterized by means of a sharp pointed soldering iron, just proximal to the intervertebral ganglion. All branches of the third and fourth cervical nerves were cauterized as close to the spine as possible, whereby close attention was paid to those running at the ventral side of the vertebrae. Destruction of the nerves C3 and C4 was preferred to laminectomy with section of the dorsal roots, as previous experience had shown that rabbits, nearly invariably, develop transverse lesions during the first week after a cervical laminectomy.

Results

Unilateral blocking of neck receptors was performed 19 times in 5 rabbits with one intact labyrinth. In 18 cases this resulted in positional nystagmus with a duration varying from 3 to 147 minutes.

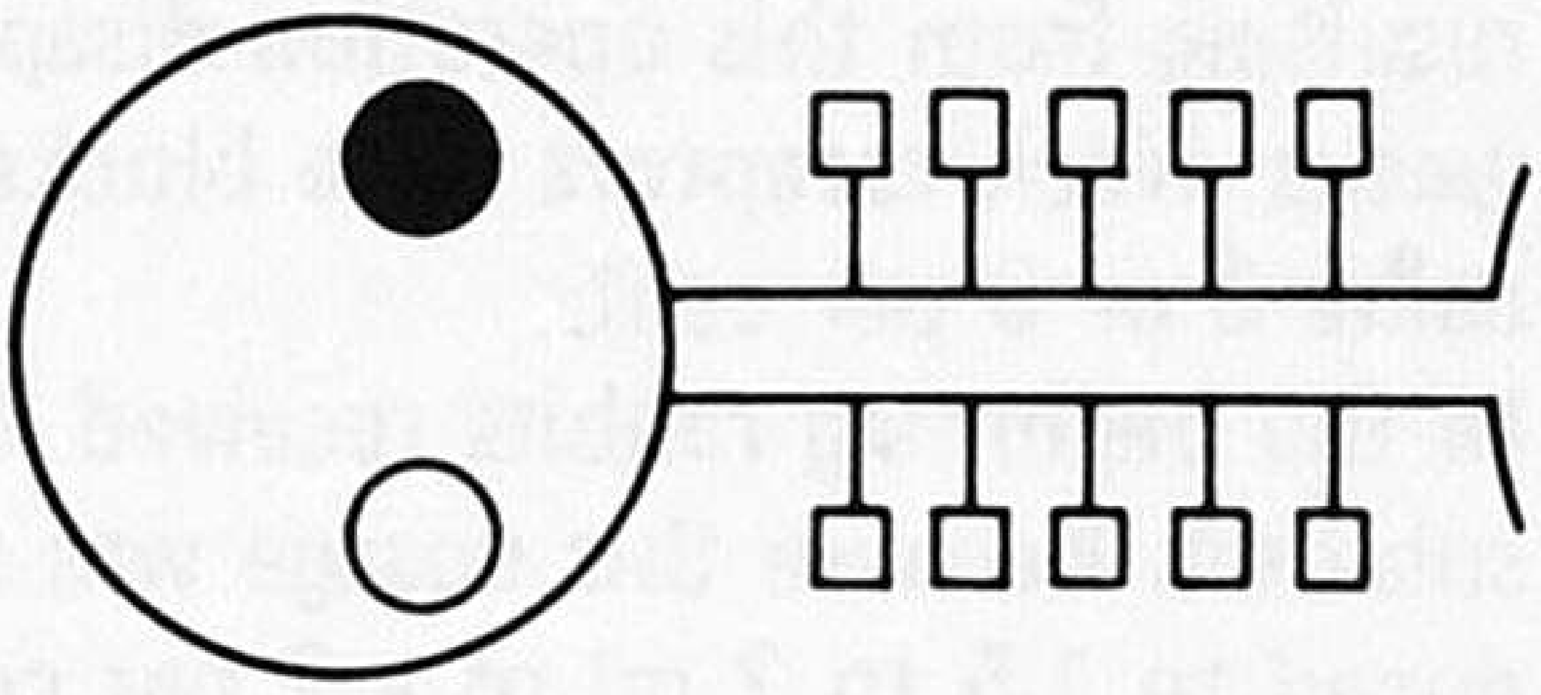
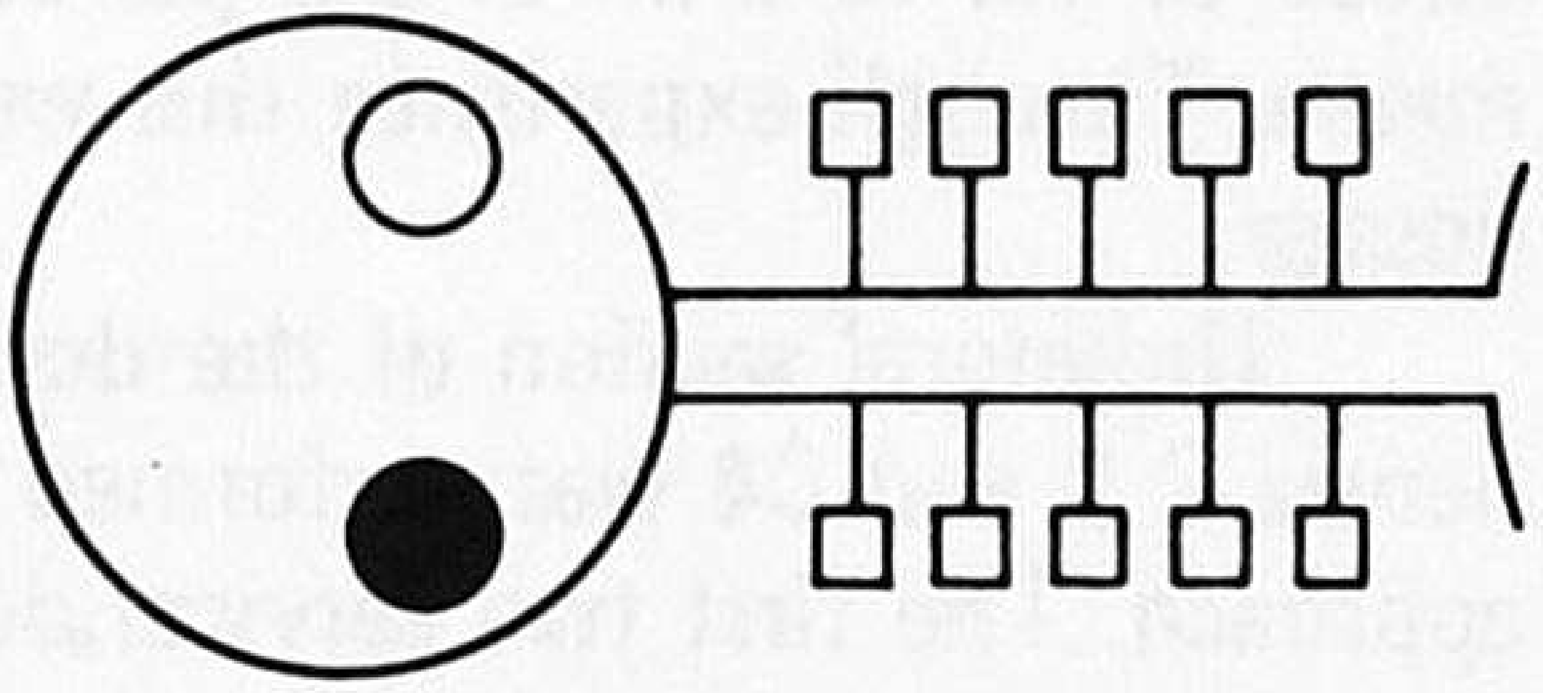
The nystagmus was equally strong in both lateral positions in 4 instances. It was stronger and lasted longer when the intact labyrinth was down after 11 injections, and in the 3 remaining trials intensity and duration of the nystagmus were largest when the intact labyrinth was up (Table 1).

The direction of the nystagmus was variable and changed in the course of 9 of the experiments. In the other 9 trials the direction was constant; there was neither any correlation between the direction and the side on which the labyrinthectomy had been performed, nor between the direction and the side on which the dorsal roots had been blocked. The direction of nystagmus also varied from trial to trial for individual rabbits.

Table 1

UNILATERAL LABYRINTHECTOMY IN RABBITS

Lateral position with more pronounced nystagmus after procaine injection in the neck of 5 rabbits

no preference	4	
intact labyrinth down	11	
intact labyrinth up	3	
no nystagmus	1	
Total number of experiments:	19	

Legend: white circle : intact labyrinth
black circle : destroyed labyrinth

white square : intact cervical nerve or dorsal root
black square : destroyed cervical nerve or dorsal root

Unilateral denervation, i.e. destruction of the first two cervical dorsal roots, and of the third and fourth cervical nerves was performed in 5 rabbits, two times on the opposite and three times on the same side as the labyrinthectomy. Immediately after surgery the animals with ipsilateral neck denervation exhibited rolling about the longitudinal axis of the body. The rolling movements started with a fall to the operated side and lasted for only a few minutes. Thereafter, the animals walked in circles towards the operated side, while the hind limbs sometimes remained standing on the same spot. When laid on their flank with the cut roots and nerves down, they kept themselves immobile. However, if held on their flank with the operated side up, they immediately turned their head, front feet and part of the trunk, hind limbs and pelvic girdle to the standing position as soon as these parts were released. One rabbit kept turning itself over towards the operated side. The customary rotation of the head of about 90° after labyrinthectomy decreased in these 3 rabbits to 60° - 45° in 4 to 6 weeks.

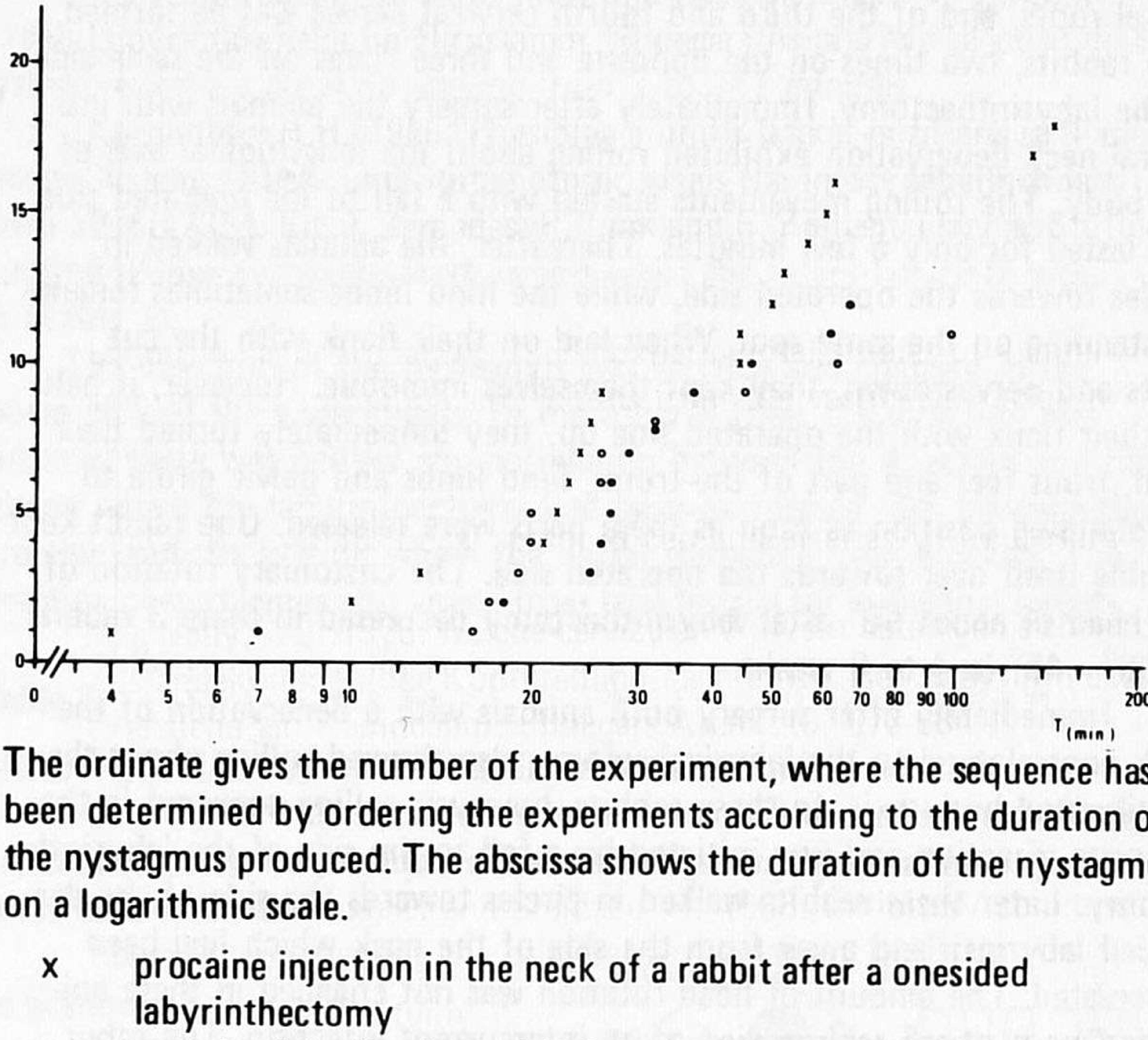
Immediately after surgery both animals with a denervation of the neck contralateral to the labyrinthectomy also showed rolling about the longitudinal body axis. In these rabbits, however, rolling occurred in the opposite direction and was initiated by a fall to the side of the labyrinthectomy. Later these rabbits walked in circles towards the side of the destroyed labyrinth and away from the side of the neck which had been denervated. The amount of head rotation was not changed in these animals. One of the 5 rabbits died of an intercurrent infection. The other 4 animals had spontaneous nystagmus during a prolonged period of 31 to 44 days after the neck operation.

Subsequently, the remaining upper cervical receptors were blocked with procaine HCl 26 times in these rabbits. This started a positional nystagmus in 23 instances, with a duration of 7 to 90 minutes. The duration of nystagmus in the individual trials is shown in fig. 1.

Nystagmus was never more pronounced in the lateral position with the intact labyrinth facing up. After 9 injections a stronger nystagmus was noted when the side of the intact labyrinth was down, while in the remaining 14 instances the nystagmus occurred without preference for either lateral position (Table 2). The direction of the nystagmus was, again, not constant and could change in the course of one experiment.

Control injections of procaine into the gluteal musculature did not produce nystagmus.

Figure 1



The ordinate gives the number of the experiment, where the sequence has been determined by ordering the experiments according to the duration of the nystagmus produced. The abscissa shows the duration of the nystagmus on a logarithmic scale.

x	procaine injection in the neck of a rabbit after a onesided labyrinthectomy
o	procaine injection in a rabbit's neck after a onesided labyrinthectomy and a neck deafferentation on the same side
●	as o but with a neck deafferentation opposite to the side of the labyrinthectomy

Summary

1. Five rabbits had a unilateral labyrinthectomy.
2. The ensuing spontaneous nystagmus disappeared after 8 to 12 weeks.
3. After this, blocking of the neck receptors by way of procaine injections in the neck caused nystagmus in 18 out of 19 experiments.
4. In 4 of these rabbits the neck was thereafter denervated on one side.
5. Again, a spontaneous nystagmus arose, disappearing after 31 to 44 days.
6. Blocking of the remaining cervical dorsal roots and nerves by procaine injection started a nystagmus in 23 out of 26 experiments.

Discussion

The most striking result of this investigation is that interference with neck receptors in rabbits who have recovered from the acute sequelae of unilateral labyrinthectomy produces disturbances that are mainly determined by the predominance of the intact labyrinth.

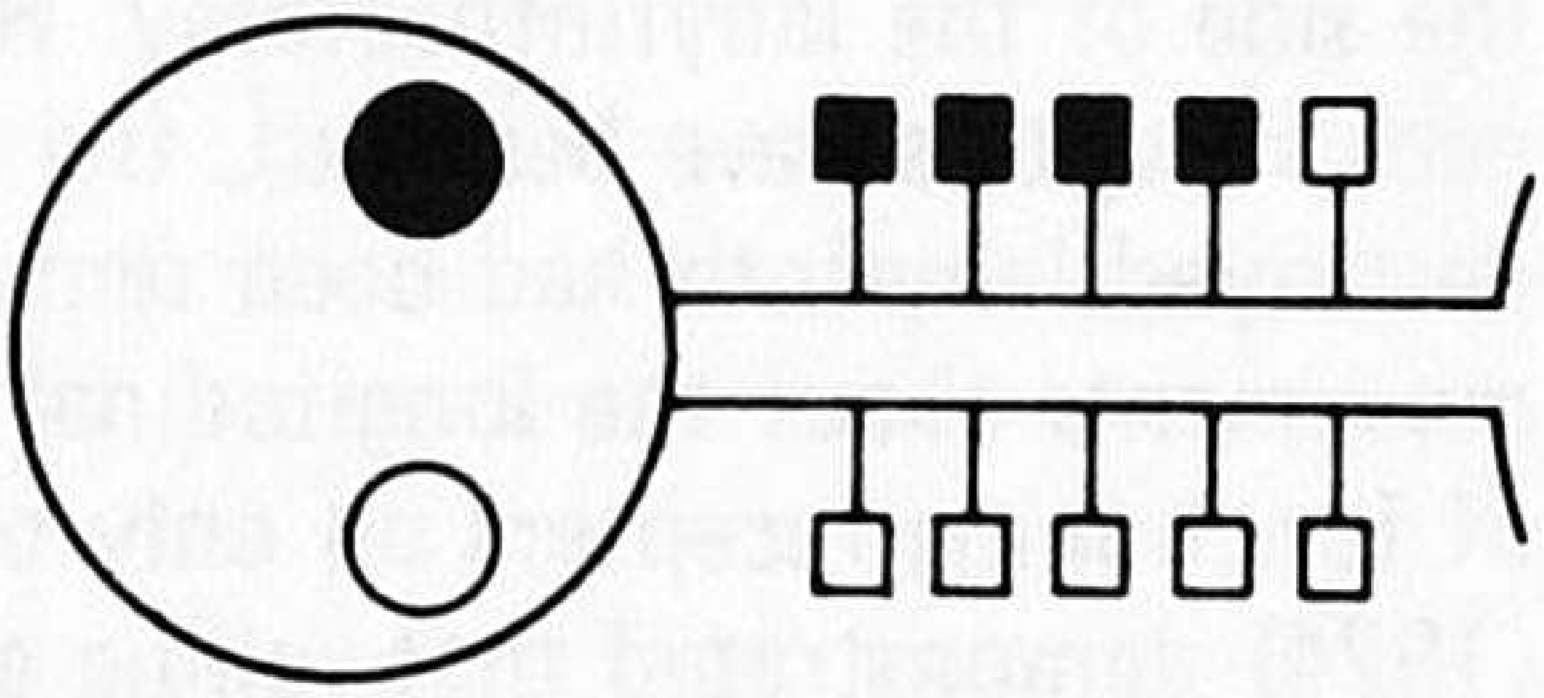
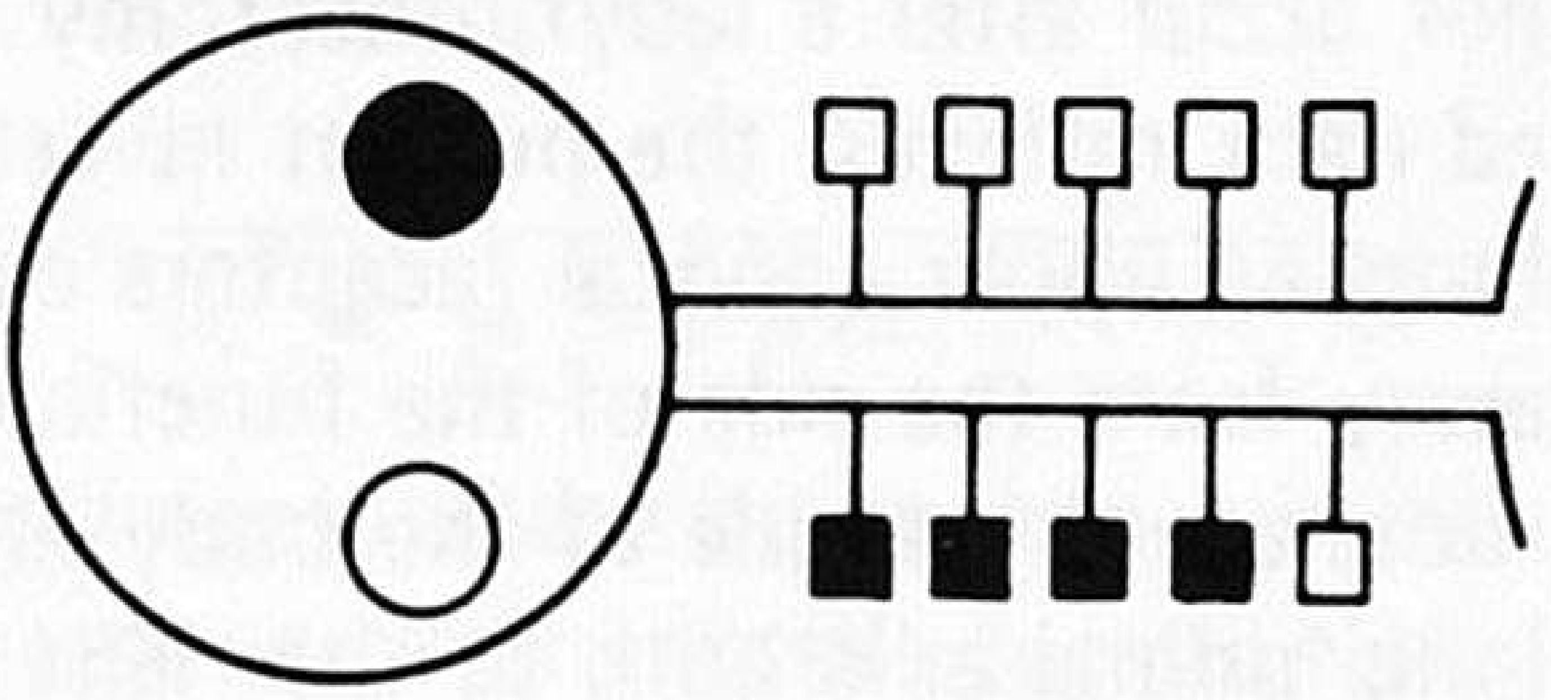
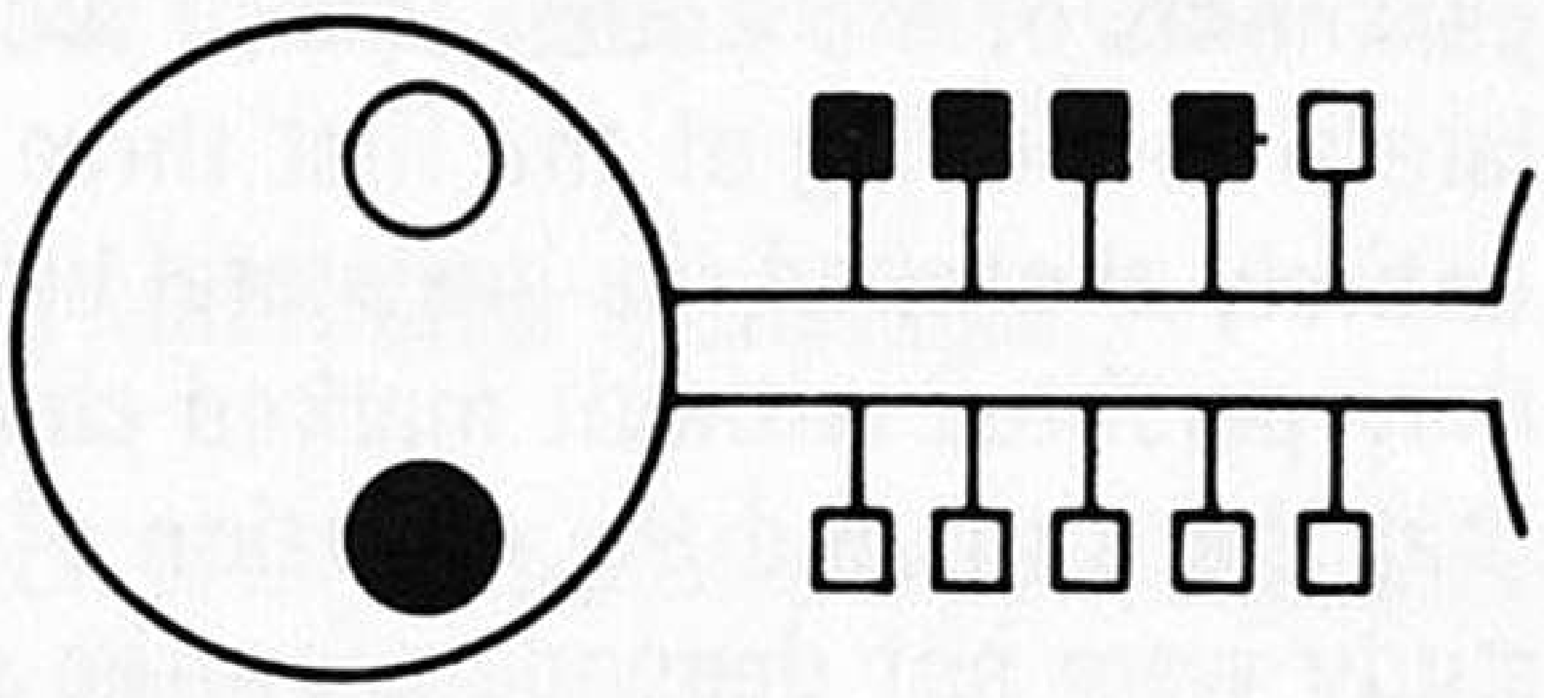
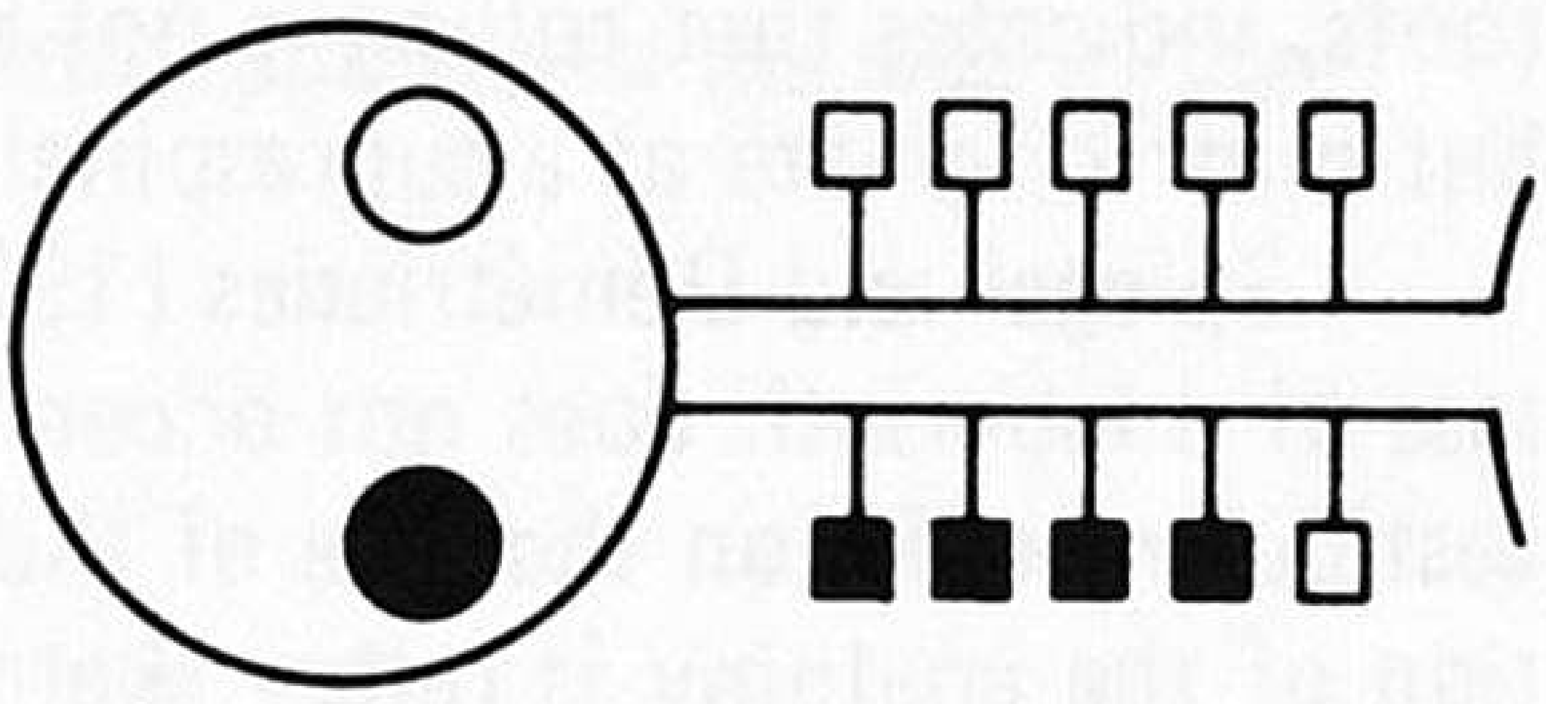
Immediately after unilateral neck denervation, the animal shows rolling about the longitudinal axis of the body, initiated by a fall to the side of the destroyed labyrinth. Next, it walks around in circles towards the side of the labyrinthectomy. Regardless of the side on which the neck receptors have been cut, the animal behaves as if the previously destroyed labyrinth had been removed again. It thus happens that rolling movements about the longitudinal axis of the body occur in the presence of functioning receptors on only one side of the neck. While Magnus (1924) demonstrated that rolling about the longitudinal body axis does not occur after a labyrinthectomy in a rabbit with symmetrically decreased neck reflexes, the present investigation proves that one set of partially blocked upper cervical receptors can mediate rolling both towards and away from the side of the functioning cervical roots. That the cervical roots on either side of the body are sensitive to neck rotation around a longitudinal axis both to the right and left, is also evident from the experiments of Mc Couch et al. (1950). These authors observed that unilateral sectioning of the first three cervical dorsal roots in decerebrate cats entirely abolished the ipsilateral limb responses to neck torsion, while they persisted without marked change on the opposite side. The fact that the form and the direction of the rolling movements as seen in this study were not dependent on the side of the sectioning of the cervical roots, indicates that rolling is not initiated by propriospinal mechanisms but must originate at a supraspinal level.

Spiegel and Démétriades (1925) found that compensation for the loss of a labyrinth does not occur after the making of a lesion in the vestibular nuclei on the side of the destroyed labyrinth. As their description of the anatomy is rather sketchy it may be better to state that compensation fails after a lesion of the brain stem at the level of the vestibular nuclei. Conversely, Uemura and Cohen (1972) made numerous lesions in various parts of the vestibular nuclei on the opposite side of a labyrinthectomy in monkeys (Macacus Rhesus) and still found a marked degree of recovery from the effects of the loss of a labyrinth. The results of the present experiments indicate that structures that are involved in the compensation remain the Achilles heel of the posture controlling mechanism after partial recovery from labyrinthectomy. A withdrawal of non-adapting excitatory influences on structures in the medulla oblong-

Table 2

UNILATERAL LABYRINTHECTOMY AND UNILATERAL NECK DENERVATION IN RABBITS

Lateral position with more pronounced nystagmus after procaine injection in the neck of 4 rabbits

no preference	13	
intact labyrinth down neck denervation up	4	
intact labyrinth down neck denervation down	5	
intact labyrinth up neck denervation up	0	
intact labyrinth up neck denervation down	0	
no nystagmus	4	
total number of experiments	26	

Legend: see Table 1

ata on the labyrinthless side can explain all of the observed symptoms. Of course, disinhibition of equivalent structures on the opposite side provides an equally probable explanation.

Like MacNally (1926) I found that the spontaneous rotation of the head of the animal about the naso-occipital axis decreased from 90° to 50° or 60 ° after the cervical roots on the side contralateral to the labyrinthectomy had been cut. Neck root section on the side of the destroyed labyrinth caused no marked change in the head rotation of our rabbits, but MacNally found an increase of the rotation to about 120°. The difference can be explained by the fact that MacNally examined his animals in the hanging position with dependent head and measured the head rotation relative to the pelvis, while I observed rotation of the neck with respect to the upper thoracic aperture in free sitting rabbits.

Electrical stimulation of the upper five cervical roots (MacNally, 1926) caused turning of the head about a dorso-ventral axis and rotation about a naso-occipital axis towards the stimulated side (in Magnus' nomenclature turning is 'Wendung' and rotation is 'Drehung').
The rotations of the head that are actually observed after unilateral section of nerve roots in rabbits with one labyrinth occur despite the effects of paralysis of the cervical muscles, which would favour rotation in the opposite direction. MacNally's technique involved complete section of the anterior and posterior roots. This explains why he found greater changes in head position after unilateral neck operations than later investigators (Biemond, 1940; J. de Jong, 1967) who tried to save the anterior roots C1 and C2 as much as possible.

The results of microelectrode studies, as reviewed by Wilson (1970), indicate both that the changes in excitability of cells in the lateral and medial vestibular nuclei due to stimulation of peripheral afferents are facilitatory most of the time, and that units in the vestibular nuclei may respond to stimulation on either side of the body. The experimental evidence would be consistent with the assumption that blocking of neck afferents induces nystagmus by the withdrawal of an excitatory influence from the upper cervical receptors on nuclei of the medulla oblongata. The decisive acute effect of local anesthesia of the neck in rabbits with one labyrinth appears to be a withdrawal of excitatory influence acting on the vestibular nuclei.

The similarity of the changes produced by labyrinthectomy and by neck deafferentation on one side (J. de Jong, 1967) would tend to indicate that the link between the upper cervical roots and the ipsilateral brain stem nuclei is stronger than the crossed pathway. If there is any preference, nystagmus is stronger in the lateral position with the intact labyrinth facing down, regardless of the side on which the neck receptors have been eliminated (Table 2). While cutting of C1 and C2 in otherwise intact rabbits causes nystagmus for no more than a few hours at most (Biemond and J. de Jong, 1969), in rabbits with only one labyrinth, unilateral neck deafferentation is followed by positional nystagmus for thirty-one to forty-four days. The balance between the neck receptor systems is possibly corrected by the same mechanism that provides a partial compensation for the loss of one labyrinth. Wyke and Molina (1973) described three types of receptor nerve ending that are found in the capsules of the apophyseal joints of the cervical spine.

The inconstant direction of the nystagmus is not due to blocking of receptors across the midline, as was thought before (J. de Jong, 1967), since it occurs both after and before deafferentation of one side of the neck. It can be explained by the fact that the cervical kinesthetic receptors on either side give information about neck movements in all directions, while procaine has a differential blocking effect on the afferent fibres, blocking the thinner ones first.

An equivalent to Bechterew's nystagmus was observed by Biemond and J. de Jong (1969). After the nystagmus produced by cutting the dorsal roots C1 and C2 on one side had disappeared, sectioning of the remaining dorsal roots C1 and C2 on the other side caused a weaker nystagmus in the opposite direction, lasting for a quarter of an hour at most. In the present study it appears that blocking of intact receptors on one side of the neck in animals with one labyrinth causes nystagmus with a duration of up to ninety minutes.

Conclusions

In the presence of only one functioning labyrinth, blocking of cervical receptors causes nystagmus. After unilateral denervation of the afferent fibres of the neck of these animals an equivalent of Bechterew's nystagmus can be elicited by blocking the remaining cervical receptors.

In the chronic stage following unilateral labyrinthectomy, deaffentation of one side of the neck causes long lasting positional nystagmus.

CERVICAL NYSTAGMUS IN THE CEREBELLECTOMIZED RABBIT

Introduction

Högyes (1881, 1912) was the first to establish that cerebellar lesions which did not involve the eighth nerve nuclei, did not affect vestibular nystagmus and compensatory eye movements.

De Kleyn (1912) could elicit vestibular nystagmus after complete cerebellectomy. However, Allen and Fernandez (1959) found that cerebellar lesions did not produce positional nystagmus in cats whose labyrinths had been destroyed previously. At the synaptic level the relationship between the cerebellum and the vestibular nuclei has been the subject of several detailed studies by Ito and collaborators (1964a, 1964b, 1966a, 1966b, 1971, 1972). The cerebellar control of the vestibular pathways to the extraocular muscle neurons has extensively been reviewed by Cohen and Highstein (1972). Cohen and his collaborators also studied and reviewed the influence of the cerebellum on ocular movements (1969, 1971).

Pompeiano and Cotti (1959) as well as Giaquinto et al., (1963), thought that the connections of the spinal cord with Deiters' nucleus would course through the cerebellum. Although previous investigations (Magnus, 1924; Wilson et al., 1966, 1967; Fredrickson et al., 1966, and Gernandt, 1967) had demonstrated that the cerebellum was not essential for spinovestibular interaction, I wanted to investigate in the present series of experiments whether cervical nystagmus could be induced after cerebellectomy, as is known to be the case with vestibular nystagmus. If cervical nystagmus did not occur after cerebellectomy, it could not be due to disturbances of the input to the direct spino-vestibular fibres alone, and J. de Jong's (1967) hypothesis that these kinds of nystagmus use the same elementary circuit would be incorrect. Since the cerebellum is the 'head ganglion of the proprioceptive system' (Sherrington, 1947), the fact that experimental cervical nystagmus is mostly due to blocking of joint and ligament receptors (J. de Jong, 1967; Biemond and J. de Jong, 1969) could indicate that absence of cerebellar function eliminates neck nystagmus.

Materials and methods

With intravenous pentobarbitone sodium anesthesia and aseptic surgery, an occipital craniectomy in nine rabbits was performed, as described in chapter II. Then the cerebellum was removed with a suction cannula, and special attention was paid to disconnection of the lobulus petrosus from the brain stem (Magnus, 1924). The operation was continued until the floor of the fourth ventricle was exposed from the inferior colliculi to the obex. As the anesthesia wore off, all animals showed marked opisthotonus. After surgery the animals were fed by orogastric tubes and received a powdered baby food formula to which a minimal amount of water had been added. Nevertheless, the animals did not survive for more than fifteen days postoperatively, perhaps because they still received unphysiologically large quantities of fluid. In seven of the nine rabbits postoperative nystagmus had not yet subsided at the time they were injected with procaine, according to the technique described in chapter II.

As cerebellectomy in the rabbit caused a nystagmus which usually persisted until the time of death, it was not possible to evaluate in a simple way whether procaine block had resulted in nystagmus. Instead, the following, somewhat arbitrary, method was used to evaluate the effect of the injection: one minute after the rabbit was placed in position, the total distance moved by the eye in the fast phase was measured for the following one minute interval; this was repeated after procaine block of the dorsal roots. If the total distance, measured in any one lead, with the animal in the same position, had increased by at least a factor of two after injections, this was taken to mean that a cervical nystagmus had been caused by the injection.

In order to check on the surgical technique of cerebellectomy the brain and cervical cord of six consecutive animals were fixed in 10 per cent formalin (3.5 per cent aqeous formaldehyde solution) for a month. Macroscopic study showed that minimal remnants of cerebellar tissue were left at the site of the cerebellar pedunculi. Klüver-Barrera sections were made at the level of the largest amount of remaining cerebellar tissue. Diagrams of these sections of the medulla oblongata are reproduced in fig. 2.

The effect of darkness on cervical nystagmus was studied in two cerebellectomized rabbits.

Results

In 9 rabbits I infiltrated the neck 30 times in the period between the fourth and the fourteenth postoperative day. Three ml of procaine HCl were used; the strength of the solution was 1 per cent in 14 and 2 per cent in 16 of the trials. Nystagmus with a duration of 10 to 163 minutes occurred in 13 instances (fig. 3). The results were negative in 17 experiments. At least one positive trial was obtained in each of the animals.

In 2 trials nystagmus was more pronounced in the lateral position with the blocked roots down, in the other 11 there was no difference between the nystagmus seen in both lateral positions. Procaine injections only twice produced nystagmus when the animals were in the prone position. Control injections into the gluteal musculature did not induce nystagmus.

In 2 experiments I switched off the light; no effect on positional nystagmus could be found.

Fig. 4 shows an example of neck nystagmus in a cerebellectomized rabbit, that was free of nystagmus before the injection. Fig. 5 shows the increase of the nystagmus in a cerebellectomized rabbit after blocking of the neck receptors.

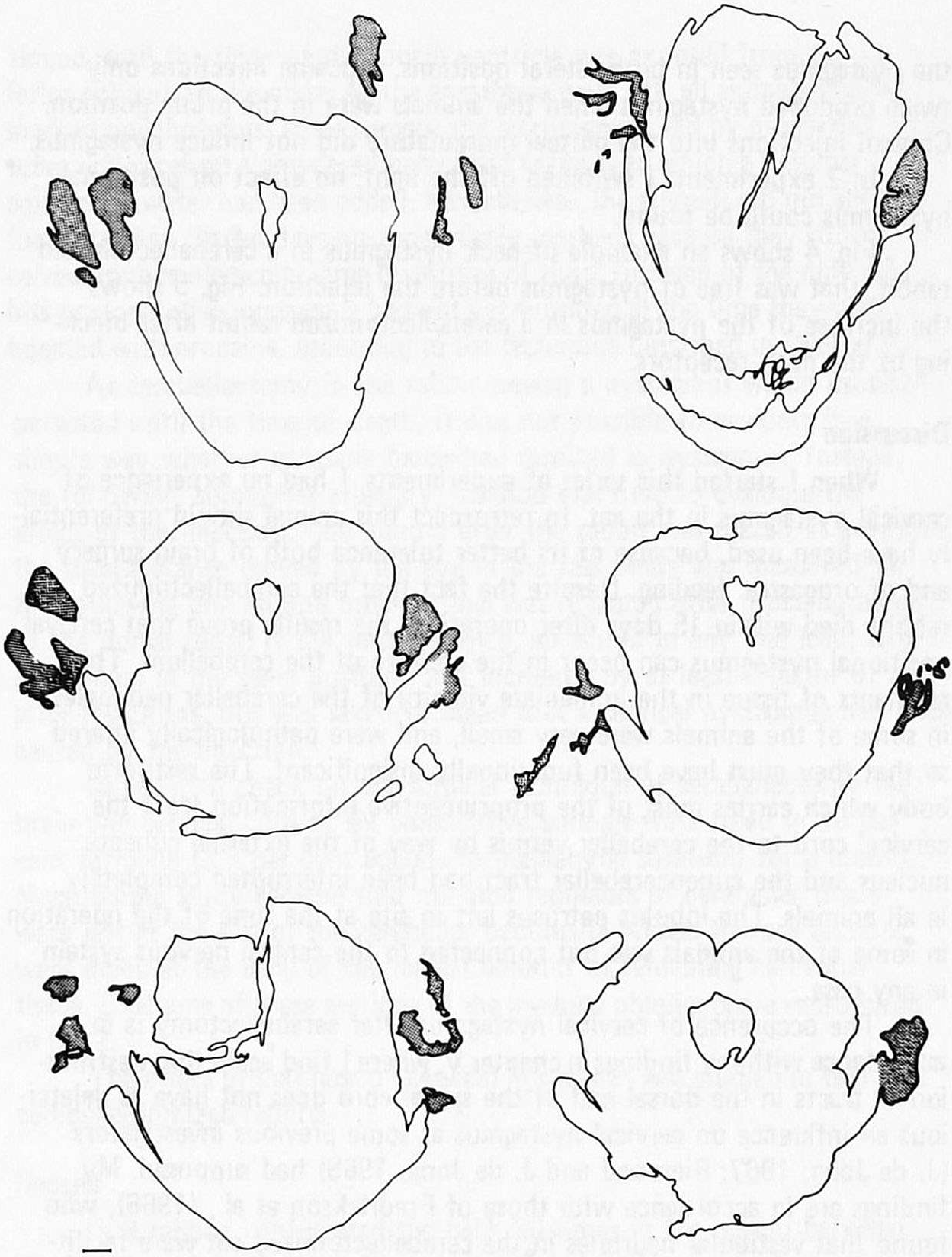
Discussion

When I started this series of experiments, I had no experience of cervical nystagmus in the cat. In retrospect this animal should preferentially have been used, because of its better tolerance both of brain surgery and of orogastric feeding. Despite the fact that the cerebellectomized rabbits died within 15 days after operation, the results prove that cercival positional nystagmus can occur in the absence of the cerebellum. The remnants of tissue in the immediate vicinity of the cerebellar peduncles in some of the animals were very small, and were pathologically altered so that they must have been functionally insignificant. The restiform body which carries most of the proprioceptive information from the cervical cord to the cerebellar vermis by way of the external cuneate nucleus and the cuneocerebellar tract had been interrupted completely in all animals. The lobulus petrosus left in site at the time of the operation in some of the animals was not connected to the central nervous system in any case.

The occurence of cervical nystagmus after cerebellectomy is in accordance with my findings in chapter V, where I find again that destruction of tracts in the dorsal half of the spinal cord does not have as deleterious an influence on cervical nystagmus as some previous investigators (J. de Jong; 1967; Biemond and J. de Jong, 1969) had supposed. My findings are in accordance with those of Fredrickson et al., (1966), who found that vestibular neurones in the cerebellectomized cat were facilitated nearly exclusively by joint movements, especially of the cervical vertebral column.

Cerebellectomy blocks a number of important pathways from the spinal cord to the vestibular nuclei. Primary spino-vestibular fibres are few in number and end in the most caudal part of the descending and lateral vestibular nuclei and in the group X (Pompeiano and Brodal, 1957) which does not receive primary vestibular fibres. Part of these

Figure 2

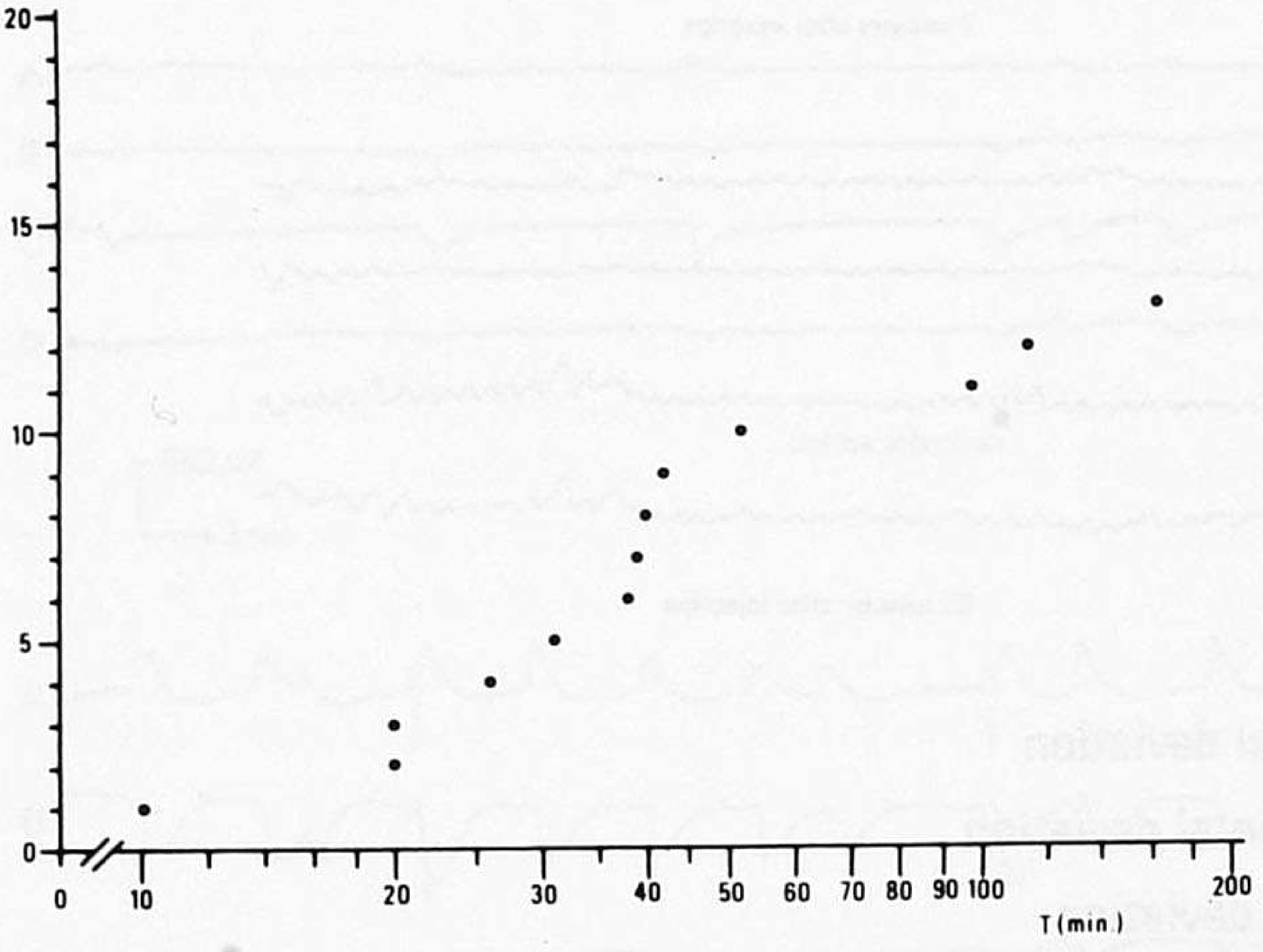


Legend: Shaded: remnants of cerebellar tissue

Each drawing represents a transverse section of the medulla oblongata of each of six consecutive experimental animals at the level at which the largest amount of cerebellar remnants was found.

spino-vestibular fibres can be left out of the present discussion, as they are collaterals of the dorsal spino-cerebellar tract which does not receive afferent fibres at the cervical spinal level. Crossby, Humphrey and Lauer (1962) situate the spino-vestibular tract in the ventromedial part of the cord, lateral to the ventral spino-thalamic tract. These, however, are spino-reticular fibres ascending ipsilaterally and on the opposite side, together with the spino-thalamic axones to end by way of reticulo-vestibular fibres in all of the vestibular nuclei. Probably the spino-reticular fibres are the main remaining connection of the cervical cord to the vestibular nuclei, since the cuneo-cerebellar, the rostral spino-cerebellar, and the dorsal and ventral spino-olivo-cerebellar tract have been interrupted by cerebellectomy. Another cervico-vestibular pathway could consist of collaterals to the vestibular neurons given off by olivo-cerebellar axones. Even so, the two animals that survived the period of positional nystagmus after cerebellectomy prove that cervical nystagmus does occur in the absence of the cerebellum.

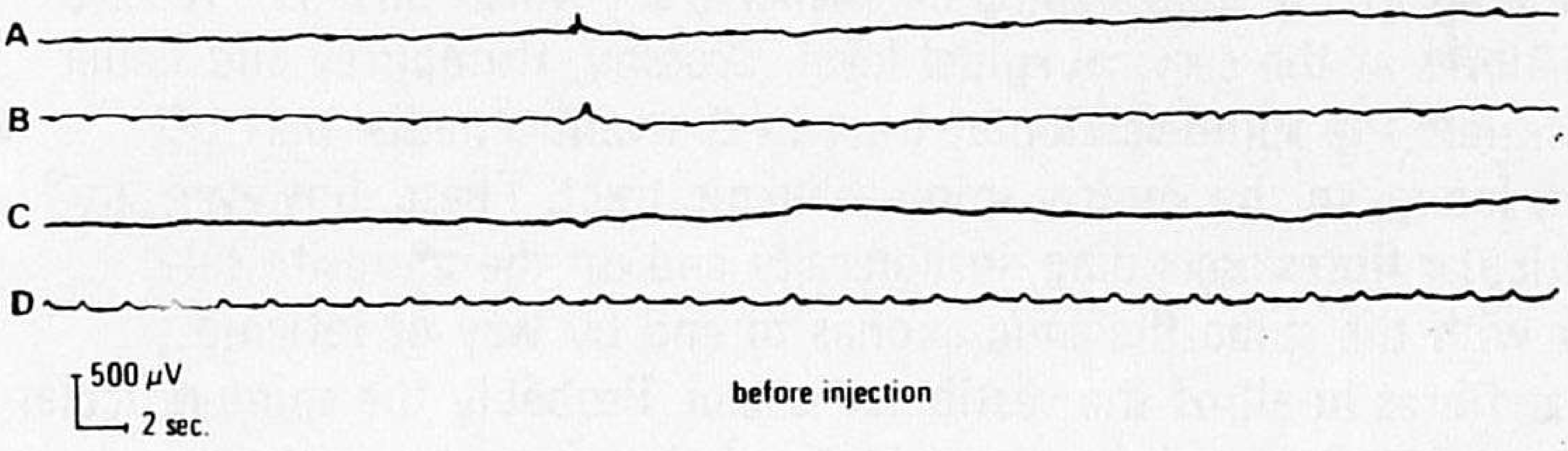
Figure 3



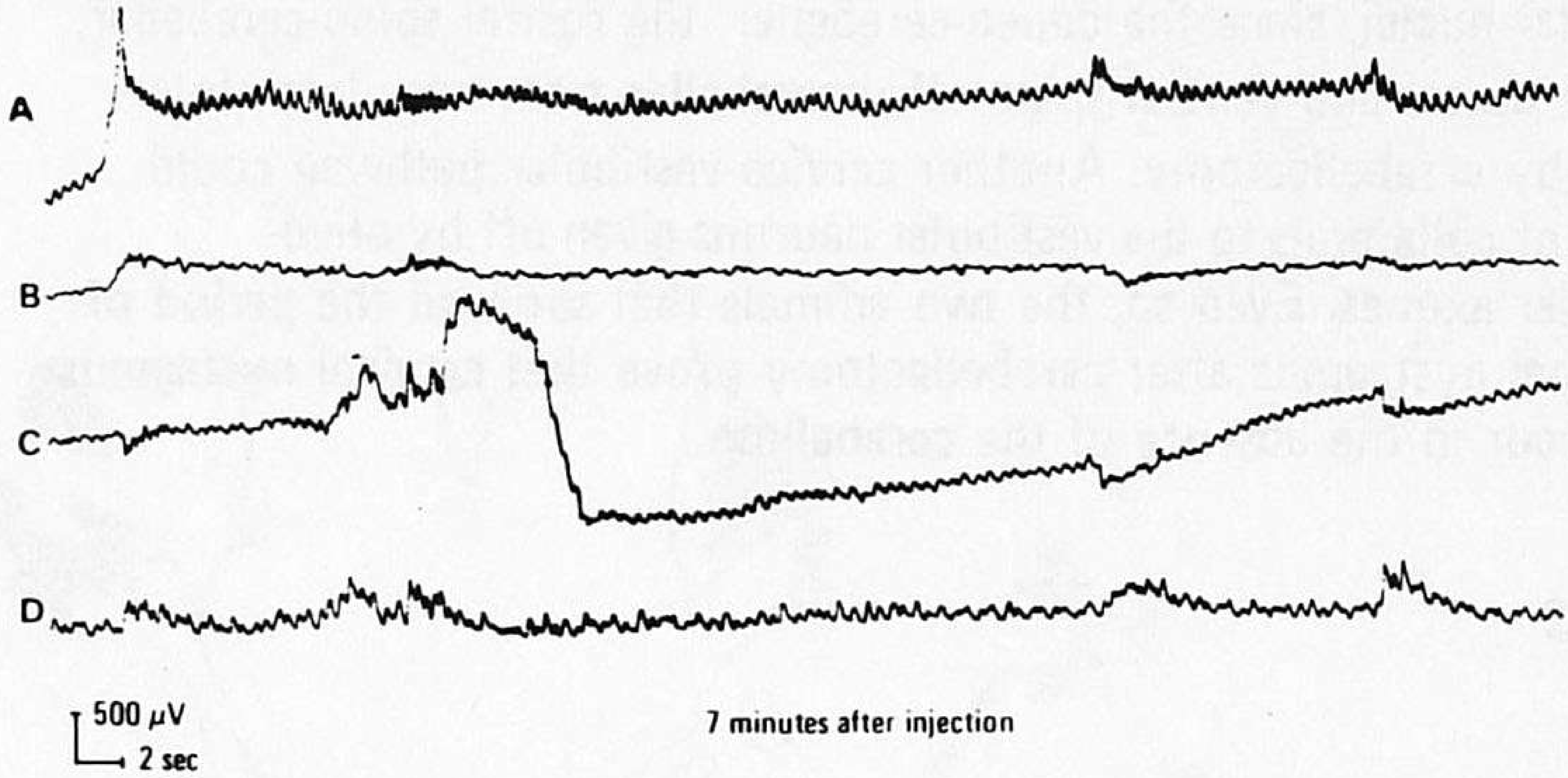
The ordinate gives the number of the experiment, where the sequence has been determined by ordering the experiments according to the duration of the nystagmus produced. The abscissa shows on a logarithmic scale the duration of the nystagmus after procaine injections in the neck of rabbits whose cerebellum had been removed.

Figure 4

E.N.G. of a cerebellectomized rabbit in prone position before and after injection of procaine HCl at the C1-2-3 dorsal roots. No spontaneous nystagmus before the injection.



before injection



7 minutes after injection

85 minutes after injection

A: right eye, vertical deviation

B: right eye, horizontal deviation

C: left eye, vertical deviation

D: left eye, horizontal deviation

In A and C: quick phase upwards: eye downwards; quick phase downwards: eye upwards

In B and D: quick phase upwards: eye to the right; quick phase downwards: eye to the left

Summary

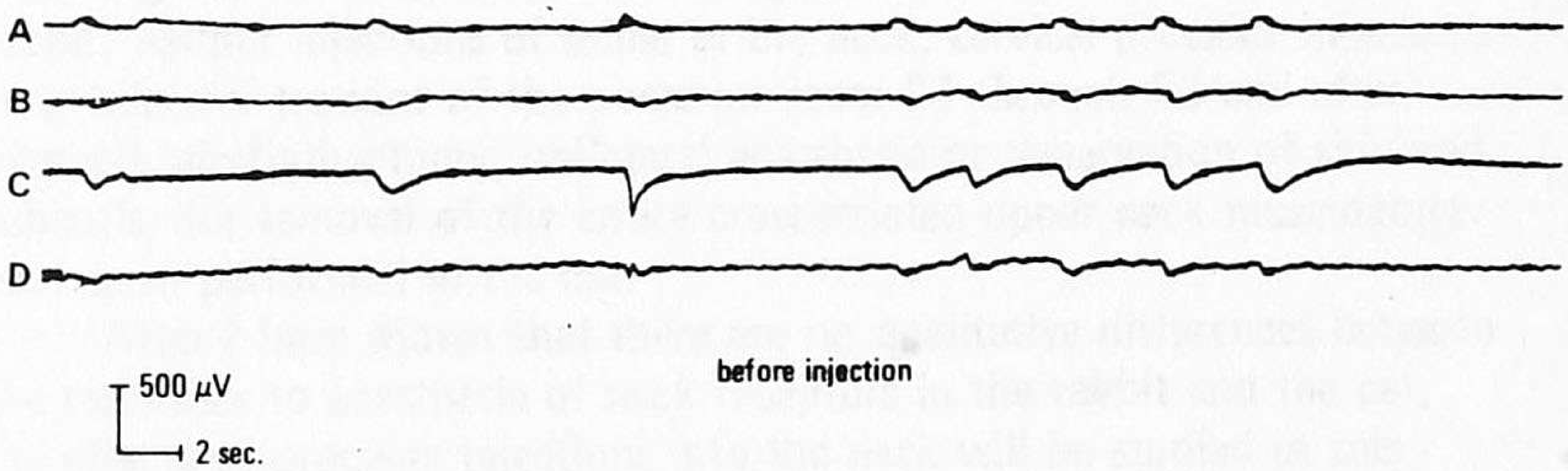
Blocking of cervical receptors in cerebellectomized rabbits produced nystagmus in 2 animals and a marked increase of spontaneous nystagmus in 7 others. In each of the 9 rabbits cervical anesthesia produced nystagmus in at least one trial.

Conclusions

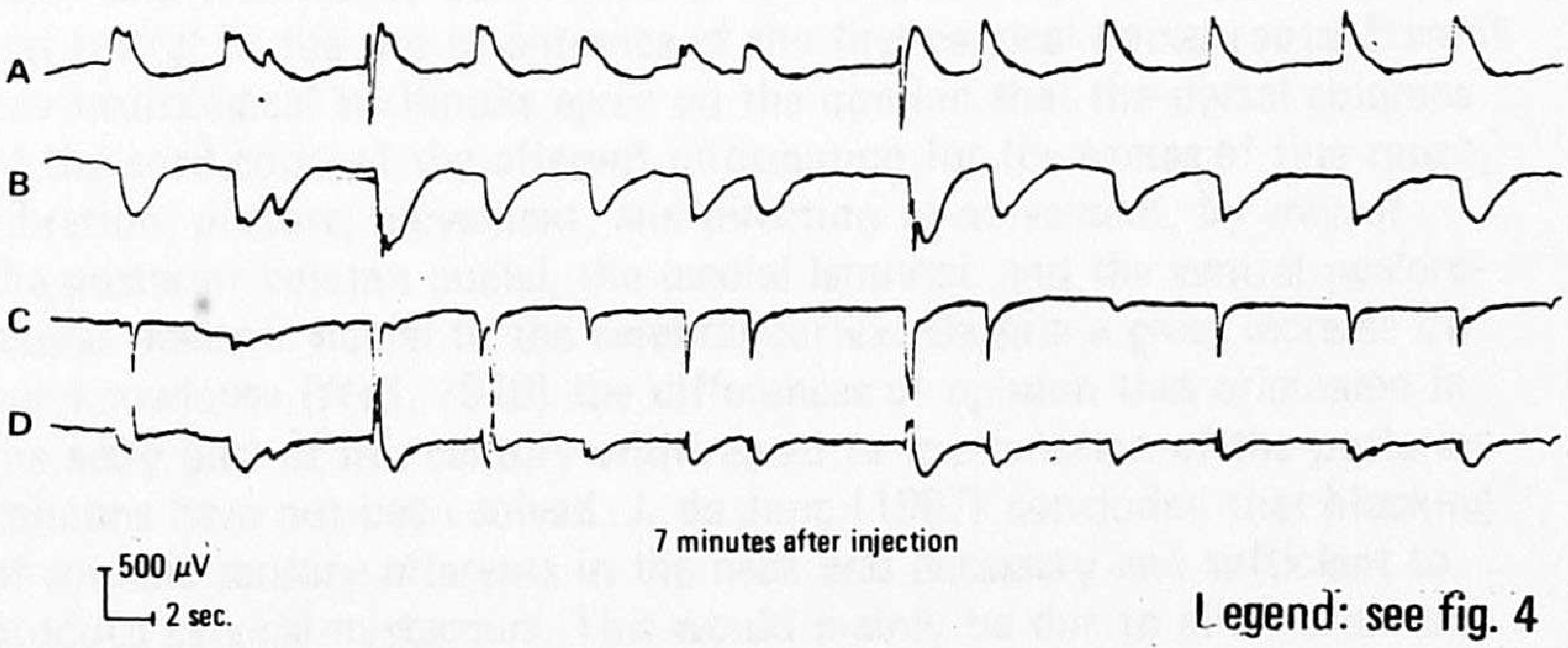
Intact cerebellar function is not a necessary condition for cervical nystagmus. The described experiments do not invalidate the hypothesis that both cervical and labyrinthine nystagmus arise in the same vestibulo-oculomotor circuit.

Figure 5

E.N.G. of a cerebellectomized rabbit in right lateral position showing the increase of nystagmus after injection of procaine HCl at the C1-2-3 dorsal roots.



before injection



7 minutes after injection

Legend: see fig. 4

CERVICAL NYSTAGMUS IN THE CAT; DESTRUCTION OF THE POSTERIOR UPPER CERVICAL CORD

Introduction

Disturbances of posture and gait are more easily detected in the cat than in the rabbit. Moreover, cats tolerate surgery better and have frontally placed eyes. Therefore, the investigation was continued in this animal.

As the spino-vestibular connections described by Pompeiano and Brodal (1957) and Brodal (1969) have a similar general distribution in all mammals, especially the cat and the rabbit (Mehler, 1969), I expected that cervical nystagmus in the latter species would have about the same properties as in the former. Nevertheless, this had to be verified before the effects of partial spinal cord destructions could be studied.

In a series of preliminary experiments I established that cervical positional nystagmus occurs in cats upon blocking of their neck receptors. It is not abolished by interruption of both cervical neuro-vascular bundles or by unilateral labyrinthectomy. The effects of darkness on cervical positional nystagmus will be reported. I have not seen the necessity of repeating the entire series of J. de Jong's (1967) experiments on the rabbit: neither injections of saline in the neck, cervical procaine injections after bilateral sections of the posterior roots C1 through C3 and after bilateral labyrinthectomy, unilateral anesthesia or denervation of skin and subcutis, nor removal of the entire cross-striated upper neck musculature have been performed in the cat.

After I have shown that there are no qualitative differences between the responses to anesthesia of neck receptors in the rabbit and the cat, the effects of procaine injections into the neck will be studied in cats both before and after destruction of the dorsal half of the spinal cord, just rostral to the site of entrance of the first cervical dorsal roots. Present day neurological textbooks agree on the opinion that the dorsal columns of the cord conduct the afferent information for the senses of fine touch, vibration, posture, movement, and direction of movement, by way of the posterior column nuclei, the medial lemnisci, and the ventral postero-lateral thalamic nuclei to the cerebral cortex. Despite a great increase of our knowledge (Wall, 1970) the differences of opinion that originated in the early part of last century with regard to the function of the posterior columns have not been solved. J. de Jong (1967) concluded that blocking of somatic sensory afferents in the neck was necessary and sufficient to produce cervical nystagmus. This would mainly be due to elimination of proprioceptive impulses from the deep ligaments and intervertebral joints of the neck. Since it has been established in chapter IV that cervical nystagmus is not abolished by cerebellectomy, the afferent information from the neck receptors could reach the vestibular nuclei by way of the dorsal columns - especially via the fibre tract described in the rabbit by Gerebtzoff (1940) - the spino-reticular or the spino-olivary fibres. The present series of experiments in the cat is set up in order to decide whether or not afferent fibres in the dorsal part of the spinal cord are essential for the production of cervical nystagmus.

Materials and methods

Healthy adult cats were used. The electronystagmogram was recorded in darkness and animals were selected that showed no nystagmus in the prone and lateral positions. When the animals that were discarded because of spontaneous nystagmus were used in other experiments, most of them appeared to have serous otitis media with chronic inflammation of the epithelium lining the tympanic bulla.

In a first series of trials an attempt was made to induce nystagmus by procaine infiltration of the deep cervical tissues. The amount of procaine varied from 1.5 to 4 ml of a 2 per cent solution, for the same reason as described in chapter III. I also studied whether a tendency to fall occurred and if so, to which side of the body. This tendency was then studied in a number of control animals after they had been tied to a board for an hour in the customary position for this experiment as described in chapter II. The influence of light and darkness on cervical nystagmus was also investigated.

For labyrinthectomy I used the technique of de Kleyn (1912a). After postoperative recovery had been completed, I studied the influence of cervical blocks on eye movements, gait, and posture.

In a last preliminary experiment both vertebral neuro-vascular bundles were destroyed in a cat at the level of the transverse processes of C1. Through a mid-line incision the foramina costotransversaria of the first cervical vertebral arch were partly exposed by milling away the bone. Fig. 6 shows part of one foramen costotransversarium of the first cervical vertebral arch from which the vertebral neuro-vascular bundle has been removed by cautious cautherization.

The dorsal half of the cord was destroyed in four cats at a level just rostral to the entrance of the C1 posterior roots. With intraperitoneal pento-barbitone sodium anesthesia and aseptic surgical technique I exposed the atlanto-occipital membrane by way of a dorso-median skin incision and blunt separation of the posterior neck musculature. After opening of the meninges and exposure of the cord, I made the lesion with the aid of a spatula. The wound was closed in layers. Upon recovery from the anesthesia, the animals showed nystagmus which disappeared in the course of two weeks in one cat, while it persisted for six to eight weeks in the other three animals.

As soon as the postoperative nystagmus had abated, I again infiltrated the cervical tissues with a 2 per cent procaine HCl solution. After this either the electronystagmogram or changes in posture, gait, and jumping movements were studied.

Eleven to thirteen months after the operation, the animals were perfused under general anesthesia, first with Ringer's solution, then with 10 per cent formalin. The medulla oblongata and the cervical cord were fixed for two more weeks in formalin; the area of the lesion was then cut into serial sections with a thickness of 7μ which were stained according to the techniques of Nissl and Holzer. The maximum extent of the area in which all axones were destroyed is demonstrated in fig. 7. The long postoperative survival period made more detailed anatomical studied useless, as the disintegrated structures of the damaged neurons would have been resorbed by this time.

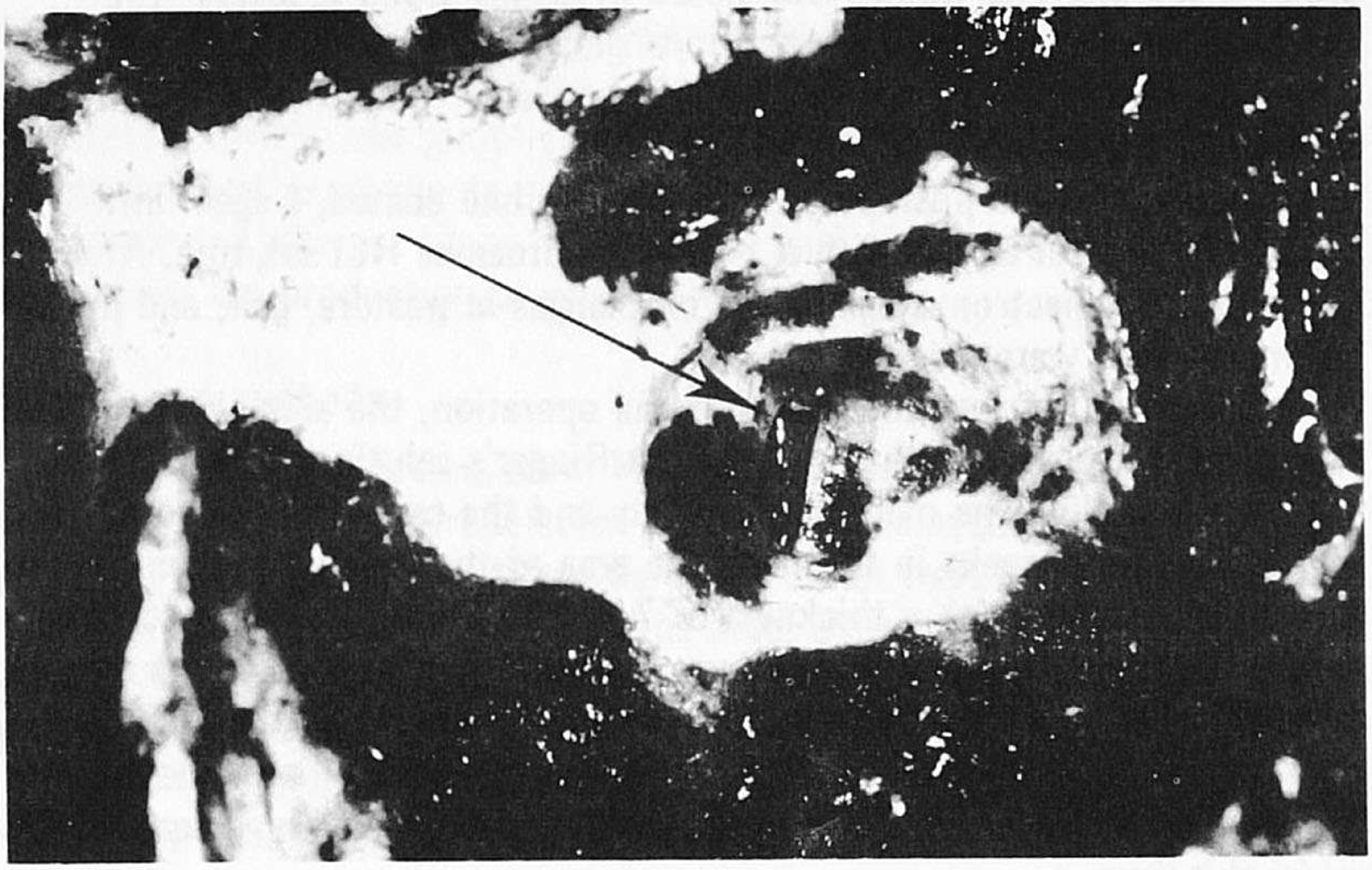
Results

Altogether 27 cats were used. A total of 77 injections was given alternately on the left or on the right side of the neck. Twenty-six injections induced nystagmus of varying direction and frequency, lasting from 4 to 66 minutes. Fig. 8 shows an example of neck nystagmus in an intact cat.

Before surgery, unilateral neck infiltration in a number of trials was followed by ipsilateral hemi-hypotonia, a staggering ataxic gait, and a tendency to fall, usually towards the side of the injection. The animal sought support with the flank on the side of the injection against stable objects. Rotation of the head, rolling about the longitudinal body axis, and compulsive circling movements were not observed. After administration of procaine injections in the neck of unoperated cats and recording of the ENG for one hour, the gait of 21 of the animals was studied. Thirteen cats showed staggering and a tendency to fall towards the injected side, 4 towards the opposite side and 4 moved quite normally; the 4 animals that moved well had shown nystagmus on the electronystagmogram. In 12 trials the cats had a tendency to fall, although nystagmus had not occurred during the previous hour.

Figure 6

First cervical vertebra of a cat from which both neurovascular vertebral bundles have been removed, showing one of the foramina costotransversaria.



Unilateral labyrinthectomy was performed in 4 cats. Beside the well-known effects described by Magnus (1924) all of them had miosis and paresis of the membrana nictitans on the side of the operation. De Kleyn (1912b) ascribed this to a lesion of the postganglionic sympathetic fibres running through the middle ear in the cat.

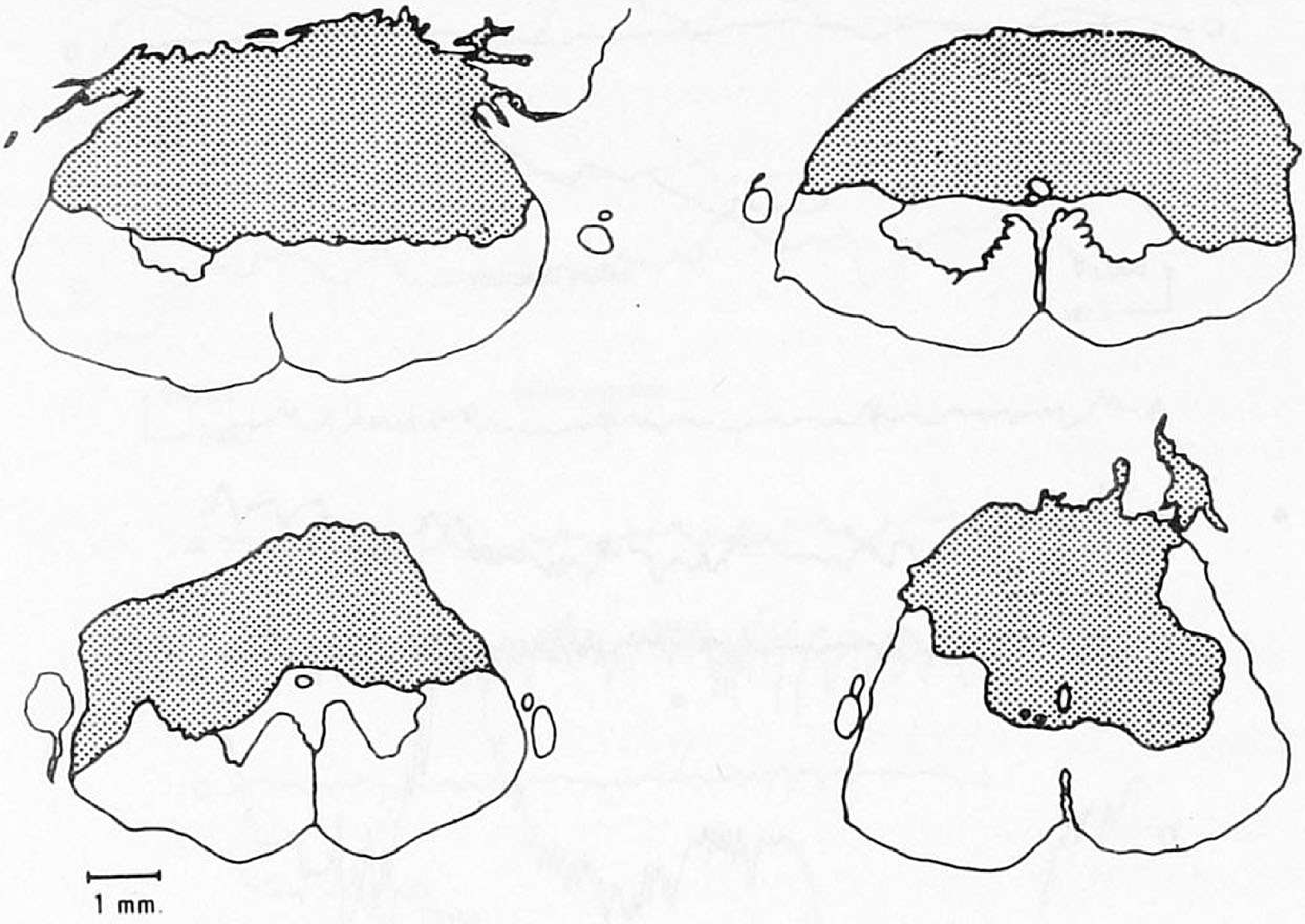
After the postoperative nystagmus had disappeared, 21 procaine infiltrations of the neck were given, 8 of which were followed by nystagmus with a duration of 3 to 50 minutes. Of the 8 positive injections, 4 had been given on the side of the destroyed labyrinth and 4 on the opposite side. There was no difference between the amount of nystagmus recorded in the lateral positions, regardless of whether the intact labyrinth was pointing up or down (Table 3).

Of the 4 animals that had one labyrinth destroyed, each received one neck injection in order to study the tendency to fall. Three animals were inclined to fall towards the side of the injection, regardless of the side of the labyrinthectomy. The fourth cat showed a staggering ataxic gait but did not tend to fall.

The cat whose vertebral neurovascular bundles had been destroyed received 7 procaine injections into the neck, 6 of which were followed by nystagmus with a duration of 13 to 38 minutes.

Figure 7

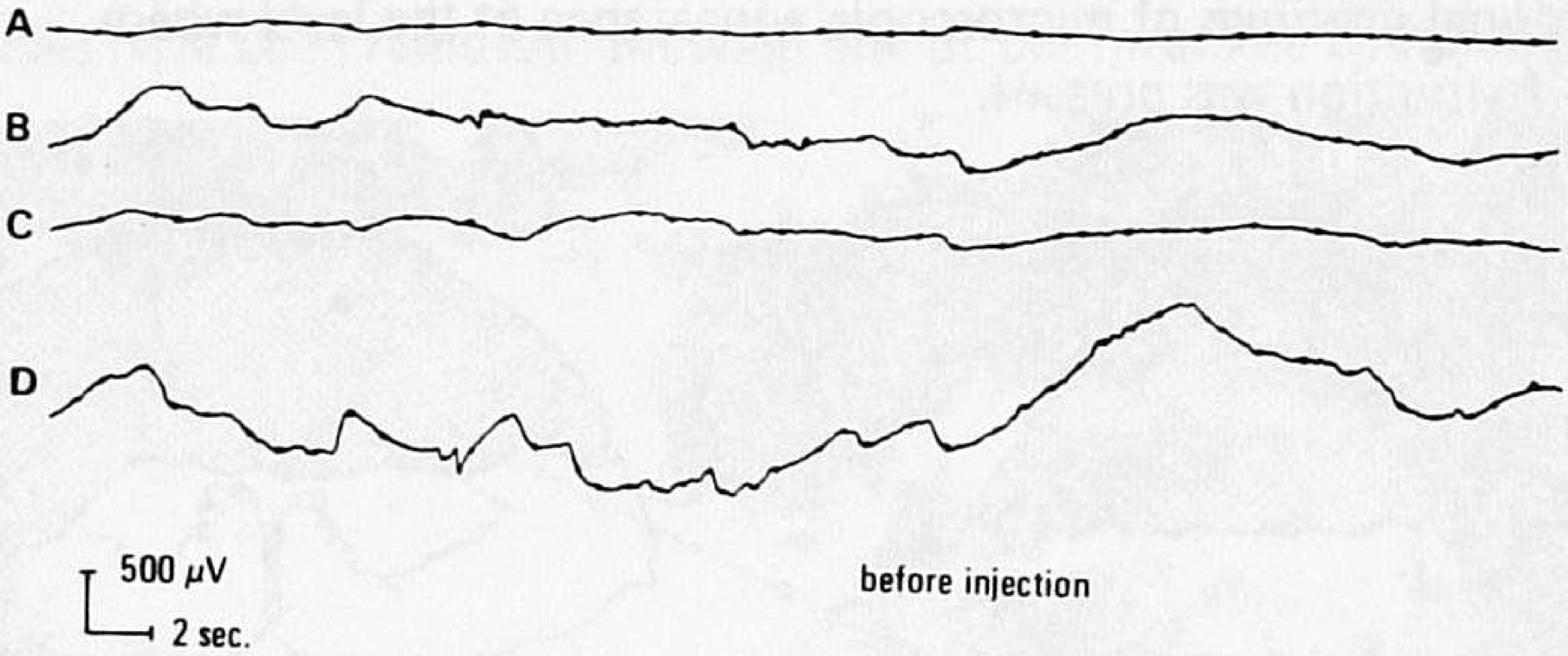
Destruction of the dorsal half of the upper cervical cord in four cats. Cross-sectional drawings of microscopic appearance at the level where maximal destruction was present.



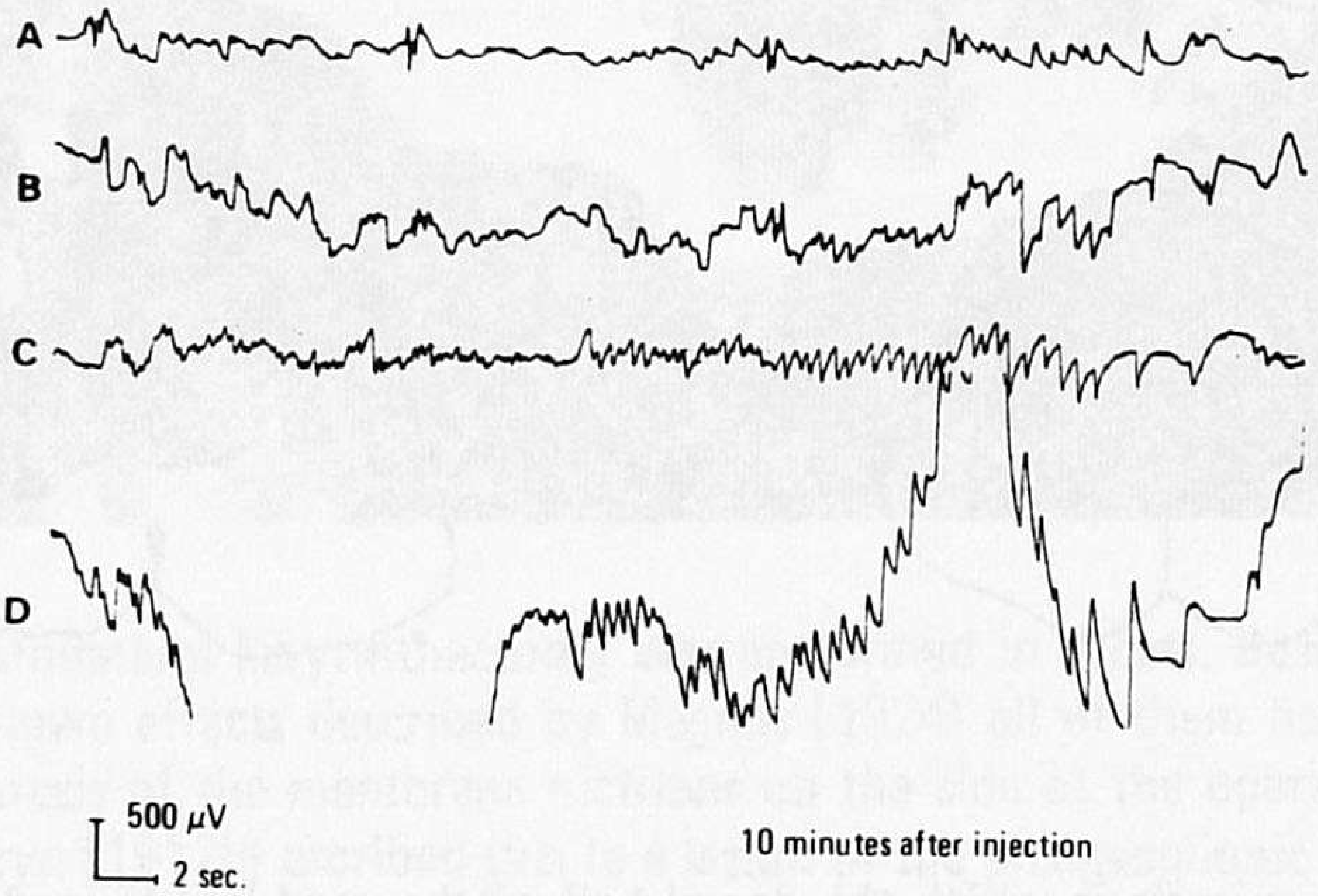
The 4 animals in which the dorsal half of the cord had been destroyed, received a total of 50 procaine injections into the neck (Table 4). In 17 trials nystagmus was recorded with a duration of 9 to 129 minutes. The duration of the nystagmus is given in fig. 9. Fig. 10 shows procaine-induced nystagmus in a cat in which the dorsal half of the upper cervical cord had been destroyed. The animals never recovered completely from their neurological deficits. Before they were sacrificed, more than a year after surgery, their locomotion showed: exaggerated and incoordinated lifting of the front paws, broad-based gait and semiflection of the hind quarters, as a result of which the centre of gravity of the trunk was abnormally close to the ground. In the sitting position the animal's head and trunk exhibited small, pendulous, sideways swaying movements. When jumping down from a table, the animals threw their hind limbs abnormally far backward and up into the air, and would make a clumsy landing with an ungainly and heavy thud. In these animals unilateral infiltration of the neck induced staggering gait and increased flexion of the hind limbs.

Figure 8

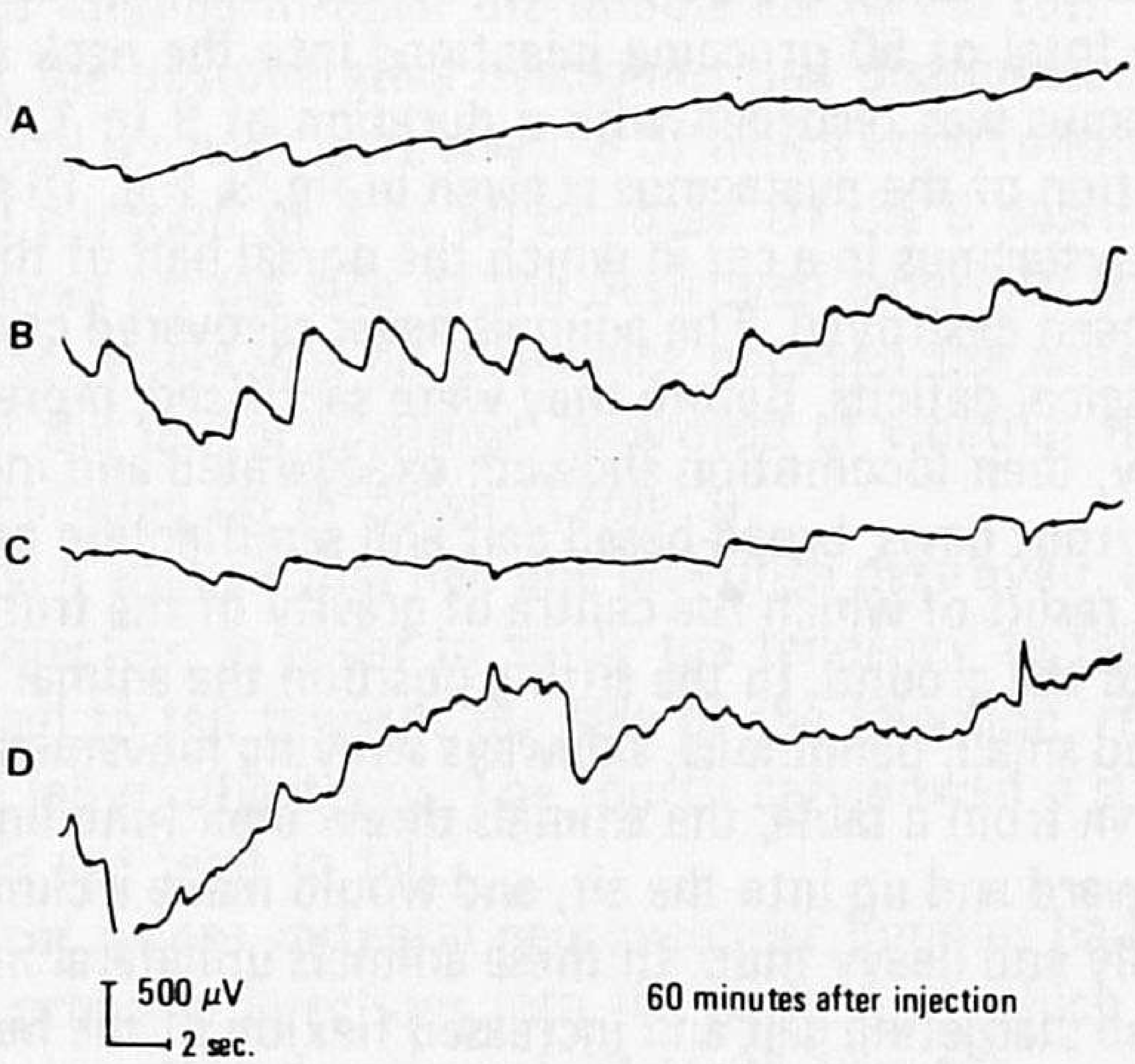
E.N.G. of an intact cat in right lateral position before and after blocking the upper three dorsal cervical roots with procaine HCl.



before injection



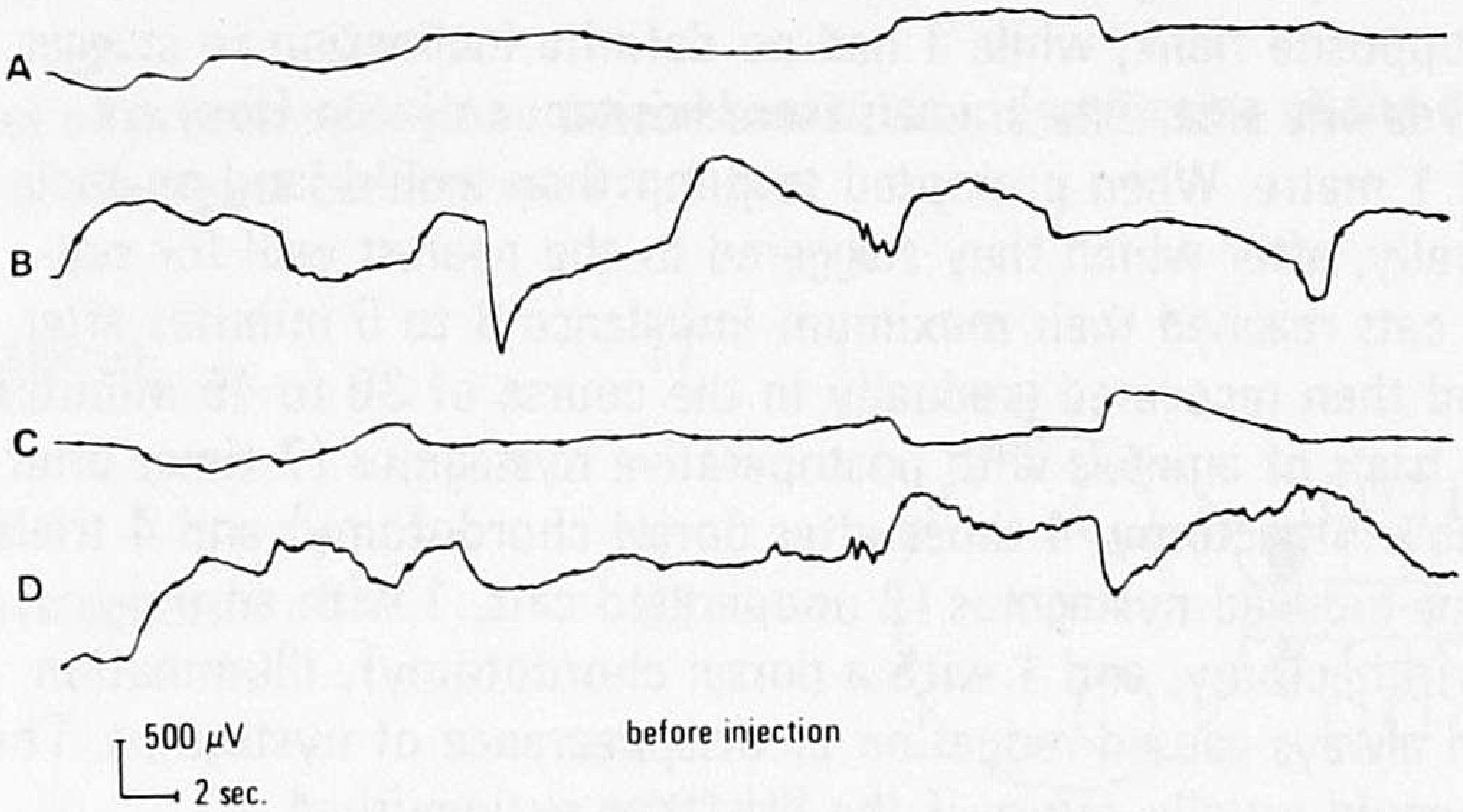
10 minutes after injection



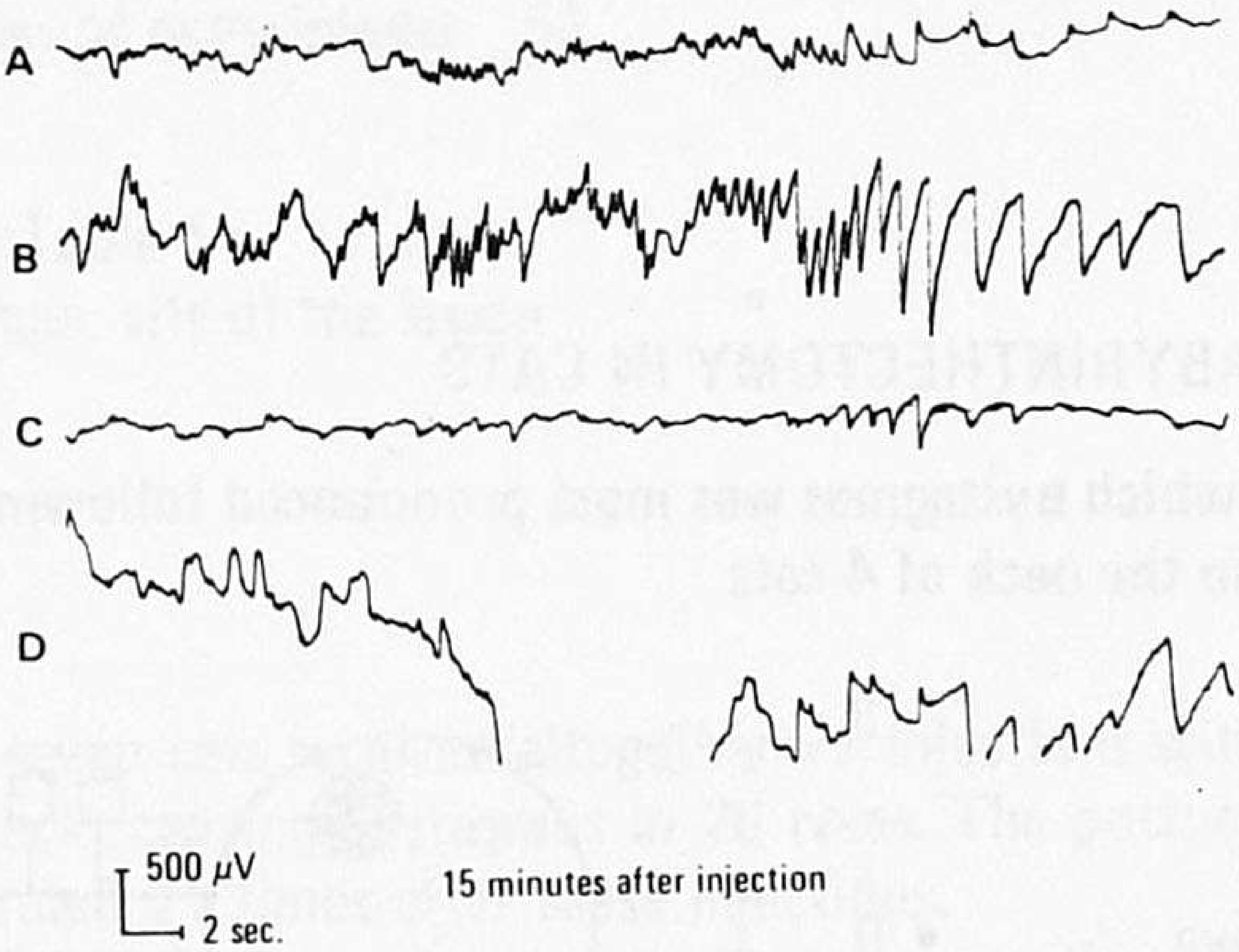
60 minutes after injection

Figure 8

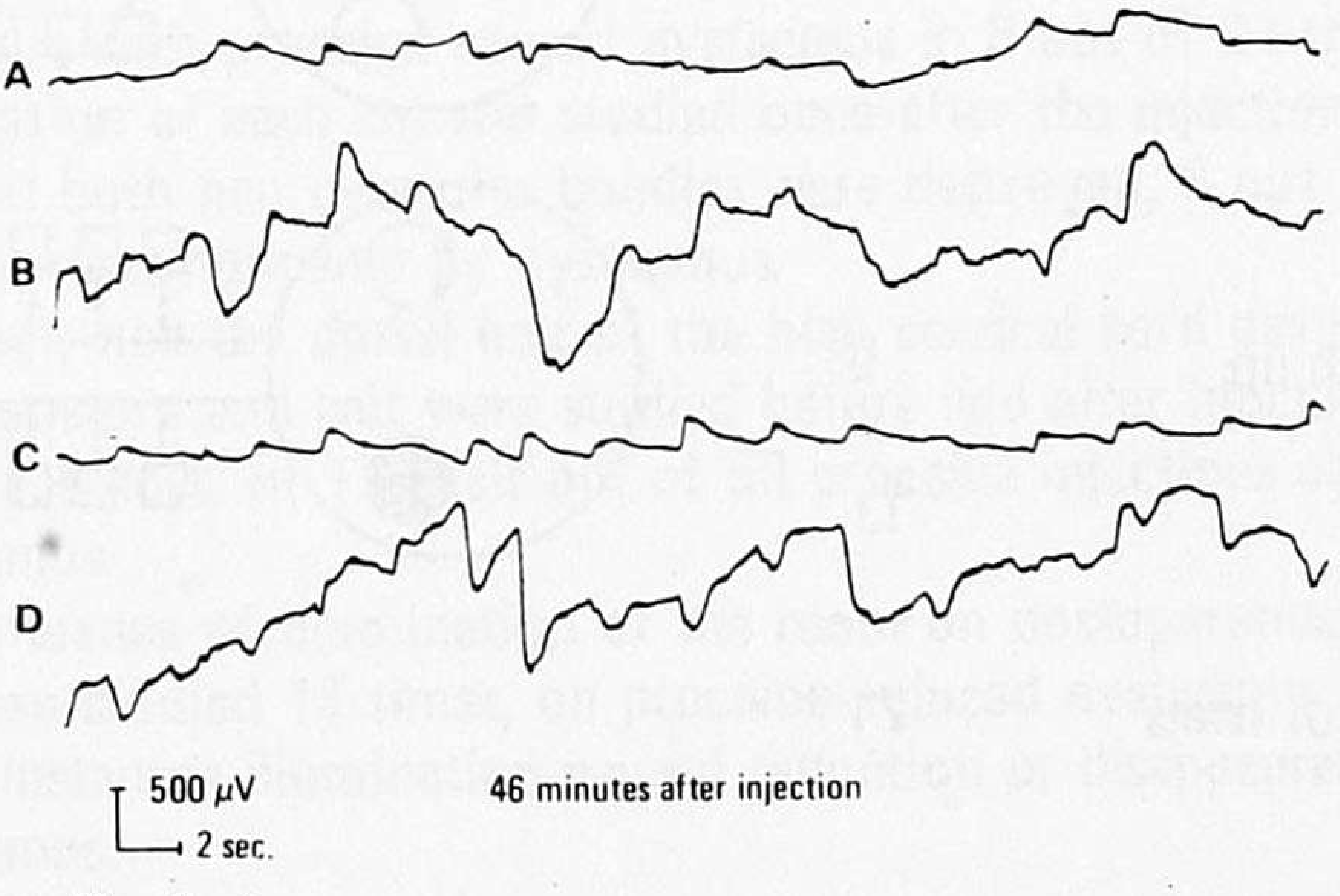
E.N.G. of an intact cat in left lateral position before and after blocking the upper three dorsal cervical roots with procaine HCl.



before injection



15 minutes after injection



46 minutes after injection

Legend: see fig. 4

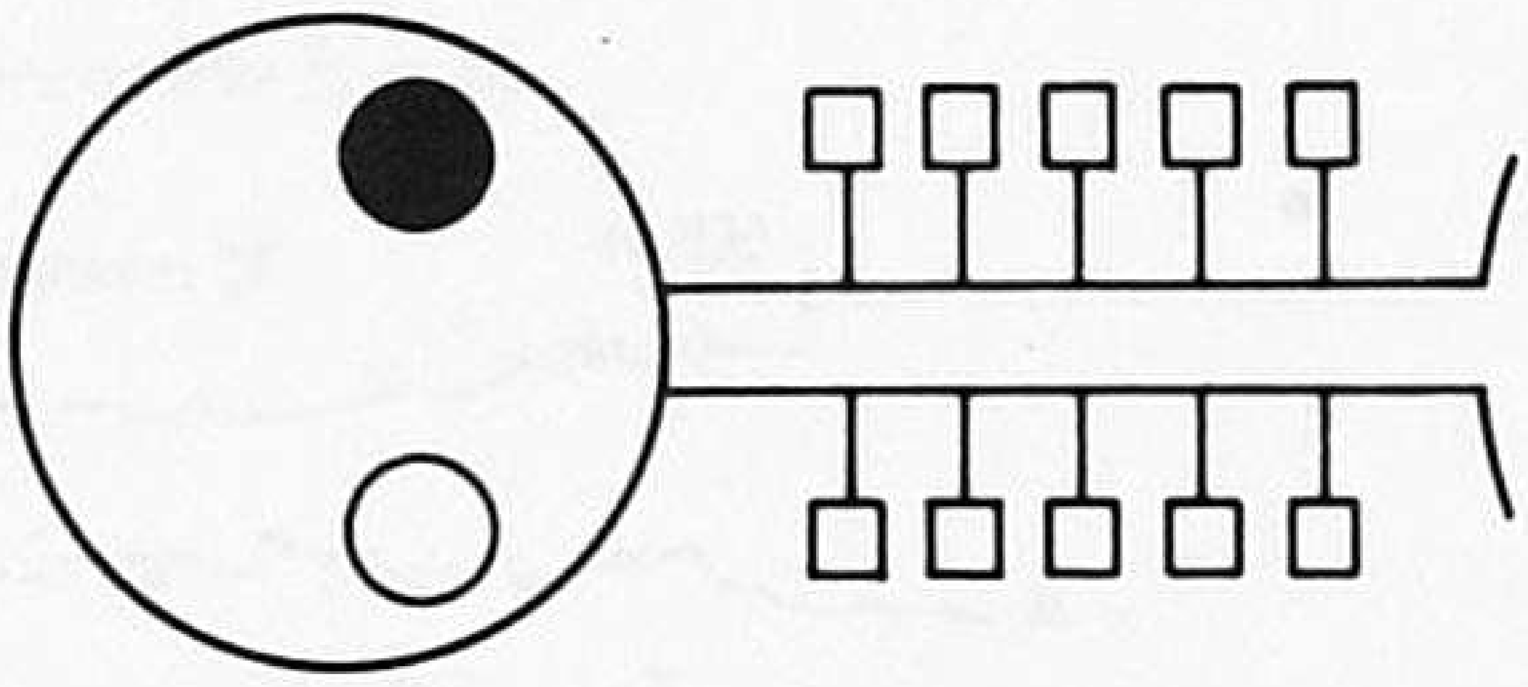
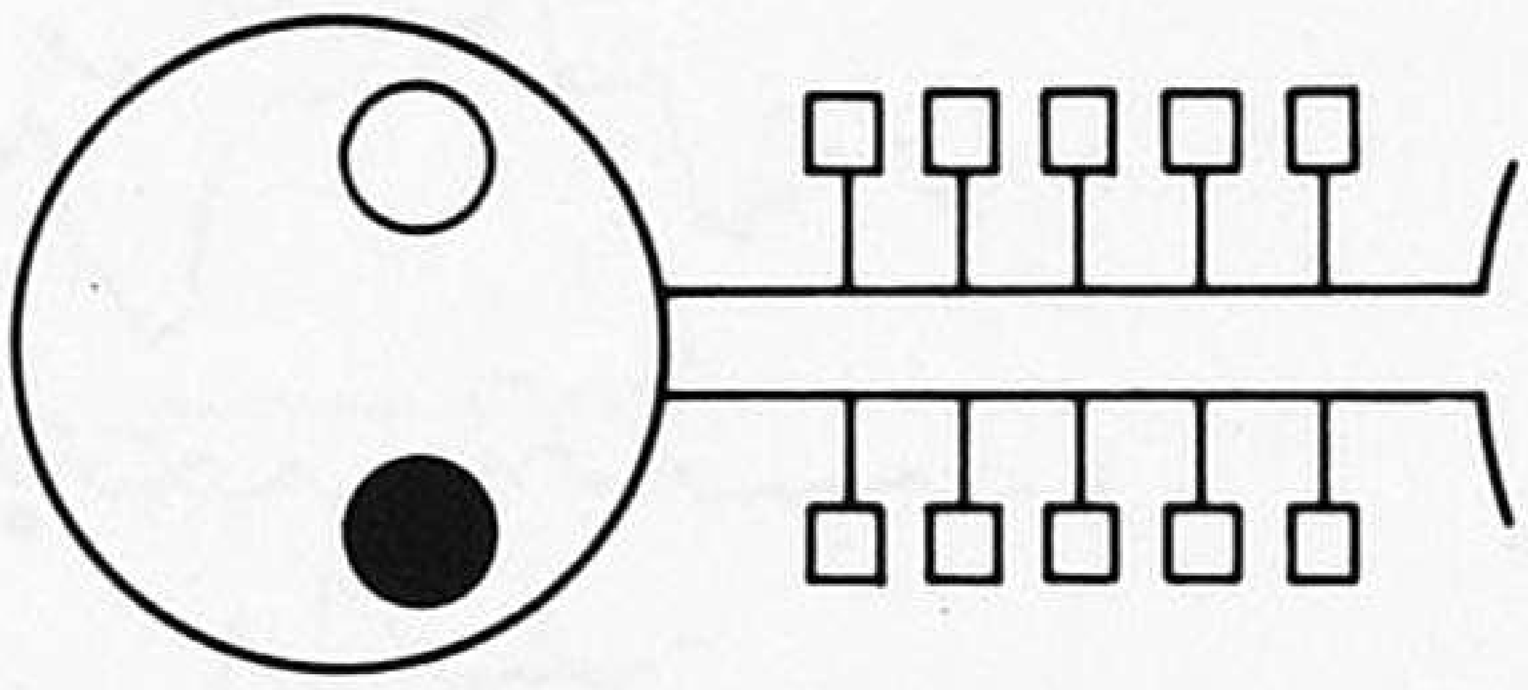
Two of them sought support with the flank on the side of the injection, 1 with the opposite flank, while 1 had no definite inclination to stagger or fall towards one side. The animals were hesitant to jump from an elevation of 1 metre. When prompted to jump they would land on their knees and belly, after which they staggered to the nearest wall for support. These cats reached their maximum imbalance 3 to 5 minutes after injection and then recovered gradually in the course of 30 to 45 minutes.

In 11 trials of animals with postoperative nystagmus (7 times after unilateral labyrinthectomy, 4 times after dorsal chordotomy) and 4 trials with procaine-induced nystagmus (2 unoperated cats, 1 with an unilateral labyrinthectomy, and 1 with a dorsal chordotomy), illumination of the room always caused reduction or disappearance of nystagmus. The nystagmus would usually return if the light was extinguished.

Table 3

UNILATERAL LABYRINTHECTOMY IN CATS

Lateral position in which nystagmus was most pronounced following procaine injection in the neck of 4 cats

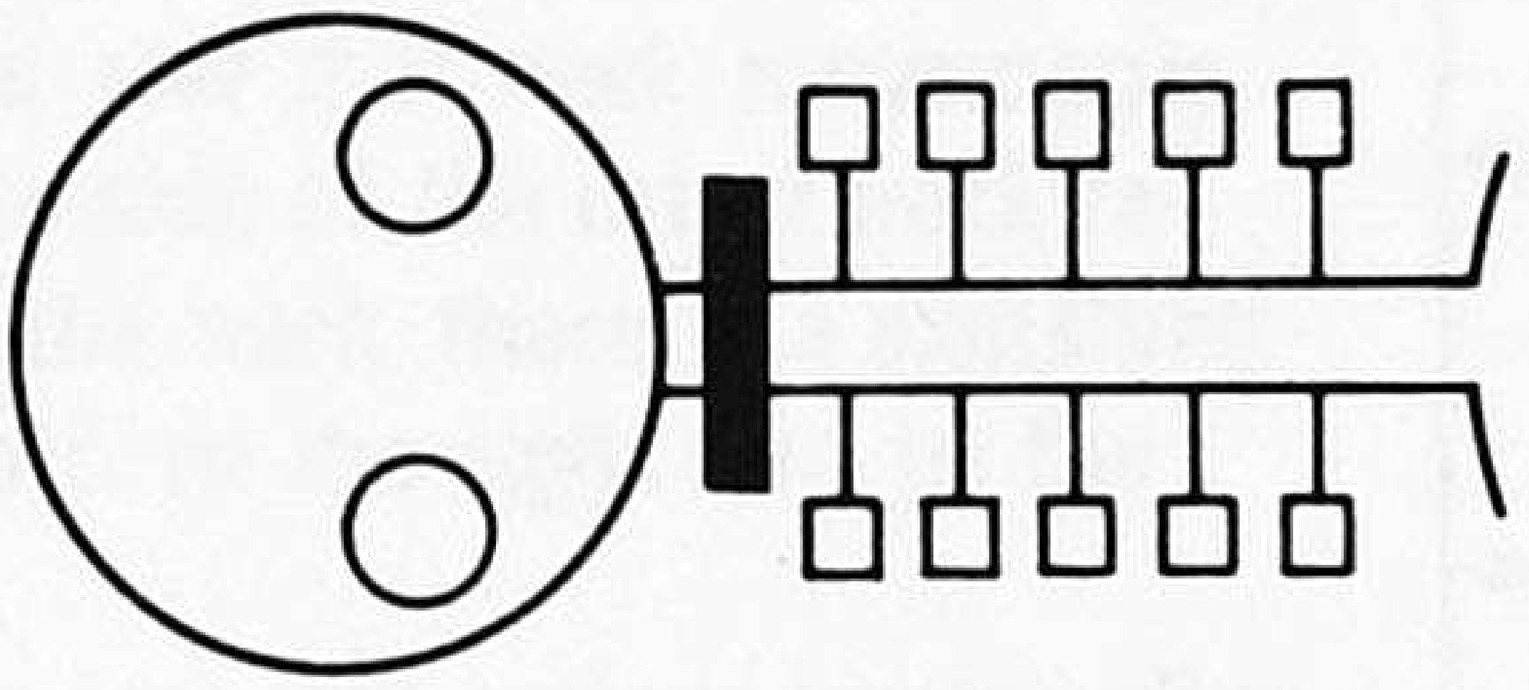
no preference	8	
intact labyrinth down	0	
intact labyrinth up	0	
no nystagmus	13	
Total number of trials	21	

Legend: see Table 1

Table 4

Effect of procaine block on cervical roots after destruction of the dorsal half of the upper cervical cord in 4 cats

nystagmus	17
no nystagmus	33
Total number of experiments	50

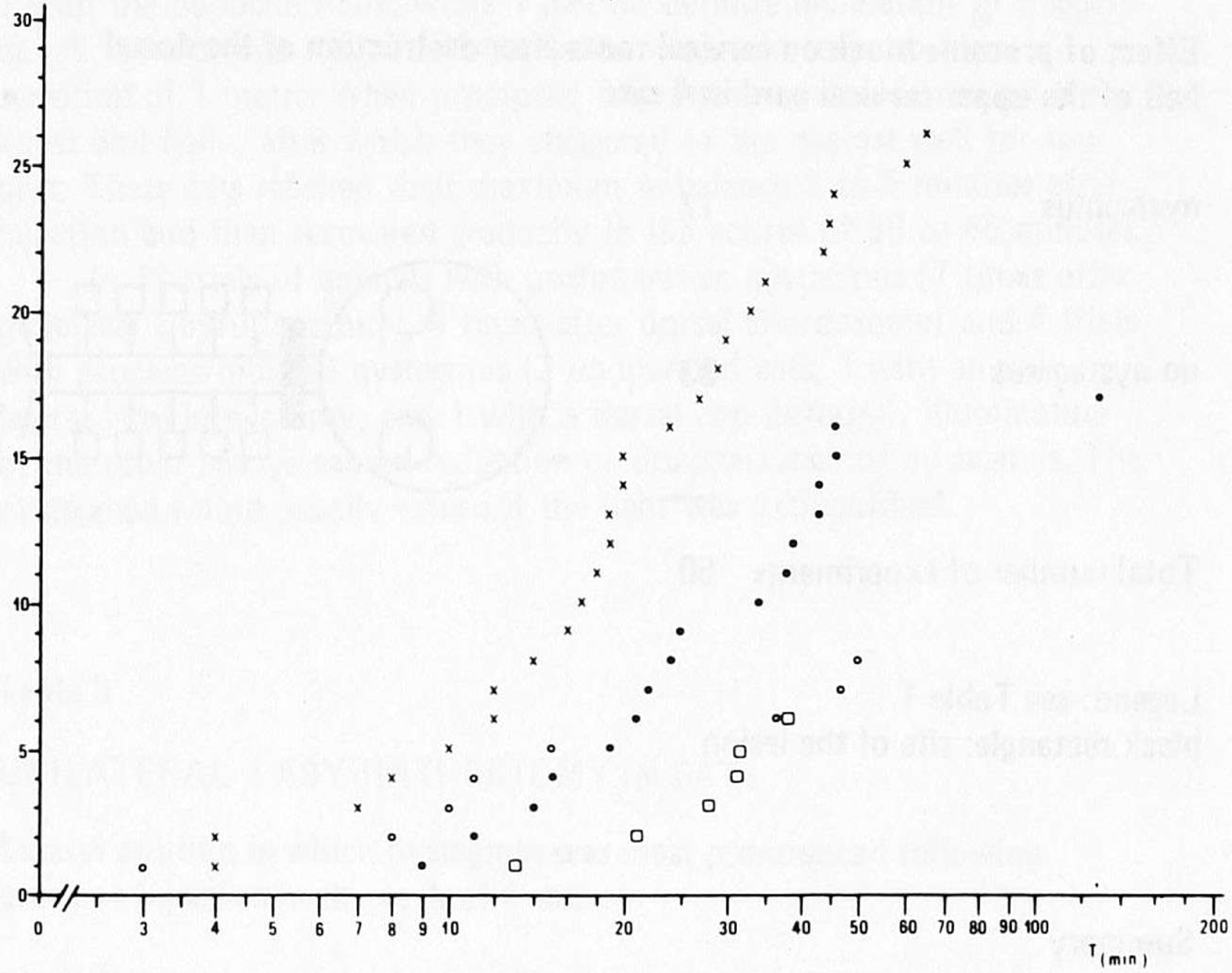


Legend: see Table 1
black rectangle: site of the lesion

Summary

1. Twenty-seven cats received altogether 77 injections with procaine in the neck, causing nystagmus in 26 cases. The posture and gait were studied 21 times after these injections.
2. Four cats had had a unilateral labyrinthectomy. Blocking the neck receptors with procaine caused nystagmus in 8 out of 21 trials. The locomotion of each cat was studied once after the injections.
3. In 1 cat both neurovascular bundles were destroyed; 6 out of 7 injections were followed by nystagmus.
4. Four cats had the dorsal half of the high cervical cord destroyed. Their posture and gait were studied before and after blocking of the neck receptors. In 17 trials out of 50 procaine injections caused nystagmus.
5. The influence of illumination of the room on postoperative nystagmus has been studied 11 times, on procaine-induced nystagmus 4 times. In all instances illumination caused reduction or disappearance of nystagmus.

Figure 9



The ordinate gives the number of the experiment, where the sequence has been determined by ordering the experiments according to the duration of the nystagmus produced. The abscissa shows the duration of the nystagmus on a logarithmic scale.

x procaine injection in the neck of intact cats

o procaine injection in the neck of cats after a onesided labyrinthectomy

● nystagmus after procaine injection in the neck of cats after destruction of the dorsal part of the upper cervical cord

□ procaine injection in the neck of a cat after destruction of both vertebral neurovascular bundles

Discussion

In the cat, as in the rabbit, frequency, amplitude, and direction of cervical nystagmus that had been induced by procaine injections often changed in the course of one experiment. Suzuki and Takemori (1971) found that electrical stimulation of upper cervical dorsal roots in guinea pigs produced horizontal ocular movements which were always directed towards the stimulated side. After unilateral deafferentation of the neck in decerebrate cats, Mc Couch et al. (1950) saw that neck movements induced a full range of limb responses on the side of the intact neck receptors. This means that on either side of the neck there is a signalling system for postures and for movements both to the right and to the left.

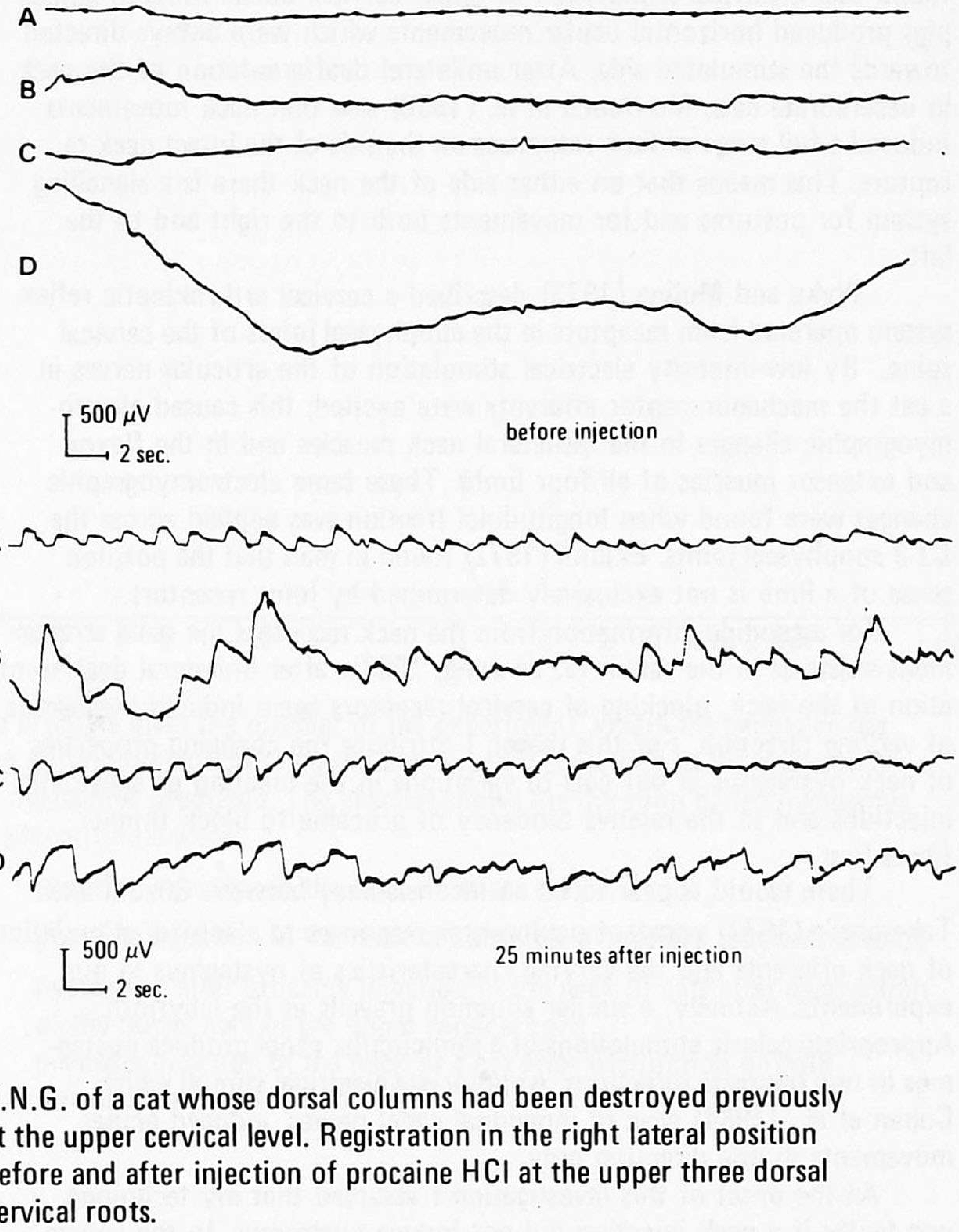
Wyke and Molina (1973) described a cervical arthrokinetic reflex system operated from receptors in the apophyseal joints of the cervical spine. By low-intensity electrical stimulation of the articular nerves in a cat the mechanoreceptor afferents were excited; this caused electromyographic changes in the ipsilateral neck muscles and in the flexor and extensor muscles of all four limbs. These same electromyographic changes were found when longitudinal traction was applied across the C2-3 apophyseal joints. Eklund (1972) found in man that the position sense of a limb is not exclusively determined by joint receptors.

For ascending information from the neck receptors,the same arrangement exists as in the rabbit (J. de Jong, 1967): after unilateral deafferentation of the neck, blocking of cervical receptors again induces nystagmus of varying direction. For this reason I attribute the changing properties of neck nystagmus in our cats to variations in the location of anesthetic injections and to the relative tendency of procaine to block thinner fibres first.

There would appear to be an inconsistency between Suzuki and Takemori's (1971) constant oculomotor responses to electrical stimulation of neck afferents and the varying characteristics of nystagmus in our experiments. Actually, a similar situation prevails in the labyrinth. Appropriate caloric stimulations of a semicircular canal produce nystagmus in two opposite directions. Appropriate electrical stimuli which Cohen et al., (1964) gave to individual canal nerves, induced ocular movements in one direction only.

At the onset of this investigation I assumed that my technique was faulty if a neck injection did not induce nystagmus. In the course of five years of experimentation, I became more confident in the technical correctness of the experiments. Nevertheless, negative trials did

Figure 10



E.N.G. of a cat whose dorsal columns had been destroyed previously at the upper cervical level. Registration in the right lateral position before and after injection of procaine HCl at the upper three dorsal cervical roots.

Legend: see fig. 4

not only occur with a persistent regularity, but became even more numerous after I had stopped using rabbits and acquired a sufficient experience with cats. The most plausible explanation for this finding is that vestibular imbalance in the cat is more readily and completely compensated than in the rabbit, as is evident if one compares the sequelae of labyrinthectomy in these species.

The amount of nystagmus provoked by neck injections was subject to marked differences within the same animal species. A similar phenomenon has been noted by Magnus (1924) who saw a wide variability in the strength of vestibular and cervical reflexes between individual animals. One would expect little cervical nystagmus in animals with weak neck reflexes.

The great difference between the lively, graceful, and agile movements of the cat and the relative poverty of the rabbit's spontaneous motility renders a comparison of motor disturbances in these animals impossible. The severity of the initial postural disorder, however, is less severe in the cat, who does not exhibit the rotation of the head, rolling about the body axis, and forced circling movements, - Magnus' (1924) Manegebewegungen - , which are seen in the rabbit. In twenty-one trials I studied motor disturbances after the electronystagmographic recording had been completed. In twelve instances the cat showed staggering without any nystagmus and in the other nine experiments the ataxia outlasted the nystagmus. Apparently the ascending cervico-oculomotor circuit has at its disposal compensatory mechanisms which do not correct disturbances of the descending cervico-spinal pathways.

Comparison of vestibular and cervical syndromes demonstrates that the cervical syndrome is characterized by striking ataxia and relatively little nystagmus. The fact that some of the neck infiltrations induced an evident ataxia without any nystagmus should be borne in mind by those who evaluate disturbances of equilibrium after traumatisms of the human neck. Since both the hind quarters and the fore limbs of these cats were equally ataxic, the disorders of gait cannot be ascribed to leakage of procaine along the cervical spine towards the brachial plexus. As it is very difficult to quantify the cervical block, I cannot on the basis of our experiments decide whether or not there is habituation to blocking of neck afferent fibres. Our control experiments show that ataxia is not significantly influenced by oedema of the foot-pads which sometimes develops while the animals are tied to a board in order to record their ocular movements.

The influence of optic fixation on nystagmus has been studied, amongst others, by Aschan (1956) in patients with nystagmus of varying origin. In 1964 he published the results of nystagmography in rabbits that frequently had no nystagmus in the light, but vigorous vestibular nystagmus in darkness. My experiments in rabbits have not been performed in darkness, as I wanted to observe the ocular movements directly. Recording in the dark probably would have yielded nystagmus with greater amplitude, higher frequency and longer duration, but could have given confusion with ocular drift (Collewijn, 1970).

Kornhuber (1966) observed ataxia, but no nystagmus after intradural cutting of cervical dorsal roots in the cat. He did not describe, however, whether he made ENG recordings in the dark. Similarly, L. Cohen (1961) described ataxia after local anesthesia of the neck in Rhesus monkeys, without mentioning nystagmus. In the same species J. de Jong (1973) has only found cervical nystagmus if records were obtained in the dark. It is improbable that the increase of nystagmus in darkness can be ascribed to changes of the so-called corneo-retinal potential which is, in fact, in man known to decrease initially and rise afterwards nearly to its starting level in the absence of light (ten Doesschate and ten Doesschate, 1956; Horsten, Philipszoon and Winkelman, 1963). The term 'corneo-retinal potential' is at least a partial misnomer as Pasik, Pasik and Bander (1965) were able to record the electro-oculogram after evisceration of the eyeballs in monkeys. These findings have been confirmed by B. Cohen (personal communication).

Procaine injections after unilateral extirpation of the labyrinth

Comparison of Tables 1 and 3 reveals two facts: in rabbits cervical nystagmus is more pronounced in the lateral position with the intact labyrinth pointing down. This is not the case in cats, a difference that can be explained by analogy to the experimental data of Jongkees and Philipszoon (1962), of Philipszoon (1962), and of Collewijn (1969). Jongkees and Philipszoon (1962) could only provoke nystagmus in rabbits and patients by linear accelerations after a previously induced eye deviation. Philipszoon (1962) observed in both the human and the rabbit that slow compensatory eye movements induced by neck torsion turned into nystagmus only when the speed of the neck torsion exceeded a certain limit. Collewijn (1969) noted that the neuronal circuits which produce quick phases of nystagmus are triggered more easily as the eyes move down from their mid-position. In the chronic stage after labyrinthectomy the rabbit's eyes dwell in the immediate vicinity of their resting position as soon as the animal has been placed on its side with the intact labyrinth pointing upward. Since there is not much non-adapting eye deviation, the slow ocular drift, induced by blocking of neck receptors, will not trigger the quick phase circuits easily and only some nystagmus occurs. In the lateral position with the intact labyrinth pointing down, the same rabbit shows a large vertical conjugate deviation of the eyes: if one looks at the eye that is facing up, the iris with the exception of a narrow upper segment is covered by the lower eyelid. Addition of a small neck-induced ocular shift to the extreme vertical non-adapting deviation of the eyes will produce much more nystagmus than is seen when the animal is placed on its other side. In the cat (Magnus, 1924) unilateral labyrinthectomy will produce non-adapting deviation of the eyeballs during the first few postoperative days only. After this initial period in which I gave no injections into the neck the biasing factor that favours nystagmus in one lateral position is not present any more.

Procaine injections after destruction of both vertebral neurovascular bundles at the C1 level

Carbone (1965) tied off both vertebral arteries at their point of emergence from the subclavian arteries in rabbits. This resulted in nystagmus for three to four seconds. The fact that we could elicit nystagmus by procaine injections in the neck of a cat whose vertebral neurovascular bundles had previously been destroyed, proves once more that a non-vascular cause for cervical nystagmus does exist too.

Lesions of the dorsal part of the upper spinal cord

As we know that cervical nystagmus is due to blocking of proprioceptive afferents, it seems a surprising finding that destruction of the dorsal columns does not abolish this nystagmus. However, it would be very rash, indeed, to state that the dorsal columns or dorsal spino-cerebellar tracts are not involved in neck nystagmus at all: in my small series of animals, nystagmus persisted for up to eight weeks after the spinal operation. This could point to an inhibitory action of the dorsal columns on the vestibular nuclei. The duration of the nystagmus which was started by procaine injections in the neck was equal before and after cutting the dorsal columns. Thus, at least some proprioceptive information must ascend in the ventral part of the cord.

This is not the first attack on the clinician's time-honoured habit to regard the dorsal columns as the main pathway carrying proprioceptive impulses. Oscarsson (1970) states that proprioceptive information also ascends in the spino-reticulo-cerebellar pathway (SRCP) and in the spino-olivo-cerebellar pathway (SOCP). The SRCP ascends in the ventral part of the lateral funicle. Miller and Oscarsson (1970) divide the SOCP in three parts: ventral funiculus (VF)-SOCP, dorsolateral funiculus (DLF)-SOCP, and the dorsal funiculus (DF)-SOCP. Wall (1970) also attacked this concept of the importance of the dorsal columns in a careful review of the literature, supported by two series of experiments. He suggested that the dorsal columns have a dual function: their first task would be to conduct impulses that control the analysis of information which reaches the brain by other somatic sensory pathways. If this analysis does not decipher the afferent information adequately, the dorsal columns would execute their second duty, which is the conduction of stimuli that are generated by active exploration of the environment. In this situation the dorsal columns would be essential for the interpretation of stimuli which can only be understood by active movements or by sequential analysis. Norton (1970) opposes Wall's concepts of posterior column function, as they would render both the somatotopic organisation and the modality specificity of the dorsal column-medial lemniscus pathway superfluous. Dubrovsky et al., (1971) and Melzack et al., (1971), however, also put emphasis on the dorsal columns' function in sequential analysis of sensory data.

Philipszoon and Bos (1963) cut the spinal cord at the C1 level partially in one rabbit and completely in seven others. Thereafter, neck torsion nystagmus was eliminated, whereas vestibular nystagmus still remained intact. Their experiments were not controlled histologically, however.

The open question remains as to which alternative tracts carry proprioceptive data to the vestibular nuclei. My lesions destroyed the dorsal columns, the dorsal spino-cerebellar tracts, the external cuneate nuclei, the dorsal-funiculus and the dorso-lateral-funiculus spino-olivo cerebellar pathway and the fibre tracts of Gerebtzoff (1940), if the latter do actually exist in the cat. I paid special attention to the possibility that the lesions could be cranial to the origin of the internal arcuate fibres, that would then surreptitiously pass the dorsal column information on to the brain stem. This was not the case in any of my cats. Thus we are left with a number of pathways which could possibly carry the proprioceptive information to the brain stem:

1. the spino-reticulo-cerebellar pathway
2. the ventral-funiculus spino-olivo-cerebellar pathway
3. the rostral spino-cerebellar tract, which is an equivalent of the ventral spino-cerebellar tract at the cervical spinal level, and has not been located anatomically so far (Brodal, 1969).

As cerebellectomy does not abolish neck nystagmus, one would be inclined to concentrate on the spino-reticular and spino-olivary pathways. Abundant connections exist between the reticular substance of the medulla oblongata and the vestibular nuclei. The olivo-cerebellar fibres give off excitatory and inhibitory collaterals to the vestibular nuclear complex.

Again, we must not forget that the spinal lesions induced longlasting nystagmus (page 35). This means that the interrupted pathways cannot be disregarded with impunity. As destruction of the ventral half of the high cervical cord would be incompatible with chronic survival, this counterexperiment unfortunately was not feasible. It has not been performed in acute experiments either: Wilson et al., (1966) who found that spino-vestibular responses were not abolished by destruction of the dorsal half of the cat's thoracic cord, did not study spino-vestibular interaction after a lesion of the ventral spinal cord.

Azzena (1969) and Giretti (1971) claim that the spinal cord compensates the sequelae of unilateral labyrinthectomy and unilateral fronto-parietal cortical lesions in guinea pigs. It could equally well be argued that the main origin of compensatory mechanism is located in the lower brainstem and that the precarious balance regained by neurons in this region is disrupted once more by spinal lesions. The experimental data presented here do not settle this argument.

Conclusions

1. Ataxia, a tendency to stagger and fall sidewards as well as nystagmus are induced by blocking afferent cervical fibres in the cat.
2. In the cat, as well as in the rabbit, neck nystagmus can be elicited after destruction of one labyrinth.
3. Cervical nystagmus is not abolished by complete destruction on both sides of the vertebral arteries, veins, and nerves.
4. Section of the dorsal half of the upper cervical cord induces nystagmus, which persisted for up to eight weeks in my series of four experimental animals. Thereafter blocking of cervical receptors with procaine again causes nystagmus.
5. Spino-vestibular information is, at least in part, carried by pathways ascending in ventral regions of the cord.
6. In clinical neurology it is incorrect to postulate that disturbances of equilibrium after neck injuries are a sign of organic disorder only if nystagmus is present.

NECK NYSTAGMUS AFTER CERVICAL MID-LINE MYELOTOMY IN THE CAT

Introduction

In chapter III I described a series of experiments in rabbits in which one of the labyrinths and the dorsal roots on one side of the neck had been destroyed. In these animals nystagmus occurred when the remaining dorsal roots C1-2-3-4 were blocked by procaine injections, even if the functioning labyrinth and the intact neck receptors were located on opposite sides of the body. This means that afferent information from the neck crosses the mid-line either in the spinal cord or in the medulla oblongata or at both these levels. Other, but less plausible possibilities, would be more rostral crossings such as the commissura colliculi inferioris, the massa intermedia, the habenular, posterior, anterior, and supraoptic commissures.

Spinal crossing fibres have been described by a number of anatomists. Cajal (1909) using the Golgi method in cats described collaterals of cervical dorsal root fibres that went to the dorsal horn on the opposite side by way of the commissura grisea dorsalis. In Marchi preparations crossing fibres were found to be less numerous by Ranson (1932), Corbin et al., (1935, 1936) in the cat and by Yee (1939) in the rabbit. Hashimoto (1928) wrote that of the fibres ascending from the cervical cord to the descending vestibular nucleus a small number crossed the mid-line. Johnson (1954) demonstrated that a few fibres of the spino-vestibular tract (Collier and Buzzard, 1903) ended in the crossed Deiters' nucleus.

Physiological evidence for crossed spino-vestibular interaction was produced by Gernandt and Gilman (1959), Feldman et al., (1961), Fredrickson et al., (1966), Wilson et al., (1966), Wilson and Yoshida (1969) as well as by Matsushita and Ikeda (1970).

A detailed anatomical description of commissural fibres between the vestibular nuclei in the cat was given by Ladpli and Brodal (1968) and Brodal (1972). Crossed connections between the vestibular nuclei were demonstrated in physiological experiments by de Vito et al., (1956), Shimazu and Precht (1966), Fredrickson et al., (1966), Gernandt (1964, 1967), Mano et al., (1968), Stroud et al., (1971), and Shimazu (1972).

As a first step towards the identification of the commissural systems that are involved in cervico-vestibular reactions, I split the three upper spinal neck segments of the cat in the mid-line.

Materials and methods

Except for one animal which had already undergone a unilateral labyrinthectomy one year previously, adult cats with normal vestibular responses were used. The animals received intraperitoneal pentobarbitone sodium anesthesia and were then, under aseptic conditions, subjected to unilateral labyrinthectomy, intradural section of the dorsal roots C1 through C3 on one side of the neck, and sagittal split of the cord extending from a level just proximal to the root entrance of C1 to the entrance of the more rostral rootlets of C4. The dorsal roots were cut on the side of the labyrinthectomy in one, on the opposite side in the other animals.

After surgery the cats were artificially fed by a nasogastric tube until they were able to eat again. During the period from five to eight months after surgery the cats received cervical procaine blocks and were studied with the techniques described in chapter II. Before being sacrified, these cats were decerebrated anemically under intraperitoneal thiopentone sodium anesthesia by J. de Jong. Decerebrate rigidity and neck responses on the extremities were studied. A Sherringtonian intercollicular cut in the plane of the tentorium cerebelli was then made, followed by additional observation of the animal.

Finally the cats were perfused with Ringer's saline followed by 10 per cent formaline. After hardening of the cord and the medulla oblongata for two weeks in formaline, the specimens were studied macroscopically, after which Klüver-Barrera and Holzer sections with a thickness of 7 μ were made, projected by a camera lucida, and drawn at a magnification of 10 times.

Results

Of the 5 animals that were used, 2 died during the first two post-operative weeks. Because of autolysis, their lesions could not be examined histologically. One early death was of the cat that had been operated upon one year after unilateral labyrinthectomy. This animal kept its four legs in extension on the first post-operative day, but, apart from this, did not show any anomalies of posture and tonus. The other 4 cats preferred to lie on the side of the labyrinthectomy. All developed a pronounced cervical lordosis and a slight increase of the dorso-lumbar kyphosis. There was a marked stiffness of the extremities with extension of the fore limbs and semiflexion of the hind limbs, which had its onset between the first and twelfth post-operative day, while it persisted until the seventh to ninth week after surgery.

On the side of the labyrinthectomy all animals had miosis and a paretic membrana nictitans. Nystagmus was directed towards the side of the intact labyrinth in 1 cat and to the side of the destroyed labyrinth in 2 cats; the cat with the previously destroyed labyrinth showed no nystagmus, and with the first cat in this series I did not look for nystagmus the first days after the operation. After disappearance of the postoperative nystagmus, the 3 surviving cats received a total of 25 injections of 2 ml 2 per cent procaine HCl into the neck (Table 5). In 18 of these trials nystagmus occurred with a duration of 15 to 84 minutes (fig. 11). Nystagmus was recorded 4 times after placing the anesthetic depot on the side of the neck where the dorsal roots had been cut. The direction of the nystagmus, as well as its frequency and amplitude were variable. In 15 trials nystagmus was stronger in one of the lateral positions. There was no correlation between this position and either the side of the labyrinthectomy or the side of the injection into the neck; this also held true in the subsequent trials with the same cat. The animals received intra-muscular control injections of 2 ml 2 per cent procaine HCl, which did not cause nystagmus. Fig. 12 shows an example of procaine-induced nystagmus in cats with a unilateral labyrinthectomy, unilateral neck deafferentation, and mid-line myelotomy.

Anemic decerebration was successfully performed in 2 cats. The third died during the surgical exploration of the basilar artery by haemorrhage from dural sinuses at the base of the skull. The surviving animals, one with the labyrinthectomy and the sectioned dorsal roots on the same side, the other with these interventions on opposite sides, developed a slight stiffness of the flexor musculature that was not influenced by passive movements of the neck in relation to the fixed head. A diagram of the spinal lesions is shown in fig. 13.

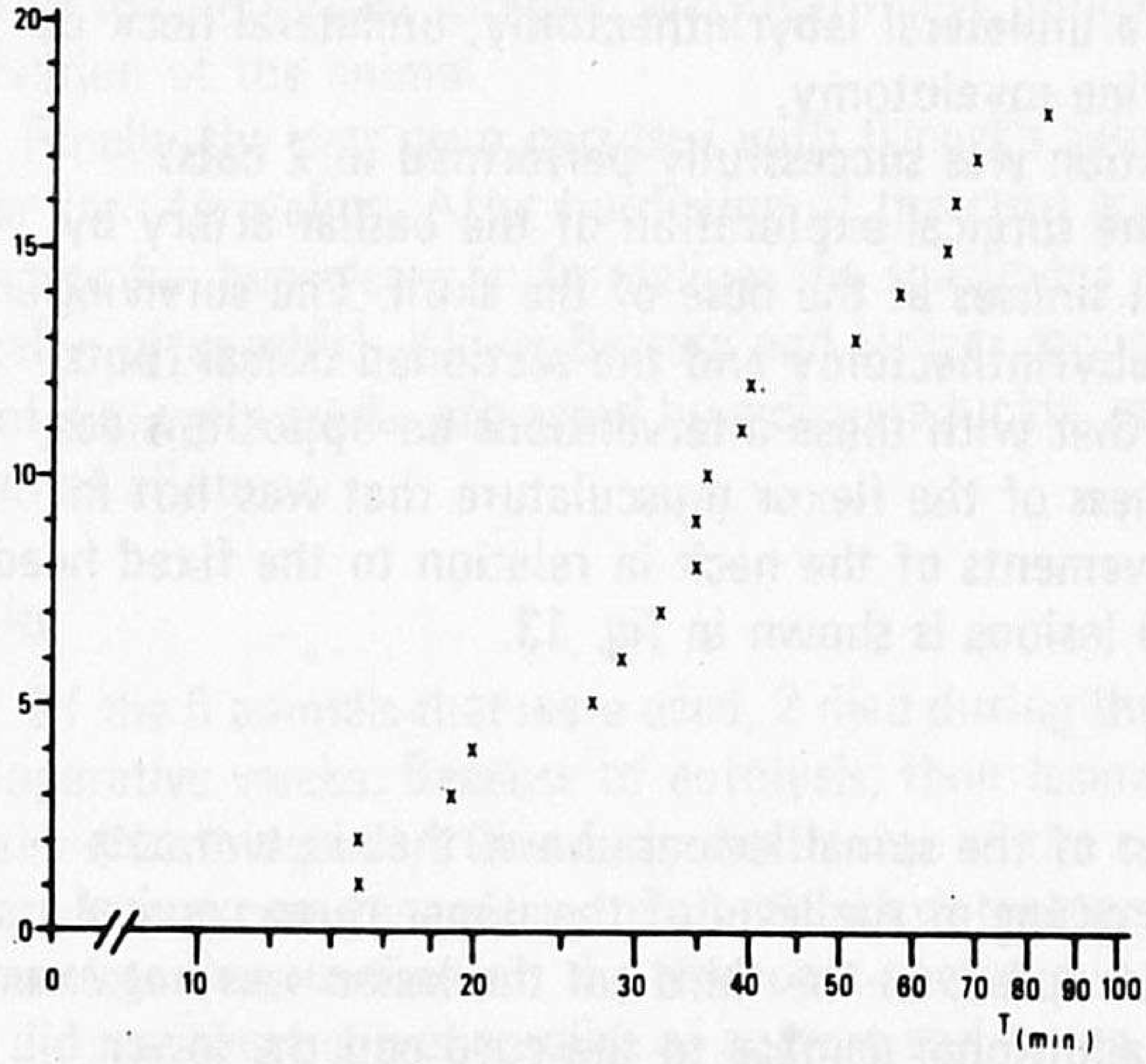
Discussion

The reconstruction of the spinal lesions shows that in two cats all commissural fibres crossing at the level of the upper three cervical segments have been interrupted. In the third cat the lesion was not exactly in the mid-line. The additional damage to the cord and the lower medulla oblongata is more than sufficient to explain the postoperative limb rigidity. It is, in fact, surprising that the animals recovered as rapidly as they did. In addition to the advantages cited in chapter V, the cervical cord of the cat offers the favourable circumstance that the lateral cervical nucleus is limited to the level of C1 to C3. The afferent fibres of this nucleus cross the mid-line in the upper cervical cord and have been cut by my lesions. This means that the lateral cervical nuclei are not an essential link in the cervico-vestibular pathway.

In one animal the neck roots and the labyrinth had been destroyed on opposite sides of the body, in the others on the same side. After the operation only one cat showed nystagmus in the customary direction, i.e. towards the side of the intact labyrinth. Two other animals had nystagmus directed towards the side of the lesion. The rather gross and asymmetrical spinal cuts render a more detailed interpretation of this finding hazardous. It may be stated, however, that the spinal input into the vestibulo-oculomotor system of the cat is strong enough, if disturbed, to change the direction of nystagmus after labyrinthectomy.

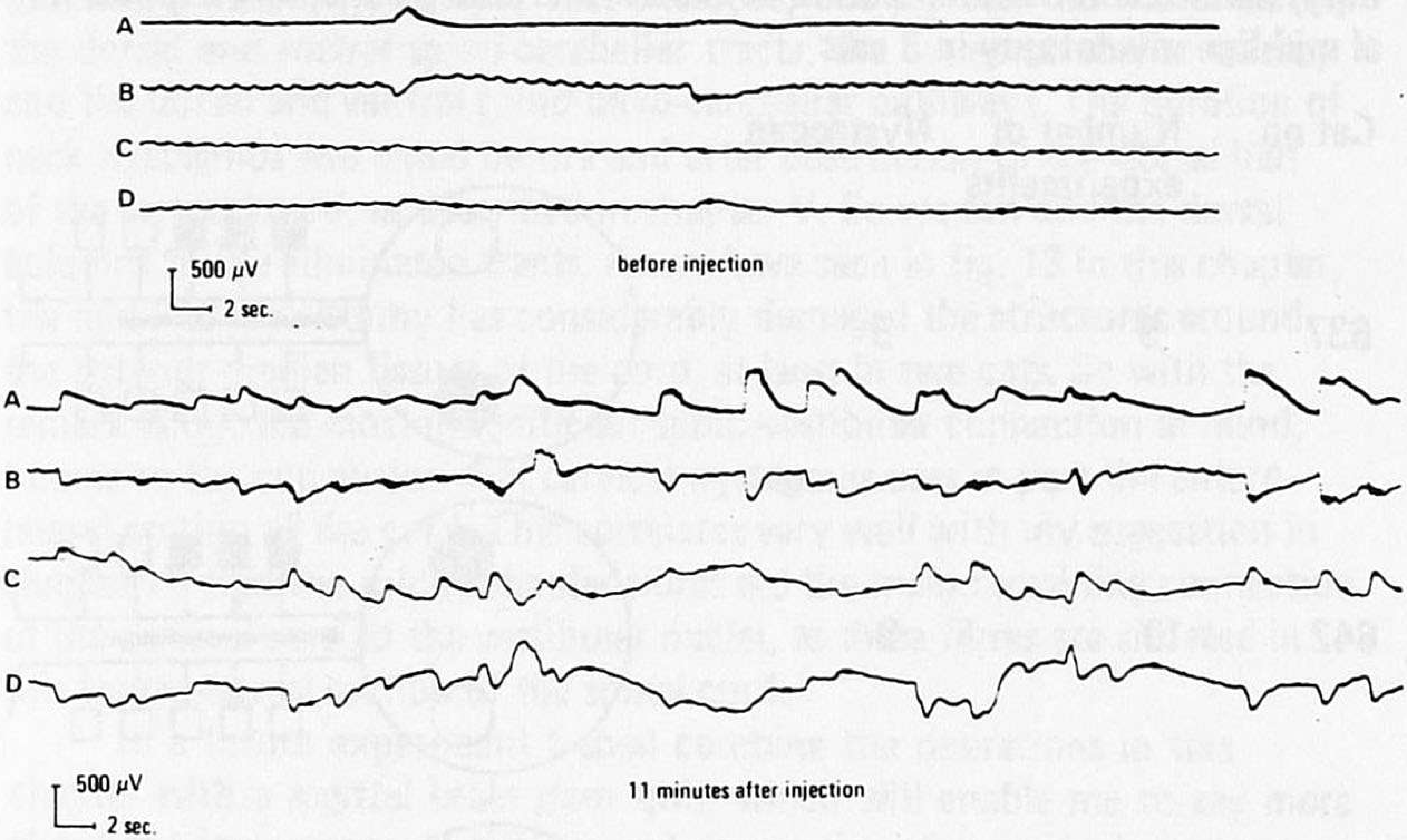
After decerebration the animals were observed for two and a half hours; it is unlikely that the absence of decerebrate extensor rigidity could be due to the thiopentone sodium. On the other hand I did not perform a control experiment. As a final check on the operation the skull was trephined and a Sherringtonian intercollicular cut was made,

Figure 11



Cats with a mid-line sagittal split of the cervical cord. Duration of nystagmus after procaine block of the dorsal roots. The ordinate gives the number of the experiment, where the sequence has been determined by ordering the experiments according to the duration of the nystagmus produced. The abscissa shows the duration of the nystagmus on a logarithmic scale.

Figure 12



E.N.G. of a cat with a unilateral labyrinthectomy, unilateral neck denervation and a mid-line myelotomy before and after infiltration of the remaining upper three dorsal cervical roots with procaine. Right lateral position. Legend: see fig. 4

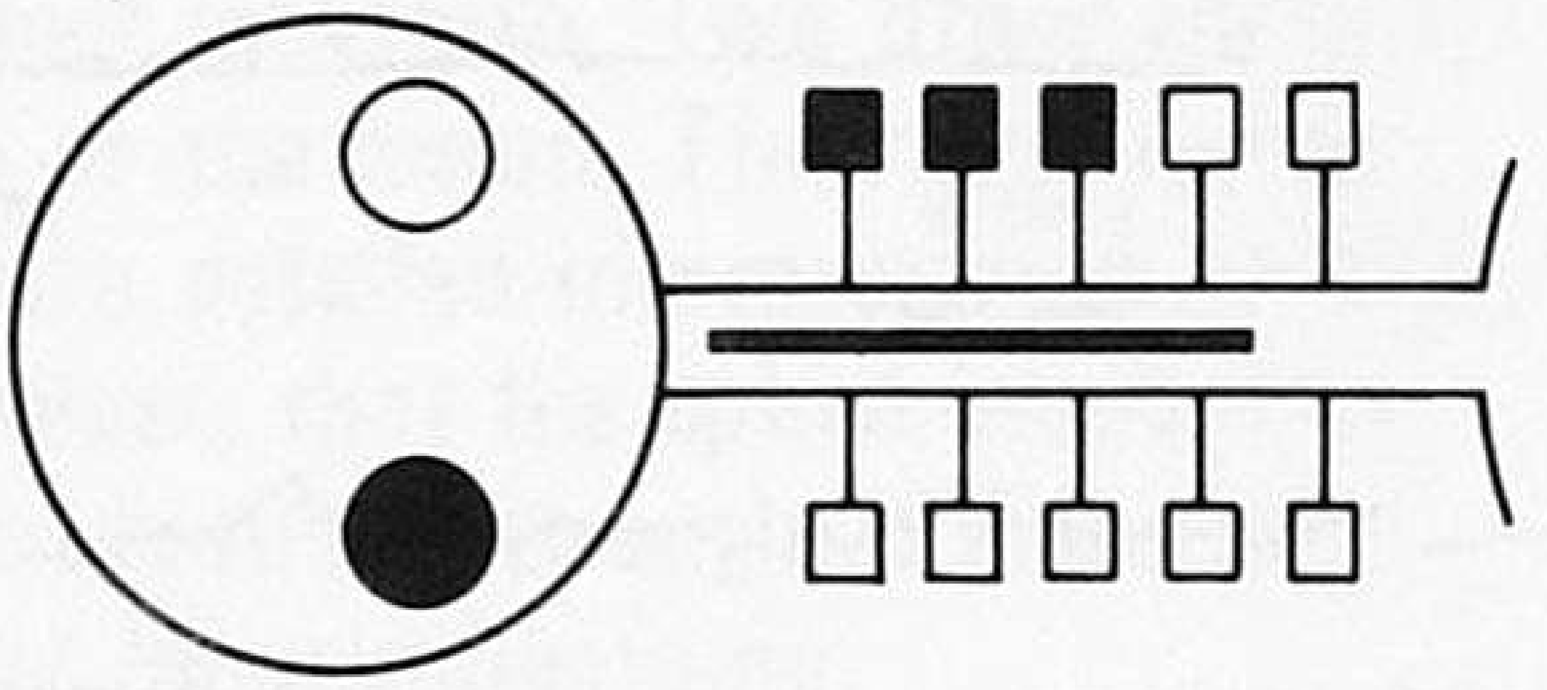
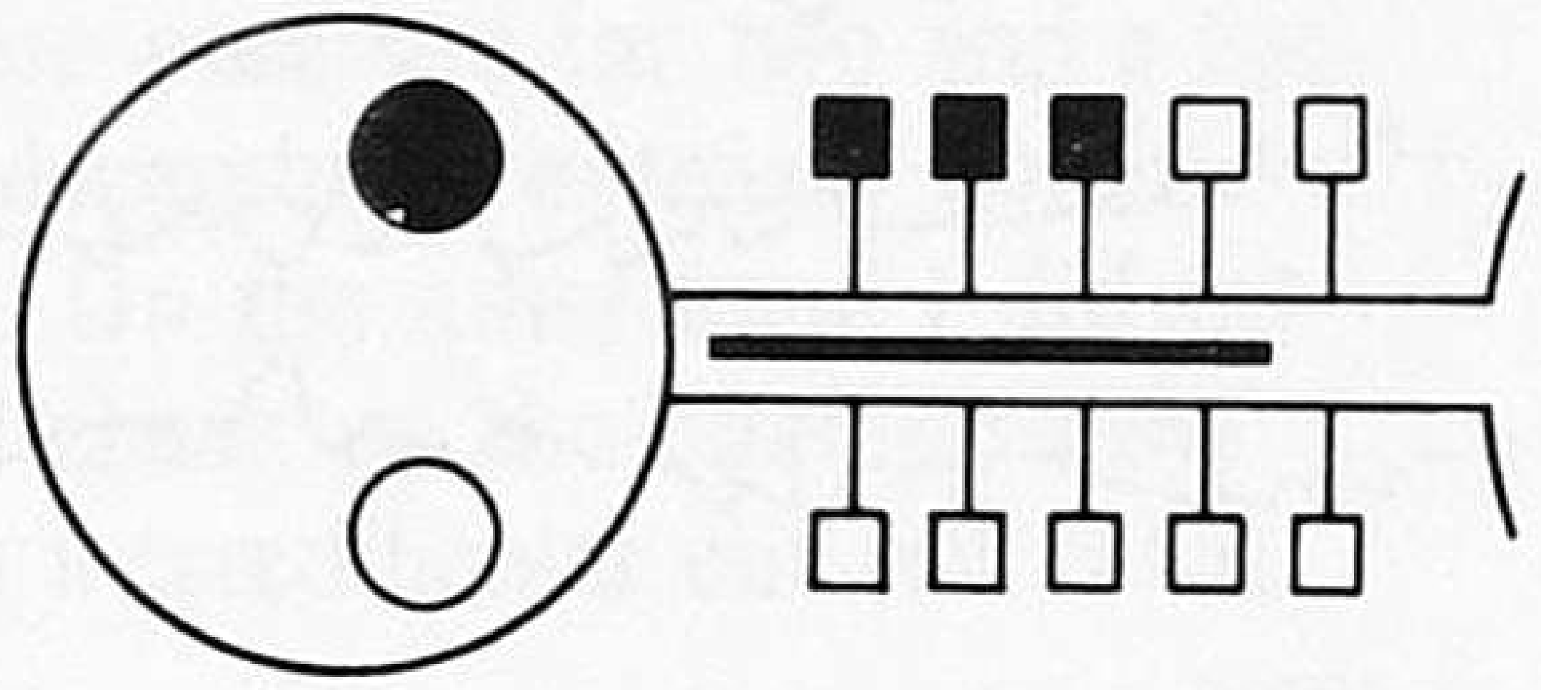
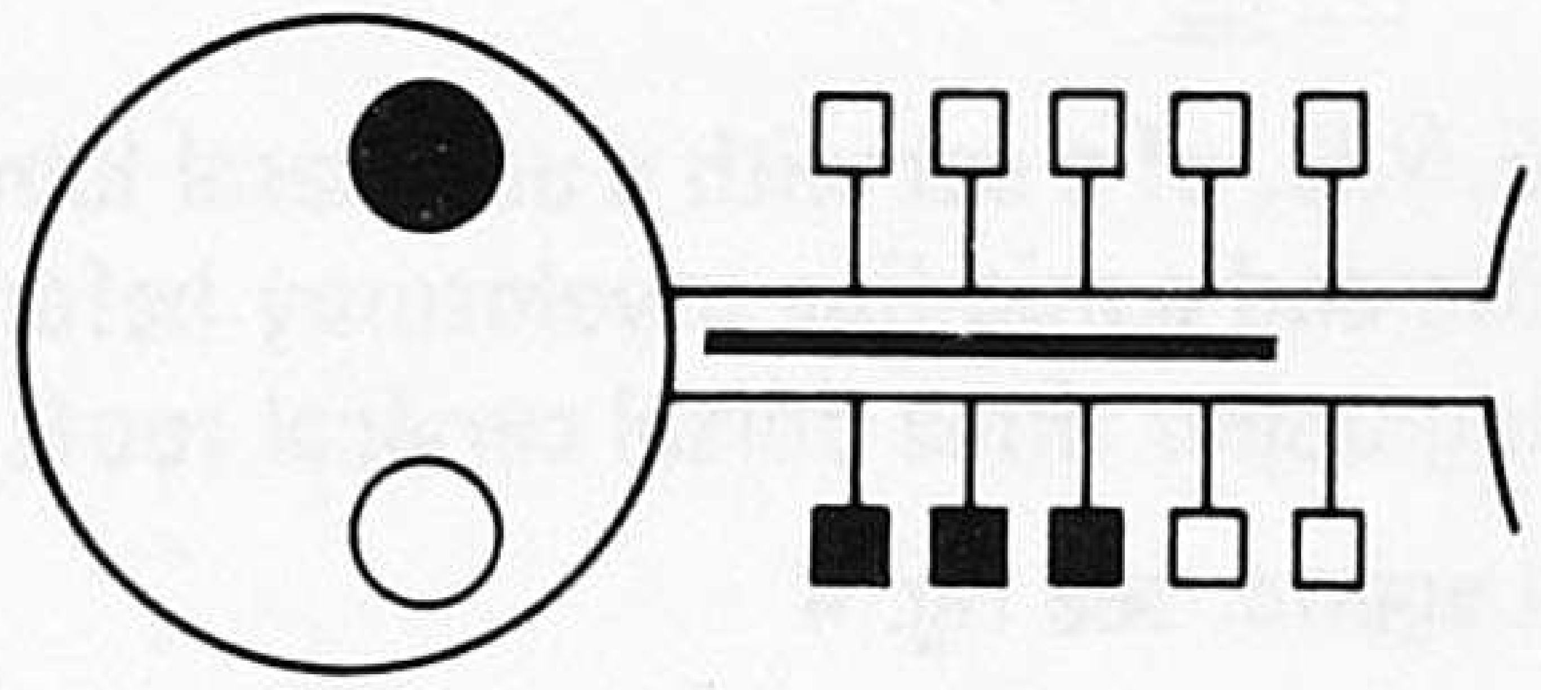
which did not affect the posture or muscle tone of the animal. When an animal is decerebrated by transection of the brain stem, no extensor rigidity will develop in a limb which has previously been deafferentated by dorsal root section (Sherrington, 1947). This is not the case with an anemic decerebration.

After perfusion of the animals and removal of the cervical cord, remnants of an old haemorrhage were seen in the mid-line on the ventral side of two specimina.

In accordance with Sherrington's (1947) findings in cats and dogs, Gilman and Denny-Brown (1966) found that monkeys with posterior column lesions developed extensor rigidity of the limbs upon decerebration. The absence of extensor rigidity in my cats is possibly an effect of damage to central motor axones originating in the brain stem and interruption of proprio-spinal pathways in the cervical cord. The absence of extremity responses to neck torsion cannot with certainty be ascribed to destruction of Magnus' (1924) centre for neck reflexes on the

TABLE 5

Effect of procaine block of cervical dorsal roots after unilateral labyrinthectomy, unilateral intradural section of the dorsal roots C1-2-3, and high-cervical mid-line myelotomy in 3 cats

Cat no.	Number of experiments	Nystagmus	
637	9	5	
642	10	8	
651	6	5	
Total:	25	18	

Legend: see Table 1

extremities as Ehrhardt and Wagner (1970) found that after laminectomy the cervical cord is very easily mechanically damaged by neck torsion. In the present series, procaine probably spread across the mid-line of the neck; this would explain why nystagmus occurred after cervical injections on the side where the dorsal roots had been cut.

Collecting the results of the preceding experiments, one meets at once with the difficulty that one cannot assume that the various lesions were made in one animal. By doing so, one runs the risk that of all the spino-vestibular connections emphasis is put on the most insignificant one. Chapter III describes how cervical procaine nystagmus can be elicited in a rabbit when one labyrinth is destroyed and the neck is denervated on the same or the opposite side. It was mentioned that the uncrossed spino-vestibular connections are probably more important than the crossed ones. From chapter IV it is clear that the cerebellum is not essential to cervical procaine-induced nystagmus. This excludes, but for their collateral fibres, the dorsal and rostral spino-cerebellar tracts, the cuneo-cerebellar tracts, and the dorsal and ventral spino-olivo-cerebellar pathways. The duration of neck nystagmus was equal before and after destruction of the dorsal half of the cervical cord, as described in chapter V. So we can add the dorsal columns to the eliminated tracts. As we have seen in fig. 13 in this chapter, the mid-line myelotomy has considerably damaged the structures around the anterior median fissure of the cord, at least in two cats. So with the remark about the most insignificant spino-vestibular connection in mind, I come to the conclusion that cervical nystagmus uses in part the antero-lateral section of the cord. This correlates very well with my suggestion in chapter IV that the spino-reticular fibres are the main remaining connection of the cervical cord to the vestibular nuclei, as these fibres are situated in this ventro-lateral section of the spinal cord.

In a future experiment I shall combine the operations in this chapter with a sagittal brain stem split, which will enable me to say more about the importance of the crossed connections for cervical nystagmus.

Summary

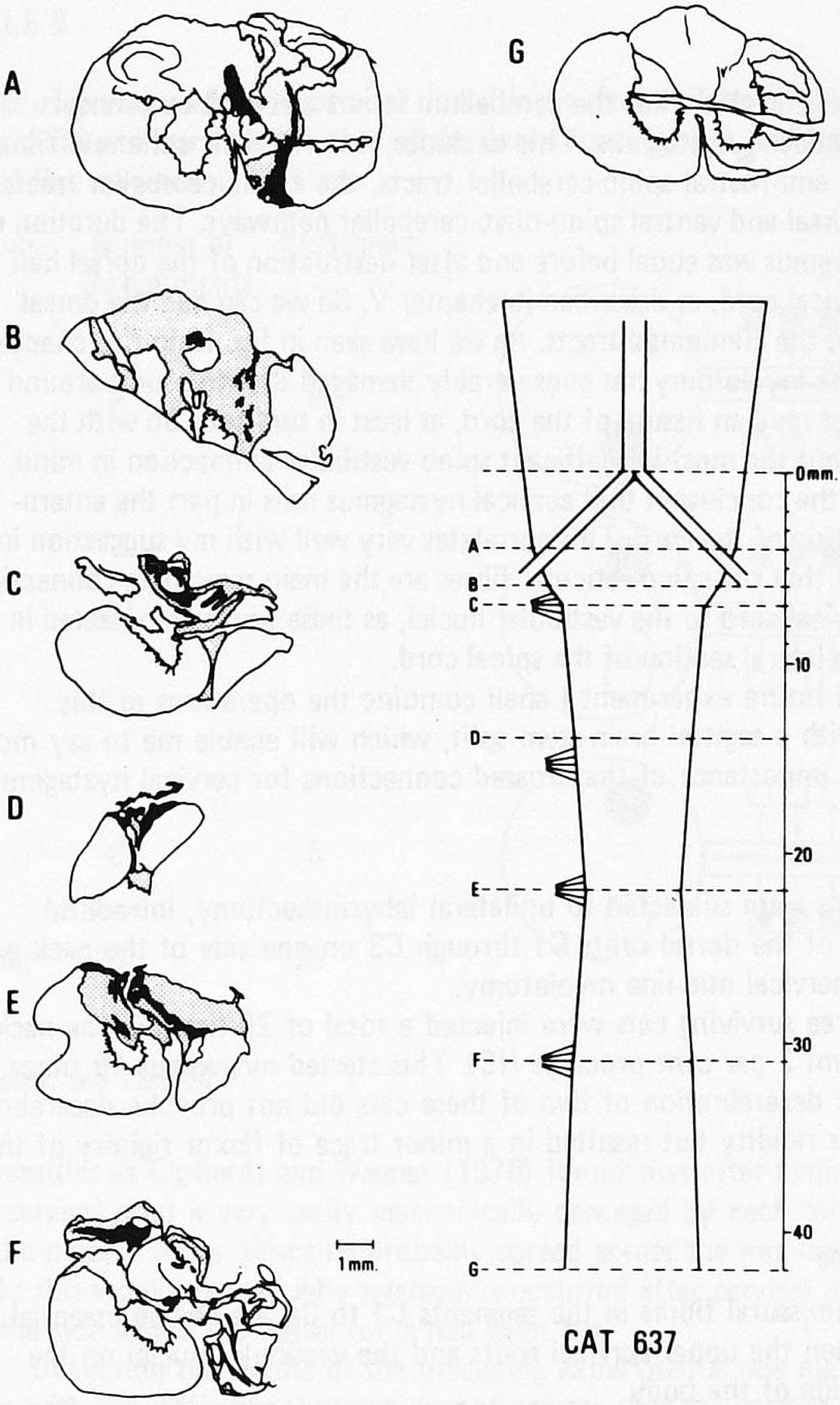
1. Five cats were subjected to unilateral labyrinthectomy, intradural section of the dorsal roots C1 through C3 on one side of the neck and a high cervical mid-line myelotomy.
2. The three surviving cats were injected a total of 25 times in the neck with 2 ml 2 per cent procaine HCl. This started nystagmus 18 times.
3. Anemic decerebration of two of these cats did not provoke decerebrate extensor rigidity but resulted in a minor trace of flexor rigidity of the limbs.

Conclusions

Commissural fibres in the segments C1 to C4 are not an essential link between the upper cervical roots and the vestibular nuclei on the opposite side of the body.

The lateral cervical nuclei do not form an essential link in the cervico-vestibular pathway.

Figure 13



Cross-sectional drawings of microscopic appearance of the high cervical cord, showing the extent of the mid-line myelotomy.
The schematic drawing on the right is a dorsal view, showing the levels at which the cross sections were made.
Black: fibrosis
Shaded: gliosis

Magnification: 10 x.

Figure 13

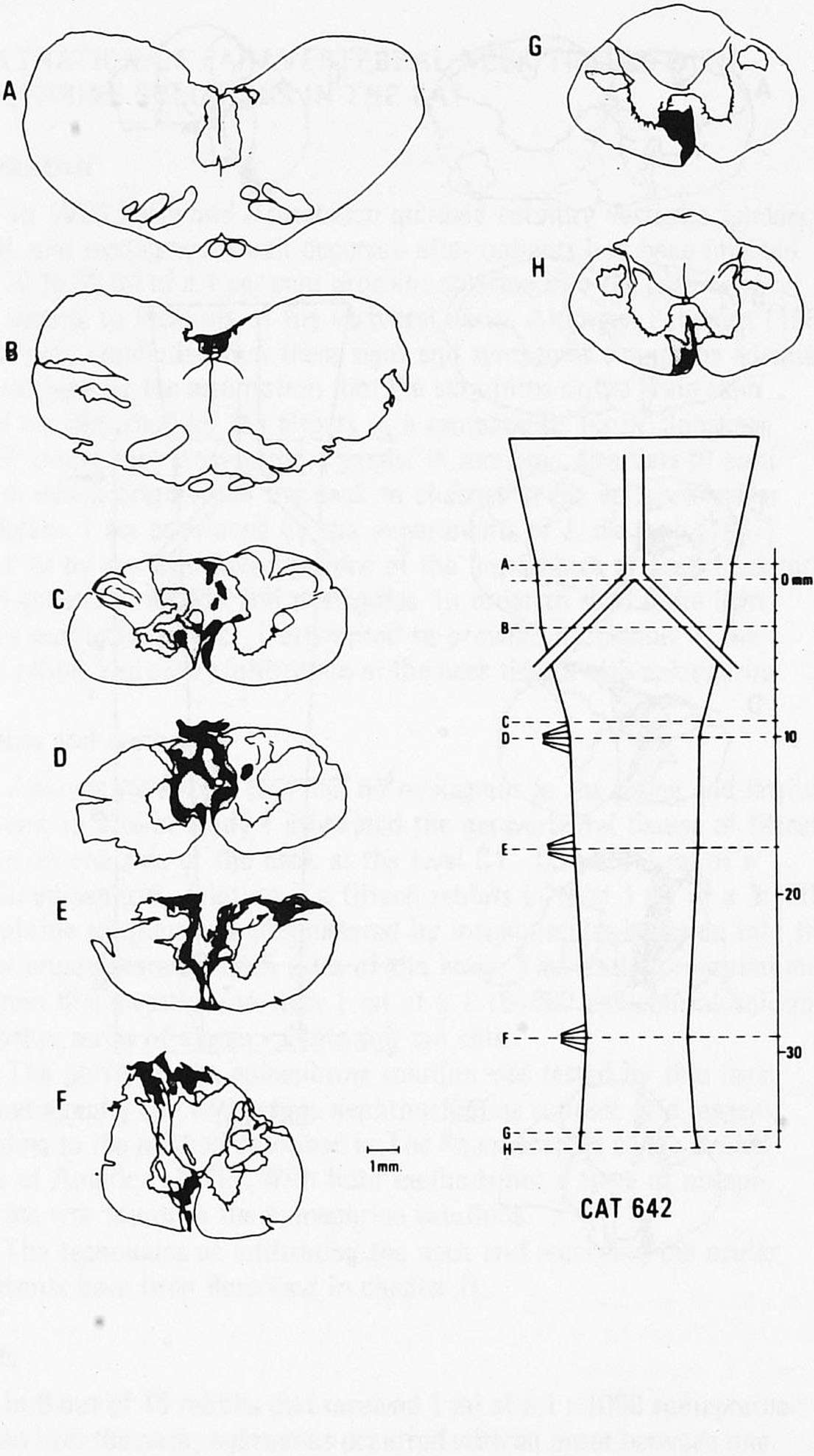
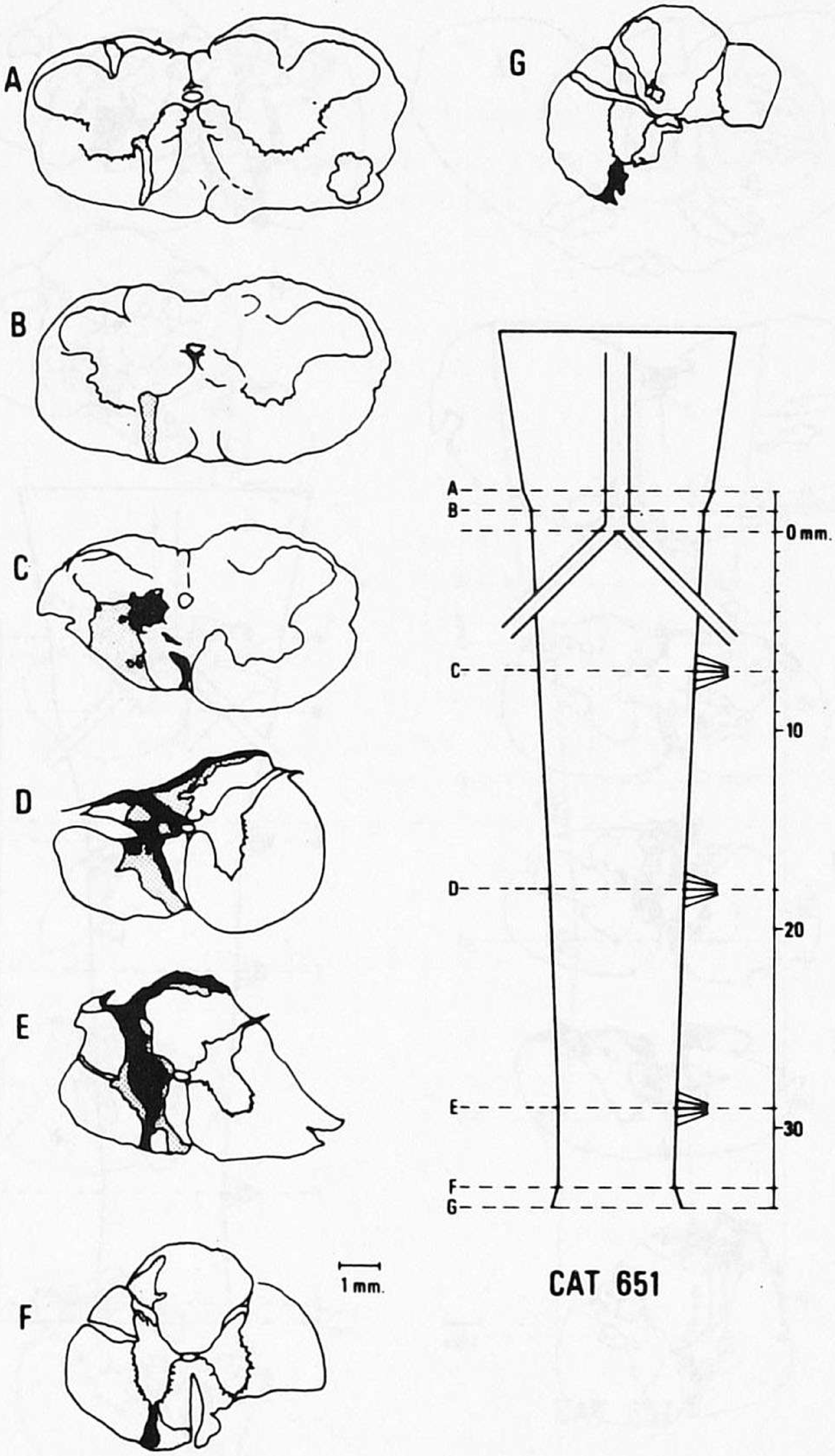


Figure 13



INFILTRATION OF PARAVERTEBRAL NECK TISSUES WITH EPINEPHRINE SOLUTIONS IN THE CAT

Introduction

In 1926 Barré and Draganesco ascribed rotatory vertigo, a tendency to fall, and nystagmus which occurred after patients had been injected with 10 to 30 ml of a 1 per cent procaine solution into the paravertebral neck tissues, to blocking of the vertebral nerve. Although Schubert (1950) had already concluded that these signs and symptoms cannot be adequately explained by the assumption that the labyrinths or the brain stem nuclei are disturbed by the effects of a sympathetic block, Jongkees (1969) stated that most authors persist in ascribing disorders of equilibrium which originate in the neck to changes in the vertebro-basilar circulation. I am convinced by the experiments of J. de Jong (1967) as well as by my own investigations of the importance of neck receptors in the genesis of vertigo and nystagmus. In order to shed more light on this confusing subject, I attempted to provoke nystagmus in the intact rabbit and cat by infiltration of the neck tissues with epinephrine.

Materials and methods

Animals were used that had no nystagmus in the prone and lateral positions. In a pilot study I infiltrated the paravertebral tissues of fifteen rabbits on one side of the neck at the level C1 - C3 with 1 ml of a 1:1000 epinephrine solution. To fifteen rabbits in total 1 ml of a 1:1000 epinephrine solution was administered by intramuscular injection into the gluteal musculature on both sides of the body. The results prompted me to repeat this investigation with 1 ml of a 1:10.000 epinephrine solution in another series of eleven rabbits and ten cats.

The purity of the epinephrine solution was tested by thin layer chromatography and with a beta-naphthochinone sulfonic acid reagent according to the method described in The Pharmacopeia of the United States of America (1970). With both methods not a trace of norepinephrine was found in the epinephrine solutions.

The techniques of infiltrating the neck and recording the ocular movements have been described in chapter II.

Results

In 6 out of 15 rabbits that received 1 ml of a 1 : 1000 epinephrine solution into the neck, nystagmus occurred with an onset between one half to 8 minutes after the completion of the injection and with a duration of 2 to 51 minutes. Direction, amplitude, and frequency of the nystagmus were variable and there was no relationship between the lateral position in which nystagmus was prevalent and the side of the neck that had been injected. Of the 6 animals that showed nystagmus, 2 died within 3 minutes after its onset.

Of the 15 rabbits that received the same amount of epinephrine into the gluteal musculature, 1 had nystagmus. This started 15 minutes after the injection and had a duration of 50 minutes. Also in this instance, the direction of the nystagmus was not constant.

None of the 11 rabbits and 10 cats that received 1 ml of a 1:10.000 epinephrine solution into the neck had any nystagmus.

The results of this investigation are summarized in Table 6.

Discussion

At the outset of these experiments my aim was to see if nystagmus could be produced by the topical action of epinephrine on the structures around the high-cervical spine. If nystagmus resulted I could then exclude ischemia of the neck receptors as the origin of nystagmus by observing the effects of epinephrine injections after afferent denervation of the segments C1 through C4. The results of the pilot study indicate that epinephrine can indeed induce nystagmus, but only in dosages that are systemically effective and sometimes lethal. For this reason I felt that continuing this series of experiments would not give meaningful results.

Eidelman et al., (1972) produced convincing evidence for a supraspinal control of cerebral vasoconstriction through a pathway in the cervical spinal cord an the sympathetic outflow above T2: the cerebral vasoconstriction which normally accompanies hyperventilation, did not occur in patients with complete traumatic transverse lesions of the cervical cord. In the same patients the reactions to induced arterial hypertension and hypercapnea indicated that the cerebral blood vessels were capable of constriction and dilatation. Hinoki (1971) described an equilibrium test by loading subjects with 0.006 mg of epinephrine per kg of body weight subcutaneously. In thirty normal people this had no effect on posture and equilibrium. In a number of patients with head trauma or cervical whiplash injury, however, increase of vertigo and ataxia was noted. The dosage of epinephrine, given subcutaneously to these human subjects, is about twenty times smaller than the quantities that I injected during the pilot study. Unfortunately, literature is poor in data on epinephrine toxicity. Bovet (1948) states that the maximum dose of epinephrine for the rabbit is 0.4 mg/kg body weight intraveneously and 20.0 mg/kg subcutaneously. For the cat these dosages are 8.0 and

20.0 mg/kg respectively.

It was realized only in 1949 (Auerbach and Angell; Goldenberg et al.) that the natural adrenal medullary hormone contains substantial but varying amounts of norepinephrine. Rosendorff (1972) estimates that most studies were performed with natural adrenal medullary hormone preparations up to the late 1950's. As the cerebral circulatory and metabolic effects of norepinephrine differ from those of epinephrine (King et al., 1952, Sensenbach et al., 1953) it is difficult to make valid comparisons between older studies and more recent experimental investigations performed with pure epinephrine. It is therefore not surprising that studies on the effect of epinephrine on the cerebral circulation have produced contradictory results. Rosendorff (1972) reviewed the literature and found that topical (brain surface) and intracarotid injections of epinephrine have been reported to produce vasoconstriction (Fog, 1939a; Dumke and Schmidt, 1943; Faucon et al., 1965) or vasodilatation (Forbes et al., 1933, Schmidt and Hendrix, 1937; Norcross, 1938).

My pilot animals had nystagmus that started as early as thirty seconds after completion of the injection and lasted up to fifty-one minutes. It is improbable that nystagmus of more than a few minutes is caused by recirculation of epinephrine as this substance is broken down radpidly in the liver, the kidneys, and other, yet unidentified, tissues (Goodman and Gilman, 1970) by catechol-o-methyltransferase (COMT) and monoamine oxidase (MAO). The vasopressor activity of the resulting metabolites is less than 1 per cent of the strength of the mother substance (Iversen, 1967). Epinephrine might have prolonged effects on the vestibular system by being slowly released into the cardio-vascular tree as a result of vasoconstriction at the site of the fluid depot. Longer lasting nystagmus could also have its origin in ischemia of neck receptors or their afferent connections, due to narrowing of the vessels that feed them. Another possible, but unlikely, mechanism would be ischemia of the labyrinth, the vestibular nerve or the brain stem as an effect of vasospasm in the vertebro-basilar territory. Such an arterial spasm could result from local effect of epinephrine on the vertebral arteries. This is probably not what happens, as Scratch et al., (1964) found that topical application of epinephrine (1:1000) over the pia caused definite vasodilatation. Vasospasm of the basilar artery or the circle of Willis has been produced by mechanical stimuli (Florey, 1925; Echlin, 1942; Pool, 1958a; Gurdjian and Thomas, 1959, 1972; Lende, 1960), electrical stimulation (Florey, 1925; Lende, 1960), topical application of a 5 per cent barium chloride solution (Gurdjian and Thomas, 1972) or

Table 6

Administration of epinephrine to rabbits and cats

Animal species	Dilution of epinephrine solution	Amount of epinephrine given (mg)	Site of the injection	Number of injections followed by nystagmus	Total number of trials
rabbit	1:1000	1	paravertebral (neck)	6	15
rabbit	1:1000	1	gluteal musculature	1	15
rabbit	1:10,000	0.1	paravertebral (neck)	0	11
cat	1:10,000	0.1	paravertebral (neck)	0	10

blood (Echlin, 1965). It is not to be expected that epinephrine solutions that do not cause spasm of the exposed basilar artery will cause spasm if applied to the adventitia of the vertebral arteries. Arterial spasm could, then, also be brought about by ischemia of the vertebral or sympathetic nerves. I have not found reports in the literature on the effects of epinephrine on automatic nerve trunks, but even if this substance would stimulate considerably the sympathetic system in the neck,it is doubtful that major circulatory changes would be the result. Again, the literature offers contradictory information: electrical stimulation of the cervical sympathetic chain produces ipsilateral narrowing of pial vessels over the cerebral convexity according to Fog (1939). Gurdjian et al.,(1958) found no change in pial vessel caliber after stimulation of the cervical and upper thoracic sympathetic system and Pool (1958b) saw no effect of stimulation of the cervical sympathetic and the dorsal roots C1 - C3 on the pial circulation. Although Poiseuille's law (Best and Taylor, 1945) states that with a constant pressure the volume of flow per time unit is proportional to the fourth power of the diameter of the tube, it is hazardous to conclude that cerebral ischemia is present when a constriction of a few pial vessels is observed through a Forbes (1928) window: Gurdjian and Thomas (1972) did cinephotomicrographic studies of pial vessels in monkeys and man that disclosed variations in vascular caliber unrelated to any specific experimental condition. These cyclic variations that may even result in a 75 per cent increase of the lumen diameter are a severe impediment to valid experimental observations and have not been discussed seriously in earlier publications. To complicate matters further, the rich sympathetic innervation of the carotid and vertebro-basilar arteries (Abrahams, 1969; Nelson and Rennels, 1970) is not uniform: in the rabbit Peerless (1971) has found different types of sympathetic fibres in the carotid and vertebral arteries. This means that conclusions from studies on the carotid circulation may not be applied to the vertebro-basilar system with impunity. The lack of dependable data concerning the pharmacological actions of epinephrine on the cerebral circulation and the vestibulo-oculomotor neuronal pathways makes this substance an undependable experimental tool that introduces a number of unknown and uncontrolled parameters into the present series of experiments. Cervical injections with 1 ml of a 1:10.000 epinephrine solution, which is a dosage currently used in veterinary medicine (Meyer Jones, 1965; British Veterinary Codex, 1965), did not produce any nystagmus. It may be more fruitful to apply a 5 per cent barium chloride solution to the vertebral arteries after deafferentation of the neck, a method with which I was not familiar before reading the publication of Gurdjian and Thomas (1972).

Summary

1. One ml of a 1:1000 epinephrine solution, injected into the neck of fifteen rabbits produced nystagmus in six, of which two died a few minutes later. In a control series of intra-gluteal injections, nystagmus occurred in one out of fifteen animals.
2. Neck injections of quantities that are currently used in veterinary medicine were not followed by nystagmus in eleven rabbits and ten cats.

Conclusion

At present the actions of epinephrine are not sufficiently known in order to use this substance as a tool in the experimental study of cervico-vestibular relationships.

of the lumen diameter are a severe impediment to valid experimental observations and have not been discussed seriously in earlier studies. To complicate matters further, the rich sympathetic innervation of the carotid and vertebro-basilar vessels [illegible] 1959; Nelson and Rennels, 1970) is not uniform: in the rabbit Pearless (1963) has found different numbers of sympathetic fibres in the carotid and vertebral arteries. This means that conclusions from studies on the carotid circulation may not be applied to the vertebro-basilar system with impunity. The lack of dependable data concerning the pharmacological actions of apomorphine on the cerebral circulation and the vestibulo-oculomotor neuronal pathways makes this substance an undependable experimental tool that introduces a number of unknown and uncontrolled parameters into the present series of experiments. Cervical injections with 1 ml of a 1:16,000 apomorphine solution, which is a dosage currently used in veterinary medicine (Meyer Jones, 1965; British Veterinary Codex, 1965), did not produce any nystagmus. It may be more fruitful to apply a 5 per cent barium chloride solution to the vertebral arteries after deafferentation of the neck, a method with which I was not familiar before reading the publication of [illegible] (197[illegible]).

Summary

1. One ml of a 1:1000 apomorphine solution, injected into the neck of sixteen rabbits produced nystagmus in six, of which two died a few months later. In a control series of subcutaneous injections, nystagmus occurred in one out of fifteen animals.
2. Neck injections of quantities that are currently used in veterinary medicine were not followed by nystagmus in eleven rabbits and ten cats.

Conclusion

At present the actions of apomorphine are not sufficiently known in order to use this substance as a tool in the experimental study of cervico-vestibular relationships.

SAMENVATTING

Nadat in hoofdstuk I uiteengezet is hoe dit proefschrift is opgebouwd, wordt in hoofdstuk II een kort overzicht gegeven over de voornamelijk door Biemond en J. de Jong verrichte experimenten over cervicale nystagmus. Daarop volgt een bespreking van enkele algemene begrippen en werkwijzen welke in de volgende hoofdstukken gebruikt worden.

In het derde hoofdstuk zien we hoe bij het konijn na vernietiging van één van zijn labyrinthen cervicale nystagmus en rolbewegingen kunnen worden opgewekt. Dit gebeurt door blokkeren van de afferente informatie in de cervicale achterwortels, zowel wanneer deze dorsale wortels beiderzijds intact zijn, als wanneer ze tevoren aan een willekeurige zijde zijn doorgesneden.

Het vierde hoofdstuk gaat over de gevolgen van cerebellectomie voor cervicale nystagmus. Het op grond van de literatuur bestaande vermoeden dat bij het konijn na cerebellectomie nog nystagmus kan worden opgewekt door procaine injecties ter plaatse van de cervicale achterwortels, kon bevestigd worden. De hypothese dat cervicale en labyrinthaire nystagmus in hetzelfde vestibulo-oculomotorische circuit ontstaan, kan gehandhaafd blijven.

Een aantal experimenten betreffende cervicale nystagmus, welke op konijnen waren verricht, werden, zoals in hoofdstuk V is beschreven, herhaald bij katten. Daarna werd overgegaan tot doorsnijden van de dorsale helft van het hoog-cervicale ruggemerg. De houding en gang van deze katten worden besproken, evenals de bevinding dat na de achterstrenglesie nog cervicale nystagmus door procaine injecties diep in de nek was op te wekken. Dit lukte eveneens na het vernietigen van de vertebrale neurovasculaire bundels aan beide zijden. Zoals te verwachten was, had een verlichte ruimte een inhiberende werking op door procaine injecties en door achterstrenglesies opgewekte nystagmus.

Hoofdstuk VI behandelt het ontstaan van cervicale nystagmus bij katten waarbij in één zitting een labyrinth werd vernietigd, de eerste drie cervicale achterwortels aan één zijde intraduraal werden doorgesneden en het cervicale ruggemerg sagittaal werd gespleten van proximaal van C_1 tot C_4. Er wordt ingegaan op het uitblijven van decerebratiestijfheid bij twee van deze geopereerde katten. Het hoofdstuk wordt besloten met een overzicht van de in vorige hoofdstukken besproken lesies en met een bespreking van eventuele andere banen welke voor de spino-vestibulaire impulsen overblijven. Vermoedelijk spelen de voorzijstrengen van het ruggemerg een rol bij het ontstaan van cervicale nystagmus.

Het zevende hoofdstuk is een relaas van een verkeerd opgezette proefopstelling waarbij werd gekeken of adrenaline injecties in de nek ter plaatse van de achterwortels nystagmus opwekken. Dit bleek het geval te zijn met doses die lethaal waren als zij in de nek werden gespoten, maar niet in de musculi glutei. Voor de veterinaire praktijk gebruikelijke doses adrenaline veroorzaakten geen nystagmus als zij in de nek werden gespoten. Er wordt ingegaan op de tegenstrijdigheden in de literatuur over de werking van adrenaline en op het verschil in innervatie en reactie van de cerebrale en vertebrale vaatsystemen. De conclusie aan het eind van dit hoofdstuk luidt dan ook dat adrenaline niet geschikt is om op het ogenblik bij het onderzoek van de cervicovestibulaire verbindingen gebruikt te worden.

SUMMARY

In chapter I the structure of this paper is outlined. The second chapter is a brief summary of the studies, chiefly those of Biemond and J. de Jong, which have been done in the field of cervical nystagmus. In addition some methods and concepts which appear in subsequent parts of the thesis are introduced in this chapter.

In the third chapter is described how nystagmus and rolling movements can be induced in the rabbit after unilateral labyrinthectomy; this is done by unilateral procaine block of the dorsal cervical roots on either side. It is shown that unilateral block following surgical deafferentation of the contralateral side is also sufficient to evoke nystagmus, again the side chosen being arbitrary.

The fourth chapter is concerned with the consequences of cerebellectomy on cervical nystagmus. The speculation that in the rabbit nystagmus could be evoked by procaine block of the dorsal cervical roots after cerebellectomy, has been confirmed. The hypothesis that cervical and labyrinthine nystagmus arise in the same vestibulo-oculomotor circuit can be maintained.

A number of experiments which were performed on rabbits were, as is described in the beginning of chapter V, repeated in cats; thereafter the dorsal half of the upper cervical cord was cut. The posture and gait of these cats are described, and the fact that nystagmus could still be elicited by procaine injection in the neck is discussed. Destruction of both vertebral neuro-vascular bundles did not prevent nystagmus being caused by the same technique. As was to be expected, light had an inhibitory effect on the nystagmus.

In the sixth chapter the following experiment is described: in cats, three lesions were created at the same time; one labyrinth was destroyed, on one side the upper three cervical dorsal roots were cut intra-durally,

and the cervical cord was sagitally split in the mid-line from the proximal end of C1 to C4. In these cats it was possible to evoke a nystagmus by procaine block of the still intact dorsal cervical roots. Two of these cats were also studied for possible loss of extensor rigidity after decerebration. The chapter is closed with a discussion of the lesions which were described in this and previous chapters; this leads to a consideration of which tracts were left intact to carry cervico-vestibular impulses. It is concluded that some ventro-lateral tracts were left intact and probably were capable of carrying the impulses which led to cervical nystagmus.

The seventh chapter is an account of an improperly designed experiment which was set up to see if epinephrine injections in the neck, in the proximity of the dorsal roots, would evoke a nystagmus. This was indeed possible, but only when a lethal dose was used; the same dose, when injected in the gluteal muscles, was not lethal and caused a nystagmus once. Doses of epinephrine which are commonly used in veterinary practice were not effective in causing a nystagmus when injected in the neck. Conflicting information in the literature, in regard to the action of epinephrine and to the differences in innervation and reaction of the vertebral and cerebral vessels, is discussed. It is concluded that at the present time, epinephrine is not suitable for use in the investigation of cervico-vestibular connections.

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