MYOTATIC, KINESTHETIC AND VESTIBULAR MECHANISMS

Myotatic, Kinesthetic and Vestibular Mechanisms

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Membership

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O. E. Lowenstein (Chairman)
Department of Zoology and Comparative Physiology, Birmingham University

D. Barker
Department of Zoology, University of Durham

G. H. Begbie
Department of Physiology, University of Edinburgh

S. K. Bosher
Ferens Institute of Otolaryngology, Middlesex Hospital, London

A. Brodal
Anatomical Institute, University of Oslo, Norway

Margaret Dix
M.R.C. Otological Research Unit, The National Hospital, London

G. F. Dohlman
Department of Oto-Laryngology, University of Toronto, Canada

E. Eldred
Department of Anatomy, School of Medicine, University of California, Los Angeles

I. Friedmann
Institute of Laryngology and Otology, London

E. Gardner
School of Medicine, Wayne State University, Detroit, Michigan

B. E. Gernandt
U.S. Naval Aerospace Medical Institute, U.S. Naval Aviation Medical Center, Pensacola, Florida

J. J. Groen
Universiteitskliniek voor Keel-, Neus- en Oorzeekten, Stichting Academisch Ziekenhuis Utrecht, Holland

C. S. Hallpike
Ferens Institute of Otolaryngology, Middlesex Hospital, London

N. G. Henriksson
Oronkliniken, Lasarettet i Lund, Sweden

J. D. Hood
M.R.C. Otological Research Unit, The National Hospital, London

J. Jansen
Neurophysiological Laboratory, Anatomical Institute, University of Oslo, Norway

P.-G. Lundquist
Department of Otolaryngology, Karolinska Sjukhuset, Stockholm, Sweden

P. B. C. Matthews
University Laboratory of Physiology, Oxford

M. Monnier
Physiologisches Institut der Universität, Basel, Switzerland

F. C. Ormerod*
98 Belsize Park Gardens, London

A. J. Philipszoon
E.N.T. Department, Wilhelmina Gasthuis, Amsterdam, Holland

O. Pompeiano
Istituto di Fisiologia, Università di Pisa, Italy

J. Purdon Martin
The National Hospital, London

T. D. M. Roberts
Institute of Physiology, University of Glasgow

Catherine A. Smith
Department of Otolaryngology, Washington University, St. Louis, Missouri

J. Wersäll
Department of Otolaryngology, Karolinska Sjukhuset, Stockholm, Sweden

* *Deceased*

The Ciba Foundation

The Ciba Foundation was opened in 1949 to promote international co-operation in medical and chemical research among scientists from all parts of the world. Its house at 41 Portland Place, London, has become a meeting place well known to workers in many fields of science. Every year the Foundation organizes from six to ten three-day symposia and three or four one-day study groups, all of which are published in book form. Many other informal meetings also take place in the house, organized either by the Foundation or by other scientific groups needing a place to meet. In addition, bedrooms are available for visiting scientists, whether or not they are attending a meeting in the building.

The Ciba Foundation owes its existence to the generosity of CIBA Ltd, Basle, who, realizing the disruption of scientific communication caused by the war and by problems of distance, decided to set up a philanthropic institution whose aim would be to overcome such barriers. London was chosen as its site for reasons dictated by the special advantages of English charitable trust law, as well as those of language and geography.

The Foundation's many activities are controlled by a small group of distinguished trustees. Within the general framework of biological science, interpreted in its broadest sense, these activities are well summed up by the Ciba Foundation's motto, *Consocient gentes*—let the nations come together.

Preface

This is the third in a series of symposia designed to cover the various areas of sensory function, the previous volumes having been "Colour Vision" and "Touch, Heat and Pain". The entire series has been planned by the Deputy Director of the Ciba Foundation in conjunction with Professor Otto Lowenstein, whose involvement in the present symposium was, however, more than usually close, for his own work has been primarily in the area of vestibular function. The Foundation is particularly grateful to Professor Lowenstein for his valuable work in the planning of the symposium and for his lively chairmanship of the meeting itself.

Illness unfortunately prevented the participation of Sir Terence Cawthorne, of The National Hospital, London, but we were glad to welcome Dr. Margaret Dix in his place.

We were sad to learn, during the preparation of these proceedings for publication, of the death of a member of the symposium—Professor F. C. Ormerod, former Director of Research at the Institute of Laryngology and Otology and previously professor in these subjects in the University of London.

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CHAIRMAN'S INTRODUCTION

PROFESSOR O. LOWENSTEIN

THE objective of this symposium, the third in the Ciba Foundation's series of meetings on sensory function, is to bring together those people who are interested in the sensory control of posture and movement. So very often these people meet separately. The "vestibular club" is a closely knit society, and those working on muscle are also nowadays beginning to form a very intimate family, but it is not often that the two can meet. This field of the sensory control of posture and movement is of course an extremely wide one, and it has obviously not been possible to invite everyone in it to this meeting—in fact, it is the strict but wise policy of the Foundation to limit the size of its meetings to roughly twenty-five people, in order that they shall be able to discuss informally together. The task of selecting the members has been a hard one, for besides those engaged in the academic pursuit of this range of interests, there are also the clinicians. The continuing discussion between clinicians and laboratory workers is a very frequently interrupted one and it is a further purpose of this meeting to bring together the two groups.

Although there is a limit set to the number of direct participants, it is our hope that by including in the published volume a record of the discussions at the meeting, we shall make accessible to all those interested in our field the thinking aloud of those actually present.

I spoke of roughly twenty-five of us at this meeting. In actual fact I feel that we shall number one more, because there will be among us during this symposium an uninvited but immensely welcome participant; the spirit of Charles Sherrington. It is strange that although it may well be that Sherrington will not often be mentioned in the formal papers, everyone of us is, I think, aware of what he owes to his pioneer work. Let us, then, make the concept of integration the guiding principle of the symposium.

Myotatic, Kinesthetic and Vestibular Mechanisms
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SECTION I
MYOTATIC AND KINESTHETIC MECHANISMS

THE INNERVATION OF MAMMALIAN SKELETAL MUSCLE

D. BARKER

Department of Zoology, University of Durham

THE classic work on muscle innervation by Ruffini, Cajal, and Dogiel, among many others, consists of observations made on nerve endings prepared by the gold chloride, silver nitrate, or methylene blue techniques. Until recently, silver impregnation, the most precise and complete of the traditional trio, was limited to sectioning methods, but by a modification of one of these (Barker and Ip, 1963) it is now possible to obtain whole, teased preparations. These are greatly superior to their gold chloride and methylene blue counterparts, and the information derived from them provides an essential guide for studies made with histochemical techniques and the electron microscope. Over the past few years these histological innovations have revealed much about muscle nerve endings that was previously inaccessible. I shall discuss some of these findings and make a general survey of the distribution and termination of muscle nerves.

MOTOR INNERVATION

The motor supply comprises skeletomotor (α) fibres that terminate in extrafusal motor end-plates; fusimotor (γ) fibres that innervate muscle spindles; and mixed (β) fibres (Bessou, Emonet-Dénand and Laporte, 1963; Adal and Barker, 1965*a*) that innervate both extra- and intrafusal muscle fibres. Intensive research on fusimotor innervation over the past decade at last seems within sight of reaching a full understanding of the complexities involved. The present position is as follows (unless otherwise stated, the information relates to work on the cat).

Spindles receive three kinds of motor ending, a diffuse, multi-terminal, trail ending (Barker and Ip, 1965), and two kinds of end-plates designated as Types I and II (Barker, 1966*b*), abbreviated as p_1 and p_2. The trail ending

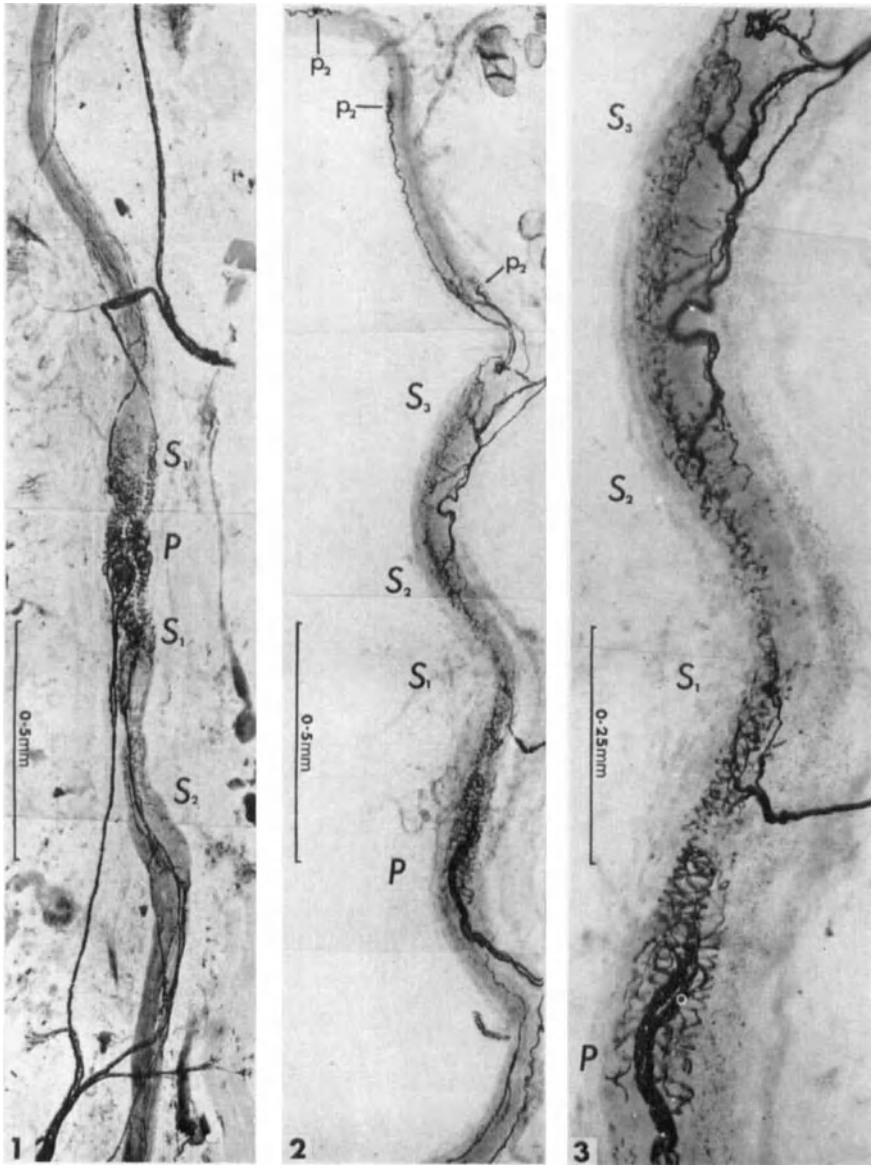
(see Figs. 19, 20 and 21) was first detected by the cholinesterase technique which revealed diffuse enzymic activity near the equatorial region, in contrast to that shown by discrete subneural apparatuses of plates located further along the poles (Coërs and Durand, 1956 [rat, cat, man]; Kupfer, 1960 [man]; Hess, 1961*a* [mouse, rabbit]; Coërs, 1962 [rat, cat, man]). Boyd (1962) provided the first information about the form of such a diffuse termination, which he described in gold chloride preparations as "a network of fine axons and small elongated nerve endings". Though figures and photographs of the trail ending have since appeared (Barker and Ip, 1965; Barker, 1966*a*), a full description has yet to be published. Two of its main characteristics are the considerable distance that usually occurs between the terminal node and the final ramification making synaptic contact, and the presence of many ramifications given off from preterminal nodes. Trail endings bear a remarkable resemblance to the extrafusal *en grappe* ending of Tschiriew (1879) that occurs in the skeletal muscles of various vertebrates (Hess, 1960, 1961*b*, 1963), and in mammalian extraocular muscles (Hess, 1961*c*, 1962; Hess and Pilar, 1963), as illustrated in Fig. 22. Work on the fine structure of the trail ending shows that this resemblance includes the nature of the myoneural junction, where postjunctional sarcolemmal folds are absent (Adal and Barker, unpublished), as in the *en grappe* terminals of the cat superior oblique muscle (Pilar and Hess, 1966). Moreover, preliminary observations on spindles in sheep extraocular muscles show that the intrafusal trail innervation and the extrafusal *en grappe* innervation frequently originate from the same motor axon (Barker and A. B. Purdy, unpublished observations). Trail endings typically occupy an area just under one millimetre long on either side of the equatorial region, extending through the S_1, S_2, and part of the S_3 regions. Jones (1966) has described diffuse spray endings in methylene blue preparations of opossum spindles; these appear to correspond to trail endings.

FIGS. 1–10. Photographs of teased preparations of cat muscle receptors. The preparations illustrated in Figs. 1 and 9 are gold chloride, the rest silver (modified de Castro technique). *P*, primary ending; p_2, end-plate of the p_2 type; pf.c., paciniform corpuscle; S_1, S_2, S_3, secondary endings located in positions increasingly distant from the primary ending; t.o., tendon organ; Ia, primary ending nerve fibre; Ib, tendon organ nerve fibre; II, secondary ending nerve fibre.

FIG. 1. Muscle spindle with primary and three secondary endings from normal flexor digitorum longus.

FIG. 2. Muscle spindle with primary and three secondary endings from normal tenuissimus. Note clarity of motor innervation in this silver preparation as compared with that in the preceding gold chloride preparation.

FIG. 3. Enlargement of the sensory innervation of the spindle shown in Fig. 2. The secondary endings are located mainly on the nuclear-chain muscle fibres (coursing through on the left-hand side of the spindle) and only to a small extent on the nuclear-bag muscle fibres.



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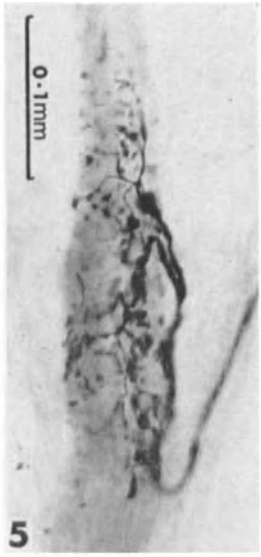


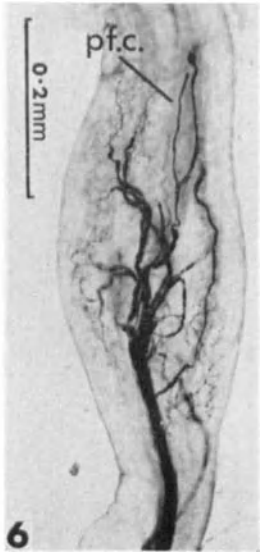


FIG. 4. De-efferentated and sympathectomized preparation from peroneal muscle showing a muscle spindle, a tendon organ and two paciniform corpuscles, one of which is associated with the tendon organ.

FIG. 5. Secondary ending of the flower-spray type in de-efferentated peroneal spindle.

FIG. 6. Tendon organ from de-efferentated extensor digitorum longus innervated by one 10 μm. Ib fibre. Six paciniform corpuscles are present underneath the receptor capsule (two only visible in photograph) innervated by a 7·5 μm. Group II fibre.

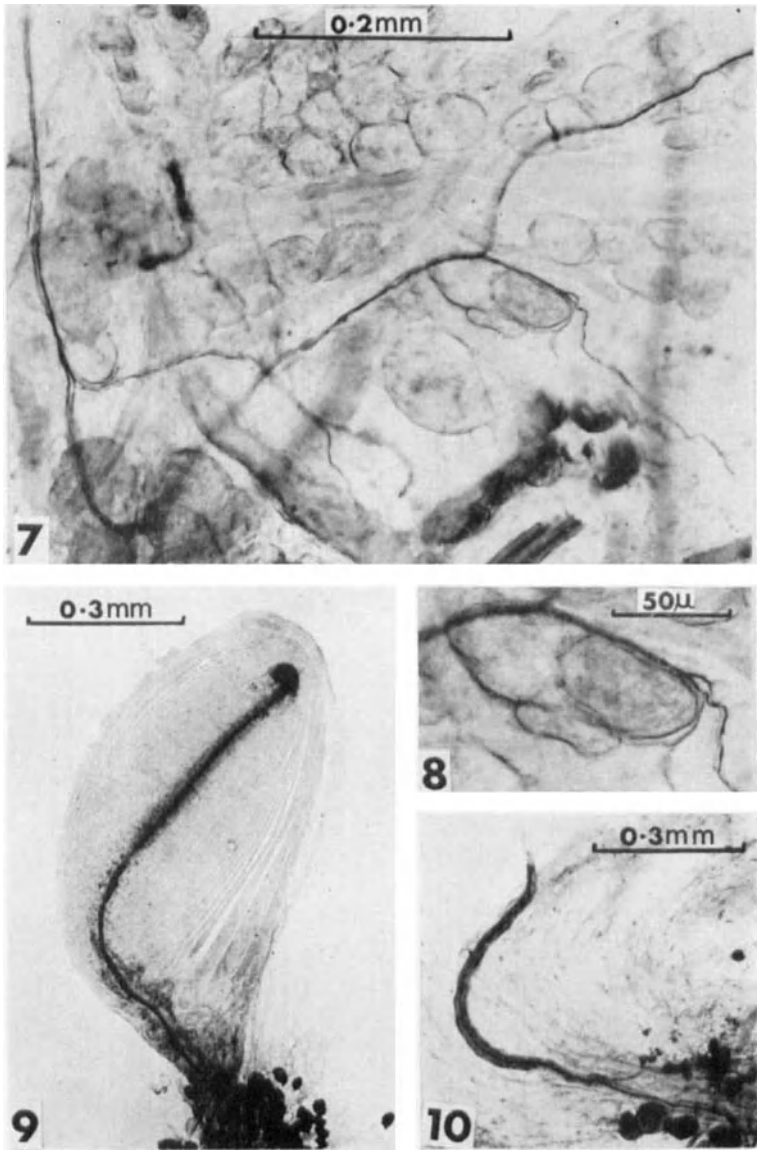
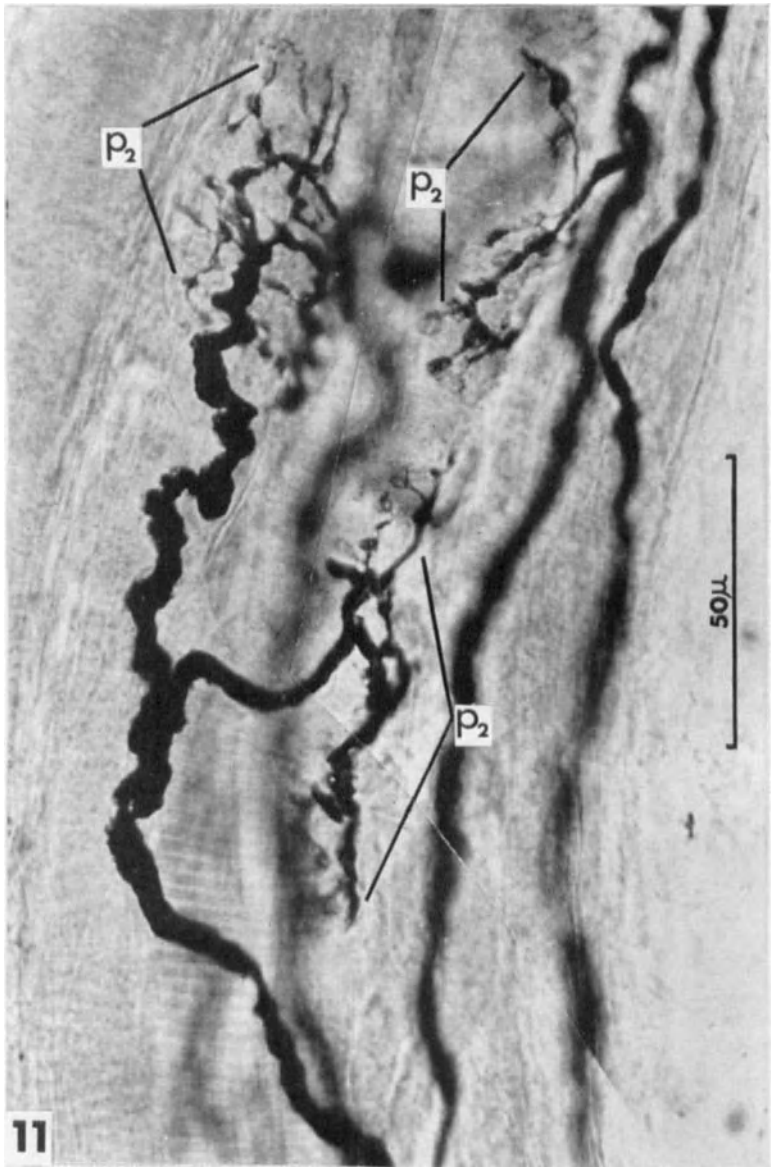
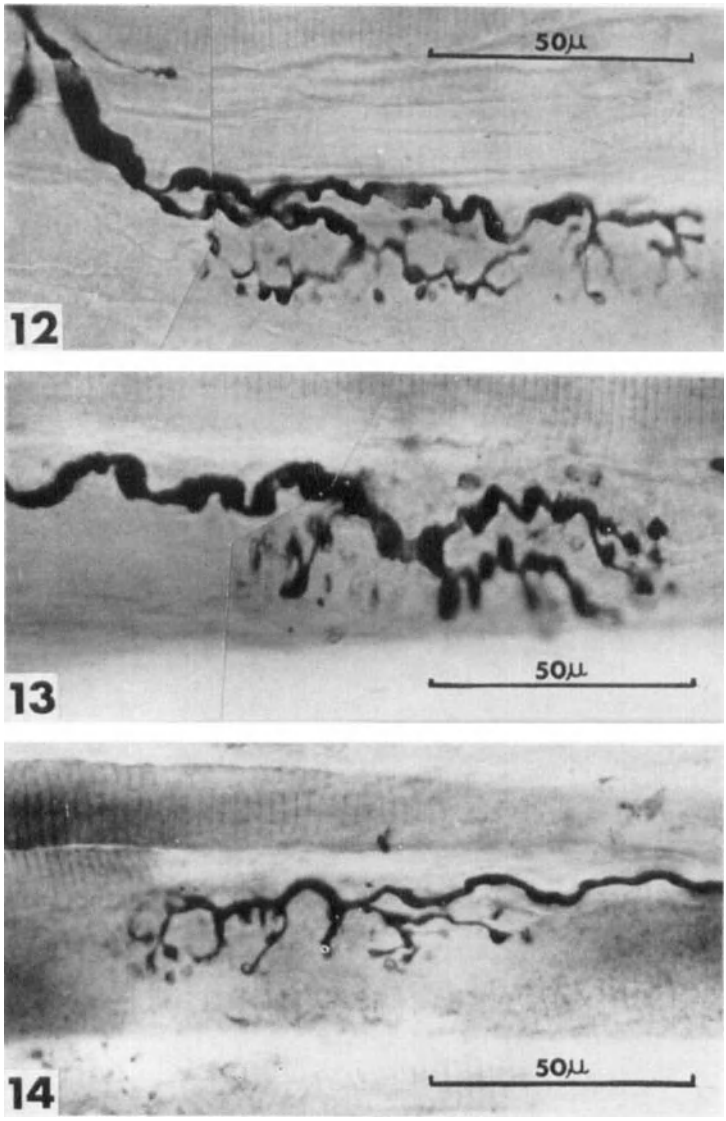


FIG. 7. De-efferentated and sympathectomized preparation of fat, connective tissue and blood vessels in tibialis posterior muscle, demonstrating innervation by two Group III fibres with stem diameters of 2·0 and 2·5 μm.
FIG. 8. Enlargement of the area just to the right of centre in Fig. 7, showing innervation of fat.
FIG. 9. Pacinian corpuscle from fascial covering of interosseous muscle.
FIG. 10. One of two paciniform corpuscles innervated by a 2·5 μm. Group III fibre.

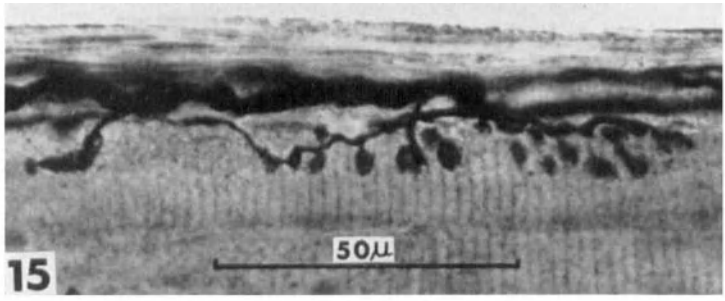


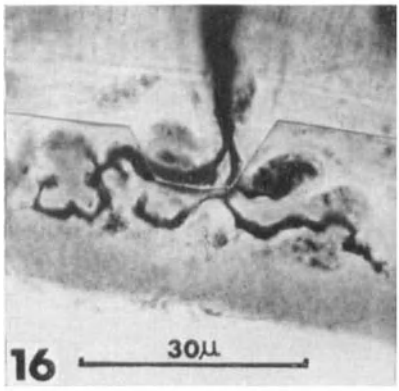
FIGS. 11-22. Photographs of teased, silver preparations (modified de Castro technique) illustrating (except Fig. 22) the motor innervation of cat muscle spindles. c., spindle capsule; j., myoneural junction formed by ramification of trail ending; *P*, primary ending; p_2, end-plate of the p_2 type; r., trail-ending ramification; tr.e., trail ending.

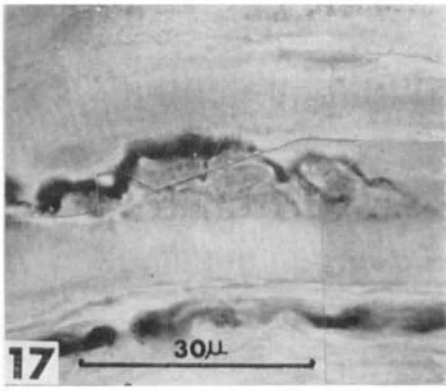
FIG. 11. p_2 plates in de-afferentated interosseous spindle.



Three examples of p_2 plates innervating de-afferentated spindles in peroneus brevis (Figs. 12 and 13) and 2nd deep lumbrical muscle (Fig. 14).







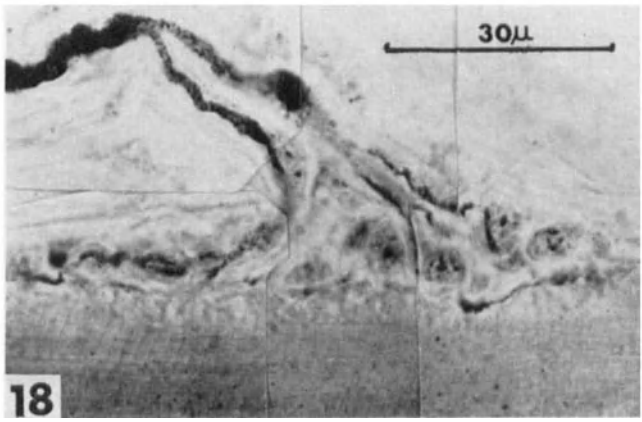


FIG. 15. p_2 plate in de-afferentated soleus spindle.
FIG. 16. Surface view of p_1 plate in de-afferentated interosseous spindle.
FIG. 17. Side view of p_1 plate in de-afferentated interosseous spindle. Note nucleated sole plate, Doyère eminence.
FIG. 18. Side view of p_1 plate in de-afferentated spindle from peroneus brevis.

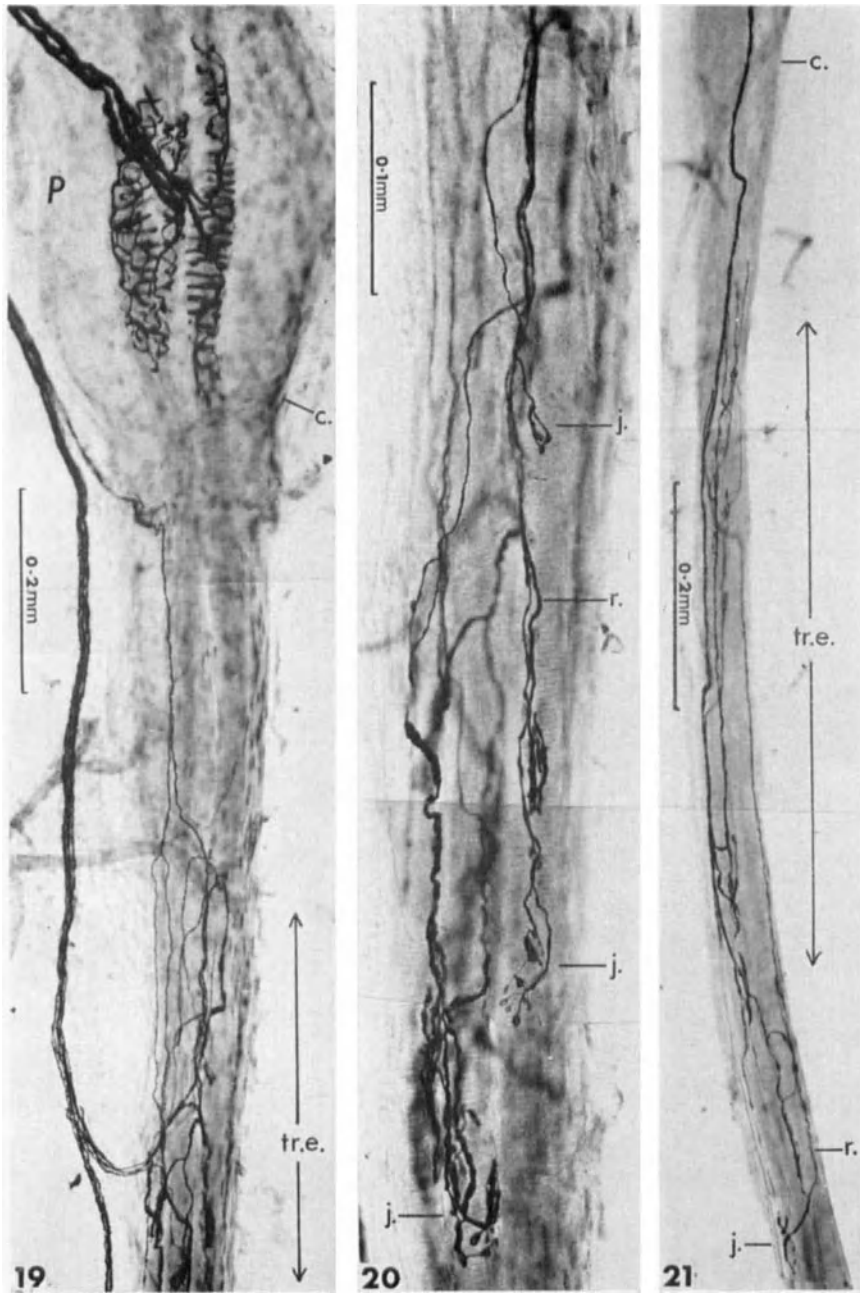


FIG. 19. Normal spindle from peroneus brevis showing primary and trail endings.
FIG. 20. Enlargement of part of the trail-ending area shown in Fig. 19. At this focus three myoneural junctions (j.) formed by trail-ending ramifications (r.) are shown.
FIG. 21. One pole of a de-afferentated peroneal spindle innervated by a single trail motor fibre.

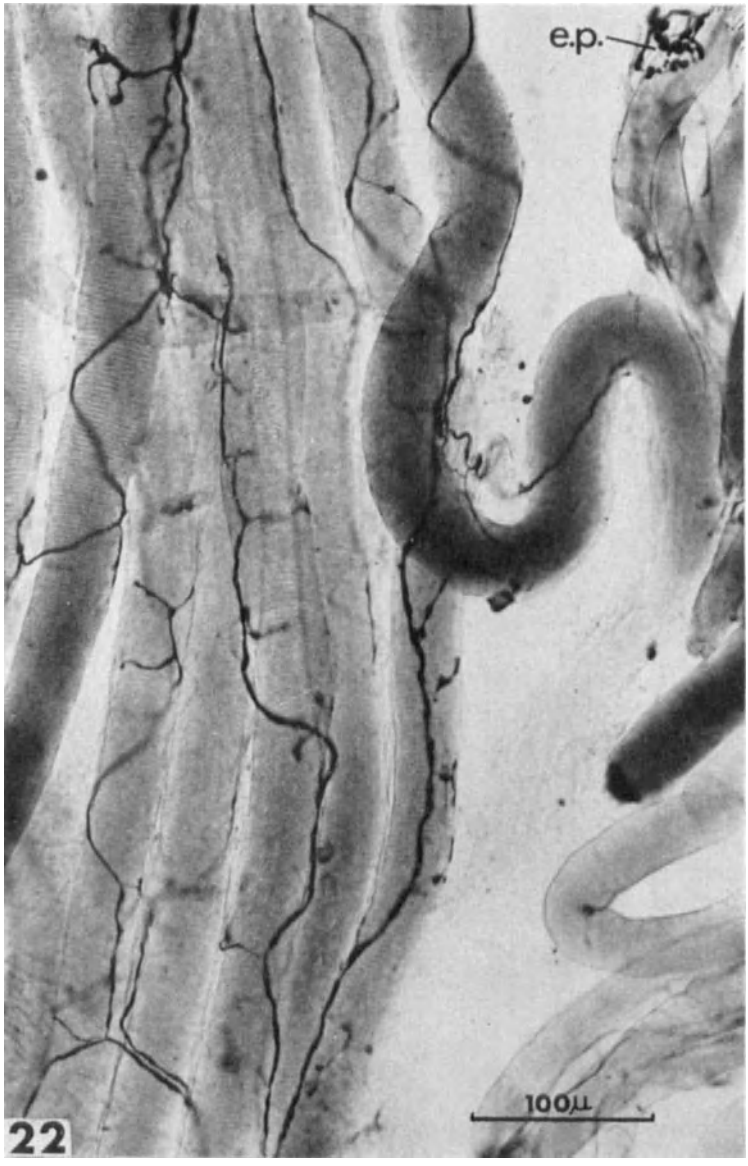
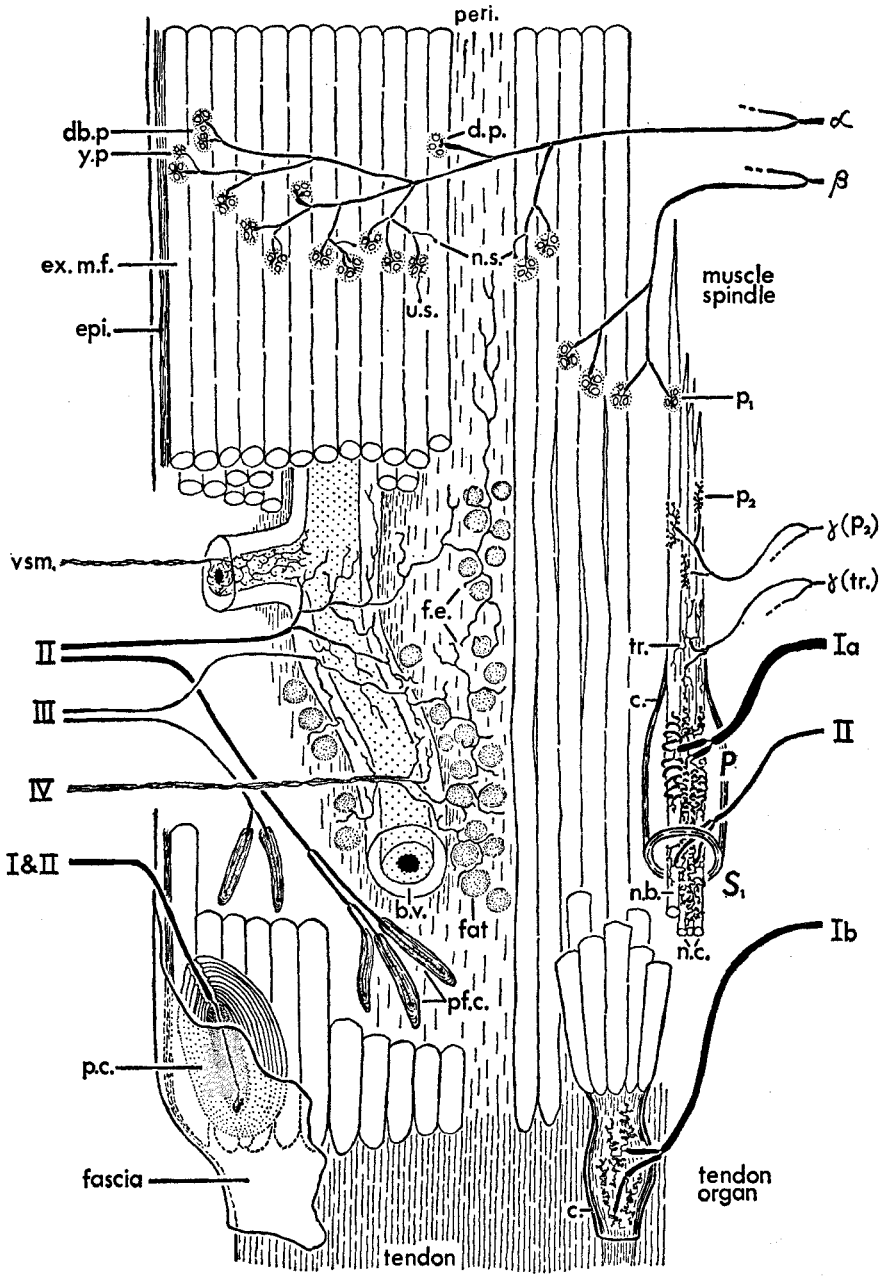


FIG. 22. *En grappe* innervation in cat inferior oblique extraocular muscle. Its diffuse multiterminal nature is similar to that of the fusimotor trail innervation, and contrasts with the discrete *en plaque* end-plate, an example of which (e.p.) is seen in the top right-hand corner of the photograph.

The p_1 plate (see Figs. 16, 17, and 18) is similar in every respect to the extrafusal motor end-plate and may on occasion be quite clearly seen to derive its axon as a collateral of a β fibre. After nerve section, p_1 plates and extrafusal end-plates degenerate simultaneously, while p_2 plates and trail endings persist for a further 24 to 36 hours (Barker and C. L. Negus, unpublished observations). This differential in motor degeneration may partly be a feature of the different kinds of myoneural junctions involved, and may also be related to axon size, since the extremities of large axons appear to degenerate more quickly than those of small ones. Taken in conjunction with other evidence, the existence of such a differential suggests that the relatively large and predominantly skeletomotor β fibres provide the p_1 innervation, while the smaller γ fibres supply the p_2 and trail endings. The location of p_1 plates is typically towards the extreme ends of the polar regions, but they may occur anywhere along the poles and may lie as close to the equator as the S_2 region. The p_1 plate occurs with less frequency than the other two fusimotor endings, and unlike them is usually supplied to only one or two muscle fibres in the spindle. The p_2 plate (see Figs. 11–15) is on average about twice as long as the p_1, and there is no nucleated sole plate or Doyère eminence. Synaptic contact is made by irregular knobs or rings applied closely to the surface of the muscle fibre somewhat like *boutons terminaux*. These plates are characteristically mid-polar and several are usually supplied to each intrafusal muscle fibre. The fine structure of p_1 and p_2 plates has not yet been described. In favourable silver preparations of p_1 plates there are indications of a subneural apparatus with postjunctional sarcolemmal folds. These do not appear to be present in p_2 plates whose synaptic knobs seem to lie on simple cushions of sarcoplasm.

The distribution of three kinds of motor ending to cat muscle spindles results in the occurrence of seven different patterns of polar innervation, and there is an eighth variant in which one of the two poles sometimes receives no motor innervation at all. Jones (1966) has also encountered such barren poles in opossum lumbrical spindles. Of 64 possible combinations of polar innervation in complete spindles, I have so far found 19 in analysing a sample of 59 spindles teased out from various hindlimb muscles. The most common pattern of innervation in this sample was for trail endings and p_2 plates to be distributed to both poles: 91 per cent of the spindles received trail endings, usually at both poles; 78 per cent received p_2 plates; and 58 per cent received p_1 plates. None of the endings is exclusively distributed to one type of intrafusal muscle fibre, though trail endings are more frequently located on chain than on bag fibres, and p_1 plates more


peri.
db.p
y.p
d.p.
α
β
ex. m.f.
n.s.
u.s.
muscle spindle
epi.
p1
p2
γ(P2)
γ(tr.)
vsm.
f.e.
II
III
IV
tr.
Ia
c.
II
P
I&II
n.b.
S1
b.v.
fat
n.c.
Ib
pf.c.
p.c.
fascia
tendon organ
c.
tendon

frequently on bag than on chain fibres. The p_2 plates, however, are more or less equally distributed to both bag and chain fibres. Boyd (1966) still adheres to his original view (1962) that one type of fusimotor ending specifically innervates one type of intrafusal muscle fibre, while Jones (1966) finds, on the contrary, that in over a third of his sample of opossum spindles motor endings were supplied to both bag and chain fibres by the same motor axon. Rabbit spindles, in which all muscle fibres are of the bag type (Barker and Hunt, 1964), receive both trail endings (Barker and Ip, 1965) and p_1 plates; the presence of a p_2 innervation awaits future analysis.

The identification of the functionally separable dynamic and static fibres of Matthews (1962) with specific fusimotor fibres and endings remains to be satisfactorily elucidated. There have been two attempts to do so:

(*i*) *The dynamic/*γ_1*, static/*γ_2 *correlation.* This was suggested by Matthews (1962; Jansen and Matthews, 1962; Crowe and Matthews, 1964*a*, *b*; Brown, Crowe and Matthews, 1965) and is based on the concept developed by Boyd (1962; Boyd and Davey, 1962; Boyd and Eccles, 1963) of two γ motor systems in which large, fast γ-stem fibres reach the spindle as large branches ("γ_1 fibres") terminating as end-plates on bag muscle fibres, while small, slow γ-stem fibres arrive as thin branches ("γ_2 fibres") to supply a network of endings on the chain muscle fibres. One difficulty in the way of this interpretation is that the ranges of the conduction velocities of static and dynamic fibres overlap (Crowe and Matthews, 1964*b*) instead of giving the bimodal distribution that would be expected on the basis of a γ_1/γ_2 correlation. Moreover, by tracing the intramuscular course of γ fibres, Adal and Barker (1965*a*) showed that there is no correlation between the diameters of γ fibres in the muscle nerve and those of their branches at spindle entry, and found the distribution of γ fibres to be such that many cat spindles are innervated by large γ-stem fibres only. Further doubts were raised by work on rabbit spindles which, though composed of bag muscles only, nevertheless proved to be innervated by both large and small γ-stem fibres (Adal and Barker, 1965*b*), static and dynamic fusimotor fibres (Emonet-Dénand, Laporte

FIG. 23. Schema of the innervation of mammalian skeletal muscle based on a study of the cat. Those nerve fibres shown on the right of the diagram are exclusively concerned with muscle innervation; those on the left also take part in the innervation of other tissues. Roman numerals refer to the groups of myelinated (I, II, III) and unmyelinated (IV) sensory fibres; Greek letters refer to motor fibres. Features of terminal sprouting and degeneration are omitted from the spindle. b.v., blood vessel; c., capsule; db.p., double motor end-plate; d.p., degenerating end-plate; epi., epimysium; ex.m.f., extrafusal muscle fibre; n.b., nuclear-bag intrafusal muscle fibre; n.c., nuclear-chain intrafusal muscle fibre; n.s., nodal sprout; *P*, primary ending; p_1, p_2, two types of intrafusal end-plates; peri., perimysium; p.c., Pacinian corpuscle; pf.c., paciniform corpuscle; S_1, secondary ending; tr., trail ending; u.s., ultraterminal sprout; vsm., vasomotor fibres; y.p., young motor end-plate ("accessory ending").

and Pagès, 1964, 1966), and two kinds of motor ending (Hess, 1961*a*; Barker and Ip, 1965). Finally, Barker and Ip (1965) found no correlation in cat or rabbit spindles between the type of fusimotor ending and the axon diameter at the entry to the spindle of the fibre, or fibre branch, supplying it, and maintained that plate and trail endings are not segregated in their distribution to bag and chain muscle fibres respectively. At the Nobel Symposium held in Stockholm in 1965 (Granit, 1966), the γ_1/γ_2 concept and its dynamic/static correlation were therefore abandoned.

(*ii*) *The dynamic/trail-fibre, static/plate-fibre correlation.* This interpretation is put forward by Bessou and Laporte (1966) and is based mainly on their finding (1965) that stimulation of dynamic fusimotor fibres initiates a non-propagated potential near the equatorial region, whereas stimulation of some static fibres initiates a propagated action potential further away, more towards the middle and end of the polar region. Histological evidence (Barker, 1966*a*) suggested that the juxta-equatorial trail ending and its fibre should therefore be identified as dynamic, and that static fibres terminated in the spindle as end-plates. At the time of the Nobel Symposium, this correlation appeared to be the most probable one, even though it was at variance with the dynamic rather than static effect produced by stimulating the fusimotor collaterals of β fibres (Bessou, Emonet-Dénand and Laporte, 1963; Brown, Crowe and Matthews, 1965), an effect since shown to persist after curarization of the extrafusal myoneural junctions (Emonet-Dénand and Laporte, 1966).

Both these correlations were proposed before it was realized that there are two types of plates involved (p_1 and p_2) in addition to the trail ending. At this stage the only correlation that appears certain is to identify the p_1 plate and its β fibre as dynamic. In view of Bessou and Laporte's (1965) findings, and the close resemblance between trail and *en grappe* innervation (indeed their common identity in sheep extraocular muscles), it seems safe to conclude that trail endings produce slow, local contractions and initiate non-propagated potentials intrafusally, comparable with similar extrafusal responses produced by *en grappe* innervation in frog muscle (Kuffler and Vaughan Williams, 1953*a*, *b*) and cat extraocular muscles (Hess and Pilar, 1963). Such activity may also produce a dynamic effect, in which case the static fibres can be identified with the p_2 innervation. A possibility that has to be taken into account in future experiments is that this innervation may be capable of producing both contracture and propagated action potentials, like avian *en grappe* innervation (Ginsborg, 1960).

An essential preliminary to detailed studies of muscle innervation is to isolate the component under investigation by differential denervation. It

has also become apparent that in interpreting one's observations it is equally essential to be aware that the peripheral nervous system is undergoing continuous growth and decay, and to examine each slide as if it were one frame in a reel of ciné film. This is especially important in fusimotor analysis, where within the narrow confinements of the intrafusal bundle one is not simply dealing with three different kinds of motor ending as fixed morphological entities, but with every expression of their terminal degeneration and renewal. These include the various forms of axon sprouting, young endings, and degenerative changes that occur in the process of end-plate replacement, a description of which has been given by Barker and Ip (1966). Their study suggests that in normal, healthy skeletal muscles of the cat, collateral and ultraterminal sprouting of motor axons is shown by between 30 and 40 per cent of fusimotor plate-ending axons, and by about 20 per cent of skeletomotor axons. In further work on this phenomenon, Barker and Negus (unpublished) find that of 2,281 extrafusal motor endings in cat peroneal muscles, 10·6 per cent were either sprouts or young end-plates (previously regarded as "accessory endings"), while 14·7 per cent were in various stages of degeneration. Some fusimotor sprouts grow out from the spindle along nearby capillaries, or venture into and return from tendon, or wander up into the nerve trunk conveying the fusimotor supply. There is reason to suppose that many such sprouts from trail and p_2 endings eventually reach neighbouring spindles to assist in the replacement process. Sprouts from p_1 plates do not join in this traffic.

The existence of this cyclic renewal and decay of peripheral terminals has wide implications, some of which are discussed by Barker and Ip (1966). Some previous observations and interpretations are seen in a new light because of it, and it is clear that some of the assessments made of neuromuscular disease will have to be revised, and that new interpretations are necessary of patterns of re-innervation following nerve injury.

Finally, a word about motor innervation ratios. In Adal and Barker's (1965*a*) study of the cat's first deep lumbrical muscle it was possible to make an accurate assessment of the innervation ratio not only of skeletomotor fibres, but also of fusimotor ones. Innervation ratios have previously been calculated by dividing the number of extrafusal muscle fibres by the number of motor fibres in the muscle nerve. On this basis, the innervation ratio for the cat's first deep lumbrical is 1:98, but this makes no allowance for fusimotor innervation. The ratio of α motor fibres to extrafusal muscle fibres in this muscle is actually 1:300, and the fusimotor ratio is 1:9—that is, one γ or β fibre is distributed to nine intrafusal muscle-fibre poles located in from one to five spindles, usually in two. These ratios, of course, simply

give an average picture, for, as Henneman and Olson (1965) have shown, the size of a skeletomotor unit is proportional to the diameter of the α fibre innervating it, the largest fibres supplying the greatest number of muscle fibres. This is also true of γ fibres, the smallest of which usually innervate only one spindle as against as many as five supplied by the larger ones (Adal and Barker, 1965*a*). Henneman has also demonstrated (Henneman, Somjen and Carpenter, 1965) that the excitability of motoneurones is an inverse function of their size, and it is possible that this may be the significant factor that determines the size composition of the γ supply in different muscle nerves. Boyd and Davey (1966) have shown that the ratio of thickly myelinated to thinly myelinated γ fibres varies in different muscle nerves, and suggest that "a high proportion of thinly myelinated γ fibres in a nerve is associated with a well-developed nuclear chain intrafusal system, with its specialized γ_2 innervation, in the muscle spindles it supplies". However, there is no evidence that trail ("γ_2") endings are supplied exclusively by thinly myelinated γ fibres, and an explanation in terms of motoneurone excitability seems more likely.

SENSORY INNERVATION

The sensory component of muscle nerves, unlike its somatic motor counterpart, consists of both myelinated and unmyelinated fibres. The myelinated ones have a trimodal size distribution, falling into large, medium and small classes (Groups I, II and III), and it is convenient to refer to the unmyelinated C fibres as Group IV. By checking counts made on silver preparations against electron microscope preparations, Barker and M. J. Stacey (unpublished observations) estimate that these fibres outnumber myelinated ones by about 2:1 in the cat posterior tibial nerve. A reappraisal of Ranson and Davenport's (1931) silver counts suggests that the ratio for cutaneous nerves may be much higher, perhaps about 16:1.

Only a minor part of the total sensory fibre outflow consists of fibres that are exclusively concerned with muscle innervation, namely the Ia and II fibres that supply primary and secondary endings to the spindles, and the Ib fibres that innervate Golgi tendon organs. The rest provide an innervation that is also common to other tissues. Quantitative data on this point are provided by Barker, Ip and Adal (1962) who correlated the receptor populations of four cat soleus muscles with the diameter spectra of the sensory fibres of the nerves supplying them. After allowing for the innervation of spindles, tendon organs and paciniform corpuscles teased out in each case, they found an average of 29·2 per cent of the total number of

sensory fibres in the nerve remained unallocated, comprising over one-third of Group II and three-quarters of Group III. They suggested that these provided a supply of free endings to the muscle. Zelená and Hník (1963) likewise estimate that about 30 per cent of the myelinated sensory components supply free endings in the rat soleus. Further information about muscle free endings has since been obtained by Barker and Stacey (unpublished observations), who find that not only are Group II and III fibres engaged in this innervation, but also the whole of Group IV. The endings are located in the adventitia of blood vessels, fat and connective tissue (see Figs. 7 and 8), and occasionally ramify within receptor capsules. Their distribution to these tissues in muscle is in fact the same as in other parts of the body, such as skin. Perhaps this broad range of fibres, which extends from Group II through to Group IV, may fulfil the role of the large and small fibres proposed by Melzack and Wall (1965) in the operation of their gate-control theory of pain mechanisms.

Some features of the sensory innervation of skeletal muscle are illustrated in Figs. 1–10. The general disposition of primary and secondary endings in muscle spindles, for example, is illustrated in Figs. 1, 2 and 3. Primary endings are located on both bag and chain fibres (see Figs. 3 and 19), whereas secondary endings are supplied predominantly to chain fibres (Fig. 3). In rabbit spindles the secondaries lie on the bag fibres mainly in the myotube regions, which are three to four times longer than those in the cat (Barker and Hunt, 1964). These contain a single row of nuclei in a tube of sarcoplasm extending from the ends of each nuclear bag, and form a substratum for rabbit S_1 secondaries comparable to the nucleated region of chain fibres that carry cat S_1 secondaries. Cat spindles may carry up to four (Barker and Ip, 1961) or five (Boyd, 1959) secondaries, and the approximately 400 μm. long regions that they occupy on either side of the primary have been conveniently designated as S_1 to S_4 by Boyd (1962). Most cat hindlimb spindles receive a secondary innervation, and this usually consists of one secondary ending only (Barker and Ip, 1961). Those secondaries that lie nearest to the primary ending consist chiefly of rings and spirals and are supplied by thicker axons than those located further away, which have a more irregular "flower-spray" (Ruffini, 1898) form (see Fig. 8). Annulo-spiral secondaries are about twice as common as flower-spray secondaries in the cat (Barker and Ip, 1960). In spindles with a secondary innervation, the primary ending is generally supplied by a larger diameter Ia fibre than in those without (Adal and Barker, 1962).

Golgi tendon organs (see Figs. 4 and 6) are usually less numerous in skeletal muscle than spindles (Barker, 1962), and in some small muscles

containing only a few spindles, such as cat deep lumbricals and rat tail muscles, they may be absent. The following information about these receptors in cat hindlimb and intercostal muscles was gathered by M. Pang, who examined over 1,500 gold chloride preparations assembled during the course of a quantitative study of mammalian proprioceptors carried out by my research group in Hong Kong in 1960–1961. The average dimensions of the receptor are 0·5 mm. by 0·1 mm. and they are usually connected in series with ten extrafusal muscle fibres. A small proportion (7·6 per cent in this analysis) are located wholly in tendon. The majority are fusiform in shape, but double forms occur and the receptor may sometimes branch at one or both ends. They occasionally (10 per cent of this sample) occur in association with free endings, or spindles, or paciniform corpuscles, and the Ib fibres that innervate them usually do so without branching to supply other tendon organs.

Paciniform corpuscles, such as occur in joint capsules and periarticular tissue (see Hromada and Poláček, 1958), are scarce in muscle, and the small number present are usually associated with tendon organs, being located either on the surface or immediately underneath the thin capsule (see Figs. 6 and 10). They are innervated by Group II and III fibres, which branch to supply groups of from two to nine. Their much larger cousins, the Pacinian corpuscles (Fig. 9), occur very seldom within muscles, though a few may occur underneath the fascia of some, such as the interossei. In the cat's hindlimb about 60 of these corpuscles are supplied by the interosseous nerve, the majority occurring in a large cluster located towards the lower end of the tibia, lying between the lateral flexor digitorum longus muscle and the tibial periosteum (see Hunt and McIntyre, 1960; Barker, 1962).

SYMPATHETIC INNERVATION

This is exclusively vasomotor. At one time the presence of fine axons in cross-sections of the equatorial region of de-afferentated spindles led me to suspect an intrafusal sympathetic innervation (Barker and Cope, 1962; Barker, 1963). This seemed likely in view of Hunt's (1960) finding that repetitive sympathetic stimulation caused significant changes in the threshold of the receptor to applied stretch. However, such effects might equally well be produced indirectly via spindle blood vessels, and it has since become clear that the fine axons in our 1962 de-afferentated preparations belong to trail endings. The unmyelinated ramifications of these that are produced from the terminal and preterminal nodes of the trail fibre sometimes run through and make occasional synaptic contact within the area of equatorial nucleation.

SUMMARY

The motor supply to mammalian skeletal muscle comprises skeletomotor (α) fibres that provide extrafusal end-plates; fusimotor (γ) fibres that innervate spindles; and mixed (β) fibres that innervate both extra- and intrafusal muscle fibres. Spindles receive three kinds of motor ending, a diffuse, multi-terminal trail ending, and two kinds of end-plates, p_1 and p_2. The evidence indicates that trail endings are homologous with the *en grappe* innervation that occurs in mammalian extraocular muscles and some skeletal muscles of other vertebrates. In sheep extraocular muscles the intrafusal trail innervation and the extrafusal *en grappe* innervation frequently originate from the same motor axon. The p_1 plates are identical with extrafusal end-plates and may occasionally be seen to have β fibre connexions. The p_2 plates are larger, lack a nucleated sole plate, and consist of irregular knobs and rings. Extrafusal and p_1 plates degenerate more rapidly after nerve section than p_2 plates and trail endings. In the cat the most common pattern of fusimotor innervation is for trail endings and p_2 plates to be distributed to both spindle poles. Trail endings are more frequently located on chain than on bag fibres, p_1 plates more frequently on bag than on chain fibres, and p_2 plates are more or less equally distributed to both bag and chain fibres. None of the endings is exclusively supplied to one type of intrafusal muscle fibre, or supplied by axons that fall into specific size groups at spindle entry. The dynamic/γ_1 fibre, static/γ_2 fibre correlation and the dynamic/trail-fibre, static/plate-fibre correlation are discussed. At this stage the only correlation that appears certain is to identify the p_1 plate and its β fibre as dynamic. The trail fibres may also prove to be dynamic, leaving the static role to be played by the p_2 innervation.

A process of continuous growth of all motor fibres ensures the replacement of their peripheral terminals, which have a limited life-span and periodically degenerate in a normal cycle of decay and renewal. Quantitative assessments of the degrees of sprouting and of degeneration of terminals in normal muscle suggest that extrafusally these are of the order of 10 to 20 per cent, while intrafusally they may be about twice this.

The sensory supply to mammalian skeletal muscle comprises the myelinated fibres of Groups I, II and III, and the more numerous unmyelinated C fibres of Group IV. Only a minor part of the total sensory fibre outflow consists of fibres that are exclusively concerned with muscle innervation, namely the Ia, Ib and II (secondary) fibres. The rest provide an innervation that is also common to other tissues. About one-third of Group II, three-quarters of Group III and all Group IV fibres supply free

endings to the adventitia of blood vessels, fat, connective tissue and tendon. Some Group II and III fibres innervate paciniform corpuscles, but these receptors are more abundant in joints than muscles. The larger Pacinian corpuscles are rarely intramuscular. The sympathetic innervation is exclusively vasomotor.

A schema of the innervation of mammalian skeletal muscle based mainly on a study of cat hindlimb muscles is shown in Fig. 23. This is intended to replace the schema published in two previous reviews (Barker, 1962, 1963).

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DISCUSSION

Roberts: Have you any views, Professor Barker, on whether the secondary endings always lie over the trail endings?

Barker: There is usually some degree of overlap between the trail endings and the secondary innervation in the juxta-equatorial region, but this rarely occurs further along the poles.

Hallpike: Does the term "trail" ending imply that this fibre is always long and thin?

Barker: It is characteristic of trail endings for there to be a considerable distance

between the terminal node of the trail fibre and the places where the long, thin and often branched axon terminals finally make synaptic contact. It was this feature that suggested the term "trail".

Smith: Are they naked axons? And have they what Hess described in extra-ocular eye muscle—bulbous enlargements on the preterminal nerve which seem to make the synaptic contact with the muscle fibre (Hess, A., and Pilar, G. [1963]. *J. Physiol., Lond.*, **169**, 780–798)?

Barker: The terminals are naked axons, and the regions that make synaptic contact with the muscle fibres do so in the form of knobs, brushes and tapers.

Eldred: What is your viewpoint on the relationship of the p_1 and p_2 endings to the regeneration of motor end-plates, which you have reported to be evident on intrafusal fibres (Barker, D., and Ip, M. S. [1966]. *Proc. R. Soc. B*, **163**, 538–554)? And as a corollary, in renewal of the extrafusal motor end-plate is there a period of time when the axon has ramified and made contact with the extrafusal fibre, but does not show an associated nucleated end-plate?

Barker: My observations suggest that a nucleated sole plate appears very early on in p_1 and extrafusal end-plate formation. There is no difficulty in distinguishing between such young plates and the much larger p_2 endings. There is some resemblance between the axon terminals of a p_2 ending and those of an extrafusal end-plate in the earliest stages of degeneration. Both are knob-like, but the p_2 is larger and lacks a nucleated sole plate.

Smith: Have you evidence that this continual degeneration and regeneration of the peripheral nervous system occurs under normal conditions? Do you believe that the entire motor end-plate degenerates, or just a part of it?

Barker: As far as one can tell, natural degeneration of motor terminals parallels up to the last stages that which can be produced experimentally by cutting the nerve. It starts at the tips of the axon terminals, which begin to roll up and back, and then to inflate and retract, and finally the axon starts to blow up and the terminal portion to disintegrate. After nerve section, the process goes a stage further, for the axon actually vanishes and leaves an empty sole plate, whereas in normal muscle new sprouts may by that time have come round to make new axon terminals in that sole plate.

Smith: Is this initiated peripherally at the nerve endings, or in the axons?

Barker: According to M. V. Edds ([1953]. *Q. Rev. Biol.*, **28**, 260–276) such sprouting is probably in response to the solating action of a humoral agent released by the Schwann cells of the degenerating axon.

Lowenstein: Is there this same fluid innervation in ordinary extrafusal motor end-plates?

Barker: I believe it occurs in all motor endings—mammalian ones, anyway.

Matthews: You said that over one-third of the Group II afferent fibres do not come from spindles, and might come from free nerve endings. This is, of course, of crucial importance for electrophysiological experiments. Could you say more about the preparations on which this estimate was based?

Barker: If you cut all the afferents to the soleus muscle, you can then tease out and count all the spindles, tendon organs and paciniform corpuscles, and compare this receptor population with the afferent fibre-diameter spectrum. We did this for four cat soleus muscles (see Barker, D., Ip, M. C., and Adal, M. N. [1962]. In *Symposium on Muscle Receptors*, pp. 257–261, ed. Barker, D. Hong Kong: Hong Kong University Press). We made various assumptions—for example, we assumed a one to one ratio of Ia fibres to endings—and we concluded that about a third of the Group II afferent fibres were engaged in free-ending innervation and about three-quarters of Group III. Zelená and Hník in the following year arrived at an equivalent finding (Zelená, J., and Hník, P. [1963]. *Physiologia bohemoslov.*, **12**, 277–290). We calculated that on average 29·2 per cent of the myelinated fibres were engaged in free-ending innervation in the cat soleus, and they estimated it as 30 per cent in rat soleus.

Matthews: One is left with Professor C. C. Hunt's experiments of 1954 (*J. gen. Physiol.*, **38**, 117–131) in which he found no sign of these on recording single units from dorsal root filaments in the cat.

Barker: We find that when these free-ending fibres are traced back, as one can do with some certainty in teased silver preparations, they are of reasonable dimensions, up to 7 or 10 μm.

Eldred: It might be of interest to describe Hník's findings in more detail here. He found that after tenotomy (Hník, P., Beranek, R., Vyklicky, L., and Zelená, J. [1963]. *Physiologia bohemoslov.*, **12**, 23–29) and also after de-efferentation (Hník, P. [1964]. *Physiologia bohemoslov.*, **13**, 405–410) and exercise of the muscle (Hník, P., and Payne, R. [1965]. *J. Physiol., Lond.*, **181**, 36–37*P*) there is an increase of afferent discharge from the muscle which is not ascribable to either tendon organs or annulo-spiral or flower-spray endings, but is probably from this category of free, relatively large myelinated fibres. His work was done in rats and cats. We have been examining the discharge from tenotomized muscles in the cat, but so far have not seen this late enhancement in discharge (Yellin, H., and Eldred, E. [1965]. *Anat. Rec.*, **151**, 436).

Matthews: Most of Hník's responses were recorded mass discharges. Have single-unit studies been made?

Eldred: When Hník came to analyse single units he turned to the cat's dorsal roots. On the basis of these findings he said that the tendon organs and spindle afferents do not increase their discharge (Hník, P. *et al.* [1963]. *Loc. cit.*). He does not say that activity of any dorsal root units is increased in the cat, but he and Payne do for the rat (Hník, P., and Payne, R. [1965]. *J. Physiol., Lond.*, **180**, 25–26*P*).

Wersäll: We have tried to find muscle spindles in the tensor tympanus and stapedius muscles of the rabbit. These are peculiar in that they have extremely small motor units and very short muscle fibres. Our small endings of secondary type form afferent endings mainly on the muscle fibres. It appears that no separate encapsulated spindles are to be found (see p. 38).

Barker: The innervation you describe sounds similar to that in cat extraocular muscles where the stretch afferents end freely among the muscle fibres rather than in spindles, which are absent. I do not think it is helpful to think of such muscles functioning as their own spindles.

Lowenstein: People working on the vestibule have often discussed the significance of the paucity of spindles in eye muscles. You said that spindles exist in sheep eye muscles; can you say more about this?

Barker: Spindles have been reported in the eye muscles of man and the chimpanzee (Cooper, S., and Daniel, P. M. [1949]. *Brain*, **72**, 1–24); in the macaque monkey (Greene, T., and Jampel, R. [1966]. *J. comp. Neurol.*, **126**, 547–550); and in a number of artiodactyl ungulates besides the sheep (Cilimbaris, P. A. [1910]. *Arch. mikrosk. Anat. EntwMech.*, **75**, 692–747). Cilimbaris, who made the most extensive search of this kind in mammals, found no spindles in horse eye muscles, or those of rats, lagomorphs, or certain carnivores. This distribution is curiously sporadic; for example, Cilimbaris found spindles absent in pig eye muscles, but present in those of the wild boar, and Greene and Jampel found them in the rectus muscles of the macaque but not in the oblique muscles.

Lowenstein: Among the lower vertebrates, fishes have little sensory innervation of the eye muscles. The interest by vestibular physiologists in the muscle spindles of eye muscles may have been misguided, in that there may be no need for the vestibular part of the eye muscle function. But generally speaking in visual orientation there would be room for a feedback.

Barker: S. Cooper and M. Fillenz ([1955]. *J. Physiol., Lond.*, **127**, 400–413) have recorded from the freely ending stretch afferents in the eye muscles of the cat and mangabey monkey.

Jansen: In your analysis of the motor innervation of 59 muscle spindles have you obtained the comparable figures for the individual intrafusal muscle fibres?

Barker: The analysis has not been taken as far as that yet.

Eldred: May I raise a point about the innervation of Pacinian corpuscles? An accessory unmyelinated fibre has been described classically in Pacinian corpuscles, and recently O. B. Il'inskii has obtained results supporting its existence electrophysiologically. He suggests that the afferent discharge of the Pacinian corpuscle can be modified as a result of electrical stimulation of this small fibre (Il'inskii, O. B. [1966]. *Bull. exp. Biol. Med.*, **61**, 1–6).

Barker: Loewenstein has described and recorded from C afferent fibres innervating cat mesenteric Pacinian corpuscles (Loewenstein, W. R., Goto, K., and Noback, C. [1962]. *Experientia*, **18**, 460). My impression is that these "accessory" fibres are really only part of the web of free endings that innervates fat, connective tissue and blood vessel adventitia throughout the body. One occasionally sees such free endings within the capsules of spindles, tendon organs and Pacinian corpuscles. The axons supplying them in these situations have been referred to as satellite fibres, accessory fibres, concomitant fibres, and so on, but I think their presence there is just incidental.

Lowenstein: You illustrated two kinds of lamellated corpuscle in your Fig. 23, Professor Barker—the true Pacinian corpuscle and the elongated paciniform corpuscle. Is there any information about their speeds of adaptation? The rapid adaptation of the Pacinian corpuscle is now attributed to the mechanical properties of the lamellae (Loewenstein, W. R. [1966]. *Ciba Fndn Symp. Touch, Heat and Pain*, pp. 186–201. London: Churchill), and the paciniform corpuscle with fewer lamellae might be expected to be less rapidly adapting.

Roberts: The paciniform corpuscle in the joint capsule is certainly a rapidly adapting corpuscle, but perhaps not quite so rapid as the Pacinian proper; it gives 2 or 3 impulses for each sudden deformation whereas the Pacinian corpuscle gives only one, except in special conditions.

Barker: One can recall here the work of C. C. Hunt and A. K. McIntyre ([1960]. *J. Physiol., Lond.*, **153**, 74–87) on the interosseous nerve, in which they distinguish between vibration and tap receptors. When Adal and I were studying this nerve, we were interested to see that the Pacinian corpuscles that it innervated occurred in two distinct size groups. The classical types measure about a millimetre long and have around 60 lamellae, in contrast to smaller ones about half a millimetre long with a dozen or so lamellae. The frequency of occurrence of these two types suggests that they correspond to the vibration and tap receptors, respectively, in Hunt and McIntyre's recordings.

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ON THE FUNCTIONAL PROPERTIES OF STRETCH RECEPTORS OF MAMMALIAN SKELETAL MUSCLES

JAN K. S. JANSEN

Neurophysiological Laboratory, Anatomical Institute, University of Oslo, Norway

THE identification and the main functional properties appear to be reasonably well established for three types of stretch receptors in mammalian skeletal muscles. These are the Golgi tendon organs and the primary and the secondary endings of the muscle spindles. In addition there are a number of other sensory endings in skeletal muscle with thin (group III) or unmyelinated afferent fibres. The properties and significance of these thin muscle afferents are less well understood and will not be considered in the present review.

In his classical paper, B. H. C. Matthews (1933) described two main types of stretch receptors in mammalian muscle, his A and B endings. The main difference was in their response to muscle contraction. The discharge of the A endings was interrupted during a muscle twitch whereas the B endings were excited. This fundamental difference between the two types of receptors was ascribed by B. H. C. Matthews (1933) to the localization of the receptors with respect to the extrafusal muscle fibres—the B response originating in Golgi tendon organs in series with the extrafusal muscle fibres, the A response in muscle spindle receptors coupled in parallel with the main muscle fibres and thus unloaded during contraction of the muscle. This interpretation has been accepted by all later investigators, and it is still the main criterion for the functional identification of tendon organ and muscle spindle receptors.

The physiological identification of afferent fibres from primary and secondary endings of muscle spindles is based on the histological observation (Ruffini, 1898) that the afferent fibre from the primary ending is thicker (group I) than that from the secondary ending (group II). Physiologically the identification of the two types of fibre is achieved by measuring their conduction velocity and, following Hunt (1954), the division line between group I and group II afferent fibres has commonly been placed

at 72 m./sec., corresponding to an axon diameter of 12 μm. Possible overlaps in the conduction velocity of afferent fibres from primary and secondary endings have been discussed by P. B. C. Matthews (1964).

The subject of muscle stretch receptors has received considerable attention in recent years and several notable reviews have been published (Granit, 1955; Hunt and Perl, 1960; Matthews, 1964). The subject has also been extensively discussed at several recent symposia, the proceedings of which have been published (Barker, 1962; Granit, 1966; Andrew, 1966). Even so there may be some justification for a summary of the rapidly accumulating knowledge and controversial points concerning the physiology of muscle stretch receptors.

GOLGI TENDON ORGANS

The characteristics of the tendon organs are relatively simple and I shall accordingly deal with them first. The main qualitative features of the tendon organ response were established by B. H. C. Matthews (1933), who showed that they were tension receptors, commonly with fairly high thresholds to passive stretch of a muscle. This was confirmed by Hunt and Kuffler (1951), who also demonstrated that the afferent fibres from the tendon organs all belonged to the group I of muscle afferents (12–20 μm. diameter).

Certain additional features and a more quantitative description of the response of the tendon organs have been obtained in recent studies of soleus (Jansen and Rudjord, 1964) and anterior tibial tendon organs (Alnæs, 1966) in this laboratory. It appears that some tendon organs may respond differently to tension produced by passive extension of a muscle and to the tension of active contraction. Thus, in the soleus, tendon organs were found that did not respond at all to passive extension up to the maximal *in situ* length of the muscle, the corresponding tension being more than 500 g. To twitch contractions, on the other hand, the soleus tendon organs were all excited at small to moderate tensions. The thresholds to active contraction for 42 soleus tendon organs ranged from 6 to 160 g. with a mean value of 44 g. (Jansen and Rudjord, 1964). This difference between the exciting effects of active and passive tension was ascribed to a differential effect of the two types of stimuli on differently located tendon organs. This is easily seen in a bipennant muscle like the soleus, and it was in fact found that all the tendon organs that did not give a maintained response to full passive extension were localized in the proximal end of the muscle.

Certain differences between soleus and anterior tibial tendon organs were found by Alnæs (1967). The latter were all excited and gave a main-

tained discharge to passive stretch of the muscle within its physiological limits. Their thresholds to active and passive tension were rather similar, except for a few proximally located receptors with slightly higher thresholds to passive extension. The anterior tibial tendon organs also differ from those of the soleus in that some of them fire "spontaneously" without any load on the muscle. This was found for 4 out of 27 anterior tibial tendon organs examined.

The stimulus–response relation

The discharge frequency of the tendon organs increases with increasing tension on the muscle. To steady tensions the receptors adapt very slowly. The steady-state firing frequency of soleus tendon organs is an approximately linear function of muscle tension. This applies to active as well as passive muscle tension, but the frequency increase tended to be less for a given increment of tension when the muscle was passively extended. Thus, the mean slope of the frequency–passive tension relation was 5 impulses/sec./100 g., whereas that of tetanic contraction was 8 impulses/sec./100 g. This again is most easily explained by an attenuation of the passive tension due to the architecture of the muscle.

Another unexpected feature of the response of the soleus tendon organs to tetanic contractions of the muscle was the influence of the initial tension of the muscle. Whenever this was appreciable (more than 300 g.), the receptor behaved as if it was mainly excited by the active component of the tension (Jansen and Rudjord, 1964).

Alnæs (1966) again found notable differences among the anterior tibial tendon organs. For the majority of them the response to passive stretch and tetanic contractions with different initial tensions was described by a continuous curve consisting of an initial steeper part merging smoothly with a less steep part at higher tensions. This is consistent with the fact that most of the anterior tibial tendon organs had similar thresholds to active and passive tension, and is most easily explained by a more favourable distribution of passive tension to the tendon organs of this muscle.

When plotted against tension on log–log coordinates the firing frequency of anterior tibial tendon organs is well described by a straight line. This suggests that a power function of the form:

$$R = K \cdot P^n$$

is a useful description of the steady-state response of anterior tibial tendon organs. In the equation R is the response measured as frequency, K and n

are constants and P is total muscle tension. The value of n was found to vary between 0·4 and 0·8, with a mean of 0·5 (Alnæs, 1966).

In the upper range of tensions produced by tetanic contractions, for example from 500 to 1,500 g., the response curves of the anterior tibial tendon organs is an approximately straight line with a slope varying from 4 to 20 impulses/sec./100 g. for different receptors (Alnæs, 1966). This is about the same range of variation as that of soleus tendon organs.

The differences in general form of the response curves of soleus and anterior tibial tendon organs might suggest fundamental differences in the properties of the receptors of the two muscles. However, the problems introduced by the distribution of passive tension in the muscles make any such inference doubtful. The linear relation of the soleus tendon organs refers to one or the other kind of stimulus (contraction or passive extension), and the usual finding was a smaller sensitivity to passive stretch. This is explained by the "attenuation" of this stimulus in the soleus. In tibialis anterior, on the other hand, the more favourable mechanical coupling of the tendon organs reveals the entire range of their steady-state response as an approximate power function.

Dynamic properties of tendon organs

The response of the tendon organs depends not solely on muscle tension itself, but also on the rate of change of tension. This is easily seen during a muscle twitch. The firing frequency is then commonly maximal during the rising phase of the twitch and has already fallen by the time of peak tension. In soleus many tendon organs respond well to transient increases in passive tension, but do not fire at all during maintained passive extension at higher muscle tension.

Alnæs in this laboratory found an interesting difference in the transient response of soleus and anterior tibial tendon organs. When excited by a tetanic contraction of the muscle, the anterior tibial tendon organs showed a marked overshoot during the period of increasing tension. The peak frequency of firing during a tetanus might be three times the steady-state response during maintained contraction. The response of the soleus tendon organs, on the other hand, usually does not contain such a transient overshoot. Their firing frequency increases early to a maximum value at which it remains during the maintained contraction.

This difference between the tendon organ response of the two muscles may be due to a greater dynamic sensitivity of the anterior tibial tendon organs, or it may simply be a consequence of the greater speed of contraction of the tibialis anterior muscle. To distinguish between the two alterna-

tives the tendon organ response was examined during periodic variations in tension produced by a sinusoidal stretch of the contracting muscle. During sinusoidal stretches the peak tension developed is relatively independent of the frequency of stretch, whereas the rate of change of tension changes greatly (Rack, 1966). To sinusoidal stretches the tendon organ response varies periodically with the tension. The time of peak frequency is clearly earlier than that of peak tension, another indication of the dynamic sensitivity of the receptors. At low frequencies of stretching (less than 1 cyc./sec.) the peak frequency corresponds approximately to the steady-state value for the same tension. At higher stretch frequencies there is a rather steep increase in peak frequency of firing, and, as mentioned, this occurs without any comparable increase in peak tension. When the peak frequency of firing is plotted against the stretch frequency the response areas of the anterior tibial and soleus tendon organs occupy the same region of the plot and exhibit similar types of curves (Alnæs, 1966). This indicates that the explanation for the difference in transient response of the anterior tibial and soleus receptor is largely the difference in contraction rate of the two muscles, and the conclusion is reached that the receptor properties of the two groups of tendon organs are rather similar, during static as well as dynamic conditions.

MUSCLE SPINDLE RECEPTORS

The muscle spindles contain two types of receptors closely associated with the specialized intrafusal muscle fibres. In mammals the intrafusal muscle fibres have an independent efferent innervation, and activity in these fibres has a significant effect on the properties of the receptors. The complexity of the muscle spindles is therefore appreciable and many features of their mode of functioning are still incompletely understood. As described in the preceding paper of this volume (p. 3), important controversies exist with regard to the morphology of the muscle spindles, but general agreement has been reached on the following main points.

(1) There are two types of receptors in the mammalian muscle spindle.

(2) There are two types of intrafusal muscle fibres in most spindles.

(3) There are several different types of efferent nerve fibres to the intrafusal fibres.

The primary ending

The main characteristics of the response of the primary endings were demonstrated by B. H. C. Matthews (1933). These receptors respond with

an increasing frequency of firing to increasing muscle length, and, equally important, they respond to the rate of change of length, that is to say, to the velocity of stretch as well. The static response of the primary endings—that is, their frequency of firing to maintained extension of the muscle—increases approximately linearly with the length of the muscle (Eldred, Granit and Merton, 1953; Whitteridge, 1959; Harvey and Matthews, 1961; Bessou and Laporte, 1962; Jansen and Matthews, 1962*b*). The slope of the frequency–extension relation determines the length sensitivity of the primary ending. To the extent that the published values for the static sensitivity of primary endings can be compared, it has been shown to be rather similar for soleus (Jansen and Matthews, 1962*b*) and anterior tibial primary endings (Alnæs, Jansen and Rudjord, 1965).

The sensitivity of the primary endings to the velocity of stretch has commonly been measured as their so-called dynamic index (Jansen and Matthews, 1962*a*; Matthews, 1962; Bessou and Laporte, 1966). This is the reduction in frequency of firing at the transition from a linear dynamic stretch to static extension at the same length. It has been shown by P. B. C. Matthews (1963) that the dynamic index increases with increasing velocity of stretch, as required from a measure of velocity sensitivity. Furthermore, Crowe and P. B. C. Matthews (1964*a*) have shown that the assessment of the dynamic properties of the receptor from the dynamic index is consistent with other measurements of the velocity sensitivity, such as their peak frequency of firing during a ramp stretch. The shape of the relationship between the dynamic index and the velocity of stretch has been determined for soleus primary endings only. The relationship is usually nonlinear, consisting of an initial steeper part merging gradually with a less steep, almost linear curve at the higher velocities of stretch (Matthews, 1963). Very little information exists on the dynamic sensitivity of the primary endings of other muscles. The response curve of a posterior tibial primary ending, published by Brown, Crowe and P. B. C. Matthews (1965), falls with the range of variation of the soleus receptors. The dynamic index of anterior tibial primary endings appears to be in the lower range and slightly less than that of soleus receptors (Alnæs, Jansen and Rudjord, 1965).

The effects of fusimotor activity. B. H. C. Matthews (1933) had already observed that some primary endings would be excited during a muscle twitch when the muscle nerve was stimulated by a supramaximal shock, and he suggested that the excitation was due to contraction of the intrafusal muscle fibres innervated by thin efferent nerve fibres. Many years later this view was established by the experiments of Leksell (1945) and Hunt,

Kuffler and Quilliam (1951). By stimulating thin efferent fibres in the ventral roots the latter group showed conclusively that these fibres did not produce appreciable extrafusal contraction. They did, however, evoke electrical activity in intrafusal muscle fibres and at the same time excited the muscle spindle receptors. Hunt and Kuffler (1951) further demonstrated that all muscle spindles appear to receive several fusimotor fibres and that the excitatory effects of each of them are summated.

The morphological observations of Boyd (1962) of two types of γ-efferent fibres to the spindles stimulated the interest in possible functional differences within the γ-efferent group of nerve fibres. On indirect evidence it was suggested that there might be two types of fusimotor fibres differing in their effect on the dynamic sensitivity of the primary ending (Jansen and Matthews, 1962*a*). On stimulating single γ-efferent fibres in ventral roots and studying their effect on the dynamic and static properties of soleus primary endings, P. B. C. Matthews (1962) and subsequently Crowe and P. B. C. Matthews (1964*a*) indeed demonstrated that the γ fibres consisted of two groups with different effects on the receptor properties. The one group of fibres, called dynamic γ fibres, consistently increased the dynamic sensitivity of the primary endings, whereas the other group, called static γ fibres, decreased or had no effect on the dynamic sensitivity of the receptors. Both types of fibre excited the receptors at constant muscle length. In a similar study of fusimotor effects on posterior tibial primary endings Brown, Crowe and P. B. C. Matthews (1965) could show that virtually all accessible γ-efferent fibres could be classified as either static or dynamic fibres. The functional distinctness of the two types of fibres has been established by a number of observations. The difference persists over the entire physiological range of velocities of muscle stretch. It is present also during sinusoidal stretches and during ramp releases of the muscle. And finally, one particular γ fibre had the same effect, either static or dynamic, on all primary endings which it excited (Crowe and Matthews, 1964*b*). Many of these observations have been confirmed by Laporte and collaborators on different preparations (Bessou, Laporte and Pagès, 1966).

A rather detailed account of the fusimotor effects on primary endings has been given by P. B. C. Matthews and collaborators. They find that the effect of activation of dynamic fusimotor fibres increases with increasing velocity of stretch. Dynamic fusimotor activity, therefore, increases the slope of the relationship between the dynamic index and the velocity of stretch. The steepness of this slope also increases with increasing frequency of fusimotor activation. Activation of static fusimotor fibres, on the other

hand, usually reduced the slope of the dynamic index against velocity of stretch.

Crowe and P. B. C. Matthews (1964*a*) also examined the fusimotor effects on the length sensitivities of the receptors. Examined under static conditions both types of fusimotor fibre usually caused an approximately equal increase in the frequency of firing at different lengths. That is to say, the slope of the static frequency–extension relation remained unchanged. This is rather surprising in the light of observations on decerebrate cats (Jansen and Matthews, 1962*b*). The fusimotor background activity prevailing in the decerebrate preparation regularly increased the static sensitivity of the primary endings. The explanation of this apparent discrepancy is not obvious. It might possibly be a consequence of activation of only one single fusimotor fibre, presumably causing contraction of only one-half of the intrafusal muscle fibres.

In addition to the γ-efferent innervation discussed above, the muscle spindles may also be innervated by collaterals of motor nerve fibres which supply ordinary extrafusal muscle fibres as well. This has long been a controversial subject (Hunt and Kuffler, 1951; Granit, Pompeiano and Waltman, 1959*a*, *b*), but is now firmly established by Bessou, Emonet-Dénand and Laporte (1963, 1965). They used the small lumbrical muscles of the cat and were able to isolate in the ventral roots the majority of its motor fibres. The smaller α motor fibres were found to supply small and relatively slowly contracting extrafusal motor units. In addition some of them also appeared to have a specific effect on the muscle spindles, as judged by their exciting effect on the primary ending. The specificity of the spindle effect was demonstrated by its high optimal frequency, three to four times the tetanic fusion frequency of the extrafusal fibres. The spindle activation was, furthermore, still present after selective curarization blocking the extrafusal neuromuscular transmission while the intrafusal synapses were still functioning. Such α innervation of the spindles was not found in all the preparations they examined. It has later also been demonstrated in the tibialis posterior muscle (Brown, Crowe and Matthews, 1965), but it is still unknown to what extent it commonly occurs in other muscles. In a later study it has been demonstrated that the effects of the α fusimotor fibres on the primary endings are very similar to the effects of dynamic γ fibres. They may cause a large increase in the dynamic sensitivity of the receptor, while their effects at constant length are less pronounced (Bessou, Emonet-Dénand and Laporte, 1965).

It appears clear that the α innervation of the spindles occurs in addition to the innervation by static and dynamic γ fusimotor fibres (Brown, Crowe

and Matthews, 1965). Without more information about the frequency of occurrence of additional α innervation in spindles of various muscles, its functional significance is difficult to assess.

The secondary ending

Spindle afferents of slow conduction velocity were first demonstrated by Merton (1953). They were studied more extensively by Hunt (1954), who showed that soleus secondary endings on the average had slightly higher thresholds for extension than the primary endings. There was, however, considerable overlap in the values for the two types of receptors, and the difference in threshold cannot be regarded as fundamental. In tibialis anterior, for instance, the average threshold of the secondary endings appears to be as low as or lower than that of the primary endings (Fehr, 1962; Alnæs, Jansen and Rudjord, 1965).

One important difference between primary and secondary endings has been established in later work. The secondary endings are much less sensitive to the velocity of muscle stretch. This was first described by Cooper (1959, 1961) and has later been confirmed for the spindle receptors of a number of different muscles (Harvey and Matthews, 1961; Matthews, 1963; Bianconi and van der Meulen, 1963; Renkin and Vallbo, 1964; Alnæs, Jansen and Rudjord, 1965). Most convincingly, this difference has been demonstrated for primary and secondary endings of the same spindle of the tenuissimus muscle by Bessou and Laporte (1962). When measured by their dynamic index there is some overlap in the dynamic sensitivities of primary and secondary endings (Matthews, 1963; Alnæs, Jansen and Rudjord, 1965). Bianconi and van der Meulen (1963) have tentatively attributed the differences in dynamic properties of the various secondary endings to different receptor regions within the spindle.

The small dynamic sensitivity of the secondary endings has also been demonstrated for other types of mechanical stimuli, such as tendon taps (Lundberg and Winsbury, 1960) and vibration of the tendon (Bianconi and van der Meulen, 1963). A further characteristic of the response of the secondary endings is that they often continue to fire during slow releases of the muscle. This is in contrast to the behaviour of the primary endings, which are usually silent during muscle release (Harvey and Matthews, 1961).

To static extension the firing frequency of secondary endings increases approximately linearly with muscle length (Harvey and Matthews, 1961). For soleus and anterior tibial receptors the average slope of the static frequency–extension relation of secondary endings is very similar to that

of the primary endings (Jansen and Matthews, 1962*b*; Alnæs, Jansen and Rudjord, 1965). For tenuissimus receptors, however, the secondary endings have a higher average static sensitivity than the primary endings (Bessou and Laporte, 1962).

The effects of fusimotor activity. Hunt (1954) demonstrated that secondary endings were excited by activation of intrafusal muscle fibres by stimulation of single small efferent fibres in the ventral roots. Quite recently Appelberg, Bessou and Laporte (1966) have described the differential effects of static and dynamic fusimotor fibres on the response of the secondary endings. The experiments were performed on their elegant tenuissimus preparation. This permitted comparison of the effect of individual fusimotor fibres on primary and secondary endings of the same muscle spindles. The static fusimotor fibres, identified by their action on the primary ending, also uniformly coactivated the secondary ending of the spindle. In contrast, the dynamic fusimotor fibres with one exception did not influence the response of the secondary endings to stretch. (The one exceptional dynamic fibre had its effect on a secondary ending with a larger than usual dynamic index.) This finding of Appelberg and his co-workers must be of considerable importance for deductions about structural and functional relationships within the muscle spindles and it is supported by observations on reflexly induced changes in the response of muscle spindle receptors (Jansen, 1966).

No information is available on the effects of α fusimotor fibres on secondary endings.

CORRELATION OF SPINDLE STRUCTURE AND FUNCTION

In view of the present controversies about muscle spindle histology, it appears at the moment most appropriate to put the emphasis on the existing physiological observations of muscle spindle mechanisms. B. H. C. Matthews (1933) originally suggested that the dynamic sensitivity of the primary ending was due to differences in visco-elastic properties between the receptor region and polar region of the intrafusal muscle fibres. If the nuclear bag receptor region was relatively less viscous that the rest of the intrafusal fibre, the receptor would be subjected to additional deformation during a dynamic stretch, due to the viscous force, and the dynamic sensitivity of the receptor would be explained. This explanation appears to have been accepted as the most plausible one by all subsequent investigators, and P. B. C. Matthews (1964) has aptly summarized the arguments in its favour.

B. H. C. Matthews' hypothesis has recently been strongly supported by

Smith's (1966) direct observations and cinematography of intrafusal muscle fibres during small step changes in length. Smith employed isolated spindles of rat hindleg lumbrical muscles. Although the identification of the two histological types of intrafusal muscle fibre was not always possible in the preparation *in vivo*, it will be accepted for the present discussion that Smith's thick intrafusal fibres were nuclear bag fibres and his thin fibres were nuclear chain fibres, as indeed appears entirely likely. The two types of intrafusal fibres behaved differently following a step stretch of the muscle spindles. Following the stretch a slow relaxation lasting approximately 0·5 sec. occurred in the large, nuclear bag fibres. It indicates a region of low viscosity in the central region of bag fibres, just as postulated by the "visco-elastic hypothesis" of the origins of the dynamic response of the primary endings. Very much less, if any such relaxation was seen in the thin, nuclear chain fibres. Smith also points out that the time-course of the visco-elastic effect in the bag fibres is similar to the time-course of the decay of the response of the primary ending after a step stretch.

Histologists agree that the primary ending has receptor terminals on the nuclear bag as well as on the central region of the nuclear chain fibres. Smith's observations on the passive mechanical properties of the two kinds of fibre suggest that these two receptor regions may have very different properties. The nuclear bag receptor region may be the origin of the dynamic response of the primary ending, whereas the nuclear chain receptor region generates the static response of the receptor. The same suggestion has been made previously on indirect evidence (Jansen and Matthews, 1962*a*; Matthews, 1963). The absence of obvious viscous relaxation in the nuclear chain fibres also agrees with the small dynamic sensitivity of the secondary endings, which are known to have their main receptor terminals on these fibres.

To explain the effects of fusimotor activation on the spindle receptors one needs to know the mechanical properties of contracting intrafusal muscle fibres. Only fragments of this are known, and there is still a long way to go before the complete chain of events from intrafusal muscle fibre activation to receptor excitation is accounted for. But certain initial important observations have been presented. Smith (1966) recorded the time-course of contraction of the two types of intrafusal fibre to direct electrical stimulation of his isolated rat spindle preparation. To single shocks the small muscle fibres, presumably the nuclear chain fibres, exhibited vigorous, rapid twitch contractions, lasting about 100 msec. The bag fibres, on the other hand, gave only small and much slower contractions to single shocks. When the preparation was stimulated tetanically the

contraction of the chain fibre reached its plateau about twice as fast as the bag fibre. Comparing his observations with those of Crowe and P. B. C. Matthews (1954*b*), Smith found a striking similarity in the time-course of contraction of the bag fibre and the time-course of activation of the primary ending by dynamic γ fibres. A similar agreement was found between the time-course of contraction of the chain fibres and the time-course of static γ fibre activation of the primary ending.

Although very suggestive, Smith's observations leave unanswered the question of whether the intrafusal muscle fibres contract in the same way when activated through their motor nerves. Boyd (1966) has recently presented observations on the activation of intrafusal muscle fibres of tenuissimus spindles by stimulating their γ fibres. Single shocks did not produce visible intrafusal contractions. On repetitive stimulation some γ fibres produced contractions of nuclear chain fibres, others activated the nuclear bag fibres. Only exceptionally did he find activation of both chain and bag fibres from a particular γ fibre. The chain fibre contraction was rapid compared to the bag fibre contraction, which Boyd describes as weak and sluggish, with contraction and relaxation phases lasting 0·5 sec. or more.

These observations on the behaviour of the intrafusal muscle fibres appear to justify the following conclusions. There are functionally two types of intrafusal muscle fibre, differing among other things in their speed of contraction. The slow and fast types of intrafusal fibre presumably correspond to the histologically defined nuclear bag and nuclear chain fibres, respectively. The motor innervations of the two types of fibre appear to be largely independent and separate. The dynamic fusimotor effects can reasonably be expected from activation of nuclear bag fibres; the static fusimotor effects similarly from nuclear chain fibres. This scheme, which in principle is similar to earlier suggestions by Matthews and co-workers (Matthews, 1964; Crowe and Matthews, 1964*a*, *b*), also accounts for some additional observations. The discharge of both primary and secondary endings can be driven in synchrony with the fusimotor activation. Such driving is produced by stimulation of static fusimotor fibres and is not seen on stimulation of dynamic fusimotor fibres (Matthews and Crowe, 1964*b*; Bessou and Laporte, 1966; Appelberg, Bessou and Laporte, 1966). The finding that the secondary endings are excited by static but not by dynamic fusimotor fibres (Appelberg, Bessou and Laporte, 1966) is easily fitted into the picture. Another recent finding should also be mentioned in this context. Rack and Westbury (1966) have shown that the action of succinylcholine on the response of the primary endings closely imitates the effects

of dynamic γ fibre activation, and Smith (1966) has observed succinylcholine to cause strong and prolonged contractures on the nuclear bag fibres, while its action on the nuclear chain fibres was much weaker.

In spite of this apparently consistent picture of the mode of action of the muscle spindles there are certain physiological observations which, at the moment, are very difficult or impossible to fit into the picture. This has been emphasized particularly by Laporte and his collaborators. There are two groups of observations that are particularly relevant here. Histologically there are no nuclear chain fibres in rabbit hindleg muscle spindles (Barker and Hunt, 1964). In spite of this, Emonet-Dénand, Laporte and Pagès (1966) were able to demonstrate two kinds of γ fibres to rabbit spindles with effects closely similar to the dynamic and the static γ fibres of cat spindles. This observation shows that static fusimotor effects can be obtained without nuclear chain fibres in the spindles.

Important observations have also been made in the study of the electrical activity of intrafusal muscle fibres. On stimulating identified dynamic γ fibres to tenuissimus spindles, Bessou and Laporte (1965) recorded non-propagated junction potentials in the central third of the spindle. This agrees well with the other evidence presented above that the dynamic fusimotor effects are caused by activation of a slow muscle fibre. Activation of static γ fibres evoked propagated action potentials in the intrafusal muscle fibres. These action potentials originated at points 2 to 3 mm. from the location of the primary ending. This is beyond the end of the nuclear chain fibres, and accordingly the propagated action potentials were generated by the nuclear bag fibres. As is well known, propagated action potentials are commonly accepted to be associated with twitch contractions and Laporte and Bessou's finding is difficult to reconcile with the direct observations of slow contractions in the bag fibres.

On account of these difficulties Laporte and collaborators (Bessou and Laporte, 1966; Appelberg, Bessou and Laporte, 1966) introduce a new interpretation of the action of the fusimotor fibres. This interpretation is partly based on Barker's (1966) histological picture of the muscle spindle. Barker accepts two kinds of γ-efferent fibres to the spindles, the one terminating as a γ plate ending, the other as a γ trail ending, but his description differs fundamentally from Boyd's (1962) in that both kinds of intrafusal muscle fibre usually receive both kinds of motor terminals, and Laporte's suggestion is that the same intrafusal fibre may produce the dynamic or static fusimotor effects according to which type of motor terminal is activated. The dynamic fusimotor fibres would cause localized and weak contractions in the central region of the intrafusal fibres. The

static fibres would cause twitch contractions activating one pole of the intrafusal fibres. By postulating appropriate and different mechanical changes in the muscle fibres under the two types of fusimotor activation, the static and dynamic fusimotor effects could be explained. It is, however, difficult to incorporate the recent observations on the behaviour of the intrafusal muscle fibres into Laporte's hypothesis.

More experimental data are needed for a final decision as to the validity of Laporte's or Matthews' hypothesis of the mechanism of the dynamic and static fusimotor effects. In particular, more detailed knowledge of the mechanical properties of the two kinds of intrafusal muscle fibre would be valuable. This should also be investigated in rabbit muscle spindles. It is possible that these intrafusal muscle fibres may turn out to be of two functionally distinct types even though their histological differences are not as obvious as those of the cat. Our understanding of the electrical activity of the intrafusal muscle fibre is also far from satisfactory. In particular, a study of possible interaction between the electrical activity evoked from dynamic and static γ fibres should yield valuable information. With such additional information there is reason to believe that the still pending controversial issues in muscle spindle physiology will be resolved.

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DISCUSSION

Pompeiano: Dr. Jansen has mentioned the results of Dr. Smith's work (Smith, R. S. [1966]. In *Nobel Symposium I. Muscular Afferents and Motor Control*, pp. 69–80, ed. Granit, R. Stockholm: Almqvist and Wiksell) on contraction of isolated muscle spindles from the rat in response to direct stimulation. Evidence was presented in this paper for twitch and slow intrafusal muscle fibres and it was stated that the slow fibres were probably nuclear bag fibres and the fast twitch fibres, nuclear chain fibres. The nature of the contraction of intrafusal muscle fibres of isolated curarized lumbrical muscle spindles from the dog has also been investigated recently by Dr. K. Diete-Spiff ([1966]. *Archs ital. Biol.*, **104**, 387–405). In this work intrafusal muscle fibres have been studied at random and no evidence

for fast contraction to direct stimulation has been obtained. Since the fibres reported in this paper were almost certainly what would be classified by histologists as nuclear bag fibres, further experiments on isolated spindles are probably required in order to ascertain the modality of contraction of the nuclear chain fibres. It would also be advisable to know whether the contraction of the so-called fast intrafusal fibres differs from that of the extrafusal muscle fibres.

As to the fusimotor control of muscle spindles, we can give additional evidence that large-diameter fusimotor fibres end in intrafusal muscle fibres which also have a γ fusimotor supply (Carli, G., Diete-Spiff, K., and Pompeiano, O. [1966]. *Experientia*, **22**, 583–584; [1967]. *Archs ital. Biol.*, **105**, in press). In this series of experiments performed in decerebrate cats we examined the effect of γ-nerve block, produced by the local application of dilute solutions of procaine hydrochloride, on the excitatory response of muscle spindle receptors of the gastrocnemius muscle resulting from repetitive stimulation of the lateral vestibular nucleus of Deiters. In six muscle-spindle receptors the afferent discharge to stimulation of Deiters' nucleus was abolished by γ-nerve paralysis. In four others, however, the spindle acceleration persisted after γ-fusimotor block and the subsequent block of extrafusal end-plates with gallamine triethiodide, administered intravenously at the height of γ-fusimotor paralysis. It is concluded that the effect from Deiters' nucleus is mediated by γ fusimotor fibres in all the cases studied, but that in some it is also mediated by fusimotor fibres larger in diameter than γ fibres. This conclusion is supported by the anatomical observations of Professor Barker showing the existence of large-diameter nerve fibres (β fibres) which branch to supply extrafusal as well as intrafusal muscle fibres.

Barker: In connexion with these interesting quantitative findings it is perhaps also relevant to mention Kidd's work on the rat tail muscles, where the fusimotor innervation appears to be largely supplied by β fibres (Kidd, G. L. [1964]. *Nature, Lond.*, **203**, 1248–1251). Also, if one looks at rabbit muscle, one gets the impression that β innervation is more prevalent, particularly in the lumbrical muscles of the foot, where on one occasion we found (Adal, M. N., and Barker, D. [1965]. *J. Anat.*, **99**, 918–919) one β fibre supplying a whole muscle with just one spindle in it.

On the controversial and crucial point of whether the intrafusal muscle fibres of a spindle that has both bag and chain fibres are in two separate efferent systems or not, it should be said that in the only other independent pronouncement so far (beyond those of Boyd and myself), E. G. Jones ([1966]. *J. Anat.*, **100**, 733–759) found in the oppossum that in over one-third of his sample, the motor endings on the bag and chain fibres were supplied by the same axon. This should be recorded as part of the histological picture.

Lowenstein: Are the corresponding neurones missing from the ventral horn in cases without γ innervation?

Barker: I don't think anyone has looked at this.

Jansen: The problem is that there are so many other small cells in the ventral horn.

Matthews: I would echo Dr. Jansen's main conclusion that we need more studies on isolated spindles. Already there is quite strong evidence for two kinds of intrafusal fibres with different contractile properties. This does seem to be the simplest explanation of how the rather different actions of the static and dynamic fusimotor fibres are mediated.

Roberts: A film* made by Professor I. A. Boyd demonstrates the difference in the structure and innervation of nuclear bag muscle fibres and nuclear chain muscle fibres in isolated spindles stained with gold chloride (Boyd, I. A. [1962]. *Phil. Trans. R. Soc. B*, **245**, 81–136). The behaviour of isolated living spindles when stimuli of graded strength were applied to the muscle nerve is illustrated.

Both types of intrafusal fibre developed local contractions beneath the motor nerve endings at the ends of the lymph space, with resultant stretch of the whole sensory region, when the appropriate fusimotor fibres in the nerve were activated; the separation of the turns of the spirals of the primary ending could be seen clearly. The bundle of nuclear chain intrafusal fibres contracted with a rapid time-course and little viscous damping. The nuclear bag intrafusal fibres contracted with a slow time-course and viscous damping was marked. The two types of intrafusal muscle fibre were usually activated by different γ nerve fibres, but sometimes both types were activated either by separate γ fibres with similar thresholds, or possibly by the same γ fibre.

Single stimuli applied to the appropriate γ fibre produced local twitching of intrafusal fibres, most obvious in the nuclear chain fibres, which had a higher fusion frequency than the nuclear bag fibres. Maintained contraction of both types of fibre, graded with the frequency of stimulation, reached a maximum at about 100 pulses/sec. (Boyd, I. A. [1966]. *J. Physiol., Lond.*, **186**, 109–110*P* and **187**, 10*P*). Therefore, although we have previously spoken of the action potential of the plate ending as being a propagated action potential, we do not know whether this is what is happening in these spindles. But certainly the mechanical change does not propagate over the whole length of the fibre. The poles contract smartly and the equatorial region becomes stretched out in both types of fibre; there is no sign of a markedly slower, smoother change such as one would have expected to be associated with "trail" responses.

Pompeiano: Dr. Roberts, have the speeds of contraction of nuclear bag and nuclear chain fibres been measured and compared with the speed of contraction of extrafusal muscle fibres of the same preparation?

Roberts: Such measurements have not been made so far, but the impression is

* "The behaviour of isolated mammalian muscle spindles on stimulation of fusimotor nerve fibres" (1966) by I. A. Boyd, Institute of Physiology, University of Glasgow; 16 mm.; "quarter-track" magnetic sound strip. The film was shown during the symposium and also at the Physiological Society Meeting, Glasgow, September 1966.

that the intrafusal fibres are all a little slower than the extrafusal ones. It would perhaps be possible to do a frame-by-frame analysis of the contraction speeds on this film, and so far as I can see that would be the only way to get speeds of contraction for the intrafusal fibres. We cannot just record their length changes directly. Professor Boyd will eventually be able to record the time-course of tension changes in the spindle, but so far we do not know even that.

Barker: Was it possible to make histological preparations of these spindles after the filmed experiment in order to see what type of motor innervation was present?

Roberts: Professor Boyd has not stained any of the spindles which were photographed in this particular film; the ageing of the preparation might rule this out technically, of course, but it would be worth trying.

Matthews: We should perhaps highlight here the magnitude of Professor Boyd's achievement, which is to stimulate the nerve fibres of the spindle and to see the contraction. R. S. Smith has already observed spindles in which the intrafusal fibres are contracting after direct electrical stimulation and has also found the difference in the time-course of contraction of the bag and chain fibres, as Dr. Jansen was telling us, and it is nice to have these two sets of experiments showing the same thing.

Roberts: Another point which is relevant to the question whether the "driving" should be a function of the chain or of the bag fibres is that although from the film it looks as though the chain fibres are moving faster, the previous idea, as developed during the discussions in the Nobel Symposium at Stockholm (see pp. 115–119 in [1966]. *Nobel Symposium I. Muscular Afferents and Motor Control*, ed. Granit, R. Stockholm: Almqvist and Wiksell), was that the bag fibres should be faster.

Matthews: But Smith showed clearly that with direct electrical stimulation small intrafusal fibres, presumed to be chain fibres, contract faster than the larger intrafusal fibres, which were presumed to be bag fibres (Smith, R. S. [1966]. *Ibid.*, pp. 69–80).

Roberts: That is not the same as saying that the chain fibre is associated with driving, because the conclusion arrived at in Stockholm (*Loc. cit.*, pp. 115–119) was that "driving" is a function of the static γ efferent. At the time of that symposium the static γ was associated with the plates, and at that stage it was supposed that the plates would give propagated action potentials which would presumably be occurring only on the bag fibres, and that the dynamic effects would be produced by the trail endings, and these were supposed to lie mainly on chain fibres.

Eldred: I don't doubt that this difference in the speeds of contraction of the two kinds of intrafusal fibre is real, but a more complete proof would be the demonstration that the lengths of the sarcomeres alter in a manner consistent with the hypothesis. What happens to the ends of these fibres will, of course, influence the appearances of the contractions. Has anyone attempted to measure the time-courses of the sarcomere changes?

Jansen: R. S. Smith recorded the changes in sarcomere length of the bag fibres of his spindles. This, unfortunately, was not possible for the chain fibres since these were covered with nerve fibres at his point of observation.

Roberts: It is of course possible that the film does not show the whole range of available γ effects. There may have been no static fibre represented, or perhaps no dynamic fibre.

Eldred: Before the dynamic and static components of the spindle discharge are firmly attributed to the intrafusal fibres, we should take into consideration what the attachments of those fibres and the capsule itself are doing. Is the capsule being deformed? We have attempted to determine this by taking measurements on serial sections of spindles in one "experimental" muscle which had been either stretched or subjected to lateral pressure or extrafusal or intrafusal contraction, and comparing these with measurements from the opposite "control" muscle (Bridgman, C., Sweeney, S., and Eldred, E. [1967]. *Am. J. Anat.*, in press). Cross-sectional areas of the two types of intrafusal fibres were taken and deductions made of what had happened to the fibre lengths, and also to the capsule. With extrafusal contraction, for example, there was found to be a shortening of the capsule, but we would like to know also what happens to the capsule after intrafusal contraction. In the cat, many of the intrafusal fibres, which are of the chain group, insert to the capsule, so that changes in the capsule should influence the discharge of endings associated with chain fibres. Such intrafusally activated, or perhaps slow, viscosity-modulated changes in capsule conformation, might be the cause of the secondary pause often seen in twitch responses of primary endings.

Wersäll: Dr. Jansen's excellent survey seems to provide the answer to my point (p. 17) about the rabbit middle ear muscles which appear to have secondary endings only. These are entirely statically responding muscles with very short fibres, innervated mainly by thin nerve fibres which could be regarded as γ fibres. We have here an excellent system of secondary afferent and efferent fibres co-operating on a static basis; there are no muscle spindles and no primary endings. This system corresponds well physiologically with the findings presented here. Maybe that is also the explanation for the fish muscle system, where there is a feedback system but one working under very specific conditions. Apparently Nature has been able to apply the findings from the muscle spindles of these very simple muscles and so avoid the complicated pattern!

Barker: But in the stapedius muscle perhaps there are two types of extrafusal innervation? Could you not describe it in terms of *en plaque* and *en grappe* endings, as in the extraocular muscles of the cat?

Wersäll: There is some variation but I would not call any of them typical *en grappe* endings, either in the stapedius or the tensor tympani.

Barker: As a matter of interest, B. Csillik ([1965]. *Functional Structure of the Post-synaptic Membrane in the Myoneural Junction.* Budapest: Akademiai Kiadó) states that the tensor tympani is another mammalian muscle with *en grappe*

innervation, but when I looked at it I became certain that the only type of motor innervation there is *en plaque*. Blevins also found plates only (Blevins, C. E. [1963]. *Am. J. Anat.*, **113**, 287–301). Primarily as a result of Hess' work, the *en grappe* innervation is now a very precise entity, and can be demonstrated as a diffuse multi-terminal type of innervation in both cholinesterase and silver preparations. We also know something about its fine structure.

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VIBRATION AND THE STRETCH REFLEX

P. B. C. MATTHEWS

University Laboratory of Physiology, Oxford

FOURTEEN years ago at an earlier Ciba Foundation symposium, Dr. P. A. Merton (1953) gave a paper entitled "Speculations on the servo-control of movement". The ideas he, Dr. Roberts, and others then discussed have been a continued stimulus to neurophysiologists working on myotatic mechanisms, but his suggestions still remain controversial. Inevitably, such discussions on the part played by reflexes in the control of movement have usually been largely qualitative, but it is unlikely that the precise role of proprioceptive reflexes will be resolved until they can be studied quantitatively. I am going to discuss one small facet of the problem of the possible servo-control of muscles, namely the need to know the "gain" of the servo-loop in order to assess its efficacy. As will emerge, I do not know how this figure can be measured with any certainty.

The servo hypothesis is largely described by Fig. 1, which is copied unchanged from Merton's paper. Some movements, "urgent movements" in the figure, are supposed to be produced by impulses from the higher centres impinging directly on to the large α motoneurones, thus causing the muscle to contract. Other movements, "ordinary movements" in the figure, were suggested to be produced rather indirectly by impulses from the higher centres exciting the fusimotor or γ motoneurones. These cause contraction of the specialized intrafusal muscle fibres inside the muscle spindle, thereby exciting its primary or annulo-spiral afferent ending. The resulting afferent discharge then monosynaptically excites the large α motoneurones of the muscle, and so it contracts. The suggested advantage of this indirect route for producing muscle contraction is that it employs the stretch reflex, which is looked upon as a powerful servo automatically holding the muscle at the particular length "demanded" by the fusimotor discharge, in spite of any disturbances produced by variations in the load or in the strength of the muscle. Contractions mediated by the more direct α route would not have this property, unless they were continuously modified by some form of afferent feedback. Merton supported his speculations

with definite experimental evidence, and in the years since a certain amount more has been obtained (cf. Angel, Eppler and Iannone, 1966; Eldred, Granit and Merton, 1953; Hammond, Merton and Sutton, 1956).

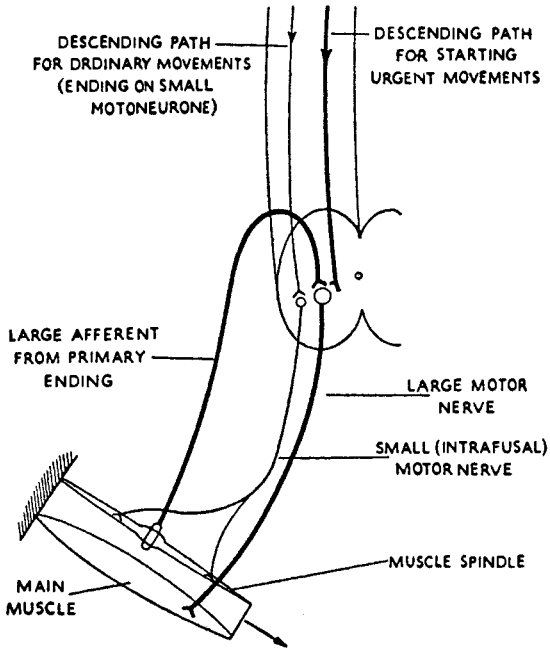

FIG. 1. Merton's (1953) diagram of the two possible motor pathways to skeletal muscle. (Reproduced by permission of the author.)

The recent findings on the structural and functional complexity of the muscle spindle make it unlikely that things can be as simple as Merton originally suggested (cf. Brown and Matthews, 1966; Matthews, 1964), but in no way invalidate his main idea. However, basic to the whole concept is the implicit assumption that the gain of the servo-loop is high. In other words, a small extension applied to the tendon must reflexly call forth a large restoring muscle contraction by means of the stretch reflex. If the gain of the loop were not high, the indirect method of producing contraction would lose many of its advantages, for the length of the muscle would still be rather dependent upon any load on it.

The stretch reflex is particularly well demonstrated in the decerebrate cat, and the qualitative observation familiar to most physiologists is that an experimenter needs to exert a considerable manual force to flex its limbs against the resistance set up by the stretch reflex of the opposing extensor

muscles. However, when the stretch reflex is measured myographically it is less impressive. Granit (1958) and I (Matthews, 1959) both made measurements on the tonic stretch reflex of the soleus muscle of the decerebrate cat; this is of course a red muscle, which Denny-Brown (1929) showed to have a well-developed stretch reflex, rather better than that of its white synergist gastrocnemius. Fig. 2 shows a fairly typical stretch reflex,

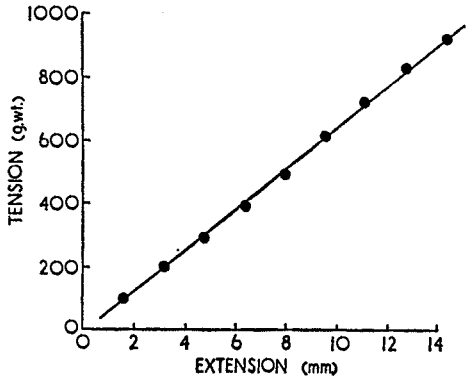

FIG. 2. The linearity of the stretch reflex. The relation between the extension applied to the soleus muscle of a decerebrate cat and the resulting "active" tension produced by its stretch reflex. The results were obtained during the course of a single stretch (14 mm. at 1·6 mm./sec.; redrawn from Fig. 3 of Matthews, 1959.)

elicited by slow progressive stretching at 1·6 mm./sec. The abscissa shows the extension applied at a series of times. The ordinate shows the resulting reflex tension, over and above that obtained when the nerve to the muscle was cut. Similar results were obtained by suddenly stretching the muscle to a new length and then holding the length constant. The reflex response is seen to be rather linearly related to the extension, and in this particular case the slope was 75 g. wt./mm. extension. In different preparations, some decerebrated by the classical intercollicular brain section and some by anaemia, the reflex stiffness varied from 40 to 200 g. wt./mm. Granit's (1958) values were on average slightly lower (20–100 g. wt./mm.). These reflex stiffnesses are not at all great in relation to the power of the muscle, for when stimulated tetanically soleus will produce up to about 2·5 kg. wt. tension. The maximum change of length of soleus in the body is about 2·5 cm., so even with the stiffest reflex seen (200 g. wt./mm.) the muscle would have to be displaced through about half its available range to develop its maximum tension. Thus in the decerebrate cat the stretch reflex of soleus does not seem to be particularly well-adapted to maintain the length

of the muscle constant in the face of a varying load, or of muscle fatigue. (Assuming that one may extrapolate from these results in which the muscle was connected to an isometric myograph and its length forcibly varied; Dr. Roberts, I suspect, will have something to say on this.)

The reflex stiffness of the gastrocnemius and soleus muscles combined together is only slightly above that of soleus. Smith, Budris and Paul (1962) found a mean value of 74 g. wt./mm. (range 22 to 170) for the maintained tonic stretch reflex of these muscles in response to extension applied at 22 mm./sec. The mean stiffness of the peak of the phasic stretch reflex developed in response to this velocity of stretching was 171 g. wt./mm. (range 95 to 257), and there was no further increase in stiffness on increasing the velocity of stretching. Roberts (1963) and Jansen and Rack (1966) studied the stretch reflex of soleus in response to sinusoidally varying extensions of a peak to peak amplitude of 0·7 mm. upwards, and inspection of their records suggests that the reflex stiffness in response to this form of phasic input is little greater than that for the tonic stretch reflex. Partridge and Glaser (1960) obtained similar results on the gastrocnemius combined with the soleus. Pompeiano (1960), studying the long head of the triceps of the forelimb, usually found stiffnesses of below 100 g. wt./mm. to stretches of up to 14 mm. In one experiment, in response to stretch at about 15 mm./sec., the triceps muscle developed a phasic reflex of 415 g. wt./mm., but as it can develop up to 7 kg. wt. on tetanic stimulation, this is still not a very high figure. Thus it must be concluded that in relation to the available strength of a muscle the stretch reflex does not appear to be particularly stiff, and thus not particularly well adapted to act alone in controlling the length of a muscle by servo action.

However, the stiffness of the stretch reflex, as measured in the decerebrate cat, cannot be simply equated with the gain of the postulated servo operating from the primary endings of the muscle spindle. For, as well as the primary endings, the stretch must excite the secondary afferent endings of the muscle spindle (flower-spray) and the Golgi tendon organs. The afferent discharge of both of these would be expected to inhibit the α motoneurones of extensor muscles, and thus the measured stiffness of the stretch reflex would be expected to be below that which would be obtained by activation of primary endings alone. These other endings would be expected to be excited in the normal animal as well as in the decerebrate, so the additional gain could only be of use if these inhibitory reflexes could be blocked, as by an inhibition of the interneurones through which they relay. But these endings must be supposed to be present for some good reason, and it should not lightly be assumed that their discharges are ever normally ineffective;

it is more likely that we have not yet grasped their full role. Before this line of argument is pursued, another complication must be faced, namely that the force developed by a contracting muscle, activated to a constant extent, depends upon the length of the muscle—the classical length–tension relation. Granit (1958) and I (Matthews, 1959) found that for soleus the tetanic tension produced by low-frequency stimulation of its nerve increased markedly as the length of the muscle was increased over the same range of lengths at which a stretch reflex had earlier been observed in the same preparation. Thus it must be supposed that only a part of the increase in tension produced on stretching a muscle with a stretch reflex is truly reflex, resulting from the recruitment of fresh motor units and the acceleration of the discharge of those already firing; part of the increase in tension must be due to the increasing contractile strength of those motor units which are already active, giving what may be called a "pseudo reflex" (Granit, 1962). The relative contributions of the true and of the pseudo reflexes to the increase in tension seen in any particular stretch reflex seem almost impossible to assess, and from the point of view of determining the stiffness of the servo may not matter very much. It is puzzling, though, that two independent factors (the true and the pseudo reflexes) interact in such a way as to produce the common linear relation between the active tension and the applied extension. One possibility, suggested earlier (Matthews, 1959), is that the stretch reflex observed in the decerebrate cat represents the balance between an excitatory reflex from the spindle primaries and an inhibitory reflex from the Golgi tendon organs. If so, the tension developed in the stretch reflex would no longer be dominated by variations in the contractile strength of the muscle with its extension, as the efferent discharge would be appropriately adjusted by the inhibitory feedback. Jansen and Rudjord (1964) have recently shown that the Golgi tendon organs have such a low threshold to active contraction of the soleus that they are certainly powerfully excited in quite moderate-sized stretch reflexes.

Some experiments of Pompeiano's (1960) definitely suggest that the stretch reflex contains a concealed inhibitory component. Fig. 3 is redrawn from some of his results on the stretch reflex of the long head of the triceps muscle of the forelimb of the decerebrate cat. The open circles show an apparently typical stretch reflex with a stiffness of 70 g. wt./mm. obtained in a decerebrate cat with post-brachial section of the spinal cord (this enhances the stretch reflex). The closed circles show the increase in active tension produced in the same muscle by the same extension later in the experiment after various further surgical manipulations of the preparation. The two sets of points are the same for all practical purposes. The paradox is that this

second set of points shows not a true stretch reflex but an entirely pseudo stretch reflex, for the ipsilateral dorsal roots of the appropriate segments of the spinal cord had been cut. Thus the increase in tension under both conditions must have been due to the strength of the muscle being increased by the stretching, thereby increasing its response to a pre-existing steady motor discharge. Thus stretching the muscle while the dorsal roots were

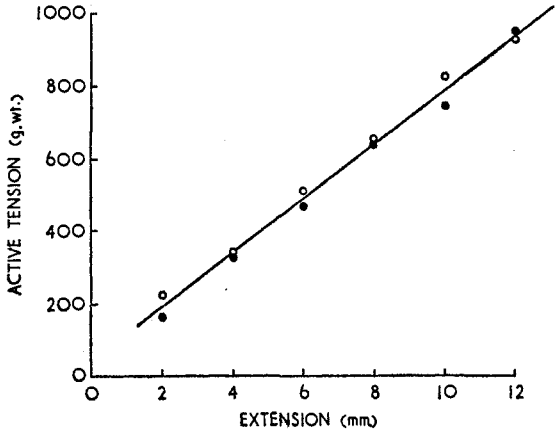

FIG. 3. Pompeiano's paradox. The relation between the extension applied to the triceps muscle of the forelimb of the decerebrate cat and the resulting "active" tension. O, precollicular decerebrate with a post-brachial section of the spinal cord. ●, same preparation, stretched over same range, after de-afferenting both forelimbs (including the triceps) by section of the appropriate dorsal roots, and after complete cerebellectomy. (Redrawn from part of the data presented in Fig. 9 by Pompeiano, 1960.)

intact seems to have produced no reflex response at all. The simplest explanation of this paradox is that stretching the muscle excited an afferent discharge in several kinds of receptor, some with autogenetic excitatory effects and some with autogenetic inhibitory effects, and that these effects just balanced out. There was no doubt that the dorsal roots were initially active, for on their section the amount of contraction of the muscle decreased greatly and was only restored to the original high level by the two facilitatory procedures of cutting the dorsal roots to the contralateral forelimb and ablating the cerebellum. At the very least, Pompeiano's paradox, as it may be called, is a warning to us not to underrate the complexity of the reflex mechanisms controlling skeletal muscle.

Another way of studying the "gain" of the reflex response to excitation of the primary endings, is to excite them by means of vibration applied to the tendon of the muscle. Granit and Henatsch (1956) showed that

primary endings could be driven by appropriately large amplitudes of vibration to discharge one impulse for each cycle of the vibration. Thus vibration applied to a muscle tendon would be expected to excite a stretch reflex in the decerebrate cat, and it has recently been shown that it does indeed do so (Matthews, 1966*a*, *b*). An example is shown in Fig. 4. Vibration at 200/sec. of 10 μm. peak to peak amplitude applied longitudinally to the tendon of soleus excited a reflex contraction of about 100 g. wt.

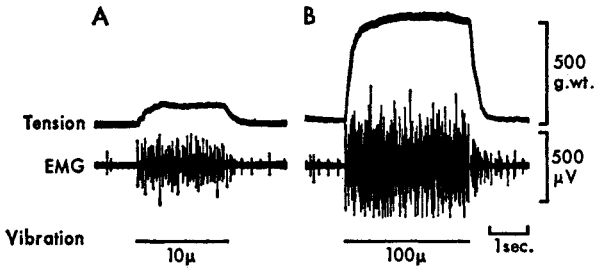

FIG. 4. The reflex response to vibration. Vibration at 200 cyc./sec., of peak to peak amplitude shown below the records, was applied longitudinally to the tendon of the soleus muscle of the decerebrate cat. (From Matthews, 1966*a*.)

accompanied by considerable electrical activity of the muscle. 100 μm. amplitude vibration caused a contraction of 500 g. wt. accompanied by a massive electrical discharge. Various controls showed that this was a genuine reflex response of the muscle to the vibration applied to it and the reflex had the properties of the classical stretch reflex, albeit excited by a rather unusual form of stretching. On increasing the amplitude of the vibration at any particular frequency the reflex response came to an approximate plateau for amplitudes of vibration of 100–200 μm. This plateau is most likely due to the vibration driving the majority of the primary endings to discharge one spike for each cycle of vibration. Increasing the frequency of vibration would then be expected to increase the plateau value of the reflex, and the relation between the plateau tension and the frequency of vibration should give a measure of the "gain" of the reflex loop from the primary endings to muscle contraction. Fig. 5 shows an example of the relation between plateau tension and frequency. The reflex does increase progressively with the frequency of vibration, and the relation is approximately linear with a slope of 1·6 g. wt. tension per cyc./sec. increase in vibration frequency. The range in seven experiments was from 0·8 to 3·1 g. wt. per cyc./sec. It is interesting to compare these figures with the stiffness of the stretch reflex, on the assumption that the vibration reflex is due to excitation of the primary endings. In the decerebrate cat a stretch of

1 mm. may increase the discharge of a primary ending by up to about 10 impulses/sec. (Eldred, Granit and Merton, 1953; Granit, 1958; Jansen and Matthews, 1961). The vibration figures suggest that this would lead to up to 30 g. wt. of reflex tension, a figure which is about the same as that for a

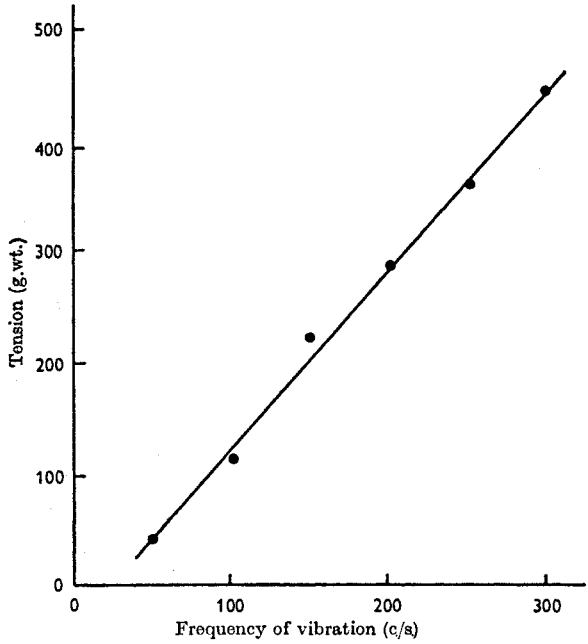

FIG. 5. The relation between the size of the reflex contraction and the frequency of vibration, for vibrations of 150 μm. amplitude. (From Matthews, 1966*b*.)

small stretch reflex, though often the stretch reflex may be rather larger. It would obviously be of interest to make the two measurements on a single preparation. However, the vibration experiments offer no suggestion that the gain of the stretch reflex from the primary endings has been greatly underestimated by measuring the stiffness of the classical stretch reflex. Of course, any reflex inhibition from the Golgi tendon organs excited by the contraction will influence the response to vibration as well as the response to stretch, so the vibration experiments throw no light on any modulating role of the Golgi tendon organs in reducing the gain.

The vibration experiments rest on the assumption that vibration of the particular amplitude used is a reasonably specific stimulus for the primary endings. This is now being investigated by Dr. M. C. Brown, Dr. I. Engberg and myself by recording the responses to measured vibration of primary endings, secondary endings and Golgi tendon organs. We have

confirmed the remarkable sensitivity of primary endings that has already been shown by others (Granit and Henatsch, 1956; Bianconi and van der Meulen, 1963). An example is shown in Fig. 6, where the ending followed vibration at 300 cyc./sec. when the peak to peak amplitude was only 17 μm. Fusimotor stimulation has been found to increase the sensitivity of the primary ending yet further, again confirming earlier work (Granit and

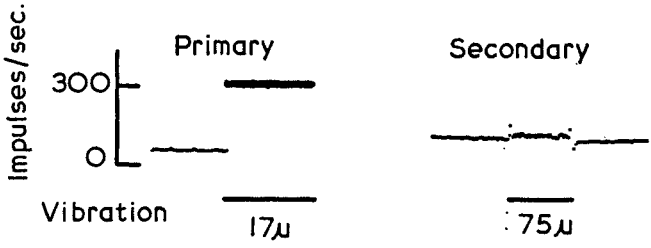

FIG. 6. The different effects of vibration on a primary ending and on a secondary ending (the conduction velocities of their afferent fibres were 96 and 39 m./sec. respectively).

The records give a direct display of the frequency of discharge of the endings, as shown by the scale on the left. The muscle was stretched by 5 mm. just before the beginning of each record to make it taut, and a period of vibration of approximately 1 sec. duration was then applied; the vibration was at 300 cyc./sec., and its peak to peak amplitude is given below the records. (The spindles lay in the soleus muscle of the same anaesthetized cat in which the ventral roots supplying the soleus had been cut. Records obtained in collaboration with M. C. Brown and I. Engberg. Technique generally similar to that of Crowe and Matthews, 1964.)

Henatsch, 1956; Crowe and Matthews, 1964). In contrast, as further illustrated in Fig. 6, the secondary ending of the muscle spindle is proving to be rather insensitive to vibration applied to the tendon, as expected from the work of Bianconi and van der Meulen (1963). During passive stretch none have been driven by amplitudes of vibration below 100 μm. for frequencies above 100/sec., and most have not had their mean frequency of discharge appreciably altered by vibrations of such amplitude, though vibration of larger amplitude sometimes does so. Fusimotor stimulation produced no increase in the sensitivity to vibration in all but one out of nine secondary endings, and this one was then only moderately sensitive in comparison with the primary endings. (For example, it then required an amplitude of vibration of 75 μm. to drive it at 200/sec.) The Golgi tendon organs are about as insensitive as the secondary endings when the muscle is stretched passively and then vibrated. However, when the muscle is made to contract by stimulating ventral root filaments, the Golgis become more easily influenced by vibration. Vibration of 100–200 μm. amplitude at frequencies up to about 50/sec. above the frequency at which

a Golgi tendon organ is firing in response to the contraction will then often cause driving; though lower amplitudes of vibration at these frequencies, or higher frequencies at moderate amplitude, have very little excitatory effect. These preliminary results show that the primary ending is the only muscle receptor with a low-enough threshold to be responsible for the reflex contraction in response to vibration. Unfortunately, when the amplitude of vibration is increased to 100–200 μm. to give a plateau of reflex contraction, a few secondary endings and some Golgi tendon organs will also be excited by the vibration; the amount of excitation of the tendon organs by vibration will probably depend upon the amount of the reflex contraction. Therefore, as with stretching, the response to vibration cannot be taken simply as the response of the postulated length servo from the primary endings. Thus neither stretching nor vibration can be used to give an unequivocal figure for the gain of the servo, though on the present findings it would be rather surprising if the gain should prove to be high in relation to the strength of the muscle. It should be pointed out finally that I have largely been concerned with the measurement of the d.c. or steady-state gain of the system. The a.c. or transient gain of the system under phasic conditions may well be higher, but its measurement presents yet further problems. The main conclusion is that the hypothesis of the follow-up length servo and the fusimotor pathway as a normal, self-sufficient route for producing muscle contraction cannot be considered to be established by the mere existence of the negative feedback pathway provided by the primary endings of the muscle spindles and the monosynaptic reflex. This very real pathway has yet to be shown quantitatively to have the right properties to fulfil such a particular role.

In parenthesis, it may be added that the failure of vibration applied to human muscles to produce rapid movements is also against the hypothesis of a simple servo-control of movement by means of the monosynaptic pathway. The movements produced by vibration in man are notably slow (Hagbarth and Eklund, 1965; De Gail, Lance and Neilson, 1966; Rushworth and Young, 1966), though as yet only a limited range of conditions of vibratory stimulation has been investigated.

SUMMARY

The hypothesis of the servo-control of voluntary muscles by the fusimotor fibres and the primary endings of the muscle spindles is based on the implicit assumption that the "gain" of the feedback loop is high. There are, however, no satisfactory measurements of this gain available and it is not clear how such measurements could be obtained. The interpretation of the

tension–length relationship of the stretch reflex is complicated by the tension–length properties of muscle contracting under a constant motor drive; and other receptors beside the primary ending of the spindle would be expected to be excited by stretching. Recently, vibration has been shown to elicit a stretch reflex in the decerebrate cat and a study made of the variation in the size of the reflex with alteration in the frequency of the vibration, in the hope of avoiding some of these difficulties. It is concluded that the "gain" of the feedback loop from the primary endings has yet to be shown to be great enough for the system to be well adapted to act alone in controlling the length of a muscle by servo action.

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DISCUSSION

Roberts: In the experiments in which you stimulated the soleus muscle by applying vibration to the tendon, what was happening to the behaviour of the individual motor units? In the experiments I have done (Roberts, T. D. M. [1958]. *J. Physiol., Lond.*, **144**, 2–4*P*), leaving as much as possible of the innervation intact

and recording from single motor units, in the majority of cases the motor unit does not increase its firing frequency during increase of tension, and this would fit in very neatly with the behaviour described as the "pseudo stretch reflex", which is purely a tension–length effect. When you put in increased primary-ending firing by vibration, what is happening to the motor units, and why does the Renshaw feedback not suppress the firing, as it does in the intact animal?

Matthews: We know that an increase in the amplitude of vibration gives an overall increase in motor-unit activity. We should now follow your example and study the individual motor unit to see whether its frequency of firing alters as we change the amplitude and frequency of vibration; we have not done this yet. As far as the Renshaw system goes, like any inhibitory feedback system it need not turn the response "on" or "off" but may graduate its amount. The Renshaw system is presumably operative in these vibration reflexes and is causing there to be less reflex than otherwise.

Roberts: I am perhaps over-influenced by my hypothesis that the saturation seen in the firing frequency of the motor units is due to Renshaw feedback, which one would expect to cause saturation. And if it produces saturation in my conditions, why does it not do so in yours? Perhaps your Renshaw cells are less active as a result of denervation.

Matthews: There is widespread denervation, so the soleus is the only active muscle, but then in your case the stretched muscle should be the only one having an appreciable amount of extra contraction, and therefore the only one providing much Renshaw feedback.

Roberts: If the innervation is intact and one muscle is pulled, increased responses in muscles not being pulled can be demonstrated (Roberts, T. D. M. [1952]. *J. Physiol., Lond.*, **117**, 5*P*), so there is a good deal of interaction between muscles. However, the majority of the feedback would be expected to be from the stretched muscle, as you suggest.

Eldred: Did you pull at frequencies below 50 cyc./sec.? At shivering frequencies, apparently the ratio of afferent discharge from primary and secondary endings is altered to favour the secondary afferent discharge (Stuart, D., Ott, K., Ishikawa, K., and Eldred, E. [1965]. *Expl Neurol.*, **13**, 82–95).

Matthews: At lower frequencies the reflex response to vibration falls off badly and the interpretation becomes much harder, because at these frequencies each cycle of vibration should give more than one spindle spike. At 30 cyc./sec. one might be exciting 3, 4 or 5 impulses in each cycle of vibration, and therefore one would be putting in quite a high frequency. But the increase in the secondary discharge at low frequencies is only relative, I think. At all frequencies of vibration there is always more primary than secondary discharge.

Eldred: What happens to the amplitude of the H wave?

Matthews: I have done no experiments on this myself. E. C. Alvord and M. G. F. Fuortes ([1953]. *J. Physiol., Lond.*, **122**, 302–321) stimulated the nerve to the medial gastrocnemius repetitively while recording from the nerve to the

lateral head of gastrocnemius. They used weak stimuli so they were probably putting in repetitive Ia afferent activity, as does vibration. They found that the reflex response often bore little phase relationship to the stimulus.

Monnier: Have you tried to stimulate Pacinian corpuscles by vibration?

Matthews: I have seen that done in John Gray's laboratory. They are even more sensitive than the muscle spindles, so that any Pacinian corpuscles in soleus would have been excited in these experiments, but there are rather few corpuscles in soleus, as Professor Barker told us.

Eldred: How do you avoid those on the interosseus membrane?

Matthews: They are denervated. Most serious are those up in the pelvis, which are not denervated.

Lowenstein: On the other hand, the picture described by Dr. Matthews is exactly that obtained from the insect stretch receptor when exposed to vibration (Lowenstein, O., and Finlayson, L. H. [1960]. *Comp. Biochem. Physiol.*, **1**, 56–61). At low frequencies a number of impulses are obtained per cycle of stimulation, the number of impulses being in proportion to the degree of extension. With the upper limits of following there is one response per cycle. So we have exactly the same picture from the insect stretch receptor, where we have a modified muscle fibre innervated by a peripheral sensory neurone. Under those conditions, Dr.

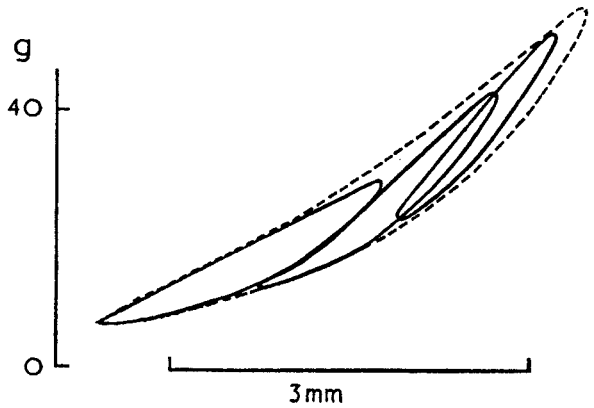

FIG. 1. (Roberts). Tension–length curves for the reflexly active soleus muscle of a decerebrate cat.

The tendon has been dissected free and is subjected to rhythmically fluctuating tensions. The working point follows a different curve according to whether the muscle is lengthening or shortening. Curves for smaller ranges of tension-change fit snugly within the guide-curves formed by the upper and lower limbs of the curve for a larger range (broken line). The loops are traced in a clockwise direction. (From Roberts, T. D. M. [1963]. *Q. Jl exp. Physiol.*, **48**, 328–345.)

Matthews, how does the sensory ending discriminate between a very powerful stretch producing 100 cycles of response in one cycle, and a 100 cycles' stimulus with one response per cycle?

Matthews: I don't think it can distinguish these two situations.

Roberts: A factor that you did not bring out with regard to the stiffness of the stretch reflex is one of the consequences of the peculiar mechanical properties of muscle. What I am referring to must apply also to intrafusal muscles and may therefore run right through the stretch reflex. The point is that the tension–length curve for stretching is not the same as the tension–length curve for relaxing (Fig. 1). If a movement starts in the direction of stretching, the working point

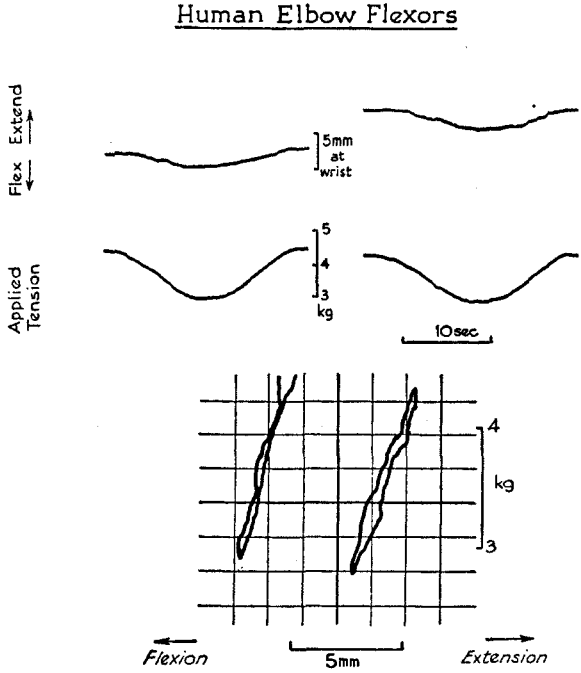

FIG. 2 (Roberts). *Above:* Records of the displacement of the wrist (upper traces) when the human elbow flexors work against a fluctuating tension (lower traces).

Below: Plots of tension against length. The right-hand traces were obtained first; the wrist was raised about 5 mm., and then the left-hand traces were recorded. (From Roberts, T. D. M. [1966]. In *Control and Innervation of Skeletal Muscle*, pp. 160–170, ed. Andrew, B. L. Dundee: Thomson and Co.)

moves up on to the stretching curve, but if its starts in a direction that allows the muscle to relax, the working point moves down on to the relaxing curve. This gives a very steep intermediate portion on the curve for a displacement from a rest position, and this may account for the apparent stiffness of the reflex. I have measured the stiffness with which my own biceps muscle adjusts to changing the weight of an object held in the hand, and I find that it must be several tens of kilogrammes per millimetre.

Matthews: Other estimates of stiffness in the human reflex have been lower than this. Did you allow for friction of joints?

Roberts: My experiment on the elbow flexors is illustrated by Fig. 2. I stabilize my upper arm in the vertical position by rigid supports, one at the shoulder and the other at the extreme tip of the elbow, and I hold my forearm out approximately horizontally. Hanging from my wrist is a bottle connected by flexible tubing to a reservoir of water. A crane alternately raises and lowers the reservoir and the bottle attached to my wrist is consequently filled and emptied, thus altering the gravitational force tending to extend the elbow. I measure this force and also the small vertical excursions of the wrist. In the figure, the upper

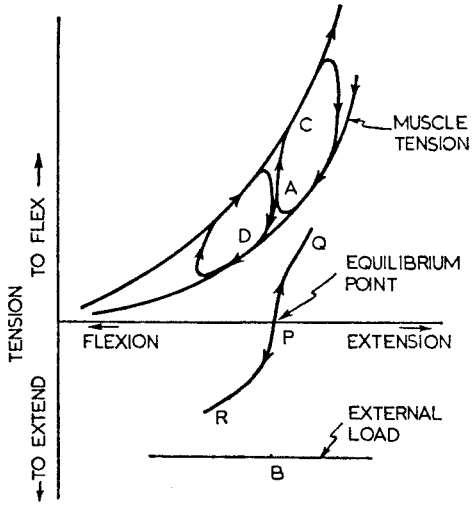

FIG. 3 (Roberts). Scheme to account for the stiffness with which the muscles of the elbow resist disturbances of joint-angle.

records show the time-courses of the tension-changes and of the resulting displacements. The lower records are the direct plots of tension-change against length-change. The displacement between the two tension–length diagrams is about 5 mm. at the wrist so that, with a multiplication factor of 15 or 20 for the effect of leverage, the slopes of these diagrams indicate a very large value for the stiffness at the tendon.

Matthews: What is the subject doing at these times? What feedback is available to him? These are relatively slow sinusoids; I wonder if you can be certain that all the stiffness is coming from muscle proprioceptors. Could there be any visual feedback?

Roberts: The subject is watching the pen of the recording device, but it would not be possible to produce the curve by moving the pen by voluntary control of the position of the wrist, because as soon as one tried to do anything with the

wrist, the pen would go off the paper. Voluntary movements which you could control by eye would be well off the scale. I think this effect is due to the cross-overs—to hysteresis in the muscle properties.

Matthews: In that case would you not expect it to be more of a step-function?

Roberts: Not necessarily. Fig. 3 shows a scheme by which one might explain the effect. The force developed by the elbow flexors is indicated in the upward direction, using the guide-curves for the soleus of the cat from Fig. 1, with joint-angle as abscissa.

We are to suppose that the arm is at rest with the flexors exerting a force at A which is in equilibrium with an externally applied constant load shown at B. These forces are equal and opposite, so that the working point for the resultant effect on the joint will be at P. Now suppose that some external agency tries to extend the joint. The force developed by the muscle will increase along the curve AC. If the external agency tries to flex the joint, the muscle-force will fall off along the curve AD. The locus of the resultant for small perturbations about the equilibrium position can then be represented by the curve QPR. It will be seen that this has an extremely steep portion in the neighbourhood of the rest position, showing that the system is very stiff in its resistance to perturbation.

For the biceps, I am sure these curves would have to be much flatter, because we have Wilkie's evidence that when the elbow is at a right-angle we are at the flat top of the tension–length diagram for the flexors (Wilkie, D. R. [1950]. *J. Physiol., Lond.*, **110**, 249–280). However, the loops are a constant finding in my experiments, and it is the cross-over from one loop to another that we are interested in here.

Myotatic, Kinesthetic and Vestibular Mechanisms
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SPINAL CORD AND BRAIN STEM PATHWAYS FOR AFFERENTS FROM JOINTS

ERNEST GARDNER

School of Medicine, Wayne State University, Detroit

THE importance of the nerve supply of joints lies in: (1) the subjective effects (pain) and reflex changes that may accompany joint disease, and (2) the role of articular nerves in posture, locomotion, and the appreciation of position and movement. The distribution of nerves to joints was the subject of a monograph more than a century ago (Rüdinger, 1857). Most of the studies since then have been limited to anatomical investigations or have dealt with pain from joints.

It is only in the last two decades that major interest in other functional properties of articular nerves has developed. We now know that, aside from the contributions of the vestibular and visual systems, the perception of position and movement is dependent chiefly and probably entirely upon sensory endings in joints and associated ligaments and their central nervous system pathways and connexions.

The role of joint receptors in the appreciation of position and movement was recognized by Goldscheider (1889, 1898), although his use of the term "*Muskelsinnes*" was confusing. Stopford (1921), in a study of lesions of the nerves to the hand, concluded that accurate localization of a finger in space depends on the stimulation of endings in joints. Browne, Lee and Ring (1954) and Provins (1958) came to similar conclusions on the basis of experiments in which joint capsules in human subjects were anaesthetized.

Sarnoff and Arrowood (1947) showed that as spinal anaesthesia was induced, position sense persisted after stretch reflexes had disappeared. They concluded that pathways subserving stretch reflexes were not involved in position sense. In a review of the nerve supply of joints (1950*b*), I suggested that joint afferents might play a key role. In 1950 also, Mountcastle, Covian and Harrison reported that potentials could be evoked in the cerebral cortex by stimulation of periosteum and joint capsule, but not by muscle stretch. Furthermore, Lloyd and McIntyre (1950) demonstrated

that Group I afferents from hindlimb muscles ascended but a relatively short distance in the dorsal funiculi and then ended in grey matter. Cohen (1958) reported that afferent impulses from joints formed the chief contribution to position sense in the human shoulder. Finally, Mountcastle and Powell (1959) and Rose and Mountcastle (1959) presented cogent arguments for assigning to receptors in joint capsules and pericapsular tissues a major role in the appreciation of position and movement.

Some muscle afferents do project to the cerebral cortex. These include hindlimb afferents, but not by way of dorsal funiculi (Gardner and Morin, 1953, 1957), and Group I afferents from the forelimb (Amassian and Berlin, 1958; Landgren and Wolsk, 1966). However, these projections play little if any role in the appreciation of movement and position. For example, the rate of firing of a neuromuscular spindle gives no clue to the length of the muscle and therefore of the position of the joint. Furthermore, the spindle may be quiet while the muscle is contracting. Likewise, changes in muscle tension may alter the rate of firing of neurotendinous endings, but changes in tension may occur at any position of a joint.

That modality which subjectively is a sense or recognition of space has a component from both skin and deep tissues. Furthermore, the normal appreciation and recognition of an object held in the hand depends upon the stimulation of endings in the skin and in deep tissues (now known to be joints). Renfrew and Melville (1960) point out that this ability to identify objects held in the hand is generally explained as a synthesis of touch and kinesthesia. They, however, distinguish between touch and the dermal component of the sense of space; the dermal component and joint sense are combined to form the somatic sense of space, which they term choraesthesia (the term kinesthesia is commonly used to refer to the perception of changes in joint angles).

The present review deals chiefly with the spinal cord and brain stem pathways for the deep (articular) component of the sense of space. These pathways must, however, be considered in the context of their peripheral connexions and receptors and their projection to the cerebellum and to the thalamus and cerebral cortex.

NERVE ENDINGS IN JOINTS

The origin, distribution and termination of articular nerves have been determined chiefly by gross dissection, by microscopic study of serial sections of foetal joints, and by microscopic study of nerve endings (for studies and pertinent references, see Gardner, 1942, 1948*b*, *c*, *d*, *e*, 1950*b*, 1956). The joints studied have been mostly those of the limbs, although

the basic pattern of nerve supply seems to hold for the joints of the vertebral column (Pedersen, Blunck and Gardner, 1956; Stilwell, 1956; Lewin, Moffett and Viidik, 1962). The general features of origin and distribution are not pertinent to the present review.

Articular nerves resemble cutaneous nerves in their fibre spectrum. Some of the myelinated fibres are as large as 16 or 17 μm. in diameter, but most are smaller and fall into what in muscle nerves would be classified as Group II and III fibres. The fibres in articular nerves form the following types of endings (excluding vasomotor endings).

Free endings

These are formed by nonmyelinated and small myelinated fibres and occur in ligaments, in the joint capsule (especially near its junction with the periosteum), in the adventitia of blood vessels, and to some extent in synovial membrane. It is likely that a significant number of the sensory free endings are pain endings, that is, are sensitive to tissue injury. Many, however, may be mechanoreceptors (see proprioceptive triad, p. 59).

Complex, non-encapsulated endings

The most numerous complex endings in joints are the spray endings (Ruffini type), which were first described in detail for joints and associated structures by Sfameni (1902). They may be several hundred micrometres long, and they arise from the larger myelinated fibres (especially the 7–10 μm. group). They are found chiefly in the joint capsule, predominantly in regions that are compressed or deformed during movement (Gardner, 1944; Boyd, 1954; Gardner, 1956; Stilwell, 1957*a*, *b*). In forming these endings, axons lose their myelin and divide into filaments which undergo repeated expansions and anastomoses in a small area. Connective tissue elements and capillaries are prominent around such endings, but layers characteristic of Pacinian or paciniform corpuscles are not found. Variations according to species and activity have been described (Sklenská, 1965).

Golgi tendon organs, which also occur in ligaments such as the collateral ligaments of the knee joint, are similar to or identical in structure with the spray endings, although their parent fibres tend to be somewhat larger (Andrew, 1954*a*; Gardner, 1956; Skoglund, 1956).

A few small myelinated fibres form coiled endings in the adventitia of articular blood vessels. They resemble simple spray endings and are presumably vasosensory, but their precise functions are unknown.

Complex, encapsulated endings

The classical type of large lamellated ending, the Pacinian corpuscle, is rarely found within a joint (Gardner, 1944, 1953; Samuel, 1952; Boyd, 1954). It is, however, often seen in peri-articular tissues, in some instances directly adjacent to the joint capsule, and is present before birth (Gardner and Gray, 1950, 1953; Gray and Gardner, 1950, 1951; O'Rahilly and Gardner, 1956).

Simpler, smaller types of encapsulated endings, termed paciniform corpuscles, do occur in joints (Gardner, 1956; Skoglund, 1956; Stilwell, 1957*a*, *b*), although they have often been overlooked, for example, by Gardner (1944). They arise from the larger myelinated fibres, and are present in small numbers in ligaments and joint capsule. In some joints, such as those of the laryngeal cartilages, they may be the predominant ending. Variations in the size and degree of lamellation of the encapsulated endings have been correlated with the size and location of the joint and with the species (Hromada and Poláček, 1958; Poláček, 1961, 1966). Some of the variations are named, for example, the Golgi-Mazzoni corpuscle, which tends to be spherical and whose terminal axon is branched.

It has been noted that in many deep tissues, spray endings, lamellated endings and free endings tend to occur together in what has been termed a proprioceptive triad (Stilwell, 1957*a*, *b*, *c*, *d*). The association had been noted before, for example, by Policard (1936), who describes previous work in this area. It has been suggested that the free endings of the triad may be mechanoreceptors.

FUNCTIONS OF JOINT NERVES

Response to injury

Studies of human joints opened under local anaesthesia indicate that the fibrous capsule is highly sensitive to painful stimuli, whereas the synovial membrane is relatively insensitive (Kellgren and Samuel, 1950). The most effective painful stimulus to a joint is twisting or stretching. Joint pain, which presumably develops from the stimulation of free endings, is usually diffuse and poorly localized. It may be referred and it may be accompanied by marked reflex effects on the vasomotor system and skeletal muscles (Gardner and Jacobs, 1948; Gardner, 1950*a*).

Control of blood flow

Although the blood vessels in joints, including the arteriovenous anastomoses, are supplied by postganglionic sympathetic fibres, little is known of the nervous control of blood flow through joints.

Response to position and movement

While recording from the posterior knee joint nerve of the cat (Gardner, 1948*a*), I found that spontaneous spikes were present whose discharge frequency increased with light pressure on the back of the capsule. It seemed likely that these spikes arose from receptors in the capsule and it was determined that they adapted slowly. It is now known that similar recordings made during joint movement include spikes arising from receptors in ligaments as well as the joint capsule. The spray endings in the capsule and the Golgi type of endings of ligaments are very sensitive to the stretch induced by movement or tension or by an increase in intra-articular pressure (Andrew and Dodt, 1953; Andrew, 1954*a*), although the Golgi type of endings usually show no resting discharge. When a joint is moved, certain spray endings fire off, rapidly at first, and then at a rate that is dependent upon the speed and extent of movement. Boyd and Roberts (1953) demonstrated that there is a characteristic discharge frequency for particular positions and rates of movement. Cohen (1955–56), in recording from the posterior knee joint nerve of the cat, found that the manner of the response depends upon the position of the receptor and its relationship to joint tissues. He found proprioceptive firing at all angles. Each receptor had a limited angular range, the threshold of which was precise and accurate. Skoglund (1956) provided confirmatory evidence that receptors in joints are accurate indicators of movement. Also, when a joint is at rest, the spray endings most sensitive at that position continue to discharge for long periods of time. Hence, they are accurate indicators of position as well as of movement.

The encapsulated receptors in joints are also sensitive but they adapt rapidly (Boyd, 1954). In some joints, rapidly adapting receptors seem to be of special importance. In the larynx, for example, they are probably involved in the reflex control of movement (Kirchner and Wyke, 1964*a*, *b*, *c*, *d*; 1965). However, slowly adapting receptors have also been noted in certain laryngeal joints, such as the thyro-epiglottic (Andrew, 1954*b*), and Gracheva (1963) has described spray endings in the crico-thyroid joint.

The fibres which give rise to the complex endings, and perhaps those which contribute free endings to the proprioceptive triad, establish reflex connexions throughout several segments of the spinal cord and participate in several ascending pathways. The local connexions clearly are involved in the reflex control of movement and posture (Gardner, 1950*a*; Skoglund, 1956; Ekholm, Eklund and Skoglund, 1960). The endings in vertebral

joints are the key receptors in tonic neck reflexes (McCouch, Deering and Ling, 1951). Furthermore, there is evidence that receptors in joints of the thorax may be important in the reflex control of respiratory muscles (Yamamoto, Sugihara and Kuru, 1956). However, the ascending pathways which carry impulses to brain stem, cerebellum and cerebral cortex are the specific aim of the present review.

CENTRAL PATHWAYS

The afferent impulses that arise from mechanical deformation of skin and deep tissues and from the movement of joints have similar central pathways. Many of the primary afferent fibres which carry these impulses ascend in the dorsal funiculi to the medulla oblongata and constitute the first limb of the dorsal funiculus–medial lemniscus system. First, however, they give collaterals which, together with terminal primary afferents, establish widespread synaptic connexions (Gardner, 1948*a*; Gardner, Latimer and Stilwell, 1949). Impulses destined for the brain stem and cerebral and cerebellar cortex by other than the dorsal funiculus–medial lemniscus system arise from these connexions and ascend by way of several pathways. These include spinothalamic fibres, the spinocervicothalamic system, the spinocerebellar tracts, spino-olivary and spinoreticular fibres, and the dorsal funiculus–lateral cuneate nucleus system.

Dorsal funiculus–medial lemniscus system (Fig. 1)

This system has been studied experimentally chiefly in cats and to some extent in monkeys. It has traditionally been considered to carry impulses concerned with touch, position sense (previously called muscle-joint-tendon sense), and certain complex modalities such as appreciation of vibration. That it does so is well documented. However, section of dorsal funiculi, even at high cervical levels, may result in surprisingly little sensory deficit, even in man (Ferraro and Barrera, 1934; Lassek, 1954; Gardner and Morin, 1957; Cook and Browder, 1965). Nor does section of the medial lemniscus appear to alter proprioceptive functions significantly (Sjoqvist and Weinstein, 1942). Furthermore, after dorsal funiculi are sectioned, low threshold skin, deep tissue, and joint afferents still project to the cerebral cortex. This was first demonstrated by Gardner and Noer (1952) (who, however, still believed that position sense was dependent solely on the dorsal funiculus–medial lemniscus system) and shortly thereafter confirmed by Gardner and Haddad (1953). Although Ruch, Patton and Amassian (1950), Bohm (1953) and Skoglund (1956) found evoked potentials to

disappear upon cutting dorsal funiculi, the results of Gardner and Noer have nevertheless been confirmed repeatedly.

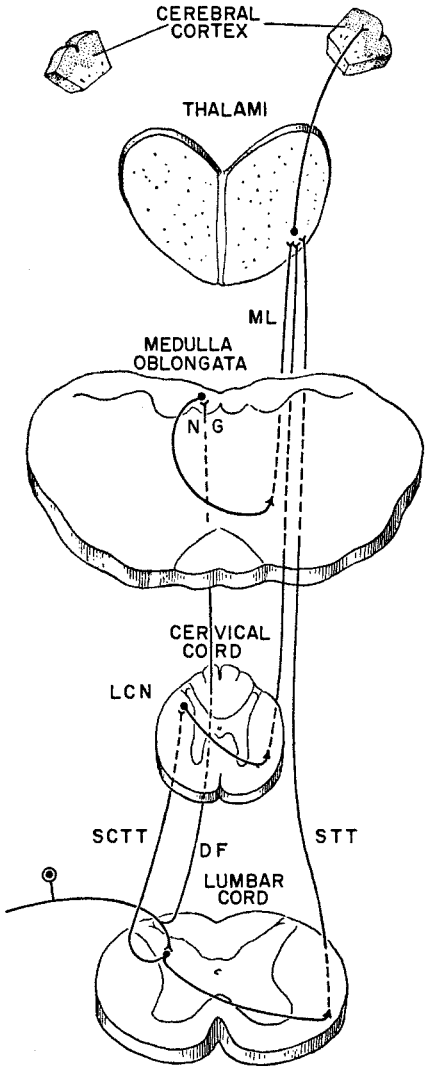

FIG. 1. Simplified representation of pathways to the cerebral cortex, showing only a single primary afferent fibre and eliminating ipsilateral projections. The chief pathways, as shown here, are (1) the projection via dorsal funiculus (DF), nucleus gracilis (NG), and medial lemniscus (ML) to opposite thalamus and cerebral cortex, (2) the spinocervicothalamic tract (SCTT) *via* the lateral cervical nucleus (LCN), and (3) the spinothalamic tract (STT).

The concept that the dorsal funiculi are solely responsible for transmitting impulses concerned with position sense stems chiefly from clinical observations that posterior column (dorsal funiculus) disease is accompanied by proprioceptive defects, including loss of position sense. However, the posterior column disease which characteristically has such sensory defects is that resulting from tabes dorsalis, which is a primary dorsal root rather

than posterior column disorder. Hence, the sensory deficits cannot be assigned exclusively to the posterior column lesion.

Spinothalamic fibres

It is doubtful that a significant classical spinothalamic system for fast afferents exists except in primates (Fig. 1). In cats, it seems to be of little importance for low-threshold, fast impulses travelling over myelinated cutaneous and deep fibres (Morin, 1953; Mark and Steiner, 1958). Getz (1952), using the method of terminal degeneration, reported that spinothalamic fibres exist in the cat and that they end in nucleus VPL. However, it is likely that these are chiefly nonmyelinated fibres. In monkeys, and probably also in man, myelinated spinothalamic fibres are more numerous and carry impulses concerned with touch, pressure and position sense. However, even in man, relatively few spinothalamic fibres reach the thalamus (Gardner and Cuneo, 1945; Morin, Schwartz and O'Leary, 1951; Poirier and Bertrand, 1955; Mehler, Feferman and Nauta, 1960).

Spinocervicothalamic system

This system, which is also termed Morin's path (Fig. 1), consists of fibres which arise from spinal grey matter and ascend in the dorsal part of the lateral funiculus, chiefly ipsilaterally, to the lateral cervical nucleus. Axons from cells in this nucleus cross in the upper cervical cord, join the medial lemniscus in the lower brain stem, and end in the thalamus. This pathway ultimately projects to somato-sensory areas I and II (SI and SII) (Andersson, 1962). The spinocervicothalamic system has been studied most thoroughly in cats, but it is present in all species so far studied, with the possible exception of man. It is now known to carry a variety of modalities, and to be involved in local, segmental and supraspinal mechanisms, and perhaps pain also (Kennard, 1954; Taub, 1964). It is interesting that the spinal afferents to the lateral cervical nucleus conduct at a faster rate than do those of the dorsal funiculi (Mark and Steiner, 1958; Norrsell and Voorhoeve, 1962). Impulses ascending by this system reach the cerebral cortex 2–4 milliseconds sooner than do those ascending by the dorsal funiculus–medial lemniscus route. However, Taub and Bishop (1965) point out that the small-fibred half of the Aα fibres which ascend in the dorsal funiculi give collaterals which excite cells projecting to the lateral cervical nucleus. Thus, the slower conducting primary cutaneous afferents project to the faster central path.

The initial clarification of the anatomy and functions of the spinocervicothalamic system is due chiefly to the work of Morin (1955) and

Morin and Catalano (1955). Ramon y Cajal (1909) had described a special nucleus, the *noyau du faisceau cerebelleux*, in the upper cervical segments, with collaterals to it from dorsal spinocerebellar fibres. Rexed and Brodal (1951) reported chromatolysis in this nucleus after cerebellar lesions and concluded that it relayed to the cerebellum. Subsequently Rexed (1954), in his report on the cytoarchitectonics of the spinal cord, termed it the lateral cervical nucleus. Then Morin and Catalano (1955) found that midbrain lesions in cats were followed by chromatolysis in the lateral cervical nucleus opposite to the side of the lesion, whereas cerebellar lesions were without effect. Morin (1955) found that in cats the dorsal part of the lateral funiculus carries tactile impulses, and that when the dorsal funiculi are cut, either a subsequent section below the lateral cervical nucleus or a median commissurotomy at C1–3 will usually abolish evoked potentials in the opposite cerebral cortex. Morin also reported chromatolysis in the lateral cervical nucleus of monkeys after midbrain lesions. Furthermore, Morin and Thomas (1955) traced degeneration to the contralateral thalamus by way of the medial lemniscus after lesions of the lateral cervical nucleus. They also reported that the ascending fibres gave collaterals to the inferior olive. They confirmed that lesions of the medial lemniscus, but not of the cerebellum, are followed by chromatolysis in the opposite lateral cervical nucleus.

These studies of the lateral cervical nucleus explained many previous findings on multiple pathways to the cerebral cortex. Gardner and Noer (1952) had found that in cats superficial and deep afferents (including joints) still projected to the cerebral cortex after section of dorsal funiculi, and also after section of dorsal funiculi and the contralateral lateral funiculus. However, evoked potentials were greatly reduced or abolished after the dorsal funiculi and both lateral funiculi were cut. They also recorded surface-positive spikes from the dorsal half of the ipsilateral lateral funiculus and the ventral part of the contralateral funiculus with stimulation of joint and other nerves. Gardner and Haddad (1953) confirmed these findings and reported that bilateral projections to both SI and SII for low threshold afferents, including joints, persisted after section of the dorsal funiculi and contralateral lateral funiculus.

It is now clear that section of the ipsilateral lateral funiculus cuts afferents to the lateral cervical nucleus. A section immediately below the nucleus cuts most if not all of the afferents, which here are collected dorsally. In the thoracic region, however, some of the afferents lie more ventrally and might well be spared by an ipsilateral incision.

Subsequent experiments showed that the spinocervicothalamic system

is available for touch from large and small fields (Catalano and Lamarche, 1957; Kitai, Ha and Morin, 1965), and for deep modalities, including low-threshold joint afferents (Gardner, Kitai and Morin, 1961; Morin, Gardner and Kitai, 1962). It had been reported that section of this system abolishes the tactile placing reaction (Lundberg and Norsell, 1960), but Norrsell and Voorhoeve (1962) were unable to confirm this.

There is also evidence that some of the fibres in the spinocervicothalamic system are activated by stimuli that damage tissue (Lundberg and Oscarsson, 1961). Furthermore, the system gives collaterals to the midbrain reticular formation and thus plays a role in reticular activation (Morin, 1953; Morillo and Baylor, 1963).

Lateral cervical nucleus

This nucleus is found in the lower medulla and upper two or three cervical segments, adjacent to the dorsal grey matter (Fig. 2). Its size varies

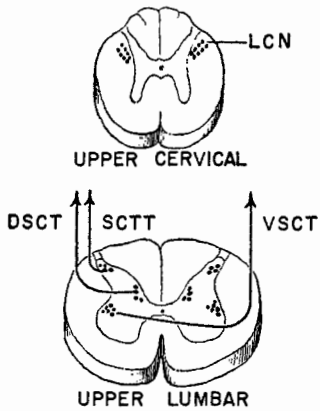

FIG. 2. Simplified representation of upper cervical and upper lumbar spinal cord. The position of the lateral cervical nucleus (LCN) is shown in the cervical cord. The section of the lumbar cord is a composite of several levels showing the cells of origin of the spinocervicothalamic tract (SCTT), of the dorsal spinocerebellar tract (DSCT) and of the ventral spinocerebellar tract (VSCT).

according to species (Kitai, Ha and Morin, 1965; Ha, Kitai and Morin, 1965). It is present in many primates (Ha and Morin, 1964), but is small in the monkey (Morin, 1955; Gardner and Morin, 1957) and is small or absent in man (Gardner and Morin, 1957; Ha and Morin, 1964). Its synaptology has been described by Ha and Liu (1963). Brodal and Rexed (1953) pointed out that its spinal afferents seem to be derived from all levels of the spinal cord and that they ascend in the lateral funiculus, chiefly in its dorsal part. Its spinal afferents (Fig. 3) appear to be derived from three chief sources (Ha and Liu, 1962, 1966). These are: (1) dorsal grey matter, especially ipsilaterally and especially in lumbosacral region. The axons, which probably constitute about 75 per cent of the spinal afferents (Taub and Bishop, 1965), end in the lateral cervical nucleus. That these fibres are terminal is

indicated by the fact that they cannot be invaded antidromically by cerebellar stimulation (Lundberg and Oscarsson, 1961). It is probably these fibres that are activated by the collaterals of those small primary afferents which ascend in dorsal funiculi. (2) Collaterals from dorsal spinocerebellar fibres, and (3) collaterals from ventral spinocerebellar fibres. (For a contrary view about collaterals from spinocerebellar fibres, see Lundberg, 1964.)

The lateral cervical nucleus also receives afferents from the brain stem. Wall and Taub (1962) have shown that the most medial part of the nucleus

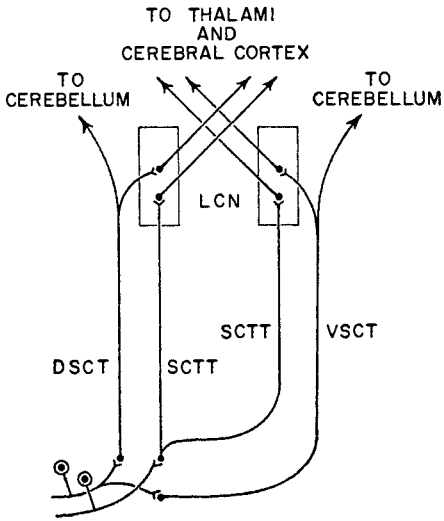

FIG. 3. Diagrammatic representation of spinal afferents to the lateral cervical nucleus (LCN). These are terminal fibres (spinocervicothalamic tract, SCTT) and collaterals from the dorsal and ventral spinocerebellar tracts (DSCT, VSCT). Note that the diagram shows some of the ipsilateral projections to the cerebral cortex (ipsilateral with respect to stimulated site).

is the caudal end of the descending trigeminal nucleus. Hence, the body is represented from medial to lateral in the lateral cervical nucleus by head and neck, forelimb, and hindlimb.

Cells in the lateral cervical nucleus respond chiefly to ipsilateral stimuli, especially to skin and hair (Gordon and Jukes, 1963), but also to pressure and sometimes to joint movement (Morin, Gardner and Kitai, 1962; Morin *et al.*, 1963*b*). However, Oswaldo-Cruz and Kidd (1964) report that no cells respond to true joint receptors.

Thalamus and Cerebral Cortex

Potentials are readily evoked in the cerebral cortex of cats by stimulation of joint nerves. They have also been demonstrated in monkeys (Gardner, unpublished observations, 1956*). However, what is more important is

* Work done at Dept. of Anatomy, University of California at Los Angeles.

that neurones driven by physiological stimuli, namely joint movement, are a prominent feature of both thalamus and sensory cortex. They are closely related to neurones driven by light mechanical stimulation of the skin and hairs. Mountcastle (1957), in a single-unit analysis of the somatic sensory cortex in cats, found that all the cells studied were activated by mechanical deformation of some peripheral tissue, with three subgroups: (1) hair movement, (2) skin pressure, and (3) joint movement, including other deep tissues. The cells driven by joint movement signalled steady position and phasic changes in joint position and were never activated by muscle stretch. It is surprising that Norrsell and Wolpow (1966), in confirming the existence of multiple pathways to the cerebral cortex, failed to find cortical activity evoked by stimulation of low-threshold joint afferents. They suggested that the type and depth of anaesthesia were responsible for the failure. There is little doubt that the cortical neurones driven by joint movement are involved in the appreciation of position and movement. The question is whether this sensory modality is served only by the dorsal funiculus–medial lemniscus system, as Mountcastle, Poggio and Werner (1963) believe, or whether the other pathways (spinothalamic and spinocervicothalamic) are also involved. This facet of an important problem has been somewhat clarified by Vierck (1966). He trained macaques to respond discriminatively to leg position, and found, by the persistence of responses after a variety of cord lesions, that multiple pathways were involved.

About 80 per cent of the cortical neurones that are driven by joint movement are activated by slowly adapting receptors. Their excitatory angles (about 60°–90°), like those of thalamic neurones driven by joint movement, are nearly four times wider than those of primary afferent neurones (Mountcastle and Powell, 1959; Mountcastle, Poggio and Werner, 1963). Hence, during the full range of movement, each cortical neurone must be driven by successively excited receptors. Although not specifically studied with respect to joint afferents, much of this convergence must occur in the spinal cord (Wall, 1960), medullary (Perl, Whitlock and Gentry, 1962) and thalamic levels.

The cortical activity referred to above was recorded from the primary sensory cortex. Carreras and Levitt (1959) recorded from units in the second somato-sensory area of cats that responded to movement of hairs, pressure on skin, or movement of a joint. About 2 per cent of the units responded to ipsilateral stimulation. Gardner and Noer (1952) and Gardner and Haddad (1953) reported that low-threshold joint afferents projected to the opposite SI in the cat, but also to the opposite SII and occasionally

to the ipsilateral SII. These responses persisted after section of dorsal funiculi. However, Andersson (1962) found that small skin units and some deep receptors projected to SII, but found no joint receptors that did so.

Motor cortex

Evoked potentials are readily recorded from the motor cortex of cat and monkey upon stimulation of cutaneous and deep nerves (Gardner and Morin, 1953; Malis, Pribram and Kruger, 1953). The latency of such potentials is longer than that of potentials evoked from sensory cortex by stimulating the same nerves. The potentials persist after section of dorsal funiculi, and after bilateral removal of sensory cortex and complete removal of the cerebellum (Kruger and Pribram, 1954). However, the extent to which joint afferents may project to motor cortex remains to be determined.

Thalamus

The multiple pathways from joint and cutaneous receptors relay in the ventrobasal complex and adjacent nuclei of the thalamus. Recordings have been made from thalamic neurones which respond to movement of hairs, light touch and mechanical stimulation, contralaterally and ipsilaterally (Gaze and Gordon, 1954), and after section of dorsal funiculi (Gaze and Gordon, 1955). It seems likely that the dorsal funiculus–medial lemniscus system relays chiefly through the opposite ventrobasal complex (Poggio and Mountcastle, 1960, 1963). However, this matter is still not clarified. Perl and Whitlock (1961) recorded from cells in the ventrobasal complex and found cells that responded to rotation of joints. This activity persisted after section of dorsal funiculi. Kruger and Albe-Fessard (1960) had reported that potentials evoked in the ventrobasal complex may be reduced or abolished by section of the dorsal funiculi, but such a section has little or no effect on potentials evoked in adjacent thalamic nuclei.

In addition to being a contralateral relay, the ventrobasal complex seems to deal with small, specific body fields and rotation of joints, whereas the posterior thalamus deals with large, bilateral body areas, but not joints (Poggio and Mountcastle, 1960, 1963; Whitlock and Perl, 1959, 1961). Whitlock and Perl also found that posterior thalamic activity persists after section of dorsal funiculi. However, in their 1961 paper they also reported that in monkeys with dorsal funiculi cut, evoked unitary discharges were routinely recorded from the external segment of the contralateral ventrobasal complex, following stimulation of discrete parts of the body.

Projections to Cerebellum

Spinocerebellar tracts

These are traditionally grouped into dorsal and ventral tracts, the dorsal arising from Clarke's column ipsilaterally, and the ventral arising contralaterally from "border cells" in central, intermediate and dorsal grey matter (Hubbard and Oscarsson, 1962).

A widely held view is that dorsal spinocerebellar fibres transmit chiefly Group Ia muscle afferents and that ventral spinocerebellar fibres transmit chiefly Group Ib afferents (Lundberg and Oscarsson, 1956; Oscarsson, 1956, 1957, 1958). Spinocerebellar fibres from the forelimb use the dorsal funiculus–lateral cuneate nucleus route as well as other spinocerebellar paths which, according to Oscarsson (1964, 1965), include a rostral spinocerebellar tract. Some fibres may reach the cerebellum by a dorsal funiculus–nucleus gracilis–cerebellum route. Oscarsson (1965) also holds that low-threshold joint afferents do not project via the dorsal spinocerebellar tract.

The classical view of the cerebellum as primarily a muscle-afferent receiving station began to be challenged when Dow and Anderson (1942) recorded surface potentials from the cerebellum upon movement of hairs, and when Snider and Stowell (1944) found tactile, auditory and visual receiving areas in the cerebellum. Also, cerebellar cortical potentials can be evoked by stimulation of low-threshold joint afferents in the cat (Haddad, 1953). However, the latency of these joint-nerve potentials, and also of those evoked by stimulation of muscle nerves, is greater than that of potentials evoked by stimulation of mixed and superficial nerves (Morin and Haddad, 1953). Similar findings with regard to muscle afferents in the monkey have been reported (Morin and Gardner, 1953). Finally, micro-electrode studies of the dorsal spinocerebellar tract indicated the presence of fibres related to touch, pressure and joint movement (Laporte and Lundberg, 1956; Laporte, Lundberg and Oscarsson, 1956*a*, *b*; Yamamoto and Miyajima, 1959; Kitai and Morin, 1962.)

In summary, the spinocerebellar tracts carry low-threshold touch and joint afferents as well as muscle afferents, the dorsal fibres arise chiefly ipsilaterally and the ventral contralaterally, there is some shift of the ventral fibres dorsally as they ascend, and spinocerebellar fibres from the forelimb are said to differ in not arising from Clarke's column and in not ascending with either the dorsal or the ventral tracts (Morin and Lindner, 1953; Morin, Lindner and Catalano, 1957; Morin *et al.*, 1962; Holmqvist and

Oscarsson, 1963). Also, there is a dorsal funiculus–lateral cuneate pathway (Holmqvist, Oscarsson and Uddenberg, 1963).

However, the situation may seem more clear-cut than is actually the case. Liu (1956) reported that the primary afferents which enter over the 5th cervical to the 5th thoracic dorsal roots connect with both Clarke's column

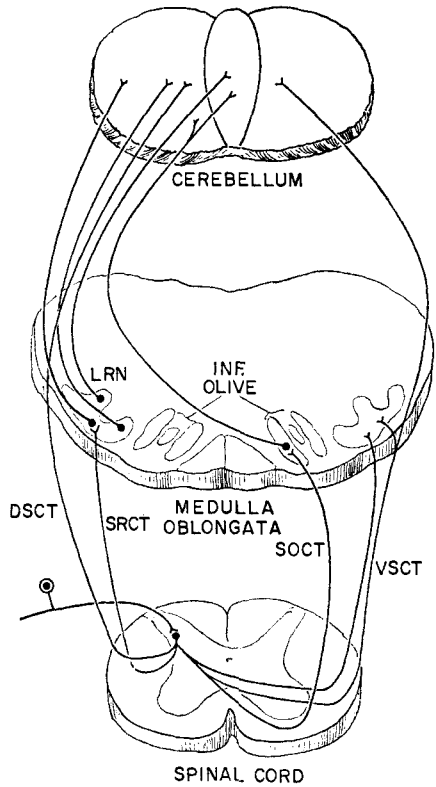

FIG. 4. Simplified representation of some of the afferents to the lateral reticular nucleus (LRN), the inferior olive, and the cerebellum. A single primary afferent represents the various modalities and the cell with which it synapses represents the source of the various spinal afferents: dorsal spinocerebellar tract (DSCT), spinoreticulocerebellar tract (SRCT), spino-olivocerebellar tract (SOCT) and ventral spinocerebellar tract (VSCT).

and the lateral cuneate nucleus. He concluded that Clarke's column represented all of the body except the head and upper neck. Smith (1957, 1961), in studies of an extensive series of human cordotomies, emphasized variations, differences from other species, the dorsal shift of ascending fibres, the lack of clear-cut separation into dorsal and ventral tracts, and the problems in transferring data from lower animals to man. Vachananda (1959), for example, in a study of these tracts in monkeys, did not find the dorsal shift of ascending fibres which Smith did in man.

Spino-olivary fibres (Fig. 4)

Afferents to the inferior olive arise from many levels of the spinal cord and ascend chiefly in the ventrolateral region (Morin, Lamarche and Ostrowski, 1957). These fibres carry a variety of modalities and are relayed by the olive chiefly to the midline of the anterior lobe of the cerebellum (Morin, Lamarche and Ovshinsky, 1958). Some of the spinal afferents may be relayed to the inferior olive by the lateral cervical nucleus.

Spinoreticular fibres (Fig. 4)

The lateral nucleus of the medulla (also termed lateral reticular nucleus) is a prominent group of cells just deep to the ventrolateral surface of the medulla, between the spinal tract and nucleus of the trigeminal and the inferior olive. It is present in all mammals, including man, and may be present in reptiles. The pertinent literature is reviewed by Kennedy (1966*b*). The lateral reticular nucleus receives a bilateral spinal input as well as descending fibres from the cerebral cortex and midbrain, and projects ipsilaterally to all parts of the cerebellum.

The nucleus consists of a parvicellular part which projects to the vermis, a magnocellular part which projects to the cerebellar hemispheres, and a subtrigeminal part which projects to the flocculonodular lobe. On the basis of silver degeneration studies, Brodal (1949) concluded that afferents ascending in the lateral funiculus ended in the parvicellular portion, and that spinal afferents to the magnocellular portion probably did not exist or were not significant. These findings suggested that the parvicellular part probably was responsible for the somatotopic projection of cutaneous sensory information to the anterior lobe and paramedian lobule of the cerebellum, whereas the magnocellular part would function as a relay for the suprasegmental inputs to the nucleus and thence to the cerebellar hemispheres.

Recently, however, silver degeneration studies of the nucleus following lesions of the lateral funiculus in cats (Morin, Kennedy and Gardner, 1966; Kennedy, 1966*b*) and in monkeys (Mehler, Feferman and Nauta, 1960) have shown that spinal afferents end in the magnocellular as well as in the parvicellular portion of the nucleus. Hence, there may well be a spinal inflow to the neocerebellum, as reported by Morin and co-workers (1963*a*). Furthermore, potentials have been recorded throughout the nucleus following stimulation of various nerves (Grundfest and Carter, 1954), more specifically, by stimulation of cutaneous and muscular nerves in hindlimb and forelimb, and the posterior nerve of the knee joint (Kennedy,

1966*a*). These responses were evoked by contralateral and ipsilateral stimulation. Also, single-unit responses to physiological stimulation have been recorded (light touch, bending of hairs, pressure and joint movement); the most prominent responses were to pressure and joint movement (Kitai and Morin, 1966).

SUMMARY

The sensory fibres in joint nerves form: (1) spray endings, (2) encapsulated endings, usually paciniform in nature, and (3) simple free endings. The first two occur chiefly in joint capsules and ligaments; free endings also occur in joint capsules and ligaments, and to a lesser extent in the synovial layer. The first two are especially sensitive to deformation induced by movement. Encapsulated endings adapt rapidly to deformation; spray endings adapt slowly and are accurate indicators of position as well as of movement. Joint nerves resemble cutaneous nerves in fibre spectrum and central connexions. Impulses can reach the cerebral cortex by the dorsal funiculus–medial lemniscus system, by the spinocervicothalamic system, and, in primates so-far studied, by the spinothalamic system. The multiple pathways provide for projection to ipsilateral as well as contralateral cerebral cortex, and to motor cortex as well as sensory. Also, joint afferents have multiple routes to the cerebellum, including the spinocerebellar tracts and via the olives and the lateral reticular nuclei of the medulla. Afferent impulses from muscle, at least those arising from spindles and tendon organs, play little if any role in the appreciation of position and movement.

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DISCUSSION

Brodal: You mentioned that the ascending fibres to the lateral cervical nucleus were partly crossed, Professor Gardner. When Rexed and I studied these fibres experimentally many years ago (Brodal, A., and Rexed, B. [1953]. *J. comp. Neurol.*, **98**, 179–211) we found no degeneration in the contralateral nucleus following lesions restricted to the dorsolateral part of the lateral funiculus, and were inclined to think that this is a rather pure ipsilaterally ascending pathway. After lesions which involve the dorsal horn, there are, however, some fibres which ascend on the other side and reach the contralateral nucleus. Secondly, we found these fibres to degenerate even when lesions were made below the level of the column of Clarke. From this we concluded that even if fibres to the lateral cervical nucleus ascend in close proximity to those of the dorsal spinocerebellar tract, the cells of origin are probably not, or at least not only, those in the column of Clarke. In fact, fibres from lower segments of the cord appear to be rather numerous. I wonder on what evidence you base your statement that there are collaterals of the dorsal spinocerebellar tract to the lateral cervical nucleus. In our experiments (with the Glees method) we found fine degenerating fibres (presumably collaterals) entering the nucleus at right-angles to the descending fibres, but we were unable to say whether these belong to the spinocerebellar tract.

Gardner: The contralateral representation in the lateral cervical nucleus is not prominent; most cells respond only to ipsilateral stimulation. However, the results of single-unit recording from cells in this nucleus indicate that a few cells respond to contralateral stimulation. Also, H. Ha and C. N. Liu ([1966]. *J. comp. Neurol.*, **127**, 445–470) present anatomical evidence, based on chromatolytic and degeneration studies, of some contralateral projection to the lateral cervical nucleus. It is clear from your comments that there is no general agreement yet that some of the afferents to the lateral cervical nucleus are collaterals of spinocerebellar fibres. Cajal described collaterals coming off at right-angles from large ascending fibres and going to the cells of the lateral cervical nucleus. I have seen such fibres in silver preparations, and Ha and Liu, in the paper referred to above, report that right-angle collaterals enter the nucleus from both its dorsolateral and medial aspects. However, there seems little doubt that most (75 per cent) of the afferents

are not collaterals of spinocerebellar fibres. They arise below the level of Clarke's column, and they end in the nucleus, as A. Taub and P. O. Bishop ([1965]. *Expl Neurol.*, **13**, 1–21) have reported.

Brodal: I am not sufficiently familiar with the recent physiological studies to discuss them, but I would like to stress the difficulties involved in deciding anatomically the sites of origin of ascending spinal pathways. In a paper appearing about a year ago the authors had made lesions in various places in the cord and drew the—certainly unwarranted—conclusion that the spinocerebellar tracts were feeding into the lateral cervical nucleus. It is evident that their lesions were far too large and unsuitable for the purpose. The same warning has been given by Taub and Bishop ([1965]. *Loc. cit.*).

Gardner: Certainly the results of recording from the cells in the dorsal grey matter giving rise to the afferents to the lateral cervical nucleus, and of recording from the nucleus itself, as well as of attempting to stimulate the spinocerebellar fibres antidromically above the level of the nucleus (most of the units cannot be invaded by antidromic stimulation of the spinocerebellar tracts) indicate that 75 per cent or more of the afferents go directly to the nucleus ipsilaterally and end there. But I believe that there is sufficient anatomical and experimental evidence to support the thesis that some of the afferents arise contralaterally and that some are collaterals of spinocerebellar fibres.

Monnier: Have you any thoughts on the significance of the ipsilateral and contralateral pathways? And have you done experiments in which only the ipsilateral pathway has been interrupted?

Gardner: Multiple pathways may well serve as reserve mechanisms in case of injury, but I don't know why some are ipsilateral and some contralateral. In monkeys, if the dorsal funiculi are cut, say at the upper cervical level, the sensory deficit is surprisingly small. Likewise if the dorsal part of the ipsilateral lateral funiculus is cut, the sensory deficit is small. That is to say, if any *one* of these systems is destroyed surgically, with clean lesions, the sensory deficit is often slight.

Purdon Martin: You have no human observations, so you do not know how much of this comes into consciousness. You may therefore be interested in a case recorded by R. Lipschitz and J. Block ([1962]. *Lancet*, **2**, 169–172) in which an African had had his posterior columns damaged through a needle being stuck in under one of his cervical spines. The patient lost all his sense of position; he did not lose pain and temperature appreciation. He eventually became able to walk, as long as he kept his eyes open; he could start himself by putting his hands out. I argued that he must have some proprioceptive impulses coming up by pathways other than by his posterior columns, assuming that the posterior columns were entirely divided, in order to activate his anti-gravity mechanism and also his stepping mechanism.

Gardner: A. W. Cook and E. J. Browder ([1965]. *Archs Neurol., Chicago*, **12**, 72–79) have reported a series of eight patients in whom the dorsal funiculi were

cut in an attempt to relieve pain (five at upper thoracic levels and three at upper cervical levels). There seemed to be no permanent, significant sensory deficits. The remaining pathways which continued to function in sensory mechanisms certainly included the lateral spinothalamic tract. There seems to be an unequivocal lateral cervical nucleus in man. The nucleus is smaller in monkey than in cat, while the spinothalamic tract is correspondingly more prominent in monkey, and still more so in man. There may be a reciprocal relationship between the spinocervicothalamic tract in sub-primates and the spinothalamic tract in primates.

Pompeiano: I should like to know first, whether there is evidence for supraspinal control of transmission of sensory volleys through the lateral cervical nucleus, and secondly, whether the joint receptor afferents are able to influence the activity of the second-order vestibular neurones, either directly or indirectly by way of the cerebellum. So far only the responses of second-order vestibular neurones localized in the lateral vestibular nucleus to repetitive electrical stimulation of the different types of muscular and cutaneous afferent fibres have been investigated in precollicular decerebrate cats (Giaquinto, S., Pompeiano, O., and Santini, M. [1963]. *Boll. Soc. ital. Biol. sper.*, **39**, 524–527). In this study, unit responses occurred only by stimulating Group II and III cutaneous and muscular afferents, but no evidence was found of effects from Group Ia muscle afferents. These results have recently been confirmed by V. J. Wilson, M. Kato, R. C. Thomas and B. W. Peterson ([1966]. *J. Neurophysiol.*, **29**, 508–529). It would be advisable to study the response of single vestibular neurones to different natural sensory stimulations, including that of the joint receptors.

Gardner: Some work has been done by G. Gordon and M. G. M. Jukes ([1963]. *J. Physiol., Lond.*, **169**, 28–29*P*) on the supraspinal control, or lack of it, of the lateral cervical nucleus, but I am not familiar with the details of this work. I know of no work on the projection of low-threshold joint afferents to Deiters' nucleus or to any other vestibular nucleus. We were rarely successful in recording low-threshold muscle afferents from the lateral cervical nucleus. Touch, light pressure and a few deep modalities, including joints, were recorded, although low-threshold joint afferents are few compared with tactile impulses to the lateral cervical nucleus.

Jansen: Is there any convergence of joint and skin afferents in the lateral cervical nucleus or are they independent systems, as they are apparently in the dorsal column system?

Gardner: The predominance of tactile units over joint units is so great that I cannot be positive about this, but my impression is that tactile and joint afferents converge, somewhat as they do in the cerebral cortex.

Eldred: Where precisely does the lateral cervical nucleus projection go in the thalamus?

Gardner: I am not sure. The medial lemniscus with its predominantly (or entirely) contralateral projection goes to the ventrobasal complex of the thalamus;

the lateral cervical nucleus projects to the same general area. Mountcastle and his co-workers (for example, Poggio, G. F., and Mountcastle, V. B. [1960]. *Bull. Johns Hopkins Hosp.*, **106**, 266–316) believe that the extralemniscal pathways project chiefly outside the ventrobasal complex, particularly to the posterior thalamus. D. G. Whitlock and E. R. Perl ([1959]. *J. Neurophysiol.*, **22**, 133–148), however, reported that a fairly extensive part of the thalamus, including the ventrobasal complex, receives impulses from peripheral nerve stimulation after the dorsal funiculi are cut. A critical experiment would be to carry out single-unit recording from thalamic neurones during physiological stimulation and with the dorsal funiculi cut.

Eldred: I. S. Cooper now localizes his lesions in Parkinsonian patients to the zone between the ventrobasal complex and the ventrolateral nucleus ([1965]. *Bull. N.Y. Acad. Med.*, **41**, 870–897), which is exactly where Dr. J. S. Buchwald and I find increased activity following excitation of spindle afferents in the cat with succinylcholine. I wonder if that site is on the pathway for joint receptors as well.

Gardner: It might be, but so far as the joints are concerned, I don't know.

Matthews: You quoted Sarnoff and Arrowood's experiments in which intrathecally injected procaine blocked muscle reflexes before it blocked joint sensation, and you implied that this showed that the muscle afferents were also being blocked early. But an alternative explanation is that procaine blocks the small γ fusimotor fibres, thereby making the muscle spindle rather less sensitive (Matthews, P. B. C., and Rushworth, G. [1957]. *J. Physiol., Lond.*, **135**, 245–262).

Gardner: That is true, but in any event, position sense may be intact when afferent impulses over spindle afferents are absent.

Myotatic, Kinesthetic and Vestibular Mechanisms
Edited by A.V. S. de Reuck and Julie Knight

SOME PROBLEMS OF POSTURAL SWAY

G. H. Begbie

Department of Physiology, University of Edinburgh

Most clinical investigations of neurological patients include the Romberg test, in which the patient is asked to stand upright with feet together and eyes shut. A greater amount of sway than some arbitrarily chosen minimum is taken as a positive Romberg sign. Romberg (1853) himself considered it as a test for the integrity of the posterior columns of the spinal cord, but it has been much more generally used since his day. In its simple form it suffers from the disadvantage of being very dependent on the examiner's experience and acumen. Ideally one would like a test of postural sway which would be easy to administer and which would give simple quantitative results without encumbering the patient with extra bits of apparatus. At the same time, it would be an advantage if the test sharpened up the difficulty of standing still so that even the most stable subject would find it exacting, and therefore very minor degrees of instability would show up.

These introductory considerations are mentioned because, although the experiments to be described are largely concerned with healthy subjects, the investigation originally started as an attempt to quantify the Romberg test itself. For this reason, the experimental conditions have been kept very simple in design so that they might afterwards be applied, without modification, to patients.

Many methods of measuring postural sway have been used in the past. Mitchell and Lewis (1886) measured movements of the head against a horizontal scale; Hellebrandt (1938) estimated movements of the centre of gravity; Travis (1944) measured the oscillations of a spring-loaded platform on which the subject stood; Miles (1950) tied threads to the head and recorded the integrated sway in different directions; Orma (1957) photographed a light strapped to the head of the subject; Joseph (1960) and many others have used electromyography of the postural muscles. For the present purpose, a different approach was tried. The platform on which the subject stood was made unstable and records were taken of the movements of this platform as the subject strove to keep his balance.

The instability was produced by supporting the platform on a system of two crossed struts (Fig. 1), so that it could rock from side to side. The movement can be described mathematically as the rolling of one ellipse-like curve on another similar one, and the instantaneous centre of rotation is at the point of intersection of the struts. The system is in equilibrium by itself, but when someone stands on it the combined centre of gravity is raised sufficiently for it to be unstable. The subject has therefore to make correc-

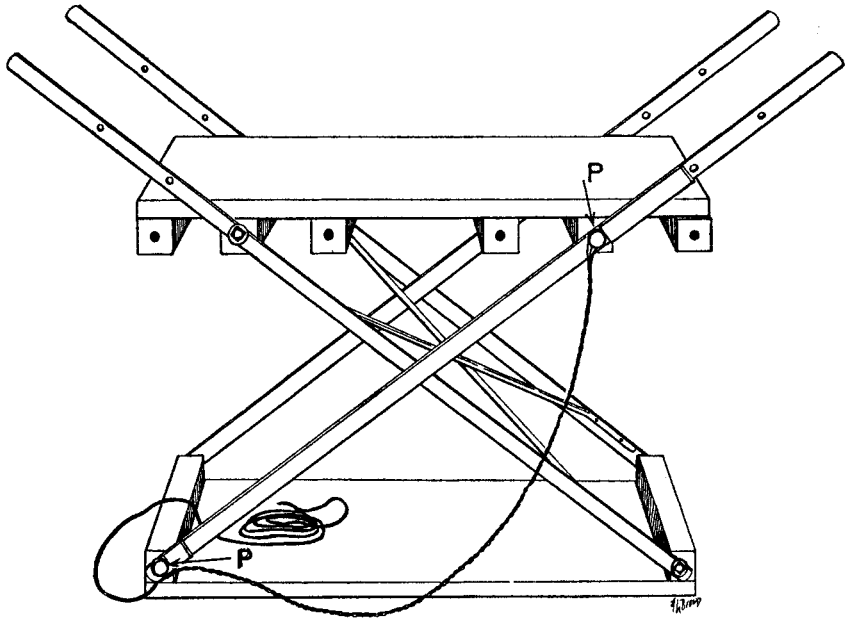

FIG. 1. General view of the oscillating platform. P—potentiometer. The subject stands on the upper platform. The normal safety surround and limiting stops have been omitted from this diagram.

tive movements as soon as there is any departure from the exactly central position. The apparatus is enclosed partially in a padded surround, and stops are arranged to limit the excursions of the platform. The movements of the system are recorded by two potentiometers fixed to two of the pivots. A d.c. voltage signal, proportional to the angle which the platform makes with the horizontal, is fed to an oscilloscope and photographed. In general, each test lasted for 60 seconds, and Fig. 2 gives an idea of the type of record obtained.

Three measurements have been made on the records. Firstly, the largest angular displacement between rightward and leftward sways which

occurred during the middle 40 seconds of the record was noted. This was called shortly the *sway*. The other two measurements are related to the fact that two distinct frequencies of oscillation can be seen in the records. One is at $\frac{1}{2}$–1 cycle per second and will be called the *slow oscillation*. It can be seen at the beginning of the eyes-open record in Fig. 2. The other has a frequency of $1\frac{1}{2}$–$2\frac{1}{2}$ cycles per second and is most evident in the eyes-closed record of Fig. 2. It will be called the *fast oscillation*. The amount of these two oscillations was estimated by assigning a numerical value to the middle

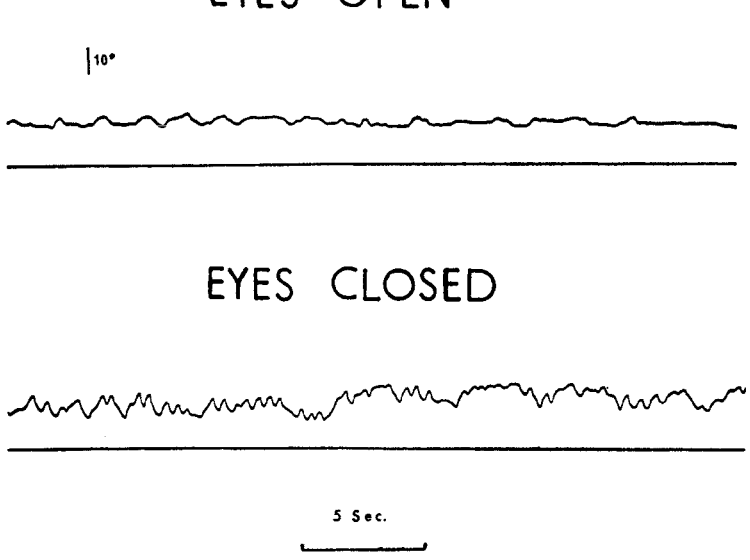

FIG. 2. Typical record, showing the amount of sway and the evidence of regular oscillations.

40 seconds of each record. If the oscillation was present for the entire time the number was 3. If it was present for less than this but for more than half the time, the number was 2. If it was present for less than half the time, the number was 1. Zero was assigned to those records with no trace of the oscillation.

It might be thought that these oscillations were primarily due the mechanical properties of the platform. But the evidence is against this. With a man on it, the platform is unstable and has no natural frequency of its own. The oscillations were not altered when the length of the struts and the width of the base were changed within quite wide limits. On the

other hand, as we shall see, the oscillations are altered by changing the physiological and anatomical conditions of the experiment.

It is possible to correlate the results on body sway with those obtained by earlier workers who used a stable base on which the subjects stood. There is an appreciable difference between subjects, although it was not easy to relate this to height and weight. This agrees with Fearing (1924), Frucht (1952) and Orma (1957) but disagrees with Travis (1944) and Miles (1950). An extreme instance may be cited of a four-foot high achondroplasic dwarf who produced records on the present apparatus that were indistinguishable from that of a normal person in amounts of sway and oscillation.

In general, the sway from front to back is more than, sometimes twice as much as, the sway from side to side, as Fearing (1924) has shown. In our apparatus the antero-posterior sway is quite energetic, not to say dangerous. For this reason, it is the transverse sway which is examined in all that follows.

As Fig. 2 shows clearly, the amount of sway increases greatly when the eyes are shut, as has been known for a long time with the simple Romberg test.

The present test was therefore broadly comparable to standing on a fixed base, and this was sufficiently encouraging to make one think that it could be used for experimental work. There is, however, one way in which standing on an unstable base produces a paradoxical result. Putting the feet apart—a distance of 14 inches was used—increases the amount of sway. This kind of balancing is thus rather like trying to stand upright in a small boat. It will be necessary to bear in mind this difference from standing on a fixed base, where putting the feet apart increases stability.

The fact that shutting the eyes increases the amount of sway can be interpreted in more than one way. One might, for example, argue that this is not directly due to a lack of vision but to the fact that darkness is a stress to which we are less accustomed. In that case one might think that practice at the task would lessen the effect. I tried practising on the apparatus for two quarter-hour sessions every day for three weeks (except Sundays). At the end of that time, closing the eyes had just as bad an effect as at the beginning. Other, slightly less persistent subjects showed the same pattern. This task is therefore not like some sensori-motor ones such as knitting, where vision can be discarded after an initial learning period. It is more like golf where not keeping the eye on the ball can be deleterious even to a champion. Practice, in general, has surprisingly little effect on performance on the present apparatus. After a short period of familiarization, most subjects maintain a fairly constant plateau of performance. This may be because standing still is already a fairly well practised activity.

The two oscillations which we have mentioned differ in other respects than their frequency. The fast one, at 1½–2½ cycles per second, is increased by closing the eyes, but the slow one, at ½–1 cycle per second, is decreased. Clearly, the fast oscillation cannot be due to any reflex associated with vision. If it is corrective in nature, it must be linked with information either from the vestibule or from proprioception in its most general sense, involving inputs from muscles, tendons, joints and skin. One can look at these possibilities a little more closely by studying the relative effects of standing, kneeling and sitting on the platform.

Kneeling and sitting are found to eliminate all traces of the fast oscillation. There is one red herring which complicated the work for some time. Kneeling introduces a faster frequency of 3–4 cycles per second, not present in either standing or sitting. From subjective experience, it seemed likely that this was due to the curvature of the knees, that is, the subjects did not have a flat base as when standing or sitting. This was later confirmed by showing that the 3–4 cycles per second oscillation vanished when the subject was given a firm cushion on which to kneel.

The suggestion is therefore that the fast oscillation is somehow bound up with information from the ankles or feet. Now, if you stand with your feet apart, the cutaneous sensations from the feet are much the same as with feet together, but the ankle joints are more stable. Therefore, if the fast oscillation were linked with the ankle joints one might expect it to diminish with feet apart. And so it does—to almost half its previous value (see Table II, p. 88).

Sitting and kneeling not only eliminate movement at the ankle joints. They also lower the centre of gravity. To get round this, experiments were tried with three subjects who had their ankle joints splinted. The results were that splinting abolishes the fast oscillation, as one might expect. It is worth noting that in the splinted condition, total sway is larger than average, which one might also expect.

To postulate that the fast oscillation is linked in some way to the ankle joints is, of course, not to say that one need only consider the ankle joints when considering postural sway in general. Even from the feet themselves, we may get other information. Heyd, quoted by Harris (1938), and Orma (1957) have shown that cooling the feet in iced water increases sway, thus indicating that cutaneous sensation from the feet has a part to play.

The slow oscillation presents quite a different picture. It is decreased by closing the eyes, but increased by putting the feet apart (see Table II). It can be obtained at some time in all subjects whether standing, kneeling or

sitting. It cannot therefore be based on information from the ankles, feet or legs. The frequency of ½–1 cycle per second is close to that found in some tasks where a hand lever has to be moved to make a pointer follow another pointer which is moving in a random fashion—that is, an eye–hand co-ordination task. Is our test an eye–postural muscles co-ordination task? Unfortunately, the slow oscillation can occur with eyes shut, though rarely. We shall return to this point.

It should be added that kneeling and sitting have a noticeable effect on total body sway. Kneeling diminishes it appreciably, and sitting diminishes it still further. This suggests that the task is easier, either because of the lowering of the centre of gravity or, more likely, because there are fewer joints to control.

These preliminary experiments have thrown up more questions than answers. I should like to describe a composite experiment which was designed to throw more light on the problems of the upright stance. Again the various conditions were kept simple so that if necessary at a later date patients could accomplish the tests without too much difficulty.

Each of 25 subjects came to the laboratory on two separate days. On one of these, he or she performed the tests with feet together and on the other day with feet 14 inches apart. Their instructions were to keep the platform as stable as possible in a central position. If they fell against the side of the surround they were to regain their balance as quickly as possible. There were five one-minute tests preceded and succeeded by a control test. The five conditions were: fixating an external point in the room, looking at the feet, reading from a paper attached to a stand on the platform, continuously rolling the head around, and finally with eyes shut. During the control tests they could adopt whatever technique they thought best, and no doubt many of them fixated an external point in the room. The 25 subjects were divided into 5 groups and the order of presentation of the 5 tests was based on a Latin square arrangement.

There are conflicting opinions in the literature on the relationship between sex and postural sway (cf. Frucht, 1952; Orma, 1957; Miles, 1950; Joseph, 1960). In our experiment, 16 of the subjects were men and 9 were women, and no significant difference between the sexes was found. Nor was any correlation found between the test scores and the heights, weights or ages of the subjects. Thirteen of the subjects did the feet-together tests on their first day and the feet-apart tests on their second day. The remaining 12 did the tests the other way round. Unfortunately, the records of four of the subjects were technically imperfect, and the final results are therefore based on 21 subjects.

In these tests, the sway and oscillation were measured in the way that has already been outlined. Let us first consider the sway (Table I).

The stops on the apparatus were arranged to allow $12\frac{1}{2}^{\circ}$ of sway to either side. Therefore a mean score of 25° meant that all the subjects had hit the stops at some time. An analysis of variance was applied to the scores and only those features which were statistically significant are mentioned below.

It will be noticed that all conditions improved a little with practice, in the sense that those subjects who tried a given condition on their second day did better than those who tried it on their first day. The difference between initial and final control tests on any one day, however, was not always significant.

TABLE I

MEAN SWAY PER PERSON (IN DEGREES)

	Control			*Looking at*			
	Initial	*Final*	*Fixating*	*feet*	*Reading*	*Moving head*	*Eyes shut*
Feet together							
Tested first	9·90	10·40	11·10	12·70	14·15	25·00	25·00
Tested second	8·65	7·20	8·80	10·30	11·65	14·60	25·00
Feet apart							
Tested first	16·50	14·30	11·65	18·95	22·45	22·75	25·00
Tested second	15·50	11·20	10·40	15·35	15·70	25·00	25·00

21 subjects. Maximum sway—25°.

The most obvious point about the test results was that, as usual, shutting the eyes had a bad effect—feet together or feet apart, tested first or tested second—on the amount of sway. Although this indicates that some degree of visual information is necessary for normal performance, it does not yet answer the question of what kind of information is required.

Moving the head in a rolling fashion gives poor results—almost as bad as eyes shut. This could be due to a number of causes. The head movements prevent fixation and continuous perception of a stable visual field. Then again, the extra stimuli to the vestibules and from neck structures are likely to make the information from these sources difficult to interpret. Thirdly, the rolling alters not only the position of the centre of gravity of the head but also that of the whole body. So the nature of the task is changed to some extent. On the latter two counts alone, one would expect that head movements would give a worse result than eyes shut. The fact that the head-rolling condition turns out to be slightly *better* than the eyes-shut condition means that subjects, when they roll their heads, are still getting

and using some visual information—and therefore carrying out some, no doubt impaired, righting reflexes.

Consider now a further two of the tests—looking at the feet and reading the paper attached to the platform. These were worse than either of the control tests and worse than fixating an external point in the room. Now, both involve fixating on a point which is moving with the platform. This means that they are, in effect, cancelling out the results of the vestibulo-ocular reflexes which are "attempting" to stabilize the eyes with respect to external space. Both tests also prevent fixation on an external point of space, which normally also helps to keep the eyes steady in space. The result is that in both conditions there is more relative movement of the eyes with respect to space, and therefore the optical righting reflexes are disorganized to the extent that they are getting misleading information for their working. This could be expected to lead to an increase in sway. So much seems reasonable.

Now, looking at the feet, in addition to tending to nullify the vestibulo-ocular reflexes, also suffers from three further disabilities that do not afflict the task of reading. The bent position of the head produces (*a*) an alteration of the normal orientation of the visual field, (*b*) an alteration of the orientation of the vestibule and a change of position in neck structures, (*c*) an alteration of the balancing task by the displacement of the head downwards and forwards. Therefore, in looking at the feet, all reflexes would have to be, as it were, recoded—once for all, not continuously as in head rolling. So one might expect that looking at the feet would be worse than reading. But the exact opposite is the case. Reading is always worse than looking at the feet in all subjects. Why should this be?

Here one is compelled to invoke a difference between the two tasks which is perhaps difficult to define accurately. Bursill (1958) and others have shown that if subjects are presented with two tasks, one in the centre of their visual field and one at the periphery, they can direct their attention in different ways between the two tasks. In particular, in conditions of stress there is a funnelling of attention on to the central task and a neglect of the peripheral task. In reading and looking at the feet, the subject has a central fixation task to perform, while his peripheral task is to be aware of and respond to relative movements of the peripheral visual field. But reading is a more exacting task than looking at the feet, and any lack of fixation is immediately apprehended as an inability to read, whereas a certain amount of wobble of fixation on the feet might be tolerated and even pass unnoticed. Therefore one might say that in looking at the feet one had some spare attention left for perception of the peripheral visual field, but in

reading there was more funnelling of attention on to the central task. The clear implication is that peripheral vision is an important factor in balancing.

Before leaving this set of experiments, the results on the oscillations should be mentioned. Table II presents some of the facts.

The fast oscillation of 1½–2½ cycles per second was more prominent with feet together than feet apart. This is the opposite of sway and we have already commented on it. Otherwise the results for the fast oscillation follow those of sway. The five conditions could be arranged in order of decreasing occurrence of the fast oscillation, thus: eyes shut, rolling the head, reading, looking at the feet, fixating an external point. The results indicated that the oscillations appeared most when there was least accurate information as input to righting reflexes. The opposite order was apparent

TABLE II

OCCURRENCE OF FREQUENCIES OF OSCILLATION

	Feet together	*Feet apart*
1½–2½ *cycles/sec.*		
Tested first	49	22
Tested second	42	14
½–1 *cycle/sec.*		
Tested first	35	48
Tested second	28	42

21 subjects. Units explained in text.

with the slow oscillation of ½–1 cycle per second. It appeared to the greatest extent when there was the most opportunity for visual checking.

It seemed worthwhile to follow up the problem of the importance of peripheral vision. The question was asked: if we present centrally extra visual information about performance, can it compensate for a lack of peripheral vision? Ten highly practised subjects were presented with three different conditions. In all three, they had a monitor oscilloscope within range of their central vision. In the first condition, they saw two vertical lines on the screen. One of these was fixed centrally. The other moved to and fro and reproduced the movements of the platform, so that the subject could see his own performance. In the second condition only the fixed line was presented. In the third condition, the subject could only see the moving line. A fourth control test with no visible oscilloscope was also given. The conditions were presented in the light and the dark. The results are summarized in Table III.

For sway in the light, that is to say, when there is full peripheral and central vision, additional central information makes little difference. In the dark, without peripheral vision, all additional central information

makes some difference, but it was never sufficient to make the dark condition as good as the light condition. This appears to confirm that full peripheral vision is a necessity for best performance. It should be noted that in this experiment the stops were arranged to limit the permissible maximum of sway to $7\frac{1}{2}^{\circ}$ to either side.

The results on the fast oscillations follow those on sway almost exactly. The slow oscillation shows the opposite kind of effect. When peripheral and central vision are both present, there is usually some slow oscillation and it is slightly increased by giving a fixation line. When peripheral vision is not possible, the slow oscillations are only present to any extent if there is some central vision. Their complete absence in the dark in Table III is not always typical.

TABLE III

EFFECT OF EXTRA INFORMATION ON PERFORMANCE

	Control	*F.L.+M.L.*	*F.L. alone*	*M.L. alone*
Mean sway in degrees				
In light	6·75	6·25	6·13	6·50
In dark	15·00	8·88	9·34	10·25
Amount of 1½–2½ cycles/sec. oscillation				
In light	17	18	16	15
In dark	27	20	21	24
Amount of ½–1 cycle/sec. oscillation				
In light	13	16	17	14
In dark	0	12	12	13

F.L. = Fixation line; M.L. = Monitor line. 10 subjects. Units of oscillation explained in text. Maximum sway—15°.

The idea of giving the subject knowledge of results by means of a monitor oscilloscope can be extended to those types of experiment in which one tries to interfere artificially with the balancing mechanism. One of the best disruptors of balance is alcohol and some tests were conducted on its effects. These have been reported elsewhere (Begbie, 1966), and a brief summary will suffice. Subjects were given 31·5 g. of alcohol per 65 kg. of body weight, by mouth in the form of whisky. The dose was taken on an empty stomach at the beginning of the day, and the subjects were then tested for balance and blood alcohol at hourly intervals for the next six hours. The dose is a moderate one and is equivalent to a little more than two whiskies. The peak blood alcohol was never above 75 mg. per 100 ml. Each subject also carried out the regime on another day without alcohol, as a control. The hourly tests consisted of the following four conditions: eyes open, eyes shut, looking at the monitor in the light, looking at the monitor in the dark.

The previous results on peripheral vision were again confirmed. In addition it was shown that alcohol increases both sway and fast oscillation. This correlates well with the blood alcohol level, and decrements of performance were found with blood alcohols as low as 25–35 mg. per 100 ml. There are two conclusions about the slow oscillations. If we have peripheral vision, then there is an appreciable amount of slow oscillation, and alcohol makes very little difference. If we have no peripheral vision, then the amount of slow oscillation decreases, and again alcohol does not make much difference.

It will be noted that the effect of alcohol on sway and the fast oscillation is very like the effect of lack of peripheral vision. It is known that alcohol causes a certain decrease of peripheral vision. One might ask: could the effect of alcohol on balance be primarily due to its effect on peripheral vision? It seems unlikely, since the effect on the slow oscillation is not compatible with this theory.

Another drug which has been tried is hyoscine. It has sometimes been postulated that the efficiency of hyoscine in motion sickness might be due to a raising of the threshold of movement sensation. On this view, people ought to perform worse on the platform after hyoscine. So far, however, no effect at all has been found in half-hourly testing for four hours after the ingestion of 0·6 mg. of hyoscine hydrobromide.

None of the experiments so far described indicates unequivocally a role for the vestibule in balancing of this kind. Indeed there have been statements in the literature to the effect that it has no part to play. As a contribution to the discussion of this problem, I should like to offer the evidence of four patients with vestibular defects. One of these had been very severely affected by large doses of streptomycin given for a tuberculous infection. Although not appreciably deaf, she had great difficulty in walking, especially over rough ground. Her vision was "jumbled" when she rode in a car. She showed a greatly increased sway on the platform, and in fact lurched against the stops even with her eyes open. It might be argued that she was an extreme example in whom the difficulty of locomotion had induced a panic reaction to any balancing test. The other three patients had much less serious defects, and were in fact not at all incommoded in their ordinary life, although they all had abnormal caloric reactions. They showed fairly large amounts of sway but on the whole no larger than that produced by the worst of the normal people who had been tested. However, when they were tested with the monitor oscilloscope, a very interesting difference was obtained. None of the normal people had gained any advantage from the extra visual information provided by the monitor oscilloscope when

they were tested in the light. But the vestibular patients produced significantly (in the statistical sense) better scores in both sway and fast oscillation when they had the help of the monitor oscilloscope in the light. This suggests that their vestibular defect had had an effect on their method of balancing, and that this defect could be partly compensated for by extra visual information.

It is not possible to draw all these results into a neat and tidy theory. The one thing that is clear is the importance of vision, and attention has been drawn to the significance of peripheral vision. Even though, from the latencies involved, it is likely that any vestibular reflexes would come into action first, their adjusting action is comparatively coarse compared to that of the more accurate visual reflexes.

It has been tentatively suggested that the fast oscillation has been coming from the ankle joint. This may be an over-simplification. Movements at the ankle joints are not possible without a movement elsewhere to keep the centre of gravity over the base of support. In the transverse movements which we have been studying, ankle-joint movement will be accompanied by hip-joint movement, and the latter must be implicated in the fast oscillation. In this connexion, it is of interest to recall the finding of Goldscheider (1889) that proximal joints are more sensitive to movement than distal ones. It is, however, not possible to be dogmatic about whether the afferent contribution is coming from receptors in the ankle and hip joints or from muscles around these joints. A tiny, but perhaps misleading, clue is that when the stretch reflexes are enhanced, as in ankle clonus in man, they do produce a frequency of around 2–3 cycles per second.

It is, however, possible to think of the fast oscillation as operating, not in a directly corrective manner, but in a rather different way. Whatever the mechanism of balance may be, it involves sense organs with quite definite thresholds of excitation. An engineer might suggest that the way to get round the consequent occurrence of effects like "backlash" would be to bracket the dead zone by introducing an oscillation. The fast oscillation might then be equivalent to the engineer's "dither". This would also explain why it tends to increase when sensory information is scanty.

The slow oscillation is a more irregular affair. As we have seen, its frequency corresponds to that of an eye–skeletal muscle co-ordination system. But since it can occur in the dark, it would be necessary to postulate that the afferent information could be gained from other than visual channels. Walsh (1962) has given a reaction time for otolith–hand co-ordination, namely $\frac{1}{4}$–$\frac{1}{2}$ second. It would therefore be tempting to think

of the slow oscillations as being due to corrections based on consciously appreciated vestibular information. But these are very speculative matters on which I should be glad to have advice and suggestions.

SUMMARY

A platform of controllable instability has been used to study postural sway under a number of different conditions, which included differing amounts of visual information, different positions of the head and the consumption of alcohol. Two particular frequencies of oscillation are characteristic of the records, and the possible origin of these is discussed.

Acknowledgements

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DISCUSSION

ROLE OF THE VESTIBULAR SYSTEM IN THE CONTROL OF POSTURE AND MOVEMENT IN MAN

Purdon Martin: It has been observed by Magnus ([1924]. *Körperstellung.* Berlin: Springer) and others that as one ascends the animal scale the vestibular mechanism seems gradually to become of less importance. It gives rise to two kinds of reflexes, ocular and somatic; in man the former have been very much studied but not much attention has been paid to the latter, with which I am now concerned.

It will be convenient first to classify very briefly the postural reflexes that are concerned in the upright posture and locomotion in the normal individual.

In the first place we must be able to support the weight of our bodies against gravity: we are provided with what Sherrington called an "anti-gravity mechanism".

Secondly, each part of the body must be supported for postural purposes on the adjoining (usually lower) parts—as, for instance, the postural fixation of the head on the trunk. Also, if any part of a dummy figure, such as the head or trunk, is bent forward or otherwise comes out of perpendicular, its weight creates a "moment" which tends to make the figure fall down, rotating about its feet as a centre. The human subject, however, does not fall down, so that the weights and the postures of the various parts are co-ordinated in such a way that equilibrium is maintained—that is to say, there is a postural fixation of the body as a whole.

Thirdly, against a horizontal force, the body may simply be braced, but if the force is great enough to displace it from its base, "staggering" reactions come into play which enable it to get a support under its centre of gravity, and the upright posture is protected.

Fourthly, the creature must be able to regain the upright posture—there are "righting" reactions. In man these are brought into action voluntarily but they obviously involve many of the preceding reactions.

Fifthly, there are special postural reflexes involved in our peculiar mode of locomotion. In the first place the centre of gravity must alternate from over the right foot to over the left foot and back again; secondly, as the left leg swings it is counterpoised by a tilt of the upper part of the body to the right and *vice versa*, and thirdly, the centre of gravity must be delicately controlled in the antero-posterior direction in such a way that when we have been enabled to take a step forward it is checked when that movement is finished, so that we do not fall over (Martin, J. P., and Hurwitz, L. J. [1962]. *Brain*, **85**, 261–276).

In all these reflexes there has been the assumption that the subject is on a stable base, but (sixthly) there is another group of reflexes that enable him to retain the upright posture when the base is unstable. If a normal individual is tilted in a sitting or standing position he maintains the upright posture and makes certain other adjustments.

We may therefore tabulate these groups of reflexes as follows:

1. The anti-gravity mechanism.
2. Mechanism of postural fixation.
3. Staggering and other reactions to horizontal forces.
4. Righting reactions.
5. Reflexes concerned in locomotion.
6. Tilting reflexes or reactions to instability of the base.

I have examined eleven patients who were devoid of vestibular function with regard to their disabilities under each of these headings. One patient had had both her eighth nerves divided and so provided a criterion of complete vestibular

loss, but the reactions of all the other patients were the same and so I am satisfied that they had no vestibular function.

I may say at once that in everyday life these patients showed surprisingly little disability that was attributable to their vestibular defect. A number of them were, of course, deaf and had the disabilities attributable to that cause. Some had suffered from meningitis or had been treated with streptomycin and so might have some disability additional to that due to the vestibular loss. Finally, I am not concerned here with the ocular disturbance that most of these patients have in the early years, as a result of which the eyes do not adapt themselves to the vertical movement of the head during walking and the patient consequently has to stop in order to see objects at a distance clearly.

With these provisos, most of the patients live normal lives. Several of them drive motor cars; one has until recently ridden a motor cycle. The woman whose eighth nerves had been divided many years previously brought with her a neighbour beside whom she had lived for ten years, and the neighbour did not know that she was unsteady. Provided that he has full use of vision the patient without vestibular function can do almost everything except, perhaps, walk along a line.

However, it should be said that these conditions prevail among city-dwellers who walk on smooth pavements and after dark in well-lighted streets. In darkness or in a fog, if the surface is at all uneven, they are unsteady and when coming down stairs, with no visual point of reference immediately in front of them, they may feel uncertain. One patient said that he would not trust himself to walk on a plank across a stream.

Since vision can to a great extent compensate for the lack of vestibular function, the effects of vestibular deprivation are better demonstrated if the patient is blindfolded. It should be noticed that the patient is then depending for purposes of posture and movement on proprioception alone.

Under these circumstances:

1. The patient shows no disturbance of his anti-gravity mechanism.

2. He supports his head and trunk normally and he maintains his equilibrium; that is, he co-ordinates the weights and postures of the individual parts of his body normally. He can stand steadily with his feet together. That the vestibular mechanism plays some small part in the posture of the head is shown by the fact that if the labyrinth is destroyed on one side the head is held for a time slightly rotated towards the side of the lesion.

3. He staggers normally when pushed and otherwise reacts normally to horizontal forces.

4. He is able to rise normally from the lying or sitting position and to turn over quite easily from the supine to the prone position and *vice versa.*

5. He can walk on a firm smooth surface, that is to say, he makes the normal movements of walking and the various reflexes peculiar to walking appear to be normal. If he closes his eyes while walking on a smooth pavement he continues

to walk steadily, but if he is blindfolded and then started off he is uncertain and apt to widen his base or falter in his progress and make little "dancing" movements. In any case he is very sensitive to unevenness of the surface, so that a relatively slight irregularity causes him to stagger. He cannot make any reasonable attempt to walk in a line putting the heel of one foot against the toe of the other. When walking up a slope he falters after a couple of steps and then bends forwards to regain his propulsive momentum; descending the slope he is somewhat more liable than the normal blindfolded individual to increase his pace and is more unsteady. (This should perhaps be related to his disabilities under the next heading.) He is quite incapable of walking over very rough ground. As a rule he negotiates the same ground quite easily with his eyes open but some patients state that walking over rough ground is difficult at all times.

Even on a soft surface the patient without vestibular function again performs very well with his eyes open (for example, if he stands or walks on springs—"jumping jacks"—or on a mattress laid on the floor). However, when he closes his eyes he is at once very unsteady and falls over in any direction. If he is walking (blindfolded) on a firm surface and then steps on to the mattress he comes to a halt after one double step and would fall over. This may be attributed either to diminution of the proprioceptive information from his feet and lower limbs (on which he is entirely dependent) or to the instability of the base (see below). One patient said he felt quite disorientated, so the former is perhaps the major factor. He may perform well if he walks holding the examiner's hand.

6. It is under conditions of instability that the patient without vestibular function shows his real disability. I have in mind here, primarily, tilting or wobbling of the base, but immersion or floating in water is a particular case of instability in which the patient is at a great disadvantage.

All the patients without vestibular function are very vulnerable on the tilting apparatus, especially when they are blindfolded. They are overthrown at an angle of tilt and at speeds of tilting with which the normal subject (blindfolded) has no difficulty in coping. In the sitting positions they fail to maintain the upright posture and in the "all fours" positions they fail to react against the tilt and slide down with it. With their eyes open they perform better, particularly if the tilting is slow and the patient is sitting, and under such conditions their reactions may be quite good, but in the "all fours" positions, when there is less content in the visual field, having their eyes open makes less difference.

It is clear that in general the effective postural reflexes excited by tilting depend on the vestibular mechanism, and if the vestibular reflexes are lost there are no others that can compensate for them in any adequate fashion (Martin, J. P. [1965]. *Brain*, **88**, 855–874).

Suppression of vestibular reflexes

On the tilting apparatus large reflexes involving the whole body are apparently excited by stimulation of the vestibular mechanism, but if, instead, the subject is

standing or sitting on a firm base, natural stimulation of the vestibular mechanism by movement of the head excites no bodily movements whatever.

It appears therefore that the tilting reflexes are produced only when the body is unstable and that there is some factor in addition to the excitation of the vestibular mechanism that is responsible for their occurrence (Martin, J. P. [1965]. *Brain*, **88**, 855–874).

The postural reflexes that are active when an individual is standing or sitting on a firm base and blindfolded are excited by somatic proprioception, and so, under conditions of stability, proprioception is dominant and the vestibular reactions are suppressed; under conditions of instability the vestibular influence predominates and proprioceptive reactions are relatively in abeyance.

Conclusions

From this evidence we may deduce that in the human subject:

1. The vestibular mechanism plays no essential part in static posture or in the righting reactions.

2. In walking it comes into action when the surface is uneven and is in reserve when vision cannot be used.

3. The only condition so far recognized in which the subject is greatly dependent on his vestibular mechanism is when his supporting base is unstable (including when he is in water).

EXPERIMENTAL STUDY OF THE CONTROL OF POSTURE IN MAN

Henriksson: Dr. Begbie, may I briefly mention another method for studying postural mechanisms which I shall come back to in my paper (p. 233). The patient puts one foot on each of two scales and we record the difference in pressure from the right and left feet and also integrate those variations. We have found that there is a tendency in normal subjects to put more weight on one foot than on the other; some put more weight on the right and some more on the left foot. This was one of the difficulties we encountered when trying to correlate the deviation in the Romberg test with vestibular disorders.

Begbie: F. A. Hellebrandt in the 1930's mentioned that an individual's centre of gravity tends to be over to one side or the other (Hellebrandt, F. A., Topper, R. H., Braun, G. L., and Elliott, M. C. [1938]. *Am. J. Physiol.*, **121**, 465–470). She related it to right-handedness and left-handedness. There would be more muscle weight on the side of the body normally used. The centre of gravity of a right-handed person would therefore be more to the right, and he would tilt to the left in order to compensate. I have looked through my records but could find no difference between left-hand and right-hand sways.

Henriksson: We also found no correlation with right or left-handedness.

Lundquist: Dr. Begbie, if you increase the mass of the swaying table and therefore damp it, do you still get very regular frequencies? If normal subjects have a tendency to put more weight on one side than the other, when a person is

standing on the table he will at first relax and put his weight over to one side and then the compensating mechanisms will make him change over to the other foot. Perhaps this will vary in frequency if you damp the table?

Begbie: I have not increased the mass of the apparatus, which I could do, but I have altered the positions of the struts and the width of the top platform, which alters some of the physical properties, including what one might call the "damping" of the platform, quite considerably. However, this makes no difference to the regularity of the frequencies. The tendency for normal subjects to place more weight on one side or the other can be exaggerated. In 1953 J. W. Smith took photographs of people standing which showed that they never stand in one position for longer than a minute anyway, so I would not place too much importance on this point (Smith, J. W. [1953]. *Acta orthop. scand.*, **23**, 159–168).

Groen: What is the strict relationship between your experiments and the Romberg test, Dr. Begbie?

Begbie: The strict relationship would be difficult to define. My experiments started as an attempt to make the Romberg test a little more difficult. Normally, the only feedback which we have from the ground is the constant pressure on the soles of our feet. This test introduces a more dynamic feedback. When engineers investigate control systems, like those involved in standing, they often use the technique of opening a feedback loop in order to study the simpler system that results. The present test does the opposite. It closes a loop that was not there before—if one may use such a phrase. The experiments have some relation to the Romberg test since the results on shutting the eyes and on the effects of sex, age, weight and height all correlate reasonably well with the established literature on the Romberg test. But I would, of course, readily admit that my test is not the same as the Romberg test.

Eldred: Ito has recently reported that righting reflexes arise from receptors in the mesenteries and viscera of the monkey, so we should not necessarily ascribe reflexes to the muscle and joint proprioceptors (Ito, T., and Sanada, Y. [1965]. *Jap. J. Physiol.*, **15**, 235–242).

Lowenstein: This is why I prefer to avoid the term "proprioceptor". This term is beset with difficulties and we should avoid using it in an explanatory sense, although it is a convenient portmanteau description of what we mean. The visceral receptors are extremely interesting and should not be overlooked. The degree of filling of the viscera might make a difference to posture, for example.

Eldred: I wonder if stance in man is helped at all by the auditory system, especially in the individual suffering from a long-standing vestibular deficit? Sensitive detection of sounds and sound shadows should furnish very helpful cues.

Purdon Martin: Magnus, of course, said that all postural reflexes were dependent on proprioception or on the vestibular mechanism or on vision or contact. This is usually satisfactory for practical purposes, but there are postural reflexes which depend on other afferent systems. André-Thomas, for instance, showed

postural reflex reactions in the very young baby that depended on sound (André-Thomas and Autgaerden, S. [1963]. *La locomotion de la vie foetale à la vie post-natale.* Paris: Masson).

Lowenstein: In many animals, especially insects, even olfactory stimuli can be potent factors in posture. So nothing is impossible in this field, especially in a person who has suffered from a deficiency for a long time. Have you tested subjects immediately after they have lost their vestibular sense?

Purdon Martin: Nearly all the patients I mentioned have been without their vestibular sense for a long time but in one or two the loss was recent, and there is no significant difference except in the ocular reactions. In an animal the vestibular mechanism plays a part in the position of the head, but in man by my method we have no evidence of the vestibular mechanism playing any major part in the position of the head, except that if one labyrinth is destroyed the head rotates towards the side of the lesion, but for a few weeks only.

Groen: Jongkees and I studied people who had lost their vestibular function, and we found that they differ from normal people in several respects other than those mentioned by Dr. Purdon Martin (Jongkees, L. B. W., and Groen, J. J. [1942]. *Ned. Tijdschr. Geneesk.*, **86**, 1876–1879). We used a waggonette which could be accelerated and we measured the amount of linear acceleration that the subject could cope with before falling over. The best of our patients who had completely lost vestibular control achieved up to 70 per cent of the control of normal subjects. We also investigated gait. If one records a normal person's walk, for instance by measuring the vertical acceleration, one finds a strict time-pattern; the deviation is not more than 3 per cent. But a subject who has lost his labyrinthine function shows deviations from the strict time-pattern of the order of 10–20 per cent (Jongkees, L. B. W., and Groen, J. J. [1942]. *Ned. Tijdschr. Geneesk.*, **86**, 2898–2902). These tests were made with the eyes closed and on a smooth surface. This therefore corroborates our impression that such people do not have such a strict gait as normal subjects.

Henriksson: We have been using a similar approach with patients without vestibular function in traffic tests. We used a traffic simulator, a rotating device that could be controlled by the "driver". My hypothesis was that subjects with no vestibular function would be poor drivers. We tested them on this device, comparing them with a control group, and found that most of these subjects with no or impaired vestibular function controlled their "car" very well. The complexity of these problems can also be illustrated by the fact that some of these patients say when they come to us: "I was so dizzy that I had to drive the car the whole way up to the hospital, otherwise I couldn't possibly have managed"!

Purdon Martin: I found this too. One patient until recently had ridden a motor cycle, and an elderly man, who reacted well visually to tilting, still drives although he is now over seventy. Of course patients who lose their vestibular function have a disturbance of their ocular control and some give up driving a car because of this.

Gardner: Do any of your patients play golf?

Purdon Martin: I have said that these patients are very sensitive to unevenness of the surface. One particular patient whom I asked what he was unable to do with his eyes open replied that it was difficult to think of anything, but that he had fallen down on the golf links twice. These patients seem to be much influenced by the peripheral visual field, and when my patient was concentrating on the golf ball and paying less attention to his peripheral field, apparently he sometimes fell down.

Begbie: Although the vestibular patients whom I tested on my apparatus swayed quite a lot, it was not more than in the worst of the normal subjects. It was interesting that when I added the monitor oscilloscope, so that they had extra information about their performance, they improved in the light, whereas it makes no difference in normal people. This suggests that there is some defect that can be improved by extra visual information.

Monnier: The sway described by Dr. Begbie must have something to do with a very basic process, connected with the state of wakefulness of the subject. Have you any information on this state? I am thinking of the importance of the pendulum movement of the gaze in the paradoxical phase of sleep, in which body sleep is very deep and brain sleep is very superficial.

Begbie: All these tests of course lasted for one minute only. I am afraid I have no information on states of wakefulness, but this is clearly a possibility.

Lowenstein: What was the frequency of this phenomenon, Professor Monnier?

Monnier: It was about 78 per minute in paradoxical sleep, that is, close to the upper limit of Dr. Begbie's slow component, which was 60 per minute.

Henriksson: The importance of studying voluntary eye movements should be stressed. When we make vestibular examinations we could well include a recording of voluntary eye movements. We have found that such tracking tests can be very informative.

Brodal: From what has been said here, it would appear that the vestibular apparatus is not very important for maintaining the upright posture in man. In the cat (Walberg, F., Bowsher, D., and Brodal, A. [1958]. *J. comp. Neurol.*, **110**, 391–419) it is striking that the primary vestibular afferents terminate only in that region of the lateral vestibular nucleus (of Deiters) which gives off descending vestibulo-spinal fibres to the cervical cord and thus supplies the neck and the fore-limb. We do not know yet whether the same restriction of primary vestibular fibres is found in man, but if so, this might fit in with the observation that man can stand and walk quite well even without receiving vestibular impulses. We are at present preparing a map of the human vestibular nuclei, and it appears that the lateral vestibular nucleus, which gives off all the vestibulo-spinal fibres, is rather modest in size.

Roberts: There seems to be a possible confusion between labyrinthine positional reflexes and those from the limbs, which one might think of as supporting reactions. I have the impression that these are acting in opposite senses. It seems

to me that the labyrinthine reflexes are aimed at keeping the head steady in space, so that when the platform moves, the feet move away with the platform and the body is left in the same place. This would eventually cause the subject to fall over, because the withdrawal of the platform deprives the body of its support on that side. The movement of toppling over then leads to propping reactions which restore the balance. Rademaker's dogs from which the labyrinths had been removed were evidently quite good at keeping their upright posture, and in fact they were better than normal animals at walking across a rotating turntable. They differ from Dr. Purdon Martin's labyrinthless and blindfolded people in that, on the tilting table, they managed to get into a more or less upright position, although not quite so well as a normal dog. As a result of the tilting, the weight tends to slide downhill, and an increased propping reaction develops in the "downhill" legs which brings the weight more or less back up to where it was before. One tends to confuse these secondary reflexes with the labyrinthine reflexes. This fits in with Professor Groen's observation that when a labyrinthless person stands on a trolley and the trolley is moved, he does not do too badly.

Groen: He is maximally only 70 per cent as efficient as the normal subject.

Roberts: The fact that he is able to do anything at all on a moving trolley shows that he must be using the propping reaction. If the reflex support in these conditions depended on the labyrinth, he would fall over.

Philipszoon: Dr. Purdon Martin has said that there are only a few differences between people with and without labyrinthine reflexes. One situation in which there is a very marked difference is in water. One must warn people without labyrinthine reflexes not to swim. We always examine the function of the labyrinth in patients who have been given streptomycin therapy (for meningitis) because patients without these reflexes drown. When one is swimming one does not see what is going on above or below and one cannot make use of proprioception; labyrinthine reflexes are relied on entirely.

Bosher: Dr. J. A. V. Bates and his colleagues at the National Hospital have investigated the reactions of people when support is removed from the limbs on one side, as when they rest on all fours and the support of the right arm and right leg is removed. This is a very severe tilt and the body tends to drop to that side. The interesting finding from their preliminary observations, which are to be published shortly, is that although the majority of people make the correct compensatory actions, deviating their bodies against the direction of the tilt much as Dr. Purdon Martin showed with the tilting table, there are a number of people who appear to be normal yet do the opposite to what one would expect and lean towards the direction of the tilt, as it were hurling themselves to destruction on the floor. Dr. Begbie, have you come across anything in your studies comparable to this situation?

Begbie: No, except sometimes with subjects under the influence of alcohol. Some people then simply sway to one side and remain leaning against the side

of the apparatus. J. H. Sheldon ([1963]. *Geront. clin.*, **5**, 129–138) draws attention to the fact that when old people fall they often express their feelings in terms like: "Once you're going, you've got to go". He ascribes this to an increased reaction-time which one may also have with alcohol. The mechanical properties of the tilting platform would probably enhance any effect from such a cause.

Bosher: After drinking alcohol, then, some of the subjects' reactions would, in fact, appear to be inappropriate although the majority do tend to make the correct compensatory movements.

VESTIBULAR CONTROL OF MUSCLE REFLEXES

Eldred: I am having difficulty in seeing the bridge between muscle spindles, which we have already discussed, and vestibular function. Has anyone information about the stepping-stones in between, such as H-reflexes, tendon jerks, or electromyograms from slow and fast muscle? There would be good opportunity to gather such data, I would think, from patients with unilateral vestibular deficits, where one side could be used as a control for the other.

Roberts: We have done some experimental work which links the labyrinth with the stretch reflex. We have been measuring the sensitivity of the stretch reflex either by tension–length diagrams or by firing-frequency–tension diagrams, at the same time tilting the head after denervating the neck, in order to get undiluted labyrinthine reflexes; and it is possible to show a well-coordinated stabilizing system of reflexes coming from the labyrinth to the limbs which differs quite dramatically from Magnus's scheme. Magnus's reflexes were reported to have the same effect on all four limbs, in marked contrast, as he repeatedly emphasized, to the neck reflexes, which produce different effects on forelimbs and hindlimbs or different effects on the limbs of the two sides, according to which way one tilts the animal. I found that tilting the head with the neck denervated produces the appropriate changes in the four limbs for stabilizing the head; that is to say, when the head is tilted back, stretch-reflex activity in the extensors of the hindlimbs is increased and stretch-reflex activity in the forelimbs decreases; tilting the head to the left gives increased stretch-reflex activity in the extensors of the left side and decreased activity on the right. So the labyrinth produces stabilizing reflexes.

Fig. 1 is based on a series of photographs of animals in various positions, illustrating all these effects. Consider the situation with the head in the normal position and the neck straight; there is an equal distribution of forces and supporting reactions in all four limbs. If the head is tilted back and the neck kept straight, extensor activity increases in the hindlimbs and flexion takes place in the forelimbs, as in a horse rearing or a dog about to jump over an obstacle. (The conclusion that this is a labyrinthine effect is supported by electrophysiological experiments in which the body was horizontal but the neck was denervated.) If the head is tilted forward there is forelimb extension and hindlimb flexion. If the neck is bent back but the head is in the normal position there is forelimb extension

and hindlimb flexion, as when a cat comes down stairs or when a horse lands after jumping over an obstacle. With the neck bent forward but the head in the normal position there is forelimb flexion and hindlimb extension, such as is

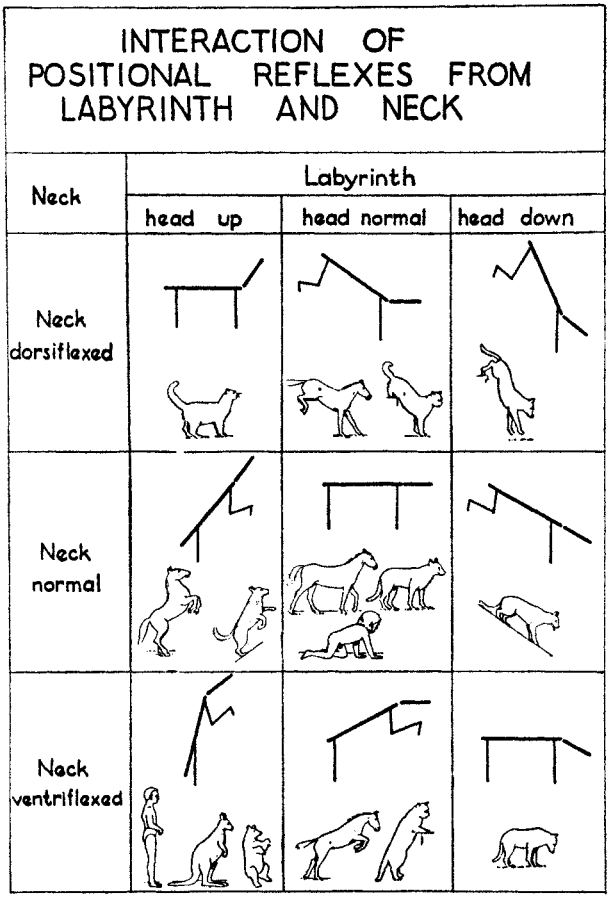

FIG. 1 (Roberts). Scheme, combining photographic and electrophysiological evidence, to show the positional reflexes from the labyrinth upon the limbs and the way these reflexes interact with the reflexes from the intervertebral joints of the neck. (From Roberts, T. D. M. [1967]. *Neurophysiology of Postural Mechanisms.* London: Butterworth.)

seen in a horse taking off to jump over an obstacle or a cat going upstairs. It is interesting to note that a horse jumping over an obstacle does not move its head much, whereas the dog does; it looks up to go over and down as it comes down.

When the head is tilted back, which should produce hindlimb extension, and the neck is also back, which should produce forelimb extension, the two reflexes oppose one another and there is an equal distribution of forces in all four limbs. When the reflexes co-operate, for example when the head is down, which should give forelimb extension, and the neck is back, which should also produce forelimb extension, there is extreme forelimb extension and extreme hindlimb flexion, as when an animal leaps down from a height. When the reflexes co-operate in the opposite direction, they give forelimb flexion and hindlimb extension, which is the normal position for a man or for the kangaroo, or for an animal sitting up. When a man puts his head into the true normal position he must tip his head forward. If he also straightens his neck by bringing his body round (otherwise the neck would be bent further) he reaches a position with an equal distribution of forces in all four limbs like any quadruped.

Wersäll: Could you complete the picture by pushing the head to the right or the left? If the head is pushed to the side in a guinea pig without a labyrinth the animal starts rotating.

Roberts: If the head of an animal is turned towards the left shoulder by a movement in the horizontal plane, there is extension of the left limbs and flexion of the right limbs as though to prepare the body to start turning to the left. (Presumably, if you push hard enough the flexed right limbs will show stepping reflexes.) With torsion about the longitudinal axis, the effect on the body is such as to relieve the torsion on the neck; for example, if the fore-quarters are held stationary and the head is rotated in one direction, the hind-quarters will rotate in the opposite direction, whereas if you hold the hind-quarters, the fore-quarters will rotate into an intermediate position. There is reflex movement by the body to relieve the torsion on the neck and the relative movements are in the same sense at each of the intervertebral joints all down the vertebral column. If the head moves in relation to gravity the labyrinth produces extensor movements which tend to push the head back into the normal position. When there is no labyrinth one just gets the neck reflexes.

Purdon Martin: None of these reflexes resulting from rotation of the head is present in the normal human subject, or perhaps it would be better to say that the conditions under which they occur in the normal subject have not yet been discovered. They are found under certain conditions of disease which may bring them out. In the chronic hemiplegic, for instance, there may be movement of the limbs such as you have described.

Roberts: The normal maintenance of the upright position must depend on reflexes of this kind. I suspect that they are difficult to bring out in the adult but I think they are visible in the child.

Purdon Martin: If they were tested under conditions of instability they might come out, but so far the conditions under which they occur have not been discovered.

Monnier: Some of these head reflexes are demonstrable in man; for instance

the phenomenon of Magnus and de Kleijn can be demonstrated in the newborn (extension of the arm on the side of the face, when the head is turned passively).

Roberts: It would be interesting to put a person into water and see whether turning his head would make him move his limbs to straighten out the neck. I believe that it would. This would correspond exactly to the rotational reflexes you find in the frog, where the movements of the limbs against the water tend to bring the body into a position which relieves the torsion on the neck.

Myotatic, Kinesthetic and Vestibular Mechanisms
Edited by A.V. S. de Reuck and Julie Knight

SECTION II
VESTIBULAR MECHANISMS: FINE STRUCTURE

ULTRASTRUCTURE OF THE VESTIBULAR END ORGANS

J. WERSÄLL, L. GLEISNER and P.-G. LUNDQUIST

Department of Otolaryngology, Karolinska Sjukhuset, and King Gustaf V Research Institute, Stockholm, Sweden

THE sensory cells in the vestibular sense organs and the lateral line canal organs are secondary receptor cells. They function as transducers characterized by a high degree of directional sensitivity, high sensitivity to mechanical stimulation, slow adaptation and wide dynamic range. Considering these characteristics, it seems likely that the structural composition of the cells and their nerve terminals would reflect the special physiological requirements in one way or another. The present paper attempts to summarize our knowledge of the fine structural organization of these sensory receptors and to serve as a background for the discussion of possible transducer mechanisms.

In mammals two distinct types of sensory cells are found (Wersäll, 1956) (Figs. 1 and 2). The type I sensory cell is a flask-shaped cell with a round bottom and a flat upper surface facing the endolymphatic space. The major part of the cell surface is enclosed by a nerve chalice. This chalice is formed by a terminal branch of a dendritic axon from one of the bipolar vestibular ganglion cells. The type II cells are cylindrical in shape and are innervated by small nerve terminals located at the base of the cell.

Each sensory cell is provided with a sensory hair bundle protruding from the cuticular plate on the cell surface. The hair bundle is asymmetrical in shape. It contains one kinocilium-like sensory hair, protruding from one of the centrioles located in a less dense area on one side of the cuticular plate. The centriole is composed of nine triplet tubules arranged in a ring perpendicular to the cell surface (Wersäll, Flock and Lundquist, 1965; Flock and Duvall, 1965; Wersäll and Lundquist, 1966) (Figs. 3 and 4). In cross-sections through the centriole a number of spokes are found to surround the triplet tubules, forming a shovel-wheel-like formation around the centriole close to the plasma membrane of the cell (Fig. 4). On

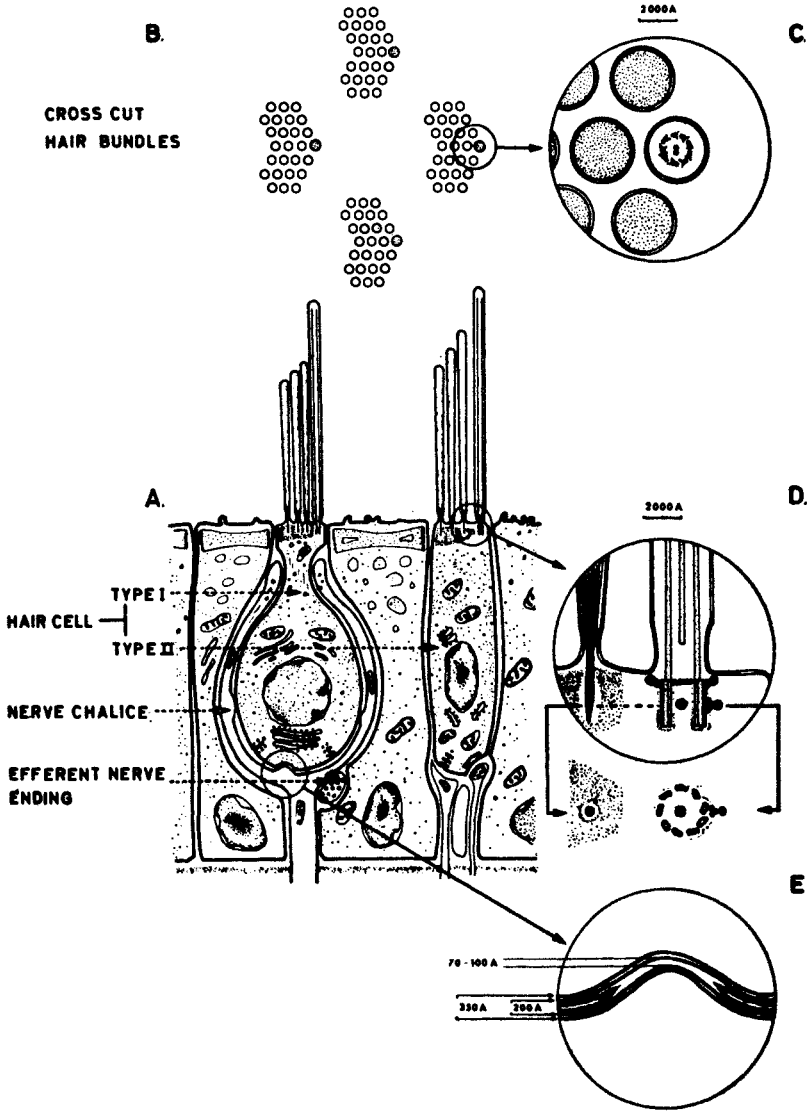

FIG. 1. Schematic drawing of the two types of hair cells in the vestibular epithelia of mammals and birds (A).

The asymmetric organization of the hair bundle, with one kinocilium located in the periphery of the hair bundle, is illustrated (B, C). The kinocilium protrudes from a centriole in the hair cell lying close to the cell surface in a less dense area in the periphery of the cuticle. The axial core of the sensory hairs proper is finely fibrillated and protrudes into the cuticle, which it penetrates in the form of a rootlet (D). The synaptic complex in relation to afferent and efferent nerve endings is illustrated (A), as is the close apposition of the plasma membrane of the hair cell and nerve chalice in certain regions (E).

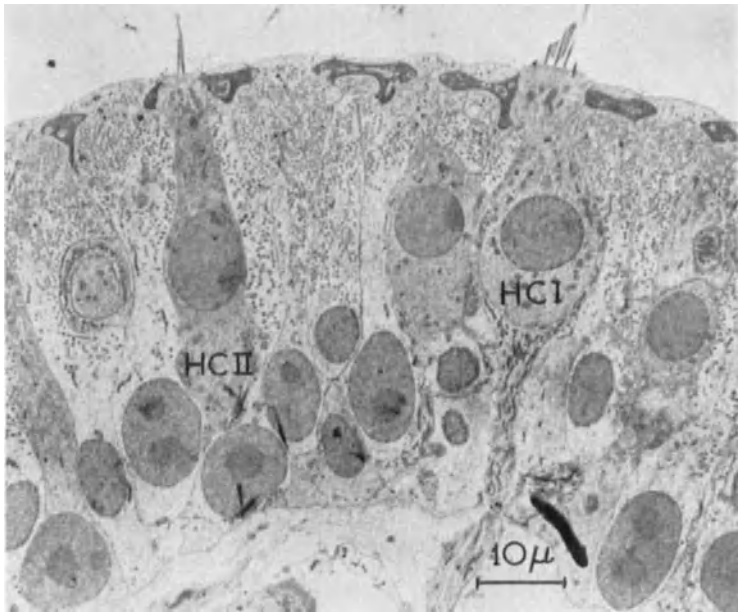

FIG. 2. Survey picture of a section through the sensory epithelium in the crista ampullaris in the guinea pig.
HC I: Hair cell type I, surrounded by its nerve chalice. HC II: Hair cell type II, provided with small nerve endings at the bottom of the cell. × 1,160.

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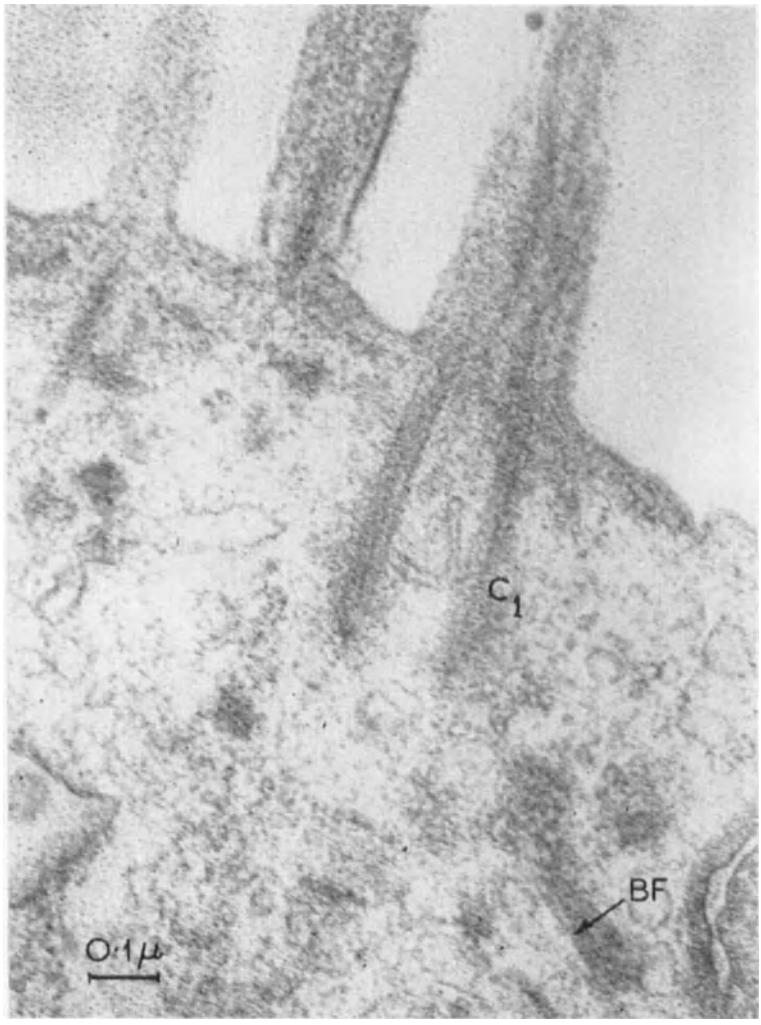

FIG. 3. Higher magnification of longitudinally cut centriole (C_1) of the crista of the guinea pig, illustrating the multibarrelled structure of the centriole, forming the kinocilium and the basal foot (BF) which is orientated in the direction of stimulation of the hair cell. × 144,000.

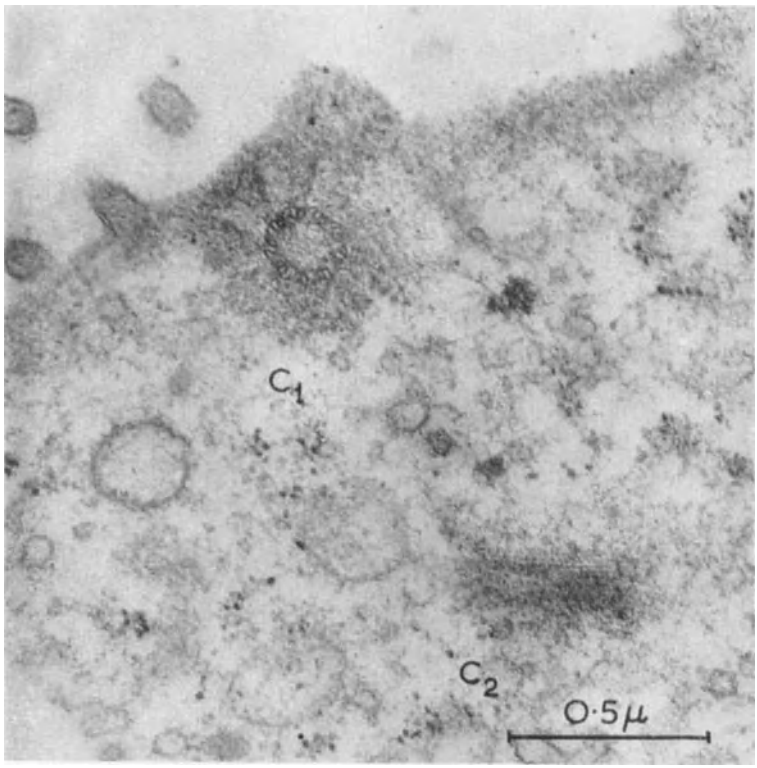

FIG. 4. Cross-section through the distal part of a hair cell of the crista of the guinea pig, showing the triple tubules of the centriole, C_1, forming the kinocilium. Spokes radiate from the centriole in a shovel-wheel fashion. The second centriole of the cell, C_2, is often located at some distance from C_1 and orientated in a different way. × 48,000.

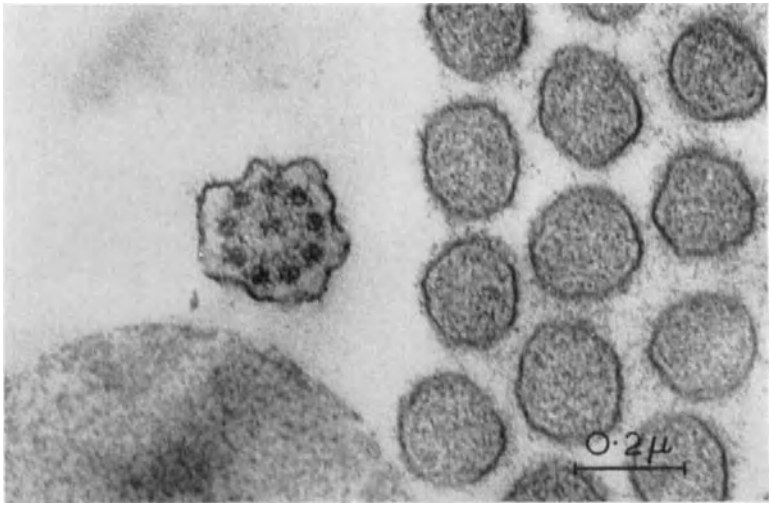

FIG. 5. The micrograph illustrates a portion of a cross-section through a hair bundle from the crista of the guinea pig. The ring of nine double tubular filaments surrounding a pair of filaments in the centre of the kinocilium is seen. The regular arrangement of the stereocilia is evident as well as thin strands of a substance of low density, connecting the stereocilia. × 72,000.

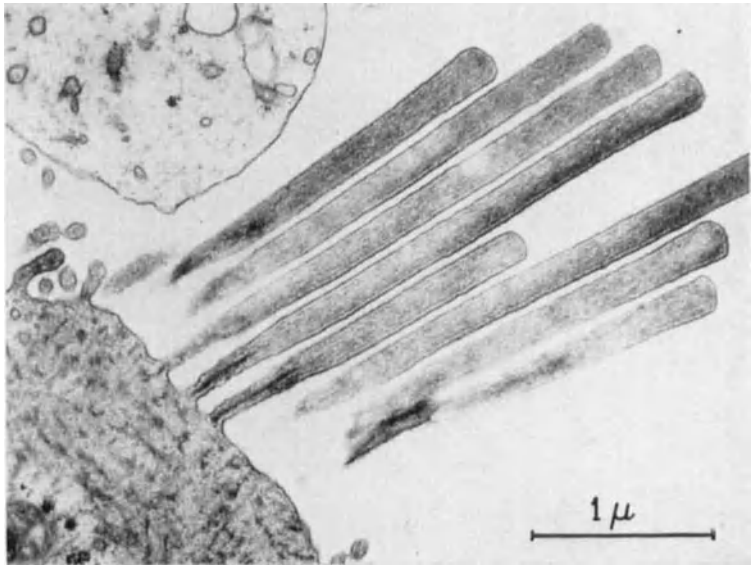

FIG. 6. A few short sensory hairs are shown, cut from the base to the top of the hairs. Note the filamentous structure of the axial core of each hair and the condensation of the fibrils to a fibre in the basal part of the hair. This fibre forms the rootlet further down in the cuticle. (Crista of guinea pig.) × 24,000.

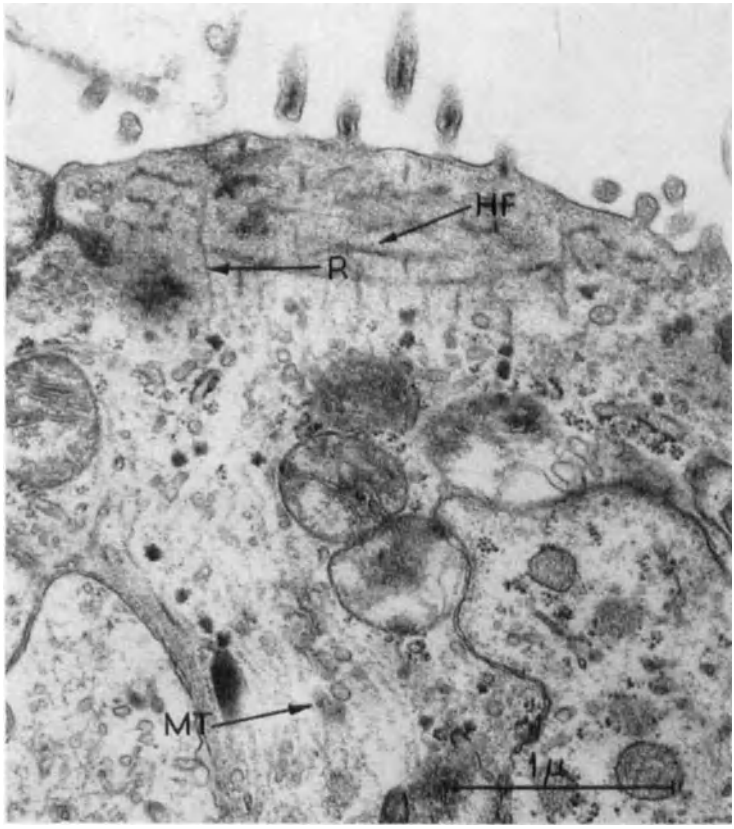

FIG. 7. The apical part of a hair cell of type I from the guinea pig crista is shown, with horizontal fibres in the cuticle (HF) and the hair rootlets (R) in continuity with microtubules (MT) filling up the neck of the cell. × 29,920.

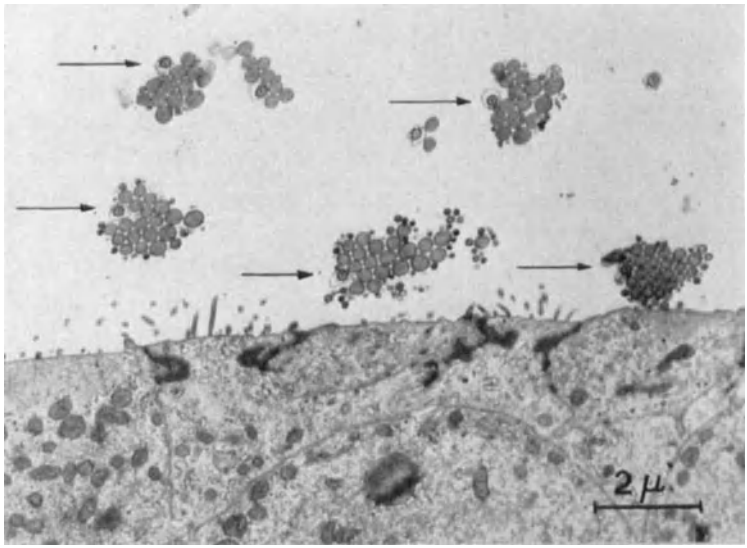

FIG. 8. The arrows indicate the kinocilium in the hair bundles of sensory cells on the crista ampullares horizontalis in the frog. All bundles are orientated with their kinocilium towards the utricle. × 6,800.

one side of the centriole, facing away from the rest of the hair bundle, is found a basal foot (Lowenstein, Osborne and Wersäll, 1964; Flock, 1964) (Fig. 3). From each one of the triplet tubules protrudes a double tubular filament which passes through the surface, forming the axial core of the kinocilium proper (Fig. 5). The plasma membrane covering the fibre bundle of the kinocilium is continuous with that of the rest of the cell surface.

The sensory hairs proper are arranged in parallel lines in the bundle. Each hair is composed of a fibrillar axial core surrounded by a plasma membrane sheath (Fig. 6). The hair row closest to the kinocilium contains the longest hairs and the length of the hairs decreases successively with increasing distance from the kinocilium. The axial core of each sensory hair forms a rootlet which can be followed through the cuticle down into the subcuticular area (Fig. 7). From there, microtubules go down through the supranuclear part of the cell towards the region of the nucleus. In the type I cells these microtubules are fairly densely packed in the thin neck of the cell, but diverge from each other closer to the nucleus. It seems likely that the microtubules are of importance for the transducing mechanism, as was also recently suggested by Jande (1966) for the equivalent structures in the receptor cells in the lateral line organ of frog tadpoles. An even more complicated structure connects the base of the hairs with the synaptic region in the hair cells of the labyrinth of the ammocoete larva, studied by Lowenstein and Osborne (1964).

The area immediately below the cuticle contains a large number of mitochondria. In both type I and type II cells a Golgi apparatus is found in the supranuclear part of the cells and a varying amount of ergastoplasmic membranes. These membranes are often well organized in type I cells, forming a number of parallel flat thin spaces in the cytoplasm surrounded by membranes covered with ribosomes.

Each sensory area in the labyrinth has a characteristic organization with regard to the orientation of the hair bundles, as originally demonstrated by Lowenstein and Wersäll (1959) in the labyrinth of the thornback ray (*Raja clavata*). Thus the kinocilium is regularly found on the utricular side of the hair bundle in the crista of the horizontal canal and on the opposite side in the crista of the vertical canals (Figs. 1 and 8). In the utricle the hair bundles are organized in a characteristic fan-shaped fashion, with a peripheral part where the orientation is rotated through 180° so that the bundles in that area face the rest of the hair bundles (Flock, 1964). In the saccule the hair bundles face away from a slightly bent line along the long axis of the saccular macula close to the middle of the macula, equivalent to the striole

of the macula (Spoendlin, 1965) (Fig. 9). There is a close relation between the function of the various parts of the labyrinth and the orientation of the hair bundles on each sensory area, as discussed in earlier papers by Lowenstein and Wersäll (1959), by Flock and Wersäll (1962), by Lowenstein, Osborne and Wersäll (1964), by Flock (1964) and by Wersäll, Flock and Lundquist (1965) and by Spoendlin (1965). In the lateral line organ of fishes and amphibia each sensory area contains groups of cells facing towards the head of the animal and other cells where the kinocilium faces towards the

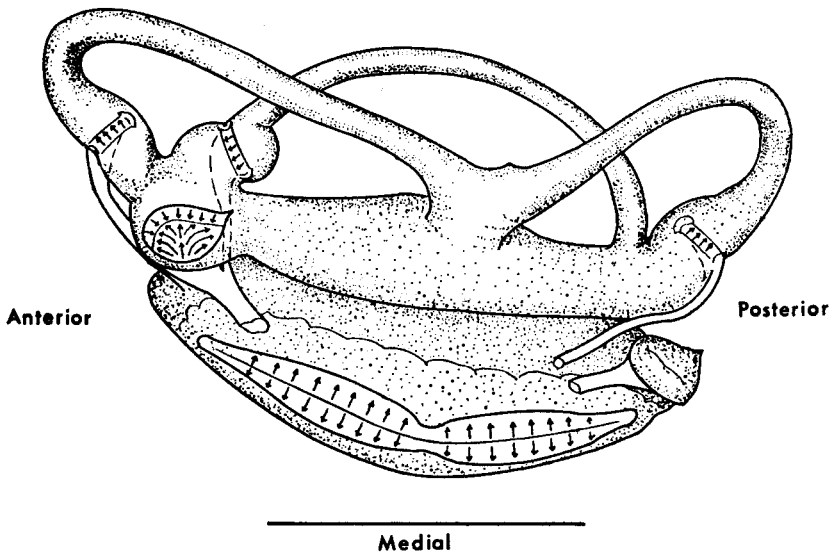

FIG. 9. Schematic drawing of the fish labyrinth, illustrating the orientation of the sensory cells in the sensory areas with regards to the kinocilia in the hair bundles.

tail. A definite relation has been established between the microphonic output of the mechanoreceptor cells in the lateral line organ of fish and the direction of stimulation of the sensory cells (Flock, 1964), maximum output being achieved when the bending forces are acting upon the sensory hairs in the direction of orientation of the kinocilium of the hair bundle. Görner (1963) also demonstrated that the nerve fibres innervating one group of sensory cells in the lateral line organ of *Xenopus laevis* decreased their rate of discharge when the hairs were moved away from the kinocilium and increased the rate of discharge when the hairs were moved in the opposite direction (Harris and Milne, 1966). The directional sensitivity of the various sensory areas in the labyrinth thus depends on the directional sensitivity of the sensory cells or the groups of sensory cells, as reflected in the organization of the hair bundles on the cell surface (Fig. 10).

Each sensory cell in the vestibular sensory epithelia as well as in the sensory epithelia of the lateral line organs is innervated by afferent and also efferent nerve fibres (Fig. 11) (Petroff, 1955; Wersäll, 1956; Engström, 1958; Rasmussen and Gacek, 1958; Rossi, 1961). The afferent fibres are the end terminals of the dendritic axon of bipolar ganglion cells located in the vestibular ganglion. These fibres as well as the axons of the ganglion cells themselves are heavily myelinated. Each fibre loses its myelin sheath during its passage through the basement membrane of the epithelium. Some of the fibres form nerve chalices around the type I sensory cells;

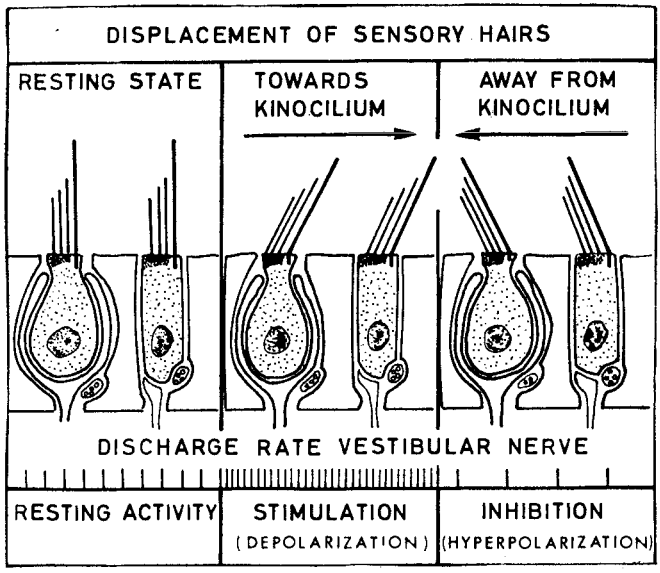

FIG. 10. Schematic illustration of the relation between hair-cell orientation and the pattern of stimulation of the innervating nerve fibres in the mammalian crista.

others form a branching network of fine fibres ending on sensory cells of type II.

The synaptic membrane formed in the contact between the sensory cell of type I and the nerve chalice varies in different parts of the chalice (Engström, Ades and Hawkins, 1965; Spoendlin, 1965). Thus large areas of these synaptic contacts are formed by four distinct opaque membrane layers, separated by less dense interlayers. In other areas the two opaque middle layers disappear or are reduced to form one single irregular layer (Fig. 12) (Wersäll and Lundquist, 1966). At these points a rather large vesicle is often found on both sides of the synaptic membrane. In the guinea pig, synaptic rods surrounded by vesicles are found in the hair cell, resting on

the plasma membrane (Fig. 13). The plasma membrane opposite the synaptic rod is slightly thickened, forming a typical synaptic complex. Similar complexes are also found in the synaptic contact between the type II hair cells and their afferent nerve endings. In the frog, the hair cells are of type

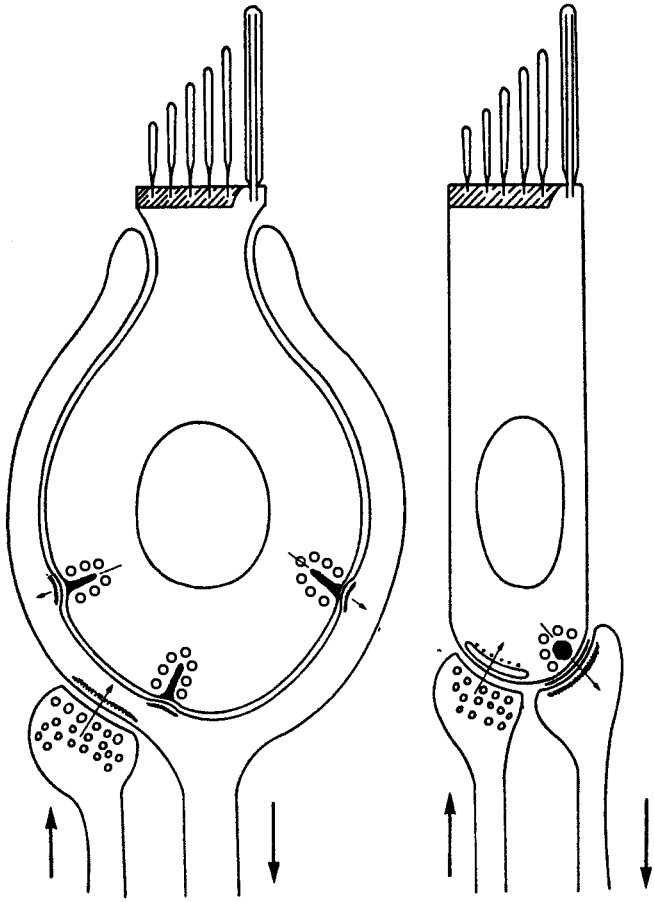

FIG. 11. Schematic drawing of the relation between afferent and efferent nerve fibres and the vestibular sensory cells in the mammalian labyrinth.

II, as in fishes, and the synaptic complex at afferent endings is composed of the plasma membrane of the hair cell and that of the sensory cell, each covered by an opaque layer. The hair cell contains one or several globular synaptic bodies and a large number of synaptic vesicles in the synaptic area. Around the synaptic body are also short tubules and vesicles surrounded by a membrane coated by an irregular, less-dense layer. Some of these vesicles and tubules open up on the cell surface, suggesting a pinocytotic or

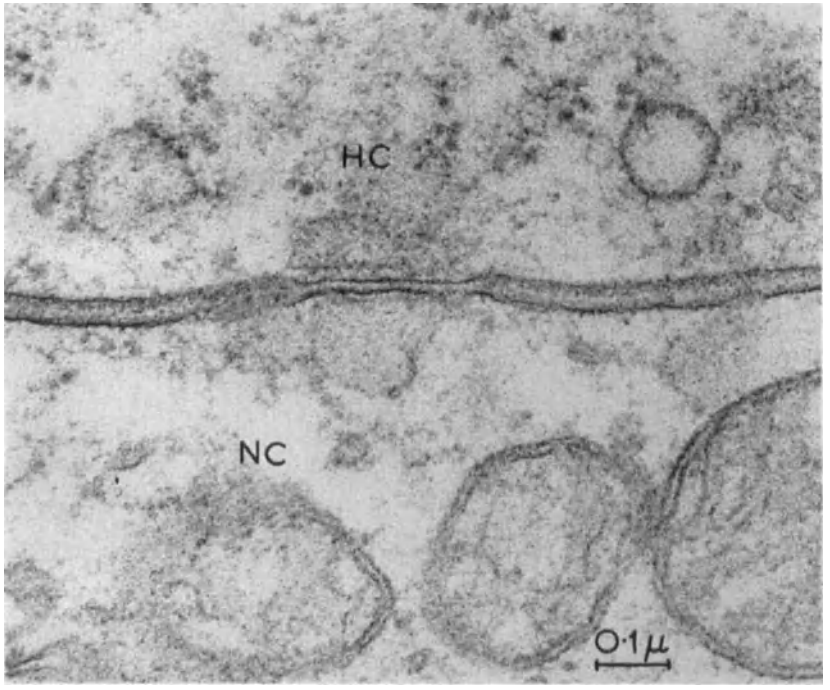

FIG. 12. The micrograph illustrates a region where the plasma membranes of the sensory cell and of the nerve ending are closely apposed and the two dense intermediate layers are reduced to one irregular layer. HC: Hair cell. NC: Nerve chalice. × 92,000

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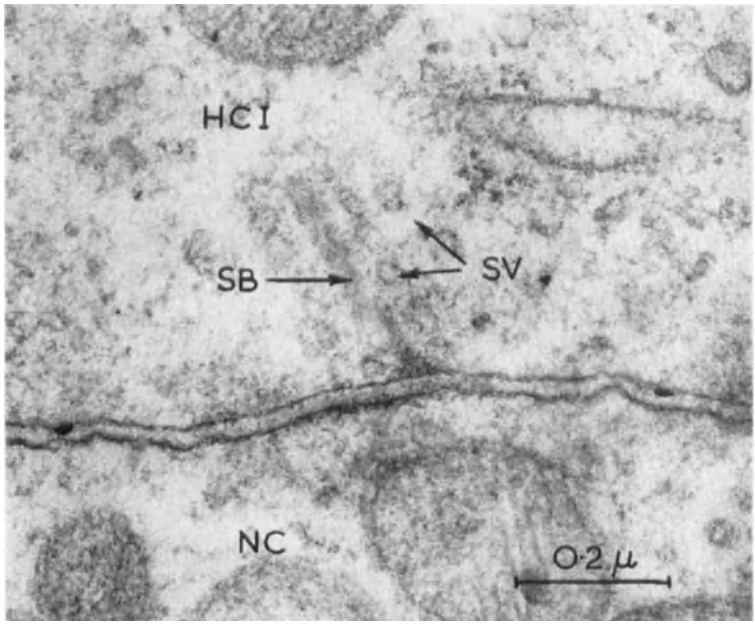

FIG. 13. A synaptic bar (SB) is resting on the plasma membrane of a hair cell of type I from the guinea pig crista. A condensation of dense substance is found on the plasma membrane of the nerve chalice (NC). Synaptic vesicles (SV) surround the synaptic bar. × 100,000.

secretory function of the cell (Gleisner, Lundquist and Wersäll, 1967). A similar system of pinocytotic coated vesicles was recently described in the synaptic area of the afferent nerve ending on the outer hair cells of the organ of Corti of the guinea pig, by Wersäll (1967).

The efferent nerve supply to the inner ear was first demonstrated by Petroff in 1955. In 1956, Wersäll demonstrated the existence of two morphologically different types of nerve fibres in vestibular sensory epithelia. Besides the sparsely granulated nerve fibres forming the afferent nerve

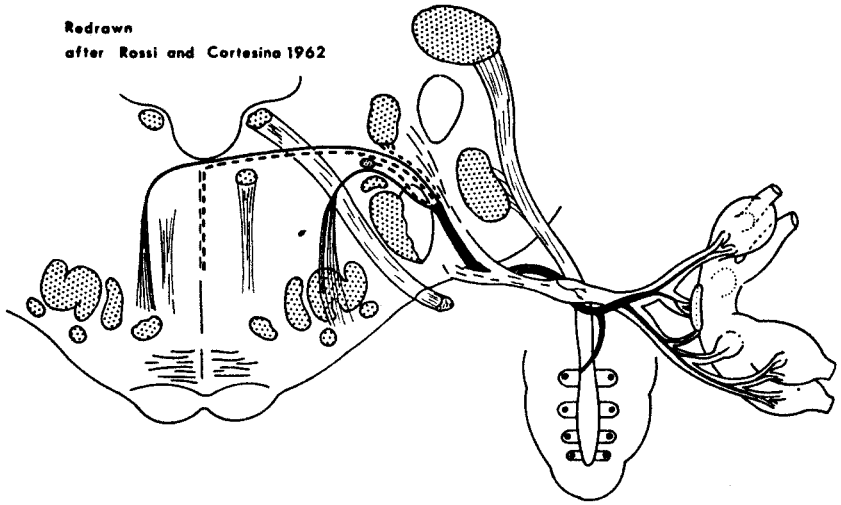

FIG. 14. Schematic drawing of the efferent nerve fibres from the superior olivary nuclei to the cochlea and from the restiform body and vestibular nuclei to the vestibular sensory cells, as shown with Koelle's cholinesterase staining method. (Guinea pig.) (After Rossi and Cortesina, 1962.)

endings, all labyrinthine receptor areas were found to contain heavily vesiculated nerve fibres. These vesiculated nerve fibres were considered by Engström in 1958 to be efferent. He compared the richly vesiculated presynaptic endings described by De Robertis (1955) and by Palade and Palay (1954) with the vesiculated fibres and nerve endings first observed by Engström, Sjöstrand and Wersäll (1953) and drew the conclusion that all heavily vesiculated fibres and nerve endings in the labyrinthine epithelia would be efferent. A system of nerve fibres staining intensively with Koelle's method for demonstrating specific cholinesterase was shown in the vestibular system by Dohlman, Farkashidy and Salonna (1958). Hilding and Wersäll (1962) traced these fibres, by means of a combination of the Koelle stain and electron microscopy, to heavily vesiculated nerve endings

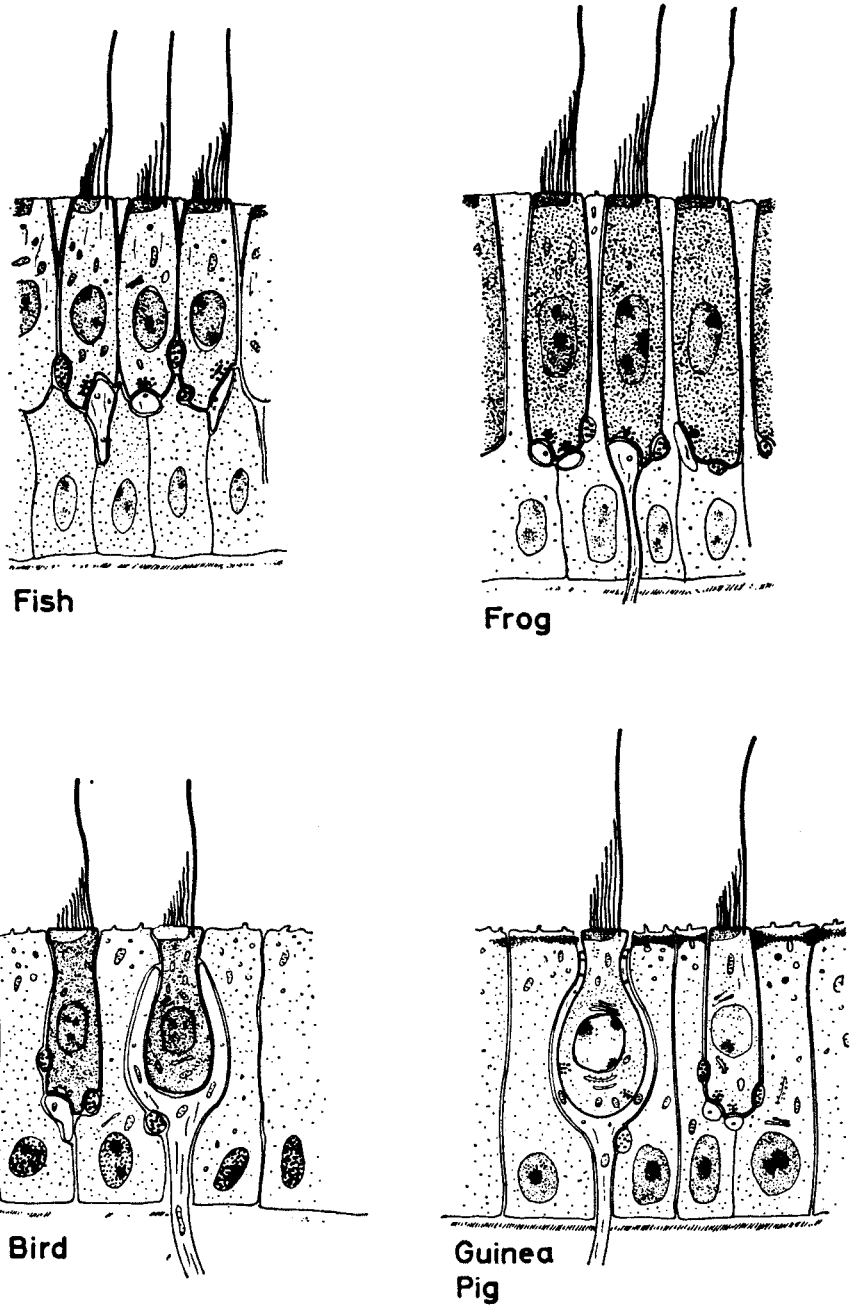

FIG. 15. Schematic drawing summarizing the morphology of the innervation of the sensory cells in fish, frog, bird and mammal.

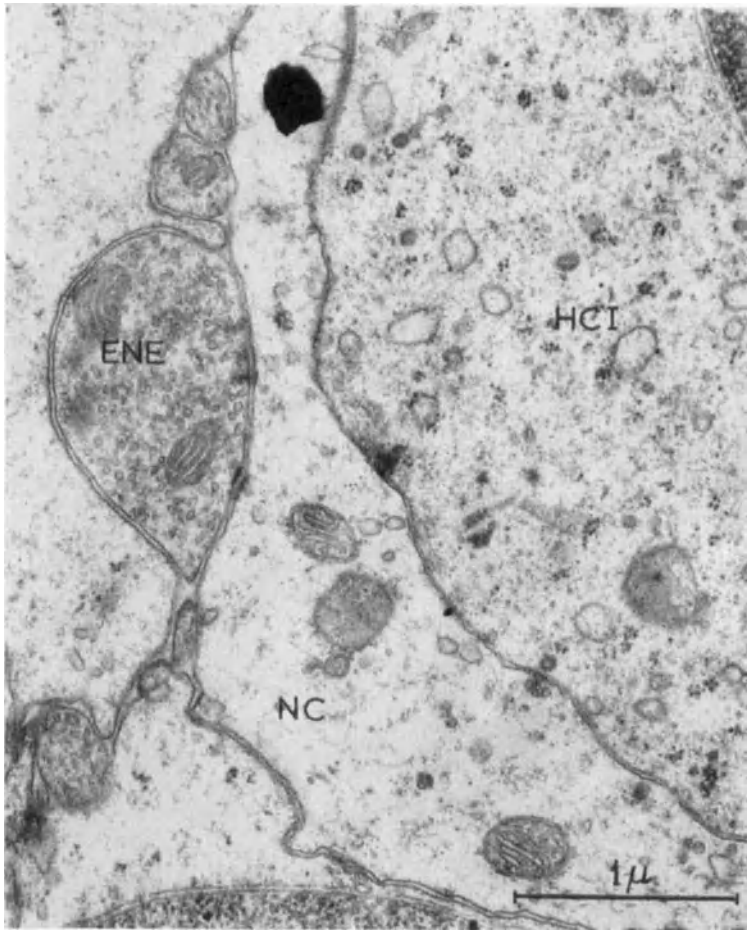

FIG. 16. An efferent nerve ending containing an accumulation of synaptic vesicles (ENE) is illustrated in synaptic contact with a nerve chalice (NC) surrounding a hair cell of type I (HC I). (Guinea pig crista.) × 29,464.

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on the outside of the nerve chalices as well as on hair cells of type II. Rossi and Cortesina (1962) described how these fibres arise from nerve cells in the lateral vestibular nucleus and from a group of cells located a certain distance from this nucleus. They also found efferent fibres going from the reticular substance to the vestibular as well as the cochlear sensory cells (Fig. 14).

In a comparative anatomical study of the sensory cell innervation of frogs, fishes, birds and mammals, Wersäll, Flock and Lundquist (1965) identified vesiculated efferent endings in the sensory epithelia of the labyrinthine sense organs of all these groups, as well as in the lateral line organs of fishes and frogs (Fig 15). The efferent nerve endings, which are partly formed as *en passant* endings of branched efferent fibres and partly as true terminal boutons, are provided with a characteristic synaptic complex which varies slightly from animal to animal. All efferent endings contain an accumulation of round and oval vesicles. When the efferent ending terminates on the sensory cell surface, the synaptic membrane of the nerve ending sometimes shows a slightly wavy appearance. In the grooves thus formed a dense substance is often found in the nerve ending, closely attached to its plasma membrane. The hair cell regularly contains a synaptic sac, a somewhat irregular flat space in the cytoplasm surrounded by a thin membrane and located close to and parallel with the plasma membrane of the hair cell. This membrane is sometimes coated with ribosomes on the side facing the hair cell. Those efferent nerve endings and nerve branches forming synapses with afferent dendrites are provided with a simpler synaptic complex, formed by a condensation of dense material on both sides of the synaptic membrane and an accumulation of synaptic vesicles on the presynaptic side (Figs. 16 and 17).

The question of synaptic transmission and transmitter substances is still unresolved for the labyrinthine receptors. The complex formation of the synaptic areas does, however, suggest chemical rather than electrical transmission. In the synaptic contact between the hair cells of type I and the nerve chalice the synaptic structures vary considerably along the cell surface. As mentioned above, both typical synaptic rods and also simpler synaptic complexes are found. As pointed out by Engström, Ades and Hawkins (1965), by Spoendlin (1965) and by Wersäll and Lundquist (1966), there are, however, some areas where the two opposing membranes of the sensory cell and nerve chalice are closely attached in a way similar to the electrotonic junctions described by Bennett and co-workers (1963) between teleost spinal neurones. Spoendlin (1966) suggests that a leakage of current would occur through these synaptic areas and cause the resting

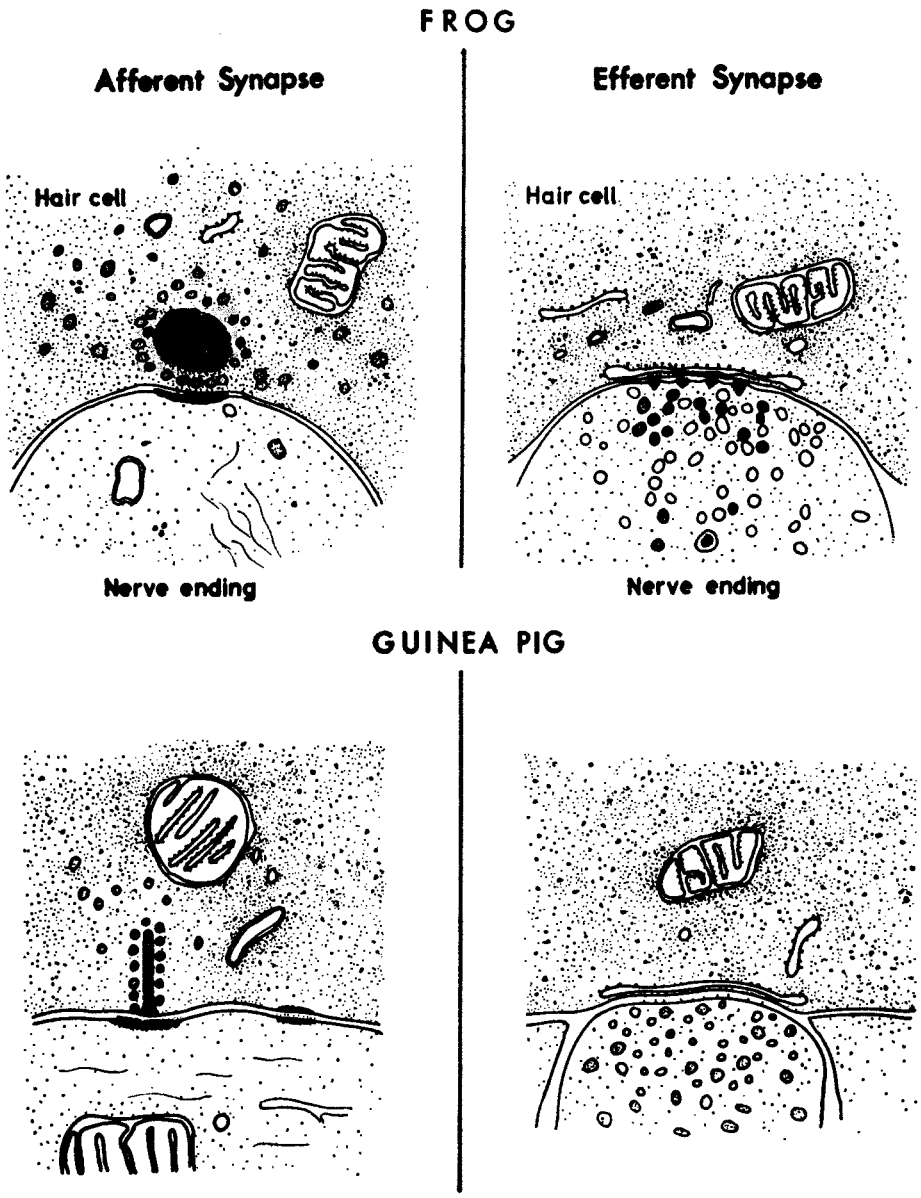

FIG. 17. Schematic drawing of the synaptic complex in efferent and afferent synapses in frog and guinea pig.

discharge of the afferent vestibular nerve fibres. So far this has to be considered purely hypothetical, since the actual site of this phenomenon has not yet been located physiologically. Possibly a combination of microelectrode studies and electron microscopy might lead to further knowledge about this phenomenon.

SUMMARY

The vestibular end organs are mechanoreceptor cells responding to shearing forces acting via movement of sensory hair bundles protruding from the fluid surface of the cell.

These sensory hair bundles consist of regularly arranged stereocilia and a kinocilium. The former are composed of an axial core of dense fibrillar material, tapering down into a root. This root passes through a dense cuticular plate located immediately below the plasma membrane of the cell and into the apical cytoplasm.

The kinocilium in the periphery of the bundle is composed of an axial core of two central fibres, surrounded by nine peripheral double filaments passing into the apical cytoplasm and ending in a centriole-like basal body. One other centriole is found further down in the cytoplasm.

In mammals and birds two types of cells can be found. The type I cell is flask-shaped with a narrow apical part and is surrounded by an afferent nerve chalice. The type II cell is elongated with a basally located synaptic region. Only cells similar to this second type can be found in lower species, such as fishes and frogs. The afferent nerve endings form large chalices around the type I sensory cells, and smaller club-shaped endings in the synaptic region of type II and similar cells. Dense synaptic bodies are found in the sensory cells close to the afferent nerve endings.

The efferent nerves form *en passant* synapses or button-shaped terminals filled with synaptic vesicles.

The functional polarization of the sensory cells is indicated morphologically by the orientation of the hair bundles. In the horizontal canal, the cells are orientated with their kinocilia towards the utricle, and in the vertical canals, towards the canal.

In the saccule and utricle a curving boundary zone can be followed over the surface, the kinocilium facing this zone in the utricle and facing away in the saccule.

A deviation of the sensory hairs towards the kinocilium produces a depolarization of the sensory epithelium and a movement in the opposite direction produces a hyperpolarization.

Acknowledgements

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DISCUSSION

Lowenstein: Dr. Wersäll, you implied that the electrotonic tight synaptic structures might comprise a mechanism of conduction from hair cell to nerve fibre, but it occurs to me that they could alternatively be feedback synapses, replacing what we know in the central nervous system as recurrent collaterals. Is there any morphological evidence *against* transmission from nerve cell to hair cell?

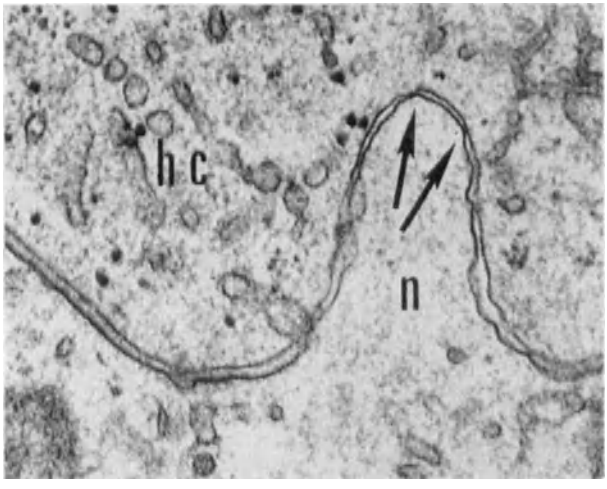

FIG. 1 (Smith). Synapse between chalice cell (n) and hair cell (hc) from the utricle of the chinchilla. Apparent fused junctions are indicated by arrows. × 61,000.

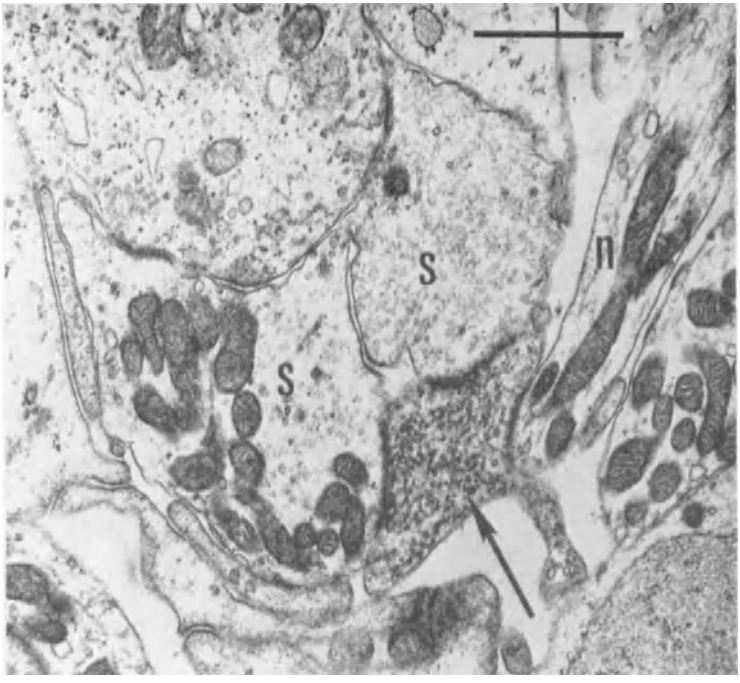

FIG. 2 (Smith). See text.

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Wersäll: There is no evidence against this possibility. The extreme selectivity in the cochlea could perhaps also be related to a feedback system in the afferent spiral neurones.

Lowenstein: In such cases there would be two feedback systems, one from the central nervous system—by the efferent sense endings—and the other a local one, which might simply be a smoothing or stabilizing feedback rather than a co-ordinating feedback. But this is quite speculative, in the absence of direct information.

Smith: May I enlarge on what Dr. Wersäll said about the narrower synaptic gaps in some places between hair cells and chalice nerve fibres. One often sees small invaginations of the nerve into the hair cell, as Dr. Wersäll demonstrated, and at these points there is likely to be a thinner synaptic cleft, as he pointed out. In the guinea pig there seem to be very small, or punctate fused junctions in the invaginations (Fig. 1), rather than the longer lengths of fusion which have been demonstrated elesewhere by Robertson and co-workers and are believed to be related to electrical transmission (Robertson, J. D., Bodenheimer, T. S., and Stage, D. E. [1963]. *J. Cell Biol.*, **19**, 159–199). We do not know if this can be considered to be evidence for electrical transmission in the chalice and hope that electrophysiological studies will supply the answer. These small areas of fused membranes are not present at the synapses of the hair cells with the boutons.

Lowenstein: Dr. M. P. Osborne in my laboratory recently investigated the central nervous system of insects and was at first elated to find typical ion-tight junctions—judged by the reduction of the two inner opaque layers to one layer—where he would have expected them on physiological grounds, namely, where there are field effects. But when he investigated this further he found these places in such profusion that he became doubtful whether one can conclude that whenever one finds such junctions they must have a synaptic function. This of course is all in the air at the moment, but one should be cautious in interpreting such morphological findings.

Friedmann: Dr. Wersäll, one occasionally sees a calyx surrounding two or three type I cells. What might be the significance of this?

Wersäll: This system is formed, as you know from your own beautiful studies on the otocyst, by branches which start as small nerve endings and which are so close to the accumulations of sensory cells of type I that it must be highly likely that as the nerve grows out it will enclose a whole group of sensory cells. I don't know whether there is any physiological significance. It could be that this condensation of a number of hair cells would make a more sensitive system. This is a very different type of innervation from the much finer fibres forming the branched system innervating the type II cells, and a difference in function seems likely.

Lowenstein: That there is such extensive convergence built into the vestibular organs is illustrated in the lamprey, where there are what we call the "candelabra" fibres, of large diameter, each innervating a number of sensory cells—sometimes

dozens—in the maculae and especially in the semicircular canals. This convergence seems to be fundamental and I am not surprised to find it in these chalices.

Wersäll: It is interesting that sometimes only two or three type I cells are innervated by one afferent fibre, which would give rather local representation of the sensory area, compared to the more diffuse system of type II hair cell innervation. There are also the wider branching systems which cover large areas of type II sensory cells. I suspect that we have here two rather different principles of organization, which could be compared to the different types of innervation of rods and cones in the eye.

Lowenstein: It is possible that all sensory epithelia have side-by-side an approximately one to one innervation and a convergent innervation.

Dohlman: The "candelabra" fibre serving several hair cells might be connected functionally with the summation of stimuli.

Friedmann: This pattern of convergent innervation starts very early in the development of the isolated fowl embryo otocyst in tissue culture, at the 10th to 12th day. One has the impression of an initial disorganized stage and an eventual settling down to a more characteristic candelabra pattern.

Smith: Dr. Wersäll, you described microtubules in the neck of the type I hair cell; have you found them in type II cells? I have always felt that they might be due to compression of the cytoplasm at this place where the type I cell is under pressure from the encircling nerve. The type II cell does not have a constricted neck because the nerves do not reach the apical part of the cell.

Wersäll: I have seen filaments or tubules at the outer end of the type II cells but because they are more widely spread they are difficult to see. But it could be that they do not exist in type II cells.

Monnier: Dr. Wersäll, in earlier papers you pointed out that one type of hair cell is more suited to phasic and the other to tonic activity. What is your present conception?

Wersäll: I would not like to draw any firm conclusions about the functions of the two types. I have said that the type I hair cell, with its one to one or at most three to one representation, could reflect the response from one local area of the macula or the crista. This is perhaps not so important in the crista but very important in the macula. The type II cell is more likely to represent, as Professor Lowenstein has pointed out, a summing up of the physiological status of the whole macula. The possibility of phasic or tonic response in one type or the other is still open for discussion.

Smith: I wonder if there might be possibilities for peripherally initiated inhibition, by means of the efferent fibres—a sort of "lateral inhibition"? The efferent fibres are very long and have synaptic bulbs along their naked axons (Iurato, S., and Taidelli, G. [1964]. In *Proc. Third Europ. Reg. Conf. on Electron Microscopy* (Prague), vol. B, pp. 325–326. Prague: Czechoslovak Academy of Sciences) which probably touch a number of nerve fibres. If a sensory nerve ending is set off by the hair cell, possibly it could in turn activate an adjacent efferent nerve ending

which might inhibit a second sensory nerve with which it makes synaptic contact. Fig. 2 shows two nerve endings (s), apparently sensory, on a hair cell. An efferent nerve (arrow), as determined by numerous vesicles in the neuroplasm, is in contact with both of them as well as with a nerve fibre (n) on the right.

Wersäll: Such a system might be possible. As far as I know, there is however no experimental evidence for this yet.

Lowenstein: Dr. Wersäll, have you found anywhere a situation where there is an enormously long, absolutely rigid kinocilium accompanied by a normal stereocilial bundle? A very elongated kinocilium is found in the maculae, but not in the cristae, of the ammocoete larva of the lamprey.

Wersäll: In the macula of the guinea pig the kinocilium is always longer than the rest of the bundle, but not to the extent you are describing. We have seen a few cases in the guinea pig where the afferent fibres from the vestibular system have been cut and a change occurs in the population of the sensory hairs. The kinocilium becomes very large—but I do not know whether it is a newly formed kinocilium or not—and the rest of the hairs disappear. There thus seems to be some relation between the presence of the nerve fibre and the formation of this kinocilium and also the hair bundle. Of course, it would be nice to think that the outgrowing nerve fibre determines the orientation of the hair bundle, or perhaps the opposite, but we don't know! I might add that in the octopus there are no stereocilia, according to V. C. Barber ([1966]. *Z. Zellforsch. mikrosk. Anat.*, **70**, 91–107; [1966]. *J. Anat.*, **100**, 685–686). All the sensory hairs have the same kinocilium-like appearance and are orientated in the same direction. Many insect mechanoreceptors (which of course are *primary* sensory receptors) have one dendritic projection forming a kinocilium-like structure which is the only transducing mechanism between the mechanoreceptor and the afferent fibres.

Friedmann: We have seen the opposite situation to the "giant" kinocilium, namely the "dwarf" or rudimentary kinocilium on the supporting cells of the macula in tissue cultures of isolated fowl embryo otocysts. They also occur in the organ of Corti.

We have also managed to obtain specimens of the human macula, from patients operated on for Ménière's disease by Sir Terence Cawthorne, and here as in other mammals we find type I cells with a large calyx-like embrace of the afferent nerve fibre, and also occasional button-shaped nerve endings (Friedmann, I., Cawthorne, T., and Bird, E. S. [1965]. *J. Ultrastruct. Res.*, **12**, 92–103; [1965]. *Nature, Lond.*, **207**, 171–174). But we have not been able to examine an entirely normal human macula yet: there were no volunteers!

Lowenstein: These short kinocilia on the supporting cells are the rule in the vestibular epithelium; they have a short peg-like kinocilium with an even more complex basal body than that of the normal kinocilium of the sensory cell and they are all of the same length, which spans the height of the subcupular space. One is tempted to think that they function as spacers.

Lundquist: We often find a centriole close to the fluid surface all over the labyrinthine cells, and both in the supporting cells of the ampullae and also in the endolymphatic sac I have several times seen "rudimentary" kinocilia such as Professor Friedmann has described, originating from these centrioles. So it might be that when the centriole is located close to the fluid surface we can often expect to find a primitive kinocilium-like structure.

Lowenstein: But it is not "primitive", because despite its short length it is a perfectly honest kinocilium in its structure.

Lundquist: There is a basal body and something like a basal foot.

Lowenstein: Basal feet are present but in the supporting cells they point in random directions.

Dohlman: Turning to a different subject, Professor Barker emphasized that nerve fibres are structures which grow, die and are replaced. I have been trying to get evidence for a similar turnover in the vestibular organ but so far without result. However, I cannot believe that we are born with one set of hair cells and nerve endings which will survive from birth to perhaps 90 or 100 years of age! Has this problem been investigated for other sensory areas?

Barker: The only evidence I know on the sensory side is some work by J. F. Tello ([1932]. *Trab. Lab. Invest. biol. Univ. Madr.*, **28**, 1–58) in which he describes normal and degenerating paciniform corpuscles in human external genitalia. M. J. T. FitzGerald ([1961]. *J. Anat.*, **95**, 495–514 and [1962]. *J. Anat.*, **96**, 189–208), working on free nerve endings and on paciniform corpuscles in the pig's snout, found evidence of cyclic growth and decay. There is also work by L. M. Beidler ([1961]. *Am. Scient.*, **49**, 421–431) on taste receptors, in which he shows a turnover of the receptor cells. He says nothing about the nerve endings, but presumably there must be reconnexions. So far as I know, no observations have been made on replacement in the vestibular organ. Some work by A. Weber ([1950]. *Bull. Histol. appl. Physiol. Path.*, **27**, 73–80) suggests that replacement may occur centrally, there being a cycle of degeneration and renewal of *boutons terminaux*. I have tried to follow this up, but so far without success.

Myotatic, Kinesthetic and Vestibular Mechanisms
Edited by A.V. S. de Reuck and Julie Knight

FUNCTIONAL ASPECTS OF VESTIBULAR STRUCTURE

O. LOWENSTEIN

Department of Zoology and Comparative Physiology, University of Birmingham

THE ultrastructure of the vestibular hair cell, the overall functional significance of the orientation of its hair bundle, and the specific features of the topographic orientation of the hair cells within the sensory epithelia in semicircular canals and otolith organs have been outlined in the communication by Wersäll (p. 105). It is my task now to speculate on the role played by the hair cell in the process of mechano-electric stimulus transduction. Naturally the hair cell cannot be considered in isolation. The cupula or the otolith membrane, as the case may be, closely ensheathes the hair processes and is, in turn, surrounded by endolymph, a fluid with remarkable physico-chemical properties. All these may well be closely involved in the ultimate transduction process, besides playing their part in the gross mechanical events that focus the effect of angular acceleration or positional dislocation of the head on to the receptor cell.

Let us look at what happens when an angular acceleration takes place about a dorso-ventral axis with the horizontal semicircular canals lying in the plane of rotation. We know that such an acceleration produces an inertia movement of the fairly rigidly coupled cupula–endolymph system in ampulla and canal and that this brings about a displacement of the cupula either away from or towards the junction between ampulla and utriculus (utriculo-petal or utriculo-fugal displacement). In the crista of the horizontal canal the hair cells are arranged in a strictly uniform manner so that the kinocilium of every hair cell all over the crista stands on the utricular side of the hair bundle. Utriculo-petal acceleration thus deforms the hair bundle, by shearing rather than bending, in the direction of the utriculus. The hair bundle protruding into a tubular space within the mass of the cupula is thus subjected to a shearing force which dislocates both kinocilium and stereocilia from their resting position. It is not known whether the kinocilium and the stereocilia are rigidly coupled or whether the distance between the kinocilium in front and the stereocilia behind is diminished in this case. It must be remembered that the kinocilium stands

free of the population of stereocilia in a roughly triangular gap present among the regular rows of stereocilia, the distance between the kinocilium and nearest stereocilium being significantly greater than the inter-stereocilial distance.

It may be mentioned here that the cupula does not reach down to the apical surface of the sensory epithelium. A subcupular space separates the two and this is filled with a clear viscous substance differing from the cupula in refractive index and homogeneity. Whether this substance extends into the intracupular tubular space surrounding the hair processes is not known. It is believed that this substance is secreted by the supporting cells of the sensory epithelium. Nothing is known of its chemical composition, especially of the presence or absence in it of the mucopolysaccharide found in endolymph and cupula.

Let us return now to the mechanical events. The cupula–endolymph system behaves like an overcritically damped spring-loaded torsion pendulum. It therefore returns to its resting position as soon as acceleration gives way to constant velocity rotation. The hair bundle does likewise. We know from single-unit recordings of the electrical activity in the afferent ampullary nerve that utriculo-petal dislocation of the hair bundle increases the impulse frequency from a pre-existing resting level, the increase in activity being over a considerable range a linear function of the acceleration. On the contrary, ampullo-fugal displacement of the hair bundle from its resting position inhibits the resting activity (Lowenstein and Sand, 1940; Ledoux, 1949). Under these circumstances the kinocilium follows the stereocilial bundle, again with a possible change of kinocilio-stereocilial distance.

The differences in the root structure of kinocilia and stereocilia are striking and have been described by Wersäll. The kinocilium with its true cilial filamental make-up has a polarized root with a "basal foot". This projects in a direction perpendicular to the axis going through the two central filaments of the cilium and points away from the stereocilial bundle, towards the utricular end of the ampulla in the case of the horizontal canal. It may be recalled that in the vertical canal the whole situation is reversed. Here the kinocilial side of the hair bundle faces the canal-end of the ampulla. This situation can be easily understood on a developmental basis, when one takes into account the origin of the cristae of the vertical and horizontal canals from a common rudiment (Groen, 1960). The functional consequences of this topographic situation are spectacular, insofar as utriculopetal dislocation of the cupula brings about an increase of electrical activity in the horizontal canal, whereas the activity of the vertical canal

increases on utriculo-fugal dislocation of the cupula. Of course, in both cases the excitatory effect is brought about by a displacement in which the kinocilium moves in advance of the stereocilial hair bundle.

Before we deal more closely with the significance of the strict polarization of the transduction mechanism, let us have a look at the connexions of the hair cell with the afferent nerve from which the electrical recordings of impulse activity are made.

The hair cells described are so-called secondary sensory cells—"epithelial ciliated" cells which "are innervated" by the dendritic processes of first-order sensory neurones situated somewhere in the course of the afferent pathway, but often well outside the medulla.

What we now know of the ultrastructure of the synaptic connexions between hair cell and afferent nerve calls for a revision of this description. The hair cell is not just purely and simply "a ciliated epithelial cell". The typical presynaptic structures inside its cell body entitle it to neuronal status despite the fact that no axonal process is continuous with it.

The presence of typical synaptic bars surrounded by a halo of synaptic vesicles in the hair cell make the assumption unavoidable that this cell initiates chemical transmission on to the postsynaptic endings of the so-called first-order neurone. The hair cell does in fact receive presynaptic endings from cells belonging to an efferent pathway, but these differ quite characteristically from those associated with the presynaptic structures within the hair cell. A third type of ending may exist in the form of tight membrane formations resembling what are usually described as structures associated with electrical transmission. Whether this transmission, if it exists at all, takes place from hair cell to nerve ending or in the opposite direction can at present only be a matter of conjecture.

Let us turn now to the existence of the resting activity in the afferent nerve. This is generally found on recording from stationary preparations. Before we discuss its possible origin, quite apart from its well-documented overall functional significance (Lowenstein and Sand, 1940), it must be emphasized that peripheral recordings of it were obtained from isolated preparations in which all efferent pathways were severed and thus all naturally intervening feedback from the central nervous system was abolished. Such open-loop analyses may be useful in studying the transduction process within the receptor, but they do not necessarily allow assertions to be made about the significance of an observed resting activity in the afferent pathway, which might quite likely be under the control of the efferent part of the system.

However, there is good evidence from the electrophysiological study

of the behaviour of second-order neurones in vestibular nuclei (Adrian, 1943; Schoen, 1957) to show that resting activity is manifest under normal circumstances, that is to say, in the intact loop.

How is this resting activity generated? The most reasonable assumption is to ascribe it to a leakiness of the chemical synapses between the presynaptic hair cell and the postsynaptic processes of the first-order vestibular neurones. It must be remembered that in the isolated preparation the recording electrode makes contact with a dendrite of the bipolar first-order neurone.

The relatively low-frequency resting discharge from vestibular endings is often astonishingly regular and protracted and, therefore, very unlikely to be due to chance-firing of a structure precariously poised at the mercy of random molecular events. Its functional importance as the basis for bi-directionality of response and as an important source of vestibular tonus makes it most likely to be an integral part of the functional picture. Let us therefore assume that in the unstimulated state secretion of neurotransmitter goes on at the hair cell synapses at a certain not at all insignificant and fairly constant rate. This results in a certain level of electric activity in the afferent pathway. The ultimate effect of mechanical stimulation so far as the hair cell is concerned should then be an increase or decrease in the amount of transmitter substance liberated from the hair cell.

We have now to ask how such changes in synaptic activity are brought about. Such changes may be due to an increase or decrease in the amount of transmitter substance intracellularly available and/or to a change in membrane permeability at the synaptic site. The latter is usually assumed, and one thinks in terms of depolarization or hyperpolarization of synaptic membranes.

If such changes in the state of polarization are the result of the now generally postulated sodium–potassium mechanism somewhere in the membrane of the hair cell, we may assume that they are steered by mechanical interference with this membrane. Our attention must therefore turn again towards the apical part of the receptor cell where these mechanical events take place. We return to the hair bundle and its ancillary structures, such as the cupula and the surrounding chemical medium of the subcupular substance on the one hand and the endolymph on the other.

Analyses of the endolymph in mammals have brought to light the astonishing fact that the relative concentrations of potassium and sodium in the endolymph closely resemble those found in the cell interior (Smith, Lowry and Wu, 1954; Citron, Exley and Hallpike, 1956; Murray and Potts, 1961; Enger, 1963).

Trincker (1965) points out that this makes it appear unlikely, if not

impossible, that the normal sodium and potassium mechanism can be operative across the apical part of the hair cell membrane, that is, across the membrane of the hair processes. This membrane could thus not be considered to function like ordinary receptor membrane as the locus for electrogenesis based on sodium and potassium batteries. In elasmobranch fishes, for which very complete electrophysiological data are available, the potassium content of the endolymph is also higher than that of the perilymph (Murray and Potts, 1961). But the difference is not so pronounced as in mammals (18 times instead of 30 times). Moreover, there is no drop in the sodium content, which is roughly equal in endolymph and perilymph, the surplus potassium being made good by a proportionally lower urea content. In contrast to mammals, therefore, the elasmobranch hair cell is surrounded by a medium providing the conditions for a normal sodium battery, but with a greatly reduced potassium concentration gradient. Unfortunately, there are so far no measurements of resting potential between endolymph and the interior of the hair cell. Whether in these circumstances the absence of a sodium–potassium mechanism at the apical part of the hair cell, postulated by Trincker, can be considered as a universally valid generalization, is a very open question.

The wall of the labyrinth separating perilymph and endolymph may be considered to be absolutely impermeable to ions. The positivity of the endolymph with respect to the perilymph could not otherwise be maintained either in mammals or in elasmobranchs. An ion-tight seal may likewise be assumed to exist between the apical and basal exterior of the hair cell, and there exists some as yet imperfect ultrastructural evidence for this. There is evidence that the low sodium concentration in the endolymph is maintained by active sodium absorption (Dohlman, see p. 142) and that the cells of the so-called plana semilunata are probably the source of potassium ions. The mechanism of the maintenance of the endolymph positivity against the perilymph is at present unknown.

The well-defined gradient of increasing positivity from ampullar wall towards the core of the cupula and the hair processes ensheathed in it, and the fact that this gradient is affected by cupula displacement in parallel with similar potential changes in close proximity to the hair cells of the crista, suggests that it may be closely associated with the transduction process (Trincker, 1957). A plot of the changes in the distribution of electric charge in the endolymph during cupula movements against direction and degree of cupula displacement represents a close analogue to the course of electric activity recorded in an afferent nerve during similar cupula displacement, as described by Groen, Lowenstein and Vendrik (1952).

If we accept with Trincker the proposition that the apical part of the hair cell is *de facto* ion-impermeable, the scope of our search for possible links in the mechano-electric transduction mechanism must be widened. Mucopolysaccharides have been shown to respond to displacement by electric potentials (displacement potentials) which are purported to differ essentially from either piezo-electric effects or flow potentials. These displacement potentials have been investigated biophysically by Christiansen, Jensen and Vilstrup (1961), and Christiansen (1964) has made an attempt to build such potential changes into a mechano-electric transduction hypothesis applicable to the vestibular system. His hypothesis is based on the assumption that thin layers of mucopolysaccharide, the presence of which in appreciable concentration in the endolymph has been demonstrated (Dohlman, 1960; Dohlman and Ormerod, 1960), surround the apical structure of the hair cell. Deformation of the hair bundle could under these circumstances be expected to result in changes in static potential of up to 40–60 millivolts. Such changes are completely reversible on return to the original shape of the system after deformation. If then—Trincker argues in discussing this hypothesis—the surface of the hair behaved like an insulator, might deformation not capacitatively generate a corresponding but opposite potential change in the interior of the hair processes? The effect of this would be the introduction in the cell interior of a change of potential, representing the first step in the generation of a receptor potential, representing an electrical analogue of the mechanical events. The release of transmitter substance at the chemical synapses in the body of the hair cell would then be the penultimate process leading ultimately to the depolarization of the afferent postsynaptic ending and the modulation of the discharge of the frequency-coded all-or-nothing impulses. All this rests on very meagre factual evidence and may, for all I know, not even be physico-chemically feasible.

Assuming that one way or other the apical end were the immediate transduction site, the question arises of whether the kinocilia or the stereocilia are the more likely transducers. It has been postulated that the kinocilium, on account of its close structural resemblance to a freely mobile cilium, might be considered to function as a mobile cilium in reverse. A mobile cilium responds to some, very likely electrical, signal arriving at its root with movement, that is, with mechanical deformation. The kinocilium on the other hand, incapable of active movement by being closely contained within the cupula, might be imagined to respond to passive deformation with an electric change on or near its root, from which may then start the events ultimately leading to changes in the rate

of chemical transmission at the synapse. This hypothesis would fit in with the topographic arrangement of the hair cells, not only in the canal cristae, but also in the maculae, where the population of hair cells is elaborately mapped out so as to cover responses to positional changes in all possible directions. However, the hair cells in the cochlea of adult mammals lack the kinocilium proper. Only its root structure is present in the usual position relative to a stereocilial bundle. Yet these hair cells are mechano-electric transducers like their counterparts in the vestibular sense endings, and the only hair processes that can be made responsible for this are stereocilia. There is a possible difference. The cochlear hair cell need not necessarily be direction-sensitive, although von Békésy (1954) assumed this when comparing outer and inner hair cells of the mammalian cochlea.

If the presence of a kinocilium is not a necessary condition for successful transduction, we might switch our attention to the stereocilia. These are anchored in the so-called cuticular plate by simple elongated conical roots. Could it be that displacement of the hair bundle dislocates the whole basal plate? In this case the movement of the substance of the cuticular plate may be thought to affect the rest of the cytoplasm of the hair cell either directly or via the basal structure of the kinocilium which lies outside the cuticular plate, but sufficiently near it to be within range of such a disturbance.

It is interesting, however, that the hair cells in the octopus statocyst, which are primary sensory cells, have an assembly of hair processes all of which are typical kinocilia (Barber, 1965, 1966*a*, *b*).

In a recent study of the ultrastructure of the hair cells of the labyrinth of the ammocoete larva of the lamprey (*Lampetra fluviatilis*), Lowenstein and Osborne (1964) found associated with the cuticular plate and the roots of the stereocilia a striated organelle with average periodicity of 1,300 Ångström units (130 nm.). This organelle branches and reaches far down into the body of the hair cell, ending in close proximity to the synaptic sites. Such a structure has so far not been reported from any other vertebrate labyrinth. We have conducted a special search for it in the labyrinth of the ray (*Raja clavata*), but so far without success (unpublished observations). It would have to be universally present to encourage the attribution of a transductive function to it.

What is the upshot of all this? It must be conceded that, despite the number of conflicting clues that I have been able to muster in this paper, at least my own understanding of the mechano-electrical transduction mechanism is wholly unsatisfactory. This would be rather disturbing, were it not for the fact that our understanding is not significantly more complete in other sensory fields. It is regrettable that it has been impossible

so far to record the receptor potential from the hair cell. These cells are small and penetration by micro-electrodes is difficult. The chemical nature of the afferent synapses has only recently been demonstrated circumstantially by means of the electron microscope and the search for the neurotransmitter is still going on. Acetylcholine is being strongly tipped as a favourite but the last word has not been spoken yet on that problem.

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DISCUSSION

MORPHOLOGICAL ASPECTS OF STIMULUS TRANSDUCTION

Smith: I was interested in the striated organelle that Professor Lowenstein described in the hair cells of the labyrinth of the ammocoete larva, that is an extension of the cuticular plate. In the cochlea, we have seen extensions of the cuticular plate running down through the cytoplasm of the hair cell, but they showed no periodicity (Smith, C., and Dempsey, E. [1957]. *Am. J. Anat.*, **100**, 337–368). Whether they are present in all hair cells I do not know.

Wersäll: In the bat, R. S. Kimura ([1966]. *Acta oto-lar.*, **61**, 55–72) has demonstrated that the rootlets of the sensory hairs in the cochlear hair cells bend and make contact with the fenestrated membranes along the sides of the hair cells. The hair cells in the bat have no kinocilium. So here we have a different system where a part apparently moves towards the periphery rather than going down to the nerve endings at the base of the cell, as in the ammocoete larva.

It is tempting to assume that the sensory hairs are actually produced by the outgrowth of fibres formed by the protein-synthesizing mechanisms of the centrioles. Each sensory cell has two centrioles, one of which is found close to the surface. Even in the cochlea a kinocilium appears in the embryonic stage although it disappears later. (In birds, or in the chicken at least, a few cochlear sensory cells do have a kinocilium in the adult stage.) The second centriole is often located below the other. One of the centrioles might form the fibrils which make the filiform processes on the surface grow into sensory hairs.

Lowenstein: We might then be justified in assuming that the kinocilium is an organization centre of the cell rather than directly involved in transduction, if it were not for the evidence from the octopus (Barber, V. C. [1966]. *Z. Zellforsch. mikrosk. Anat.*, **70**, 91–107; [1966]. *J. Anat.*, **100**, 685–686).

Henriksson: You mentioned the question of the existence of a sodium-potassium battery. In experiments on frogs, performed to look into other problems, we injected fluid into the endolymphatic system of one semicircular canal and recorded the vestibular activity in the nerve from another canal (Henriksson, N. G., and Gleisner, L. [1966]. *Acta oto-lar.*, **61**, 380–386; Henriksson, N. G., Gleisner, L., and Johansson, G. [1966]. *Acta oto-lar.*, **61**, 281–291). We rotated the preparation at different endolymphatic pressures to study the effect of pressure on nerve activity. When we began the experiments we injected distilled water, and this had very little effect on vestibular activity. This makes me doubt that the primary physiological meaning of the high potassium concentration of the endolymph concerns the modulation of the frequency of the impulses in the vestibular nerve.

Lowenstein: Those who believe in the importance of mucopolysaccharides say that the high potassium concentration may have the function of keeping the mucopolysaccharides in order!

Wersäll: With Dr. Flock I have studied the effect of streptomycin on the lateral line organ (Wersäll, J., and Flock, Å. [1964]. *Life Sci.*, **3**, 1151–1155). This is an ideal model system from many points of view—one can expose it, put a tubule with which to move the hairs right on the cuticle and get a comparatively well-calibrated input–output system, and one can record from the neighbourhood of the lateral line organs the shift in the microphonic potentials of the sensory cells. During experiments with drugs we studied the effect of 1 in 100,000 streptomycin solution on the sensory cells and found that the microphonic potential disappeared very rapidly when the streptomycin solution was diluted with Ringer's solution. If we replaced the Ringer's solution by a potassium-enriched medium containing the equivalent potassium concentration of endolymph, the microphonic potential returned. In fact, we found the same as Dr. Henriksson: when we started, it did not matter whether we applied endolymph collected from the lateral line organ or Ringer's solution or distilled water; the organs still functioned. As soon as streptomycin was added we had to replace the potassium in order to restore the function. It looks as if initially there is enough

potassium in the cupula for normal functioning, whichever fluid is added, but that streptomycin "disconnects" the potassium and to make the system function again one must replace the potassium. So I think that the potassium is important for the functioning of the hair cells.

Lowenstein: I would suggest that the mucopolysaccharides are present as potassium salts and that the potassium is dissociated from the mucopolysaccharides in your experiments.

Wersäll: I have difficulty in relating mucopolysaccharide to the transducing system because I cannot imagine how polysaccharide could provide an organized direction-sensitive system, although it would be easy to produce the potential shift. From a purely morphological point of view I would rather put the transducer into the cell, where we know that we definitely have an organized, directional system. I would compare this with the beating cilium, which we know transforms the energy of the cell to mechanical energy in a protein system organized in one direction. On stimulation the kinocilia of the respiratory ciliated cells beat in one direction only. Here we have the same kind of system in reverse. We have an organized system in the cell, as reflected in the gross morphology of the hair bundle. It is not easy to see how the connexion with mucopolysaccharides can be made.

Dohlman: The cilia of the hair cell are of different lengths ranged in order of increasing height, and the line of slope is always in one direction. If mucopolysaccharide molecules are present between the cilia, it is apparent that the effect at the top of the cilia will differ in its electrical orientation according to the direction of bending. So there is a possibility of a directional response to change in a system in which mucopolysaccharides might play a more or less significant part.

Lowenstein: Although I have been extremely sceptical about the significance of mucopolysaccharide, which after all is found all over the body, I would agree with Professor Dohlman that one can imagine a directional coupling of a longitudinally organized array of mucopolysaccharide molecules to the directional arrangement of the stereocilia. So there is no insurmountable difficulty here. J. A. Christiansen has also pointed out that an up-and-down microphonic change is easily conceivable ([1964]. *Acto oto-lar.*, **57**, 33–49). The slow-phase events in the vestibular organ are more tied up with actual directional polarization, and there the mucopolysaccharides may be harder to bring in.

Hallpike: If mucopolysaccharide is significant in the vestibular apparatus it should equally be significant in the cochlea. But whereas in the cupula there is plenty of mucopolysaccharide, the cupula being strongly PAS-positive, my impression of the tectorial membrane is that PAS staining is comparatively feeble.

Friedmann: The tectorial membrane is strongly PAS-positive, with little variation. It depends on the technique, of course.

Lowenstein: This means that the mucopolysaccharide explanation could apply to the cochlea as well as to the cupula.

Lundquist: A recent investigation in the guinea pig by K. Rodgers and J. T.-Y. Chou ([1966]. *J. Lar. Otol.*, **80**, 778–790) has shown a large difference between the potassium and sodium contents of the vestibular and cochlear endolymph. They found about 130 m-equiv./l. potassium and 30 m-equiv./l. sodium in utricular endolymph, whereas cochlear endolymph contained 80 m-equiv./l. sodium and the same amount of potassium. This shows that it is probably the high level of potassium that is important for the functioning of the labyrinthine receptors.

Smith: There is considerable variability in the results from different investigators who have analysed cochlear endolymph for sodium and potassium. This is due mainly to the difficulties encountered in withdrawing endolymph from the cochlea. Johnstone and his co-workers found that the sodium content of the cochlear endolymph in guinea pigs was extremely low (1·8 m-equiv./l.) (Johnstone, C., Schmidt, R., and Johnstone, B. [1963]. *Comp. Biochem. Physiol.*, **9**, 335–341), contrary to the recent observations by Rodgers and Chou. It is easier to remove endolymph from the vestibule and the variability is not so great there. Our analytical values for vestibular (utricular) endolymph in the guinea pig were 15·8 m-equiv./l. sodium and 144 m-equiv./l. potassium (Smith, C., Lowry, O., and Wu, M.-L. [1953]. *Laryngoscope, St Louis*, **64**, 141–153).

Lundquist: This is also illustrated by the recent investigation by H. Silverstein ([1966]. *Ann. Otol. Rhinol. Lar.*, **75**, 48–63; [1966]. *Laryngoscope, St Louis*, **76**, 498–512) who found a very low sodium concentration in cochlear endolymph, 25 m-equiv./l.

Lowenstein: The fact remains that in elasmobranch fishes the sodium concentration is at blood level in the ampulla whereas the potassium is 18 times higher than in the blood. The sampling procedure here is easy (Murray, R. W., and Potts, W. T. W. [1961]. *Comp. Biochem. Physiol.*, **2**, 65–75).

Eldred: I am still musing on Professor Dohlman's comments about the directional response of hair cells, and trying to draw helpful insight from the greater information available for spinal motoneurones. The position of a synapse on a motoneurone, whether on dendrite, soma, or initial segment, is thought to influence greatly the effect of the synapse upon the membrane potential and net excitability of the cell. Thinking now of the hair cell, might not this mechanism work in reverse? That is, if the soma experienced a differential in potential over its surface, afferent synaptic terminals would be excited in patterns reflecting this potential gradient.

This mechanism would require generation of a potential gradient over the hair cell surface. It is certain that the hair cell has some orientation, since the cilia are arranged in strict ranking by length. Let us suppose that the mucopolysaccharide between the cilia is electrically charged, as was mentioned, but at different potential levels going from the cuticula outwards, so that the cilia sample a varying potential according to how far they extend into the polysaccharide. These potential effects on the "dendrites", as it were, would lead to a potential gradient

over the soma cell surface. Then as the cilia are bent during acceleration and the tips shift to shallower layers of mucopolysaccharide, a change in gradient of potentials over the cell surface would result. The multiple afferent synapses would be excited after a different pattern, and so information on the direction and degree of acceleration would be started on its way centralward.

Smith: I was most interested in Professor Lowenstein's suggestion that the cuticular plate of the hair cell might shift. I have always been struck by the manner in which the top of the chalice spreads out like a collar into which the head of the hair cell fits. Is it possible that, particularly on excessive stimulation, the head of the hair cell may be moved and may stimulate one particular part of the nerve ending? This would of course depend on whether this nerve fibre is sensitive to deformation.

Lowenstein: The nerve cell comes up very close to the surface at the neck of the hair cell; is there really provision for an ion-tight junction there? Clearly endolymph must not trickle down on to the nerve endings because of its high potassium content.

Smith: There is apparently a tight junction between the hair cell and the supporting cell. The intercellular gap at the surface of the macula is approximately 80 Å (8 nm.). This is widened just below to 175 Å (17·5 nm.) (Smith, C. [1967]. In *Submicroscopic Structure of the Inner Ear*, ed. Iurato, S. Oxford: Pergamon Press). The nerve endings are always separated from the cell surface by a space of about one micrometre.

Wersäll: Although it might be, as Professor Smith suggests, that under specific conditions very large movements take place in the crista whereby the cuticular plate of the hair cell is moved, the morphology suggests that while the hair is a rather stiff rod it is condensed into a very thin structure just where it enters the cuticle. This suggests that the hair does not bend, but is displaced in one direction or another and the transducing mechanism will act upon the region of the cuticle to one side or the other. This seems to be the important point from a mechanical point of view. Whereas any shifting of the whole cuticle would take place only when there are enormous pushes on both sides.

Dohlman: We have destroyed the cupula with ultrasound. The hairs are still seen to be standing up in the subcupular space, but the cupula is destroyed and hairs are seen scattered on the surface. This seems to indicate that the subcupular space is more viscous than the endolymph in the cupular meshwork where we find the hair bundles in their canals. Therefore it seems difficult to decide what part could bend.

Lowenstein: The bending at the tips would be transformed into a shearing force which would act at the base of the hair, tangentially to the cell.

Wersäll: In fact one can demonstrate these shearing forces by taking the crista with its cupula, which is a fairly rigid substance, and displacing the cupula sideways. This gives a characteristic microphonic curve from the crista similar to that obtainable from the organ of the Corti, because all the cells are directed the

same way. If the cupula is pushed up and down a double microphonic is recorded, of the same type as one records from the lateral line organ, because some hairs will be displaced one way and some the other. This shows that the bending is a shearing force which acts on the basal part of the hair. (Incidentally, one wonders whether one should speak of movement when dealing with magnitudes of a few Ångströms. When one gets down to the lowest possible degree of stimulation one is practically out of the realm of movement.)

Dohlman: This experiment does not remove the possibility that you are bending the tips of the hairs.

Lowenstein: On this point of size, if we take von Békésy's calculations at all seriously and even if we increase them by two powers of ten, we are still within the radius of a hydrogen atom—that is the effective movement in the cochlea. So that many of the microscopic images are not very relevant to the problem.

CHEMICAL OR ELECTRICAL TRANSMISSION: THEORETICAL ASPECTS

Matthews: Professor Lowenstein referred to the extreme regularity of the resting discharge of the endings in the vestibular apparatus. With Dr. Stein, I made similar measurements on the muscle spindle and found that the discharge of the secondary ending has a similarly low variability (Stein, R. B., and Matthews, P. B. C. [1965]. *Nature, Lond.*, **208**, 1217–1218). (The average value of the coefficient of variation of the inter-spike interval for six secondary endings was 0·02 when they were discharging at 25/sec.; that is, the standard deviation of the intervals was 2 per cent of the mean interval.) Dr. Stein has made an extensive theoretical analysis of the causes of variability in neuronal discharge which is of great importance for the mechanisms of transmission (Stein, R. B. [1965]. *Biophys. J.*, **5**, 173–194).

He has analysed the transmission across a junction in which transmission depends upon a number of unitary events or quanta. If only one quantum is required to initiate an all-or-none impulse on the far side of the junction, there is likely to be a high degree of variability. As the number of quanta involved in transmission goes up, the variability is less and there is a definite relationship between the coefficient of variation determined over the whole range of mean frequencies of firing and the number of quanta required to fire an impulse.

For the secondary ending of the cat muscle spindle the number of quanta required on this theory to initiate an impulse—and it is quite hypothetical what these quanta are—is over a thousand. In the case of the vestibular hair cell also, if the degree of regularity is the same, a thousand quanta or so will be required to achieve transmission. But if one thinks in terms of a chemically transmitting synapse, the quantum should be the vesicle, and on the grounds of its size it is inconceivable that 1,000 quanta can be released from the sensory cell across on to the nerve cell in order to cause firing. The high degree of regularity of the nervous discharge does therefore throw into doubt simple quantal transmission by a chemical transmitter.

Dohlman: May I present preliminary pharmacological data in favour of chemical transmission in the vestibular apparatus? Many investigators have looked for a chemical transmitter in hair cells using mammals in their experiments. This has been difficult because so many structures in the body are affected by the inhibitors and stimulants injected that one may not detect any effect. We have therefore used frogs, which appear to be more suitable for such experiments because the substances used can be applied topically to the ampullae of the semicircular canals and the response recorded from the vestibular nerve.

If botulinum toxin is applied topically at a concentration which paralyses the rat diaphragm, a decrease in and total inhibition of the vestibular nerve response and the resting potential frequency is observed, and even after one-tenth of this dose the same reaction is again noted. Atropine causes a decrease in resting potential frequency and response to rotation. Tubocurarine applied topically to the vestibular organs paralyses transmission, although it does not do so when injected systemically, which means that it cannot pass the blood–labyrinthine barrier. This seems to indicate that the transmission of stimulation is probably mediated by a cholinergic transmitter.

The problem remains of where the spontaneous resting potential frequency is elicited, in the hair cell or in the neurone. Some experiments towards solving this problem have been made by injecting into the endolymph substances which might change the function of the endolymphatic cell membrane of the hair cells.

If γ-aminobutyric acid (GABA) is injected into the endolymph we might expect that this would increase the conductivity of the cell membrane. The response from the vestibular nerve decreases rapidly and after a few minutes the resting frequency has also disappeared. We have also injected saponin, which is known to produce a pattern of fine holes in the cell membrane. This also causes the resting potential to disappear.

These are only preliminary experiments but they seem to indicate that if we interfere with the endolymphatic cell surface of the hair cell the normal response to rotation as well as the resting potential frequency will disappear. If transmission were purely or mostly due to electrical conduction between the hair cell and the nerve ending we should not expect this result. In that case the resting potential frequency would be a property of the neurone and not of the hair cell. Therefore these experiments seem to suggest that the source of the resting potential frequency is in the hair cell and that it is probably due to a chemical mediator of the cholinergic type. This is in accordance with the investigations of Dr. Wersäll and others which have provided morphological evidence for the presence of a chemical transmitter mechanism.

Matthews: The problem remains, despite these pharmacological findings, of how to explain the extreme regularity of discharge if the hair cell is exciting the nerve cell by liberating discrete quanta of transmitter.

Lowenstein: It is true that for long periods there may be this apparent regularity in the resting discharge in the vestibular nerve. It is followed periodically by

fluctuations, but the problem still remains: for the period of time in which it is regular, how is it driven? Minute analysis will of course always show certain fluctuations.

Wersäll: Is the possibility of quantal release really excluded, for these periods of regularity?

Matthews: The problem is that if just one quantum is released and is sufficient to excite, how is it that it is always released at just the right time? What we know about quantal release at other synapses is that the process controlling it is a probability one—that is to say, when the impulse reaches the neuromuscular junction, it increases the probability of the release of quanta of transmitter substance.

Lowenstein: It is always assumed that during the release of transmitter from a vesicle there is a violent event in which the membrane of the vesicle breaks and the entire contents come out. Dr. M. P. Osborne (unpublished observations) in my department is sceptical about this because he finds ducts from the vesicles on to the cell membrane. He thinks that although there may be a certain finite amount in the vesicle, it may trickle out gradually.

Matthews: That would certainly solve this particular problem.

Wersäll: There is another possibility. H. Spoendlin has suggested that the resting discharge could be caused by electrotonic spread through the tight junction ([1966]. In *Second Symposium on the Role of the Vestibular Organs in Space Exploration*. Moffett Field, California, Ames Research Center: National Aeronautics and Space Administration). Would you accept that?

Matthews: This would overcome the problem of variability, because an electrotonic process can be continuously graded, whereas a quantal process is a unitary all-or-none affair.

Wersäll: But would the cell find it easier to control this?

Matthews: Yes, because the unit size will then depend upon the reaction of an individual polysaccharide molecule, or other molecular process, and there will be a great many of these.

Wersäll: But perhaps these molecules could lead to the release of quanta. I agree with Professor Lowenstein that to equate these big vesicles with quanta is just a simple way of applying the morphological data directly; but as far as I can see there is nothing to say that the quantum is the vesicle, or that each contains the same amount of transmitter; they might contain different dilutions.

Matthews: There is the extensive work on the neuromuscular junction where this idea was born and where it is reasonably watertight (Katz, B. [1962]. *Proc. R. Soc. B*, **155**, 455–477), but it should not be uncritically applied to every place in which vesicles are seen.

Wersäll: No one has seen that what is released after a minute stimulation is the vesicle. It has been demonstrated that a small amount of transmitter substance will give a potential but nobody has demonstrated that the small amount applied

is the amount contained in one vesicle. There is still a large gap between the granule and what the electrophysiological data show.

Lowenstein: One might have many such small unitary packets within the vesicle, so that release would still be quantal. The vesicle seen with the electron microscope need not be the ultimate unit; there might be quantal units inside it.

Matthews: The moment one leaves the neuromuscular junction these objections become of crucial importance. At the neuromuscular junction one cannot get so very many packets inside an individual vesicle. By calculation, the amount of transmitter needed to produce the end-plate potential comes out at the same order of size as the vesicle containing this amount of transmitter in isotonic solution (Eccles, J. C. [1964]. *The Physiology of Synapses*, p. 32. Berlin: Springer; Katz, B., and Miledi, R. [1965]. In *Studies in Physiology*, pp. 118–125, ed. Curtis, D. R., and McIntyre, A. K. Berlin: Springer).

Roberts: Is it not possible to reconcile this question of quantal transmission by supposing that the transduction in the first place occurs in the neuromast itself, at the junction between the hairs and the soma, that it is an electrical, continuous transduction, and that it is followed by chemical transmission from the cell body to the nerve fibre? There would then be no question of having to provide a continuous stream of quanta to explain the resting discharge, because the transmission could be per impulse. There could be fine gradation in this first transduction, and then, when the nerve is reached, the quanta come in.

Matthews: Yes, if the hair cell gives impulses, this would solve the problem.

Wersäll: In this connexion, the synaptic rod is an interesting structure, found only in the sensory cells and never at the true synaptic junctions between afferent and efferent fibres. The continuity between the hairs and the synaptic bar with its condensation of synaptic vesicles, which is also found in some of the mechanoreceptors, is interesting from this point of view, in that this may be the mechanism along which the transformation of electrical energy into chemical transmitter takes place.

Roberts: Is it possible to put a microelectrode into a hair cell?

Lowenstein: Many people including myself have tried it, but firstly the cells are very small and, secondly, the vestibular wall is like cotton wool. The only way the microelectrode might go in more easily is along the pathway of the nerve. One could probably by chance penetrate a hair cell by that means.

Smith: When we were measuring d.c. potentials in the semicircular canals, the microelectrode sometimes went through the cells in the cristae and we momentarily measured a negative of -30 to -70 mv. Of course we could not determine whether these were sensory cells or supporting cells.

Lowenstein: Trincker also found these rather dramatic steps when he penetrated. But to hold this during rotation on a torsion swing or tilting on a tilting apparatus is another matter.

Smith: Our measurements of the vestibular d.c. potential do not agree with Trincker's. We never found a positive potential in the endolymph of the vestibule

higher than about +5 mv (Eldredge, D. H., Smith, C. A., Davis, H., and Gannon, R. P. [1961]. *Ann. Otol. Rhinol. Lar.*, **70**, 1024–1037). Of course, we were not measuring, as he did, changes after movement of the cupula.

Wersäll: Am I right in thinking that this is mainly a question of zero point and that the actual shift from negative to positive recorded by Trincker could still be right? You used different electrodes and the different positive values you obtained could be due to the different zero points.

Smith: Partly yes and partly no. Our measurements were made relative to perilymph. We never recorded any high positives in the cupula, as Trincker reported.

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EXCRETION AND ABSORPTION OF ENDOLYMPH IN THE VESTIBULAR APPARATUS

G. F. DOHLMAN

Department of Otolaryngology, University of Toronto, Canada

THE classical investigations on the circulation of the endolymph by Stacy Guild in 1927 demonstrated that a flow of endolymph takes place in a direction from the scala media in the cochlea via the endolymphatic duct to the endolymphatic sac. Microscopic studies revealed three parts of the sac, each with its characteristic type of epithelium, and showed the presence of numerous free cellular elements in the lumen of the intermediate part of the sac. Since then evidence has been accumulated in support of this concept by the use of various methods. Different dyes, pigments, radioactive isotopes or labelled enzymes have been injected into the endolymph of the cochlea and have been found to accumulate in the endolymphatic sac (Yamakawa, 1929; Engström and Hjort, 1950; Lundquist, 1965; Ishii, Silverstein and Balogh, 1966). Injections into the canals have given identical results with regard to the flow of the endolymph (Doi, 1939). Dyes or isotopes have been administered parenterally and have been traced to the endolymphatic sac after passing the secretory epithelium in the cochlea or vestibular apparatus and the endolymph of the membranous labyrinth (Andersen, 1948; Dohlman, Ormerod and McLay, 1959). Other investigators have reported observations on the structure of the saccular walls strongly suggesting an absorptive function (Yamakawa, 1929; Siirala, 1942; Secretan, 1944).

More recent electron microscopic investigations (Lundquist, Kimura and Wersäll, 1964*a*, *b*; Lundquist, 1965) of the endolymphatic sac not only confirm the observations made by Guild but also add further important information. Lundquist injected colloidal silver or bacteria into the cochlear duct and found these particles in macrophages within the lumen of the endolymphatic sac. With the electron microscopic technique it was possible to show that the lining epithelium of the intermediate part of the sac consisted of two different cell types, the "dark" and "light" cells.

The light cells have numerous microvilli and rich vacuolar contents.

They show several morphological criteria for the absorption of fluid from the lumen of the sac. The "dark" cells, on the other hand, were found to produce pseudopodia embracing injected material or cellular debris and forming membrane-bounded vacuoles around these elements, thus demonstrating a phagocytotic activity by which digested material is removed from the lumen of the sac. This was further emphasized by the investigations by Ishii, Silverstein and Balogh (1966) using labelled protein and enzymes, which confirmed the phagocytotic and pinocytotic activity of these cells.

The function of this area can be illustrated further by investigations by Silverstein (1966), who analysed the endolymph from the cochlea and from the endolymphatic sac. The comparison showed a high concentration of total protein and lactic and malic dehydrogenases and a considerably lowered potassium level in the sac.

All the experiments in which foreign material is introduced into the cochlear or vestibular endolymph have always shown an accumulation of the particles or solutes in the endolymphatic sac and a clean endolymph in the remaining parts of the labyrinth. The functional activities of the endolymphatic sac might then support the image of it as an organ which absorbs fluid, so leading to an endolymph flow clearing away particles and cell debris from the entire endolymphatic system, and also leading to a concentration of proteins and solutes which then are removed by excretory and phagocytotic cells in the saccular walls.

However, several morphological findings as well as experimental results have been reported indicating absorptive functions in other parts of the endolymphatic system also, suggesting a local circulation of endolymph in the cochlea (Naftalin and Harrison, 1958).

In light microscopic studies, von Fieandt and Saxén (1936*a*, *b*, 1948) came to the conclusion that the epithelial cells of the external spiral sulcus must be absorbing or even phagocytotic cells. In their experiments with injections of iron salts, Altmann and Waltner (1950) found that absorption took place through the external spiral sulcus.

In an electron microscopic study of the fate of iron-dextran particles injected into the scala media, Yamamoto and Nakai (1964) found that the cells of the spiral prominence and the outer spiral sulcus allowed the passage of iron particles from the endolymph to the capillaries through the intercellular spaces and the pinocytotic vesicles of the cytoplasm.

From these investigations it seems evident that some cell areas in the cochlea are able to remove fluid as well as finely dispersed particles. It has therefore been assumed that similar functions could possibly be attributed to

cell groups in the vestibular parts of the endolymphatic system also. C. A. Smith (1956, 1957) has described cells in the utricle which in electron microscopy resemble the cells found covering the spiral prominence, suggesting a functional similarity.

However, in the vestibular apparatus there seems to be a great deal of confusion regarding the cell types surrounding the hair cell areas and their functional significance. The morphological description of these cells (Retzius, 1884; Iwata, 1924; Kolmer, 1927; Hazama, 1928; Werner, 1928; Berggren, 1935; von Fieandt and Saxén, 1936*a*) can be summarized as follows.

All sensory areas in the labyrinth are surrounded by high cylindrical cells. At both ends of the crista these cells are most pronounced in their differentiation and are found to cover two half moon-shaped areas in the side walls of the ampullae, called the plana semilunata. These areas are mostly described as continuing on the canalicular as well as utricular sides of the crista, linking together the cells of the two plana semilunata and thereby forming a closed lining around the hair cell region of the cristae. The same arrangement is found around the maculae of the sacculus, utricle, lagena and so on. Further away from the hair cell regions these high cylindrical cells change to low cylindrical or cubical cells before going over into the squamous epithelium of the labyrinthine walls. Iwata (1924) has regarded all these cells surrounding the sensory areas as secretory and has given them the name "regiones secretoriae". Others have stressed the difference in morphology between the high cylindrical cells on the planum semilunatum and the cells on both sides of the crista. The latter have been called "*protoplasmatische Zellen*" by Retzius (1884), "*Randepithelien*" by Werner (1928), and cells of the "intermediate zone" by Berggren (1935). Only von Fieandt and Saxén (1936*a*), using osmium-containing fixatives, reported morphological differences in the cells on the slope of the cristae which they, however, explained as due to different phases in the secretory process of these cells.

By using osmium fixation for light and electron microscopic studies of the cells surrounding the sensory areas of the vestibular apparatus in the pigeon, it was possible to further differentiate these cell areas from a morphological as well as functional point of view (Dohlman, 1964).

It was possible to show that the cells of the plana semilunata on the side walls of the ampulla consisted of very high slender cells containing organelles characteristic for secreting cells. After parenteral injection of radioactively labelled sulphur into pigeons, these cells selectively took up the sulphur and secreted it as mucopolysaccharides into the endolymph, as

could be shown with autoradiography (Dohlman, Ormerod and McLay, 1959). The cells on the canalicular as well as the utricular sides of the crista, which had earlier been described as part of the plana semilunata and were regarded as the same kind of cells, did not take up the radioactive sulphur and showed morphologically an entirely different appearance (Dohlman, 1964, 1965).

This region contained two kinds of cells in a regular sequence, "dark" and "light" cells. The "dark" "osmiophilic" cells were characterized by a dense osmiophilic cytoplasm filled with mitochondria, an abundance of infoldings of the plasma membrane in the basal parts of the cells, many vacuoles and vesicles in the cytoplasm and a brim of microvilli on the endolymphatic surface of the cell. The light cells showed no basal infoldings, no microvilli, and a "light" "osmiophobic" cytoplasm with few mitochondria but containing several lysosomes and small vesicles.

The presence of these two cell types in this region has also been shown in reptiles by Hamilton (1965) and in guinea pigs by Wersäll (1966, personal communication). Hamilton has coined the name microvillous cells, which is another name for what are known as dark cells in other tissues but stresses the presence of microvilli, which have generally been regarded as a morphological sign of an absorptive function. However, he calls the light cells supporting cells, which is misleading, as there is no reason to believe that they support any other cells of vital importance and there is more evidence for their having a secretory function. These cells do not produce the same secretion of mucopolysaccharides as the planum semilunatum cells, as is clearly shown by the autoradiographs after the injection of labelled sulphur, but they do produce a secretion which appears as eosinophilic globules over their cell surface in light microscopy (Dohlman and Boord, 1964).

This gives the impression that the "dark" cells, abundantly equipped with microvilli, and with all the signs of being engaged in pinocytosis, are absorbing cells, whereas the "light" cells seem to resemble secretory cells.

In experiments made for other purposes in which the membranous ampulla had been opened, so allowing the sodium-rich perilymph to mix with the endolymph, the dark cells showed a considerable increase in the number and size of their vacuoles.

On the assumption that in this experiment these cells had been stimulated to an increased uptake of fluid and perhaps also sodium, saline solution was injected into the canals. Methylene blue was added to follow the fate of the injection. If the pigeon was killed 10–15 min. after the injection, microscopic investigation of the dark cells showed an increase in vacuoles and it could also be seen that methylene blue had been taken up in these vacuoles.

When the animal was sacrificed ½–1 hr. after the injection, the methylene blue could be traced to the walls of the subepithelial capillaries.

The vesicles in the light cells showed no sign of the dye at this early stage but after a longer period of survival, in some of these cells a faint stain could be seen in some large vesicles. This could perhaps be interpreted to mean that the light cells were able to secrete back into the endolymph some substances earlier absorbed by the dark cells.

In marine birds, a glandular organ, the so-called "salt glands", secretes a 4–5 per cent solution of sodium chloride, apparently to rid the organism of the large amount of salt taken in from food and sea-water. These glands are composed of cells which resemble most closely the "dark" cells in the labyrinthine walls, the only difference being that they have no microvilli.

Komnick (1962; Komnick and Komnick, 1963) has developed a method of sedimenting sodium ions with an antimony compound to show the presence of these ions in the cells of the salt glands. By using this method on the labyrinthine cells it was shown that the sodium-antimony compounds were sedimented in the cytoplasm of the dark cells only, and not in the light cells. When chloride ions in the specimen were precipitated with silver lactate solution it could be demonstrated that the chloride ions were confined to the intercellular spaces and to the vacuoles of the dark cells.

Thus these experiments have shown that the dark cells are engaged in the transport of sodium. Their morphology supports the idea of pinocytotic activity and the microvilli on their surface suggest absorption. The injection experiments support the view that these cells are removing substances, including solutes such as sodium chloride, present in the endolymph.

How far the excretory activity of these cells extends has not been studied in these experiments. After injections of Indian ink and fine silver crystals made for other purposes a survey of the dark cells did not reveal any obvious sign of phagocytosis, but this does not exclude the possibility that very fine corpuscular elements are removed by these cells.

The unique chemical composition of the endolymph, with its high content of potassium and low content of sodium, is still a matter for conjecture as far as its functional significance is concerned. However, the dark cells, which are engaged in removing sodium chloride and probably other substances from the endolymph, are located in the close vicinity of all the sensory areas in the labyrinth, and only in these places. Thus both the location and the excretory function of these cells seem to be factors working toward a reduction of the sodium concentration close to the sensory area. That this must be of importance for the normal physiological functioning of the hair cells is also suggested by the known fact that the hair

cells cannot tolerate the high concentration of sodium chloride of a Ringer solution for their normal performance (Tasaki, Davis and Eldredge, 1954).

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DISCUSSION

Lundquist: We have seen dark cells in the cristae of guinea pigs and also the frog which are very similar to those demonstrated by Professor Dohlman in the pigeon; they have many cytoplasmic projections towards the basement membrane which are filled with mitochondria.

I would also stress the similarity of these dark cells to the stria vascularis cells so beautifully demonstrated by Professor Smith (Smith, C. A. [1957]. *Ann.*

Otol. Rhinol. Lar., **66**, 521–535). As we think that the stria vascularis has something to do with the regulation of sodium and potassium concentrations, they are probably in the same functional category.

Dohlman: I believe you have said that the dark cells are collected in one area of the guinea pig crista and the light cells in another?

Lundquist: In the guinea pig crista the dark cells are accumulated in a band at the bottom of the crista and especially towards the utricular side, where I believe they are continuous with the dark cells observed by Professor Smith in the utricular body (Figs. 1–4). There is also a light cell layer.

Lowenstein: If I understood Professor Dohlman correctly, the stria vascularis of the cochlea corresponds to the planum semilunatum of the ampullae, yet while no dark cells are found in the planum semilunatum, the stria vascularis apparently has both the cylindrical light cells and the dark cells.

Wersäll: In the stria of guinea pigs and mice there is a mixture very similar to what Professor Dohlman has shown in the bird, with the processes of the dark cells interdigitating with those of the light ones. A paper by K. Kikuchi and David Hilding demonstrates how they develop embryologically ([1966]. *Acta oto-lar.*, **62**, 277–291).

Dohlman: The term planum semilunatum has been given both to the cells of the sides of the ampullae and to cells on the slope of the cristae, but these are two totally different things. I would prefer to call only the cells on the lateral walls, which are purely secretory, the planum semilunatum cells, and to call the dark and light cells on the slopes perhaps juxta-crista cells, to distinguish them from the planum semilunatum cells. One finds the same two types of cells in man as in the bird on the slopes, even if not in the same regular sequence as we see them in birds.

Smith: In the stria vascularis the marginal cells (dark cells) and the light cells surround the capillaries. Below, in the spiral prominence there are also dark cells. But these latter are separated from the capillaries by the basement membrane and cells of the spiral ligament. The dark cells in the spiral prominence are similar to those in the vestibule in that their basal plasma membranes have many finger-like processes which abut upon large extracellular spaces (Smith, C. A. [1957]. *Ann. Otol. Rhinol. Lar.*, **66**, 521–537). Incidentally, the same mixture of light and dark cells is found in the ampullae of the squirrel monkey.

Lundquist: In the guinea pig also we have seen dark cells surrounding the capillaries lying inside the stria, as Professor Smith describes. The protrusions of the dark cells are intermixed with those of the light cells. There are large numbers of pinocytotic vesicles in the cytoplasm of the cells adjacent to the capillary endothelium.

Dohlman: I assume that these dark cells in the stria vascularis are not absorbing cells as they are not shown to have microvilli, whereas the light cells in the intermediate portion of the endolymphatic sac have microvilli and are absorbing

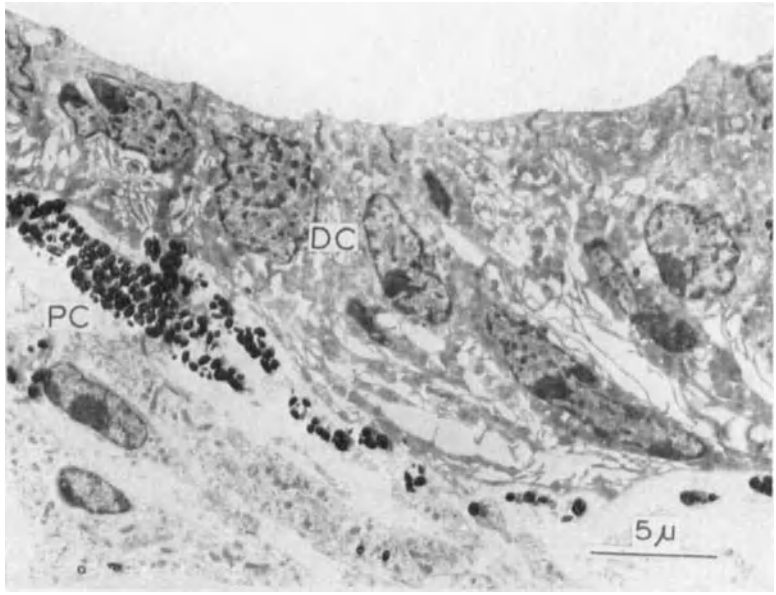

FIG. 1 (Lundquist). A dark cell (DC) in the bottom part of the crista ampullaris of the guinea pig, exhibiting many cytoplasmic projections. The fluid surface is smooth. Many pigment cells are found in this region (PC). Osmium tetroxide. × 4,200.

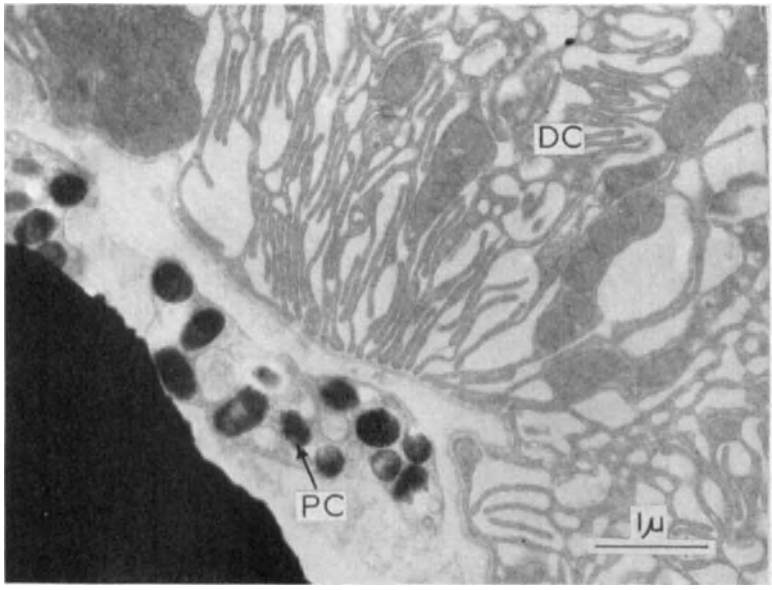

FIG. 2 (Lundquist). In higher magnification, the slender cytoplasmic projections of the dark cells (DC) are filled with rounded mitochondria, an appearance similar to the dark cells of the stria vascularis of the organ of Corti. Osmium tetroxide. × 18,000.

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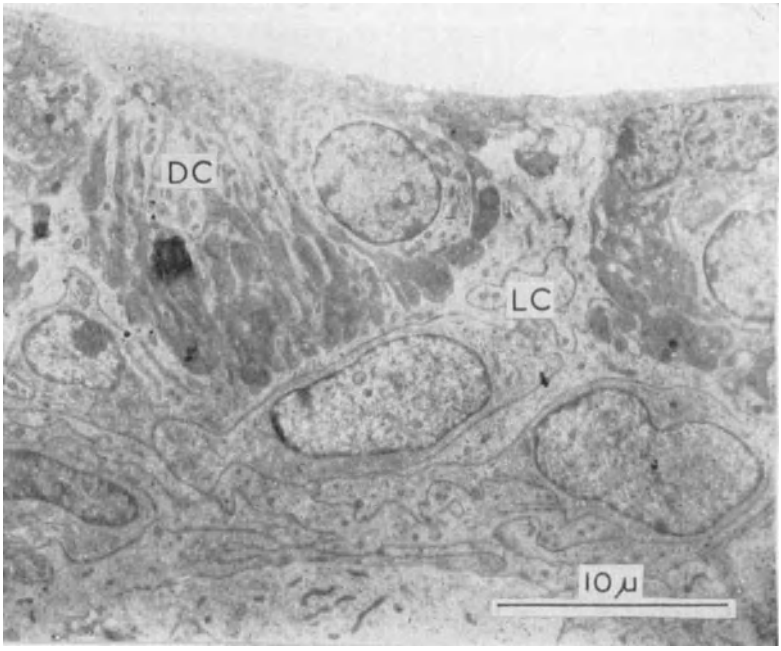

FIG. 3 (Lundquist). Electron micrograph from the stria vascularis of the guinea pig cochlea demonstrating light (LC) and dark cells (DC), as described by C. Smith (1957). The dark cells exhibit long basal cytoplasmic projections filled with mitochondria. Osmium tetroxide. × 3,800.

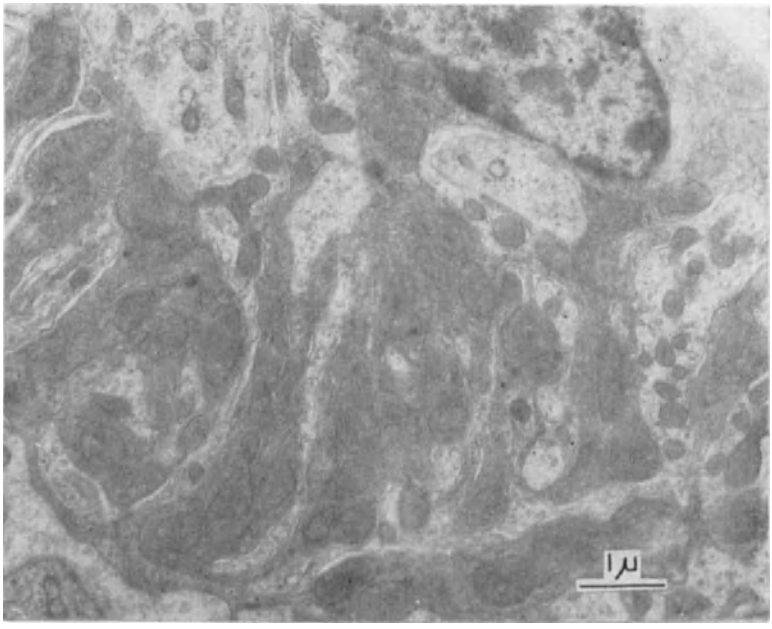

FIG. 4 (Lundquist). Detail of dark cells from the stria vascularis demonstrating the long cytoplasmic projections, extending basally, and filled with mitochondria. Osmium tetroxide. × 13,000.

and phagocytozing cells, as Dr. Lundquist has shown. The dark cells in the salt-secreting glands of sea birds have exactly the same appearance as the dark cells in the labyrinth, except that the secretory cells have no microvilli; whereas the absorbing cells in the labyrinth have a thick rim of such hairs.

Smith: Dr. R. Hinojosa has found that ferritin is taken up by the cells in the stria vascularis (personal communication, 1966).

Lowenstein: I would be interested to know whether dark cells exist around the sensory areas in the elasmobranch labyrinth, where the sodium content of the endolymph is normal.

Professor Dohlman, you quite rightly said that the endolymph is in flux! It starts in these areas we have been discussing: what happens in the endolymphatic duct and sac?

Dohlman: That has been excellently studied by Dr. Lundquist, so I shall mention only some experiments with radioactive sulphur injected into the pigeon for other purposes. The labelled sulphur is secreted by the planum semilunatum cells into endolymph but is then found, even as long as four days after the injection, as a dense condensation in the endolymphatic duct when radioactivity is no longer found in the endolymph of the labyrinth. As Dr. Lundquist has shown, absorption takes place in the endolymphatic sac. The condensations in the duct and sac are therefore probably mucopolysaccharides and protein residues from the desiccated endolymph which are apparently then phagocytozed by the free cells and light cells in the sac.

Lundquist: I have studied the normal ultrastructure of the guinea pig endolymphatic duct and sac (Lundquist, P.-G. [1965]. *Acta oto-lar.*, Suppl. 201). It turns out that the descriptions by Guild in 1927 are still valid. In the intermediate portion of the sac, and also in part of the distal portion close to the sigmoid sinus, we find light cells active in resorption, with large numbers of microvilli protruding into the lumen of the sac and the formation of pinocytotic vesicles.

I repeated the experiments of S. R. Guild ([1927]. *Am. J. Anat.*, **39**, 1–56, 57–81) in which substances were injected into the cochlear duct. When I injected colloidal silver particles into the scala media, I was able to trace them up into the endolymphatic sac and to see large cytoplasmic protrusions of the dark cells of the intermediate region engulfing the silver particles. The particles can be traced downwards into histiocytes lying in the connective tissue below the cell; the whole process of transportation from the surface towards the mesenchyme below can be demonstrated (Lundquist, P.-G., Kimura, R. S., and Wersäll, J. [1964]. *Acta oto-lar.*, Suppl. 188, 198–201; Lundquist, P.-G. [1965]. *Loc. cit.*).

Lowenstein: This is extremely interesting phylogenetically, when we consider that in the early stages, in the elasmobranchs at least, we find a unique open endolymphatic system. There are elasmobranch fishes that take up their otoliths, which are sand grains, from the outside, presumably in their youth, and the only way in is through the endolymphatic duct. Thus at that evolutionary stage the traffic was either both ways or went inwards.

Dohlman: In the frog the endolymphatic system is closed, but there is a very elaborate endolymphatic sac system filled with calcium crystals like those in the otoliths. The sacs are filled with these particles in the autumn but they seem to disappear during the winter, presumably being used in the calcium metabolism of the body.

Henriksson: In the course of the experiment mentioned earlier (see p. 129 for references) we injected fluid into frog semicircular canals and studied the sacs and the endocranial opening of the endolymphatic duct microscopically. On a few occasions we saw a minute amount of fluid coming out through the endolymphatic duct towards the endolymphatic sac. However, in some cases the distension of the sacs slowly subsided during periods of two or three minutes in spite of the fact that no fluid passed through the endolymphatic duct. However, we found no rise in the potassium of the perilymph in these experiments. This indicates a regulation of the "hydrops" through the membranes as well as through endolymphatic vessels.

Smith: We should also direct our attention to the possibility of other cellular membranes in the membranous labyrinth being active in the ionic exchange into endolymph and from endolymph to perilymph. We have examined the non-sensory saccular membrane and find that the epithelial cells have many basal cell-processes adjacent to large extracellular fluid spaces. These latter are closed off from the perilymph (at least partially) by the mesothelial cell layer. Dr. S. Iurato has recently been working on Reissner's membrane in the cochlea and has found a similar structure (Iurato, S., and Taidelli, G. [1967]. *Boll. Soc. ital. Biol. sper.*, in press). Cell membranes which do not look quite so specialized at a light-microscopic level may therefore also be active in maintaining the relative levels of potassium in the endolymph and perilymph.

Dohlman: Experiments by R. S. Kimura in which the endolymphatic sac was destroyed in order to produce a picture like that in Ménière's disease, have all been negative and I therefore believe that the dark cells in the resorptive areas of the labyrinthine walls can take over the function in an emergency to avoid a pathological increase in endolymph. However, more recently Kimura has shown in guinea pigs that if the endolymphatic sac is destroyed in this animal, distension of the whole endolymphatic system occurs, but in about six months (Kimura, R. S., and Schuknecht, H. F. [1965]. *Practica oto-rhino-lar.*, **27**, 343–354).

Friedmann: We can confirm Professor Smith's observations on the Reissner's membrane. We have studied this in guinea pigs treated with ototoxic antibiotics. Neomycin sulphate in particular produces a very enhanced activity of the microvilli and one can also see membrane-bound vacuoles appearing in these cells even with reasonably good fixation, and one has the impression that these membrane-bound vacuoles are dripping or passing into the endolymphatic space.

Lundquist: One might recall here that there are two different theories, said to be antagonistic, concerning endolymphatic flow. These are the radial flow theory proposed by L. Naftalin and S. Harrison ([1958]. *J. Lar. Otol.*, **72**, 118–136) and

supported by the experiments of M. Lawrence, D. Wolsk and W. B. Litton ([1961]. *Ann. Otol. Rhinol. Lar.*, **70**, 753–766), and the longitudinal flow theory of S. R. Guild ([1927]. *Am. J. Anat.*, **39**, 57–81), which is supported by my experiments (Lundquist, P.-G., Kimura, R. S., and Wersäll, J. [1964]. *Loc. cit.*; Lundquist, P.-G. [1965]. *Loc. cit.*) and also by the study of the effects of obliteration of the lymphatic duct and sac already mentioned by Professor Dohlman (Kimura, R. S., and Schuknecht, H. F. [1965]. *Loc. cit.*). But I suspect that we are all right, because it seems unlikely that Nature would provide only one outlet for endolymph! It must rather be that we have a dynamic fluid system with resorption and secretion of the necessary metabolites all round the sensory areas. I believe that the function of the endolymphatic sac is to be a waste-basket for the endolymphatic system, in which there is a slow continuous movement of fluid towards the sac, so that substances of high molecular weight and cellular debris can be moved out of the system into this small part with its very high phagocytic and resorptive activity.

Dohlman: Is there any evidence of the secretion of enzymes which can break down this accumulating debris?

Lundquist: T. Ishii, H. Silverstein and K. Balogh, Jr. ([1966]. *Acta oto-lar.*, **62**, 61–73) have studied the distribution of proteolytic enzymes in the endolymphatic system and have found the highest activity in the endolymphatic sac, about ten times higher than any other part of the endolymphatic system. Silverstein also found a protein content in the fluid of the sac about 40 times that of the contents of the other parts containing endolymph—about 5·2 g./100 g. compared with 144 mg./100 g. (Silverstein, H. [1966]. *Ann. Otol. Rhinol. Lar.*, **75**, 48–63; [1966]. *Laryngoscope, St Louis*, **76**, 498–512).

Dohlman: Silverstein also measured the potassium content of the endolymph and found it much lower in the endolymphatic sac than elsewhere in the labyrinth, so there is apparently also absorption of potassium.

Friedmann: The late Dr. J. C. Seymour working at the Ferens Institute interpreted all this as secretory activity rather than resorbing activity by the endolymphatic sac (Seymour, J. C. [1954]. *J. Lar. Otol.*, **68**, 689–711). Has Dr. Lundquist any comment on this?

Lundquist: Those investigations were made with light microscopy, and it is very difficult to evaluate such things as inclusions in the cells as indicative of either an absorptive or a secretory capacity. From the ultra-structural point of view as well as from our experimental results I believe the sac to be a resorptive organ and not a secretory one.

Myotatic, Kinesthetic and Vestibular Mechanisms
Edited by A.V. S. de Reuck and Julie Knight

SECTION III
VESTIBULAR MECHANISMS: NERVOUS PATHWAYS

ANATOMICAL ORGANIZATION OF CEREBELLO-VESTIBULO-SPINAL PATHWAYS

A. BRODAL

Anatomical Institute, University of Oslo, Norway

IN a general way it may be said that the vestibular nuclei give off fibres to the same parts of the brain from which they receive their afferents, namely the vestibular apparatus, the spinal cord, the cerebellum, the reticular formation and certain nuclei in the rostral brain stem. There is, however, no simple relationship between the afferent and efferent components within the various reciprocal connexions. Although systematic fibre counts have not been made it appears that of the *efferent* connexions those passing to the spinal cord are quantitatively most important. On the *afferent* side the fibres from the cerebellum far outnumber those from any of the other sources of afferents. These data are morphological indications that the vestibular nuclei are important links in the mediation of cerebellar influences on the spinal cord.

Recent studies make clear that the anatomical organization of the cerebello-vestibulo-spinal pathways is far from simple. There are still gaps in our knowledge, particularly concerning the cerebello-vestibular projections, but some major features are at present fairly clear. My account of the anatomical organization of these pathways will be based largely on studies performed in our laboratory, and attention will be focused especially on two aspects: the somatotopical organization of the pathways and synaptic relationships. Attempts will be made to correlate the anatomical data with functional observations. Some of the data to be presented as well as accounts of other vestibular connexions have been dealt with more fully in a monograph (Brodal, Pompeiano and Walberg, 1962) and in previous reviews (Brodal, 1960, 1964*a*, *b*, 1966*b*).

The methods used for tracing the sites of origin and termination of fibres have been the Marchi method, the silver impregnation methods of Nauta

(1957) and Glees (1946) and the modified Gudden method (Brodal, 1940*a*) for the study of retrograde cellular changes. In recent years electron microscopical studies of experimental degeneration have been made in addition.

VESTIBULO-SPINAL PATHWAYS

There has been some diversity of opinion as to the origin, course and termination of the vestibulo-spinal fibres. Results of recent research permit us to obtain a clearer picture, as presented diagrammatically in Fig. 1. There are two vestibulo-spinal fibre tracts, the classical vestibulo-spinal tract and a smaller bundle in the region of the medial longitudinal fasciculus. Following a suggestion of Nyberg-Hansen (1966) I shall refer to them as the *lateral* and *medial vestibulo-spinal tract*, respectively.

The *lateral*, classical, vestibulo-spinal tract takes origin exclusively from the lateral vestibular nucleus of Deiters (Fig. 1A). This appears from studies of the retrograde changes in the vestibular nuclei following lesions of the cord (Pompeiano and Brodal, 1957*a*) as well as from studies of degenerating descending fibres following isolated lesions of the individual vestibular nuclei (Nyberg-Hansen and Mascitti, 1964). The tract is purely ipsilateral, descends throughout the whole length of the cord in the ventral funiculus and is composed of fibres of varying diameters and conduction velocities (Ito *et al.*, 1964; Wilson, Kato and Thomas, 1965; Wilson *et al.*, 1966). Two other features of interest appear from our study (Pompeiano and Brodal, 1957*a*) of the retrograde cellular changes in the nucleus following lesions of the cord. Not only giant and large cells give off fibres to the cord but small cells do so as well, since these are typically affected in the experimental animals. Furthermore, the origin of the fibres shows a clearcut somatotopical pattern (Fig. 1B): fibres ending in the cervical cord arise from the rostroventral part of the nucleus, those to the lumbosacral cord come from the dorsocaudal part. This localization has been confirmed in further anatomical (Nyberg-Hansen and Mascitti, 1964) as well as physiological studies (Pompeiano, 1960; Ito *et al.*, 1964; Wilson, Kato and Thomas, 1965). Within the nucleus of Deiters one may, therefore, speak of a neck and forelimb region, a trunk region and a hindlimb region. Contrary to what has been often assumed, the lateral vestibulo-spinal fibres do not end on the perikarya of the motor ventral horn cells. After lesions of the nucleus (Nyberg-Hansen and Mascitti, 1964) degenerating fragments are seen in Nauta sections in the areas which Rexed (1952, 1954) labels VII and VIII (Fig. 1C) in contact with somata and particularly with large dendrites of cells of various types, while only an occasional fibre is

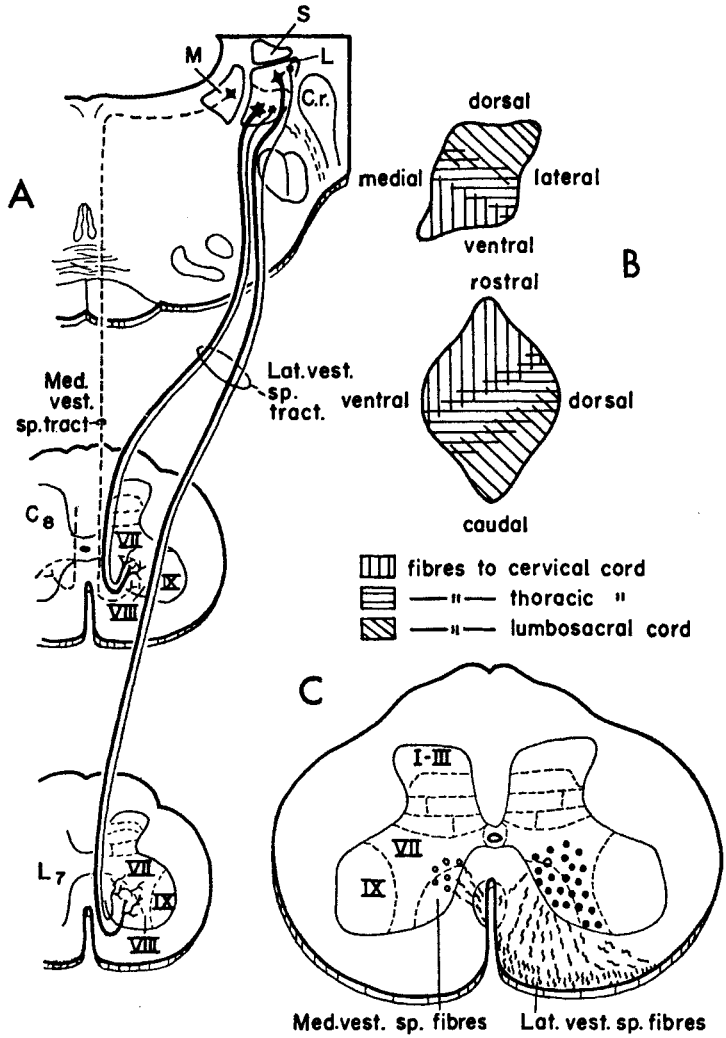

FIG. 1. A diagram summarizing some data on the organization of the vestibulo-spinal pathways in the cat as determined experimentally.

A shows the sites of origin and the course of the two vestibulo-spinal tracts. Small as well as large cells of the lateral vestibular nucleus (L) give rise to the classical lateral vestibulo-spinal tract which descends ipsilaterally throughout the cord. The medial vestibular nucleus (M) is the sole origin of the medial vestibulo-spinal tract, descending in the area of the medial longitudinal fasciculus to upper thoracic levels. A few fibres are crossed. C.r.: restiform body. S: superior vestibular nucleus. Based on studies of Nyberg-Hansen and Mascitti (1964) and Nyberg-Hansen (1964).

B shows the somatotopic organization in the lateral vestibular nucleus, above as seen in a transverse section, below in a sagittal reconstruction of the nucleus. Based on observations of Pompeiano and Brodal (1957*a*).

C shows the sites of termination in the grey matter of the cord of the two vestibulo-spinal pathways. Roman numerals refer to Rexed's zones. Based on observations of Nyberg-Hansen and Mascitti (1964) and Nyberg-Hansen (1964).

found in Rexed's lamina IX, which harbours the α as well as the γ motoneurones (Eccles *et al.*, 1960; Nyberg-Hansen, 1965).

The other vestibulo-spinal pathway (Fig. 1A), the medial one, is quantitatively less impressive than the lateral. It takes origin exclusively from the medial vestibular nucleus and can be traced only to mid-thoracic levels (Nyberg-Hansen, 1964). Its fibres are on the whole thinner than those of the lateral tract and descend chiefly—but not exclusively—ipsilaterally in the ventral funiculus close to the anterior median fissure. They end in laminae VII and VIII, approximately in the same location as the lateral vestibulo-spinal fibres (Fig. 1C).

The superior and descending vestibular nuclei do not give off fibres to the cord.

Even if cells of the vestibular nuclei may influence the spinal cord via axons or collaterals to the reticular formation it appears that their principal action on the cord must be mediated by the two vestibulo-spinal tracts. These differ in important respects in their anatomical organization and, therefore, presumably are functionally dissimilar as well.

CEREBELLO-VESTIBULAR PATHWAYS

As referred to above, the part of the central nervous system which is most amply provided with fibres ending in the vestibular nuclei is the cerebellum. For the problem concerning us here, it follows that our interest has to be focused on those components of the cerebello-vestibular pathways which end in the medial and lateral nuclei, while the others are of less immediate importance. As we shall see, the lateral nucleus stands out as the main station in the cerebello-vestibulo-spinal pathways.

There are two regions of the cerebellum which are provided with efferent pathways to the vestibular nuclei: the anterior and posterior vermis and the flocculonodular lobe. The former regions send fibres directly to the vestibular nuclei but in addition dispose of an indirect route, since they project on to the fastigial nucleus, from which second-order neurones pass to the vestibular nuclei. From a functional point of view it is important that the flocculonodular lobe is provided with (primary and secondary) vestibular afferents, while the anterior and posterior vermis appear to lack such afferents. They are dominated by afferent fibres which transmit impulses from the spinal cord. (However, the flocculonodular lobe as well appears to receive spinal impulses, namely via the group x [Brodal and Pompeiano, 1957] since this projects on to this part of the cerebellum [Brodal and Torvik, 1957] and receives a massive spinal influx [Pompeiano and Brodal, 1957*b*].)

The pattern within these cerebello-vestibular connexions is rather complex, and many details are as yet not known. Only a sketchy outline can be given here. As concerns the vestibular part of the cerebellum, Dow (1936, 1938) concluded from his Marchi studies that the nodulus and adjoining folia of the uvula send fibres to all four vestibular nuclei, while the flocculus supplies only the lateral and superior nuclei. However, at this juncture it is appropriate to mention that the vestibulo-cerebellum, defined as that

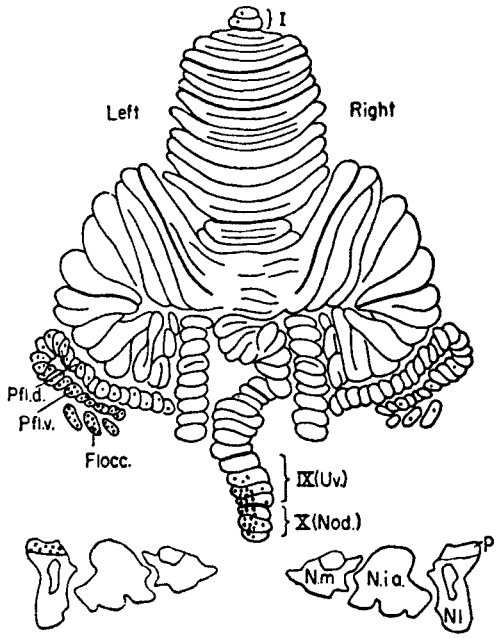

FIG. 2. The dots in the diagram of the cerebellar surface (imagined unfolded) and of the intracerebellar nuclei show the sites of termination of primary vestibulo-cerebellar fibres and thus indicate the territory of the "vestibulo-cerebellum". (From Brodal and Høivik, 1964, by permission of the Editors of *Archives italiennes de biologie*.)

region of the cerebellum which receives primary vestibular fibres, extends beyond the confines of the flocculonodular lobe and includes the major ventral part of the uvula and the ventral paraflocculus. This appears from our (Brodal and Høivik, 1964) experimental study of the cerebellar distribution of primary vestibular fibres in the cat (Fig. 2). Recent studies (Angaut and Brodal, 1967) made with the method of Nauta (1957) indicate that there are probably no fibres from the paraflocculus to the vestibular nuclei. However, they have shown that some fibres pass

from the flocculus to the medial and descending nuclei which may have been missed in Dow's studies, since the fibres are uniformly very fine. While this indicates similarities between the two divisions of the flocculonodular lobe, it appears from other findings that they are not functionally equivalent (see Brodal and Jansen, 1954, p. 289 ff;

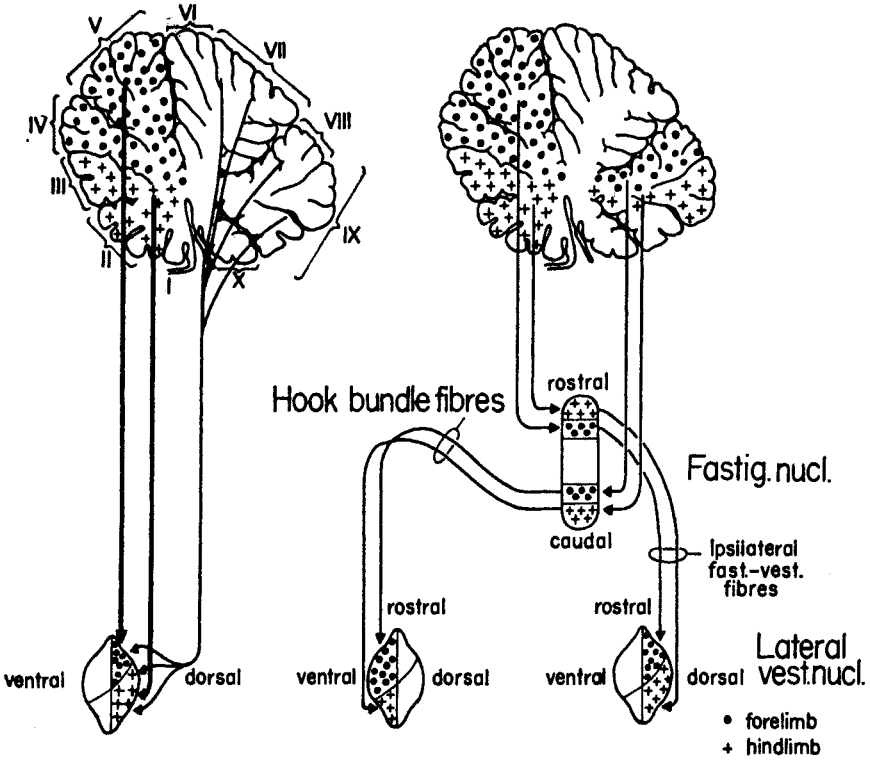

FIG. 3. Diagram illustrating major features in the projections from the cerebellar cortex on to the nucleus of Deiters (to the left) and (to the right) in the projections from the cerebellar cortex on to the fastigial nucleus and from this to the lateral vestibular nuclei.

Note that the direct cerebello-vestibular fibres and the projection from the rostral part of the fastigial nucleus end in the dorsal half of the ipsilateral lateral vestibular nucleus, while the fibres from the caudal part of the fastigial nucleus via the hook bundle supply the ventral half of the contralateral lateral vestibular nucleus. Within each of these projections there is a somatotopic localization. See text. (Slightly altered from Brodal, Pompeiano and Walberg, 1962.)

Fernández and Fredrickson, 1964, for some data), and our study indicates that within some of the nuclei the distribution of fibres from the two divisions of the "vestibulo-cerebellum" is not identical. Judging from their fibre connexions both divisions may thus influence the activity of the spinal cord, since they give off fibres to the medial as well as the lateral vestibular nuclei. However, in view of the quantitatively modest connexions to

the medial and lateral vestibular nuclei the influence of the flocculonodular lobe on the cord must be assumed to be less potent than the influence of the anterior and posterior lobe, the "spino-cerebellum".

Turning to the latter, it should be noted that the direct pathway from the vermis proper of the cerebellum to the vestibular nuclei is fairly massive and contains a number of thick fibres. Its terminal distribution within the vestibular nuclei, as determined experimentally with the Nauta and Glees methods (Walberg and Jansen, 1961) is restricted to the ipsilateral descending and lateral nuclei. Furthermore, as seen from the diagram of Fig. 3, within the latter the fibres end only in the dorsal half, while the ventral half is free. Finally, there is a somatotopical pattern within the projection from the anterior lobe: the forelimb region of the anterior lobe sends its fibres to the forelimb region of Deiters' nucleus, the hindlimb region to the hindlimb region. (The results for the posterior vermis are not decisive.)

This direct cortico-vestibular pathway from the "spinal part" of the cerebellum is supplemented by the other, having a synaptic interruption in the fastigial nucleus. The first link of this pathway, the projection from the cerebellar cortex to the fastigial nucleus, is arranged in an orderly manner (Jansen and Brodal, 1940, 1942). Even if subsequent studies (Eager, 1963, 1966; Walberg and Jansen, 1964) indicate that the projection is not as sharp as may appear from the original Marchi study of Jansen and Brodal the general principle seems to be valid (for some comments on this question see Brodal, 1967). By making lesions restricted to small parts of the fastigial nucleus it has been possible to determine the main principles of organization in the second link in the pathway, the projection of this nucleus on to the vestibular nuclei (Walberg *et al.*, 1962*a*). In contrast to the direct cerebello-cortical vestibular fibres, those from the fastigial nucleus end in the medial as well as the descending and lateral nucleus, although only in certain parts of them. (A few fibres appear to end in the superior nucleus.) Here only the fibres to the lateral nucleus of Deiters will be considered. As seen from the diagram in Fig. 3, fibres from the rostral third, approximately, of the fastigial nucleus pass ipsilaterally and end in the dorsal half of the nucleus of Deiters, in the same area where the direct cerebellar cortico-vestibular fibres terminate. Those from the caudal third, approximately, of the fastigial nucleus cross in the hook bundle and end in the ventral part of the contralateral nucleus. Furthermore, there is evidence that both components are somatotopically organized. It should be noted (see Figs. 3 and 4) that the border between the region receiving fibres from the anterior lobe and the rostral part of the fastigial nucleus and the region receiving fibres from the caudal part of the fastigial nucleus crosses the border between

the fore- and hindlimb regions. Accordingly, each component of the projections may act on both limbs. This may be an indication that the anterior and posterior vermis, although rather similar with regard to their afferent connexions, differ functionally on certain points.

The somatotopical patterns in the cerebello-vestibulo-spinal pathways from the vermis through the nucleus of Deiters make it possible to understand that stimulation or ablation of appropriate areas of the cerebellum give rise to somatotopically localized effects (see also Pompeiano, 1967). The opinion that was formerly held, that a pathway via the reticular formation is involved in this mechanism, does not receive support from recent physiological studies, and is also at variance with the anatomical observations that neither the reticulospinal (Torvik and Brodal, 1957) nor

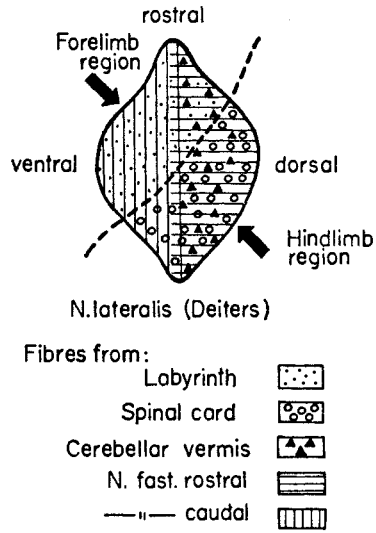

FIG. 4. Simplified and diagrammatic representation of the distribution within the lateral vestibular nucleus of afferent fibres from different sources. Only the main contingents of afferents are included (see key). Varying densities of terminations are not shown. The nucleus of Deiters is represented in the sagittal plane. Note particular areas of termination of the various afferent contingents.

the fastigioreticular projection (Walberg *et al.*, 1962*b*) betrays any somatotopical pattern. The existence of a localization within the projections of the cerebellum on to the nucleus of Deiters has been conclusively demonstrated in single-unit recordings by Pompeiano and Cotti (1959). In addition, it appears from physiological studies (Moruzzi and Pompeiano, 1957; Batini and Pompeiano, 1958; see also Pompeiano, 1967) that there are mediolateral functional differences within the fastigial nucleus (as well as within the vermis) to which so far no anatomical counterpart has been found.

SOME OTHER AFFERENT CONNEXIONS OF THE VESTIBULAR NUCLEI

The complexity of the organization of the vestibular nuclei is further borne out by other data (see Brodal, Pompeiano and Walberg, 1962, for

particulars), such as some findings on the distribution of other afferent connexions. In general each of these has its restricted site of termination within the individual vestibular nuclei. For example, in the nucleus of Deiters the primary vestibular fibres (Fig. 4) supply only its rostroventral part—that is, the neck and forelimb (and part of the trunk) region (Walberg, Bowsher and Brodal, 1958). The spinal afferents, on the other hand, are restricted to the hindlimb (and part of the trunk) region (Pompeiano and Brodal, 1957*b*, in the cat; Mehler, Feferman and Nauta, 1960, in the monkey; Bowsher, 1962, in man). This presumably indicates that vestibular control of the neck and forelimb is more immediate than that of the hindlimb. The medial nucleus receives primary fibres only in its medial region, and scanty spinal afferents supply chiefly its most caudal part.

SYNAPTIC RELATIONSHIPS WITHIN THE CEREBELLO-VESTIBULO-SPINAL PATHWAYS AND INTRINSIC ORGANIZATION WITHIN THE VESTIBULAR NUCLEI

These subjects are of immediate relevance for the interpretation of physiological observations. An attempt will be made to discuss some data bearing on these problems.

There appear to be no data on the synaptic actions of the *medial vestibulo-spinal fibres*, coming from the medial vestibular nucleus, which do not appear to contact motoneurones (Nyberg-Hansen, 1964). On account of the restriction of the tract to the cervical and upper thoracic cord it appears a likely assumption that the spinal pathway from the medial nucleus may be concerned especially in the control of proprioceptive mechanisms of the upper segments of the spinal cord.

The *lateral vestibulo-spinal tract* is better known and is obviously a very specific pathway. The somatotopically organized tract acts on α as well as γ motoneurones (Andersson and Gernandt, 1956; Gernandt, Iranyi and Livingston, 1959), and exerts a facilitatory action on extensor motoneurones. The facilitatory effect is concluded to occur monosynaptically as well as polysynaptically (Lund and Pompeiano, 1965). Recently Grillner, Hongo and Lund (1967) have brought forward evidence that vestibulo-spinal impulses activate monosynaptically interneurones which mediate disynaptic inhibition from extensor group Ia fibres to flexor motoneurones. The latter finding fits in with the anatomical demonstration that the vast majority of the vestibulo-spinal fibres do not end in lamina IX. However, since dendrites of motoneurones extend far dorsally in the grey matter of the cord (Aitken and Bridger, 1961; Sprague and Ha, 1964) it is possible that motoneurones may be acted upon monosynaptically by endings of vestibulo-spinal fibres on such dendrites.

Whether there are different fibres which mediate the effects on α and γ neurones is not known. It is of interest, however, that after vestibular nerve stimulation γ neurones have been found to discharge at a lower strength of stimulation than α fibres (Andersson and Gernandt, 1956). The suggestion may be ventured that this may perhaps be correlated with the presence of large and small cells, respectively, in the nucleus of Deiters, since both send their axons to the spinal cord (Pompeiano and Brodal, 1957*a*), although other explanations may also be sought. The presence of two types of cells in the nucleus is of relevance from other points of view as well.

Thus we have found in our experimental studies that the various groups of afferent fibres do not differ only with regard to their sites of ending but in addition present differences with regard to the cells on which they end. Primary vestibular afferents (Walberg, Bowsher and Brodal, 1958) as well as the fastigial afferents (Walberg *et al.*, 1962*a*) terminate largely, if not exclusively, on small cells, while the fibres from the cerebellar cortex (Walberg and Jansen, 1961) and those from the spinal cord (Pompeiano and Brodal, 1957*b*) establish contact, chiefly at least, with large cells in the nucleus of Deiters. In all instances, however, it appears from silver impregnation studies that contacts are established with somata as well as with proximal dendrites. Quite often pictures of "pericellular arborizations" can be observed (Fig. 5). Whether thin dendrites as well are contacted cannot be decided in such studies. This, however, is a question of considerable interest, particularly in view of some recent neurophysiological findings. Thus Ito and collaborators have concluded that the direct cortico-vestibular fibres exert a monosynaptic inhibitory action on the cells of the nucleus of Deiters (Ito and Yoshida, 1964; Ito and Kawai, 1964) (as well as on the cells in the fastigial nucleus; Ito, Yoshida and Obata, 1964). According to current views (see Eccles, 1964) this would indicate that synaptic contacts are established with somata and proximal dendrites, and is so far in agreement with anatomical data.

When we come to the anatomical evaluation of places of synaptic contact, it is, however, necessary to be aware that a final answer cannot be expected from studies made with silver impregnation methods. In the first place, as referred to above, contacts with thin dendrites escape recognition. Secondly, the finding of a degenerating fragment in contact with a soma or a dendrite does not prove that the contact represents a synapse. The fragment may belong to a fibre and not a bouton, or there may be interposed between the supposed pre- and postsynaptic structures other elements, such as a glial sheet, which cannot be seen in the light microscope but which, when present, will exclude the contact from being a

synapse. In order to get more information on the true synaptic relationships in the vestibular nuclei we have in our department recently started experimental electron microscopical studies of the afferent connexions. This necessitates a study of the normal ultrastructural organization of the vestibular nuclei. So far we have concentrated on the nucleus of Deiters. It appears from these studies (Mugnaini and Walberg, 1967*a*), among other things, that quite often a terminal bouton is separated from a soma or dendrite by a thin glial sheet. Thus not every degenerating bouton seen in silver impregnation studies actually represents a synapse. On the other hand, fairly thin axon or collateral branches can often be seen running along a dendrite and establishing a series of true synaptic contacts with it (Fig. 6). This indicates that many of the degenerating fragments found along the surface of dendrites, for example those forming part of "pericellular arborizations" (Fig. 5), are indeed places of synaptic contact. Regular terminal boutons of varying sizes are found in great numbers, particularly on dendrites. Some of them are in contact with spines which occur on the dendrites (Fig. 9). It is of particular interest that true synaptic contacts are found in great numbers also on thin dendrites (Fig. 7).

In normal preparations it is, of course, not possible to decide to which afferent system a particular bouton belongs. However, if a fibre and its boutons degenerate, they can be identified under the electron microscope as degenerating because they undergo characteristic changes. Three and a half days after a lesion the bouton appears shrunken, its shape is often irregular, its mitochondria begin to disintegrate, the ground substance becomes granular, and the entire bouton becomes more electron-dense (Figs. 8 and 9). So far the afferents to the lateral vestibular nucleus from the cerebellar vermis and from the vestibular receptors have been studied in this way, following lesions of the anterior lobe vermis and transections of the vestibular nerve, respectively. In the former study Mugnaini and Walberg (1967*b*) found degenerating boutons in contact with somata and dendrites of giant as well as smaller cells in Deiters' nucleus. Furthermore, it is of particular interest that degenerating boutons have been seen even on very thin dendrites. Largely corresponding findings have been made in the study of primary vestibular fibres (Mugnaini, Walberg and Brodal, 1967). Degenerating boutons are particularly abundant along the thicker dendrites, in agreement with the findings made in silver impregnation studies (see Fig. 5), but also here contacts are established with thin dendrites.

The observation that the corticocerebellar fibres establish synaptic contact with small dendrites raises some problems when it is confronted with recent physiological observations and views. Either these fibres must

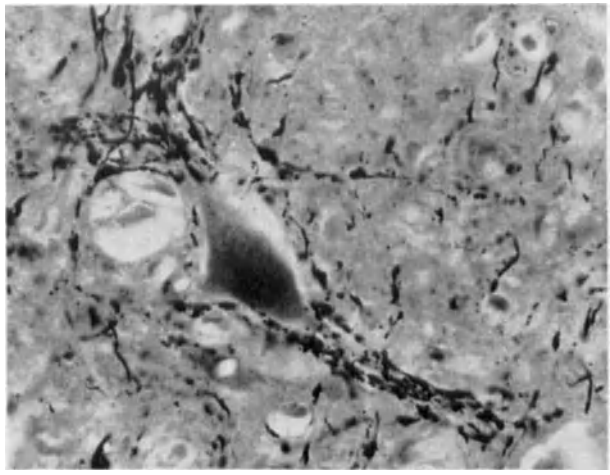

FIG. 5. Photomicrograph of a silver-impregnated section (Nauta method) from the lateral vestibular nucleus of a cat, following transection of the vestibular nerve. Degenerating fragments are seen in contact with dendrites and to some extent with the soma of a relatively small nerve cell. × 500.

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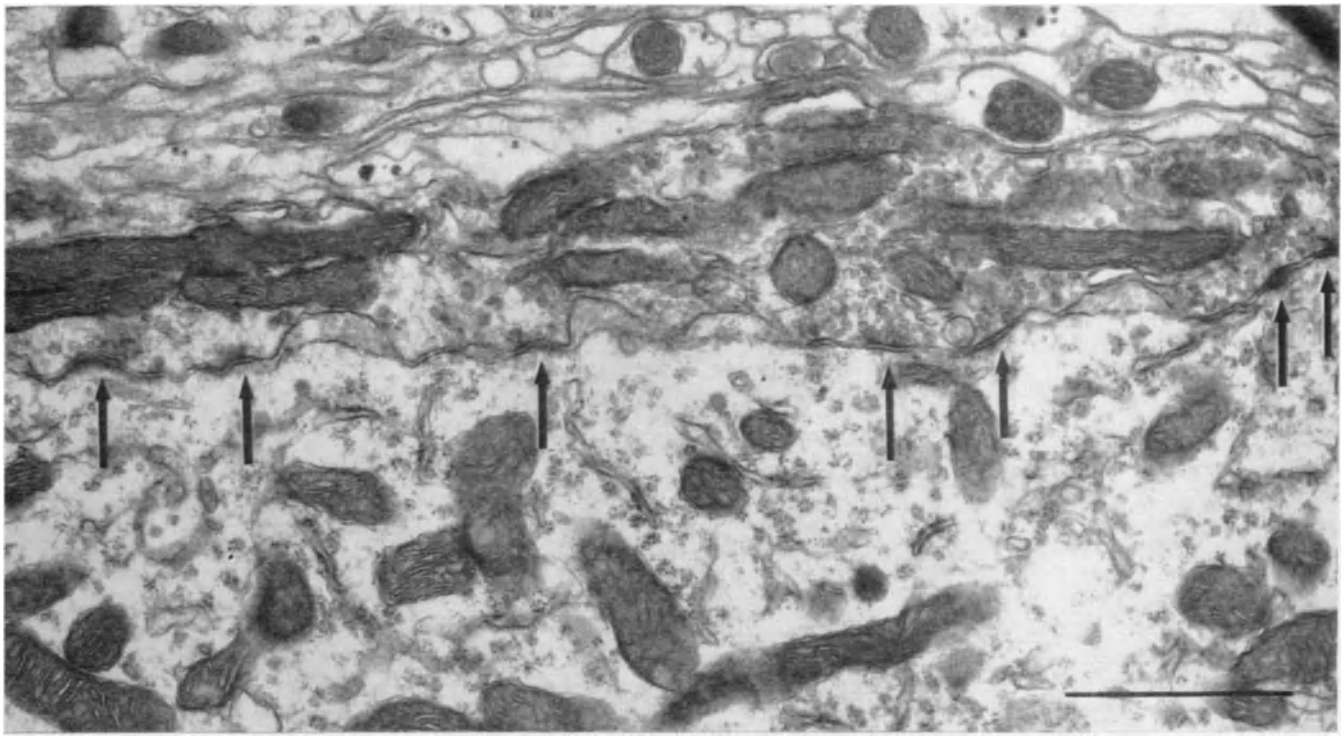

FIG. 6. Electron micrograph from the lateral vestibular nucleus in the cat.

A thin axon (above) running along the surface of a thick dendrite (below) establishes a number of synaptic contacts (arrows) with the latter. Scale line 1 μm. (Reproduced by courtesy of Dr. E. Mugnaini and Dr. F. Walberg.)

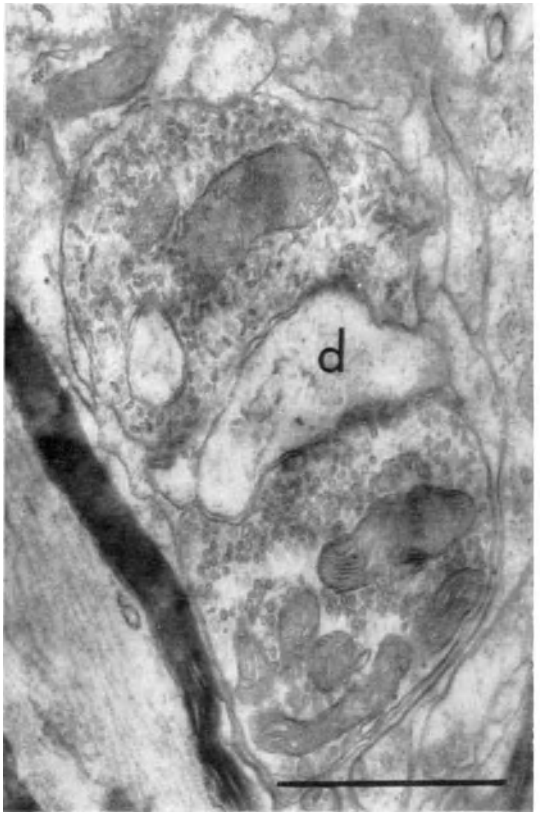

FIG. 7. Electron micrograph from the lateral vestibular nucleus in the cat.

A thin dendrite (d) is contacted on two sides by terminal boutons. Below to the left, part of a fibre with its myelin sheath. Scale line 1 μm.

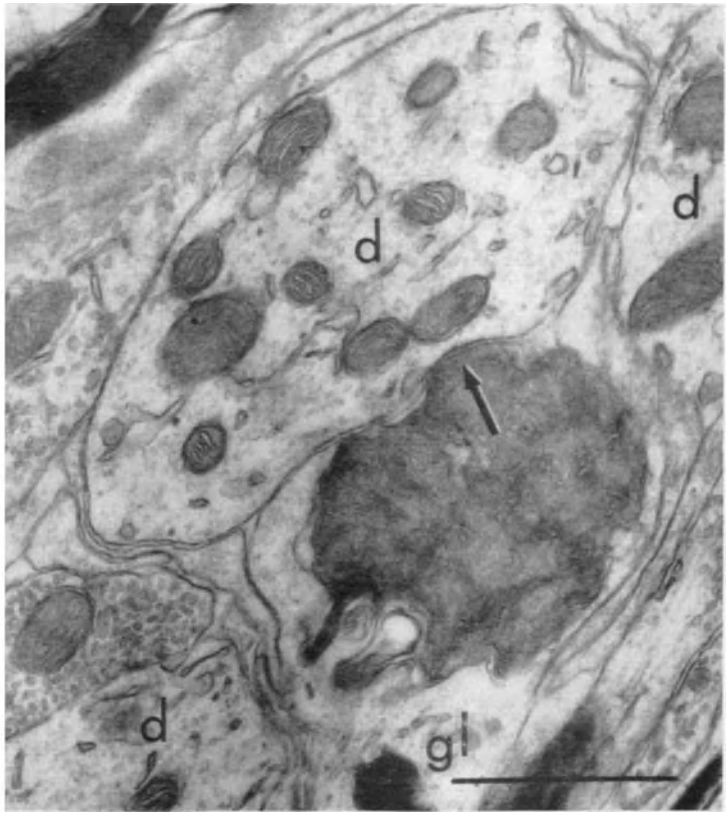

FIG. 8. Electron micrograph from the lateral vestibular nucleus in the cat, $3\frac{1}{2}$ days following a transection of the vestibular nerve.

A degenerating bouton is in contact with a dendrite (d). Arrow points to region of synapse. The degenerating bouton is partially surrounded by a glial process (gl). Scale line 1 μm.

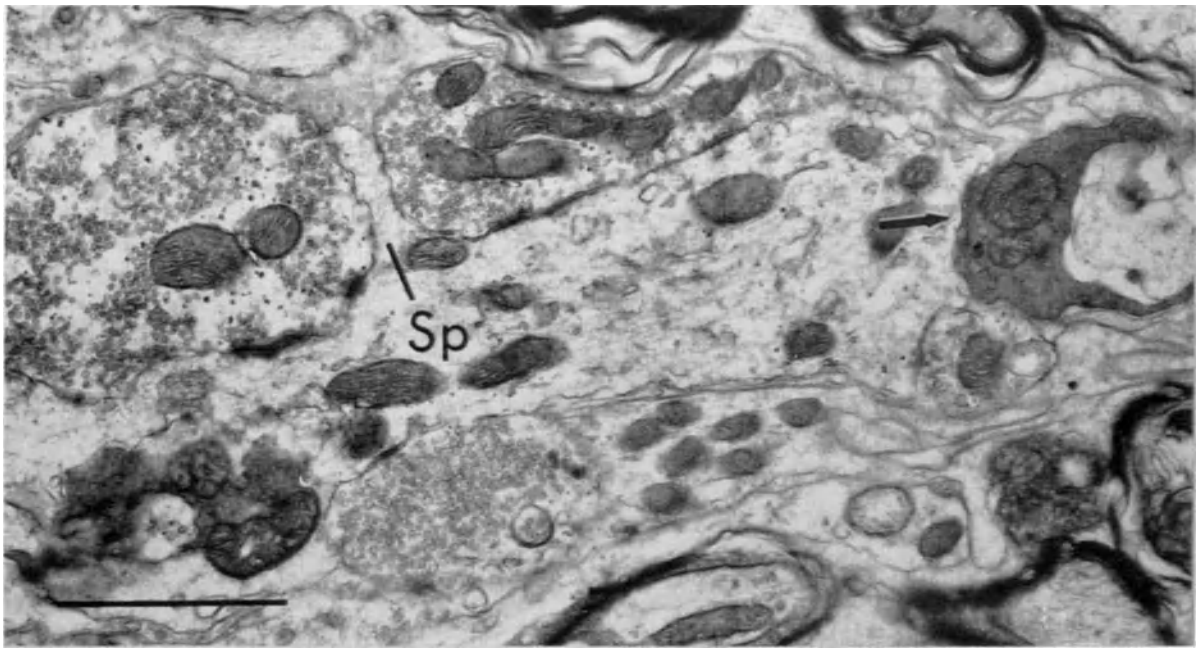

FIG. 9. Electron micrograph from the lateral vestibular nucleus of the cat 3½ days after a lesion of the anterior cerebellar vermis.

A thin dendrite provided with a spine (Sp) is contacted by normal boutons and (to the right) by a degenerating bouton. Arrow points to site of synaptic contact. Scale line 1 μm. (Reproduced by courtesy of Dr. E. Mugnaini and Dr. F. Walberg.)

establish excitatory as well as inhibitory synapses on the cells of the nucleus of Deiters, or the current view of the excitatory synapses as axodendritic is not valid for the nucleus of Deiters. Further studies will presumably solve this problem. (It may be mentioned that the electron microscopical observations in the fastigial nucleus following lesions of the anterior lobe vermis correspond to those made in Deiters' nucleus.)

There is reason to believe that continued electron microscopical investigations may throw further light on the synaptic organization of the vestibular nuclei, and give important clues for interpretations of physiological data. However, it is important to realize that it is a necessary prerequisite for electron microscopical studies of degenerating fibres and boutons, that the terminal distribution of the afferents to be studied is known in as great detail as possible. This means that the studies have to be preceded by careful light microscopical analyses, especially since the various afferents have their particular sites of ending within the various nuclei, and the pattern in the anatomical organization of the vestibular nuclei has turned out to be extremely complex (see Brodal, Pompeiano and Walberg, 1962; Brodal, 1964*a*, *b*, 1966).

One should not expect, however, that electron microscopical studies will solve all problems concerning the finer organization within the vestibular nuclei (or any other). Certain features can at present be clarified only by means of the Golgi method. For example, neither electron microscopical nor silver impregnation studies give information on whether a single axon establishes synaptic contacts with the soma and dendrites of the same cell. That this is very often the case is evident from a recent extensive Golgi study of the vestibular nuclei performed by Hauglie-Hanssen in our institute. Often an axon may be seen "climbing" along a dendrite for a considerable distance. It further appears from this work that an afferent fibre may give off a number of collaterals to a single cell, as one would indeed assume from the dense accumulation of argyrophilic particles on the surface of cells after the interruption of afferent fibres (Fig. 5). The Golgi method further may give other important information of essential importance to functional analyses. Thus, Hauglie-Hanssen, in confirmation of Ramon y Cajal (1909–11), did not find any cell of the Golgi II type which might be considered as a pure internuncial. Some small cells which have a number of branches close to the soma, and which may possibly act as internuncials, were observed only in the medial and descending vestibular nucleus. Finally it is of interest that there are in all regions of the vestibular complex dendrites which extend from one nucleus into neighbouring ones, with considerable regional variations, however (Hauglie-Hanssen,

1967). Dendrites may also be traced into adjacent nuclei or fibre bundles. However, the vast number of dendrites is contained within the particular nuclear region (see Figs. 11 and 14 in Brodal, 1964*a*). The same appears from Mannen's (1965) studies, although this author did not consider the various subdivisions separately.

FUNCTIONAL CORRELATIONS

Some functional correlations have been touched upon in the preceding sections of this paper. Thus I have mentioned that there is physiological as well as anatomical evidence that the cerebello-vestibulo-spinal pathway from the spinal regions through the nucleus of Deiters is somatotopically organized throughout its extent, making it likely that those influences which can be exerted on the spinal apparatus from the cerebellum and which are somatotopically localized, are mediated via the nucleus of Deiters (cf. Pompeiano, 1967). The fact that small as well as large cells of the nucleus of Deiters project on to the cord is presumably of some functional importance. As mentioned above, one might wonder whether the two categories of cells are concerned in the vestibular control of α and γ motoneurones, respectively. This assumption is of relevance from another point of view also. As we have seen there is a differential distribution of fibres from the anterior vermis cerebellar cortex and the rostral part of the fastigial nucleus chiefly on to large and small cells of the nucleus of Deiters, respectively. The same region of the cerebellar cortex acts directly on large cells and indirectly—via the fastigial nucleus—on small cells. It is tempting to speculate upon whether this peculiar feature may be related to the role played by the cerebellum in the α–γ linkage (Granit, Holmgren and Merton, 1955). It is well documented that in its action on the spinal cord, the vestibulo-spinal projection cooperates with other descending pathways (see for example, Gernandt, 1960). The demonstration by Erulkar and co-workers (1966) that vestibular impulses may impinge on the same internuncial cells in the spinal cord as dorsal root impulses and cerebral cortical impulses, and the mapping of the location of these interneurones, are promising steps towards a better understanding of the basis of this co-operation.

It is puzzling that the primary vestibular fibres are distributed to the forelimb region only of the nucleus of Deiters, since after vestibular nerve stimulation effects are obtained on hindlimbs as well as forelimbs. There is no evidence from Golgi studies that dendrites of cells in the hindlimb region of the nucleus extend into the forelimb region and may be affected by primary vestibular impulses in this way. Neither have internuncial cells

been identified so far in the nucleus of Deiters. A third possibility, which still remains open, may be that recurrent collaterals of axons from vestibular nuclei cells synapse with cells in the nucleus of Deiters, especially its hind-limb region.

Even if in the past attention has been devoted chiefly to the cerebello-vestibulo-spinal pathway from the vermis through the nucleus of Deiters, it should not be forgotten (1) that not only the "spino-cerebellum" but the "vestibulo-cerebellum" as well possesses a projection to the vestibular nuclei, among these the nucleus of Deiters, and (2) that there is another vestibulo-spinal route, the medial vestibulo-spinal tract, coming from the medial vestibular nucleus, which receives fibres from the vestibulo-cerebellum as well as from the fastigial nucleus.

A comparison of the anatomical organization of the two vestibulo-spinal pathways (see p. 150) makes it appear very likely that they are functionally dissimilar. This assumption is further strengthened by an analysis of Lorente de Nó's data on the distribution within the vestibular nuclei of the afferents from the various subdivisions of the labyrinth. It appears (for an account of the data and references see Brodal, Pompeiano and Walberg, 1962, p. 20) that the lateral vestibular nucleus receives fibres from the utricular macula (perhaps also from the cristae), while the medial nucleus appears to be supplied by fibres from the cristae only. The former relation seems to be easily compatible with the tonic facilitatory action of the nucleus of Deiters on extensor motoneurones. Units responding to horizontal rotation or stimulation of the horizontal semicircular canals have been found in the medial nucleus (Eckel, 1954; Duensing and Schaefer, 1958; Shimazu and Precht, 1965).

In view of the marked influence exerted by the vestibular nuclei (the lateral and medial) on the spinal cord and their importance for postural mechanisms it might be expected that they receive ample information from the muscles, tendons and joints and possibly other somatic receptors. In recent years this subject has been studied by single-unit recordings from the vestibular nuclei or by extracellular registrations. Thus Feldman, Wagman and Bender (1961) obtained responses in what are apparently the lateral and medial nuclei following electrical stimulation of the sciatic nerve. Fredrickson, Schwarz and Kornhuber (1965) observed that joint movements were particularly effective in eliciting responses. Most reacting cells were found in the medial and descending and some in the lateral nucleus. Wilson and co-workers (1966) found stimulation of mixed and cutaneous nerves to be more effective than stimulation of muscular nerves in facilitating cells in the nucleus of Deiters. The spinal pathways involved

in these effects are, however, not established. It appears puzzling that anatomically the spino-vestibular connexions are not very impressive. The direct spino-vestibular fibres are rather scanty, and as mentioned above they reach only the hindlimb region of the nucleus of Deiters (Pompeiano and Brodal, 1957*b*). Furthermore, they appear to come chiefly from lower levels of the cord, even from levels below the caudal end of the column of Clarke. According to Golgi observations by several authors the dorsal spino-cerebellar tract gives off collaterals to the nucleus of Deiters. Since this tract was interrupted as well in some of the experiments of Pompeiano and Brodal (1957*b*), it follows also that the collaterals of the dorsal spino-cerebellar tract supply only the hindlimb region of the nucleus of Deiters.

Other possible pathways from the spinal cord have been suggested, such as a route via the inferior olive, the lateral reticular nucleus, other regions of the reticular formation or the dorsal column nuclei (Wilson *et al.*, 1966). However, even if a restricted part of the medial accessory olive appears to project on to the vestibular nuclei (Brodal, 1940*b*), spinal afferents have not been traced to this part (Brodal, Walberg and Blackstad, 1950). There are some indications that a region of the lateral reticular nucleus sends fibres to the flocculonodular lobe (Brodal, 1943), but nothing is known of a possible projection to the vestibular nuclei, and spinal afferents to this region of the nucleus were not found in an experimental study (Brodal, 1949). The possibility remains open that some fibres from the dorsal column nuclei may end in the vestibular nuclei. Finally, although experimental evidence is difficult to obtain on this point, there are indications from Golgi studies (Ramon y Cajal, 1909–11; Lorente de Nó, 1933; Scheibel and Scheibel, 1958) that axons of cells in the medullary and pontine reticular formation give off collaterals to some at least of the vestibular nuclei, and spinal afferents have been traced to these parts of the reticular formation (Rossi and Brodal, 1957; Mehler, Feferman and Nauta, 1960; and others). However, it is difficult to make judgments concerning the quantity of such fibres from Golgi preparations.

In view of the apparent paucity of spino-vestibular connexions it is tempting to assume that the spinal impulses influencing the vestibular nuclei do this to a considerable extent via the cerebellum, since there are several, quantitatively massive spinal pathways to the spino-cerebellum (dorsal and ventral spino-cerebellar tracts, external-cuneate-cerebellar tract, spinal routes via the inferior olive and the lateral reticular nucleus) as well as to the vestibulo-cerebellum (via the group x of the vestibular complex, see Brodal and Pompeiano, 1957; Pompeiano and Brodal, 1957*b*; Brodal and Torvik, 1957). However, even in decerebellated animals (Fredrickson, Schwarz and Kornhuber, 1965; Wilson *et al.*, 1966) spinal impulses reach the vestibular nuclei. More studies are obviously needed to clarify along which routes these impulses travel.

GENERAL COMMENTS

The data mentioned in this presentation on the anatomical organization of the cerebello-vestibulo-spinal connexions reveal that there are still a number of open questions. For a better understanding of the functional

role of these connexions more information is also needed on the afferents from extracerebellar sources which may influence the vestibular nuclei directly or indirectly and interact with impulses from the cerebellum. In our studies of the vestibular nuclear complex we have been struck by its extremely complicated anatomical organization. In fact, it appears from these and other studies that the vestibular nuclei represent a mosaic of minor units or subdivisions, each with its specific features. It may be surmised that some of the regional peculiarities may be related to differences in the receptor organs, not only between cristae and maculae, but also between the different morphological types of receptors present (see, for example, Wersäll, 1960; Ades and Engström, 1965) and their orientation in the sensory epithelia (see, for example, Spoendlin, 1964). The complexity is further borne out by the functional differences found between units in the vestibular nuclei, where 5 types have so far been distinguished (Duensing and Schaefer, 1958) having partly different locations. Among these, tonic and kinetic neurones may be distinguished (Shimazu and Precht, 1965) with different synaptic relations (Precht and Shimazu, 1965). Furthermore, impulses from different vestibular receptors may influence the same units in a vestibular nucleus (Duensing and Schaefer, 1959). As far as studies on the function of the vestibular nuclei are concerned it follows that it will be of utmost importance, if true progress is to be made, that in physiological studies the sites recorded from or stimulated are indicated precisely, with reference to actual anatomical identification in histological sections. Diagrams showing the sites by reference to distances from the midline and the obex and so on are obviously of very limited value and may often be directly misleading. The correct identification of an electrode site in sections from the vestibular nuclei is, however, no easy task. It requires a thorough knowledge of the particular subdivisions, and often study of serial sections will be necessary.

SUMMARY

The two pathways from the vestibular nuclear complex to the spinal cord differ in several respects. The classical vestibulo-spinal tract descends ipsilaterally and originates only from the nucleus of Deiters, from small as well as large cells. It extends to the lowest levels of the cord and the projection is somatotopically organized. The fibres of the other vestibulospinal pathway come from the medial vestibular nucleus and descend chiefly ipsilaterally in the area of the medial longitudinal fasciculus to upper thoracic levels. The fibres of both pathways terminate in Rexed's laminae VII and VIII.

Among the influx to the vestibular nuclei from the cerebellum three components may be distinguished: (1) fibres from the "vestibular" part of the cerebellum; (2) fibres from the "spinal" regions of the vermis; (3) fibres from the fastigial nucleus. Each contingent has its particular distribution within the vestibular nuclei. Pathways (2) and (3) to the nucleus of Deiters are somatotopically organized but differ in their synaptic relationships. Experimental electron microscopical studies show that cortico-cerebello-vestibular fibres establish synaptic contact with very thin as well as thick dendrites and somata.

Some functional implications of these anatomical data are discussed. The complex anatomical organization of the vestibular nuclei necessitates precise histological determination of sites of stimulation or recording in physiological studies.

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DISCUSSION

Pompeiano: Professor Brodal mentioned the finding by Ito and his group that stimulation of the vermis of the anterior lobe produces monosynaptic inhibitory postsynaptic potentials in the Deiters' neurones. In 1957 we (Moruzzi, G., and Pompeiano, O. [1957]. *Archs ital. Biol.*, **95**, 31–55) found that a small electrolytic lesion limited to the rostrolateral part of the fastigial nucleus (Fig. 1*a*) abolished the typical inhibition of the decerebrate rigidity elicited by repetitive stimulation of the vermal cortex of the anterior lobe. Following the anatomical demonstration (Walberg, F., and Jansen, J. [1961]. *Expl Neurol.*, **3**, 32–52) that the long corticofugal fibres to Deiters' nucleus from the vermal cortex of the anterior lobe pass just through the rostrolateral part of the fastigial nucleus (Fig. 1*b*), the suggestion has been put forward (Brodal, A., Pompeiano, O., and Walberg, F. [1962]. *The Vestibular Nuclei and Their Connections, Anatomy and Functional Correlations.* Edinburgh: Oliver and Boyd) that these long cerebellar cortico-vestibular fibres inhibit the activity in Deiters' neurones, thus leading to abolition of the decerebrate rigidity. Since the lateral vestibular nucleus exerts an excitatory influence on the extensor motoneurones, it may be inferred that the collapse of the decerebrate rigidity elicited by vermal stimulation is not due to an active inhibitory process but rather to suppression of tonic excitatory influences upon the extensor motoneurones originating from Deiters' nucleus. This conclusion

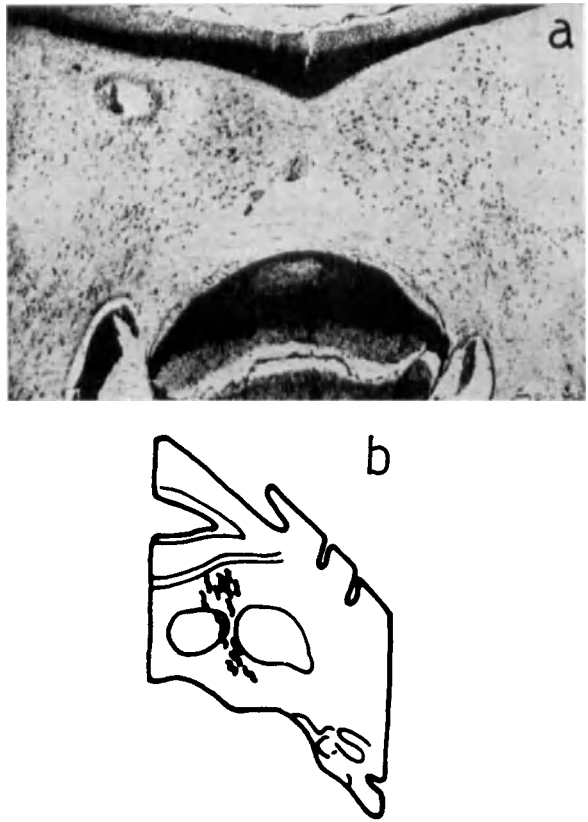

FIG. 1 (Pompeiano). Intracerebellar course of the cerebellar corticovestibular pathway.

(*a*) Micrograph showing a lesion in the rostral part of one fastigial nucleus which abolishes the typical inhibition of the decerebrate rigidity elicited by stimulation of the vermal part of the anterior lobe. The lesion occupies the rostrolateral and dorsal part of the fastigial nucleus, while the rostromedial part is intact (from Moruzzi and Pompeiano, 1957).

(*b*) Diagrammatic representation of the cerebellar corticovestibular fibres mainly directed to Deiters' nucleus, on their way through the cerebellum (Walberg and Jansen, 1961). These corticofugal fibres mainly penetrate the rostrolateral part of the fastigial nucleus, i.e., that region whose destruction abolishes the inhibitory effects induced by vermal stimulation of the anterior lobe.

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is supported by the observation (Terzuola, C. A. [1959]. *Archs ital. Biol.*, **97**, 316–339) that the hyperpolarization of the extensor motoneurones elicited by stimulation of the vermal cortex of the cerebellum is not reversed by passing hyperpolarizing current through the membrane, nor is it associated with the conductance changes which are typical of the inhibitory postsynaptic potentials.

Gernandt: Professor Brodal, can the medial vestibulo-spinal tract explain the difference in the responses we obtain at the cervical level and the lumbar level on stimulating the vestibular nerve?

Brodal: Anatomically there are only two *direct* pathways which may transmit impulses from the vestibular nuclei to the cord, one from Dieters' nucleus and the other from the medial nucleus; the latter, the medial vestibulo-spinal tract, descends only as far as the middle thoracic segments, while the other, the lateral vestibulo-spinal tract from the nucleus of Deiters, extends right down to the lower sacral segments. This may be relevant in the interpretation of the differences you mention. However, there is another problem which makes this interpretation appear rather doubtful: the primary vestibular fibres do not end in the hindlimb region of the nucleus of Deiters.

Gardner: How extensive are the dendritic fields in Deiters' nucleus?

Brodal: They are quite extensive. Dr. E. Hauglie-Hanssen has mapped the dendritic spheres in Golgi studies of the vestibular nuclei. It appears that the dendrites of the cells in a particular nucleus in general stay within the territory of that nucleus. In the nucleus of Deiters they do not on the whole go beyond the somatotopic boundaries. We have been particularly interested in this question because it might help to clarify physiological problems.

Wersäll: Is there any interneuronal connexion between the anterior and posterior parts of Deiters' nucleus?

Brodal: Dr. Hauglie-Hanssen has found no evidence of this.

Gernandt: What about the descending part of the medial longitudinal bundle? How far down have you been able to trace it?

Brodal: Dr. R. Nyberg-Hansen has been studying this subject in our laboratory. In the area which we call the descending medial longitudinal bundle there are fibres other than those from the medial vestibular nucleus. There are tecto-spinal fibres which have been followed only to the cervical levels (Nyberg-Hansen, R. [1964]. *Expl Neurol.*, **9**, 212–227); and we have the so-called interstitio-spinal fibres which come from the interstitial nucleus of Cajal in the mesencephalon. They can be traced down to the lowest part of the cord (Nyberg-Hansen, R. [1966]. *Archs ital. Biol.*, **104**, 98–111) but they appear to be rather scanty.

Pompeiano: I am not surprised that stimulation of the vestibular nerve affects the hindlimb motoneurones in spite of the absence of any direct projection of the primary vestibular afferents to the hindlimb region of Deiters' nucleus. These effects can be mediated either through the vestibulo-spinal projection originating from the medial vestibular nucleus and coursing along the medial longitudinal

fasciculus or through the reticulo-spinal pathways, since it is known that second-order vestibular neurones send some collaterals to the brain-stem reticular formation. Both these projections can reach the lumbosacral segments of the spinal cord through propriospinal pathways whose existence has been physiologically demonstrated by D. P. C. Lloyd ([1941]. *J. Neurophysiol.*, **4**, 115–134). I would like to raise the question whether the vestibulo-spinal fibres coursing along the medial longitudinal fasciculus can really be considered a motor pathway, since Professor Gernandt has shown that interruption of the medial longitudinal fasciculus does not alter the output from the ventral roots elicited by single-shock stimulation of the vestibular nerve. An alternative hypothesis is that this pathway may exert presynaptic inhibition on primary afferents in the spinal cord. It has recently been shown by Carpenter and his co-workers (Carpenter, D., Engberg, I., and Lundberg, A. [1966]. *Archs ital. Biol.*, **104**, 73–85) that in the decerebrate cat electrical stimulation of localized points of the medulla and caudal pons, including the region of the medial longitudinal fasciculus, evokes presynaptic depolarization of primary afferents, including group Ia and Ib muscle afferents and cutaneous fibres.

An entirely different line of evidence indicates that the medial and descending vestibular nuclei exert presynaptic inhibition on the primary afferents, particularly on the group Ia muscle afferents. During the desynchronized phase of sleep there is the sudden appearance of bursts of rapid eye movements. We have studied the modulation during sleep of the monosynaptic and polysynaptic reflexes in unrestrained, unanaesthetized cats and found that they are tonically depressed during the desynchronized phase (Giaquinto, S., Pompeiano, O., and Somogyi, I. [1964]. *Archs ital. Biol.*, **103**, 245–281) while a further phasic depression occurs during the bursts of rapid eye movements (Gassel, M. M., Marchiafava, P. L., and Pompeiano, O. [1964]. *Archs ital. Biol.*, **102**, 471–499). Several lines of evidence indicate that while the tonic depression of the spinal reflexes is due to postsynaptic inhibition, presynaptic mechanisms are involved in the phasic inhibition (Morrison, R., and Pompeiano, O. [1965]. *Archs ital. Biol.*, **103**, 517–537). Excitability tests made following Wall's technique have actually shown that the phasic depression of the monosynaptic reflexes during the rapid eye movements is due to terminal depolarization of the group Ia endings. Bilateral electrolytic lesions limited to the medial and descending vestibular nuclei abolish not only the bursts of rapid eye movements but also the related phasic inhibition of the monosynaptic reflexes (Pompeiano, O., and Morrison, A. R. [1966]. *Archs ital. Biol.*, **104**, 231–246). All these lines of evidence suggest that these vestibular nuclei are responsible for the terminal depolarization of the primary afferents, particularly of group Ia fibres, which occurs during sleep at the time of the bursts of rapid eye movements.

If so, one has probably to review the concept that the vestibulo-spinal projection originating from the medial vestibular nucleus acts primarily or exclusively on spinal motoneurones.

Gernandt: The large, stable responses to vestibular stimulation recorded from

the cervical and upper thoracic motor outflow bilaterally are not influenced in any way by a complete transection of the medial longitudinal fasciculus in its course along the floor of the fourth ventricle, immediately rostral to the obex. At the level of the cerebellopontine angle the medial longitudinal fasciculus can be dissected longitudinally and the free caudal portion, containing the tracts of both sides, placed on stimulating electrodes and elevated above the floor of the ventricle, suspended in mineral oil or air. Electrical stimulation thus applied does not evoke any activity in motor pools at the cervicothoracic level that can be detected by recording from the radial nerves. Neither conditioning nor simultaneous high-frequency stimulation of the medial longitudinal fasciculus under these conditions alters in any way the radial nerve responses to peripheral vestibular stimulation. These findings indicate that the functional significance of the medial longitudinal fasciculus, one of the phylogenetically oldest tracts, in the transmission of descending vestibular impulses has been exaggerated. Since this tract is probably of minor physiological importance in the transmission of vestibular impulses to the spinal cord, one or both of the other two available descending pathways, the vestibulo-spinal tract and reticulo-spinal tract, must make the most significant contributions.

Single-shock stimulation applied to the vestibular nerve evokes responses which may be recorded from both ipsilateral and contralateral peripheral motor nerves of cervicothoracic levels and from lumbosacral ventral roots. The cervicothoracic response consists of an initial spike and two successive waves. By contrast, only two waves and some later activity can be recorded from lumbosacral ventral roots. These significant differences in the configuration of the responses obtained from widely separated segments of the spinal cord suggest changes in structural organization. Either the relation of the descending vestibulofugal tracts to the motoneurones becomes weaker, or this dissimilarity of the responses might be a manifestation of temporal dispersion within the paths, and thus is not necessarily attributable to the termination of massive numbers of fibres in supralumbar regions.

Quite recently Erulkar and co-workers (Erulkar, S. D., Sprague, J. M., Whitsel, B. L., Dogan, S., and Jannetta, P. J. [1966]. *J. Neurophysiol.*, **29**, 626–664) described that at the C7 level the majority of interneurones responded with a multiple-spike discharge, in response to stimulation of the vestibular nerve. At L7, these were less frequently recorded, and the majority of interneurones responded with a single spike followed by a depolarizing after-potential.

Lowenstein: A difference in response between the forelimb and hindlimb was referred to in the discussion of Dr. Begbie's paper (see p. 92).

Brodal: Dr. Purdon Martin described cases where there was remarkably little disturbance of vestibular function in patients whose labyrinths had been destroyed. This, as I referred to earlier, may have something to do with the restriction of the primary vestibular afferents to the neck and forelimb parts of Deiters' nucleus, which seems to indicate that vestibular impulses and the vestibulo-spinal tract are not very important in the regulation of the hindlimbs.

Myotatic, Kinesthetic and Vestibular Mechanisms
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VESTIBULAR INFLUENCE UPON SPINAL REFLEX ACTIVITY*

Bo E. Gernandt

U.S. Naval Aerospace Medical Institute, U.S. Naval Aviation Medical Center, Pensacola, Florida

Vestibular impulses encounter many hazards and are affected by many influences at the points of generation, along the axons, and at the synaptic junctions before they can evoke responses in the cells upon which they impinge (Gernandt, 1967). Input–output studies can provide information relevant to mechanisms operating at the various integrating centres where transmission of these impulses can fail or succeed, thus making it possible to discuss vestibular function with a constant recourse to the concept of integration. The diverse problems of integration are tightly bound to the different choices presented, either in the processes of analysis or in the aggregate, dynamic synthesis involving function.

Vestibular activity participates in the regulation of posture and in the patterning of impulse firing on which a motor act is based (Koella *et al.*, 1956; Gernandt and Gilman, 1960*b*; Megirian and Troth, 1964). While these actions are mostly subcortical, involving particularly cerebellar, brain stem, and spinal mechanisms, the vestibular projections to the cortex, as well as interaction of vestibular with other sensory inputs in the basal ganglia, suggest a contribution of these sources to the regulation and to the strong internal coherence of motor function. During the last few years we have been engaged in the study of interaction at the spinal level between vestibular, segmental and intersegmental propriospinal, and pyramidal activities. These studies have underlined the strong projection of descending vestibulofugal connexions upon spinal motor pools, a prototype of integrating centres, and have shown that vestibular activity is influenced in a delicate and purposeful manner by messages of different peripheral and

* The experiments reported herein were conducted according to the principles enunciated in *Guide for Laboratory Animal Facilities and Care* prepared by the Committee on the Guide For Laboratory Animal Resources, National Academy of Sciences—National Research Council.

Opinions or conclusions contained in this report are those of the author and do not necessarily reflect the views or endorsement of the Navy Department.

central origin. This control of vestibular activity, as reflected by alterations in spinal motor outflow, is due to the intricate and complex convergent, divergent, bidirectional, and retrograde interconnexions which ensure co-ordination of the whole motor system and a great stability in its external manifestations. Through these channels the impulses impinge upon the synapses, some of which are excitatory and tend in turn to make the neurones fire, while some have an inhibitory action tending to prevent the initiation of impulses. These and other findings appear to contribute to an understanding of the mechanisms involved in posture, locomotion, and weight-bearing.

METHODS

Most of the experiments were performed on cats decerebrated by an intercollicular transection during ether anaesthesia. The cats were kept fully immobilized by iterative doses of gallamine triethiodide (Flaxedil) and were maintained on artificial respiration. For stimulating purposes the vestibular nerve branches were exposed in the vestibule and equipped with electrodes according to a technique previously described (Andersson and Gernandt, 1954). Laminectomy was performed and some of the ventral roots L6, L7, or S1 and at times the corresponding dorsal roots were transected intradurally, or various nerves in the hind legs were dissected and divided for central stimulation while the rest of the nerves were cut to provide a denervated extremity. The activity evoked in ventral roots was recorded either as a mass discharge, because it is as good a test of motoneurone excitability as any so far devised, short of resorting to intracellular recording, or was studied by recording from single root fibres. In some experiments the activity of single cells in the spinal motor pool was recorded extracellularly with microelectrodes.

VESTIBULAR INFLUENCE UPON SPINAL MOTOR CELLS

Tonic control

Tonic discharge of spinal motor neurones results from the integration of a multitude of influences which adjust the rate of firing in such a way as to fulfil the needs of posture and muscle tone. A spontaneous stream of impulses, originating in the vestibular organ, always traverses the vestibular nerve, impinges upon the vestibular nuclei (Adrian, 1943; Gernandt, 1949; Rupert, Moushegian and Galambos, 1962), and exerts a critical influence upon spinal motor pools. The importance of the vestibular nuclei as an excitatory source for the cord is well established, and the means by which the nuclei modulate the tonic properties of individual motoneurones have been investigated (Bach and Magoun, 1947; Ward, 1947; Kempinsky and

Ward, 1950; Gernandt and Thulin, 1953; Andersson and Gernandt, 1956). However, this question has become more crucial since the discovery of two separate, though normally co-operating motor systems in the spinal cord: one, the large and medium-sized α motoneurones responsible for extrafusal motor innervation, and the other, the small γ or fusiform neurones innervating the intrafusal muscle fibres within muscle spindles. Thus, the vestibular influence may act either directly on the α motoneurones or indirectly via the γ loop.

Section of the eighth nerve, ipsilaterally or contralaterally, in a decerebrate, decerebellate preparation whose dorsal roots have been cut, strongly reduces the α hyperactivity obtained by cerebellectomy. If a test shock is applied to an extensor or flexor nerve of the hindlimb, after the spindle loop in muscles agonistic and antagonistic to the motor pool under study is interrupted, the amplitude of the monosynaptic component of a lumbosacral ventral root response is strongly reduced by section of the eighth nerve. If the contralateral eighth nerve also is cut, the response will be further reduced and its latency more prolonged. The vestibular facilitatory influx to the cord undergoes approximately the same degree of reduction whichever vestibular nerve is cut first (Gernandt and Thulin, 1953). It may thus be concluded that spontaneous vestibular activity exerts a tonic facilitatory action on monosynaptic reflex discharge of spinal motoneurones of flexor and extensor pools, even when the γ loop has been eliminated.

Phasic control

Single-shock vestibular nerve stimulation at one pulse per second evokes responses which may be recorded from both ipsilateral and contralateral deep radial nerves, medullary and spinal accessory nerves, lumbosacral ventral roots (Gernandt, Katsuki and Livingston, 1957; Gernandt and Gilman, 1959, 1960*a*; Gernandt and Proler, 1965) and dorsal roots (Erulkar *et al.*, 1966). By intracellular recordings from interneurones at cervical and lumbar levels of the spinal cord, Erulkar and co-workers (1966) were able to demonstrate depolarizing and hyperpolarizing potentials in response to vestibular stimulation. At the cervical level the interneurones respond with a multiple spike discharge but at the lumbar level the majority of interneurones respond with a single spike. The difference is not necessarily attributable to termination of massive numbers of fibres in supralumbar regions but may be related to the greater synaptic impingement of vestibulofugal connexions on to the neurones at cervical levels and also to the distribution of input on to the receptor surface of the interneurones (Gernandt and Gilman, 1959; Gernandt, 1964).

The responses recorded from ventral lumbosacral roots consist of two volleys of impulses with a latency of 4–5 and 7–9 msec., respectively. Two principal pathways are involved in conveying impulses of vestibular origin into the spinal cord and down to lower levels: the vestibulospinal and reticulospinal paths. The spinal terminations of the descending vestibulofugal system are predominantly on interneurones which then project on to other interneurones and to presynaptic and postsynaptic membranes of motoneurones (Gernandt, Iranyi and Livingston, 1959; Brodal, Pompeiano and Walberg, 1962; Erulkar *et al.*, 1966). Impulses conducted along the vestibulospinal tract may encounter fewer synapses on their way from periphery to periphery than those in the reticulospinal tract by way of the reticular formation. Thus, the two-peak response to a single vestibular shock stimulation recorded from a ventral root may be due to motor cell activation by two separate descending volleys transmitted at α velocity (Lloyd, 1941) along different paths not having the same nuclear delays. We have attempted to separate the two peaks of the ventral root response by several means: (*i*) by cerebellar removal followed by a complete splitting of the brain stem from the inferior colliculi to the obex (thereby cutting through all pontine and bulbar crossed connexions), (*ii*) by partial transection of the spinal cord (on the assumption that the two volleys of impulses might be conducted down different quadrants of the cord), (*iii*) by splitting the lumbosacral cord, (*iv*) by intravenous injection of barbiturate in gradually increasing dose (assuming that the two sets of impulses might be differentially susceptible to the action of anaesthetics), and (*v*) by observing the response during deterioration of the animal. In each instance, however, the double response appeared to fall simultaneously. One way in which the two peaks of the response can be differentially affected is by using repetitive stimulation (10 pulses/sec.) over a period of several seconds (Gernandt, Katsuki and Livingston, 1957; Gernandt, Iranyi and Livingston, 1959). The fact that the central processes leading to the two peaks of the vestibular response are oppositely affected at the same time both during and after repetitive stimulation suggests that the two peaks probably involve different descending fibre systems. Another explanation is that vestibular stimulation causes both excitatory and inhibitory impulses to influence the motor cell activity, the second burst of impulses being due to a release from inhibition. This would mean that excitatory impulses exert their action before the inhibitory effect sets in.

If the activity is recorded simultaneously from a thin filament of a lumbar ventral root and from the parent root itself, it can be shown that the typical two-humped response represents the firing of γ impulses, grouped into two

clusters (Gernandt, Iranyi and Livingston, 1959). If the 10 pulses/sec. repetitive stimulation is applied to the vestibular nerve for some seconds the character of the evoked response is altered; the amplitude of the first peak becomes increased, sometimes to 6–10 times the height of that following single shocks, while the amplitude of the second peak may fall to zero. The growth of the first hump typically takes place in two stages. During the first stage there is a strong build-up of the γ firing superimposed on a depolarizing wave. Thus, the fusimotor neurones discharge at higher frequencies and have lower thresholds for reflex activation than do α neurones. In the second stage, large-amplitude spikes conducted in α fibres suddenly appear. Corresponding with these two stages are abrupt changes in the characteristics of the main ventral root response. The first hump grows in amplitude and then suddenly jumps to a greater height. This jump occurs at the same time as the large unit spikes appear in the root filament.

The lower threshold for γ fibres would thus indicate that the muscle spindles become stimulated before the muscle is made to contract by the impulses in the α fibres occurring in response to stronger stimulation. When the strength of vestibular stimulation is such that an unmistakable threshold response to each shock occurs in the α fibre, the response will remain practically constant even during a long period of stimulation. In contrast, it is characteristic of the γ activity that it gradually increases. Thus, the results demonstrate that the discharge in the γ fibres is not controlled by an inhibitory feedback mechanism of their own, as are impulses in the α fibres (Andersson and Gernandt, 1956). Temporal summation means more for the γ activity. These results were soon confirmed by others (Granit, Pascoe and Steg, 1957; Kuno, 1959; Eccles *et al.*, 1960).

The descending stream of impulses in response to vestibular stimulation will have an effect on spinal motor cells which is either excitatory or inhibitory or excitatory and inhibitory in parallel, each action having its characteristic distribution. The whole spectrum of facilitatory, inhibitory, or diphasic modulations of the α discharges, with intact γ loops, could similarly be obtained after elimination of the loops, although the amount of available γ support determines the threshold at which the α effects are manifested. The experimental evidence for some descending fibres (vestibulospinal and some reticulospinal fibres) being facilitatory, other reticulospinal fibres being inhibitory, is rather impressive in its volume if not in its rigour (Gernandt and Thulin, 1953; Magoun, 1958).

In the motoneurone, recovery from the effects of a preceding impulse is a relatively slow process, being related to the development of a positive after-potential which may last for longer than 100 msec. (Eccles, 1953;

Kolmodin and Skoglund, 1958). The after-potential controls recovery during repetitive activity by hyperpolarizing the membrane so that a greater excitatory synaptic drive is needed to depolarize the neurone to its critical firing level. Responses to vestibular stimulation showing a purely excitatory effect constitute a type of activity where, to high-frequency stimulation, the α fibre discharge can reach a value of about 100 impulses per sec. Natural vestibular stimulation never produces such high discharge rates in α fibres (Gernandt, 1952). Reflexly evoked discharges in large efferent fibres usually have a frequency of 20–40 impulses per sec. and may rise to 50–60 per sec. But even if certain motor cells receive nothing but excitatory vestibular impulses, their output frequency is controlled by the negative feedback mechanism of the Renshaw cells. The inhibition of the motoneurones of slow tonic muscles is particularly powerful. This may serve to stabilize the frequency of discharge of tonic muscles during maintenance of posture (Granit, Pascoe and Steg, 1957) or to suppress tonic motoneurone firing during rapid movements (Eccles *et al.*, 1961).

INTERACTIONS BETWEEN VESTIBULAR, SEGMENTAL, AND INTERSEGMENTAL PROPRIOSPINAL REFLEX ACTIVITIES

Integrative action of an isolated part of the nervous system occurs when a response is not equal to the input and, in particular, when several simultaneous or successive inputs are taken into account. Spinal motoneuronal activity is governed by three basic interplaying influences that stem, respectively, from dorsal roots, suprasegmental structures, and Renshaw cells. Some insight into these complex relationships may be obtained by examining each interaction separately through activation of the systems consecutively, in controlled temporal sequence. Stimulation of the gastrocnemius (extensor) or tibialis anticus (flexor) nerves at an intensity that is subthreshold for a ventral root response yields a clearly discernible monosynaptic response when preceded by vestibular stimulation. The same vestibular facilitatory influences upon the evoked segmental reflexes become apparent when threshold or supramaximal stimulation is applied to these functional antagonists. The facilitation appears to have a brief latency, reaches its maximum at a very early conditioning-test interval, and is still profound at 20 to 25 msec. Moreover, the descending vestibular volley may determine to some degree the proportions in which motoneurones participate in monosynaptic and polysynaptic responses. When the interval between conditioning and test shocks is increased, the enhancement changes abruptly to an interference, reaching its maximum when the two shocks are separated by about 40 msec. With still further separation

of the two shocks, there is a relief of the segmental reflex from interference and a second period of enhancement which then progressively declines during the subsequent 150 msec. After removal of the cerebellum the second period of enhancement of the spinal segmental reflex following single-shock vestibular stimulation disappears, and the period of inhibition is extended (Gernandt, Katsuki and Livingston, 1957; Gernandt, Iranyi and Livingston, 1959).

The fact that two antagonistic spinal reflex responses, the extensor gastrocnemius and flexor tibialis anticus, are both facilitated suggests that vestibular influences at the spinal segmental level contribute to co-contractional muscular patterns necessary to the pillar-like stability of a weight-bearing limb. On the other hand, muscular (gastrocnemius), mixed (tibialis anticus), and cutaneous (sural) nerve stimuli which *precede* vestibular excitation invariably cause a reduction or abolition of the vestibular response.

By employing extracellular or single-fibre recording from thin ventral root filaments it is possible to study directly the interplay of vestibular and stretch afferents upon the activity of α and γ motoneurones. This reveals the powerful autogenetic control of motoneurone activity by tendon organ afferents, which completely dominate even the most intense vestibular excitatory influences (Andersson and Gernandt, 1956).

The only kind of peripheral stimulation found to facilitate the vestibular response is that of manipulation of the tarsal-metatarsal joints of the foot ipsilateral to the recording site. Foot manipulation is uniquely effective in this way; that is, pinching, pricking, or squeezing of the foot pads (without moving the foot joints) is without such an effect. Displacement or working of the joints in the foot profoundly enhances the vestibular activity which in turn is facilitatory to both flexors and extensors and hence acts to stabilize the same extremity. Standing, stepping, springing, or landing should displace the joints in the foot and, in accordance with the degree of excitation of afferents stimulated in this way, there will be a correspondingly effective increase in the weight-bearing capacity of the same limb. This finding provides a basis for the positive supporting "magnet reaction" of Magnus.

VESTIBULAR INDUCTION OF PROLONGED SPINAL INHIBITION

A convenient method of testing for inhibition in the spinal cord is to study the effect of conditioning volleys in various afferent nerve fibres upon the height of the monosynaptic reflex response produced by a particular motor nucleus. During high-frequency vestibular stimulation (30–50

pulses/sec.) the segmental flexor or extensor test response becomes greatly augmented (Fig. 1), but after stimulation there is an enduring, powerful inhibition of the same motoneurones (Gernandt, Katsuki and Livingston, 1957; Gernandt and Gilman, 1960*a*). The inhibition commonly outlasts the cessation of stimulation by 2–3 minutes and blocks orthodromic excitation of the motoneurones at a time when antidromic excitation of the same cells is facilitated (Brooks, Koizumi and Siebens, 1956; Suda, Koizumi and Brooks, 1958). Massive, synchronous volleys are rare in

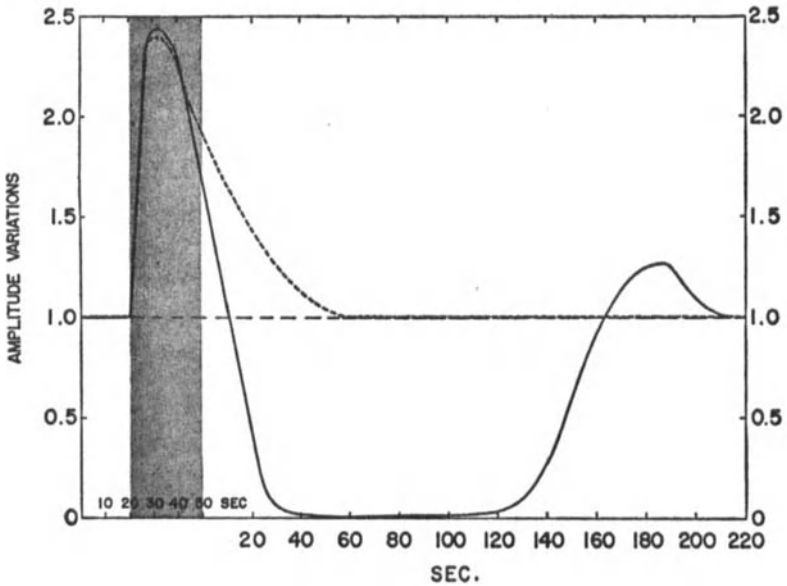

FIG. 1. Variations in amplitude of monosynaptic component of segmental lumbar reflex response, relative to control = 1·0, plotted against time in sec., during (shaded area) and following high-frequency brachial plexus stimulation before (solid line) and after (dashed line) high-spinal transection.

physiological responses, and therefore the phenomenon has not been adequately investigated with physiological stimulation.

It has been shown that vestibular stimulation leads to a gross activation of the bulbar reticular formation (Gernandt, Iranyi and Livingston, 1959) which, on direct stimulation, is known to yield facilitatory and inhibitory effects on the spinal pathways (Magoun, 1958). If it is correct to implicate the reticular formation in the elaboration of the long-lasting, non-reciprocal inhibitory action upon the monosynaptic reflex responses of flexor and extensor nerves, stimulation of other peripheral sources sending collaterals into the reticular formation should evoke the same effect by bringing into play a rapidly activated bulbar inhibitory mechanism exerting

its effect along the spinal cord. This is demonstrated by using the brachial plexus as an input lead. An identical protracted inhibition of the ipsilateral or contralateral segmental reflex response occurs following high-frequency stimulation of this plexus. The method of stimulating the vestibular nerve or the brachial plexus in order to direct impulses into the brain stem provides a more natural mode of activation than can be obtained by direct central electrical stimulation.

This inhibitory force not only affects segmental spinal reflex activity, but also, as expected, influences the motor outflow by impulses conducted intersegmentally. If the test shock is applied to the vestibular nerve and the response recorded from a lumbosacral ventral root, high-frequency brachial plexus stimulation elicits the usual inhibition of the test response (Gernandt and Gilman, 1960*a*).

The prolonged decline in amplitude of the test-response following high-frequency stimulation of the vestibular nerve or the brachial plexus is not a result of defacilitation or ordinary post-excitatory refractoriness, but is due to an active, inhibitory process which continues during the entire period of depression. If such an inhibitory process originated at a level of the neuraxis that included the bulbar reticular formation and were represented by a continuing stream of inhibitory impulses descending the spinal cord, interruption of this activity should release the segmental reflex from inhibition. This is tested by abrupt, local freezing of the spinal cord in the upper lumbar region during the prolonged depression period. When the test-response after high-frequency vestibular stimulation is abolished, a freezing spray of ethyl chloride is applied to the exposed spinal cord at L2. Within a few seconds from the start of freezing the test-response recovers completely, and there is no evidence of depression along that pathway. Further proof of an active inhibitory process originating from supraspinal structures is obtained from spinal animals. After high-spinal transection, the pattern and time-course of augmentation and inhibition of the test-response resulting from high-frequency brachial plexus stimulation in decerebrate cats are transformed into a period of augmentation without the inhibitory phase (Fig. 1). This demonstrates that the source of the enduring inhibition must be localized within the cerebellum and/or brain stem. Acute cerebellectomy, however, does not influence the effect and thus the loop through the brain stem is sufficient to evoke the protracted inhibition (Gernandt and Megirian, 1961; Gernandt and Shimamura, 1961; Shimamura and Livingston, 1963). A transverse incision through the depth of the brain stem just rostral to the obex and restricted to about 2 mm. on either side of the midline eliminates the inhibition which follows high-frequency

stimulation of either vestibular nerve or brachial plexus. Although the bulbar incision interrupts the caudal extent of the medial reticular formation, it does not necessarily follow that this region is the exclusive source of the inhibitory effects. According to current concepts, it is not correct to attribute purely facilitatory or inhibitory effects to rigidly localized portions of the reticular formation; therefore, it is not permissible to restrict the inhibitory effect to medial reticular formation only. In addition, since the incision is placed far caudally in the bulb, it is likely that continuity between rather extensive longitudinal zones of reticular formation and lower centres may be interrupted.

The neural organization of the reticular formation is well suited for self-sustained, reverberating activity evoked by afferent activation (Amassian and DeVito, 1954). Recordings from a great number of cells of various sizes within the formation or from fibres along the reticulospinal tract have clearly demonstrated such an expected post-stimulatory, repetitive firing, appearing either in bursts or at a higher rate. However, this changed firing pattern is of short duration, lasting only several seconds. The neurones vary greatly among each other in their temporal patterns of discharge, from pure onset patterns to patterns of sustained, gradually increased firing or to an initial acceleration followed by a decline to the pre-stimulus rate, even if the stimulus is not removed. It becomes apparent that an excitatory stimulus may actually set in motion a chain of excitatory and inhibitory events and that it is the final resultant of these activities which determines the drive upon a neurone. There is no reason to expect that the number of spikes should invariably, or even often, be a simple function of the strength of the peripheral stimulus. Thus, we have not been able to correlate these firing patterns with the period during which the test-response is strongly inhibited. Of course, recording from single cells or fibres cannot give a complete picture of the total activity of the reticular formation or its descending tract. In addition, an initial synchronized firing can be replaced by a desynchronized one at a *slightly* higher rate as compared to pre-stimulatory conditions, and thus be hard to detect. There is also the possibility that we have not been able to record from units possessing the maximum duration of response.

Inhibitory actions at either presynaptic (Frank and Fuortes, 1957; Eccles, 1963) or postsynaptic sites have been discussed (Gernandt and Gilman, 1960*a*). It has been assumed that special interneurones form depolarizing synapses close to the synaptic terminals of the primary afferent fibres and therefore that the inhibition exhibited in the cord in response to high-frequency vestibular stimulation has a presynaptic origin. This type of

inhibition is more potent than postsynaptic inhibition and seems to play an important role in the control of reflex movements (Eccles, Eccles and Magni, 1961). Some support for this assumption was obtained by studying the effects of vestibular stimulation upon the autorhythmic convulsive activity of the spinal cord induced by strychnine (Gernandt and Terzuolo, 1955). The inhibition of the strychnine tetanus, displayed at all levels of the cord, speaks in favour of presynaptic inhibition. Strychnine is a very effective depressant of postsynaptic inhibition but, by contrast, presynaptic inhibition is not affected (Eccles, 1963). However, Llinas and Terzuolo

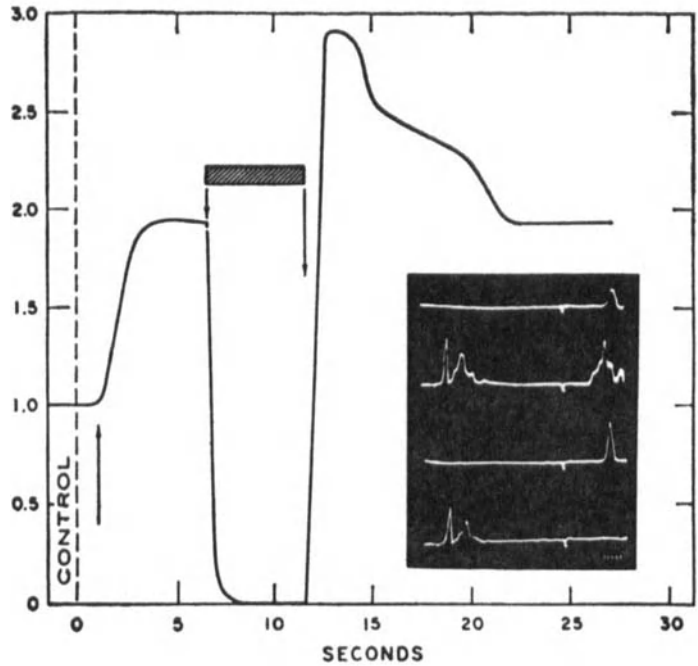

FIG. 2. Effects of vestibular stimulation upon cortically evoked responses. Inset depicts control response to single-shock cortical stimulation recorded from contralateral radial nerve, alone and when conditioned by vestibular volley (upper pair). Response to 3 pulses/sec. cortical stimulation, alone and when preceded at this frequency by conditioning vestibular volleys, is shown (lower pair). Time-scale in msec. Curve represents amplitude of cortically evoked response at 1 pulse/sec., 3 pulses/sec. (first arrow), during (marked by bar), and after conditioning vestibular stimulation.

(1964), by applying intracellular recording, were able to show that the synaptic inhibitory impingement obtained by reticular stimulation was due to a sustained hyperpolarization of the motoneurone membrane and that no clear evidence for a presynaptic inhibitory mechanism could be found.

INTERACTIONS BETWEEN VESTIBULAR AND PYRAMIDAL ACTIVITIES

Normal posture is the result of a dynamic equilibrium of central antagonistic forces continuously active in the waking state and controlled by afferent impulses. Superimposed on the lower motor mechanisms, mainly dependent upon vestibular and cervical proprioceptive influences, is a mesodiencephalic coordinating apparatus for body posture, showing an elaborate direction-specific differentiation closely integrated with the cerebral cortex and operating in the three dimensions of space. Tonic pyramidal (Adrian and Moruzzi, 1939; Calma and Arduini, 1954) and vestibular (Adrian, 1943; Gernandt, 1949; Rupert, Moushegian and Galambos, 1962) activities interact, not merely once, but again and again along the neuraxis, and if phasic pyramidal activity alters body position in space, it concomitantly induces vestibular stimulation. In the cat, the pyramidal system operates largely by influencing the interneurones mediating the segmental reflexes.

The response to single-shock stimulation of the pericruciate cortex recorded from the contralateral deep radial nerve is enhanced when preceded by a vestibular response within a time lapse of about 30 msec. (Gernandt and Gilman, 1960*b*). As the interval between the shocks is progressively shortened, the evoked cortical response is abolished at an interval of 10–15 msec. The typical augmentation of the response to single-shock cortical stimulation (1 pulse/sec.) by a conditioning vestibular volley applied at a suitable interval is depicted in the oscilloscopic tracing of Fig. 2, upper pair.

If the evoked cortical response is enhanced by an increase in stimulation frequency to 3 pulses/sec. and the vestibular conditioning volley is then delivered at the same interval and frequency, the test-response is abolished (lower pair). If the conditioning vestibular stimulation is discontinued, the cortical response promptly reappears, showing a rebound. The entire sequence of events is depicted in the curve of Fig. 2. Thus, a rather modest increase in the frequency of vestibular stimulation is capable of changing a facilitatory effect into one of interference, resulting in an extension of the time-interval during which antecedent vestibular stimulation interfered with cortically evoked activity. In the competition for access to the final common path, vestibular evoked activity clearly dominates.

SUMMARY

The spontaneous impulse discharge in the vestibular portion of the eighth nerve exerts a strong facilitatory action upon spinal motor pool activity. Vestibular stimulation can elicit responses from both ventral and

dorsal roots. Thus, the interneurones to which the descending vestibulofugal tracts are connected must project upon motor neurones and presynaptically upon incoming dorsal root fibres. Vestibular influence upon spinal motor cells is either excitatory or inhibitory or excitatory and inhibitory in parallel, each action having its characteristic distribution. The γ efferents are activated at a lower strength of vestibular stimulation than the α fibres and show a higher discharge frequency. The influence of vestibular impulses on the α motoneurones has been determined by using as an index the monosynaptic reflex discharge of extensor and flexor motoneurone pools in which the operation of the γ loops was eliminated. Interactions are analysed and a comparison is made of the influences upon lumbosacral motor pools by activation of the vestibular, segmental and intersegmental propriospinal relay systems. Vestibular excitation increases spinal segmental motor discharge. Ventral root responses evoked by vestibular stimulation are blocked by prior stimulation of spinal nerves but are greatly enhanced by slight movement of the joints of the corresponding foot.

High-frequency vestibular stimulation yields a prolonged depression of spinal reflexes by means of an active inhibitory influence. This inhibitory influence can be abruptly interrupted by local freezing of the cord some distance above the site used for spinal-reflex testing. The significance of the brain stem as a source of the post-stimulatory inhibition is discussed in the light of present and past studies.

In the competition for access to the final common path between vestibular and pyramidal activity, vestibular evoked activity dominates, and the vestibular pattern of discharge is preserved or even supplemented at the expense of cortically evoked activity.

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DISCUSSION

VESTIBULAR AND CENTRAL INFLUENCES ON SKELETOMOTOR AND FUSIMOTOR ACTIVITY

Pompeiano: May I present some evidence in support of an idea which emerges from anatomical studies, namely that the effects of stimulating the eighth nerve cannot be compared with the effects of stimulating the lateral vestibular nucleus of Deiters? Experiments were performed in precollicular decerebrate cats to study the effects of stimulation of the eighth cranial nerve on muscle-spindle afferent discharge and on extrafusal muscle tension and to compare them with the effects of stimulating Deiters' nucleus in the same experiment (Diete-Spiff, K.,

Carli, G., and Pompeiano, O. [1967]. *Pflügers Arch. ges. Physiol.*, in press). It was found in particular that repetitive stimulation of the eighth cranial nerve increased the frequency of discharge of the spindle receptors of the gastrocnemius muscle, before this muscle, fixed in isometric conditions, developed contractile

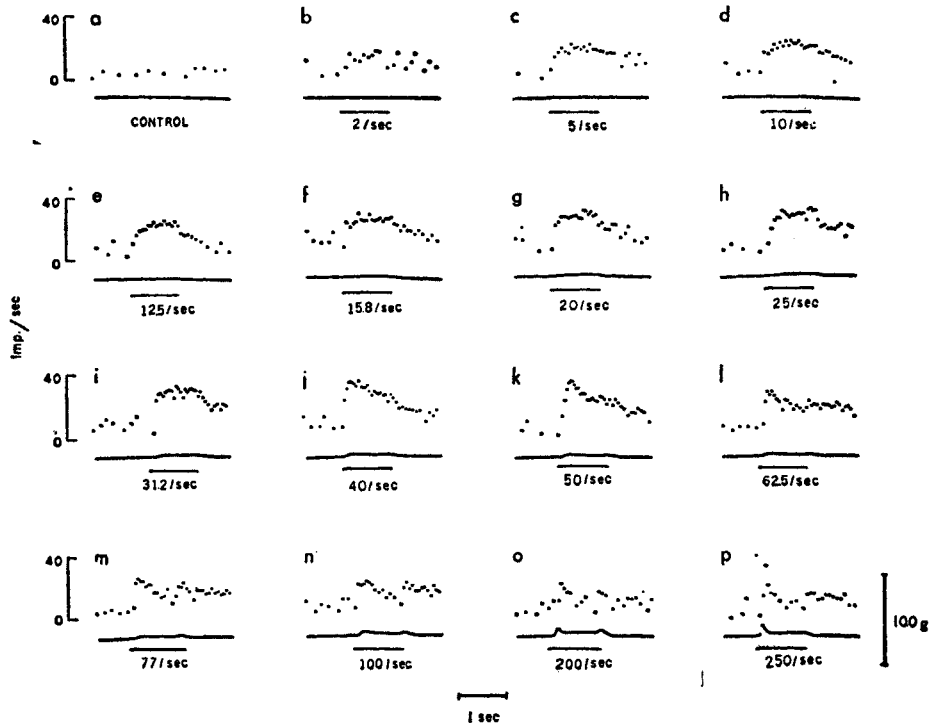


FIG. 1 (Pompeiano). Spindle-receptor activation on stimulation of the ipsilateral eighth cranial nerve at different frequencies.

Decerebrate cat with ipsilateral dorsal roots L6-S2 cut. Conduction velocity of receptor fibre, 89 m./sec. Gastrocnemius medialis muscle. Initial muscle tension: 40 g. (zero extension). The eighth cranial nerve was stimulated with rectangular pulses, 0·5 msec. in duration, 5 V, and at the frequencies indicated below each record. Note excitation of spindle receptor when the eighth nerve was stimulated at 2/sec. and the absence of extrafusal contraction at the lower frequencies of stimulation used. The upper traces of each record correspond to the spindle-receptor discharge. Each dot represents an action potential, the instantaneous frequency of which is given by its height above zero on the calibration on the left-hand scale. The lower traces correspond to the tension of the gastrocnemius medialis muscle. (From Diete-Spiff, Carli and Pompeiano, 1967.)

tension (Fig. 1). The frequencies at which spindle excitation occurred were very low (average 13 pulses/sec.). Extrafusal contraction occurred, in each experiment, at frequencies of stimulation (average 50 pulses/sec.) higher than those which caused threshold acceleration of spindle-receptor discharge. Both spindle-receptor acceleration and extrafusal contraction increased with an increase in the frequency of stimulation to an optimum value at about 100 pulses/sec. and then fell progressively with a further increase in the frequency of stimulation from

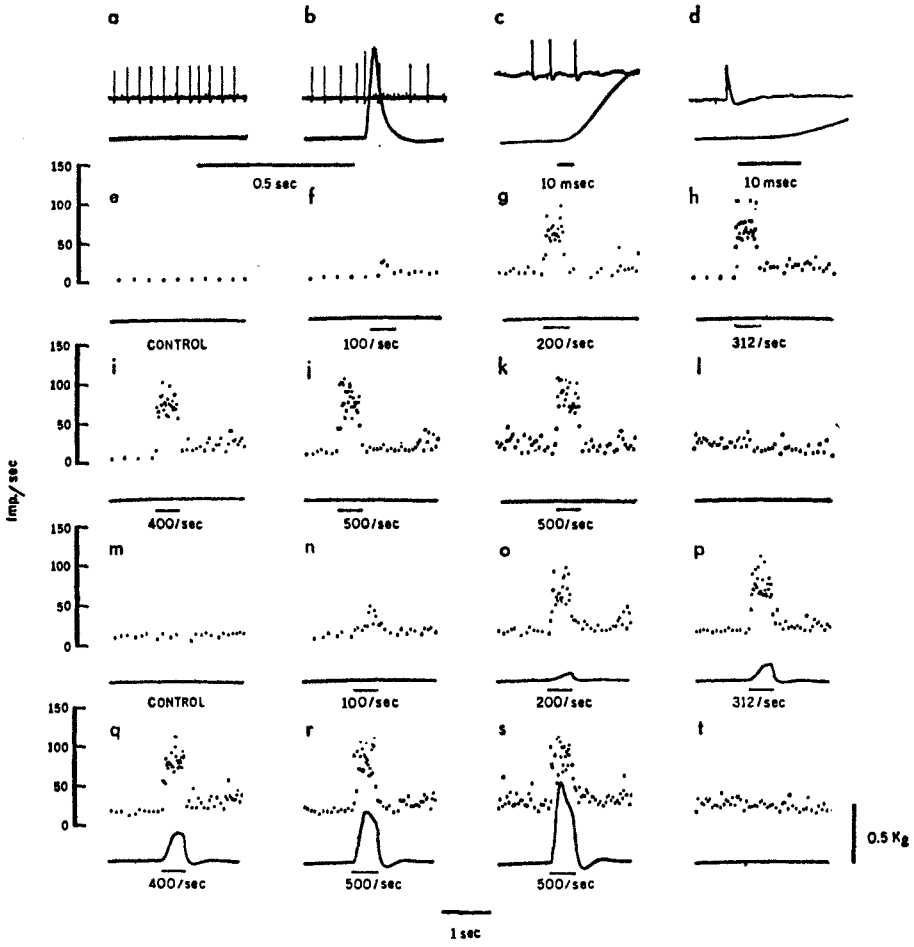


FIG. 2 (Pompeiano). Excitation of a muscle spindle receptor (conduction velocity of receptor fibre, 101 m./sec.) in isotonic and isometric conditions, on stimulation of the vestibular region close to Deiters' nucleus.

Gastrocnemius muscle afferented. Pre-collicular decerebrate cat. (*a*)-(*d*) Classification of the receptor, 4 mm. initial extension. (*a*) Control without stimulus; (*b*) the "pause" during a maximal twitch; (*c*) the "evoked" spike and an "early discharge" spike; (*d*) the evoked spike on an expanded sweep for determining conduction time. (*e*)-(*l*) Spindle excitation in slack muscle. Deiters' nucleus was stimulated at the frequencies indicated below each record (2 v, 0·5 msec. each pulse). (*j*), (*k*) and (*l*) are consecutive records taken at 4 sec. intervals. (*m*)-(*t*) excitation in isometrically contracting muscle at an initial extension of 4 mm. Same stimulus parameters as used in investigating responses in slack muscle. (*r*), (*s*) and (*t*) are consecutive records taken at 4 sec. intervals. The period of stimulation is indicated by a bar beneath each record. Upper trace, spindle-receptor discharge. Each dot represents an action potential, the instantaneous frequency of which is given by its height above zero on the calibration scale on the left-hand side. Lower trace: tension record. (From Diete-Spiff, Carli and Pompeiano, 1967.)

200 to 500 pulses/sec. Effects similar to those from the eighth cranial nerve were obtained from the medial and descending vestibular nuclei.

By contrast repetitive stimulation of the lateral vestibular nucleus of Deiters resulted in the simultaneous increase of spindle-receptor discharge and extrafusal muscle tension. There was no real difference in the threshold values needed to excite spindle receptors or the extrafusal muscle fibres (Carli, G., Diete-Spiff, K., and Pompeiano, O. [1966]. *Experientia*, **22**, 583–584). In particular the threshold frequency of stimulation which induced these changes corresponded to about 100 pulses/sec. This value is much higher than that evoking corresponding responses from the eighth nerve. Spindle-receptor activation and extrafusal contraction increased in a roughly parallel manner with an increase in the frequency of stimulation of Deiters' nucleus from 100 to 500 pulses/sec. (Fig. 2). The maximum tension changes resulting from the stimulation of this nucleus were greater than those obtained from the eighth cranial nerve and persisted in the deafferentated preparation—that is, even after interruption of the γ loop. Furthermore, the responses of the muscle spindle receptors to stimulation of Deiters' nucleus at different frequencies persisted also in slack muscle, in spite of any possible unloading effect that might have been due to shortening of the extrafusal muscle fibres (Fig. 2). It was also present after selective blocking of extrafusal end-plates by intravenously administered gallamine triethiodide.

These results show that the fusimotor system is preferentially affected when the eighth cranial nerve is stimulated. Not only is there marked spindle-receptor excitation, but the effect is produced with a range of frequencies which are ineffective for the extrafusal muscle fibres. Extrafusal muscle contraction, even when induced by increasing the frequency of stimulation, is always small. The effects of stimulating the eighth nerve can be reproduced, in part at least, by stimulating the medial and descending vestibular nuclei. The depression of both the extrafusal and intrafusal responses elicited by high-frequency stimulation of the eighth nerve or the medial and descending vestibular nuclei is likely to be due to the activation, through the vestibulo-reticular projection, of brain-stem structures inhibiting spinal cord activities. Repetitive stimulation of Deiters' nucleus, on the contrary, produces a great increase of extrafusal motor activity which is associated with a parallel increase in spindle-receptor discharge. This striking parallelism in the extrafusal and spindle receptor responses elicited by stimulation of Deiters' nucleus is likely to be due to a more direct control of the vestibulo-spinal pathway over skeletomotor and fusimotor neurones. Recent experiments in which the response of motoneurones to vestibular stimulation was recorded intracellularly (Lund, S., and Pompeiano, O. [1965]. *Experientia*, **21**, 602–603) have shown the existence of a monosynaptic connexion between Deiters' nucleus and α extensor motoneurones. The possibility of a monosynaptic connexion between the same structure and γ motoneurones is supported by some recent experiments (Pompeiano, O., Diete-Spiff, K., and Carli, G. [1967]. *Pflügers Arch. ges. Physiol.*, in press).

Lowenstein: Results such as these are extremely important because we are trying to bring together what we have learned from the first section of the symposium and what we are now learning. It may be relevant to remind you here that when people try to define vestibular "tonus", many of them in fact do not go so far as to define it in terms of tension but in terms of the rather vague concept of "preparedness for action". And the direct influence of the γ fibres seems to bear this out.

Gernandt: Since the vestibular nuclei are small and closely packed, an electrode

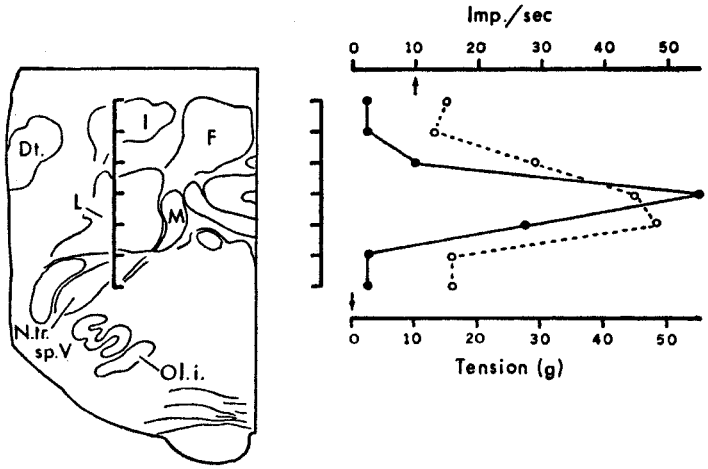


FIG. 3 (Pompeiano). Responses of extrafusal muscle fibres and a muscle spindle receptor (conduction velocity of fibre, 89 m./sec.) to repetitive stimulation (0/1 msec. pulses, 3 · 5 V, 500/sec.) at different depths along the vertical co-ordinate of Deiters' nucleus.

The scale corresponds to 1 mm. intervals. Gastrocnemius muscle, afferented. Initial extention: 6 mm. Pentobarbitone anaesthesia. The arrows indicate the control levels of spindle discharge and tension (indicated arbitrarily as 0). Note that spindle excitation and tension developed by the gastrocnemius muscle were maximum when the electrode was in Deiters' nucleus and that both responses increased in parallel. Open circles: spindle receptor discharge. Filled circles: extrafusal contractile tension.

Dt.: dentate nucleus; F: fastigial nucleus; I: interposite nucleus; L: lateral vestibular nucleus of Deiters; M: medial vestibular nucleus; N.tr.sp.V.: nucleus of the spinal tract of the fifth cranial nerve; Ol.i.: inferior olive.

(From Carli, Diete-Spiff and Pompeiano, 1967.)

tip within one nucleus readily spreads current into other vestibular nuclei and/or nearby brain-stem structures. Unquestionably the most appropriate site for applying electrical stimulation is among the peripheral branches of the vestibular nerve as they depart from the receptor structures within the vestibule. Synchronized volleys of impulses can be evoked and transmitted along the fibres as if they were a bundle of "natural electrodes" entering the brain stem, conducting orthodromic impulses which thereafter invade the ascending and descending vestibulofugal systems in a nearly natural fashion.

Pompeiano: I agree that when the peripheral branches of the eighth nerve are

stimulated one is feeding impulses into the vestibular system in a more "natural" way, although this term would apply still better to the physiological modalities of stimulation of the labyrinthine receptors. However, in order to test the function of the lateral vestibular nucleus, one has to keep in mind that the hindlimb region of Deiters' nucleus does not receive primary vestibular afferents, so that this nuclear region must be stimulated directly. The method of stereotaxic stimulation of the vestibular nuclei allowed us to demonstrate that the vestibulo-spinal influences on the ipsilateral extensor muscles originating from Deiters' nucleus are somatotopically organized (Pompeiano, O. [1960]. *Archs Sci. biol.*, **44**, 497–511) following a pattern which is in agreement with the anatomical picture. Fig. 3 is taken from our work (Carli, G., Diete-Spiff, K., and Pompeiano, O. [1967]. *Archs ital. Biol.*, in press) to show that the muscle-spindle acceleration and the extrafusal muscle contraction occur only when the stimulating electrode is strictly localized in the Deiters' nucleus. I realize, however, that when skeletomotor and fusimotor effects are elicited by stimulating the descending vestibular nucleus these effects may be due in part at least to stimulation of the descending branches of the primary vestibular fibres, which through their collaterals may excite the second-order vestibular neurones localized in the medial vestibular nucleus.

Roberts: In the "natural" condition the vestibular nerves are firing spontaneously and one would expect contrary reflex effects according to whether or not the discharge increases or decreases in frequency. It might therefore be important to know whether the effects of stimulating the vestibular nerve electrically were the same at different frequencies of stimulation. Have you considered this?

Gernandt: Usually we stimulate at a frequency of 1 shock per sec. If repetitive stimulation, 10–50 pulses/sec., is applied to the vestibular nerve the character of the evoked motor responses is altered.

Jansen: Professor Gernandt, you did not mention the differential effects of stimulating the various branches of the vestibular nerve. Was that because all these branches produce the same effect in the spinal cord?

Gernandt: The vestibulo-spinal effects are identical when electrical stimulation is applied to the nerve branches from the ampullae of the lateral or superior semicircular canals. However, when we were studying the cortical projection of the vestibular organ, selective stimulation of the different peripheral branches of the vestibular nerve made it possible to demonstrate a specific localization in the cerebral cortex of the particular end organs (Andersson, S., and Gernandt, B. E. [1954]. *Acta oto-lar.*, Suppl. 116, 10–18).

Roberts: Another possibility arises from Dr. Jansen's point, that canal stimulation might give one effect and otolith stimulation might be expected to give the opposite effect. We should perhaps suspend judgement on what we get when stimulating the eighth nerve until we know what natural situation we are imitating.

Lowenstein: Is it impossible to apply natural stimulation to the vestibule?

Gernandt: It is possible but very difficult.

Hallpike: What happens if you fire a pistol—that is, give cochlear stimulation?

Gernandt: Auditory stimulation may not necessarily activate tracts and nuclei belonging only to the "classical auditory system", but may also trigger neural activity of far-reaching systems leading finally to the activation of peripheral effectors. The familiar "startle" reaction evoked by unexpected auditory stimulation offers a striking example of how sudden recruitment of a larger population of neurones gives rise to complex and variegated motor behaviour. In anaesthetized or decerebrate cats, the physiologically available neurones of the auditory system appear to be insufficient for conducting a traceable volley of impulses, evoked by natural cochlear stimulation, into the spinal cord. In order to elicit responses from motor neurones along the extent of the cord, it is necessary to mobilize the reserve of anatomically existing connexions by establishing a high level of excitability, by giving chloralose or strychnine sulphate in a subtetanic dose.

Certain aspects of the mechanisms mediating spinal motor activity induced by auditory stimulation have been examined by recording within the bulb and from motoneurones at both cervicothoracic and lumbosacral levels (Gernandt, B. E., and Ades, H. W. [1964]. *Expl Neurol.*, **10**, 52–66). Single auditory click stimulation (147 db) elicits, in lightly strychninized cats, motor responses appearing along both sides of the spinal cord. In the competition for access to the final common path, the evoked descending acoustic volley of impulses is readily blocked by prior dorsal root stimulation. Since the ventral root responses recorded contralaterally to the side of auditory stimulation have the same appearance as the ipsilateral ventral root responses and also respond identically to higher frequency stimulation and interact with dorsal root responses in an identical way, it is assumed that the acoustico-spinal mechanisms on the two sides of the spinal cord are mirror images of each other, elicited from a common brain-stem neuronal pool. Decerebration and cerebellectomy do not interfere with the transmission of this accoustico-spinal reflex activity. Auditory projections to the brain-stem reticular formation are evidently sufficient to maintain the pattern of the descending reflexes. Partial sections of the spinal cord demonstrate that the descending connexions necessary for the transmission of activity induced by sound are part of a diffusely projecting spinal system. Bilateral motoneurone discharges following unilateral acoustic stimulation are ensured by an abundance of functional crossings in the bulb and along the extent of the spinal cord.

Dohlman: If a fistula is made on one of the semicircular canals and "clicks" are applied to the eardrum, this would be ideal as a more normal way of giving partial labyrinthine stimulation. This is the Tullio effect; one gets a very sharp stimulation.

Gernandt: We have that in mind, but we have not done it yet.

Brodal: With reference to Dr. Jansen's question concerning stimulation of the

various branches of the eighth nerve, there is evidence from the studies of R. Lorente de Nó ([1931]. *Ergebn. Physiol.*, **32**, 73–242; [1933]. *Laryngoscope, St Louis*, **43**, 1–38) that the fibres from the different vestibular receptors do not terminate in the same regions within the vestibular nuclei. In particular it appears that fibres from the utricular macula are distributed to Deiters' nucleus while the canals chiefly supply the other vestibular nuclei. Professor Gernandt, have you stimulated the nerve from the utriculus?

Gernandt: Yes, but not to the same extent as the branches from the ampullae of the lateral and superior semicircular canals. However, the vestibulo-spinal motor effects appear to be the same.

Hallpike: May I mention here a clinical condition with which I am familiar that might be related to what Professor Gernandt has told us and perhaps also to what we have heard from Professor Brodal. The patients are generally adults, more often women than men, and their trouble is as follows: they walk along quite actively and then suddenly find themselves on their knees; they fall with great force and injure their knees—a point which is worth mentioning, because it contradicts the contention that their condition is functional. They do not lose consciousness. They have no warning of any kind and never have vertigo. When they fall they are aware only of a feeling of embarassment. The condition is known as "drop attacks". The patients are on the whole rather healthy; more often than not one finds some evidence of vestibular disorder, in the form of some irregularities of the caloric responses and so on, but the attacks in question are not a feature of other forms of established vestibular disease. Most of the patients are in an age-group in which vascular insufficiency of the brain stem is beginning to make itself felt. Nobody knows the cause. It is a benign condition and does not progress. In a few patients, some of whom I have observed falling, it seems to occur when they are hurrying, or standing still, or suddenly accelerating and turning their heads. I have thought that the vestibular system might be involved but what Professor Gernandt says suggests that there might be some inhibition of the central reticular system which would fail to do what is needed, namely convert the limbs into rigid pillars to stand on.

Gernandt: The increased excitability of spinal motoneurones during vestibular or brachial plexus stimulation and the protracted inhibition after cessation of stimulation strikingly resembles the abrupt rigidity followed by transient quadriplegia which can result clinically from the impact of high-velocity missiles in the region of the brachial plexus (Livingston, W. K., and Newman, H. W. [1946]. *West. J. Surg. Obstet. Gynec.*, **54**, 131–139). It was suggested that the loss and sudden restoration of willed movements were indicative of a "temporary dys-synchronization affecting integrated neurone systems of the motor mechanism".

Hallpike: The drop attacks might then not be a vestibular disorder at all.

Gernandt: That is correct. There are many reasons for implicating the reticular formation in the elaboration of this long-lasting inhibitory influence. Thus, in

addition to the vestibular system, stimulation of any other source sending collaterals into the reticular formation should evoke the same effects.

Hallpike: Are there any clinical tests which should be done on such patients when they fall?

Gernandt: The knee-jerk reflex ought to be dead during that time.

CENTRAL REGULATION OF THE MUSCULAR AND VESTIBULAR MECHANISMS IN MAN

Purdon Martin: The observations that I want to present have a bearing on the *central control* of the muscular and vestibular mechanisms with which we are concerned in this symposium.

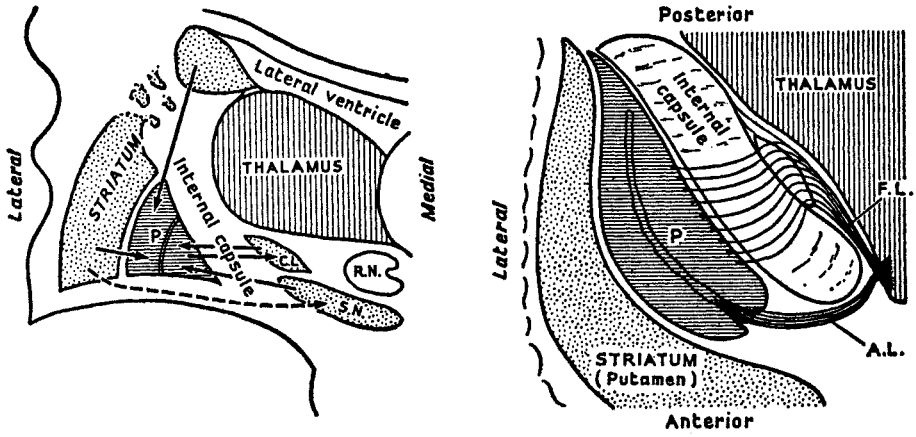


FIG. 1 (Purdon Martin). *Left:* Diagram of a vertical section through the thalamus to show the relationship of the globus pallidus (P) to the striatum, corpus Luysii (C.L.) and substantia nigra (S.N.), and the fibre connexions within this group of ganglia. R.N., red nucleus.
Right: Diagram of a horizontal section through the thalamus to illustrate the "long" efferent fibres of the globus pallidus (P). F.L., fasciculus lenticularis; A.L., ansa lenticularis. Both these bundles of fibres end in the ventral part of the thalamus.

A few years ago I set out to discover whether there were any "negative" or deficiency symptoms associated with disease of the basal ganglia, thinking that they might be related more directly to the pathological lesions than are the "positive" symptoms—the rigidity and involuntary movements—that it is customary to emphasize. I found a number of such symptoms and observed that most, and probably all of them were due to deficiencies of postural mechanisms (Martin, J. P. [1967]. *The Basal Ganglia and Posture.* London: Pitman).

As it is many years since physiologists in this country—and also elsewhere—gave up the basal ganglia as a bad job, you may be forgiven if you do not remember their anatomy (Fig. 1). The fibre connexions show that the centre of the organization is the globus pallidus. The caudate nucleus sends its efferent fibres into the pallidum, as also does the putamen; the subthalamic nucleus

(corpus Luysii) has a two-way connexion with the pallidum and even the substantia nigra sends many pallidal fibres. The outflow from the system is by way of the pallidum and it sends almost all its fibres to the ventral nuclei of the thalamus.

In the course of this investigation I came on a paper by Richter in which he described certain fixed postures in monkeys poisoned by carbon disulphide gas which were associated with degeneration closely limited to the globus pallidus on both sides. I was then engaged with Hurwitz and Finlayson in a survey of a large group of post-encephalitic patients and we had already observed in a number of them the loss of postural fixation of the head in various positions, including the "all-fours" position. This seemed to correspond to Richter's illustration (Richter, R. [1945]. *J. Neuropath. exp. Neurol.*, **4**, 324–353) of the monkey with bilateral pallidal degeneration (Martin, J. P., Hurwitz, L. J., and Finlayson, M. H. [1962]. *Lancet*, **2**, 1–6 and 62–66). This posture had also been observed in the monkey by M. B. Carpenter, J. R. Whittier and F. A. Mettler ([1950]. *J. comp. Neurol.*, **92**, 293–331) following bilateral lesions of the pallidum or of the pallido-fugal fibres, and was called by them the "somersault" posture. D. Denny-Brown has since described the same thing in a monkey with bilateral pallidal lesions ([1962]. *The Basal Ganglia and Disorders of Movement.* London: Oxford University Press). He called it the "pallidal" posture, but as there are other pallidal postures it is perhaps better to call it the "somersault" posture.

Let me give you some of our observations in patients with different kinds of disease of the basal ganglia, making use of the classification of postural reflexes that I used earlier (p. 93).

(1) In the first place, none of the patients loses his anti-gravity mechanism—his ability to support the weight of his body against gravity—but he may lose all the rest of the reflexes.

(2) One of the commonest features is that the patient allows his head to fall down—he loses the "postural fixation" of his head. Parkinson described this, but he did not describe that the patient can quite easily raise his head again and push it back quite strongly. The patient may let his trunk as well as head fall forward, but he is able to raise both trunk and head. What is lost is the fixation of the posture. This is not due to weakness of the muscles; one patient, when she has an oculogyric crisis, also has a retro-collic spasm—a released postural reflex—which bends her head and body backwards. This is a very strong and persistent spasm, and makes it quite clear that there is no weakness of the muscles in the back of her neck. When the loss of postural fixation of the head occurs in the "all-fours" position, the top of the head comes down on to the floor, in the same manner as is typical of the "somersault" position in the monkey, and I think we are justified in applying the same term to the human phenomenon.

In a patient with Wilson's disease (another disease of the basal ganglia) the head falls forward the moment the patient closes her eyes. That applies to a good many patients with conditions other than Wilson's disease. These patients have

lost the proprioceptive reflex that supports the head and are relying on the visual reflex to hold the head up. This phenomenon was also seen in an unusual case of Huntington's chorea. Many of these patients have other disturbances of their postural fixation and, in particular, disturbance of the co-ordination of the various parts which should enable them to preserve the equilibrium of the body, and they are therefore inclined to totter backwards or forwards.

(3) The third group comprises the staggering reflexes. These patients with basal ganglia disease may lose their staggering reactions and, in consequence, be unable to maintain the upright posture when pushed horizontally.

(4) Fourth comes the righting reactions, properly so-called. These are among the first reflexes to be affected in disease of the basal ganglia. The patient becomes unable to rise from a chair or from the floor and unable to turn himself over from the supine to the prone position when lying on the floor. You will recall that Magnus and Rademaker found that in quadrupeds all the righting reflexes were present in the mid-brain animals; but in the human and in the monkey they are abolished by bilateral lesions of the basal ganglia (pallidum).

(5) Patients with basal gangliar disease soon show disorders of their gait. The Parkinsonian patient shuffles along, not raising his feet from the floor. This is because in normal walking when the left leg is swinging not only must the centre of gravity move to be over the right foot but, in addition, the body has to tilt to the right, thereby counterpoising the weight of the swinging leg. Parkinsonian patients cannot achieve these adjustments of the body weight. Their stepping mechanism is unaffected and when they are rocked gently they can step out well. A patient who is unable to step forward of his own accord cannot be helped by pulling him forward, only by rocking him. Alternatively, if he is given a strong visual frame of reference, such as white lines painted on a black floor, or low obstacles placed along a pathway, the patient can walk very well by himself. It has been customary to attribute the locomotive disabilities of the Parkinsonian patient to rigidity, but these observations show that this does not provide an adequate explanation, since the patient can be enabled to walk without change in his rigidity. The fact is that he loses the postural reflexes concerned in locomotion.

(6) The last group in my classification of postural reflexes are the reactions to tilting. Many patients with basal gangliar disease behave on the tilting apparatus in the same way as patients with no vestibular reactions—that is to say they have lost the tilting reflexes which are excited by the vestibular mechanism. One patient who was otherwise extremely active had no reaction against the tilt and the same applied to many other patients whose general disabilities were greater. Three patients responded normally at first but this primary response was little more than momentary and in each case the patient quickly fell over. The response was not due to inertia because it included normal reactions of the limbs, and in any case reactions due to inertia would not have been limited to these few patients. The normal reaction is so brief ("evanescent") in these cases that it may easily be missed in viewing the cinematographic record. My interpretation is that each of

these patients has preserved the reflex excited from his semicircular canal apparatus but has lost the reflex excited from his otolith apparatus which should maintain his position. An observation of a similar kind was made by Zador but, following Rademaker, he interpreted it as due to the loss of a proprioceptive reaction. From my own observations on patients without vestibular reactions, I think it is due to the loss of the reflex that should be excited from the otolith apparatus; as far as I am aware this dissociation of the reflexes aroused from the two parts of the vestibular mechanism has not previously been recognized in the human subject. In cases where the disease of the basal ganglia is progressing gradually there may be gradual central interruption of the arcs of these various reflexes and so this dissociation may occur.

It is true that in the various conditions to which I have referred we are dealing with relatively diffuse disease, but there is considerable evidence that these reflex changes are due to disturbance of the basal ganglia. In the first place these symptoms do not (in general) occur with disease elsewhere than in the basal ganglia, and secondly there are reasons from the reported experimental work to relate these negative symptoms to bilateral disease of the globus pallidus.

I have not time here to discuss the positive phenomena of these diseases, but these deficiency symptoms are disorders of reflex mechanisms and, just as in other diseases the knee-jerk is sometimes abolished but is more often exaggerated, so some of these reflex activities may be released and may thereby cause positive symptoms.

I think it is evident that the basal ganglia are concerned with all aspects of posture other than the support of the body against gravity and we must infer that the proprioceptive, vestibular and visual postural mechanisms act through them. It has sometimes been suggested that they are the head ganglia of the vestibular system, but they are concerned with postural reflexes evoked by proprioceptive and visual mechanisms just as much as with those excited from the labyrinth. Again it has often been thought that the globus pallidus, in particular, is a motor organ, but I think it is only motor in the sense that our peculiar form of locomotion is controlled by postural influences (see Martin, J. P. [1967]. *Loc. cit.*).

Henriksson: We have had cases in our department of neurology that present a quite clear-cut tendency to fall, frequently backwards, in the Romberg test. The opinion has been that these falling tendencies must be hysteric in origin. We have examined a couple of such cases but the neurological and oto-neurological tests and examinations have been normal. It would be interesting to know if Dr. Purdon Martin has some special test which would reveal disorders in the basal ganglia in such cases.

Purdon Martin: If the condition you mention was due to disease of the basal ganglia, you would not in general have much doubt about it because there would be other signs of basal gangliar disease. However, I have known falling backwards, and consequent inability to rise from a chair, to be the first signs of bilateral pallidal lesions (as I thought) in an elderly person.

Most of the deficiencies of postural reflexes that I have mentioned are "objective" but, of course, some are more convincing evidence of organic disease than others, and if you have a number that are consistent, that naturally increases the value of the evidence. The falling down of the head when the eyes are closed is a convincing sign and so are some of the losses of the tilting reflexes. D. Denny-Brown ([1962]. *The Basal Ganglia and Disorders of Movement.* London: Oxford University Press) and others have observed that falling down of the head is most likely to occur in the monkey when it goes into a corner, and I think this may be because it comes up against a blank wall. We have noticed with patients that if there is little or no content in the visual field the effects may be much the same as those of blindfolding. Perhaps this could be made use of in testing a suspected hysterical patient.

Monnier: Dr. Purdon Martin's observations of human subjects in which the head tends to drop would interest Professor Hess, because he was able to show that coagulation of a very limited area in the subthalamus (oro-dorsally to the red nucleus) destroys the pattern which raises the head and the body. Is it possible that a lesion in the subthalamus has destroyed this righting pattern, so that the patient tends to lower the head and upper part of the body?

Purdon Martin: I do not recall Hess's observation. M. B. Carpenter, J. R. Whittier and F. A. Mettler ([1950]. *J. comp. Neurol.*, **92**, 293–331) in one of their monkeys placed lesions bilaterally by a stereotaxic technique which interrupted the pallido-fugal fibres (of the ansa lenticularis and fasciculus lenticularis) just before their entrance into the ventral thalamus, and this monkey subsequently showed the occurrence of the "somersault" posture. Later the sites of the lesions were confirmed anatomically and a photograph was published showing their very precise location on both sides. I do not know of any other subthalamic site at which the reflex arc concerned might be interrupted.

VERTIGO OF CERVICAL ORIGIN

Philipszoon: May I mention here a type of vertigo which is often forgotten to have another origin than a vestibular one. This is vertigo of cervical origin. It arises because impulses from the muscles and proprioceptors as well as labyrinthine impulses go to the vestibular nuclei.

Professor A. Biemond observed nystagmus in patients with disorders of the posterior cervical nerve roots. He reproduced this in rabbits and found positional nystagmus after cutting the posterior cervical nerve roots ([1939]. *Proc. K. ned. Acad. Wet.*, **42**, 370; [1940]. *Ibid.*, **43**, 2). We repeated this, using electronystagmography (Philipszoon, A. J. [1962]. *Practica oto-rhino-lar.*, **24**, 193–202; Bos, J. H., and Philipszoon, A. J. [1963]. *Practica oto-rhino-lar.*, **25**, 108–118; Jongkees, L. B. W., and Philipszoon, A. J. [1964]. *Acta oto-lar.*, Suppl. 189; Philipszoon, A. J., and Bos, J. H. [1963]. *Practica oto-rhino-lar.*, **25**, 339–344). We wanted a method of irritating the posterior cervical nerve roots without an operation. This was achieved by fixing the head of the rabbit in a clamp and placing its trunk

on a board which could be moved, so that the cervical nerve roots could be stimulated without labyrinthine stimulus, either to the otoliths or to the semicircular canals.

When a small stimulus was given we obtained compensatory eye movements (slow phase of nystagmus) and when the movements of the trunk were increased the quick phase of nystagmus was also seen (Fig. 1). This kind of nystagmus is peculiar in that it can be provoked in labyrinthectomized rabbits in which there is no reaction of the eyes to angular or linear acceleration (Fig. 2). The same could be done in patients without labyrinths; when the head of the subject was fixed

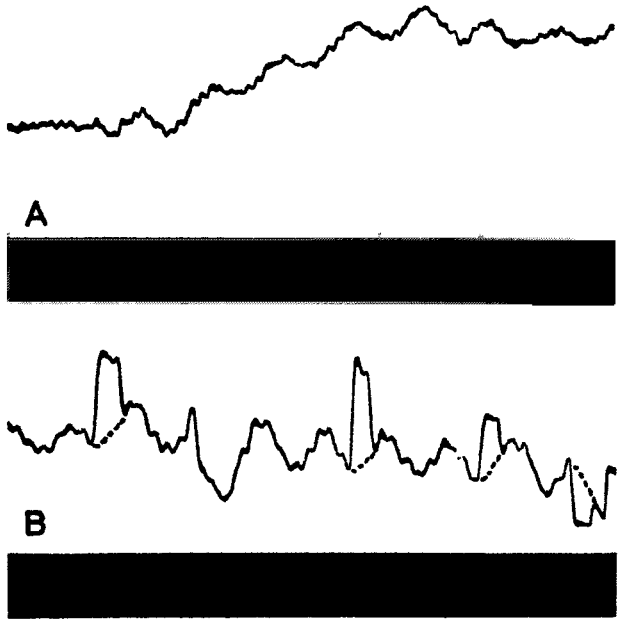


FIG. 1 (Philipszoon). A. Compensatory eye movements seen when the cervical roots are stimulated by torsion of the neck in a normal rabbit.

B. Nystagmus caused by torsion of the neck in the same animal. The dotted line indicates the eye movements expected if the quick phase of the nystagmus were not present.

in a clamp and he was sitting on a torsion swing in such a way that the trunk was rotated, neck-torsion nystagmus could be provoked even in patients without labyrinths (Fig. 3).

In another experiment we prepared a rabbit in a clamp, performed neck torsion and observed the eye movements. We then cut the spinal cord at the level of the occipital foramen, after artificial respiration by means of a tracheotomy. After total transection of the cord no eye movements could be provoked by rotating the head and thus stimulating the semicircular canals.

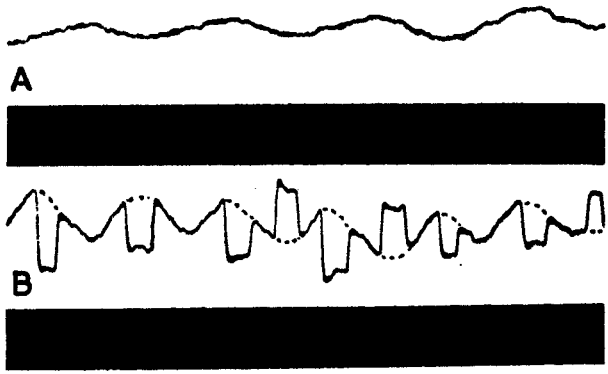


FIG. 2 (Philipszoon). A. Compensatory eye movements when the cervical roots are stimulated by torsion of the neck in a rabbit without labyrinths.

B. Nystagmus caused by torsion of the neck in the same animal. The dotted line indicates the eye movements expected if the quick phase of the nystagmus were not present.

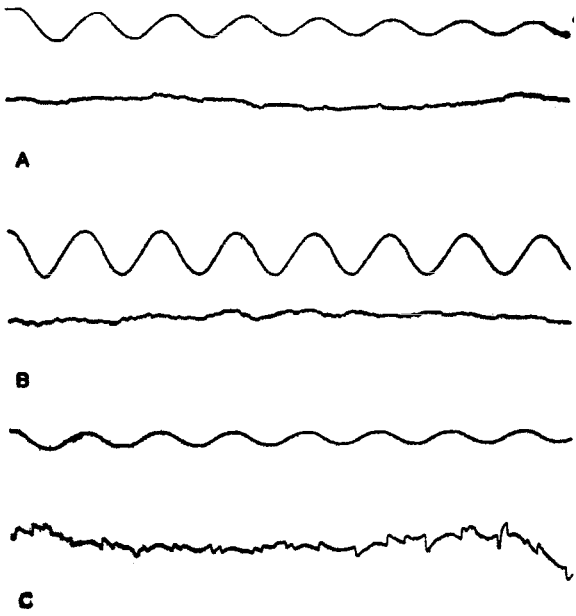


FIG. 3 (Philipszoon). Patient with two inexcitable labyrinths after trauma capitis.

A. Stimulation of the semicircular canals by angular accelerations on the torsion swing: no reaction. B. Stimulation of the otoliths by linear accelerations on the parallel swing: no reaction. C. Neck torsion: good reaction, nystagmus in both directions. The upper lines indicate the mechanical movements, the lower the eye movements.

Why is this often-forgotten source of nystagmus so important? One frequently finds patients suffering from vertigo who have normal audiograms and calorigrams and only when one uses electronystagmography does one find a spontaneous or positional nystagmus. A further difficulty is that one may not detect this by looking at the eyes because this kind of nystagmus can be inhibited by the eyes being open, even with the spectacles of Frenzel. Electronystagmography reveals that these patients have some objective basis for their complaint, and one can treat them as patients with an organic disease. One possibility of treatment is the use of antihistaminic drugs which suppress vestibular activity and also neck-torsion nystagmus (Fig. 4). These drugs suppress the nystagmus

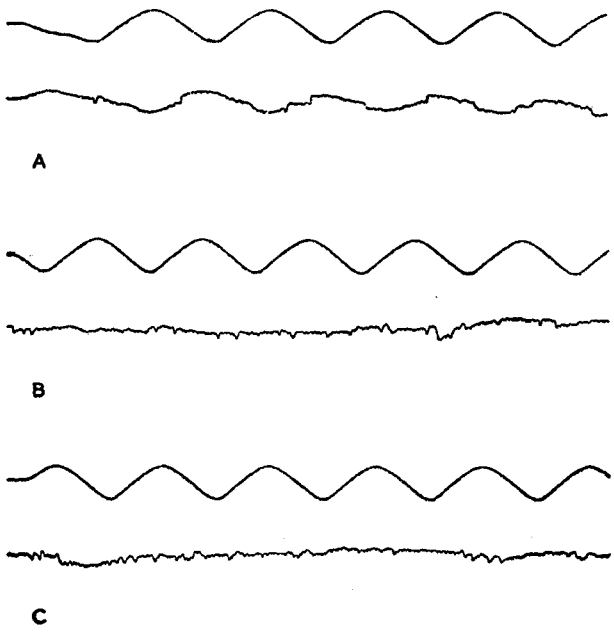


FIG. 4 (Philipszoon). The influence of cinnarizine on neck-torsion nystagmus in the rabbit.
A. Before injection. B. 20 min. after injection. C. 40 min. after injection.

seen after neck torsion in rabbits, while in patients good results are obtained in vertigo.

CENTRAL REGULATION OF VESTIBULAR RESPONSES

Groen: I hope that my contribution may bridge the gap between what we have discussed so far and the later part of symposium.

In the clinic we are often confronted with a patient whose vestibular function (or vestibular dysfunction) we must judge from his nystagmus and from his sensations and other conscious responses. In doing so, we are inclined to draw

conclusions which we assume pertain to the vestibular organ. Actually, they pertain to the whole complex of the vestibular system. In short, and to anticipate my conclusions, vestibular response is modified by central influences, and these are of at least two types. The first type is inhibitory and the second type perhaps comes from the so-called "pattern centre", which is a hypothesis I want to propose.

First of all, how do we observe the vestibular reaction? We give a rotatory stimulus and record the duration of the ocular phenomenon as a function of the

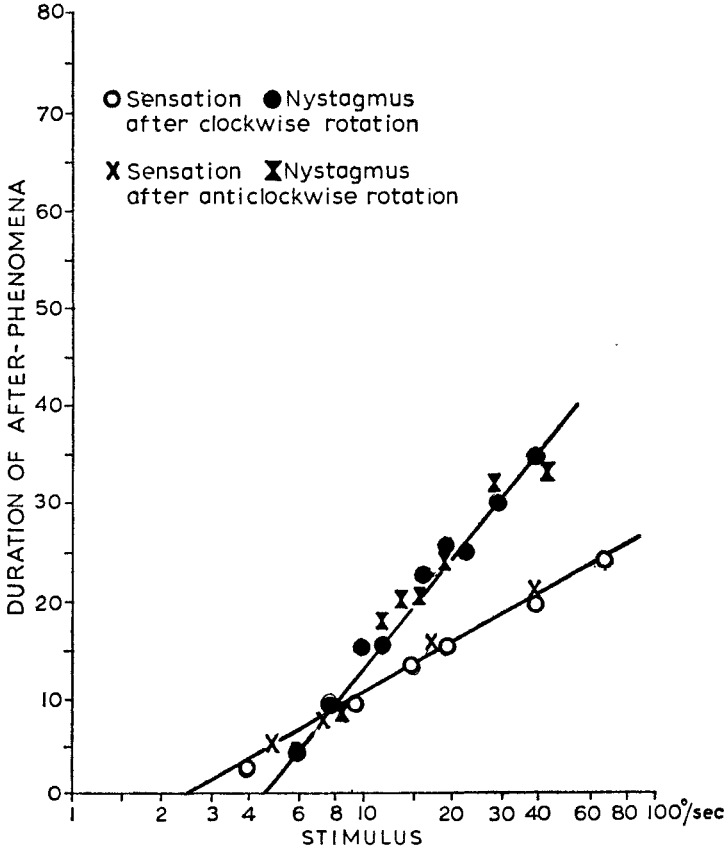


FIG. 1 (Groen). Normal cupulogram of sensation and nystagmus. The slopes of sensation (8 sec.) and nystagmus (16 sec.) are different.

stimulus. We immediately see that in so-called "normal" test subjects the duration of the sensation and the duration of the nystagmus are different in slopes (Fig. 1). Yet in so-called normal subjects they should be identical. We now submit so-called "normal" subjects to excessive vestibular stimulation. M. W. W. Krijger ([1954]. Thesis, University of Utrecht) used a group of 18 experienced fighter-pilots (that is, selected "normal" test subjects) after 2,000 hours

of "stunt" flying. Here the whole reaction pattern is far more depressed (Fig. 2). After a 14-day holiday, the curves revert to the normal type, and then after further "stunting" hours the values are again of the depressed type. There is one type of person who always produces curves that are straight and steep lines; such people will be severely motion sick on the slightest provocation (Fig. 3). They are otherwise quite normal and healthy; they are abnormal only in that they

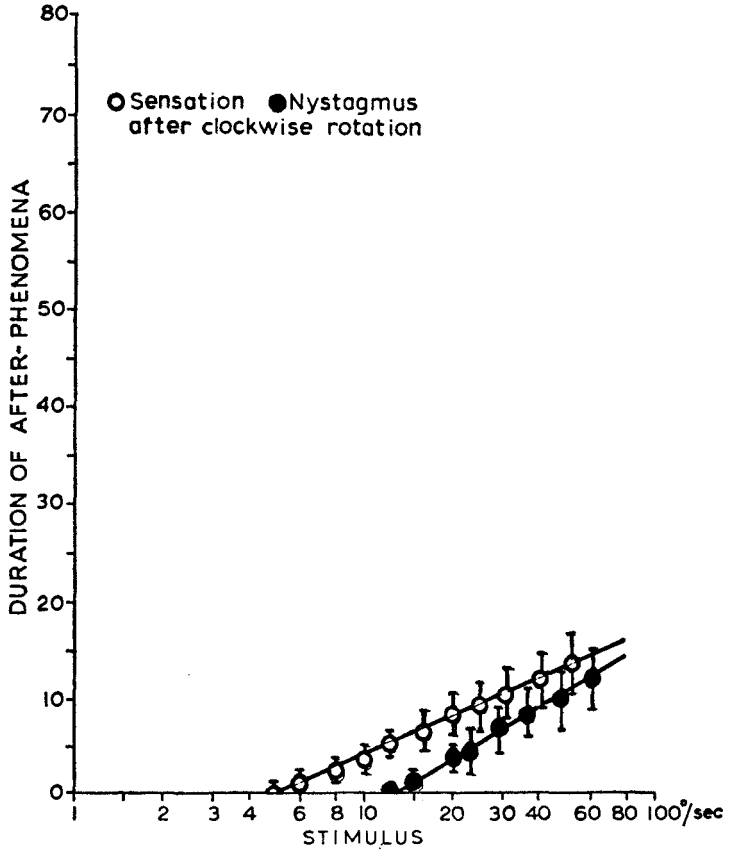


FIG. 2 (Groen). Average cupulogram of 18 experienced fighter-pilots. Threshold for sensation slightly raised. Slopes for sensation (6 sec.) and nystagmus (8 sec.) considerably lower than normal. (After Krijger, 1954.)

cannot stand any type of motion other than walking. It is not important that the thresholds for sensation and nystagmus are different; the important point is that there are normal people who have reactions which cannot be changed after excessive vestibular stimulation. I must add that not all those who tend to be motion sick have these curves, but they have this one point in common that they show the same values before and after excessive stimulation. They have no tendency for inhibition of the after-reactions.

There are only three instances in vestibular life where one can really apply one's mathematical formulae. These are the activity of the isolated peripheral organ; the ideal motion-sick man; and finally the newborn child or animal. I have studied ocular reactions in the 9-day-old baby, measuring the duration of eye

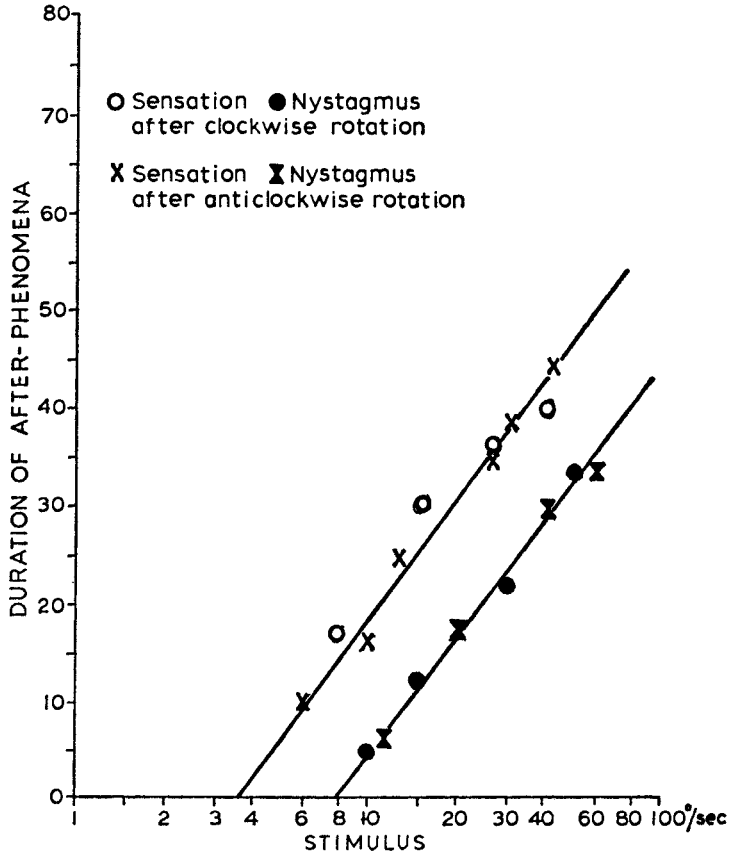


FIG. 3 (Groen). Cupulogram of an individual who is inclined to motion sickness. Thresholds are normal, but the slopes of sensation and nystagmus are identically high (18 sec.). This is not an extreme case; a value of 22 sec. or more is not exceptional.

deviation—about two minutes—and noting the low threshold. The inclination of the curve is about 18 sec. (Fig. 4). The eye deviations are enormous; the eye almost disappears round the corner and stays there! I have only seen this in the adult in one instance, in a woman who had been decorticated by anoxia. She also had enormous eye deviations and a nystagmus as well, if we stimulated her. After birth a progressive depression of the eye deviation starts to come in for

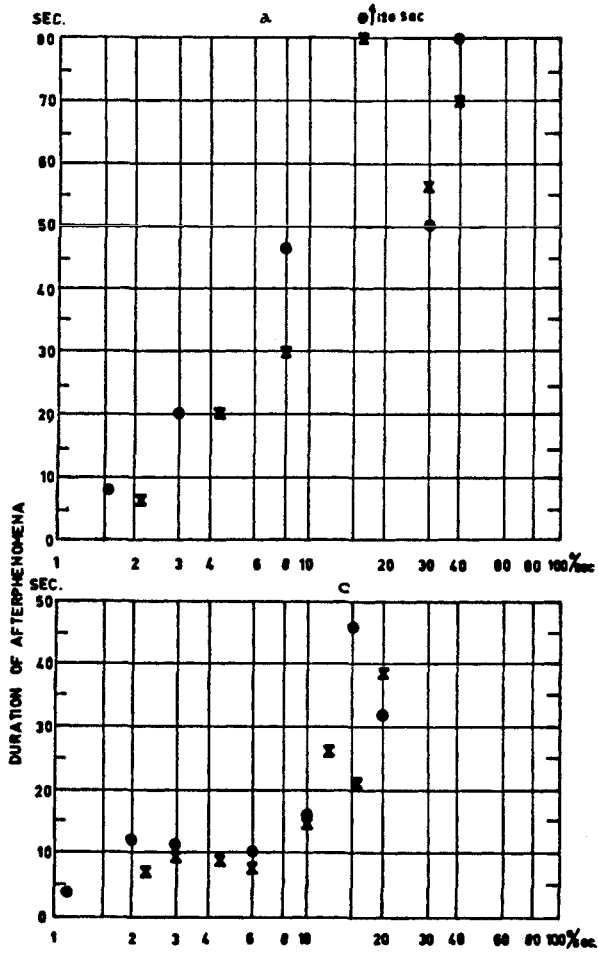
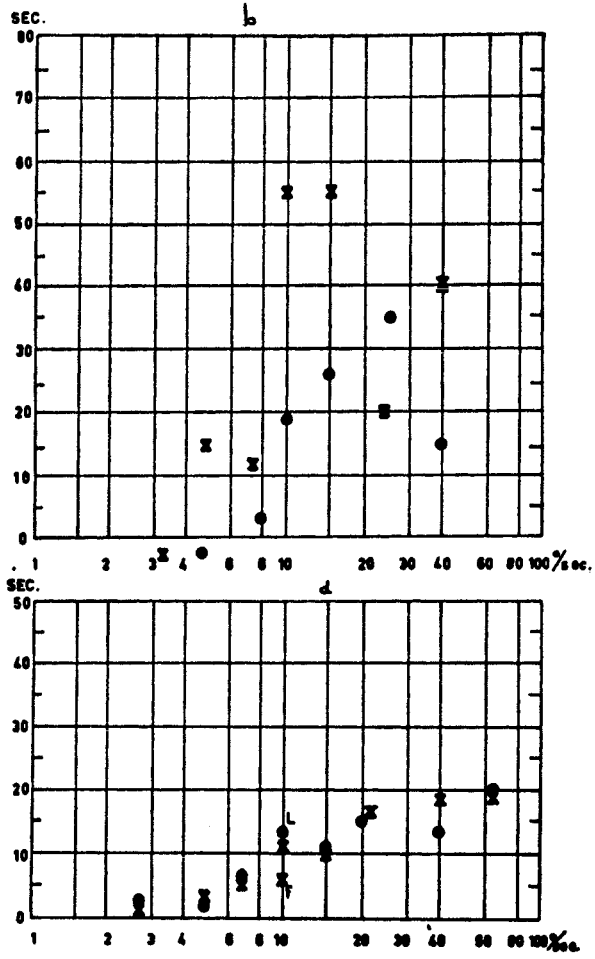


FIG. 4 (Groen). Nystagmus or eye-deviation cupulograms of a young child observed with Frenzel glasses.

(*a*) 9 days after birth. Child was awake. Measurements were started with 16°/sec. stimulus in clockwise (120 sec.) and anticlockwise (80 sec.) directions. Very sensitive reactions. Threshold at about 1°/sec. Slope = 18 sec. Slight preponderance to the left side. Responses consisted of nystagmus strokes and eye deviations.

(*c*) 36 days after birth. Child was asleep. Below 10°/sec., nystagmus was observed; above 10°/sec., merely eye deviations present. Threshold low. Slight preponderance to the left side. Inhibitory tendency for small stimuli.



(*b*) 16 days after birth. Points indicated below zero-time indicate no response. Preponderance to the right side. Threshold in the neighbourhood of 4°/sec. Inhibitory reactions present for stronger stimuli (> 20°/sec.). Child was asleep. No nystagmus below 25°/sec. stimulation; merely eye deviation.

(*d*) 82 days after birth. Child was awake. Threshold still low. Inhibition, probably by fixation, present. Slope = 7·5 sec., strongly reduced as compared to (*a*).

small stimuli. By 82 days after birth the response is like the normal adult one.

So the child is born with a normal vestibular apparatus. In the course of time inhibition develops; in man it takes about two months and in the dog it take about 28 days. The second change is that nystagmus comes in and after 16 or 20 days is a common feature. Nystagmus appears merely as a mechanism to intercept eye movement; it does not interfere with our simple concept of the peripheral organ and its mathematical and physical formulae. Inhibition, however, does, and changes the responses in such a way that my formulae do not apply to normal test subjects.

I have another suggestion and that is my "pattern" centre (Groen, J. J. [1957]. *Practica oto-rhino-lar.*, **19**, 524–530). Why is this necessary? We all know the phenomenon of becoming accustomed to the movement of a ship and then, on going ashore, finding that the ground is moving rhythmically under our feet. We feel quite sure that the ground is actually moving. I think this expresses what goes on in the central nervous system at this time. The vestibular organs have been presented for several days with a periodic or quasi-periodic stimulation. There must be some "pattern" centre in the brain where a "copy" is made of this quasi-periodic movement, and after about two days this copy becomes as active as the peripheral organ, and the two converge, in two different ways. On the boat, the coupling between the vestibular and the vegetative system is neutralized by the activity of the copy and secondly, one no longer has any sensation of moving up and down. Also, the connexion between the vestibular system and its cortical projection is suppressed because of the activity of the copy. But one's entire motor function is not impeded; in fact it is helped, and one can anticipate the movement of the ship. On going ashore, the sensation of movement is due to the "pattern" which has been constructed earlier and maintained so well; it continues to function, usually for about one day but in some cases it takes a month before the copy disappears completely.

Quite accidentally, I was given proof of this hypothesis in the data of J. A. J. Klijn and J. van Ek ([1959]. *Practica oto-rhino-lar.*, **21**, 391–393). In this experiment a pigeon had been submitted to the movement of the torsion swing for 10 minutes. By chance the pigeon was forgotten and left on the stationary torsion swing for four hours, with its head still connected to the recording drum and the recording going on. They could still see some periodicity in the record by an autocorrelation procedure although the pigeon had been motionless for four hours. They found a quasi-sinusoidal line with the same periodicity as that of the torsion swing with which the pigeon had been presented previously. This is what I would call an after-reaction due to a pattern stored in the "pattern" centre. In man, after 10 or 20 oscillations on the torsion swing, one can already see the interference of the first pattern.

So these are the two modifying central influences which I would suggest: (1) inhibition and (2) the pattern centre, to make it difficult for us to judge vestibular function proper.

Myotatic, Kinesthetic and Vestibular Mechanisms
Edited by A.V. S. de Reuck and Julie Knight

CENTRAL MECHANISMS OF VESTIBULAR AND OPTOKINETIC NYSTAGMUS

MARCEL MONNIER

Physiologisches Institut der Universität, Basel, Switzerland

MOTION of the head or motion of the surroundings results in loss of the visual object. A compensatory deviation of the gaze occurs, allowing one to keep the retinal image as long as possible. This is achieved by vestibular as well as by optokinetic oculo-motor reflexes, and it therefore seemed logical to postulate that both reflexes may have a common central mechanism.

Stimulation and coagulation experiments performed in our laboratories on monkeys, cats and rabbits provided some answers to this question. We shall try to summarize them in a diagram (Fig. 1), taking into account the mechanisms of both vestibular and optokinetic nystagmus. Experimental data on the *rabbit* will be chiefly considered, and mapped on charts of our atlas for brain research on this animal (Monnier and Gangloff, 1961).

In contrast to the clinical tradition we shall base our argument on the primary slow-phase component of the nystagmus, since it expresses its chief function, as a kind of grasp reflex.

The experimental data will be analysed in the following order:

(1) Mechanism of vestibular nystagmus. (Integration of vestibular and supra-vestibular afferents.)

(2) Mechanism of optokinetic nystagmus. (Integration of optic and supra-mesencephalic afferents.)

(3) The problem of a common central mechanism subserving vestibular and optokinetic nystagmus.

MECHANISM OF VESTIBULAR NYSTAGMUS

The *vestibular oculo-motor reflex* has a central bulbar mechanism involving three neurones, according to De Kleijn (1921, 1922) and Szentagothai (1950): (i) the vestibular afferent neurone, (ii) the central association neurone originating in the vestibular nucleus and participating in the medial longitudinal bundle, and (iii) the oculo-motor neurone, originating for example in the abducens nucleus (Nc.VI, Fig. 1).

Vestibular nystagmogenic area

The central association neurone may be stimulated not only by peripheral vestibular afferents, but also directly by electrical square pulses. In the rabbit, electrical stimulation of the medial (or superior) vestibular nucleus

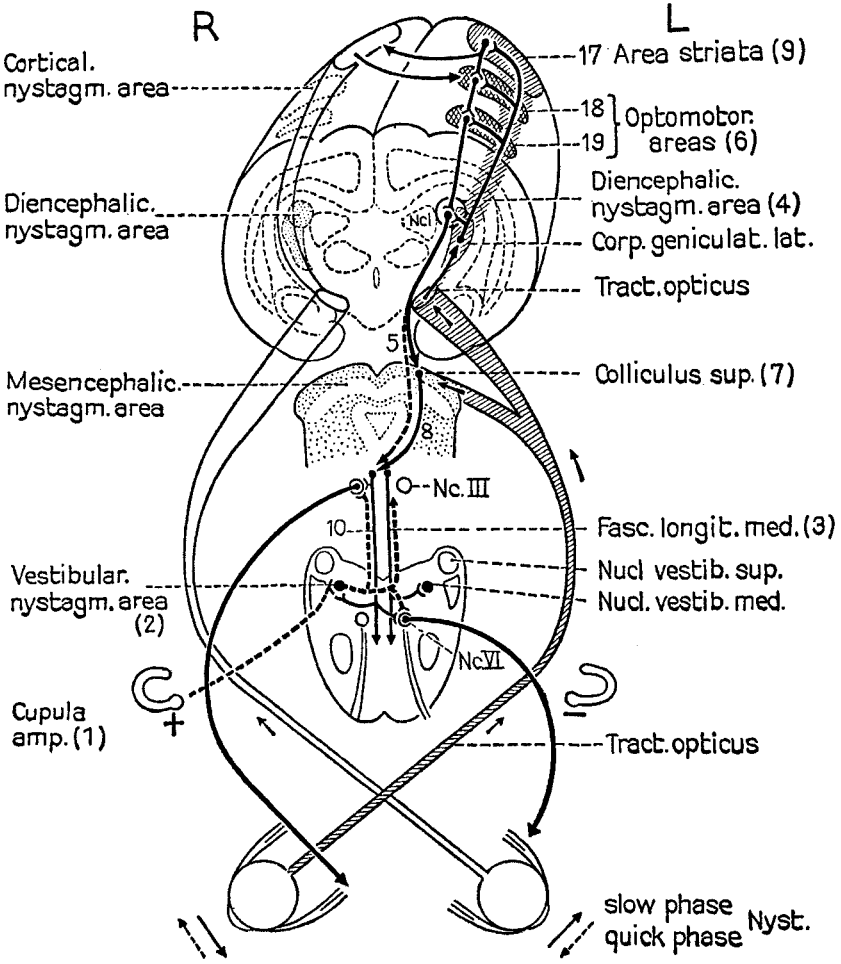


FIG. 1. Peripheral and central mechanisms of vestibular and optokinetic nystagmus. (Diagram based on experimental data.)

on the right elicits a horizontal nystagmus of eyes and head with the contraversive slow phase to the left, followed by an ipsiversive quick phase to the right (Monnier and Montandon, 1962; Montandon and Monnier, 1964; frequency 50 cyc./sec., pulse duration, 0·5 msec., voltage 0·7 v) (Fig. 1,2).

In guinea pigs and rabbits most of the axons from the medial vestibular nucleus cross the midline and run upward in the contralateral *medial longitudinal bundle* (Fig. 1,3). Stimulation of this bundle in the midline elicits mostly an ipsiversive slow-phase nystagmus of the eyes and head (Monnier, 1944; monkey; Monnier, 1946). Destruction of the bundle results in the opposite effect (Arimoto, 1958; rabbit). It follows that in order to produce the same contraversive nystagmus as that elicited by stimulation of the right horizontal canal, we must stimulate the left medial longitudinal fasciculus.

Vestibular nystagmus may be facilitated or inhibited by higher centres, namely the diencephalic nystagmogenic area—to be discussed later—and the cortex.

In man, a *directional preponderance of the vestibular caloric nystagmus* develops after destruction of the posterior temporal lobe. The preponderance consists of a prolongation of the quick phase towards the lesion, as shown by Fitzgerald and Hallpike (1942) and Carmichael, Dix and Hallpike (1954). This means that a tendency to contraversive slow deviation of the gaze has occurred. From this symptom we may conclude that under physiological conditions the cortical temporal area facilitates the ipsiversive slow deviation of the gaze.

MECHANISM OF OPTOKINETIC NYSTAGMUS

When a moving object stimulates the retina, the eyes and head move so that the image falls on the most sensitive central fovea. This initial slow pursuit movement in the direction of the moving object is interrupted by a quick flick in the opposite direction. For example, if a drum with vertical black and white stripes rotates in front of the right eye from the lateral towards the medial border of the visual field, an optokinetic nystagmus develops with a slow pursuit phase towards the medial border, to the left, followed by an ipsiversive quick phase to the right (Ter Braak, 1936). Similarly, electrical stimulation of the right optic nerve with 40 pulses/sec. elicits a horizontal nystagmus, with a contraversive slow phase and an ipsiversive quick phase (Gutman *et al.*, 1963).

Rademaker and Ter Braak (1948) distinguished a *subcortical optokinetic nystagmus* (*Stier-Nystagmus*) from a *cortical optokinetic nystagmus* (*Schau-Nystagmus*).

(a) The *subcortical optokinetic nystagmus*, well developed in lower mammals (guinea pig, rabbit), occurs when all parts of the environment move in the same direction. This nystagmus depends upon connexions between the optic tract, the superior colliculus and the eye muscle nuclei (Smith and

Bridgman, 1943). In *guinea pigs* it does not disappear after removal of the hemispheres, provided that the visual stimulus involves a large part of the retina (Smith, 1939).

In the *rabbit*, most of the afferent optic fibres from the right eye project chiefly on to the left superior colliculus (somewhat also on to the geniculate body). *Electrical stimulation* of this left structure evokes a central nystagmus in the same direction as does the optokinetic stimulation (rotation of the drum to the left) or the electrical stimulation of the right eye (Fig. 1,7). An ipsiversive slow-phase nystagmus to the left occurs (Arimoto, 1958). The optokinetic nystagmus may be enhanced by adequate stimulation of the superior colliculus (Bergmann *et al.*, 1964).

(b) The *cortical optokinetic nystagmus* occurs only when a small object moves through the visual field and induces a "grasp reaction" requiring attention. The slow pursuit movement tends to bring the axis of the eye on to the interesting object. The quick phase brings the eye back to the initial posture. This higher reaction, superimposed on the subcortical optokinetic mechanism, has a greater importance in higher mammals (dog, monkey and humans).

It involves (when the drum turns to the left) the left halves of the retinae, the geniculate body, the optic radiation, and the visual cortex (area 17; Fig. 1,9). The efferent pathway originates in the optomotor centres, that is, in the parastriate cortex (area 18), peristriate cortex (area 19) and angular gyrus. These optomotor centres (Fig. 1,6) also receive fibres from the opposite hemisphere via the corpus callosum. The higher optokinetic nystagmus is a real cortical reflex, since it is suppressed by the removal of both striate areas.

In the *guinea pig* electrical stimulation of the parieto-temporal cortex (left) evokes an ipsiversive slow-phase nystagmus (to the left), followed by a contraversive quick phase to the right (Di Giorgio, 1940*a*, *b*). The corticofugal pathway does not seem to be connected directly with the vestibular nuclei (Manni, 1952; Di Giorgio and Manni, 1963).

In the *rabbit* also, stimulation of a temporo-occipital area (15–30 pulses/sec.) produces an ipsiversive slow-phase nystagmus (Manni, Azzena and Desole, 1964).

Similarly, in the monkey stimulation of the cortex elicits contraversive quick jerks (Krieger, Wagman and Bender, 1958).

In man, *a directional preponderance of the optokinetic nystagmus* (quick phase) develops after a parietal lesion of the *supra-marginal and angular gyrus* (Carmichael, Dix and Hallpike, 1954). Thus, after lesion of the left cortex the quick phase towards the lesion is prolonged and the slow phase to the

right reduced. This means that, under physiological conditions, the left parietal centre facilitates the ipsiversive slow-phase deviation (to the left).

The directional preponderance of the optokinetic nystagmus may occur after a parietal lesion without directional preponderance of the vestibular nystagmus. According to Hallpike, this suggests that the efferent optokinetic pathway may pass to the eye muscles through systems quite separate from the vestibular nuclei.

The efferent pathway from the optomotor centres (area 18 = area parastriata and area 19 = area peristriata) runs in the posterior part of the optic radiation (pulvinar) and in the mesencephalon with or without relay in the tectum (Fig. 1,5). In the monkey, an occipito-mesencephalic bundle (Crosby and Henderson, 1948) joins the superior colliculus (striatum opticum). From this region fibres cross the midline and join an association system for conjugate gaze movement in the contralateral medial longitudinal bundle (Fig. 1, 5 and 8). A lesion of this pathway abolishes the optokinetic nystagmus to the opposite side (Hines, 1942).

In higher mammals a lesion along the pathway from the optomotor centre to the association gaze system abolishes optokinetic nystagmus and produces homonymous hemianopsia. (A lesion in the posterior optic radiation left produces a right homonymous hemianopsia with loss of optokinetic nystagmus when the drum rotates to the left.) A lesion made orally to the optic radiation also abolishes the optokinetic nystagmus, but does not produce homonymous hemianopsia.

THE PROBLEM OF A COMMON CENTRAL MECHANISM FOR VESTIBULAR AND OPTOKINETIC NYSTAGMUS

Since the vestibular and optokinetic reflexes often act synergistically, they must have some common association mechanism in close contact with the oculo-motor neurones. This mechanism, also responsible for the *rhythmic process*, must be activated by vestibular, optokinetic and supramesencephalic impulses as well. It could be located in the midbrain, since transections showed that only the midbrain is necessary for the quick phase of nystagmus (Rademaker and Ter Braak, 1948).

Two hypotheses on the nature of this common mechanism have been proposed. The first hypothesis of Spiegel and Aronson (1934) admits that the vestibular nuclei are intercalated in the pathway of corticofugal impulses for horizontal eye movements. The second hypothesis admits, as common substrate, a meso-rhombencephalic association system, acting as a gaze centre, in close contact with the oculo-motor nuclei (third and sixth cranial nerve). This classical hypothesis was chiefly based on clinical data.

The observations of Fitzgerald and Hallpike (1942), Dix, Hallpike and Harrison (1949) and Carmichael, Dix and Hallpike (1954), showing that two different cortical areas may influence the vestibular nystagmus or the optokinetic nystagmus quite independently, suggest that in man two efferent pathways must be considered.

Our personal investigations on the rabbit, with Lachmann and Bergmann on one hand and with Montandon on the other, allow us to specify certain

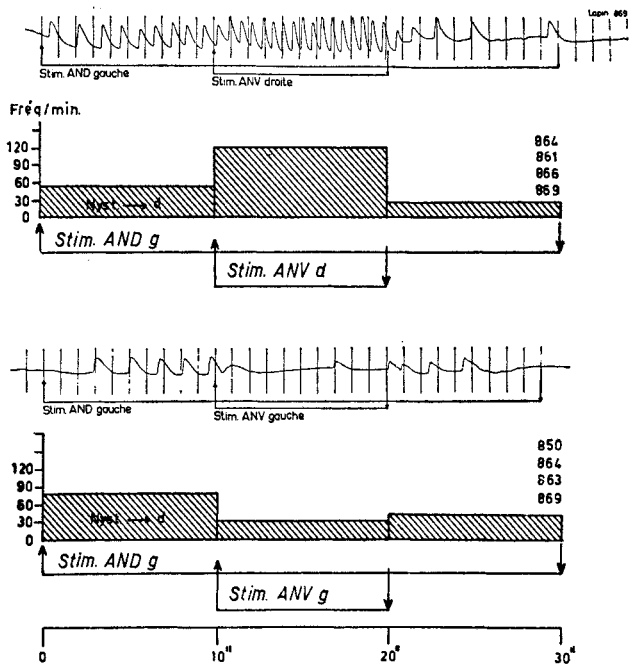


FIG. 2. Stimulation of left diencephalic nystagmogenic area. (Modified from Montandon and Monnier, 1964, Fig. 6.)

aspects of this problem. Our chief contribution with Lachmann was the discovery of a *diencephalic nystagmogenic area* in the intralaminary system, between the lateral nucleus of the thalamus and the lateral geniculate body.

In the rabbit, electrical stimulation of this diencephalic area elicits a typical ipsiversive deviation of the eyes and head (Lachmann, Bergmann and Monnier, 1957, 1958; Bergmann *et al.*, 1959). New investigations with Montandon have confirmed that stimulation of the diencephalic nystagmogenic area (left), at a frequency of 50 pulses/sec., evokes an ipsiversive deviation of both eyes (slow component of the nystagmus to the left, quick

component to the right, expressed by an upward deflexion on the electro-oculogram) (Monnier and Montandon, 1962; Montandon and Monnier, 1964). The slow component is clearly detectable only on the cathode ray oscillogram.

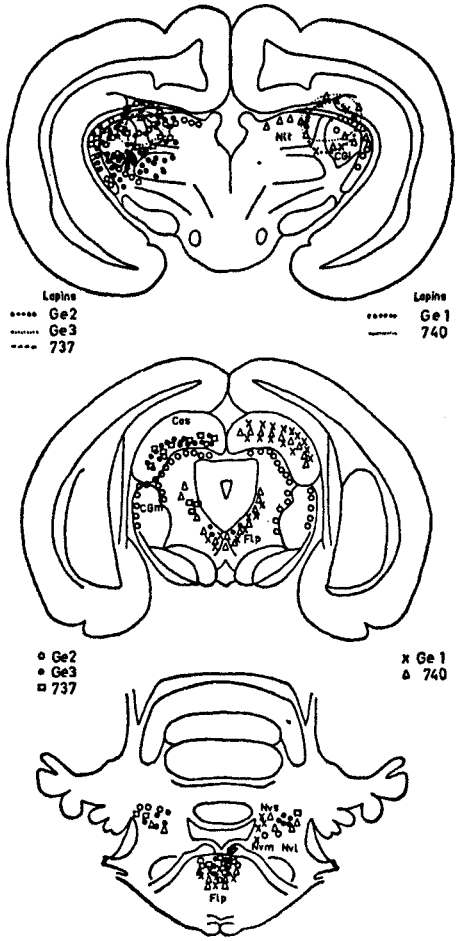


FIG. 3. Secondary fibre degenerations after coagulation of diencephalic nystagmogenic area. (Montandon and Monnier, 1964.)

The diencephalic nystagmogenic area on the left (Fig. 2, AND *gauche*) induces a nystagmus which facilitates the nystagmus induced by rotatory stimulation of the contralateral ampulla (right) or by electrical stimulation of the right vestibular area (ANV *droite*). The nystagmus frequency

increases in this case, while by contrast the left diencephalic area inhibits the nystagmus induced by stimulation of the ipsilateral vestibular system (left).

This *modulation of vestibular nystagmus* by the diencephalic area may be mediated by a descending pathway, crossing the midline and acting on the mesencephalic co-ordination centres (colliculus and medio-dorsal tegmentum) (Fig. 1, 5 and 8).

The diencephalic nystagmogenic area is intercalated between the cortical optomotor centres and the meso-rhombencephalic mechanisms of vestibular and optokinetic nystagmus. It is therefore an interesting link which provides an opportunity for analysing whether the central efferent mechanism involves the vestibular nuclei, as suggested by Spiegel and Aronson (1934), or whether it involves only an association system for conjugate movements of the eyes in the medial longitudinal bundle.

Indeed, coagulation of the diencephalic nystagmogenic area, performed with Montandon in the rabbit, showed bilateral secondary fibre degeneration in the following three regions: (*i*) colliculus superior, (*ii*) medio-dorsal tegmentum and medial longitudinal bundle, (*iii*) vestibular nuclei on both sides (Montandon and Monnier, 1964) (Fig. 3). From these findings we may postulate that the final pathway for nystagmus involves both connexions with the vestibular nuclei (supporting Spiegel's hypothesis) and connexions with the meso-rhombencephalic association system in the medial longitudinal bundle, close to the oculo-motor nuclei.

CONCLUSION AND SUMMARY

The chief anatomical and physiological data on vestibular, optokinetic and central nystagmus elicited in the rabbit have been summarized in a diagram (Fig. 1). The integrative nystagmogenic activities of distinct levels (vestibular nuclei, mesencephalic, diencephalic and cortical optomotor centres) have been considered. The fact that nystagmus can be elicited from the periphery by vestibular and optokinetic afferents as well as by various cortical and subcortical substrates evokes the possibility of a common central mechanism. This mechanism would be responsible for the rhythmic process, including the quick component of the nystagmus. It should be activated by vestibular, optokinetic and central impulses as well.

At the present time, numerous physiological and anatomical data suggest that the central mechanism for vestibular and optokinetic nystagmus involves a meso-rhombencephalic association system of intercalated neurones (in the medial longitudinal bundle) in close contact with the effector oculo-motor neurones. In addition, participation of the vestibular nuclei in this mechanism cannot be excluded.

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DISCUSSION

Gernandt: Professor Monnier, if you stimulate area 17 or 18 and 19, or remove them surgically, is there a release phenomenon?

Monnier: The results differ in each case. From stimulation of area 17 nystagmus has been reported in both directions, whereas the optomotor areas 18 and 19 always give a preponderance of the slow component towards the stimulated side. The whole system is ipsiversive as related to the slow component. This applies to the optomotor centres in the cortex and to our nystagmogenic diencephalic substrate (Montandon, P., and Monnier, M. [1964]. *Brain*, **87**, 673–690).

In the colliculus we seem to have two different situations. In the older publications stimulation of the colliculus is said to produce a contraversive oculomotor reaction. But this applies chiefly to deviation of the eyes without nystagmus and depends on the frequency of stimulation. Hess never observed nystagmus because he was stimulating with a frequency of 8 cyc./sec. As soon as we started stimulating with a frequency of 30–50 cyc./sec. with Professor Lachmann, we were able to induce nystagmus. We are probably dealing here with two different mechanisms—on the one hand, the so-called *Einstellberregung* or positioning reactions of an infant looking towards an object or a sound, and on the other hand a nystagmic process which seems to be stimulated by another frequency.

Henriksson: On your theory, where would you locate the defect in congenital nystagmus, Professor Monnier?

Monnier: I suggest that the defect would be found at the level where optic afferents are integrated by the colliculus and medial longitudinal bundle. We were able to show that congenital nystagmus reaches a minimum in definite positions of the eyes (Franceschetti, A., Monnier, M., and Dieterle, P. [1952]. *Trans. ophthal. Soc. U.K.*, **72**, 515–532).

Pompeiano: You said that after a diencephalic lesion degenerating fibres stained with the Marchi method can be followed bilaterally into the vestibular nuclei. In 1957 we (Pompeiano, O., and Walberg, F. [1957]. *J. comp. Neurol.*, **108**, 465–504) studied by Glees's silver method the distribution of terminal degeneration within the vestibular nuclei after lesions of various parts of the central nervous system. Only after destruction of the interstitial nucleus of Cajal was terminal degeneration present in these nuclei. The fibres from this nucleus descend in the dorsomedial part of the ipsilateral medial longitudinal fasciculus, from which they take off to reach the medial vestibular nucleus. No terminal degeneration, however, was found after lesions of the cerebral cortex, corpus striatum, superior colliculus, nucleus of the posterior commissure, nucleus of Darkschewitsch and central grey substance.

Monnier: Did you make lesions in the region of the intralaminary thalamic system?

Pompeiano: We did not make selective destruction of these thalamic nuclei, but those mesencephalic lesions which did not affect the interstitial nucleus of Cajal were not followed by terminal degeneration in the medial vestibular nucleus. Furthermore, this projection was strictly unilateral. Recent investigations by C. H. Markham, W. Precht and H. Shimazu ([1966]. *J. Neurophysiol.*, **29**, 493–507) are particularly valuable in this connexion, since they provide physiological evidence in favour of the existence of the unilateral interstitial vestibular path, as described by our anatomical study.

Monnier: The diencephalic nystagmogenic area is a narrow region from which fibres descend towards the colliculus and the midbrain tegmentum. If your lesion was more lateral or more medial there would be no more nystagmus.

Brodal: I gather that you locate the diencephalic nystagmogenic area in the intralaminar nuclei; is it possible to specify its position more precisely? If this "centre" is in the intralaminar nuclei it must be quite a small area, yet you showed a very massive degeneration of descending fibres. Your hypothesis appears to rest on the existence of connexions descending directly from this thalamic region to the vestibular nuclei and the cerebellum; however, I think it is almost impossible to make a small lesion of the intralaminar nuclei without damaging other nuclei or passing fibres, and this massive degeneration suggests that you may have encroached on the internal capsule or other, for example pallidofugal, fibre bundles. Have such direct connexions as you have found been described by other workers?

Monnier: The intralaminary area which produces the nystagmus is more dorsal than the internal capsule and this structure should not have been involved by our lesions, which are located between the lateral nucleus of the thalamus and the lateral geniculate body. The diencephalic nystagmogenic field is a narrow zone rather than a nucleus. Of course there are nuclear elements in it, but it certainly also contains fibres.

Brodal: I don't think anyone has made very small lesions in the intralaminar nuclei and studied possible descending pathways. W. J. H. Nauta and D. G. Whitlock some years ago ([1954]. In *Brain Mechanisms and Consciousness*, pp. 81–104, ed. Delafresnaye, J. F. Oxford: Blackwell) studied certain afferent connexions of these nuclei, but do not mention descending fibres.

Monnier: I do not know other investigators who have concentrated on the destruction of this area. Our lesions were small, since we stimulated and coagulated between two needles which are a maximum of 2 mm. apart. We used the modern high-frequency coagulator of Wyss which is now widely used for making highly localized lesions in the thalamus during stereotaxic operations in patients.

Hood: We have recently carried out an investigation of optokinetic nystagmus in normal subjects (Hood, J. D. [1967]. *Acta oto-lar.*, in press). The subjects were placed inside a large optokinetic drum so that the whole of the visual fields were excited by movement of the drum, and the resultant nystagmus was recorded electronystagmographically with d.c. amplification. The direction of movement of the drum was reversed at intervals, and a schematic illustration of our findings is shown in the upper tracing of Fig. 1. By contrast, the tracing below is of vestibular nystagmus obtained by rotating the subject in total darkness. Once again, the direction of the nystagmus has been reversed at intervals, in this case by reversal of the rotational stimulus. If the wave-forms of these two types of nystagmus be compared it will be seen that they are indistinguishable from each other and indeed, as Professor Monnier has remarked, in the presence of simultaneous optokinetic and vestibular stimulation both types of nystagmus summate. It would seem, therefore, on this account that there is some evidence for a common pathway or centre for both types of nystagmus. If, however, one examines

the points of reversal, remarkable differences between the two are apparent. In the first place, in the case of optokinetic nystagmus the eyes deviate quite markedly in the direction of the fast component. This is contrary to most textbook descriptions of optokinetic nystagmus in which it is usually accepted that the slow component takes the eyes away from the mid-line, while the fast component returns it thereto. In fact, it is a consistent finding in optokinetic nystagmus that the deviation is always in the direction of the fast component. It is as though the eyes anticipate the successive appearance of the stripes of the drum. When, however, the direction of movement of the drum is reversed, the slow component is often foreshortened and immediately replaced by a rapid fast component which

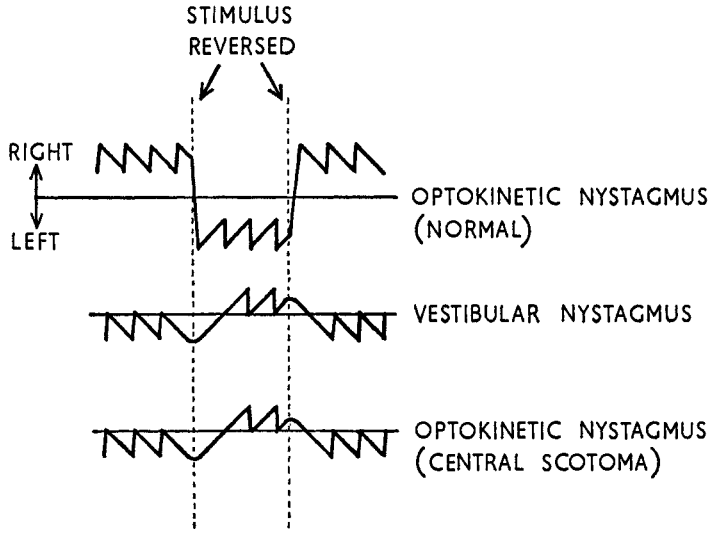

FIG. 1 (Hood). Tracings of (*a*) optokinetic nystagmus in the normal subject, (*b*) vestibular nystagmus, and (*c*) optokinetic nystagmus in a subject with a central scotoma. The centre line in each case corresponds to the straight-ahead position of gaze.

takes the eyes in the opposite direction. This is quite different from vestibular nystagmus. Here the eyes deviate in the direction of the slow component and when the direction of the stimulus is reversed there is a change in direction of the slow component. In these two respects, therefore, the mechanisms of the two types of nystagmus appear to be quite different.

This puts a quite different emphasis upon the fast component of optokinetic nystagmus. Rademaker and Ter Braak, for example, attribute the fast component to a reflex return of the eyes due to what they term the rhythmical activity of the cerebral mechanism (Rademaker, G. G. J., and Ter Braak, J. W. G. [1948]. *Brain*, **71**, 48–76). Our results, however, suggest that the fast component is the dominant component of optokinetic nystagmus, involving cerebral activity of a high order. Professor Monnier chooses to describe nystagmus in terms of the

direction of the slow component because he believes it to be neurologically most significant. This is undoubtedly true of vestibular nystagmus, but matters would seem to be quite different in the case of optokinetic nystagmus.

Further studies that we have carried out upon subjects with central scotomata are especially interesting in this respect. When the same optokinetic stimuli were applied to these subjects as to the normal subjects, the resultant nystagmus, shown in the lower tracing (Fig. 1), was strikingly different. In fact, in all respects it resembled vestibular nystagmus. In other words, by removing foveal vision optokinetic nystagmus assumes the reflex character of vestibular nystagmus. In addition, there is a further important point of difference. If, in the case of the

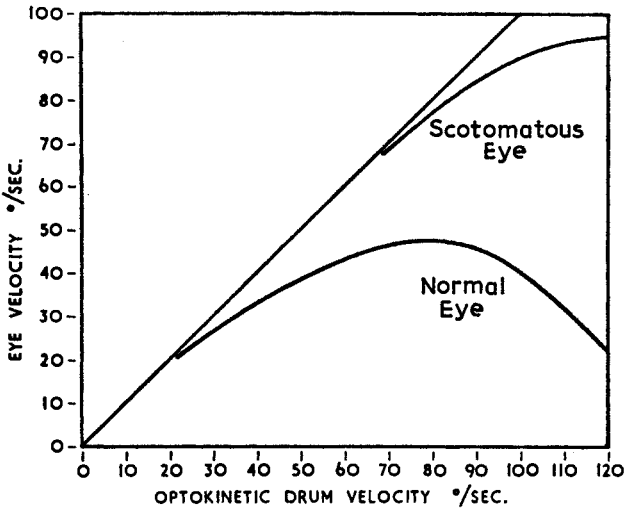

FIG. 2 (Hood). Relationship between velocity of slow component of optokinetic nystagmus and actual drum velocity. Lower curve—normal eye. Upper curve—scotomatous eye.

normal subject, the drum speed is varied and the velocity of the slow component measured and plotted against the actual drum velocity, a correlation of the kind shown by the lower curve in Fig. 2 is obtained. The eyes attain a maximum velocity of about 50°/sec. and thereafter the velocity declines with further increase of drum velocity. The upper curve of Fig. 2 was obtained from a subject with a unilateral central scotoma with the scotomatous eye viewing the drum. In contrast to the normal curve it will be seen that the scotomatous eye attains the surprisingly high velocity of 90 to 100° per sec. Similar results have been obtained from subjects with bilateral central scotoma. The impression given by these findings is of the removal of some inhibitory cortical mechanism which is dependent in some way upon the integrity of the nervous pathways subserving foveal vision. When this mechanism is removed remarkably high eye velocities result.

Monnier: These are very important observations which show the complexity of the problem. Rademaker and Ter Braak faced all contradictions. They considered the slow component as the "pursuit" movement and the quick component as the one which brings the deviated gaze back into the initial position. The basic investigations ought to be repeated in animals, and we should particularly investigate the initial "pursuit" movement and its relation to the fast component. Once the whole process is set going it becomes difficult to say what is primary and what is secondary.

Wersäll: Is it known what happens if one has two light points, one in the axis of the eye and one say 20° outside the axis of the eye from which one is looking, and one starts to move the lights? Does the eye immediately switch over to the light outside the axis or will it follow the point which is in the axis or, to put it another way, would one's attention be drawn more to an object which is moving outside the optical axis or to one in the optical axis?

Monnier: This is the famous question of subcortical and cortical nystagmus. If an object retains the attention of the subject, the whole eye will move and attempt to "grasp" this object. This is the higher type of optokinetic nystagmus. The lower type of optokinetic nystagmus is a massive reaction to a movement of the whole surroundings.

Wersäll: But if one has a drum marked with bars of the light type, with very intense illumination, can one be certain that the eye does not grasp the first bar that comes? That would explain why one begins with the quick phase. One does not think what is ahead but takes what is coming from the corner. We would then get the cortical type of nystagmus and the effect that Dr. Hood described. It would be interesting to do this experiment with two moving points of light. If the eye grasps the point outside the axis, this is Dr. Hood's effect.

Hood: I am not sure that this experiment would be very meaningful because it presupposes the existence of a subcortical optokinetic nystagmus in man. No clear-cut evidence for this has ever been adduced apart from the results of animal experiments which are not really applicable, because of the obvious marked differences in the organization of vision.

Myotatic, Kinesthetic and Vestibular Mechanisms
Edited by A.V. S. de Reuck and Julie Knight

SECTION IV VESTIBULAR MECHANISMS: CLINICAL ASPECTS

NEW TECHNIQUES OF OTONEUROLOGICAL DIAGNOSIS
I. ANALYSIS OF EYE MOVEMENTS

N. G. HENRIKSSON, A. LUNDGREN, K. LUNDGREN AND A. NILSSON

Departments of Otology, Neurology and Psychology, University of Lund, Sweden

IN the field of clinical otoneurology there has been considerable interest in nystagmus caused by stimulation of the lateral semicircular canal. We present here some of our efforts to increase the information available to the otoneurologist, using different kinds of analysis of eye movements. In the paper following (p. 231) we shall account for such efforts by presenting the results of studies of vestibular reactions other than nystagmus, particularly studies of vestibulo-spinal and postural patterns.

EYE-SPEED RECORDING BY THE DERIVATION TECHNIQUE (A.C. RECORDING)

The rhythmic eye movements consisting of fast and slow components are frequently expressions of imbalance within the vestibular system. These nystagmic movements have been exposed to careful analysis with regard to frequency, amplitude and the speed of the slow component as well as duration, by the use of different methods (Mittermaier and Christian, 1954; Mittermaier, 1954; Torok, 1948; Hallpike, 1955).

Of all these parameters the speed of the slow component has been found to have the closest relation to the vestibular stimulus, and this has been the case when both rotatory and caloric stimuli have been applied (van Egmond and Tolk, 1954).

Thus, during a constant angular acceleration the physical stimulus, being directly proportional to the product acceleration × time, will also express the angular velocity of the rotating device. During such a rotation in light the eyes will, during the slow component, more or less exactly reflect this velocity. This is mainly achieved by visual stimulation and makes possible the fixation on the retina of objects in the rotating surroundings. During

rotation in darkness the corresponding slow components, which are then induced only by stimulation of the vestibular organ, will also increase proportionally to the product acceleration × time (Fig. 1).

It is interesting, however, to note that although the vestibular organ provokes a speed proportional to the stimulus it does not seem capable of producing the "correct" speed—that matching the velocity of the rotating chair—but usually produces a much smaller velocity, often varying

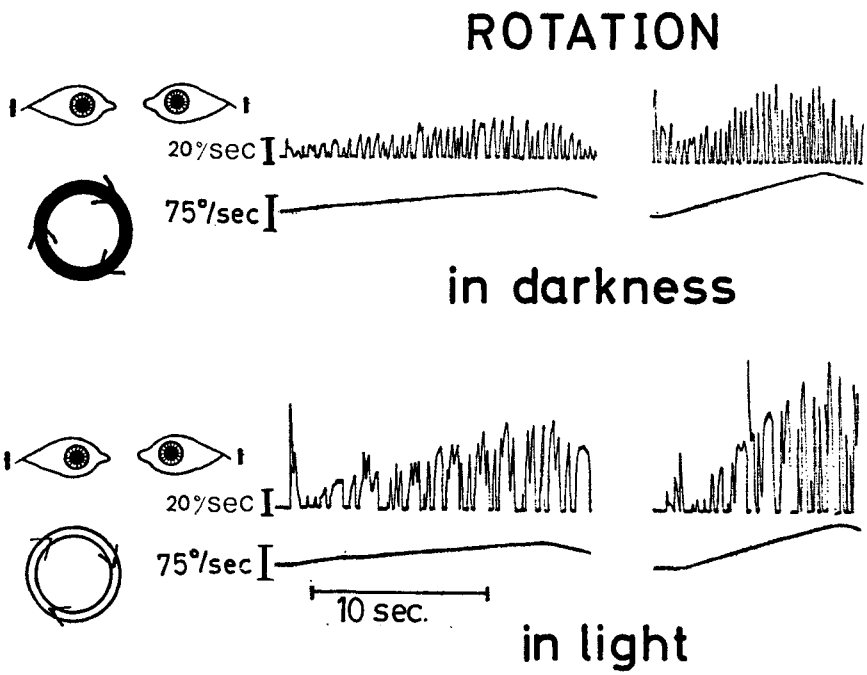

FIG. 1. Eye-speed recording of nystagmus induced by rotation at accelerations of 5° and 14°/sec.² in darkness and light. Note the linear increase of eye-speed in darkness as well as in light and the higher velocities of the eyes during rotation in light.

between 30 and 80 per cent of the velocity of the rotation (Henriksson, 1955*a*).

In caloric nystagmus a comparison between the duration and maximum speed of the slow component in recordings provoked by increasing caloric stimuli shows a more direct relationship between maximum eye-speed and stimulus than between duration and stimulus (Fig. 2) (Henriksson, 1956).

As the product of the frequency and amplitude parameters roughly corresponds to the speed of the slow component and thereby also to the stimulus, each such parameter cannot to the same extent be proportional to the

stimulus. Both, however, increase with the stimulus although neither can be as directly dependent on the stimulus as is the speed of the slow component.

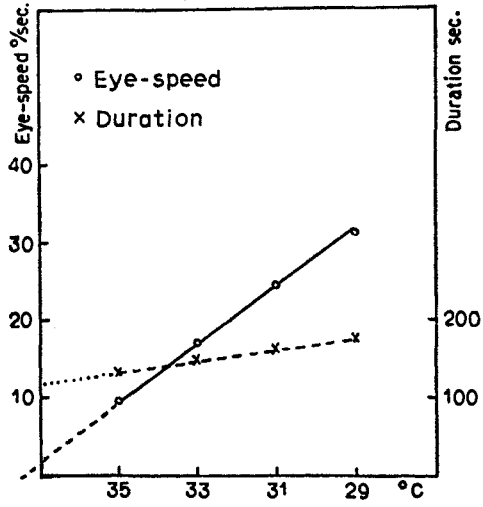

FIG. 2. Increase of mean duration (dotted line) and mean maximum eye-speed (plain line) with increase of stimulus, calculated from caloric irrigations in ten normal subjects.

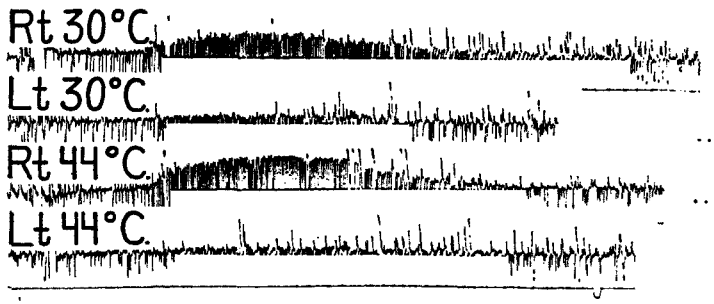

FIG. 3. Eye-speed recording of the caloric nystagmic reaction in a case of Ménière's disease. The difference in sensitivity between right and left ears is not revealed by a difference in duration but is quite clearly shown by the difference in the maximum eye-speed.

As the speed of the slow component is a direct expression of vestibular stimulus it is logical to judge the condition of the vestibular apparatus in clinical examinations from the velocity of the slow phase. In fact, modern otoneurologists agree on this (Hamersma, 1957; Preber, 1958; Stahle, 1959; Bergstedt, 1961).

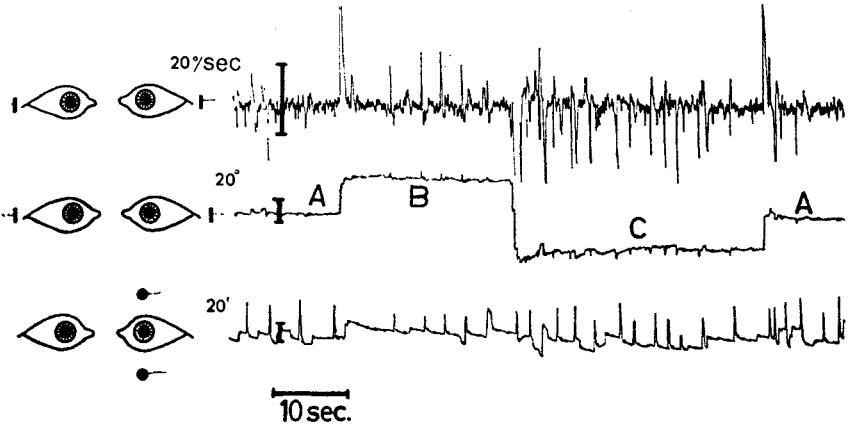

FIG. 4. Test for end-point nystagmus (healthy subject). The tracing stays in a deviated position as long as the eyes deviate.

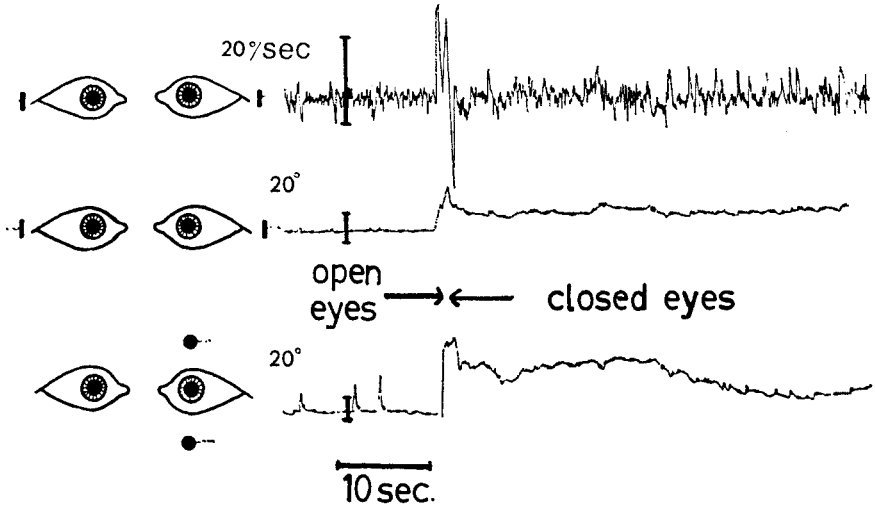

FIG. 5. The vertical recording at the bottom reveals eye-closure by a steep rise in the tracing, because the eyeballs are turned upwards when the eyes are closed and also because of an electric effect provoked by closing the eye-lids. Healthy subject.

The introduction of the derived curve of nystagmus expressing the velocity of the slow component directly has been found very useful in clinical work (Henriksson, 1955*b*; Koch *et al.*, 1959). An example of this is given in Fig. 3, in which the difference in vestibular reactivity in a case of Ménière's disease is revealed only by the difference in speed of the slow components and not by the durations. This derivation technique is gaining

in use since equipment for the electronic analysis is now commercially available (Elema, Stockholm, Sweden).

POSITION OF THE EYES RECORDED BY A D.C. TECHNIQUE

In Lund a method has been developed for determining the position of the eyes during vestibular stimulation and in other tests (Lundgren, 1967). This technique depends upon the accuracy of the electrodes in their contact with the skin, and such electrodes must not allow any drift-potentials. The method has also been introduced into our routine examinations of patients with vertigo and exploited for recording horizontal and vertical displacements of the eyes. Some of the advantages of this method will be briefly discussed here.

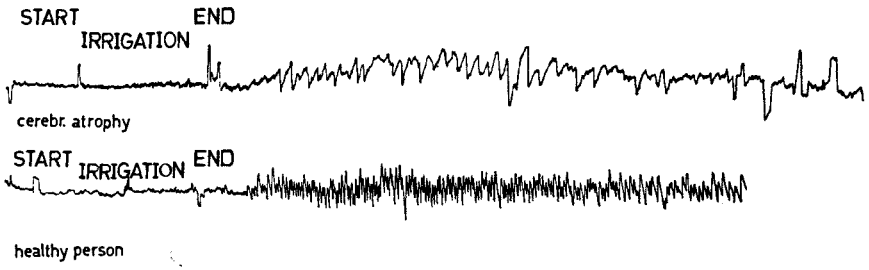

FIG. 6. Difference between a normal caloric reactivity with no deviation of the eyes in the direction of the slow phase (bottom tracing) and a pathological reactivity in a case with an ischaemic brain-stem lesion—which was revealed by this pronounced deviation.

The d.c. technique furnishes good control of the degree of deviation of the eyes during the test for end-point nystagmus and gaze nystagmus (Fig. 4). The recording of the vertical position of the eyes in the form of blinks during the tests also provides a good control of whether the patient has been closing his eyes or not (Fig. 5).

Among 20 normal students very little such deviation in the direction of the slow phase was found in the ordinary caloric tests (30°C and 44°C for 40 sec.). In clinical cases such deviations were frequently found, indicating a decrease in alertness, possibly due in some cases to a brain-stem lesion (Fig. 6).

This deviation of the eyes in the direction of the slow component could be augmented by a special technique in which an after-image was presented to the subject (Göthlin, 1927). When the subjects were exposed to such an after-image, a spontaneous deviation of the eyes towards the right frequently took place. A corresponding subjective deviation of the after-image was reported simultaneously with the recorded deviation. In other

cases the eyes stayed more or less stable gazing straight ahead and accordingly there was no subjective deviation of the after-image in these cases.

In many cases with a spontaneous deviation towards the right a scrutiny of the electro-oculographic tracing revealed a very faint spontaneous nystagmus directed towards the left. This might throw some light on the

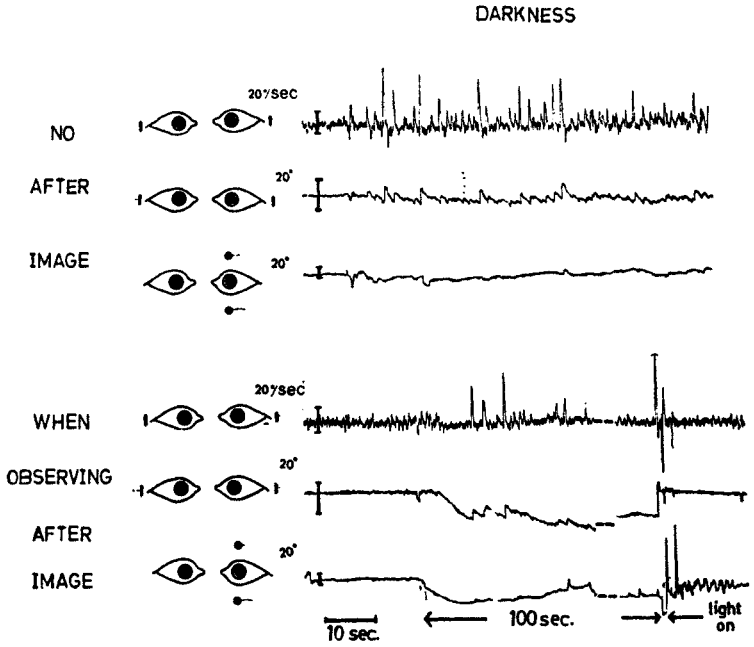

FIG. 7. *Upper curves*: Recording in darkness of spontaneous nystagmus in a patient with a vestibular neuronitis. *Lower curves*: Recording from the same patient in darkness, when observing an after-image. Note the deviations of the eyes in the direction of the slow phase of nystagmus.

problem of the existence of a spontaneous nystagmus in normal people (Bergstedt, 1961; Jongkees and Philipszoon, 1964). When a pathological nystagmus was present or a caloric reaction was induced, the eyes were always found to deviate in the direction of the slow component, with corresponding movements and positions of the after-image (Fig. 7). Thus, when a patient is exposed to an after-image, both its reported deviation and the objectively recorded deviations of the eyes will furnish information about the vestibular system. This technique is described more fully by Dr. Lundgren in his thesis (1967).

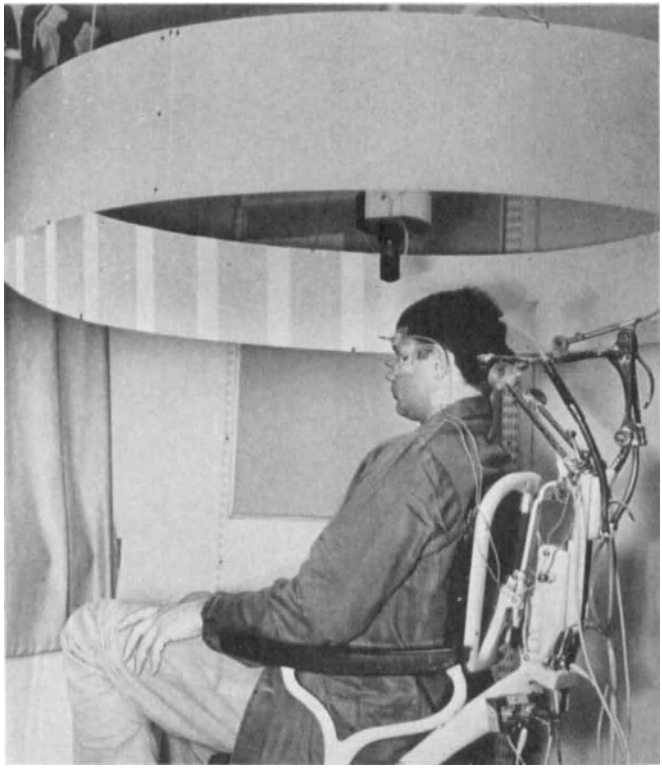

FIG. 8. The calibration test. The subject follows with his eyes as accurately as he can the moving stripes on the circular screen.

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ANALYSIS OF VOLUNTARY EYE MOVEMENTS FOR OTONEUROLOGICAL DIAGNOSIS

The two kinds of recordings of eye movements—a.c. and d.c. recordings —each demand a special method of calibration (Fig. 8). The d.c. calibration is made by having the test-subject move his eyes in the horizontal and in the vertical plane from one bright spot to another 20° away. The a.c. recording of eye-velocities requires a calibration arrangement in which the eyes perform tracking movements by following light stripes moving at a known angular velocity (in our case 20°/sec.). Fig. 9 illustrates normal

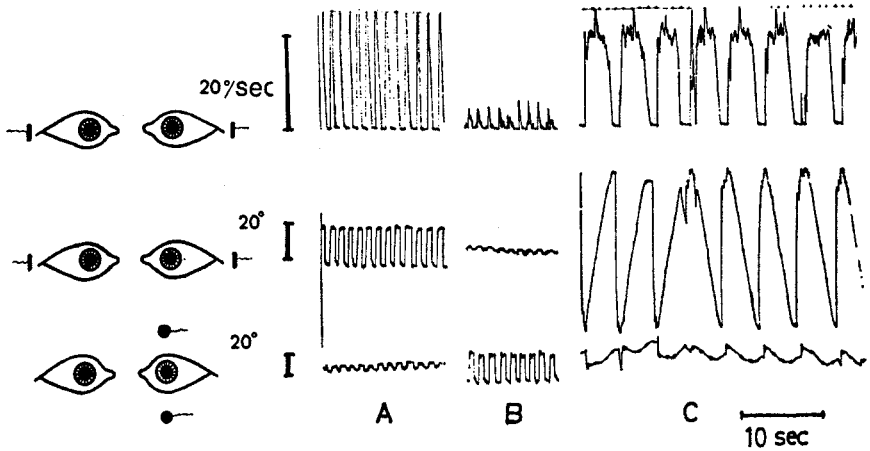

FIG. 9. Recording of voluntary eye movements for calibration, by directing the gaze by turns (A) at two bright spots 20° apart in the horizontal direction and (B) at spots 20° apart in the vertical direction, and by (C) following with his eyes the stripes moving at 20°/sec.

recordings of this kind. Note the exact movements of the eyes in all three types of calibration and note also how the smooth movements of the eyes in the tracking tests are reflected in the regular levels of the eye-speed recordings.

All these kinds of recordings, besides being calibrations, also furnish valuable information about the degree of coordination of the eye movements. We shall illustrate this with a few examples of calibrations from patients with various diseases.

In Fig. 10 is presented a curve derived from a patient with a brain-stem affection caused by arteriosclerosis. Already this patient chooses a much slower tempo in moving her eyes from one spot to another in both the horizontal and vertical directions than does a normal person. More apparent is her inability to follow the moving stripes smoothly. The eyes instead

perform quite irregular movements and only occasionally do they seem to find their target.

The tracking test reproduced in Fig. 11 reveals saccadic but not irregular movements, especially when tracking from the right towards the left. This pathological finding was not disclosed by a test for end-point nystagmus. These saccades were in fact the first objective signs of a tumour in the pontile angle. This derived type of recording is very useful because it

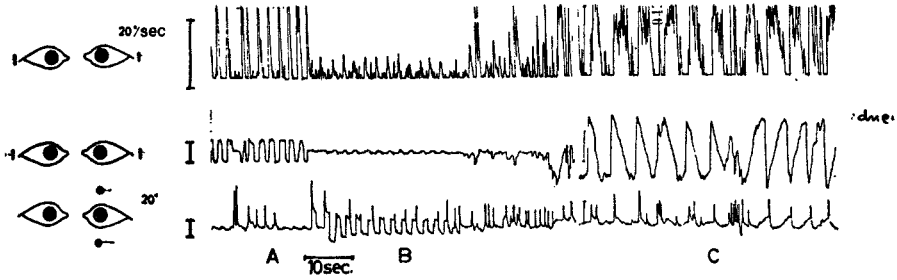

FIG. 10. Voluntary eye movements in a patient with a brain-stem lesion. See text.

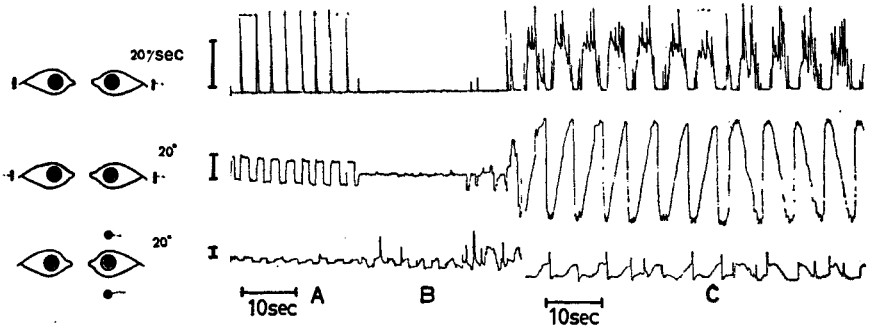

FIG. 11. Voluntary eye movements in a patient with a tumour of the pontile angle. The presence of the saccades at attempts to track the moving stripes (in the right-hand part of the figure) gave the initial hint of the diagnosis.

reveals a slight tendency for saccades by large amplitudes in the tracing. As such saccades supply information about the possible existence of diseases such as multiple sclerosis, tumours of the cerebellum or in the pontile angle as well as congenital nystagmus, the early disclosure of such phenomena is very valuable.

EVALUATION OF DYSRHYTHMIC NYSTAGMIC REACTIONS

Caloric reactions in normal people present regular nystagmic movements with a rapid but smooth increase and slower and smooth decrease of the

speed of the slow components of the nystagmic beats during the course of the reaction (Fig. 12). This regularity of the nystagmic beats can, however, be influenced by different kinds of extravestibular factors, such as variations in alertness, as well as by variations in visual impressions and also by

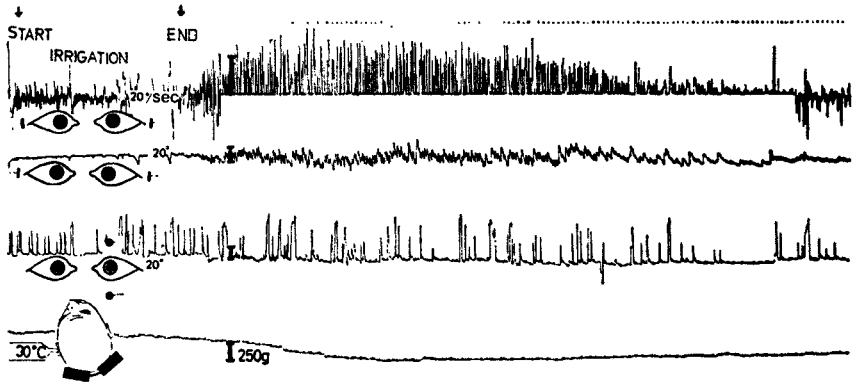

FIG. 12. The caloric response in a normal test-subject in a routine clinical recording.

The upper curve shows an eye-speed recording (by derivation) of the eye movements in the horizontal plane. The second curve is a d.c. recording of the position of the eyes in the horizontal direction. The third curve is a d.c. recording of the position of the eyes in the vertical direction. The bottom tracing is a recording of the vestibulo-spinal reflex (laterotorsion).

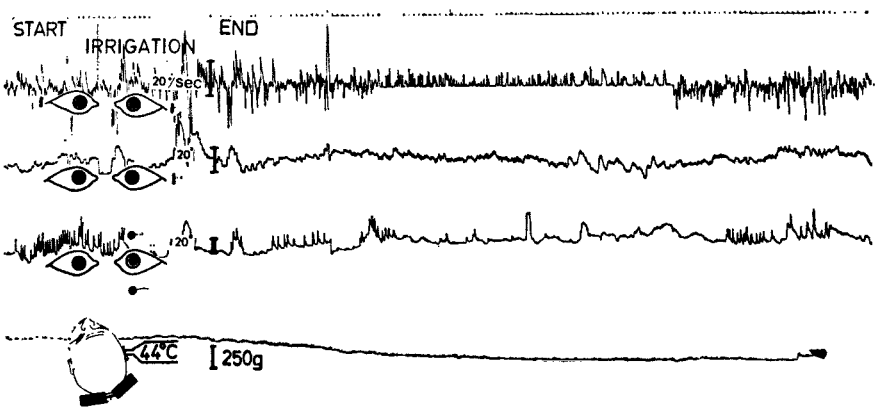

FIG. 13. Dysrhythmia in a caloric nystagmus reaction in a case with clinical indications of ischaemia of the brain stem.

frequent repetition of the test (Mahoney, Harlan and Bickford, 1957; Lidvall, 1961). Rapid variation in speed of the slow component, rapid changes in amplitude or even sudden total inhibition of nystagmus, sometimes followed by bursts of nystagmic movements, are frequently seen in clinical material, especially among elderly patients and among patients in

whom ischaemic conditions of the brain stem are suspected. Such irregularities are referred to as dysrhythmias (Jung and Kornhuber, 1964; Leidler, 1939; Pfaltz and Gulick, 1962) and seem to have been overlooked by many vestibular workers at least. However, much information may be lost by incomplete evaluation of the rhythmic pattern in a nystagmic reaction. A proper analysis of the pattern of frequency would make it possible to differentiate not only between different kinds of disorders but also between different kinds of personality within the normal range. A dysrhythmic nystagmic reaction in a case with clinical indications of ischaemia in the brain stem will serve as an illustration (Fig. 13).

OCULOGYRAL ILLUSION AND SPIRAL AFTER-EFFECT

Although a lot of information about the vestibular organ and its central connexions can be derived by analysis of the eye movements, the findings and their interpretations are constantly obscured by variations attributable to psychological phenomena (Wendt, 1951; Mahoney, Harlan and Bickford, 1957). Some studies have been made of vestibular reactions in people with neurotic disturbances (Hallpike, Harrison and Slater, 1951; Lidvall, 1963) and in schizophrenics (Angyal and Blackman, 1940). Few efforts have, however, yet been made to compare the variations in vestibular reactivity with the results from psychological tests.

The visual system on the other hand has frequently been exploited for such tests. Thus in the spiral after-effect test, the test-subject is exposed to a moving spiral and when this is replaced by a circle the test person perceives a movement of the circle towards him, and the duration of this effect can be reported. Andersson (1966*a*, *b*, *c*) found high correlations, in continuously repeated tests, between these durations and the personality characteristics of the subjects, derived from psychological questionnaires and the colour-word test (Smith and Nyman, 1962).

In similar experiments stimulated by these findings, the duration of the oculogyral illusion was studied in continuous experiments and these values were correlated with those found in the spiral after-effect test (Nilsson and Henriksson, 1967). High correlations were found between these two phenomena, indicating that the oculogyral illusion could also be expected to reveal characteristics of the personality. Following this line of thought, we chose the serial colour-word test for a direct analysis of the relation between the duration of the oculogyral illusion and personality. The colour-word test was considered to express objectively adaptability to new and unusual situations.

In this test the subject is exposed to a chart of printed words in which the

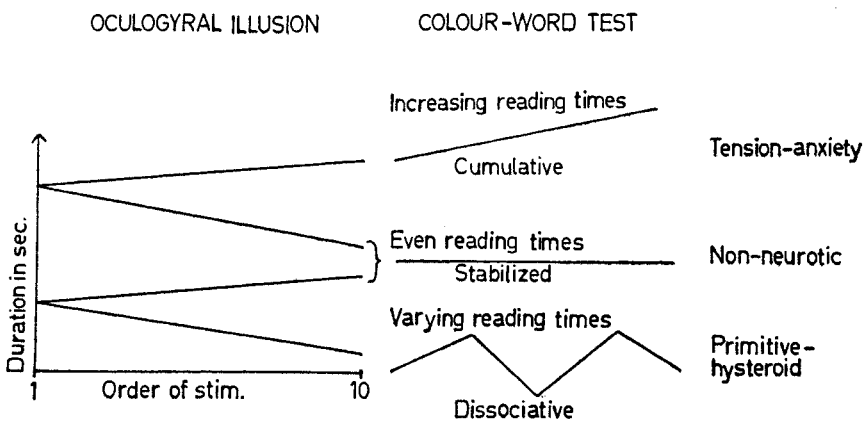

FIG. 14. Relation between regression of duration of the oculogyral illusion, the colour-word test and personality.

word blue appears in green, red or yellow, the word red in blue, green or yellow, and so on. The subject has to name the hue in which a word is printed, but to ignore the printed word. The variation in the times for reading the colour-word chart has been found to reveal important information about the personality of the person tested (Smith and Nyman, 1962). We tested 48 subjects in all, determining the duration of the oculogyral illusion at 10 repeated rotations and giving the colour-word test. According to the initial level and linear change in reported durations of the oculogyral illusion, the test subjects were divided into four different groups (Fig. 14), each group showing a prevalence of one of the three patterns found in the colour-word test. This suggests that a test based on vestibular stimulation may furnish a tool for the psychologist. Further, such studies might eventually explain the unexpected variations so frequently found in many vestibular responses. It might even be suggested that such experiments involving both vestibular and psychological engagement might be of value in selecting candidates for space-travel in different kinds of rotating space craft!

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NEW TECHNIQUES OF OTONEUROLOGICAL DIAGNOSIS
II. VESTIBULO-SPINAL AND POSTURAL PATTERNS

N. G. Henriksson, G. Johansson and H. Östlund

Departments of Otolaryngology and Neurology, University of Lund, Sweden

ANALYSIS OF THE VESTIBULO-SPINAL REFLEX

A valuable tool in the battery of tests available for vestibular examination has been supplied by the routine recording of the laterotorsion, which can be done at the same time as a recording of nystagmus (Henriksson, Dolowitz and Forssman, 1962).

Pneumatic balloons inserted beneath both sides of the occiput of supine patients record any movements of the head and neck as measurable pressure differences between the air cushions. After calibration, the pressure difference can be expressed in grams and is thus standardized (Fig. 1).

The lack of quantitative correlation between nystagmus and laterotorsion has been shown by unequal patterns of behaviour, which showed as (1) a lack of correlation between the maxima of the two reflexes, (2) unequal time for the development of the maxima and (3) unequal duration of the nystagmus and of the laterotorsion (Henriksson, Dolowitz and Forssman, 1962).

The test has been used in routine work for five years and has proved itself so valuable that we do not consider a vestibular examination complete unless we test the vestibulo-spinal reflexes. In Fig. 2 is presented a recording from a patient with a total paresis of the gaze in whom no nystagmus can be seen, but in whom not only a reactivity but also a difference in reactivity between the right and left ears was disclosed by the vestibulo-spinal reflex. We have frequently seen an opposite pattern in cases with encephalitis—that is, an intense nystagmic reaction combined with a very moderate or almost absent vestibulo-spinal reflex (Fig. 3).

We have found this test very useful, particularly as little extra manipulating is necessary for making this important addition to the caloric tests. No electrodes are necessary and the patients have simply to lie down upon the cushions.

ELECTRICAL ANALYSIS OF THE ROMBERG TEST

The well-known fact that vestibular impulses also influence the postural system has initiated a series of investigations into such interrelationships. For many workers in our field a main goal has been to derive information about the vestibular system from the postural pattern. Nyman (1945), Hirsch (1940), Fukuda (1959), Torok and Kahn (1960), Peitersen (1963) and many others have all devised more or less complicated tests for such purposes.

Among the rich abundance of postural tests the simple Romberg test is still the one most frequently used, in neurology as well as in otoneurology.

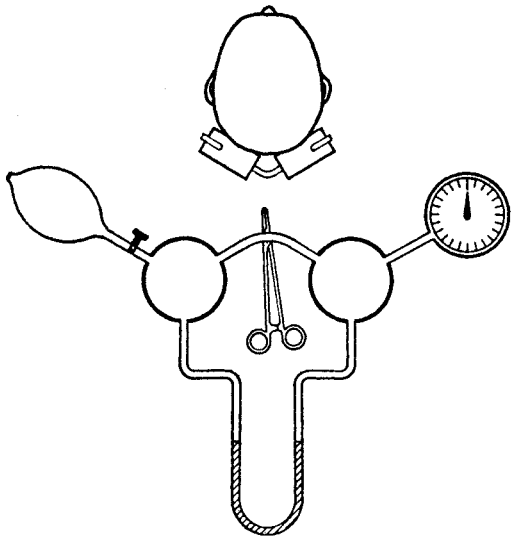

FIG. 1. Diagram of principle of recording laterotorsion.

For the neurologist this test gives valuable information but the otoneurologist gains only relatively diffuse information about the vestibular system. He can record an ability or an inability to stand erect, as well as sometimes the direction of a falling tendency, and may frequently make the very subjective statement that the performance of the test indicates some hysteric tendencies.

Many efforts have been made to make the test more objective. Thomas and Whitney (1949), using an elegant electrical method, studied the antero-posterior movements of the centre of foot pressure during normal standing in man. Electromyographic studies have also been used to elucidate postural mechanisms (Jonsson and Steen, 1963; Joseph, 1962).

METHODS

With the aim of developing a simple technique for routine analysis of the Romberg test in clinical work, two electrical commercially available scales (the Bofors Company, Sweden) were used (Fig. 4) in which a voltage was produced proportional to the weight on each scale. The difference in

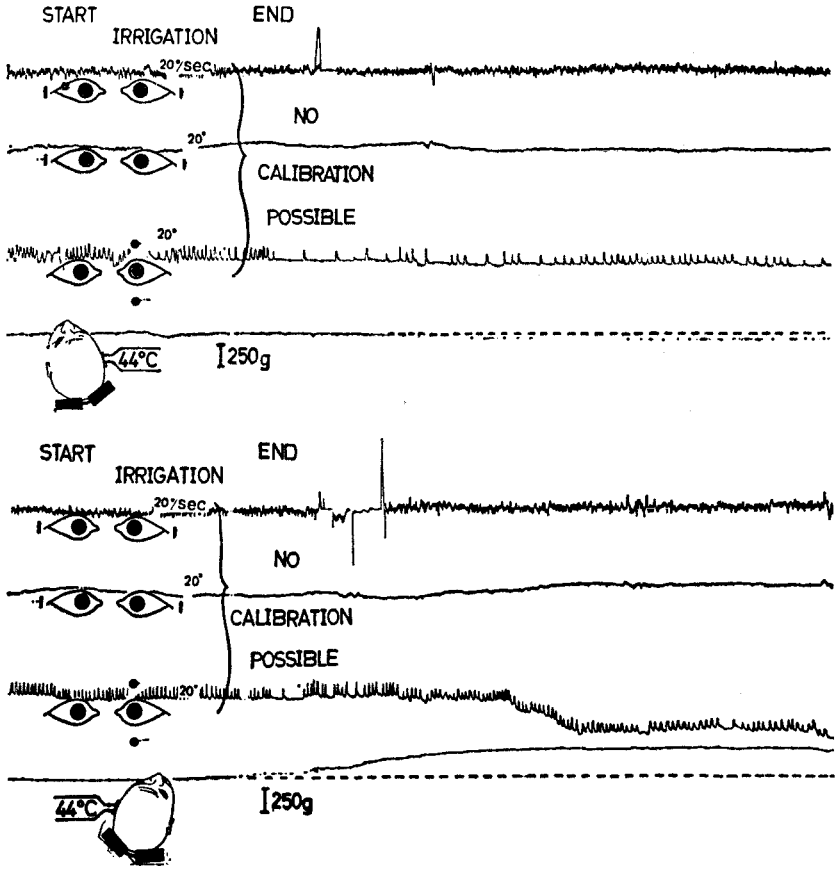

FIG. 2. A caloric response in a case with total paresis of gaze (multiple sclerosis). Vestibular reactivity is disclosed only by the recording of the laterotorsion (bottom curves).

voltage between the scales, which expressed the difference in the load on the two scales, was recorded on one of the four channels of an ink-writer.

The amplification was adjusted so that the full body-weight on either of the scales gave the same deviation of the tracing (although in different directions), independent of the actual body-weight of the subject. When the test subject stands with one foot on each scale, the potential difference

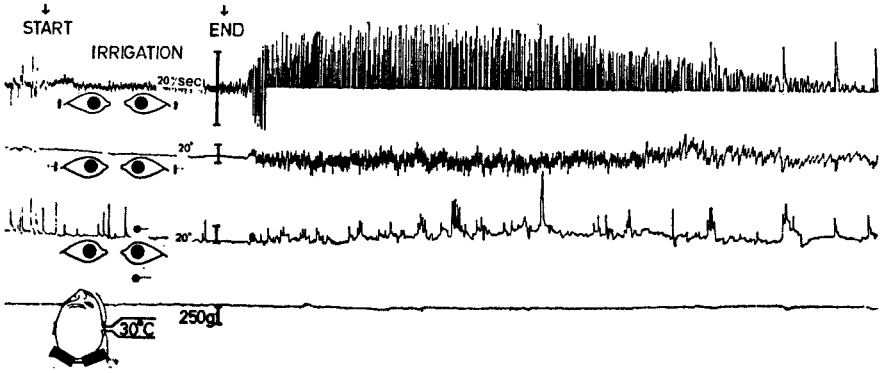

FIG. 3. Intense nystagmic reaction with a simultaneous very small vestibulo-spinal response in a case with encephalitis.

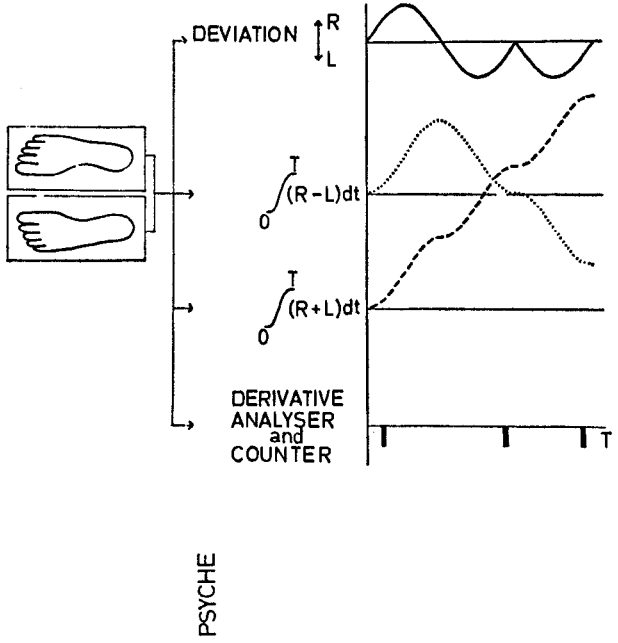

FIG. 5. Principles of the analysis of the postural rest.

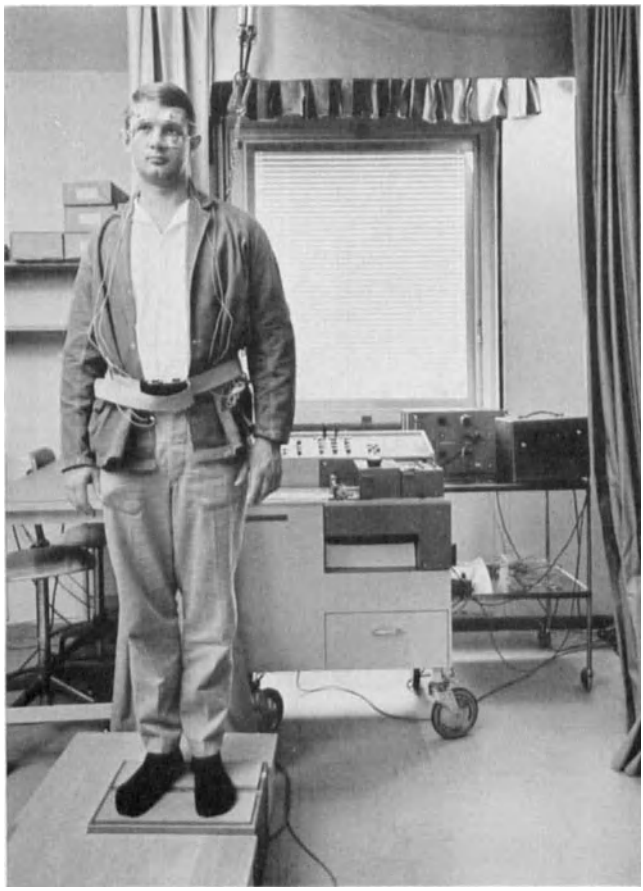

FIG. 4. Normal subject during an objective postural test (in the antero-posterior direction).

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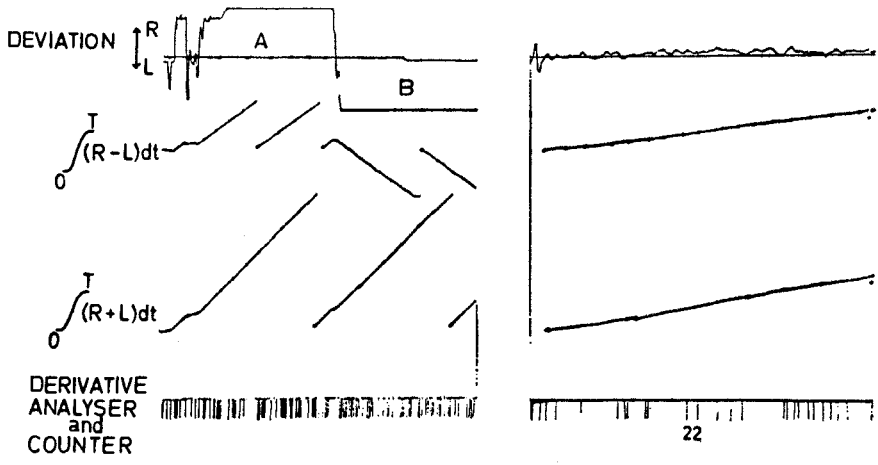

FIG. 6. An objective postural test.

The calibration is shown on the left, at A the whole weight of the test person being put on the right foot and at B on the left foot. On the right a Romberg test for one minute is shown. *Upper curve*: The potential difference between the right and left scales. *Second curve*: Recording of an integration of the difference in load between right and left feet. *Third curve*: Recording of the integrated sums of all deviations, independent of direction. *Bottom curve*: Recording of rapid distributions of weight between right and left feet.

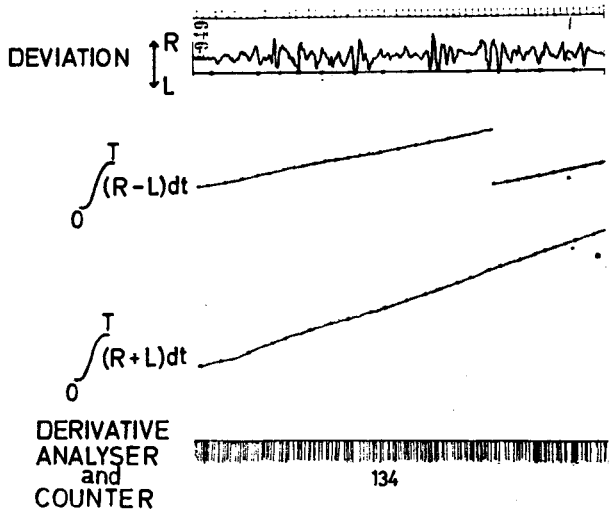

FIG. 7. The same recording as in the right part of Fig. 6, this time from a patient with vertigo due to arteriosclerosis.

recorded on the first channel then expresses, in percentage of body-weight as a function of time, the difference in the pressure exerted by the right and left feet. The algebraic and absolute values of these deviations were electrically integrated and recorded in channels 2 and 3 (Figs. 5, 6 and 7).

The purpose of this arrangement was to derive from the first integration an expression of any tendency to lean in one direction and from the other

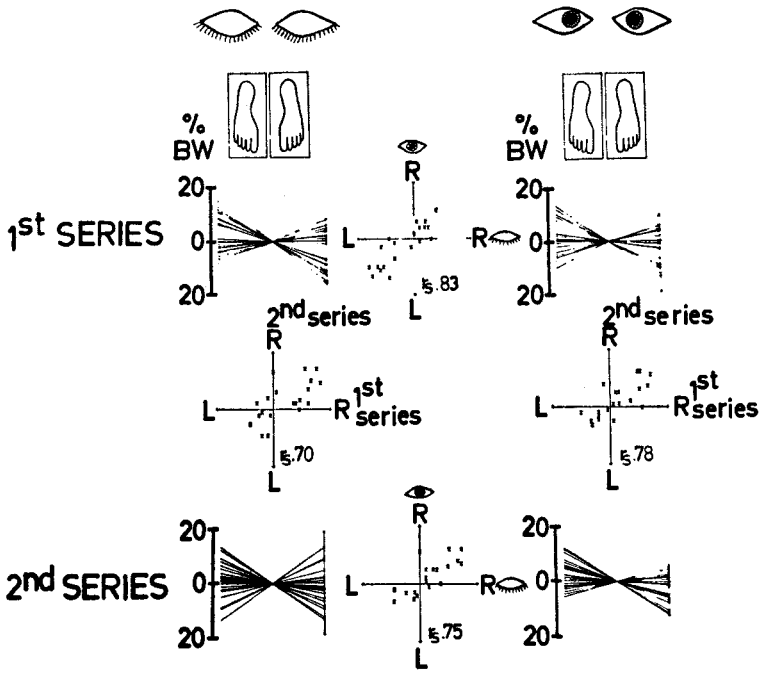

FIG. 8. Average deviation in lateral direction with closed and open eyes as percentage of body-weight, calculated by integration during periods of one minute. Correlations are presented as diagrams of the deviations with eyes open as functions of those with eyes closed and of the deviations in the repeated tests as a function of those in the first tests.

integration an expression of the average deviation in both directions. It was found, however, that most subjects chose to put more weight on one foot than on the other and that they largely kept this tendency in repeated tests, with both open and closed eyes (Fig. 8).

For that reason the second integration—expressing total deviation from an equal load on both feet—was replaced by one expressing total deviation from the deviated postition each person had chosen. This was done by introducing a time-constant of 2·5 sec., which also introduced an error

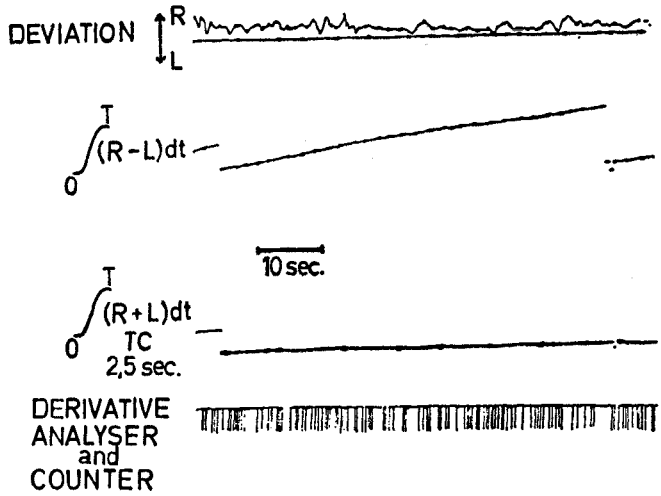

FIG. 9. The same kind of recording as in Fig. 7. Here a time-constant of 2·5 sec. is introduced into the integration of the sum of the deviations. In this way the variations from any deviated position that a test-subject may choose are integrated.

because the time-constant tends to conceal slow deviations, but nevertheless it records rapid variations adequately. Fig. 9 presents such a recording. It is believed that a total variation, as expressed by this last integration, will furnish a proper expression for the adequacy of the postural pattern. Experiments with these arrangements are in progress.

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DISCUSSION

Hallpike: Dr. Henriksson, do you do caloric tests with the eyes open and fixing on a point or with the eyes closed?

Henriksson: I use very much the same stimulus as you do, 46°C for 40 seconds. However the room is dark and I ask subjects to keep their eyes open.

Pompeiano: Have you ever recorded the caloric nystagmus with the eyes first

open and then closed? In this way one would know whether the tonic activity from the retina, which is present in complete darkness (dark discharge) but is greatly reduced by steady illumination of the retina, may affect the labyrinthine reflexes.

Henriksson: This was one of the first experiments I made because I felt that the precision of the recording was completely dependent upon the steadiness of the corneo-retinal potential. We recorded the eye deviations first when the patient was moving his eyes from one bright spot to another in a dark room and then in in a very brightly lit room, and there was no difference. So the corneo-retinal potential does not change significantly, or at least not for the type of experiments we do.

Begbie: I have noticed during d.c. recording of post-rotational nystagmus that if one measures the velocity of the slow component one occasionally finds a subject in whom the velocity of the slow component does not decline smoothly but appears to oscillate on its way down. Have you observed this?

Henriksson: We have seen such cases, and I think it might be due to fluctuation of the alertness of the patient.

Begbie: The oscillation seemed to be rather more regularly irregular than that hypothesis would account for. It is a relatively slow oscillation, with a periodicity of about two seconds.

Hallpike: Incidentally, Dr. Henriksson, you said that the curve of the speed of the slow component goes hand-in-hand with the stimulus intensity; one should perhaps say that it follows the response of the organ to the stimulus—that is, that it reflects the excitation of the end organ.

Eldred: In seeking to detect weak, residual vestibular function by caloric testing and monitoring of neck laterotorsion, is there any uncertainty about what the temperature increase is actually stimulating? One can stimulate the inside of the brain with a thermode and get motor effects. Is the gradient of heat dissipation in caloric testing known?

Henriksson: I cannot exclude the possibility that the laterotorsion in cases with no caloric nystagmic reaction could be due to a difference in temperature between the right and left side of the brain stem. The colder half of the brain stem would then cause a laterotorsion towards this side independently of whether this difference was caused by cold water in the ipsilateral ear or hot water in the opposite ear. However, I do not believe in such an interpretation.

Gernandt: The effects of prolonged caloric stimulation with hot (45°C) or ice water have been studied upon eye movements and vestibulo-spinal and segmental spinal activity (Gernandt, B. E., Igarashi, M., and Ades, H. W. [1966]. *Expl Neurol.*, **14**, 249–263). The results obtained under this variety of test conditions demonstrate that continuous irrigation with water of extreme temperatures evokes, in addition to the immediate effects upon the position of the cupula by endolymphatic convection currents according to the theory of Bárány, an initial excitatory thermal effect giving rise to an increased afferent firing (after 60 min.

of irrigation) which is followed by a paralysing effect upon the vestibular sensori-neural structures (after 130 min. of irrigation). In order to localize the site of action of thermal stimulation more specifically, experiments were carried out upon labyrinthectomized squirrel monkeys and monkeys with the three semicircular canals plugged. These results, and those obtained by recording the cochlear microphonic and neural components to click stimulation during maximal cold and warm irrigation of the ear, indicate that the effect is upon the peripheral nerve fibres somewhere along their course from the ampulla to the internal auditory meatus.

Hallpike: With reference to the pads on which you record the tendency of the head to move in the direction of the slow component, do you actually allow the head to deviate?

Henriksson: Yes.

Hallpike: We take care not to let the head move. We carry out caloric tests with the eyes open and the gaze fixed on a mark. If we allowed the head to move the eye position would also move and the nystagmus would be upset. We feel that there are still great advantages in using this older technique.

Henriksson: You say that if the patient turns his head he has to move his gaze. But in darkness a movement of the head does not necessarily change the direction of gaze with respect to the head.

Lowenstein: On the other hand it might be an advantage to allow the movement of the head. Even if one wants to turn one's head but cannot, there might be an influence, because one's intention is recorded and goes into the computer, as a so-called efference copy.

Hallpike: If, as is our custom, we perform the caloric tests with the eyes open and fixating a point, deviation of the head *must* cause deviation of the eyes and so affect the amplitude of the nystagmus. Although, as Dr. Henriksson says, head deviation in darkness *may* not cause this deviation of the eyes, one cannot be sure. The important point is that to evaluate the nystagmus we must know what, if any, deviation of the eyes is present. If the test is done with the eyes closed we need nystagmographic recording with d.c. amplification to tell us this. With the eyes open, however, this complexity is not essential.

Roberts: Benson and Bodin have obtained some surprising results in an investigation of the duration of the nystagmus produced by impulsive decelerations about the vertical (i.e. long) axis of the body (Benson, A. J., and Bodin, M. A. [1966]. *Aerospace Med.*, **37**, 144–154). In one case this axis is kept vertical and in the other the patient lies on a stretcher and the same axis of the body is now horizontal. The results are curious (Fig. 1). The impulsive decelerations are the same in each case, but the position of the curves of log angular velocity against time are very different. In the horizontal position, $\pi/\Delta = 6 \cdot 8$ sec. and in the vertical position, $\pi/\Delta = 11 \cdot 8$ sec. Therefore when two apparently similar stimuli are applied to the same sense organ with the same type of recording of the response, there are different time-constants of decay of the response.

These results are important in relation to caloric irrigations, where one is trying to stimulate the "horizontal" canal and one tips the patient back into a position where one can record the caloric effects. According to Benson and Bodin, doing this upsets the behaviour of the canal. Another odd finding is that when the patient is in a horizontal position, subjective post-rotatory effects are not present.

Lowenstein: The deceleration may stimulate the same sense organ, but it does not stimulate the same sense organ complex. In one case you stimulate the canal zone and in the other you stimulate the whole vestibulum and what comes out

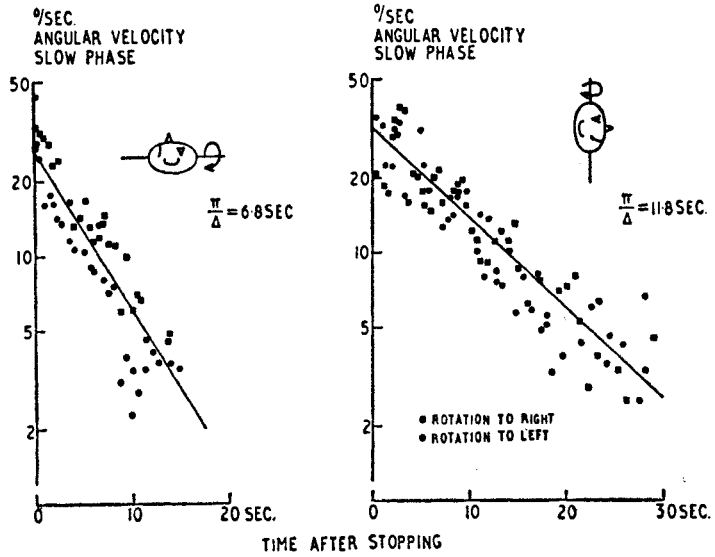

FIG. 1 (Roberts). Comparison of the patterns of decay of nystagmus following impulsive deceleration from 60°/sec., when the axis of rotation is vertical and horizontal. Angular velocity of the slow phase of nystagmus is plotted on a logarithmic ordinate scale. (From Benson and Bodin, 1966.)

from the central nervous system must be different. We know that, for instance in space flight, where there is no gravity, the nystagmus responses are very highly modified, as if the organism, not getting any static signals from the otolith organ, says that whatever signals come in from the semicircular canals are nonsense and should therefore be ignored.

Henriksson: One should bear in mind the fact that if one is rotated in darkness the vestibular organs are not capable of giving the eyes the proper compensatory eye-speed but a much smaller one. Because of habituation, the quotient between this vestibular eye-speed and the fully compensating eye-speed is always less than one. We are thus not born with definite and defined reflexes, but with a varying

ability to adapt ourselves and our reflexes to different patterns of movement and also to different physical environments such as different gravitational forces, different weight of limbs and so on.

Roberts: This is where the horrible point of these experiments comes in. It is reasonable to suppose that the sensitivity of the response to the sense organ may be changed by changing some other conditions, but the time-constant of the decay of these effects presumably reflects some property of the physical structure —of the inertia of the endolymph and of the restoring forces in the cupula and so on. How can one change the time-constant by adaptation?

Groen: This has always been my trouble also, but I think that both reflect not the properties of the peripheral organ but a modification imposed upon it by the central nervous system. These are not cupular decays; they are "central regulation" decays.

Roberts: Does not that imply that the central mechanism is producing a controlling effect which fluctuates with time and has its own time-constant?

Groen: Yes; and even worse, if the test subject is kept in a horizontal position for a long time and his eyes are closed, after half an hour he will have another decay-constant which would correspond to a far more sensitive organ than before. The situation is always changing, which causes the central regulation to change, hence giving an ever-varying response.

I would repeat that my formulae are only of value for the isolated preparation and perhaps also the newborn child and the adult who is very sensitive to motion sickness.

Lowenstein: We must not forget that by "isolated preparation" we mean "open-loop preparation", without any peripheral feedback to the organ.

Henriksson: With a peripheral vestibular preparation from the frog one finds no habituation at all. If one does ten repeated caloric stimulations to normal subjects, a quite moderate decay in the nystagmus response will be achieved, while the sensation of turning caused by the repeated stimuli will be completely abolished at the end of the caloric series (Forssman, B., Henriksson, N. G., and Dolowitz, D. A. [1963]. *Acta oto-lar.*, **56**, 663–674). In studying the duration of the oculogyral illusion after repeated rotations we even found an increase of response with repetition of the stimulus in some individuals, who differed in their type of personality from the others tested. This indicates different kinds of habituation at different levels.

Groen: Dr. Henriksson, you seem to get very low drift in your d.c. recordings; we find much more drift than you do.

Henriksson: We get very little drift, as you say. Thus, when working with eye deviation, using an after-image, we checked the spontaneous deviation after the test and found a drift corresponding to only 1° or 2°.

Groen: A second point: what relationship do you find in optokinetic nystagmus between the angular velocity of your presentation and the angular velocity of the eye? In our experience there always seems to be a "slip" in the eye, and the

eye-speed is lower than the speed of the stripes. When we present an angular velocity of the stripes of 20°/sec. we obtain in the best cases an eye velocity of only 16°/sec.

Henriksson: I would say that no such "slip" takes place. It would mean that the distance of the eye from the target is increasing by 5° or 10° during the test. I don't think it is. The tracking ability of the eye is very accurate in healthy individuals.

Roberts: W. A. Crawford finds the same sort of difference in the speeds as Professor Groen and the correction is made by saccades, so there is no cumulative error (Crawford, W. A. [1960]. Visual Acuity and Moving Objects. Ph.D. Thesis, Glasgow University; [1960]. *G. B. Fly. Personnel Res. Commun.*, **150**, 3 papers).

Henriksson: The saccades are certainly very important.

Dohlman: When I was using a secondary technique with a mirror over the corner of one eye, both the black and white stripes and the eye movements could be recorded on the same photographic paper. With this technique it was possible to assess the position of the eyes very accurately with regard to the moving stripes. I had the impression then that the eye movements followed the movements of the stripes within the limit of the image on the fovea.

Lowenstein: What were the distances of the subject from the actual stripe pattern in Professor Groen's case and Dr. Henriksson's? There may be a difference in the distances, and it may be impossible in one or the other case for the eye to follow speeds above a certain limit.

Henriksson: In our experiments the distance is about 1 m.

Groen: In our case it is larger, 130 cm.

Dohlman: I imagine that a moving light spot would produce a more accurate stimulus to the retina to incite fixation, and would result in a close relation between the movements of the eyes and the light spot.

Hood: There is a misunderstanding here between voluntary following movements and optokinetic nystagmus. Clearly, if a subject is placed inside a large optokinetic drum and its velocity is increased, a point will obviously be reached at which the eye velocity begins to depart from the drum velocity. We find that eye velocity usually follows drum velocity reasonably well up to about 40–50°/sec. but thereafter it departs quite markedly and begins to decline. Here I would agree with Professor Groen. Below this maximal velocity there is throughout a small discrepancy between the drum velocity and the velocity of the eyes, resulting in a slight slipping across the retina of the images of the stripes. It could well be that this difference is the stimulus which initiates optokinetic nystagmus.

Henriksson: As Professor Monnier pointed out, there are two kinds of optokinetic eye movements, the subcortical and the cortical ones; we should use the term "optokinetic movements" for what you are describing, Dr. Hood, and "tracking" eye movements for the other kind. But Professor Groen and I both

use tracking eye movements—we ask the patient to follow the moving stripes with his eyes.

Hood: These two kinds of eye movement are certainly quite different.

Pompeiano: In our laboratory P. L. Marchiafava has found evidence of presynaptic inhibition of primary optic afferents during the tracking eye movements which appear in the midpontine pretrigeminal cat. The presence of presynaptic inhibition of the primary optic afferent endings during these eye movements was indicated by: (1) enhancement of the antidromic response elicited by single-shock stimulation of the geniculate body or tectum; (2) decrease in the amplitude of the presynaptic component of the geniculo-cortical response to a shock applied to the optic nerve. I wonder whether these observations can help us to interpret some of the findings mentioned.

Henriksson: This might be related to the fact that after the test subject has been exposed to continuous optokinetic stimulation and then put in darkness, he will have a nystagmus which in most cases is in the opposite direction. It is an interesting phenomenon and can perhaps be correlated with these electrophysiological findings (Shanzer, S., Teng, P., Krieger, H. P., and Bender, M. B. [1958]. *Am. J. Physiol.*, **194**, 419–422).

Lowenstein: And of course it correlates well with what Professor Groen called the "pattern centre" (p. 204).

Pompeiano: Dr. Henriksson, has the behaviour of the photic pupillary reflex been investigated in your different experimental conditions? This would be a way of testing transmission of sensory volleys along the primary optic pathways, because the pupillary reflex is likely to be depressed owing to presynaptic depolarization of the primary optic afferents.

Henriksson: We have not investigated this.

Pompeiano: Presynaptic depolarization of the intrageniculate endings of the primary optic afferents, a phenomenon that occurs during presynaptic inhibition, has been found not only during the tracking eye movements but also during the eye movements elicited by vestibular stimulation (Marchiafava, P. L., and Pompeiano, O. [1966]. *Pflügers Arch. ges. Physiol.*, **290**, 275–278). Fig. 1 shows an increase in the amplitude of the antidromic response recorded from the right optic nerve on single-shock stimulation of the right lateral geniculate nucleus, following conditioning stimulation of the eighth nerve or the medial vestibular nucleus of the contralateral side. This increase in excitability of the optic nerve endings has a time-course which is typical for presynaptic inhibition.

Roberts: Is it possible to distinguish here the effects which occur during the slow and fast phases of the eye movements? There would be something to be said for switching off the visual system during the quick phase. I am not sure whether one sees anything at all when the eyes are moving rapidly.

Hood: No; Professor Ditchburn has proved that one does not (Ditchburn, R. W. [1955]. *Optica Acta*, **1**, 171–176).

Roberts: Is this suppression of the visual system in the rapid phase associated

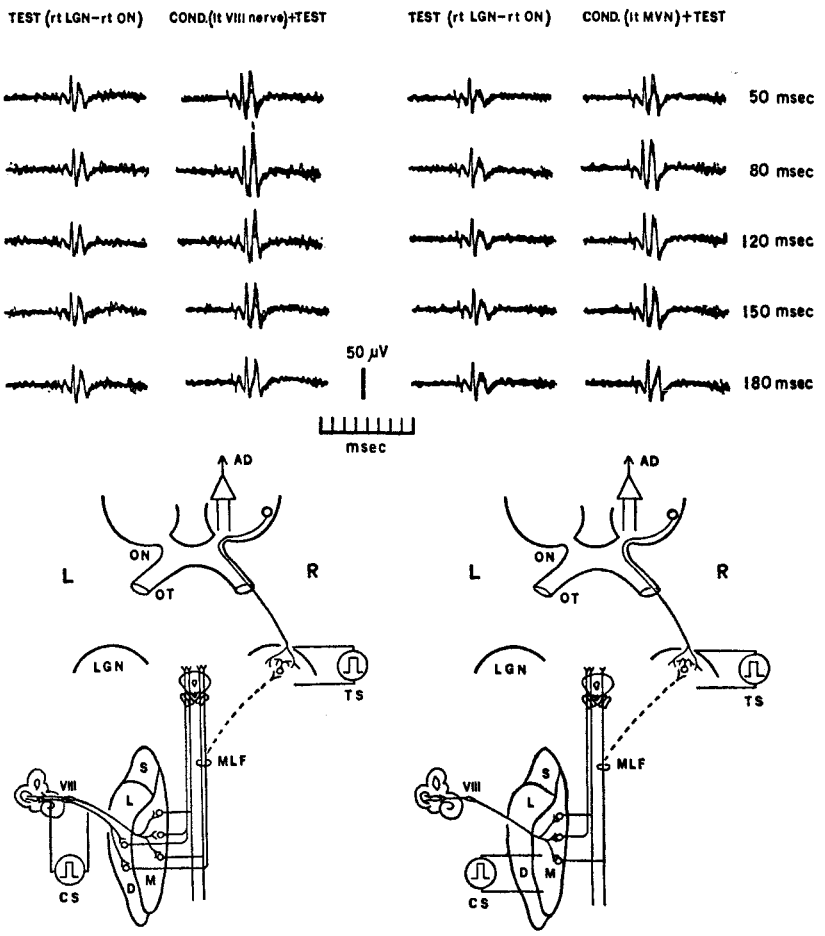

FIG. 1 (Pompeiano). Changes of the antidromic response of the optic nerve fibres to intrageniculate shocks following electrical stimulation of the vestibular system.

The terminals of the primary optic afferents are excited through an electrode inserted in the right lateral geniculate nucleus (rt LGN) while the antidromic discharge is recorded peripherally in the right optic nerve (rt ON). Conditioning stimulation of the left eighth nerve or the left medial vestibular nucleus (lt MVN) was made with 1 msec. rectangular pulses at 330/sec., for 20 msec. The lateral geniculate nucleus was stimulated with a testing shock, 0·5 msec. in duration, of strength such that the amplitude of the test responses corresponded to 41 per cent of the maximum amplitude of the antidromic volleys. The times in msec. indicate the intervals between the beginning of the conditioning stimulation and the testing shock. Each record represents a series of 5 superimposed sweeps taken at the rate of 1 every 4 sec.

AD, antidromic response; CS, conditioning stimulation; D, descending vestibular nucleus; L, lateral vestibular nucleus of Deiters; MLF, medial longitudinal fasciculus; OT, optic tract; S, superior vestibular nucleus; TS, testing stimulation; VIII, eighth cranial nerve. (From Marchiafava and Pompeiano, 1966.)

with the drive to the slow phase from the labyrinth or with the nystagmic jerk drive from the vestibular nuclei?

Pompeiano: The increase in excitability of the intrageniculate optic fibre endings elicited by repeated stimulation of the eighth nerve or of the medial and descending vestibular nuclei can still be obtained after curarization of the animal, when the somatic and the ocular movements which follow the vestibular stimulation are completely abolished.

Groen: On this inability to see anything during the quick phase, P. L. Latour ([1962]. *Vision Res.*, **2**, 261–265) found that one's attention is first switched off and then the quick phase follows, so the quick phase is itself initiated by some mechanism which turns off one's capabilities for attention and observation.

Hood: May I return to Professor Groen's pattern centre. Among the rotational tests that we carry out is the determination of the threshold of nystagmus to constant angular acceleration. We determine this much as one would assess the threshold of hearing. The acceleration is applied for about 15 sec. If this produces no nystagmic eye movements, recorded electronystagmographically, the acceleration is increased and maintained for a further 15 sec. In this way a point is established at which nystagmus is just detectable upon the recording.

In normal subjects and recording in darkness with the subject fixating a light spot attached to the chair and immediately to his front, the threshold is of the order of 1–2°/sec^2. Recently we have had the opportunity of studying the same thresholds in ballet dancers. Dr. Dix carried out caloric tests on them and found that the response was abolished in four out of five. When we applied rotational tests to these subjects the thresholds proved to be in excess of 5°/sec^2.

This, of course, is not unexpected, since the responses to rotational stimuli of ballet dancers, ice skaters and certain pilots are known to show a marked reduction or habituation, as it is termed, resulting from their repeated rotational experiences. One might, therefore, conclude that this elevation of the threshold reflects some loss of labyrinthine sensitivity as a result of habituation. As a variant of this procedure the threshold for angular acceleration can also be determined by recording the nystagmus with the eyes open in total darkness with no fixation. Since fixation, as is well known, strongly inhibits induced vestibular nystagmus the thresholds are considerably reduced and in the normal subject range from 0·1–0·2°/sec^2. When we tested the ballet dancers in this way we found, surprisingly, that their thresholds fell much within the same range. In other words their labyrinthine sensitivity appears to be perfectly normal.

It would seem, therefore, that the phenomenon of habituation is intimately connected with optic fixation, and these dancers have acquired the ability to inhibit their nystagmic responses by virtue of an enhanced fixation mechanism.

Groen: The ballet dancer is of course chosen for his or her remarkable equilibrium; it is only our means of measuring it which are inadequate. You trapped them by putting them in darkness. Incidentally, I would remark to Dr. Henriksson that in recording nystagmus in darkness there are in fact two different

situations, the first in which the patient is concentrating upon his own sensations and the second in which he is distracted by a mental calculation or by a question. In the second case, all types of nystagmus appear much more quickly and more prominently.

Begbie: Dr. E. G. Walsh, Dr. J. A. Watt and I in Edinburgh made a film of some ballet dancers pirouetting. We asked one dancer to shut her eyes at the end of the pirouette and she fell about, just as any untrained person would.

Henriksson: Ballet dancers are habituated by rotating in light. However, if one starts rotating them in darkness, they are probably habituated even to those conditions. As a matter of fact, we tried to use habituation for therapeutic purposes. We thought that we might be able to make the attacks of patients with Ménière's disease less intense by exposing them to repetition of the proper stimulus. We irrigated 12 times with intervals of five minutes, the first and last irrigation in darkness, the others in light. The nystagmus provoked by the last irrigation showed a marked decay in response in spite of the fact that most of the habituating stimulations had been given in light (Forssman, B. [1963]. *Acta oto-lar.*, **56**, 1–14). The effects on the attacks of Ménière's disease were, however, dubious.

Hallpike: From what I recall of ballet dancers, "holy rollers" and other experts in this type of activity, they favour pirouetting in one direction almost exclusively. Bárány made some observations on a sect of this kind and found that their nystagmic responses to rotation showed a preponderance in one direction which was related to the direction in which they rotated. Skaters too seem to be able to rotate best in one direction, and to be deficient in the other direction.

Hood: We were not able to establish any directional preponderance in the dancers we investigated.

Lowenstein: The choreographer presumably does not specify the direction of pirouetting; this may be left to the individual's choice.

Henriksson: This point about habituation in a particular direction is interesting. We irrigated the right ear of cats 10 times with cold water (20°C) and obtained nystagmus towards the left, diminishing with the number of irrigations. We then obtained no or very little nystagmus when we irrigated the left ear with water of 48°C, attempting to record nystagmus towards the left. When however we applied water of 48°C in the right ear, there was a brisk normal response, directed towards the right. So the habituation of nystagmus is direction-specific (Henriksson, N. G., Kohut, R., and Fernández, C. [1961]. *Acta oto-lar.*, **53**, 333–349).

Lowenstein: Would this fit in with your model, Professor Groen?

Groen: It would mean that inhibition and pattern-centre activity could be brought about by stimulating one labyrinth and that the modifying central activity would then pertain only to messages coming from that labyrinth. Stimulating the other labyrinth would provoke responses which at first would be free from retro-labyrinthine moderating processes.

The work of G. H. Crampton ([1962]. *Acta oto-lar.*, **55**, 41–44 and 515–518) may be mentioned in this context. Repeated unidirectional stimulation produced a reduced nystagmic response in cats but left the responses to stimulation in the other direction unaffected.

In contrast to these results are the earlier measurements of O. H. Mowrer ([1943]. *Comp. Psychol. Monogr.*, **9**, Serial No. 45) and W. Halstead, G. Yacorzynski and F. Fearing ([1937]. *Am. J. Physiol.*, **120**, 350–365), in which repeated unidirectional stimuli appeared to provoke bilateral inhibition. Further experiments seem therefore to be needed.

Roberts: There is an important difference between ballet dancers and ice skaters. Ballet dancers during their pirouettes move their heads in a series of jerks in order to give equal and opposite stimulations to the labyrinth in rapid succession, but ice skaters do not do this. At the end of their pirouettes they must experience very powerful post-rotatory effects, which are not seen in the ballet dancer. I wonder whether the behaviour and cupulograms of ice skaters are markedly different from those of the ballet dancers.

Groen: When the world-champion ice skater was investigated at the Leyden Clinic, she had no caloric reactions at all. She was tested in both ways: in darkness with the eyes open and closed.

Roberts: There is seldom any nystagmus in ice skaters at the end of a pirouette. Ice skaters can maintain their equilibrium even after putting their heads into a position where the rotation stimulates the vertical canals, and then, during the impulsive deceleration at the end of the pirouette, they rotate their heads back into the vertical position. This must produce the most violent coreolis effects as well. The canals must have a dreadful time!

Hallpike: What is the vestibular stimulus that is actually applied to the canals of a well-trained ballet dancer? As you say, there is a marked difference between ballet dancers and ice skaters, and it has always seemed to me that the ballet dancer might not be exciting the canals very much.

Lowenstein: They prevent it by this series of equal and opposite jerks of the head. The problem is that ice skaters apparently do not jerk the head. I have seen ice skaters exhibiting symptoms of suppressed disorientation, but not ballet dancers.

Ormerod: The experience of vertigo and instability by a skater or a dancer is not occasioned by the *velocity*, the duration or the direction of the rotation of the *body*, nor by the method or speed of ending that rotation. At the same time, neither vertigo nor instability are caused by rotation of the head at whatever speed or for whatever duration. It is the rapidity of the *deceleration*, or the suddenness of the stop of the rotation of the head which leads to these sensations, which are themselves proportionate in magnitude to the rate of deceleration.

In the case of the ballet dancer, as has been described, the slower rotation of the body can be associated with a series of jerks and stops of the head which do not lead to vertigo or unsteadiness.

In the case of the expert skater this manoeuvre is not possible and the head must rotate with the body. A sudden stop or a very rapid deceleration involving the head might lead to some instability and vertigo. The expert minimizes or eliminates these by coming out of the spin gradually, with one leg extended backwards, by gradually assuming a squatting posture, by indulging in some other form of activity or by striking a statuesque position if the performance has come to an end. These manoeuvres will all reduce the likelihood of vertigo, but it is equally possible that adaptation to the stimuli from acceleration or from

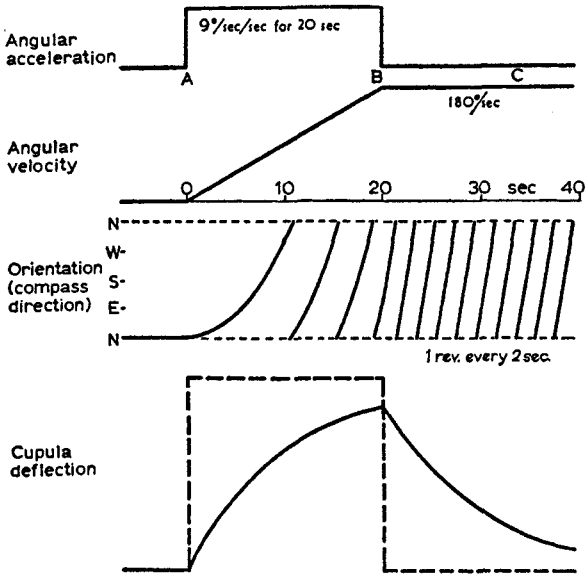

FIG. 2 (Roberts). Time-courses of the changes in angular velocity, orientation of the skull in space, and cupular deflection, arising from the application of a constant angular acceleration during the period from A to B. (From Roberts, T. D. M. [1967]. *Neurophysiology of Postural Mechanisms.* London: Butterworth.)

deceleration will also serve to eliminate the tendency to vertigo. It has already been shown that dancers and skaters do become habituated or adapted to such stimuli. When we first had an electrically propelled rotating chair in my institute, I and my collaborators tested each other so much in order to standardize the apparatus that we became almost completely adapted to the rotation tests and therefore useless as experimental subjects.

Hallpike: What ballet dancers do when they jerk their heads round is to give a transient flick to the cupula at the start of the jerk and an opposite flick at its end. That in itself might be quite enough to affect the cupula in a particular way. Has any work been done on the effects of repeated jerks of the head on the cupula?

Begbie: The movement is not quite a jerk to and fro, since it is always in the same direction. The head stays still and the body starts turning round uniformly; then halfway round the head goes round twice as fast as the body and takes up its old position again. So there is acceleration and deceleration all in the same direction. One reduces any period of uniform velocity of the head and therefore the cupula is immediately flung back after its deflection so that there is no time for it to

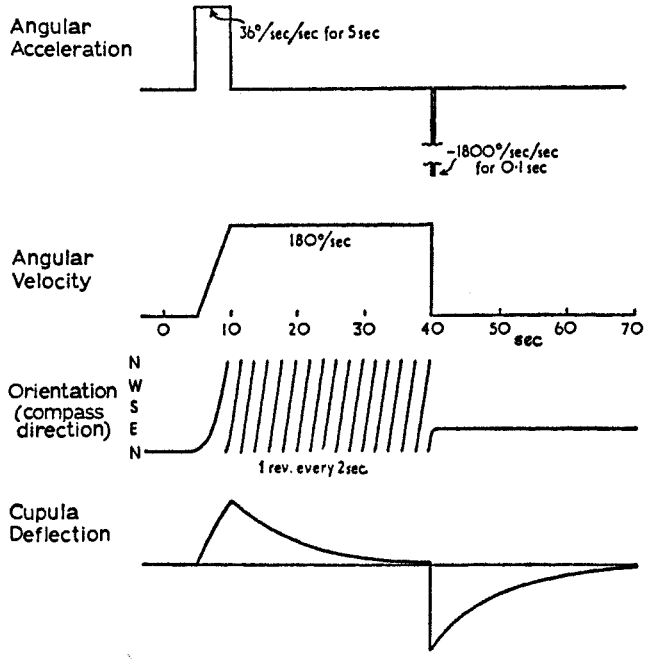

FIG. 3 (Roberts). Sequence of changes in angular velocity, orientation, and cupular deflection during the procedure for imposing an impulsive deceleration. Note that if the deceleration were spread over 1 sec., instead of occupying only 0·1 sec., the force needed would be reduced to one-tenth, yet the cupular deflection reached in the rest position would have the same value as that shown here. (From Roberts, 1967.)

steady up, as in constant velocity rotation of the head, which would give a post-rotational effect at the end of the movement.

Groen: It depends upon the cupular endolymphatic mechanism. The time-integral will end up almost at zero, so there is no residual deflection; for instance, in a head turn through 30° which is carried out quickly (by comparison with the natural time of the system) and if the body turns also, but at a constant speed, one is ready for another 30° turn; so one turns 30°, one's body goes on turning, one adds another 30°, and in every instance the total time-integral is zero; there is no residual cupular deflection because of the "stops".

Roberts: We have computed the cupular response during three different types of stimulation of the canal. Fig. 2 (p. 248) shows the results during constant angular acceleration, which is what we would like to do but usually can't. The changing orientation of the skull should follow a parabolic pathway of gradually increasing speed, and when the acceleration has finished there is a rotation at constant speed. The deflection of the cupula does not follow either the angular acceleration or the velocity exactly; it shows a sluggish response to angular acceleration. The deflection grows and then decays again. During short periods of angular acceleration there is a resemblance between the change in the angular velocity and the change

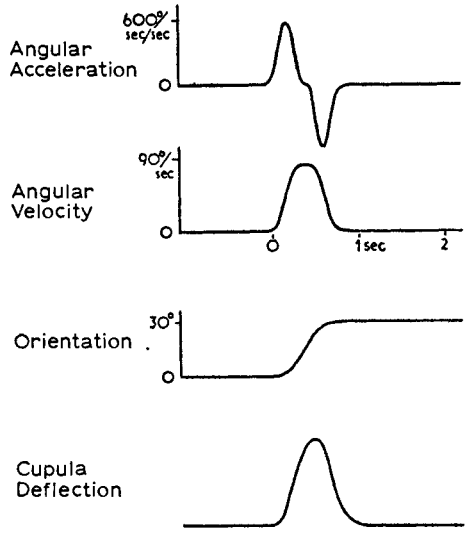

FIG. 4 (Roberts). Angular acceleration, angular velocity and cupular deflection to be expected during a normally occurring movement. (From Roberts, 1967.)

in the cupular deflection and that accounts for the reports of many clinicians that the canals may be concerned with reporting the velocity of head movements.

Figure 3 shows the Bárány-chair situation, where a period of moderate acceleration in one direction is followed by a period of rotation at constant speed during which the cupular response declines, if one waits long enough; then follows a short, sharp deceleration, bringing the head to rest, followed by the post-rotatory effects.

Figure 4 shows what happens in a normal movement. This is an imitation of a trace of my own head movement from one position to another through 30°, simulated electronically from two acceleration phases by double integration. We put that into Professor Groen's canal equation and compute what the cupular deflection would do. We see then, and this provides the answer to Dr. Hallpike,

that in the jerk from one position to another there is no bi-directional response in the cupula.

Henriksson: A possible reason why the ballet dancer turns her head is that she wants to reduce the time during which she cannot orientate herself by looking at a steady point. In other words, by both turning one's head and using one's ability to move the eyes in the horizontal direction, one can make fewer changes of the steady fixation of the eyes. For some reason and in some subconscious way, most people try to use this technique.

Hood: We questioned the ballet dancers rather carefully about their fixation. Apparently they are taught to pick out certain landmarks (either one or two) as points upon which to fix their gaze before they begin a pirouette. Then as they pirouette they deliberately fix upon one of these points that they have established beforehand.

Lowenstein: Are they told to fix their eyes straight ahead or look out of the corner of their eyes?

Hood: I think they fix their eyes straight ahead and keep their heads quite still and then move their bodies with respect to their heads. I am a little unhappy about the suggestion that rapid head movements completely eliminate the sensation of turning. Dr. Henriksson seems to give the most likely explanation for this manoeuvre.

Myotatic, Kinesthetic and Vestibular Mechanisms
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RECENT ADVANCES IN THE ELECTRONYSTAGMOGRAPHIC INVESTIGATION OF VESTIBULAR AND OTHER DISORDERS OF OCULAR MOVEMENT

J. D. Hood

Medical Research Council Otological Research Unit, National Hospital, London

One of the initial steps of a clinical otoneurological examination is the examination of the eyes for spontaneous nystagmus and if this is found to be present, the assessment of its quality and magnitude. This is usually carried out by direct scrutiny of the subject's eyes in the upright position of the head.

Now, as is well known, nystagmus resulting from peripheral vestibular disturbances is strikingly affected by the direction of gaze. It is markedly enhanced by gaze in the direction of its fast component and inhibited by gaze in the direction of the slow component. This dependence upon the direction of gaze is often referred to as Alexander's Law and it is upon it that we base the conventional gradation of the magnitude of spontaneous nystagmus—1st degree, 2nd degree and 3rd degree.

It follows that if the nystagmus is to be fully specified, any electronystagmographic recording of spontaneous nystagmus must provide accurate information not only of the character and magnitude of the nystagmus but also of the concomitant gaze position of the eyes.

This can only be achieved by means of d.c. amplification, the attendant difficulties of which are well known. Recent advances in electronic techniques have obviated many of these difficulties but there remains the problem of spurious potentials originating in the electrodes themselves. For this reason we have been at some pains to develop electrodes which are satisfactory in this respect, and the technical data pertaining to them have been fully described elsewhere (Hallpike, Hood and Trinder, 1960).

Their manner of application is shown in Fig. 1. The corneo-retinal potential is picked up by the electrodes placed as near as conveniently possible to the left and right outer canthuses. The electrode on the forehead is the earth electrode. The spectacle-like frame completes the assembly. To this the main cable to the amplifier is rigidly fixed, and the electrode

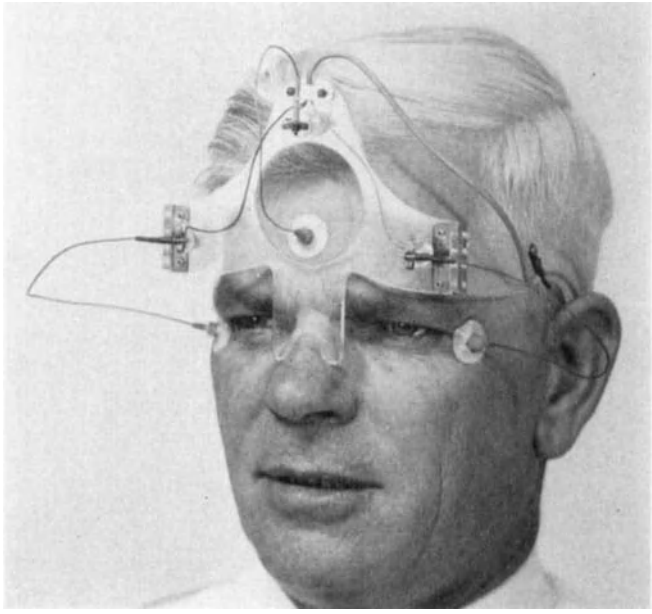

FIG. 1. Arrangement of electrodes for electronystagmographic recording.

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FIG. 2. Technique for recording spontaneous nystagmus.

connexions are separately made to spring clips attached to the frame: thus any drag on the cable is taken by the frame without disturbance of the electrodes.

The technique used for recording spontaneous nystagmus is shown in Fig. 2. The patient sits in a chair, the seat of which can be raised or lowered by means of a hydraulic jack; in this way the chin level is adjusted to a fixed and rigidly mounted chin rest. With the chin in position, a hinged support is brought forward on to the occiput, and the head is thus comfortably and efficiently immobilized. The vertical bar, shown to the front of the patient, carries a mark upon which he fixes his gaze. The bar with the fixation mark can be deviated to the patient's left or right by means of a

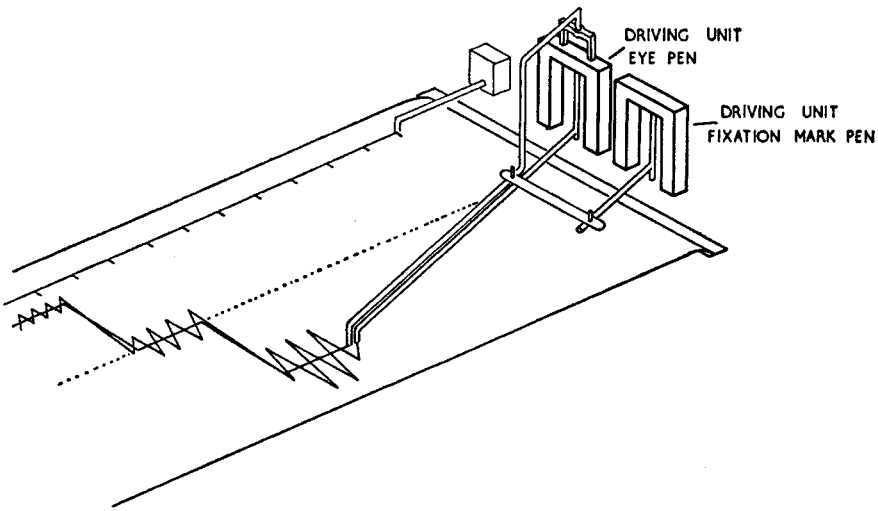

FIG. 3. Arrangement of pens for recording spontaneous nystagmus.

handle which is controlled by the examiner, seated behind the patient where he is able at the same time to observe the nystagmograph pens and operate the nystagmograph controls.

In Fig. 3 is shown the arrangement of the recording pens which has been found to be very convenient. Their rotational axes are actually, and their writing points virtually, co-incident. The outer pen records the angular deviation of the fixation mark. Upwards and downwards deflections of this pen from the central base-line correspond respectively to deviations to right and left of the fixation mark. The inner or eye pen records the conjugate eye movements in the horizontal plane. The sensitivity of its amplifier is adjusted to match that of the fixation mark pen, and both work to the same central base-line.

The recording shown is of a 3rd degree vestibular nystagmus to the left. Thus, with fixation on the mark deviated 20° to the right, slight nystagmus is present with its rapid component to the left. It increases greatly in amplitude when the eyes follow the fixation mark to a point 20° to the left. In this way, therefore, we have obtained in the recording a permanent, complete and graphic description of this subject's nystagmus. This has obvious and immediate advantages, but they are by no means the most important.

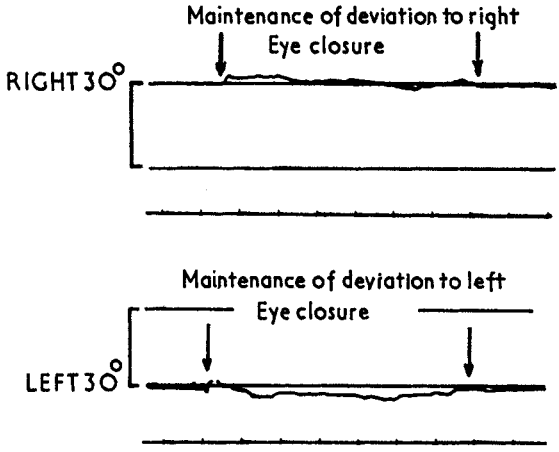

FIG. 4. Effect of eye-closure upon the maintenance of gaze deviation in a normal subject.

Nystagmus, present with eyes open, can be strikingly changed when fixation is removed either by closing the eyes or by putting the subject into total darkness. Aschan, Bergstedt and Stahle (1956) have recently described some of the changes that occur as a result of eye-closure, in particular that it brings about a marked enhancement of nystagmus of peripheral origin.

In contrast to this, Gordon Holmes as long ago as 1917 remarked upon the fact that nystagmus due to a cerebellar lesion was decreased when observed behind Frenzel's glasses. Since spontaneous nystagmus may result from a lesion at a variety of points within the vestibular system, extending from the labyrinth to the cerebrum, the possibility presents itself of effecting a differential diagnosis of the lesion based upon certain characteristic changes in the nystagmus pattern brought about by the removal of fixation either by eye-closure or darkness. Here a technical difficulty of some importance arises. Abolition of fixation whether by means of eye-closure or darkness may be, and often is, accompanied by changes in the deviation of the eyes and in accordance with Alexander's

Law, it could be to this and not the removal of fixation that any change in the nystagmus is attributable.

An essential feature of an investigation of this kind therefore must be not only the facility of controlling the direction of gaze of the eyes but also the means for its accurate measurement when fixation is removed. To this end the electronystagmographic equipment described has been found to be particularly appropriate.

Let us consider first the effects of the removal of fixation by eye-closure or darkness in the normal subject.

In Fig. 4 are shown the results of eye-closure. Above, the subject's eyes are deviated 30° to the right, fixation being maintained with the eyes open

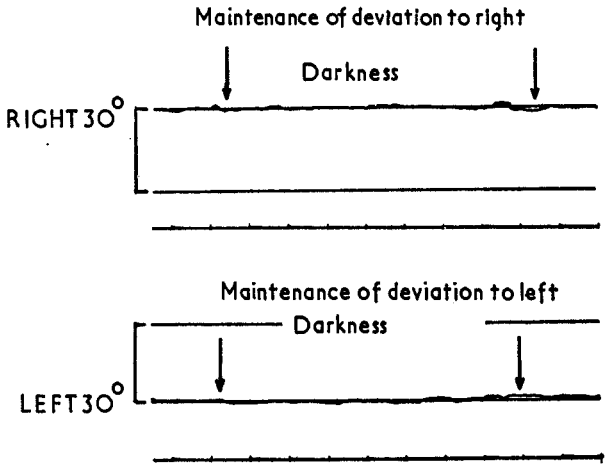

FIG. 5. Effect of darkness upon the maintenance of gaze deviation in a normal subject.

upon the fixation mark. At the point shown by the arrow, the subject closes his eyes and at the same time attempts to maintain the same gaze deviation. On opening the eyes, visual fixation upon the mark is resumed.

Apart from some slight irregularity at the point of closing and opening the eyes, it will be seen that during the period of eye-closure little change occurs in the recording, and it can be assumed that deviation of the eyes was maintained throughout this period. Similar results are shown below with gaze deviation to the left.

In Fig. 5 are shown the effects of darkness upon the maintenance of gaze deviation with the same subject. Once again it will be seen that during the period when visual fixation is removed, the recording remains remarkably steady with gaze deviation faithfully maintained both to right and to left.

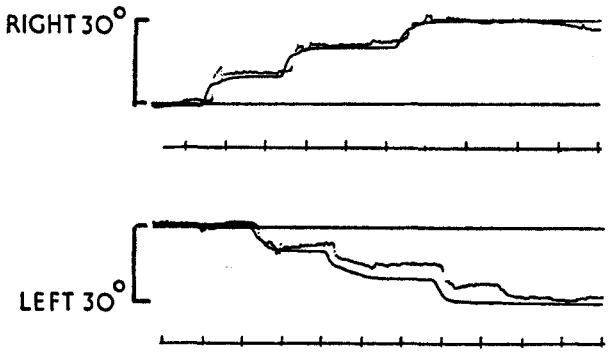

FIG. 6. Absence of spontaneous nystagmus in the presence of optic fixation in a woman patient with Ménière's disease affecting the left ear, 8 days after intracranial division of the eighth nerve.

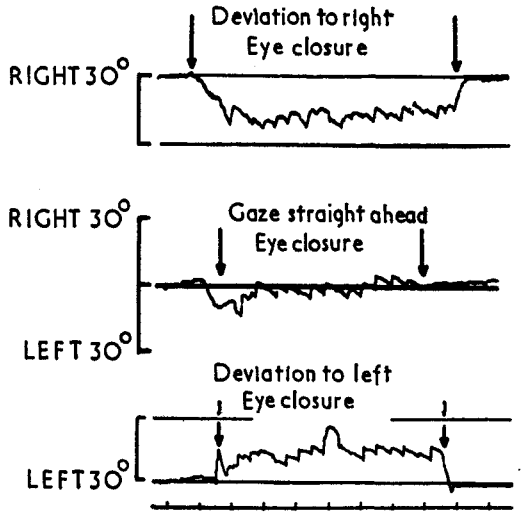

FIG. 7. Appearance of spontaneous nystagmus as a result of removal of optic fixation by eye-closure in a woman patient with Ménière's disease affecting the left ear, 8 days after intracranial division of the eighth nerve.

In fact, with both eye-closure and darkness it is clear that a normal subject can exert such a high degree of control over his eyes that, despite the absence of any visual fixation mark, he is able to maintain a gaze deviation of 30° to right or to left with an accuracy of ± 1°.

Let us now consider the electronystagmographic findings in a number of patients with a variety of otoneurological lesions at various levels within the

central nervous system. The first case is a patient with a peripheral lesion. She was a woman of 35 who had suffered for a number of years from vertigo and deafness of the left ear, attributed to Ménière's disease. Intracranial section of the eighth nerve had been carried out eight days before the recording shown in Fig. 6.

The spontaneous nystagmus of the vestibular type, with its rapid component to the right, present immediately after the operation, had subsided rapidly and, as can be seen, no nystagmic movements are apparent upon the recordings with gaze deviation in any direction.

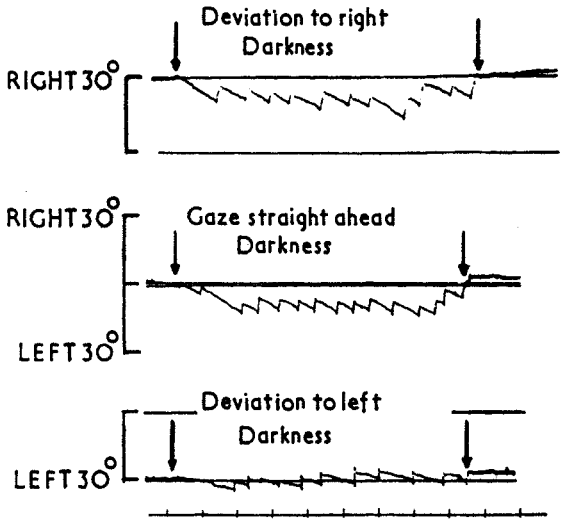

FIG. 8. Appearance of spontaneous nystagmus as a result of removal of optic fixation by darkness in a woman patient with Ménière's disease affecting the left ear, 8 days after intracranial division of the eighth nerve.

In Fig. 7 are shown the results of eye-closure. The upper recording is taken with the eyes deviated 30° to the right. The gaze is quite steady without any nystagmus. At the point shown by the arrow, the eyes are closed and the patient then endeavours to maintain the same gaze deviation. When this happens there is an immediate development of a brisk nystagmus of vestibular type to the right, beginning with a slow deviation to the left. The nystagmus disappears at once when visual fixation is restored.

In the centre and below are shown the comparable situations with gaze straight ahead and to left. In both are seen again the prompt appearance of nystagmus to the right when visual fixation is eliminated. There is in fact a 3rd degree nystagmus to the right with closed eyes.

In Fig. 8 is shown the effect when darkness is substituted for eye-closure for the removal of visual fixation. In all respects the results are similar to those of eye-closure, with the exception that gaze deviation is better maintained.

The impression derived from these records is of a primary imbalance causing the eyes to be deviated to the left followed by a rapid reflex return, the rapid component of nystagmus. With visual fixation this deviation is restrained; without it the restraint is removed and nystagmus becomes manifest.

These findings we have found to be consistently characteristic of lesions peripheral to the vestibular nuclei, whether the damage involves the labyrinth itself or the extramedullary vestibular nerve fibres. In addition,

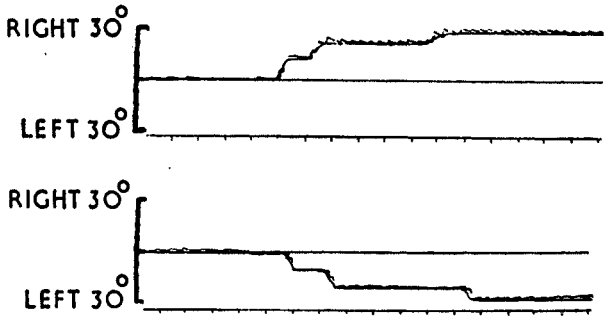

FIG. 9. Spontaneous nystagmus (visual fixation maintained) in a patient with a left acoustic neurofibroma. Second-degree nystagmus to right and first-degree nystagmus to left.

they are similar in all respects to the effects of removing fixation, either by eye-closure or darkness, upon induced vestibular nystagmus in the normal subject.

The second case is of a subject with an organic lesion at a higher level of the central nervous system.

The patient was a man of 58 with a rather advanced tumour of the left eighth nerve. The left vestibular nerve had been entirely destroyed with complete loss of the caloric responses; this had been followed by involvement of the vestibular elements within the brain stem with a resulting spontaneous nystagmus.

In Fig. 9 is shown the spontaneous nystagmus. With the gaze straight ahead slight but definite nystagmus to the right is seen. With gaze to the right, nystagmus is increased, well sustained and extremely regular. With gaze to the left, there is a 1st degree nystagmus to the left. It has a rather

smaller amplitude than that to the right. Its frequency, too, is less and also the speed of the slow component.

The effects of eye-closure upon the nystagmus are shown in Fig. 10. In the centre are shown the results with the straight-ahead position of gaze. During eye-closure the eyes deviate initially to the left and thereafter swing to the right; no nystagmus is visible with the eyes closed, but it reappears when the eyes are re-opened.

The upper record with gaze deviation to the right begins with the eyes open. Nystagmus to the right is present. At the point shown by the arrow,

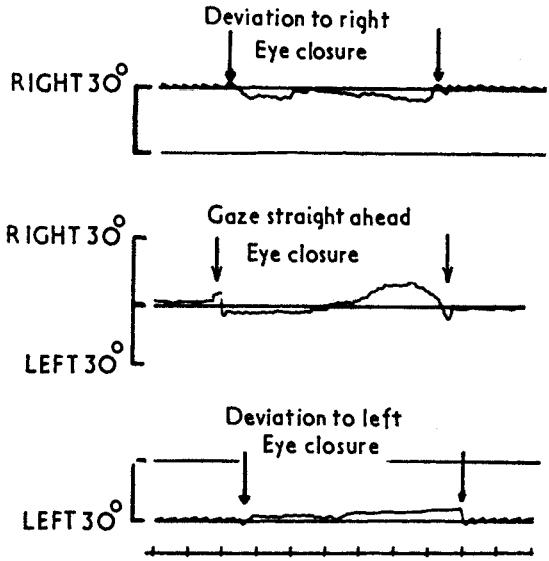

FIG. 10. Effect of eye-closure on nystagmus in patient with left acoustic neurofibroma.

the eyes are closed and the subject attempts to maintain the same gaze direction. The result is the abolition of the nystagmus with a slight deviation of the eyes towards the midline position. When the eyes are opened, nystagmus reappears immediately.

With gaze deviation to the left, as to the right, nystagmus again disappears on eye-closure.

In Fig. 11 is shown the somewhat different effect of darkness upon the spontaneous nystagmus. For gaze both to the right and to the left conjugate deviation is quite well maintained, and with this some nystagmus persists. Its character, however, changes. It now has a larger amplitude, but is irregular and a great deal slower in respect of the speed of the slow component.

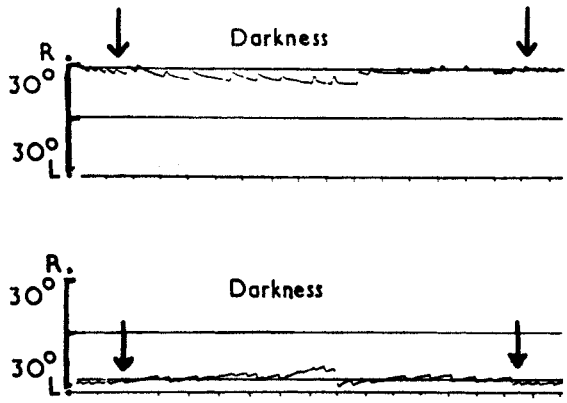

FIG. 11. Effect of darkness on nystagmus in patient with left acoustic neurofibroma.

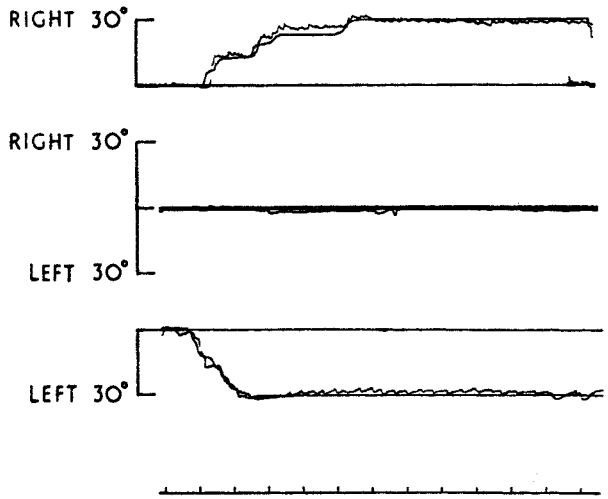

FIG. 12. Spontaneous nystagmus (visual fixation maintained) in a patient with a high brain-stem lesion. First-degree nystagmus to left and right.

The nystagmographic findings in this case thus differ conspicuously from those which follow section of the eighth nerve. The elimination of visual fixation, far from enhancing this nystagmus, abolishes it in the case of eye-closure and tends to inhibit it in the case of darkness. Expressed in reverse, the nystagmus is increased by fixation and seems, in fact, to depend upon it.

This pattern of response is one which has been found to be consistently characteristic of lesions at this higher level of the central nervous system—that is to say, lesions of the vestibular elements within the brain stem at the level of the vestibular nuclei.

Finally, let us consider the findings in the case of a lesion at a still higher level of the central nervous system, namely above the level of the vestibular nuclei in the brain stem.

The subject was a man of 55, who gave a history of difficulty in focusing with diplopia of one month's duration. Two years previously he had been

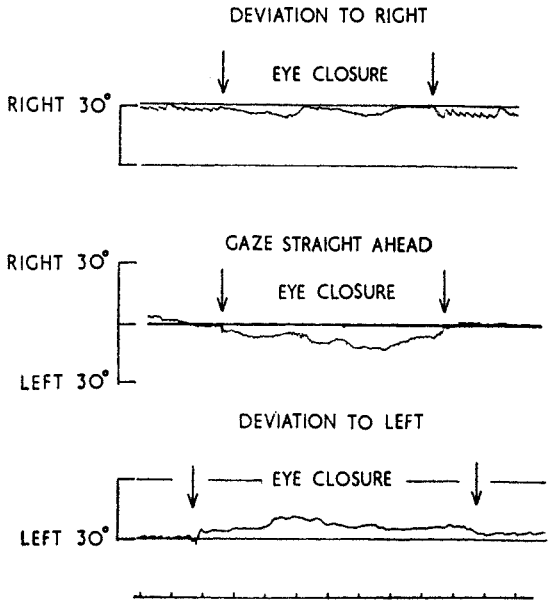

FIG. 13. Effect of eye-closure on nystagmus in patient with a high brain-stem lesion.

treated for syphilis, at which time the blood Wassermann reaction had been positive.

On examination he was found to have nystagmus. The left plantar response was extensor. Nothing abnormal was to be seen in the ears, nose or throat. Cochlear function was normal. He showed ataxia of gait and exhibited positional nystagmus of the central type. Optokinetic responses were all feeble, with directional preponderance to the right.

The caloric responses were exaggerated with marked directional preponderance to the right. The patient was seen by Dr. Hallpike, who considered these abnormalities to be indicative of an organic affection of the

vestibulo-cerebellar and optomotor connexions on the right side of the brain stem above the level of the vestibular nuclei. The neurological diagnosis was tabes dorsalis.

In Fig. 12 is shown the spontaneous nystagmus found to be present with the eyes open. With gaze straight ahead no nystagmus is present. With left and right lateral gaze, however, there is a clear 1st degree spontaneous nystagmus to the left and right.

In Fig. 13 is shown the result of eye-closure upon the nystagmus. It will be seen that during the period of eye-closure, despite the fact that gaze deviation to right and left is well maintained, the spontaneous nystagmus is

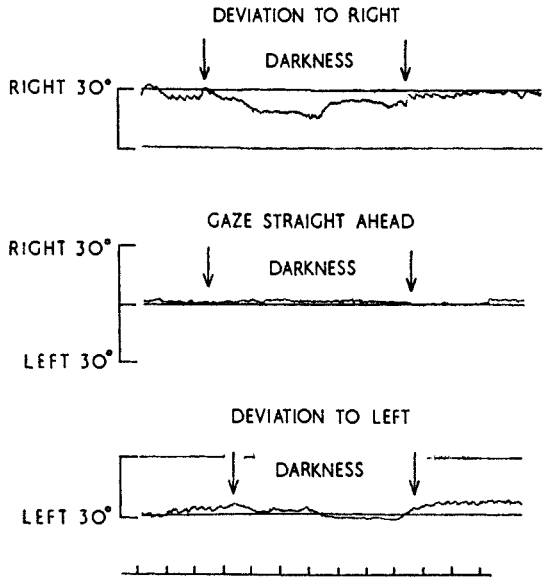

FIG. 14. Effect of darkness on nystagmus in patient with a high brain-stem lesion.

completely abolished, but reappears immediately on opening the eyes. In this respect the findings are not dissimilar to those of the previous case, in which the vestibular nuclei within the brain stem were involved.

In Fig. 14, however, is shown the effect of darkness upon the nystagmus, and it will be seen that this is quite different. Whereas in the previous case nystagmus in a modified form persisted in darkness, in this case the results are the same as with eye-closure, namely maintenance of gaze deviation of the eyes, with complete abolition of the nystagmus.

It is, of course, not always possible to specify with conviction lesions occurring at this high level of the brain stem. Nevertheless, a careful study

of the neurological findings in a large number of cases exhibiting this pattern of response has shown that there are very strong grounds for the belief that it is pathognomonic of lesions in the brain stem above the level of the vestibular nuclei.

It will be seen, therefore, that three clear and distinct patterns of response have emerged, each associated with lesions at different levels of the central nervous system. These are summarized in Table I.

Table I

EFFECTS OF EYE-CLOSURE AND DARKNESS UPON SPONTANEOUS NYSTAGMUS RESULTING FROM LESIONS AT DIFFERENT LEVELS OF THE CENTRAL NERVOUS SYSTEM

Lesion	*Darkness*	*Eye-closure*
Labyrinthine or peripheral to vestibular nuclei	Nystagmus enhanced if present or made manifest if not	Nystagmus enhanced if present or made manifest if not
At or about the level of the vestibular nuclei	Nystagmus enhanced in amplitude but decreased in respect of slow component velocity	Nystagmus abolished
Above the level of the vestibular nuclei	Nystagmus abolished	Nystagmus abolished

Little need be added as to the practical value of these findings. Clearly the electronystagmographic investigation of spontaneous nystagmus carried out in the way described can make an important contribution to the localization of lesions in otoneurological diagnosis.

The theoretical interpretation of the findings is more difficult and a subject of considerable complexity. Spontaneous nystagmus resulting from a lesion involving the vestibular pathways at any point between the labyrinth and the cerebrum is indistinguishable on direct observation of the eyes. It is, however, significant that nystagmus resulting from lesions of the labyrinth is never bilateral and as a rule is directed towards the side contralateral to the lesion, whereas lesions central to the labyrinth may result in nystagmus to both sides. In addition we know that the removal of visual fixation results in the same enhancement of induced vestibular nystagmus as with spontaneous nystagmus of labyrinthine origin. We may therefore conclude that the latter is a manifestation of an imbalance of the tonus elements of the labyrinths, for the knowledge of which we owe much to Professor Lowenstein.

When we come to consider spontaneous nystagmus of central origin, however, matters are quite different. As has been mentioned, this may be directed either to one side or to both sides and on this account it is difficult to consider it in terms of a simple imbalance.

Dix and Hallpike (1966) have dealt with nystagmus resulting from unilateral acoustic neurofibromata, and take the view that the nystagmus in these cases is not *per se* dependent upon fixation. Their suggestion is that the nystagmus is due to damage resulting from tumour pressure on certain brain-stem mechanisms which have to do with the control of conjugate eye deviations in the horizontal plane. This being so, the nystagmus results from a defect in the mechanism controlling deviation of the eyes, and accordingly is best described as a deviation-maintenance nystagmus. Their theory is well supported by their clinical observations and by the persistence of the nystagmus in darkness when deviation of the eyes is maintained.

On the other hand spontaneous nystagmus resulting from lesions high in the brain stem, with its clear dependence upon optic fixation, can best be explained in terms of some defect of the mechanisms controlling fixation.

These mechanisms have recently been the subject of a number of investigations, all of which are in agreement upon the existence of certain feedback pathways. Experimental derangement of certain of these pathways by optical techniques has been shown to give rise to nystagmic eye movements (Fender and Nye, 1961).

The possibility therefore exists that organic derangement by disease of these pathways is the cause of the nystagmus resulting from lesions above the level of the vestibular nuclei.

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DISCUSSION

Dix: Dr. Hood has spoken of the value of electronystagmography in the diagnosis of lesions of the central nervous system at different levels in the brain stem. I should like to comment on its value in the diagnosis of lesions in other situations; firstly lesions in the cerebellum and secondly, lesions of the cerebral hemispheres.

Cerebellar lesions. Fig. 1 is a record made in the straight-ahead position of gaze in light with the eyes open from a man of 52 with a long-standing history of unsteadiness and attacks of vertigo. Nothing abnormal was to be seen in the ears, nose and throat. Cochlear function was normal, apart from slight bilateral high-tone deafness. Tests of vestibular function showed a 1st degree vestibular

nystagmus to the right of the deviation-maintenance type, a directional preponderance to the right of optokinetic nystagmus and positional nystagmus of central type directed to the right in the right lateral position.

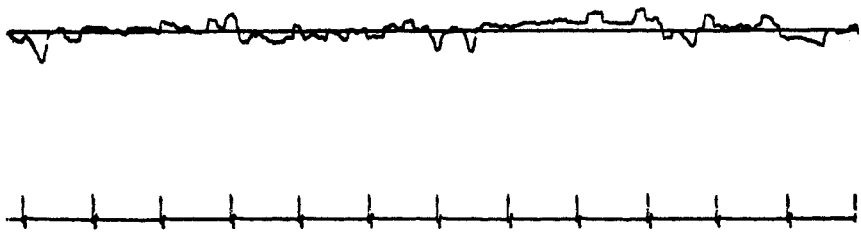

FIG. 1 (Dix). Saccadic movements in straight-ahead position of gaze of patient with cerebellar disease. Eyes open; optic fixation.

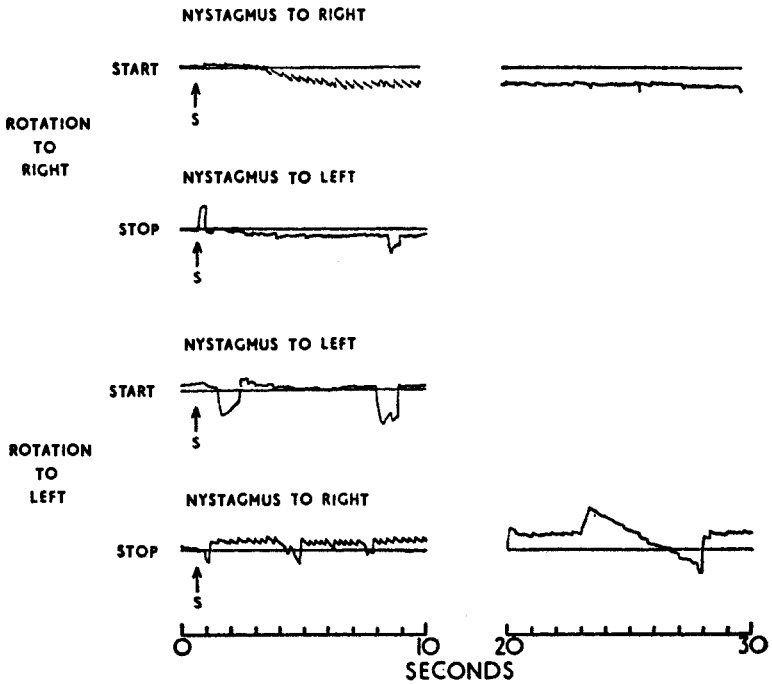

FIG. 2 (Dix). Nystagmic responses to impulsive rotational stimuli (60°/sec.) of patient after right hemispherectomy. Eyes open; optic fixation.

The record shows irregular saccadic eye movements but no definite vestibular nystagmus. These so-called "square waves" are characteristic of lesions of the cerebellum.

Subsequent neurological examination showed that this man had bilateral

cerebellar signs preponderantly on the right side with extensor plantar responses. The diagnosis was multiple sclerosis.

Cerebral lesions (Carmichael, E. A., Dix, M. R., Hallpike, C. S., and Hood, J. D. [1961]. *Brain*, **84**, 571–584). Fig. 2 is the record of induced vestibular nystagmus to impulsive rotational acceleration and deceleration stimuli up to and from velocities of 60°/sec. to right and left, from a patient on whom a right hemispherectomy had been performed. Active optic fixation was maintained upon a light source rotating with the subject in the straight-ahead line of gaze.

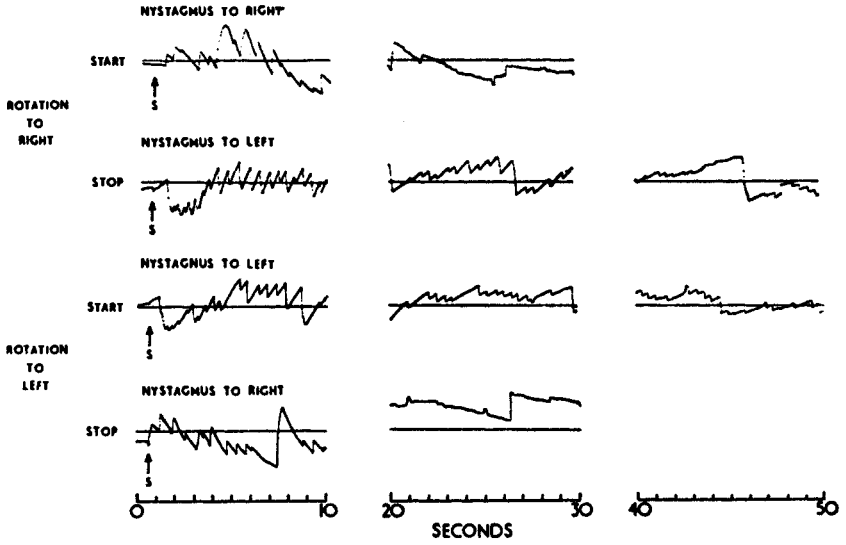

FIG. 3 (Dix). Nystagmic responses to impulsive rotational stimuli (60°/sec.) of patient after right hemispherectomy. Eyes open, in darkness; *no* optic fixation.

Responses 1 and 4 consisting of nystagmus to the right are much greater than responses 2 and 3 consisting of nystagmus to the left. In other words, there is a well-marked directional preponderance to the right, the side of the lesion.

The records shown in Fig. 3 were obtained from the same patient with the eyes open in darkness—that is, without optic fixation. The nystagmographic findings now show striking alterations. Firstly, the amplitude of the nystagmus is greatly increased. This is not surprising since vestibular nystagmus is known to be inhibited by optic fixation and we would expect its enhancement when optic fixation is removed. A second and more important difference is the effect upon the directional preponderance. Thus the directional preponderance to the right, the side of the lesion, so evident with optic fixation, is absent or reversed without it. There is, in other words, a marked directional preponderance to the left.

We have confirmed this reversal of directional preponderance in cerebral

lesions in nine other patients with hemispherectomies and, since then, in numerous other cases with unilateral cerebral lesions.

Hood: A remarkable feature of these cases with cerebral lesions is that some of them had spontaneous nystagmus towards the side of the lesion, and in a few of them when fixation was removed the nystagmus itself reversed in direction. This is in keeping with the change in the direction of the preponderance.

Roberts: Dr. Hood, have you any comments on a possible relationship between this nystagmus during the failure to maintain the deviation of gaze and the sort of things that occur in the oculogyral illusion which Whiteside has been dealing with recently (Whiteside, T. C. D., Graybiel, A., and Niven, J. I. [1965]. *Brain*, **88**, 193–210)? My impression is that in these failures to maintain the direction of gaze the fast component of nystagmus would, if continued far enough, take the eye back to the proper place. The direction of the fast component is towards the deviation which one is trying to hold, so this would fit in. Whiteside had the idea that the impression of movement of the fixation point in the dark is associated with the direction of the fast component of nystagmus occurring in the dark. According to him, the eyes drift, presumably owing to labyrinthine "noise", and corrective movements are made. The direction of these corrective movements gives rise, he suggests, to the subjective sensation of movement of the spot of light. In this case, it would mean that the direction of the movement is towards where the eye should be, and perhaps the subject believes that he has got his eyes in the right place. Does that correspond?

Hood: It would if it were true that nystagmus occurs during the illusion. Dr. Hallpike and I investigated the oculogyral illusion (Hallpike, C. S., and Hood, J. D. [1953]. *Proc. R. Soc. B*, **141**, 216–230) and we accounted for it then in terms of Graybiel's explanation (Graybiel, A., Clark, B., McCorquodale, K., and Happ, D. I. [1946]. *Am. J. Psychol.*, **59**, 259–266). It is essentially the same explanation as you have given, except that Graybiel thought that during the *slow* phase of the nystagmus there would be a tracking of the image of the fixated spot across the retina, which would give rise to the illusion of movement. But various fairly convincing experiments carried out since have shown that nystagmic movements are not necessarily present when the oculogyral illusion is present.

Roberts: On the other hand, the explanation would fit to the extent that the direction of the illusion is the direction corresponding to the correction for the labyrinthine drift. Presumably it is only when labyrinthine drift is sufficiently marked that one would get a nystagmic jerk.

Monnier: Dr. Hood, have you observed a phenomenon that I described with A. Franceschetti and P. Dieterle, namely that the frequency of nystagmus changes when the position of the eye shifts laterally, say by 10°, 20°, 30° or more? We had examples where this was the case, as if the "centre" had been informed that the eye was fixing in another direction. We had the impression that the whole system acted like a cybernetic model and that the nystagmus centre was informed that the gaze was kept in a deviated position.

Hood: Is this not just a restatement of Alexander's Law that if the eyes deviate in the direction of the fast component of the nystagmus, the frequency of the nystagmus is enhanced? We have observed this.

Roberts: Does this imply also a change in the *velocity* of the slow component?

Hood: I would have said that it does.

Groen: The velocity does not necessarily alter.

Roberts: This is why I ask. If the amplitude remains the same and the frequency goes up, the speed of the slow component must have gone up too. But one can of course increase the frequency of the jerks without affecting the velocity of the slow component, in which case one would expect the jerks to be smaller.

Hood: In any single individual or test it may not occur, but if one averaged the results from a number of subjects or tests I believe one would find that the velocity of the slow component does increase.

Henriksson: Dr. Hood, do you find any deviation of the eyes in the direction of the slow component during the caloric reaction in the normal case?

Hood: We do find this deviation but again it is an elusive phenomenon. One cannot demonstrate this consistently but if one averaged a large number of responses one would find this deviation in the direction of the slow component.

Henriksson: I agree that it is not consistently found, and I think that this is important. In the normal case with normal alertness there is hardly any deviation in the direction of the slow component; however, if the patient is sleepy or has some disorder, such as a lesion in the brain stem, perhaps due to arteriosclerosis, we frequently see a definite deviation. This is another factor in our measuring of nystagmus which we can use clinically.

Dix: I have observed this deviation of the slow component very often in brain-stem lesions, in particular, pontine lesions.

Henriksson: That is very interesting. This phenomenon should be used in clinical work, to assist the neurologists. So frequently we have cases with the "drop attacks" that Dr. Hallpike described earlier (p. 190). In these cases the neurologists often have very poor objective findings. In such cases we may find a normal peripheral caloric response which is frequently combined, however, with deviation of the eyes in the direction of the slow component during the nystagmic response. Frequently this deviation is also combined with a dysrhythmia of the nystagmic pattern. It would be interesting to know what the neurophysiologist would say about this phenomenon. Is there some kind of break-up in the synapses of the central connexions of the vestibular apparatus, due to ischaemic conditions, that causes the deviation and dysrhythmia?

Dix: Dr. Hallpike and I have recently made a study of two brain-stem mechanisms controlling horizontal deviation of the eyes which we believe to be involved in the spontaneous nystagmus of eighth-nerve tumours. The first, the vestibular tonus mechanism, was shown to be located within the vestibular nuclei below the level of entry of the eighth nerve. The brain-stem pathway of the second mechanism has been described by Bender as descending ipsilaterally

in respect of the activating hemisphere, to about the level of the nuclei of the third nerve, where it crosses the midline and continues caudally to below the level of the nuclei of the sixth nerve. The involvement of either of these pathways by tumour pressure results in deviation-maintenance nystagmus (Dix, M. R., and Hallpike, C. S. [1966]. *Acta oto-lar.*, **61**, 1–22).

Hallpike: I would suggest that the progress made in interpreting nystagmus depends very much on the methods of observing nystagmus. The particular arrangement described by Dr. Hood allows us to acquire considerable insight into the whole situation. As far as nystagmus due to peripheral disorders is concerned, one observation of great interest made possible by this instrumentation is that most of the nystagmus takes place, on the record, on the side of the baseline to which the eyes deviate in the slow component. By contrast, in optokinetic nystagmus all the recorded nystagmus lies on the other side of the baseline—that is, on the side to which the eyes deviate in the rapid component.

Turning to central nystagmus, which Holmes called "fixation nystagmus", we would prefer to avoid this term because it suggests a connexion with visual processes, whereas, as we have shown, it is not the visual processes *per se* that matter but the maintenance of the deviation of the gaze. This is why we introduced the term "deviation-maintenance nystagmus".

Myotatic, Kinesthetic and Vestibular Mechanisms
Edited by A.V. S. de Reuck and Julie Knight

ON THE DIRECTION OF SPONTANEOUS AND POSITIONAL NYSTAGMUS

A. J. PHILIPSZOON AND J. H. BOS

The Ear, Nose and Throat Clinic, Wilhelmina Gasthuis, University of Amsterdam, Holland

IN the literature we often find the opinion expressed that the direction of a spontaneous or positional nystagmus aids in the differential diagnosis between peripheral and central lesions. It therefore seems important to get a better insight into the rules governing the direction of spontaneous and positional nystagmus, as present in vestibular disorders of peripheral and/or central origin.

In one-sided cases of Ménière's disease a spontaneous nystagmus is claimed to beat in the direction of the healthy ear. Direction-changing positional nystagmus is said to indicate central disturbances, while in cases of purely peripheral vestibular disorders only a direction-fixed positional nystagmus is claimed to be present.

Recent publications (Aschan, Bergstedt and Stahle, 1956; Stahle, 1958; Jongkees, Maas and Philipszoon, 1962) giving the results of electronystagmographic recordings in vertigo, make it impossible to maintain these and other fixed rules about the relation between the direction of spontaneous or positional nystagmus and the site of the lesion.

Performing the posture test in 13 patients with unilateral Ménière's disease, Jongkees, Maas and Philipszoon (1962) found a direction-fixed positional nystagmus toward the affected ear 4 times, a direction-fixed nystagmus toward the healthy ear 6 times and a direction-changing nystagmus in 3 cases. In 41 patients suffering from Ménière's disease in both ears, they found a direction-fixed positional nystagmus toward the best ear in 14 cases, a direction-fixed nystagmus toward the most affected ear in 9 patients and a direction-changing nystagmus 18 times.

In 26 patients with a spontaneous and positional nystagmus after a radical ear operation, the same authors found a nystagmus to the operated side in 12 cases, toward the healthy ear in 8 cases and a direction-changing positional nystagmus in 6 cases. In 9 patients suffering from otitis media

they found a nystagmus to the affected ear 3 times, a nystagmus to the healthy ear twice and a direction-changing nystagmus in 4 cases (Fig. 1).

The combination of brain tumours and nystagmus is often mentioned. The determination of directional preponderance in the caloric test is considered to give information about the site of brain tumours (Carmichael, Dix and Hallpike, 1954; Sandberg and Zilstorff-Pedersen, 1961).

Jongkees, Maas and Philipszoon (1962), using electronystagmography as an indicator of caloric stimulation (by the method of Hallpike) investi-

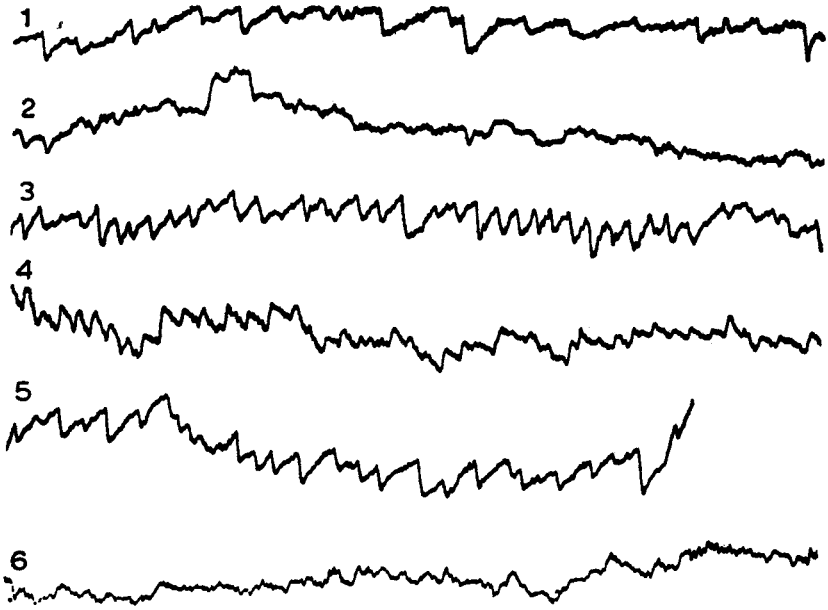

FIG. 1. Direction-changing positional nystagmus in a patient with one inexcitable labyrinth after a radical ear operation. (1) Sitting: nystagmus to the left. (2) Lying on the back: no nystagmus. (3) Lying on the left side: nystagmus to the left. (4) Lying on the right side: nystagmus to the right. (5) Lying on the stomach: nystagmus to the left. (6) Head-hanging position: no nystagmus.

gated 255 patients and found a directional preponderance without a spontaneous or positional nystagmus in the posture test only 4 times. For this reason we used the posture test with electronystagmography, as this easy examination takes far less time than the caloric test and nevertheless enables us to find a considerable percentage of cases of directional preponderance. Using the posture test we could find no rule either about the direction of the nystagmus or about the preponderance and the localization of brain tumours.

Another finding is equally strange, according to the accepted views in the literature. This is the fact that we recorded "gaze nystagmus" both to the right and to the left in the same patients with purely peripheral disorders. When we asked the patients to fix their gaze to the left—always less than 45°, to avoid nystagmus by too much deviation of the eyes—we found a nystagmus to the left, and when we asked them to gaze to the right we recorded nystagmus to the right in about 40 per cent of our patients (Fig. 2).

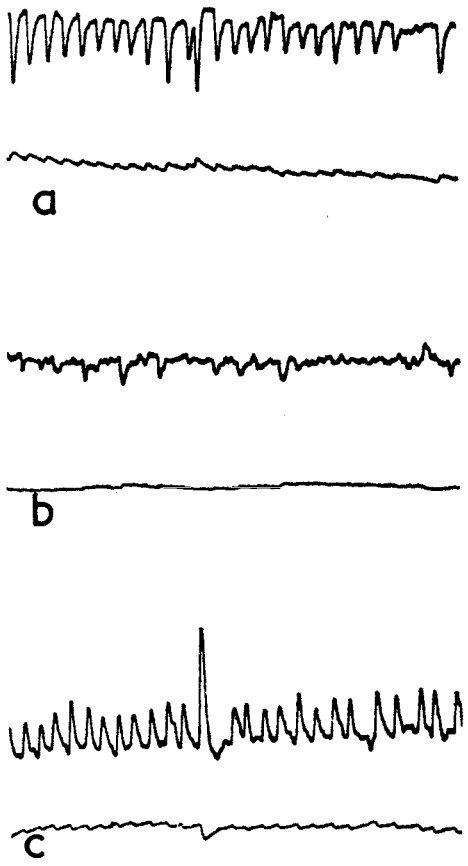

FIG. 2. Gaze nystagmus in a patient with a peripheral vestibular disorder. (*a*) Looking to the right: nystagmus to the right. (*b*) Looking straight forward: no nystagmus. (*c*) Looking to the left: nystagmus to the left. (The upper line represents the derived curve according to Henriksson, 1955.)

EXPERIMENTS

In our investigations we wanted to imitate experimentally spontaneous and positional nystagmus of peripheral and central origin in rabbits, in order

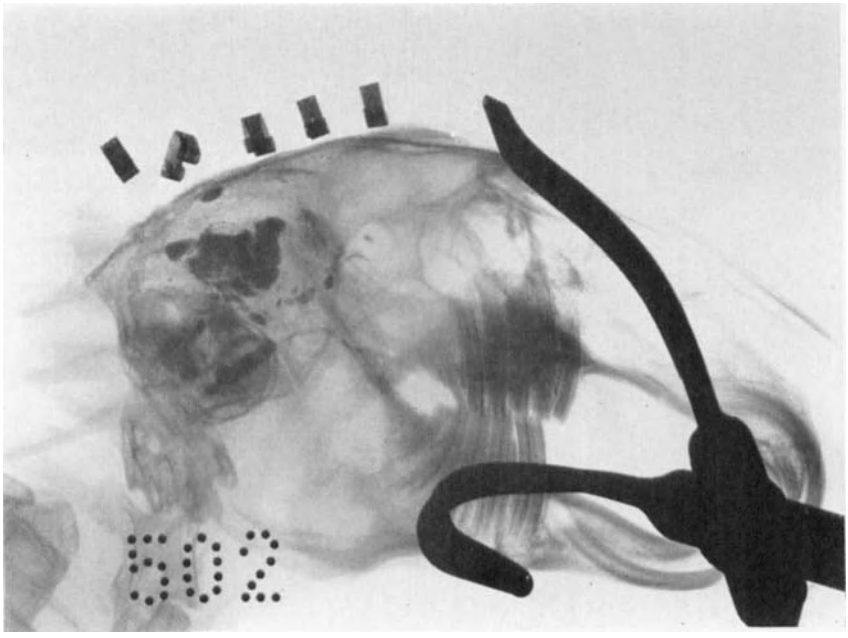

FIG. 3. Radiograph of artificial brain tumour.

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to see whether we could find rules determining the direction of that nystagmus. For this purpose we studied:

(1) Nystagmus after unilateral labyrinthectomy.
(2) Nystagmus after labyrinthectomy on both sides (Bechterew nystagmus).
(3) Nystagmus during alcohol intoxication.
(4) Nystagmus during pethidine (meperidine) intoxication.
(5) Nystagmus provoked by artificial brain tumours.

METHODS

We performed the labyrinthectomies in rabbits, following the approach of de Kleijn and Versteegh (1935). Within 48 hr. after the operation the rabbits were examined in the following positions: in the prone position, on the right and on the left side, in the supine position and upright. In order to study Bechterew nystagmus in the rabbit we did a second labyrinthectomy on the other ear about one month after the first labyrinthectomy. The movements of both eyes were recorded separately.

To study the effect of alcohol and pethidine we examined the rabbits after administration of the drugs in the same positions as described above. We gave 4 ml. per kg. body weight of a 96 per cent solution of ethyl alcohol to the rabbits by means of a gastric tube. The dose of pethidine was 100 mg./kg., which we injected intraperitoneally.

In order to study the effect of brain tumours on vestibular responses we used a method of simulating tumours by introducing a mass of foreign material into the brain substance of rabbits (Philipszoon, 1963). In these experiments we used the stereotaxic system of Monnier and Gangloff (1960) for orientation inside the skull. In order to have a good chance of being in the neighbourhood of the nystagmic pathways, we made our artificial tumours in the domain of the nystagmogenic centre of Lachmann, Bergmann and Monnier (1958). After locating this centre by electrical stimulation using an electrode we injected 0·15–0·25 ml. of a paste of Lipiodol with barium sulphate into the same spot. This paste is not absorbed and is easily localized by means of radiography (Fig. 3).

In order to inject the paste into the right place, we used special electrodes passed through injection needles from which the points had been cut off (Fig. 4). The electrode, which was led through the needle, consisted of an insulated piece of copper wire whose end was free. When we had elicited central nystagmus by electrical stimulation the electrode was retracted from the needle. The Lipiodol–barium sulphate paste was then injected with a syringe. After this we examined the rabbits in the usual positions.

RESULTS

1. *Unilateral labyrinthectomy*

We operated on 10 rabbits, 5 on the left side and 5 on the right side. Of the rabbits operated upon on the left ear, one showed a direction-fixed positional nystagmus to the right, while 4 had a direction-changing

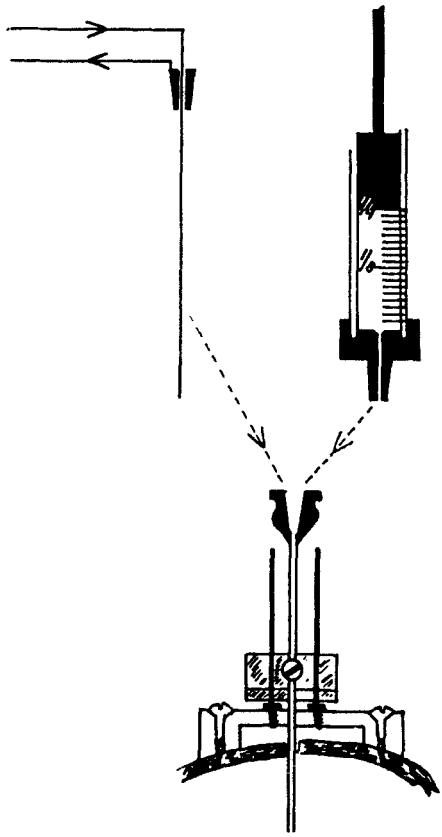

FIG. 4. Stereotaxic system used in artificial tumour experiments, showing electrode and injection needle used.

nystagmus. Of the rabbits operated upon on the right ear, two showed a direction-fixed nystagmus to the left, while the other 3 animals had a direction-changing nystagmus. Thus seven of our rabbits showed a direction-changing positional nystagmus, while three had a direction-fixed nystagmus toward the normal ear. These findings do not fit in very well

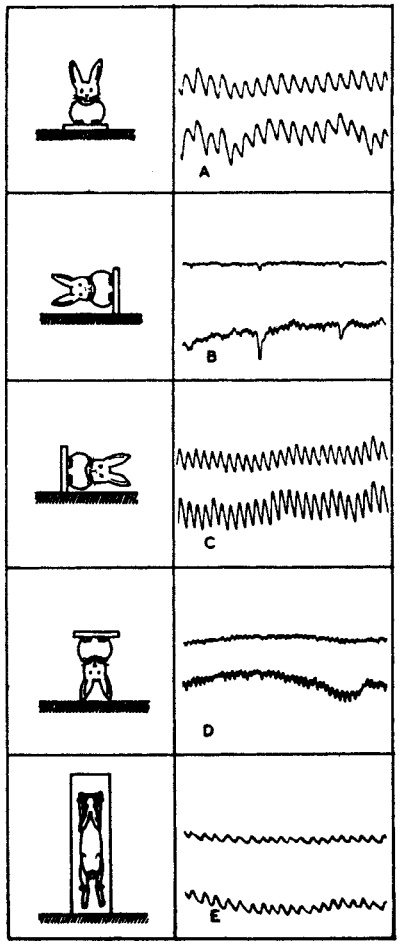

FIG. 5. Positional nystagmus in a rabbit after left-sided labyrinthectomy. A: Prone position. B: On the right side. C: On the left side. D: Supine position. E: Upright position.

In the lateral position the nystagmus is more intense when the rabbit lies on the side of the operated ear than on that of the healthy ear. Nystagmus in the prone position is greater than in the supine position. Right eye: upper curves. Left eye: lower curves.

with the old views on the direction of nystagmus after labyrinthectomy but they confirm our new clinical findings quite well.

Though these findings did not establish the existence of rules for the direction of nystagmus after labyrinthectomy, we did find, quite unexpectedly, a new "rule". In the lateral position all these animals showed a much bigger nystagmus when they were lying on the operated side; the nystagmus was very faint or absent when they were lying on the normal side. In the supine position the nystagmus was always smaller than in the prone position(Fig. 5).

Another, most unexpected, finding was the fact that in the 7 rabbits with

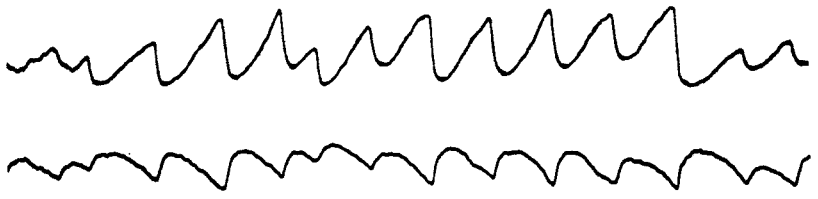

FIG. 6. Opposite nystagmus of the two eyes. The right eye (upper curve) is beating to the left and the left eye (lower curve) to the right.

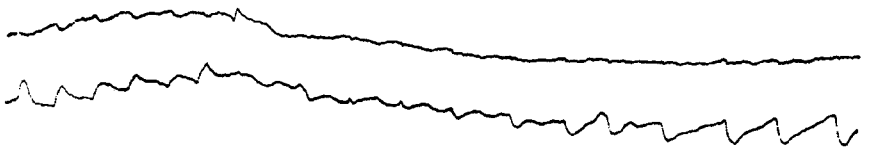

FIG. 7. Direction-changing nystagmus of the left eye. No nystagmus of the right eye.

a direction-changing nystagmus, the two eyes showed nystagmus in two opposite directions when the animal was placed in one or more positions. While one eye had a nystagmus to the left, the other eye had a nystagmus to the right (Fig. 6). One might think that this was because the eyes were both beating in the same plane but the electrodes for both eyes were not placed in exactly the same equipotential planes, resulting in the recording of an apparently "opposite" nystagmus. The fact, however, that we often found a direction-changing nystagmus in one eye while no movements of the other eye were to be recorded (Fig. 7) makes this view highly improbable. We often found no nystagmus in one eye, while a strong nystagmus was present in the other.

Another possible source of error in recording the movements of both eyes is the fact that the electrical fields of the dipoles of the eyes might

influence each other. To exclude this possibility we gave passive movements to one eye of normal rabbits, while recording the electrical field of both eyes. No influence of the moving eye could be seen upon the recording of the other eye (Fig. 8) (Philipszoon, 1959). We always recorded the movements of both eyes with both channels at the same level of amplification, obtaining identical deviations for an input step of one millivolt.

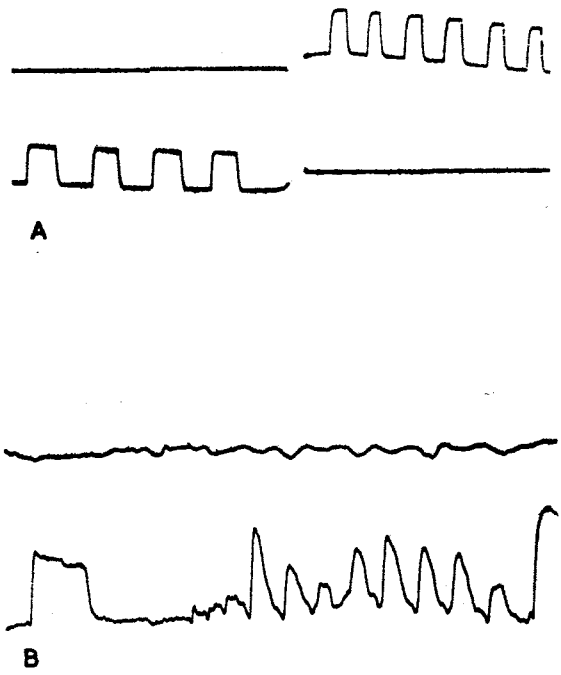

FIG. 8. A. Equal calibration of both channels for an input of 0·1 mv. B. Strong passive eye movements in the recording of the right eye.

The position of the electrodes does not influence the amplitude of the recorded eye movements either. We displaced the electrodes from the brim of the eyelids in the peripheral direction by more than 1 cm. The recording of identical eye movements remained the same (Fig. 9). Identical passive eye movements were given by means of a thread sutured into the cornea of the eye after local anaesthesia with pantocaine. One end of the thread was led via a pulley to an electromagnetic relay, while the other end was led via a pulley to a counter-weight. Switching the current on and off in the relay thus produces passive eye movements of equal magnitude in the rabbit's eye (Philipszoon, 1959).

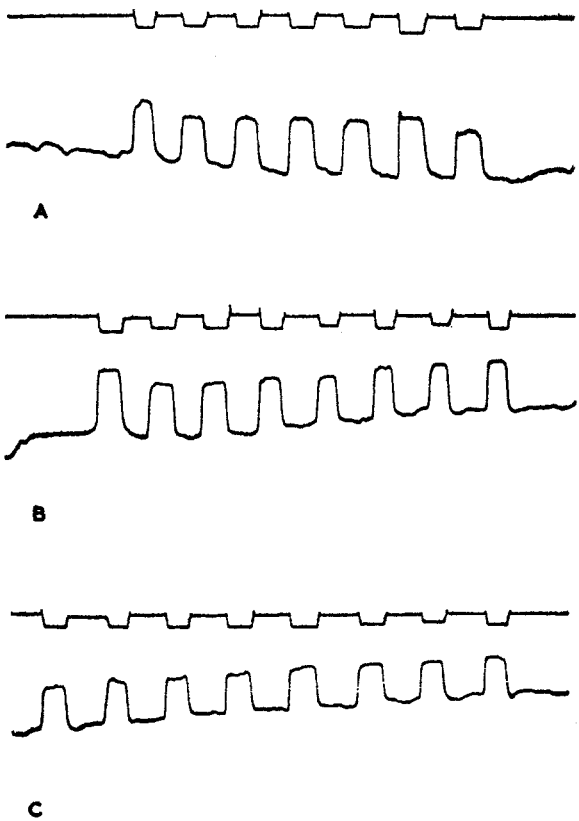

FIG. 9. A. Recording of identical passive eye movements. B. Electrodes displaced over a distance of nearly 1 cm. C. Electrodes displaced over 1·5 cm. The upper line gives the recording of the movement of the electromagnetic relay, the lower line the eye movement. Little or no influence of the displacement of the electrodes is to be observed.

2. *Bechterew nystagmus*

We studied Bechterew nystagmus in 8 rabbits. In these animals the results were similar to those obtained after one-sided labyrinthectomy.

Two rabbits showed a direction-fixed nystagmus (Fig. 10), while the other 6 rabbits had a direction-changing nystagmus. In all 6 rabbits with direction-changing nystagmus, the two eyes showed nystagmus in opposite directions in one or more positions of the animal.

3. *Nystagmus provoked by alcohol*

We gave alcohol by mouth to 11 rabbits. All the rabbits showed a distinct nystagmus. One of them had a direction-fixed nystagmus and 10

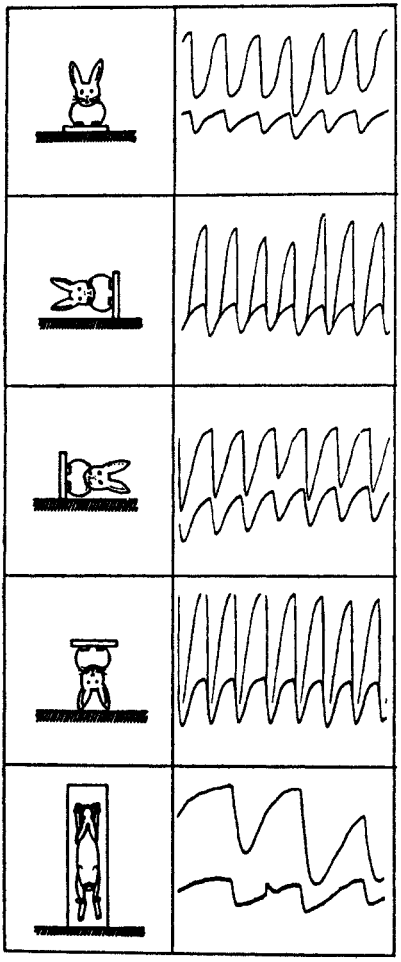

FIG. 10. Bechterew nystagmus. The nystagmus is about the same size in all positions.

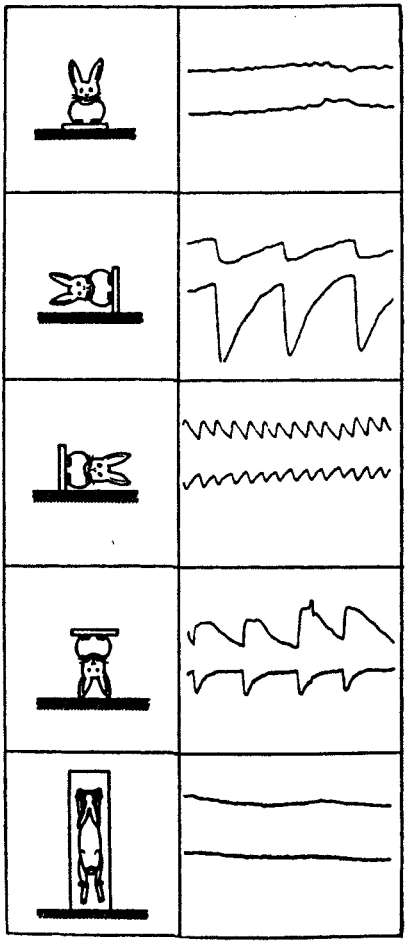

FIG. 11. Nystagmus provoked by alcohol. Note nystagmus in opposite directions in certain positions.

showed a direction-changing nystagmus (Fig. 11). Of those 10 rabbits, 6 had nystagmus in opposite directions in both eyes in one or more positions.

4. *Nystagmus provoked by pethidine (meperidine)*

Another form of chemically induced nystagmus was described by Andersen, Jepsen and Kristiansen (1953). When giving pethidine intravenously to patients, in order to produce some degree of anaesthesia, they observed nystagmic beats before the anaesthetic influence showed itself.

A certain difference in sensitivity to this drug existed among the patients but as soon as the nystagmic beats appeared, the anaesthetic influence became evident. Electronystagmography was not used in this study. We injected similar and higher doses of pethidine intraperitoneally into 35 rabbits, but we never succeeded in recording nystagmic beats. We did find very clear but unco-ordinated eye movements (Fig. 12), but these bore no relation whatever to the well-known pattern of rhythmic movements with slow and quick phases which we call (vestibular) nystagmus.

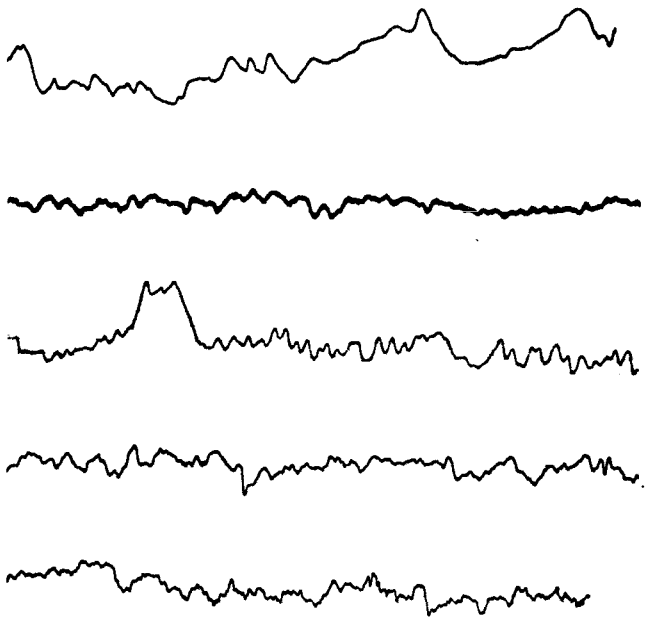

FIG. 12. "Nystagmus" after pethidine.

5. *Nystagmus provoked by artificial brain tumours*

We provoked central nystagmus by producing artificial tumours in the centre of Lachmann, Bergmann and Monnier (1957) in 12 rabbits. In all these rabbits the quick phase was beating in the contralateral direction. In seven of them a clear positional nystagmus arose after injection of the artificial tumour (Fig. 13). In 5 rabbits no nystagmus developed. In 4 rabbits the nystagmus was in the same direction as the nystagmus following electric stimulation, but the nystagmus was beating in the opposite direction in 3 rabbits. Thus up till now no rule has been found for the direction of positional nystagmus with this kind of artificial "brain tumour".

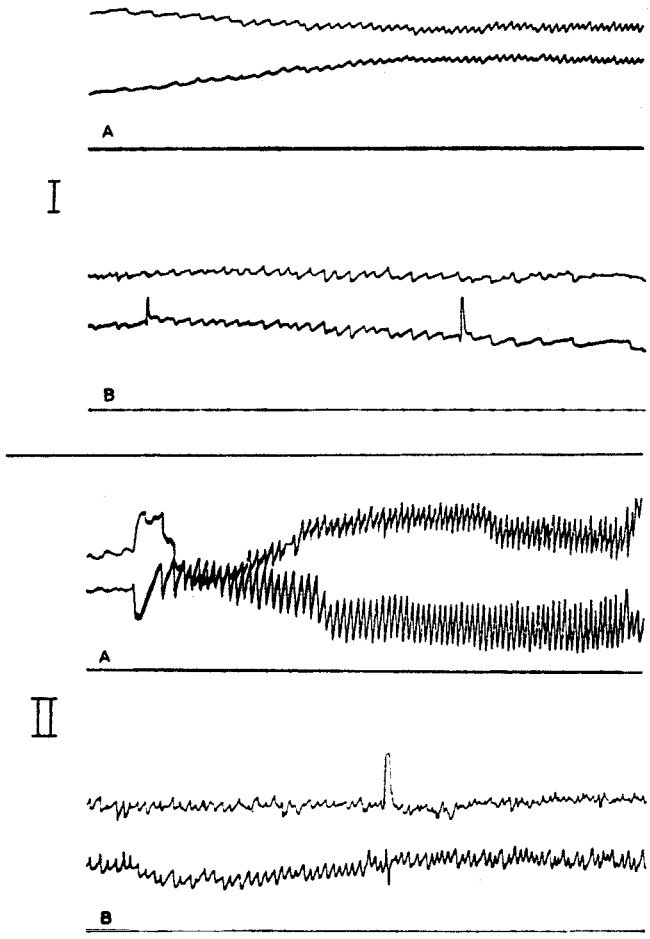

FIG. 13. Two specimens of positional nystagmus after injection of an artificial tumour. A. Nystagmus provoked by electric stimulation in the nystagmogenic centre. B. Positional nystagmus after injection of Lipiodol-barium sulphate paste.

SUMMARY

From recent publications on electronystagmography it appears that in patients with vestibular disorders there is often no definite relation between the direction of spontaneous or positional nystagmus and the site of the lesion (peripheral or central, left or right). To check these findings experimentally we decided to imitate central and peripheral spontaneous nystagmus in rabbits. We therefore studied the nystagmus after unilateral labyrinthectomy, Bechterew (bilateral) nystagmus, that occurring during

intoxication with alcohol and pethidine and nystagmus provoked by artificial brain tumours.

In 10 rabbits, after one-sided labyrinthectomy, we found a direction-fixed positional nystagmus toward the healthy ear only 3 times and a direction-changing positional nystagmus 7 times. In 8 rabbits with Bechterew nystagmus we twice found a direction-fixed nystagmus and 6 times a direction-changing nystagmus. All the rabbits with direction-changing nystagmus showed in one or more positions a nystagmus of both eyes in opposite directions (e.g. a nystagmus to the left in the left eye and to the right in the right eye).

In the lateral position, after unilateral labyrinthectomy, all rabbits showed a stronger nystagmus when lying on the side of the operation than when lying on the side of the normal ear.

Of 11 rabbits who received ethyl alcohol, one showed a direction-fixed positional nystagmus and 10 a direction-changing nystagmus. Six of these 10 rabbits showed nystagmus of both eyes beating in opposite directions, in one or more positions.

In none of 35 rabbits which received pethidine could a nystagmus be recorded. On the other hand, rough, unco-ordinated "atactical" eye movements could often be seen, though without slow or quick phases.

A method is described of making artificial brain tumours in rabbits. A paste consisting of a mixture of Lipiodol and barium sulphate is injected into the nystagmogenic centre of Lachmann, Bergmann and Monnier (1957). In 7 out of 12 rabbits this resulted in a clear positional nystagmus but without a fixed direction.

The view that no definite rules have yet been found about the relation between the direction of spontaneous and positional nystagmus and the site of vestibular lesions (peripheral or central) was confirmed by our experiments.

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DISCUSSION

Lowenstein: Dr. Philipszoon, rabbits have laterally placed eyes, and I wonder how independent the eye movements in animals with extremely lateral eyes are. Have you observed independent eye movements—even voluntary eye movements—in your animals? Do they look back over the shoulder with one eye only, for example?

Philipszoon: I have never observed such independent eye movements.

Hallpike: Yet it would seem to be rather purposeless if the movements of the rabbit's eyes were conjugate, since the eyes are placed laterally. This would mean that when the rabbit looks to the right with its right eye, its left eye could certainly not be turned on the object of interest and would be better employed looking in a different direction!

Lowenstein: So the freedom of nystagmus from conjugateness which you find may be due to the extreme lateral position of the eyes in the rabbit.

Philipszoon: Yes.

Lowenstein: On the other hand I am surprised that this could have been overlooked, because generations of people have worked on nystagmus in rabbits.

Roberts: There are, of course, the responses of the eyes from the neck that de Kleijn mentions. If the head is held still and the body is moved round towards the right ear, the right eye goes forward and the left eye comes back, or if the animal is turned to one side, one eye goes up and the other goes down. That is to say, the rabbit's eyes are probably not independent.

Monnier: It is known that in lower mammals such as the rabbit, if one attempts to obtain pure horizontal movements, as soon as one moves the animal the vertical component may interfere very strongly.

Secondly, in the instances in which you found paradoxical reactions, it is possible that some unusual deflection was due to the mode of connexion between the derivation electrode and the input of the amplifier system. Furthermore, the recording method (bipolar or monopolar) and the choice of the reference electrode may complicate the interpretation of the record. You chose the ear in your animals?

Philipszoon: No, we used the forehead.

Monnier: Another problem is that of the difference between irritative and destructive lesions. Many of the contradictions you found in patients or in

rabbits may come from the fact that your lesions were irritative or destructive, which may give quite different results.

Philipszoon: On your last point, in a patient of course one does not know what kind of stimulus the lesion is supplying. As regards the experiments in general, I wanted to demonstrate that in three or four thousand patients we found no rules about the direction of nystagmus, and that the rabbit provides a simple experimental model of this.

Myotatic, Kinesthetic and Vestibular Mechanisms
Edited by A.V. S. de Reuck and Julie Knight

OBSERVATIONS ON THE STRUCTURAL BASIS OF TWO RARE VARIETIES OF HEREDITARY DEAFNESS

C. S. HALLPIKE

Ferens Institute of Otolaryngology, Middlesex Hospital, London

MY task in this symposium is to present the results of two clinico-pathological studies: the first of a case of posterior sensory neuropathy; the second of a case of Refsum's disease.

Both of my subjects were patients at the National Hospital, Queen Square under the care of my colleagues Dr. E. A. Carmichael and Dr. M. Critchley and to them and to Professor W. Blackwood I owe the opportunity of carrying out a histological examination of the eighth nerves and labyrinths.

First, let me take the case of posterior sensory neuropathy. As originally described in 1922 by Hicks, this condition presents as two of its salient features a painless ulceration of the feet and a progressive nerve deafness. Denny-Brown in 1951 was the first to describe the histopathological changes in the nervous system. These consisted of a primary degeneration of the nerve cells of the posterior root ganglia with loss of the fibres of the peripheral nerves, the posterior nerve roots and the posterior columns within the spinal cord.

Our patient, a woman and a characteristic case, died in 1947 at the age of 41.

Ulceration of the feet and deafness both made their appearance at the age of 23. Some tinnitus was present at the onset but thereafter was not a feature. It is noteworthy that at no time was there any complaint of vertigo. On her first admission 11 years before death, otological examination revealed normal tympana and a moderate degree of bilateral nerve deafness with positive Rinne reactions. The caloric reactions were also reduced. Nine years later, 2 years before death, hearing was reduced to the perception of a loud shout and the caloric responses were abolished.

The neuropathological findings by Professor Blackwood showed characteristic degeneration of the posterior root ganglia and the posterior

columns and some fibre loss in both cochlear and vestibular divisions of the eighth nerve.

I come now to the temporal bones. The tympana and labyrinth capsules were normal. In the neurosensory apparatus, however, severe and widespread changes had occurred. The pathological changes in the two labyrinths were remarkably symmetrical in respect alike of their character, severity and distribution. Details of the changes in the left labyrinth are shown in Figs. 1–4.

In Fig. 1 is shown the cochlea. The cochlear nerve and spiral ganglion appear normal apart from some cell loss in the spiral ganglion in the basal posterior half-whorl. There is no distortion of the perilymph and endolymph compartments and Reissner's membrane is normal in position and structure.

In the organ of Corti and stria vascularis widespread degenerative changes are present, as shown in Fig. 2. There is severe degeneration of the stria, of which only part remains. Degeneration of the hair cells of Corti's organ, though considerable, is by no means complete. Thus, in spite of much distortion of the cell mass, individual cells and Corti's rods can still be distinguished. In contrast, however—and this seems a notable feature—the limbus and tectorial membrane show changes of the utmost severity, and of the limbus itself with its usually numerous cell nuclei only a ghostly outline remains.

In Fig. 3 is shown a section through the upper part of the internal auditory meatus. It shows the normal darkly staining facial nerve, together with Scarpa's ganglion and the vestibular nerve. There is a considerable cell loss in this ganglion with a severe reduction in the number of nerve fibres passing to it from the vestibular end organs.

In Fig. 4 is shown the crista of the horizontal semicircular canal. There is a severe degree of atrophy of the sensory epithelium with a reduction in the number of nerve fibres in the sub-epithelial connective tissue. Comparable changes are present in the utricle and other canals. The saccule exhibits partial collapse. Its sensory epithelium is disorganized and contains amorphous deposits.

I come now to the second of my two subjects, a typical case of the condition first described by Refsum in 1945 to which he gave the name of "Heredopathia atactica polyneuritiformis". Its clinical features, apart from deafness, include night blindness, widespread sensory disturbances and weakness and wasting of the muscles.

Much information is now available upon its neuropathology, and the chief finding is of a diffuse thickening of the peripheral nerves, a character-

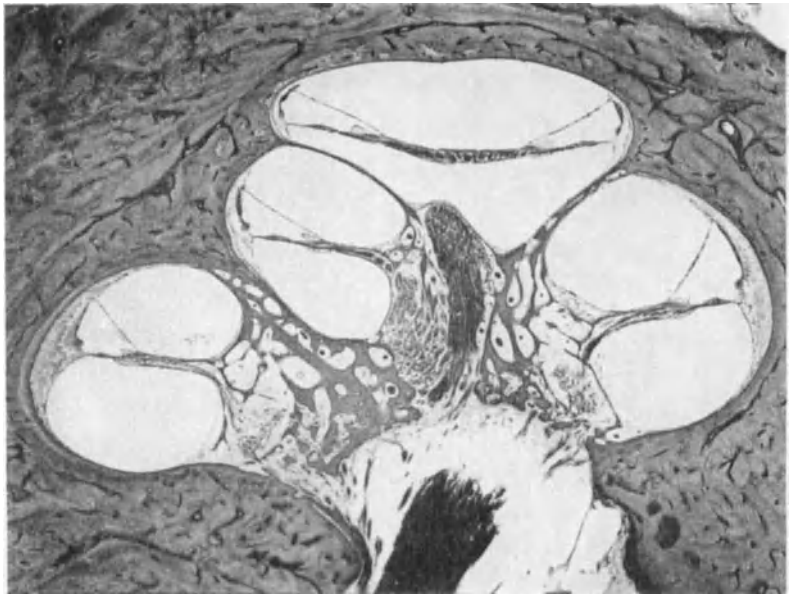

FIG. 1. Cochlea of case of posterior sensory neuropathy. Degeneration of Corti's organ and stria vascularis, with good preservation of the spiral ganglion and cochlear nerve fibres. × 16.

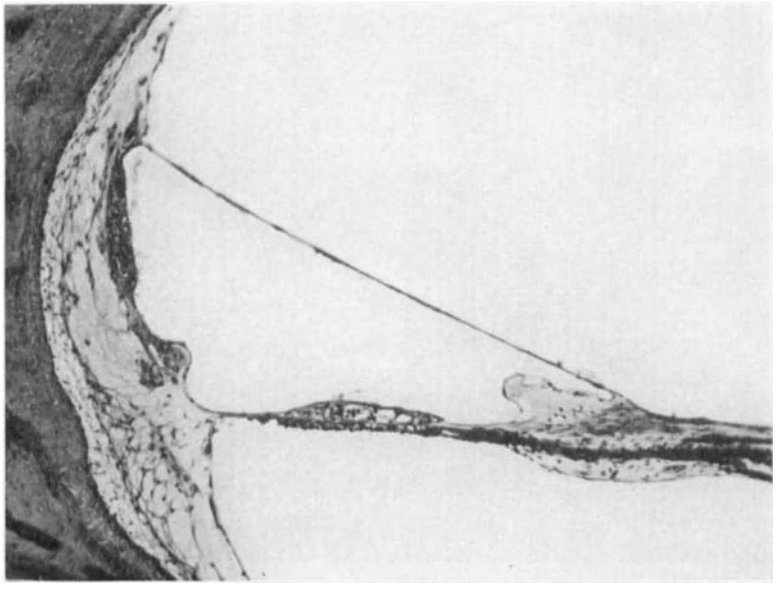

FIG. 2. Scala media of case of posterior sensory neuropathy. Degeneration of stria vascularis and Corti's organ. The cells of the limbus are very severely affected. × 95.

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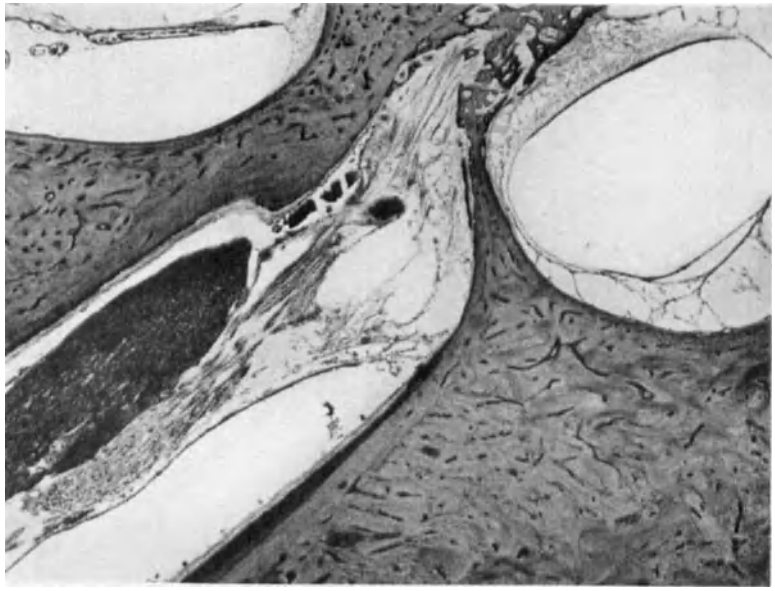

FIG. 3. Scarpa's ganglion and vestibular nerve of case of posterior sensory neuropathy. Cells and fibres are much reduced in number. × 16.

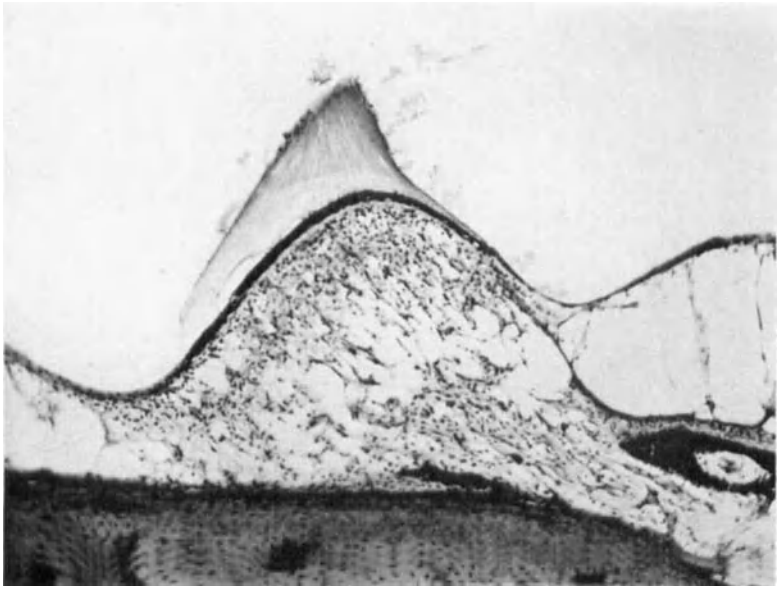

FIG. 4. Crista of horizontal canal of case of posterior sensory neuropathy. Severe degeneration of sensory epithelium and loss of nerve fibres. × 68.

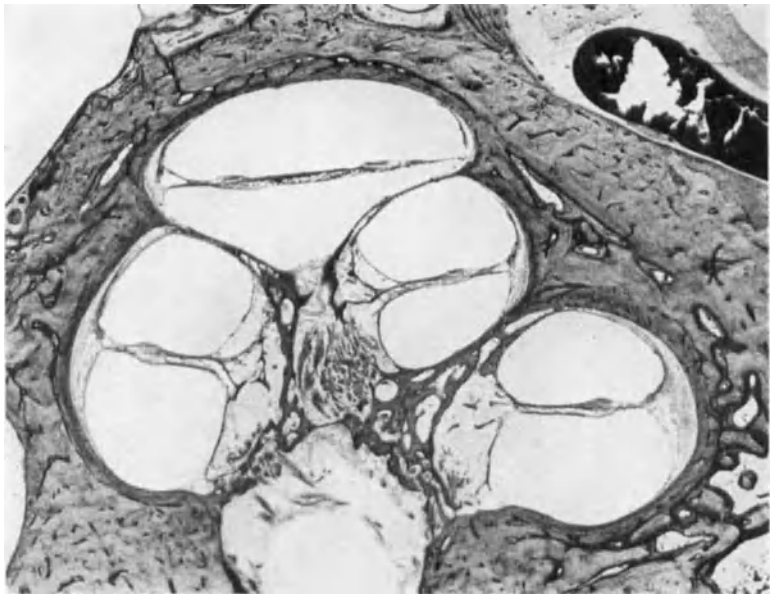

FIG. 5. Cochlea of case of Refsum's disease. Collapse of Reissner's membrane. Degeneration of stria vascularis, Corti's organ, the spiral ganglion and cochlear nerve fibres. × 14.

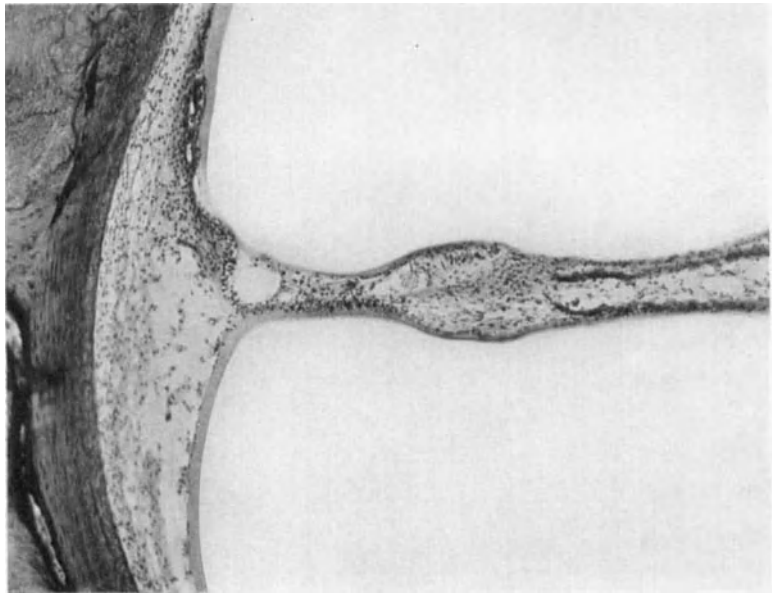

FIG. 6. Scala media of case of Refsum's disease. Degeneration of Corti's organ and stria vascularis. × 68.

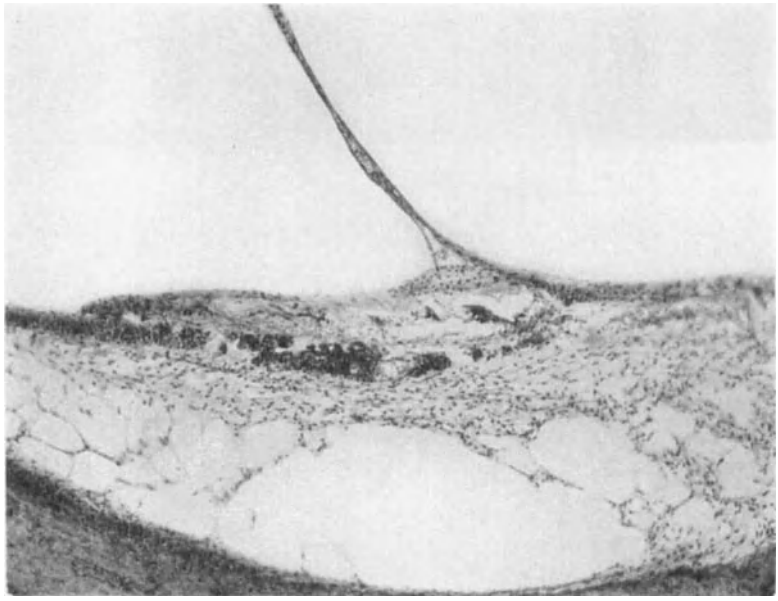

FIG. 7. Saccule of case of Refsum's disease. Partial collapse, with degeneration of sensory epithelium. × 68.

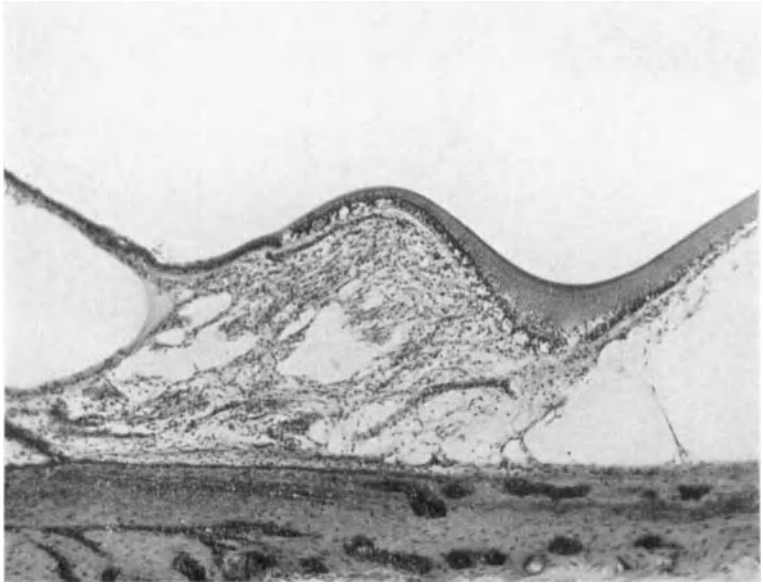

FIG. 8. Normal crista of horizontal canal of case of Refsum's disease. × 68.

istic feature being the formation around individual axons of concentrically arranged lamellae of connective tissue. Seen in cross-section these appear as the so-called "onion skin" formations. The condition therefore belongs to the group of diffuse peripheral polyneuropathies.

Our subject, a male and again a typical case, died in 1962 at the age of 38. His neurological condition was studied as an in-patient at Queen Square eight years earlier, in 1954.

Visual impairment had been present since childhood. Weakness of the legs had appeared at the age of 15 and deafness later still. The onset of the deafness was remarkably sudden and the patient is said to have awakened one morning quite deaf in both ears. The neurological findings were those of a severe and widespread peripheral neuritis with gross opacities in the eye media. The eighth nerve system was investigated by Sir Terence Cawthorne, who found normal tympana and complete deafness with normal caloric responses. There had been no complaint of vertigo. Post-mortem examination by Professor Blackwood revealed a gross diffuse thickening of the spinal nerves involving both the anterior and the posterior roots.

Histological examination of the temporal bones revealed normal tympana and labyrinth capsules. Within the membranous labyrinths however, widespread and severe changes had occurred. The changes were very similar in the two labyrinths, both in character and degree. Details of the changes in the left labyrinth are shown in Figs. 5–8.

In Fig. 5 is shown the cochlea. Reissner's membrane has collapsed, with obliteration of the scala media. The organ of Corti is disorganized throughout the cochlea, together with severe degeneration of the stria vascularis. Of the spiral ganglion cells and cochlear nerve fibres, only a few remain.

In Fig. 6 is shown the organ of Corti and stria vascularis. The cell mass of the organ of Corti has collapsed with retraction of the tectorial membrane into the internal sulcus. The nuclei of the limbus cells are still numerous and well preserved. The degenerate remnants of the stria contain some PAS-positive deposits. Both of the perilymph scalae are lined by a layer of amorphous PAS-positive material.

In Fig. 7 is shown the saccule. At one point its wall has collapsed, elsewhere it has ruptured. The sensory epithelium is grossly disorganized and contains aggregations of amorphous PAS-positive material.

In Fig. 8 is shown the crista of the horizontal canal. It shows no structural abnormality, with good preservation of the sensory epithelium and the sub-epithelial nerve fibres. The sense organs of the utricle and the vertical canals are also well preserved.

DISCUSSION

This completes the information which I have to offer. For me, at any rate, the otopathological findings have been surprising. Thus our knowledge of the neuropathology of the two conditions makes it clear that the peripheral nerves are the structures which are chiefly affected. This being so, I should have expected to find myself explaining the deafness in terms of a degeneration of the spiral ganglion and its associated nerve fibres. In fact, things have turned out otherwise. In the first of the two subjects, the case of sensory neuropathy, the spiral ganglion and cochlear nerve fibres are found to be quite well preserved, while in both subjects degeneration of Corti's organ has occurred, being very severe in degree and of unusual pattern. For instance, the extremely advanced changes in the limbus cells of the first subject must be very rare indeed. In the second subject, the case of Refsum's disease, the damage seems to be virtually confined to the cochlea and saccule with degeneration of their sense organs and collapse of their endolymphatic compartments—very much in the manner of the cochleo-saccular degeneration of Scheibe. It is tempting to consider whether we cannot explain the end-organ degeneration in these two subjects in terms of withdrawal of some nerve-conveyed trophic influence secondary to a primary degeneration of nerve fibres, but the findings do not favour this possibility. For instance, in the case of sensory neuropathy no trophic influence can have been withdrawn since there is no degeneration of the cochlear nerve fibres which would presumably convey it.

As an alternative it seems quite feasible to explain these inner ear changes in terms of gene action alone, if we may assume that each of the tissue components involved, the nerve fibres and cells, the end organs and the secretory elements of the stria vascularis, is independently subject to the otonoxic effect of the gene or genes concerned. If we can, then the resulting patterns of tissue damage could well be very complex and unusual.

Applying this to our case of sensory neuropathy we could say that gene action determines both the degeneration of the vestibular nerve and an independent degeneration of Corti's organ with especially severe involvement of the limbus cells.

In our case of Refsum's disease we find a different pattern of events. Here the otonoxic gene exerts an effect on the inner ear not unlike that responsible for the hereditary cochleo-saccular degeneration of Scheibe. An interesting feature of this effect, indicated by the mode of onset of the deafness, is that it seems to be exerted rather late in the course of the disease and with dramatic suddenness.

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DISCUSSION

Friedmann: Dr. Hallpike mentioned that he found PAS-positive material in his case of Refsum's disease, and it is of some interest that the heart is often involved in Refsum's syndrome (Gordon, N., and Hudson, R. E. B. [1959]. *Brain*, **82**, 41–55). I would like to draw your attention to a syndrome first described in Norway by A. Jervell and F. Lange-Nielsen ([1957]. *Am. Heart J.*, **54**, 59–68), a condition of congenital deafness with abnormal electrocardiograms. During the lifetime of these patients, repeated fainting attacks occur, eventually leading to death during such an attack. G. R. Fraser, P. Froggatt and T. N. James ([1964]. *Q. Jl Med.*, **33**, 361–385) have been studying congenital deafness in this country and have collected about 1,200 cases. Of these, nine were cases of this kind (which Fraser and Froggatt call "the cardio-auditory syndrome of Jervell and Lange-Nielsen"), and three of the nine children have now died. We have obtained the temporal bones and myocardium of these children.

The myocardium and heart innervation of two cases were examined by T. N. James in Detroit and showed in both cases some degeneration of the sinus node fibres and Purkinje fibres. The sinu-atrial node itself showed areas of abnormal fibrosis, infarction and haemorrhage. In each of the three cases we have examined we have seen lesions of the cochlea. The organ of Corti is extremely disorganized. Here and there one can just recognize a pillar standing. The tectorial membrane is also retracted. I have not paid too much attention to the limbus and am grateful to Dr. Hallpike for drawing attention to the possibility that the limbus may be upset and degenerated.

The principal finding is in the stria vascularis and although in parts it is obviously necrotic and degenerated, elsewhere there are large masses of granulation tissue containing deposits of PAS-positive material. This often extends into the vascular stria, where the deposits are often within expanded capillaries but may also lie on the spiral prominence and sometimes extend quite deeply into the region of the organ of Corti. One may see individual patches of PAS-positive material in the organ of Corti, the tectorial membrane and elsewhere. The region of the crista of the horizontal canal was in all three cases practically unrecognizable and contained huge masses of PAS-positive material. We hope to collect more evidence on this condition and do further histochemistry, but we are hampered by the lack of properly fixed temporal bone material from those few cases that we do obtain.

Smith: May I ask Dr. Hallpike and Professor Friedmann whether the vascular supply to the inner ear is normal in their cases? From their micrographs there seemed to be fewer blood vessels present, particularly in the spiral ligament.

Hallpike: We can always see a certain number of blood vessels, but it is difficult to make any quantitative estimation of the vascularization. Generally the disease is advanced by the time of death and the blood vessels are less prominent than in a normal subject, but we cannot be sure what they were like at the beginning of the disease.

Smith: Professor Friedmann, did you say that the PAS-positive material was inside the capillaries in the stria vascularis?

Friedmann: In the cases of cardio-auditory syndrome the material seemed to be localized in and around the distended vessels of the vascular stria. The material appeared to have a fibrinoid component, on staining with phosphotungstic acid-haematoxylin. All kinds of deposits have been described in this area in other conditions; for example they have been described as calcareous deposits in a case of toxoplasmosis by G. Kelemen ([1958]. *Archs Oto-lar., Chicago*, **68**, 547–567), but I feel that they were probably of the same kind as in our cases.

Eldred: Dr. Hallpike, is there good evidence that the peripheral motor fibres are in no way involved in posterior sensory neuropathy?

Hallpike: To the best of my knowledge there is no evidence that there is anything wrong with the motor system.

Friedmann: Dr. Hallpike mentioned the sudden onset of deafness, particularly in the case of Refsum's disease. Schuknecht and his team have emphasized that a sudden onset of deafness is often of viral origin (Schuknecht, H. F., Benitez, J., Beekhuis, J., Igarashi, M., Singleton, G., and Ruedi, L. [1962]. *Laryngoscope, St Louis*, **72**, 1142–1157). Is there any evidence for this in your cases?

Hallpike: We have seen other cases of Refsum's disease and it is interesting that the deafness increases in quite sudden steps. This does suggest labyrinthine end-organ disorder rather than a primary disorder of the nerve fibres, and it is interesting that this particular clinical feature is borne out by the histological changes. Although a viral affection might in some ways accord with the histological picture, the great frequency with which the inner ear seemed to be affected in Refsum's disease makes it likely to be of genetic rather than infective origin.

Professor Friedmann mentioned the poor state of fixation of what temporal bone material he has received. This is indeed one of the problems in establishing a scientific otology. It is certain however that we still do need "old-fashioned" low-power sections of the whole labyrinth before we can usefully go deeper into the histology.

Henriksson: In Sweden we have had a number of cases of sarcoidosis in which a slow loss of hearing was combined with a loss of vestibular function. It was sometimes possible to treat these patients effectively with cortisone preparations. Have you had any experience of such cases, Dr. Hallpike?

Hallpike: I have not met this condition.

Gardner: The thickening around the peripheral nerves in the case described by Dr. Hallpike resembles other not uncommon changes in peripheral nerves, particularly the peroneal nerves. Dyck and his co-workers at the Mayo Clinic

have now collected a number of kinship groups with a variety of peripheral nerve disorders, including significant decreases in conduction rate (Dyck, P. J., Lambert, E. H., and Mülder, D. W. [1963]. *Neurology, Minneap.*, **13**, 1–11; Dyck, P. J., Kennel, A. J., Magal, I. V., and Kraybill, E. N. [1965]. *Proc. Staff Meet. Mayo Clin.*, **40**, 685–694; Dyck, P. J., Winkelmann, R. K., and Bolton, C. F. [1966]. *Neurology, Minneap.*, **16**, 10–17).

These investigators are looking for common factors in these disorders, including connective tissue and ground substance metabolism. The primary disorder in Refsum's disease may also be in non-nervous tissue. It is interesting, in connexion with Dr. Hallpike's suggestion that gene action may explain his two cases, that Dyck's patients fall into kinship groups.

Friedmann: Fraser and his co-workers show a table of the genetic background of some of the nine cases of the cardio-auditory syndrome. The data are consistent with the hypothesis of recessive inheritance of this type of "profound childhood deafness", as Fraser calls it (Fraser, G. R., Froggatt, P., and Murphy, T. [1964]. *Ann. hum. Genet.*, **28**, 133–157). So I suppose that only a geneticist could really decide what is the basic mechanism.

Bosher: There are two points about these hereditary conditions that I would like to stress. First of all, they are mainly due to the effects of single genes, and according to modern genetic thought a single gene affects one enzyme—not even one enzyme system, but a single enzyme. Therefore, diverse manifestations in any one disease must be due to some common enzymic defect and consequent common metabolic derangement. If, therefore, one can determine, for example, the cause of the neuronal damage, it will have the same basis as the cause of the damage in the ear. If we approach these diseases in this way we may discover how the genes produce their effects and such diseases may then be amenable to therapeutic attack.

In this respect it is significant that the more thorough the search, the more commonly are metabolic defects found. For example, in Refsum's disease, a disorder of fatty acid metabolism has been reported (Richterich, R., Kahlke, W., Mechelen, P. van, and Rossi, E. [1963]. *Klin. Wschr.*, **41**, 800–801) while in Jervell and Lange-Nielsen's syndrome there is evidence of a disorder of glycogen metabolism in the Purkinje fibres (Fraser, G. R., Froggatt, P., and James, T. N. [1964]. *Q. Jl Med.*, **33**, 361–385). Professor Gardner mentioned a defect of connective tissue metabolism; there is a form of hereditary deafness, Alport's syndrome, in which proline metabolism is abnormal (Fuhrmann, W. [1963]. *Dt. med. Wschr.*, **88**, 525–532), this being, I believe, indicative of some connective tissue disorder.

Thus we have the situation in which a deficiency in one enzyme has multiple effects and we should therefore direct our attention to the analysis of the nature of the underlying metabolic defect in the most readily accessible organ.

This brings me to my second point. A problem in a number of these diseases is that although the condition may be primarily caused by a dominant gene, not

everyone who carries the gene develops the disease, a phenomenon that we term "incomplete penetrance". This can be understood if it is realized that the gene does not produce the damage that one sees; rather, it produces a susceptibility to some environmental situation and only when this situation is encountered does the bearer of the gene develop pathological changes. A clear example of this is a condition in which there is a deficiency of the enzyme pseudo-cholinesterase. This has been shown to be hereditary in nature, usually being due to a single gene (Harris, H., Whittaker, M., Lehmann, H., and Silk, E. [1960]. *Acta genet. Statist. med.*, **10**, 1–16). The enzyme normally has no discernible action in the body and those who lack it appear quite normal until they are given suxamethonium by an anaesthetist, when they develop a prolonged apnoea because they cannot detoxicate the drug. It is only in this particular environmental situation that the disease becomes manifest. Thus it appears that although the genetic defect is primary it is not sufficient in itself to cause the disease, and probably for every genetic condition there is some coexistent environmental factor which actually initiates the pathological changes. Through exploration of such combinations of metabolic defect and environmental factor we can hope not only to explain some of these hereditary disorders, but also to learn something of the physiology of the mechanisms concerned.

Lowenstein: Would you extend your understanding of "environment" to the internal physiological environment, during maturation, growth and ageing of the individual?

Bosher: The internal environment is indeed very important, for the changes occurring in the environment of the cells within the body are far more important than external changes.

Wersäll: Dr. Hallpike did not refer to his studies of hereditary deafness in white cats, but we should not forget the interesting parallels that can be drawn between experimental animal situations and inherited deafness in human beings. David Hilding has gained a lot of insight from the Shaker I mice and we ourselves are working on abnormal locomotion in the waltzing guinea pig. In particular, experience gained on those experimental animals strongly supports the idea that human diseases such as Dr. Hallpike discussed have a genetic basis.

Lowenstein: Certainly, in view of what one sees of rather localized hereditary lesions in animals, I would favour Dr. Hallpike's explanation of coincident independent gene action on the various tissue components involved in each of his two cases. For example, in animals we see lesions confined to the sacculus and cochlea which leave the rest of the vestibular organ absolutely intact. On the other hand one finds, even within the vestibular organ, localized hereditary lesions in experimental animals which make it plausible as a theory to explain the histological changes you find in these patients.

Wersäll: One sometimes even suspects not simply that there are enzyme deficiencies underlying these abnormal phenotypes but that some autoimmune reaction is involved, which accounts for the fact that, for example, in the cat,

mouse or guinea pig the organ of Corti develops in what seems to be the normal way, and functions for a few days or weeks, and then suddenly breaks down. Would you consider such changes as primarily vascular or primarily in the hair cells?

Hallpike: I cannot say. In hereditary deafness in the white cats the striking thing was what we called the "escape" phenomenon. A significant number of these animals managed to escape the condition, in one ear or in both. This we find extremely interesting, because if we knew how a few individuals escape, we might be able to arrange escape for others!

Lowenstein: This is presumably where beneficial interference with the internal environment comes in, if one can detect the condition early enough.

Lundquist: I believe that in most of the animal studies made, including those of the deaf white cats by Dr. Bosher and Dr. Hallpike (Bosher, S. K., and Hallpike, C. S. [1965]. *Proc. R. Soc. B*, **162,** 147–170), and of the Dalmatian dog by Lurie and by Ruben and his colleagues (Lurie, M. H. [1948]. *Laryngoscope, St Louis*, **58,** 279–287; Hudson, W. R., Durham, N. C., and Ruben, R. J. [1962]. *Archs Oto-lar.*, **75,** 213–219), a very severe degeneration of the stria vascularis and the organ of Corti and to a lesser extent of the spiral ganglion cells has been found. However, in Ruben's investigation the spiral ganglion cells were found to be partly normal, which indicates that perhaps these changes start in the region of the scala media, either in the stria vascularis or in the hair cell region. We are studying the deaf Dalmatian dog also and have found a vast degeneration of the hair cell and stria region and only a partial degeneration of the spiral ganglion cells.

Hallpike: I agree with you that in cats (and probably in Dalmatian dogs too—we have examined a number of these) the primary change is in the scala media. Changes in the spiral ganglion are fairly late.

I recall studying, in collaboration with Professor Hans Grüneberg, the Shaker I mouse strain. In our publication (Grüneberg, H., Hallpike, C. S., and Ledoux, A. [1940]. *Proc. R. Soc. B*, **129,** 154–173) we were able to give a detailed account of the development of the inner ear changes. The degenerative process was slower than that in white cats; the organ of Corti looks normal at first and up to 12 days or so; thereafter, degeneration started. Because the changes developed more slowly than in the cat they were easier to study. The primary lesion appeared to be in the stria vascularis; then the end organ becomes involved and later the depopulation of the spiral ganglion began.

Lundquist: In the Shaker I mice the development of the full condition is complete by about eight days after birth. K. Kikuchi and D. A. Hilding ([1965]. *Acta oto-lar.*, **60,** 287–303) have found the first signs of degeneration at about the eighth or ninth day and the Preyer reflex which usually develops at about the tenth day is delayed; after about 20 days there is total degeneration of the organ of Corti. An interesting finding was the complete absence of efferent nerve fibres going to the hair cells. This was an electron microscopic study.

Friedmann: Dr. Wersäll mentioned immunology. We can now establish

whether or not a congenitally deaf child has been infected with rubella virus in the uterus. This also links up with Dr. Bosher's comment on the susceptibility of the individual. Only 15 per cent of babies born to mothers who had contracted maternal rubella in the first trimester suffer any damage to the ear, let alone complete deafness. We recently examined the foetus of a mother who had a "therapeutic" abortion; the internal ear of the foetus was perfectly normal, both cochlea and labyrinth. So I would plead that in such cases we try to establish, both prior to and at post-mortem, the existence of rubella infection in the foetus, by isolating the virus from the endolymph or perilymph.

We have here a definite environmental causal agent which we can identify; it should narrow the wide field of congenital deafness due to unknown causes. We have studied sections of the inner ear of two babies who survived to three and five days after birth, following maternal rubella. We found peculiar granulation tissue formations in the vascular stria and concluded that the vascular stria seemed to have been still actively involved in some pathological process, and we speculated on whether the virus could act upon the fully developed organ of Corti. This is an added complication.

Another example where the internal environment may be significant is in Herpes zoster (shingles) which is more common in the middle-aged and elderly person than in the young. It may be suggested that arteriosclerotic changes in the vessels activate the latent varicella virus (which is identical with the zoster virus) and so lead to shingles.

Monnier: In connexion with these congenital diseases involving the inner ear, it is interesting that the cochlea and sacculus are closely associated and yet we know almost nothing of the functions of the sacculus. Magnus attributed to it some role in eliciting vertical eye movements and other authors have said that it is only sensitive to low-frequency vibration. Is there any new information on its function?

Lowenstein: The detailed attribution to the sacculus of certain vestibular reflexes by Magnus was of course withdrawn during his lifetime, after the work of C. Versteegh ([1927]. *Acta oto-lar.*, **11**, 393–408), but the whole story has never been clear-cut. If one were to say that the association by the inferior branch of the eighth nerve between cochlea and sacculus points in a functional direction and that, therefore, the sacculus may have an auditory rather than an equilibrium function, one must not forget that on the macula of the sacculus lies a continuous otolith. One could therefore have both functions, as we showed in elasmobranchs, where the anterior two-thirds of the sacculus macula are sensitive to vibration and elicit no vestibular reactions to tilting, whereas the posterior third is completely "deaf" but elicits clear-cut equilibrium responses (Lowenstein, O., and Roberts, T. D. M. [1951]. *J. Physiol., Lond.*, **114**, 471–489). So this is not simple and one cannot point to one sensory ending and say that it must have one function only. Potentially these are all acceleration receptors; which accelerations they receive may depend on their topographical arrangement in the ear.

Myotatic, Kinesthetic and Vestibular Mechanisms
Edited by A.V. S. de Reuck and Julie Knight

DISTURBANCE OF WATER AND ELECTROLYTE BALANCE: SOME FURTHER REFLECTIONS ON ITS POSSIBLE ROLE IN THE CAUSATION OF MÉNIÈRE'S DISEASE

S. K. BOSHER

Ferens Institute of Otolaryngology, Middlesex Hospital, London

MÉNIÈRE's striking clinical description of the disease which commemorates him was soon followed by the hypothesis that it might arise as the result of some primary disorder of the labyrinthine fluids. Knapp in 1871, directing attention to Goltz's (1870) concept that the nerve terminations within the semicircular canals are excited by pressure or tension, suggested that increase in fluid tension within the inner ear could, in some cases, be the cause of Ménière's disease, which in this way would resemble glaucoma of the eye and so be amenable to surgical drainage. However, he cautiously commented that until such increase in pressure could be demonstrated, too much should not be made of this analogy.

Subsequent workers have nevertheless been greatly attracted by this concept, which led Mygind (1926) to suggest that some disorder of water metabolism might play a part in the pathogenesis of the condition. For the first detailed clinical study of this aspect of the disease we are indebted to his co-worker Dederding (1929), whose results demonstrated not only abnormal retention of an ingested water load in patients with Ménière's disease, but also aggravation of their cochlear and vestibular disabilities during the procedure. Furthermore, she found that these patients were improved when the excess water was eliminated by the pharmacological induction of either excess sweating or polyuria.

However, 5 years later Furstenberg, Lashmet and Lathrop (1934) were unable to relate the acute vertiginous attacks in their subjects to the body water content, but were able to relate them to an increase in body sodium. They also reported that a low-salt diet had, in 14 patients, abolished these acute episodes.

As a result of such studies, dietary restriction of salt and water was widely adopted in the treatment of the disease and many clinicians considered it to

be of value. This subsequently led Perlman, Goldinger and Cales (1953) to undertake a comprehensive and careful re-investigation of the effect of these measures in 15 patients with active Ménière's disease. Their findings failed to demonstrate any consistent effect upon these patients of either water depletion and loading or salt depletion and loading, the latter being induced by administration of de-oxycorticosterone acetate (DOCA).

These findings were subsequently confirmed in part by Naftalin and Harrison (1958), who were unable to produce any increase in the frequency or intensity of the acute episodes by DOCA-induced retention of sodium. In 1961, however, these authors reported the results of another study using aldosterone instead of DOCA, as the latter, being long-acting, interfered with the normal cycle of sodium homoeostasis. They found that when extra salt was given (without aldosterone) typical vertiginous attacks occurred in their patients, in an early and labile stage of the disease, in that phase of the normal homoeostatic cycle when sodium diuresis took place, and argued from this that the main factor responsible was a decrease in aldosterone secretion. Dietary salt restriction, they concluded, might thus produce clinical improvement by maintaining a high level of aldosterone secretion.

More recently Naftalin and Harrison (1966) have suggested that fluctuation of body electrolytes and so of aldosterone secretion might be a more important factor and, if so, could probably best be avoided by the administration, in divided doses, of up to 3 g. of both sodium and potassium chloride daily, a method of treatment which had produced good results in their patients.

However, at the present time, although many clinicians no longer advocate dietary measures, in the experience of many others restriction of salt and water intake is still of value in the treatment of Ménière's disease. Certainly it has been my experience at the National Hospital, Queen Square and elsewhere that while in many patients it is difficult to demonstrate any improvement specifically due to such dietary restriction, in a few the results are clear and worth while.

It would therefore seem that despite the rather inconclusive and contradictory nature of the clinical evidence, the possibility that in some patients at least, alterations in body salt and water might play a part in the pathogenesis of the acute attacks in Ménière's disease, merits further attention. For this reason consideration of the effects of dietary changes upon the body fluids appears worth while and I shall therefore discuss, firstly, the effects of dietary restriction of salt and water upon the total body content of these substances and, secondly, the alterations in body fluid and

electrolytes which follow ingestion of relatively small quantities of salt and water.

THE EFFECT OF DIETARY RESTRICTION OF SALT AND WATER

In an adult weighing 70 kg. (11 stone) the total unavoidable daily fluid loss under comfortable environmental conditions is of the order of 1,500 ml. while, in an average diet, the water contained in solid food and that released by oxidation of food substances together provide about 1,100 ml. of fluid daily (Marriott, 1950). Thus the additional ingestion of only some 400 ml. (approximately $\frac{2}{3}$ pint) of fluid is needed each day to maintain the water content of the body unchanged, provided renal function is normal. As it is not usual to advocate fluid restriction of this degree in the treatment of patients with Ménière's disease, little change in their total body water content would seem likely to occur as a result of the restriction normally recommended.

Furthermore, it would appear that much the same can be said of the dietary salt restriction. Benedict published in 1915 his famous study of Levanzin, who existed solely on distilled water for 31 days. During the second and third weeks of this period his total renal excretion of sodium was only 1·48 g.—that is, the unavoidable urinary sodium loss averaged 106 mg. a day. Now, under comfortable environmental conditions, the total daily extra-renal loss of sodium amounts to about 150–250 mg., so the minimum daily dietary intake necessary to preserve normal balance in average circumstances would seem to be of the order of 250–350 mg. This view is supported by the demonstration that in a normal adult subject a daily intake of 300 mg. of sodium produced no instability in sodium balance, after a slight initial reduction in body sodium content (Newburgh and Leaf, 1950). Since a diet from which all foods with a high salt content are eliminated and in which all butter, bread, biscuits and cereals are salt-free, milk-intake is limited and no salt is added either in cooking or at table, still provides a daily sodium intake of 500 mg. (Davidson and Passmore, 1963), it is evident that even such extreme dietary restriction of sodium in patients with Ménière's disease is unlikely to result in any appreciable permanent reduction in total body salt content, provided adverse environmental conditions producing excess sweating are avoided.

This conclusion that the limitation of salt and water intake usually practised in Ménière's disease does not produce significant long-term depletion of the total body content of fluid and electrolytes is perhaps not surprising, for if such depletion did occur these patients would, sooner or later, develop severe and potentially fatal complications. Hence any

improvement resulting from these dietary measures must, almost certainly, be due to more complex and subtle changes.

BODY FLUID CHANGES FOLLOWING INGESTION OF SALT AND WATER

In order to determine the nature of the mechanism whereby dietary measures might produce an improvement in Ménière's disease it is necessary to consider what alterations in the body fluids are produced by ingestion of water and salt.

Here much valuable information has been provided by the careful and detailed studies of Baldes and Smirk (1934), who were able to show, with others, that relatively small alterations in water intake normally resulted

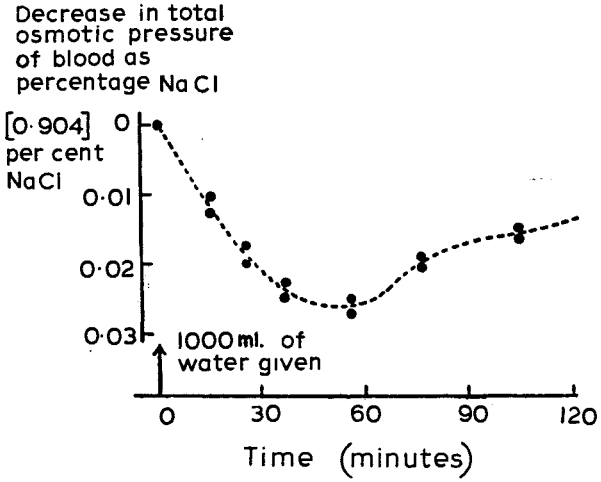


FIG. 1. Changes in total osmotic pressure of the blood resulting from the ingestion of one litre of water in an adult human subject. (From Baldes and Smirk, 1934, by permission of the Editorial Board of *The Journal of Physiology*.)

in changes in blood osmolality. They found, for example, that the ingestion of one litre of water in adult human subjects (weight range: 64–75 kg.) produced an immediate and progressive fall in the total osmotic pressure of the blood which, as shown in Fig. 1, on average proceeded at first rapidly for 35 min. and then more slowly for a further 13 min., reaching a maximum of $1\frac{1}{2}$–$2\frac{3}{4}$ per cent. The total osmotic pressure slowly returned to its previous level in the succeeding 3–5 hr. There was also a corresponding temporary increase in the total body water content.

Thus it seems clear that ingestion of even a relatively moderate volume of fluid is followed by compensatory changes requiring some hours to restore the body fluids to their original state.

The compensatory changes following the ingestion of salt are still more complex and are illustrated by one of Gamble's classical studies (Gamble, 1951), in which he observed the adjustments in sodium balance in a normal adult following the daily addition of 5 g. of sodium chloride to a constant diet. Such an increase is relatively small and is equivalent to that occurring when a patient abandons the strict diet outlined above in favour of one merely avoiding excessive salt intake. Gamble calculated the daily cation

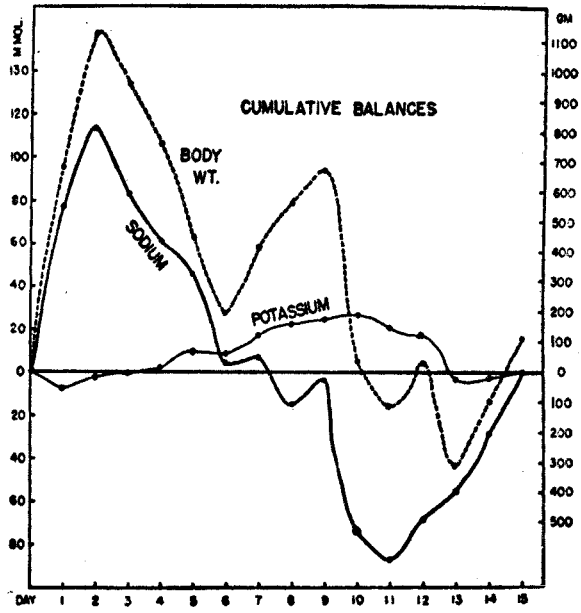


FIG. 2. Changes in body weight and sodium and potassium cumulative balances in a human subject weighing 75 kg., following the addition of 5 g. of salt daily to a constant diet. (From Gamble, 1951, by permission of Stanford University Press.)

balances in his subject by comparing the urinary cation excretion each day with the daily average during a preliminary observation period, a method avoiding errors due to unknown changes in extra-renal loss, and his results, plotted as cumulative balances, are shown in Fig. 2. It will be seen that this small additional salt load produced at first accumulation, then, as so often happens in physiological adjustments, over-shooting—so-called sodium diuresis—and finally reparative retention. Although the total body sodium content did eventually return to its previous level no less than 15 days were necessary for the compensatory changes to be effective, an indication of the

surprisingly slow rate of operation of the regulatory mechanisms governing the extracellular electrolytes.

During the same period alterations in total body water content, as indicated by the changes in body weight, roughly paralleled those in the total sodium content, but it is self-evident that quite large discrepancies occurred and, furthermore, that at times the two curves either diverged (e.g. days 7 and 8), on the one hand, or converged, on the other (e.g. days 12 and 13),

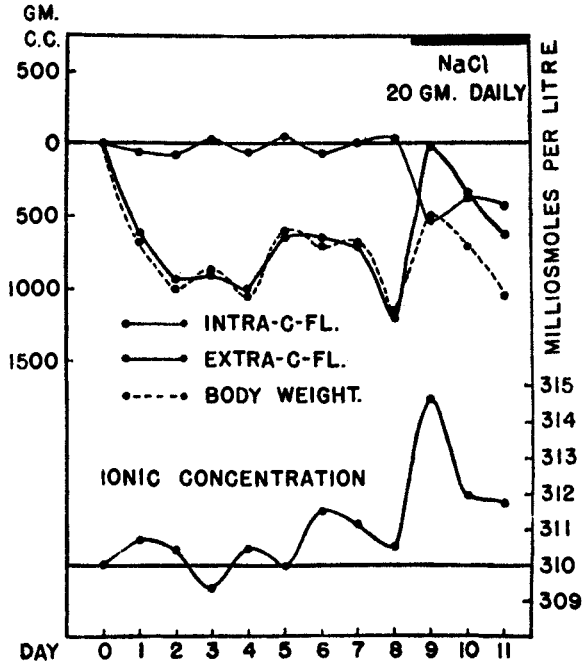


FIG. 3. Changes in body fluid volume and ionic concentration in a human subject while on a constant diet and following the daily addition of 20 g. of salt. (From Gamble, 1949, by permission of Harvard University Press.)

revealing that changes in salt concentration must also have taken place in spite of the compensatory reactions. Unfortunately variations in body weight alone do not provide sufficient information to estimate such changes accurately, a point of some importance which will be discussed later.

Attention has principally been directed in these studies to alterations in body sodium and hence, as this is largely though not exclusively extracellular, the oscillating fluctuations in fluid volume and composition described have affected mainly the extracellular fluid. It is thus evident that

the ingestion of water and/or salt leads to complex compensatory changes requiring, for the restoration of the normal balance, some hours in the case of extracellular fluid osmolality and several days in the case of extracellular fluid volume and salt content.

In addition, these changes in the extracellular fluid lead in turn to complex alterations in the intracellular fluid compartment, so further complicating the effects of such dietary ingestion. In this respect the increase in renal potassium excretion (Fig. 2), a feature recognized almost 100 years ago by Bunge (1873), is of the highest significance. This increase, it is now known, is due to loss of potassium from the cells, the kidneys having no ability to conserve the potassium content of the body. In turn it is reasonable to expect that an accompanying volume of water will also be transferred from the intracellular to the extracellular fluid, but this reciprocal volume change is modified by another important effect of the increased extracellular sodium, namely the passage of sodium into the cell, the so-called sodium shift (Gamble, 1951).

Nevertheless, considerable movement of water between extracellular and intracellular fluids does occur, as is shown by another of Gamble's beautiful investigations (Gamble, 1949). In this a normal adult, after a preliminary observation period, was given a rather large daily dietary addition of salt, namely 20 g. As shown in Fig. 3, a marked increase in extracellular fluid volume occurred and it should be noted that although this was partly due to dietary water retention, as shown by the increase in body weight, approximately half of the increase resulted from loss of water from the cells, as shown by the decrease in intracellular fluid volume, an observation of much significance. It is this reciprocal interrelationship between the two main fluid compartments which renders body weight determinations alone an inaccurate indicator of fluid volume changes.

Another significant feature, which is well shown in Fig. 3, was the inability of the compensatory measures completely to prevent a rise in the ionic concentration and hence osmolality of the body fluids, although the rise was, of course, minimized by these measures. The ionic concentration values obtained in this study apply to the extracellular fluid but it is probable that similar, though possibly less severe, changes occur in the intracellular fluid. In this respect it is of interest that evidence has been adduced suggesting that changes occur in the organic constituents of the cell which, by altering the number of osmotically active intracellular particles, constitute a protective mechanism reducing the changes in cell volume that would otherwise result from changes in extracellular fluid osmolality (McDowell, Wolf and Steer, 1955).

Finally, although consideration in general of the detailed mode of operation of these various mechanisms, which are as yet not completely understood, does not seem fruitful, attention must be drawn to one of the effects of aldosterone, a hormone concerned with the regulation of extracellular fluid volume. Wrong and his co-workers at the Postgraduate Medical School (Richards *et al.*, 1966), in confirming and extending previous studies, have shown that this hormone *in vitro* produced a significant transfer of sodium from the intracellular to the extracellular fluid in undifferentiated cells. It is of interest that no concomitant change in either intracellular potassium or water content could be detected. Hence, it seems reasonable to suppose that the intracellular composition may also be directly modified *in vivo* by aldosterone and possibly by other hormones concerned in fluid regulation.

Thus, in summary, it is evident that the ingestion of salt and/or water produces not only alterations in the volume and composition of the extracellular fluid extending, in some circumstances, over several days, but also complex intracellular changes leading in turn to variations in both cell volume and composition. In the examples used to illustrate the nature of these changes in both the cells and their environment, appropriate additions to the subjects' usual diet were made. However, the ingestion of salt and water is normally sporadic and often independent one of the other, a fact resulting unavoidably from our mode of life, and this sporadic intake in itself will therefore result in continuous, irregular fluctuations in the volume and composition of both the extracellular and intracellular fluids of a similar nature to those outlined above, because of the considerable time-intervals required for compensatory readjustment. These fluctuations, as stressed by Gamble (1949) and others, are a normal feature of the regulation of the body fluids and are relatively large in relation to the dietary intake. They are well illustrated in Fig 3, where the irregular oscillations in intracellular and extracellular fluid volumes and ionic concentration taking place even when the subject is on a fixed, unvarying diet can be clearly seen during the preliminary observation period. Indeed, Gamble (1951) has humorously likened these oscillating peregrinations to the ebb and flow of an extracellular fluid tide.

Hence, it would seem highly probable that one of the essential functions of the inner ear homoeostatic mechanisms is to maintain the constancy of the endolymph despite the continual irregular fluctuations in the state of the body fluids and the associated complex intracellular changes. Should the inner ear mechanisms be impaired, it is conceivable that such general body changes would then constitute a potential hazard, since by producing

alterations in the constitution of the endolymph they might initiate some pathological process. It is in this way that the changes resulting from the ingestion of salt and water appear most likely to precipitate the acute vertiginous attacks in Ménière's disease.

Direct supporting evidence of the possible deleterious effects of body fluid changes upon the inner ear is hard to come by. For this reason the results of two recent investigations undertaken in association with Dr. C. S. Hallpike are of interest, because in both instances cochlear degeneration appears to have been initiated by aberrations in water and electrolyte homoeostasis.

PATHOGENESIS OF COCHLEAR DEGENERATION IN THE DEAF WHITE CAT

A full account of the first investigation, an extensive histological study of the labyrinthine degeneration of the deaf white cat, will be found in another publication (Bosher and Hallpike, 1965). The results are of much interest for, besides confirming that the condition was due to a single dominant gene and that the deafness, which occurred in only 80 per cent of the white animals, was due to cochleo-saccular degeneration of the Scheibe type, we demonstrated that the pathological changes did not make their appearance until about the fifth day after birth, at a stage of cochlear development when Corti's organ became dependent for the first time solely upon the inner ear fluids for its nutrition, the nutritive supply previously being largely a direct one via the vas spirale.

One finding of great importance was that even in normal animals both the stria vascularis and the external spiral sulcus, two structures which undoubtedly play a vital part in the elaboration of the endolymph, were not fully developed morphologically at this stage. It seems reasonable to argue that this incomplete anatomical differentiation must be associated with functional immaturity and that as a result of this immaturity the endolymphatic system would normally be severely handicapped in dealing with any excessive demands imposed upon it during the neonatal period. The stability of the inner ear fluids would thus be seriously threatened at this time both by congenital lesions of the inner ear mechanism and by generalized body changes.

Consequently, it seems highly significant that investigation of the kidney immediately after birth in mammals, including cats, has revealed both incomplete anatomical development and marked functional immaturity in practically all aspects of its activity. This renal inadequacy of the newborn has been emphasized by McCance (1964) who, with his co-workers, has so clearly demonstrated that fluid and electrolyte stability in the neonatal

period is largely dependent upon the utilization in tissue growth of almost all the dietary constituents, a mechanism which would appear incapable of either quick or accurate adjustments. McCance also stresses that the control of extracellular fluid volume and composition is demonstrably less exact during the first days after birth than in adult life, and although it is self-evident that this imperfect control does not usually result in any morbid manifestation, evidence is accumulating that greater alterations in

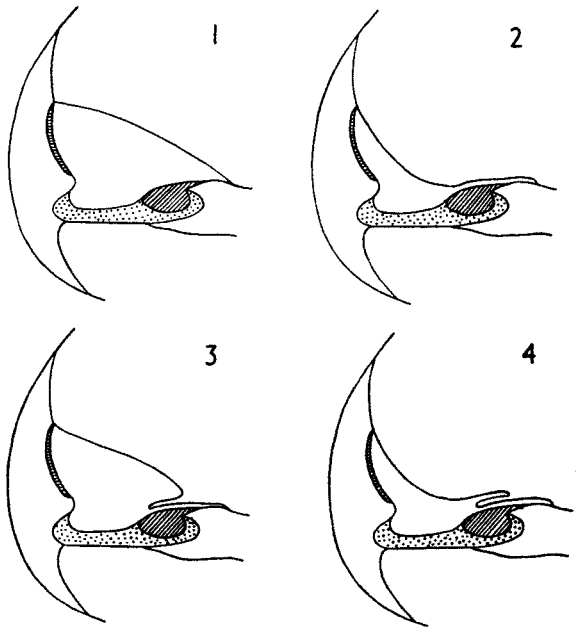


FIG. 4. Diagrammatic representation of the volume oscillations of the endolymph occurring during the cochlear degeneration of the deaf white cat, showing the folding of Reissner's membrane upon the limbus. (By permission of the Royal Society.)

the body fluids normally occur in the neonatal period than in later life. Thus Gautier (1964) has shown that hydropenia and hyper-osmolality usually develop in newborn infants, there being, on average, a rise of 3½ per cent in blood osmolality at 12 and 48 hr. after birth. As well as these relatively prolonged alterations in body fluid it also seems likely that the more transient fluctuating changes described already in adults will be greatly exaggerated during the first few weeks of extra-uterine life.

In this connotation, another feature of the cochlear degeneration in the deaf white cat which was of interest was the evidence of oscillations in the

volume of the endolymph. Sometimes distension of Reissner's membrane was present but at other times, and always in the later stages, there was collapse, and systematic study provided interesting evidence of an alternation between these phases. A reconstruction of the process, based upon the findings in a number of animals, is presented in diagrammatic form in Fig. 4, where it will be seen that one result of these oscillations in volume was the folding of Reissner's membrane upon the limbus. This folding is clearly visible in the two views of Corti's organ in a 43-day-old cat shown in Fig. 5.

The results of this investigation suggest that the cochlear degeneration in the deaf white cat is due to the inability of the immature inner-ear fluid-regulating mechanisms, hampered by some congenital hereditary enzymic defect, to maintain adequately the special constitution of the endolymph, and hence the nutrition of Corti's organ, in the presence of the relatively gross changes in the extracellular fluid occurring during the neonatal period. Furthermore it appeared that these changes, when severe, might alone be capable of inducing cochlear degeneration in genetically normal individuals.

PERCEPTIVE DEAFNESS COMPLICATING RENAL FAILURE TREATED BY HAEMODIALYSIS

The second investigation of interest is a clinico-pathological study of a case of sudden perceptive deafness apparently precipitated by excessive water ingestion, a full account of which will be found elsewhere (Ransome *et al.*, 1966).

The patient, a 32-year-old woman, presented in February 1962 with terminal renal failure due to chronic glomerulo-nephritis which was treated, with good effect, by periodic haemodialysis. In August 1962, while at home, she suddenly developed severe bilateral tinnitus and deafness associated with a slight sensation of imbalance, 11 days after her 13th haemodialysis. Three days later, at the patient's next visit to hospital, it was discovered that she had ignored instructions to restrict salt and fluid intake and investigation revealed a gain in body weight of 21 lb. (9·5 kg.) since her previous haemodialysis, which was considered to be entirely due to an increase in the volume of the body fluid. Furthermore, this increase in body fluid was approximately iso-osmotic and the serum sodium and potassium levels were within normal limits. There was no hypertension, no evidence of water intoxication and no significant deterioration in her general medical condition.

Despite an immediate 10-hour haemodialysis there was no improvement

in either the tinnitus or the deafness, which a pure-tone audiogram subsequently revealed to be perceptive in nature, the hearing being severely affected on each side for all frequencies within the range 125–8,000 cyc./sec., as shown in Fig. 6. In addition, there was complete abolition of the caloric responses on each side. Apart from further slight deterioration in the hearing, the patient's aural condition subsequently remained unchanged.

After her death from an unexpected sub-arachnoid haemorrhage in March 1963, seven months after the onset of the deafness, a detailed histological examination of the temporal bones was made. This revealed that

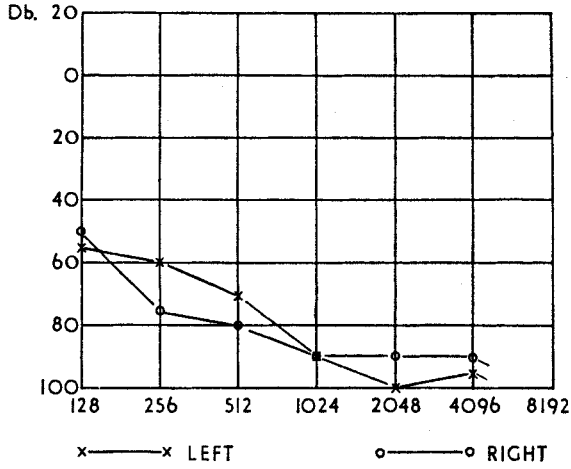
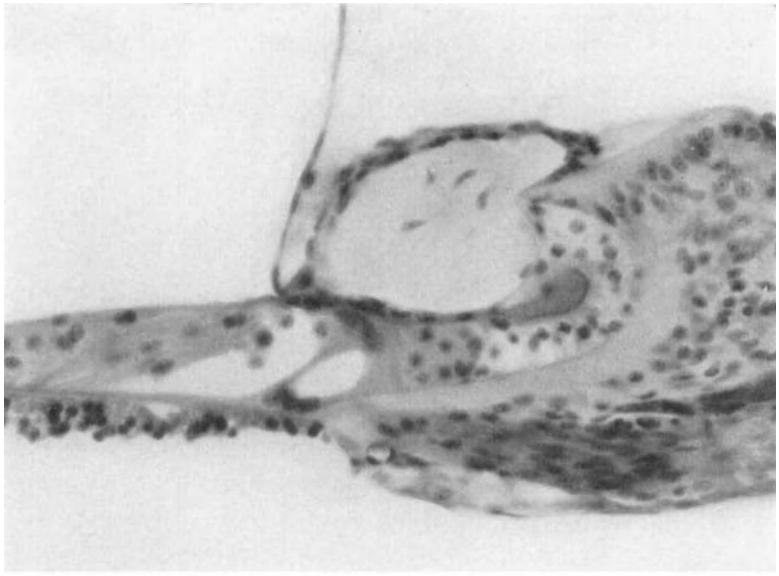


FIG. 6. Pure-tone audiogram showing the severe deafness following excessive fluid ingestion during the course of renal failure treated by periodic haemodialysis. (By permission of the Editor of *The Journal of Laryngology and Otology*.)

the pathological changes in the temporal bones were confined to the membranous labyrinth, preponderantly affecting the cochleae.

Here the scalae mediae presented no marked alterations in their dimensions, although that in the left cochlea was slightly distended while on the right there was slight collapse, most marked in the basal half-turn. In both cochleae, however, severe widespread degeneration of Corti's organs was present, in the basal coils there being only some shrunken, ill-differentiated cell masses, although at the apex the remainder of the inner rods of Corti could still be distinguished, as shown in Fig. 7. There were also slight degenerative changes apparent in the cells of the spiral ganglia.



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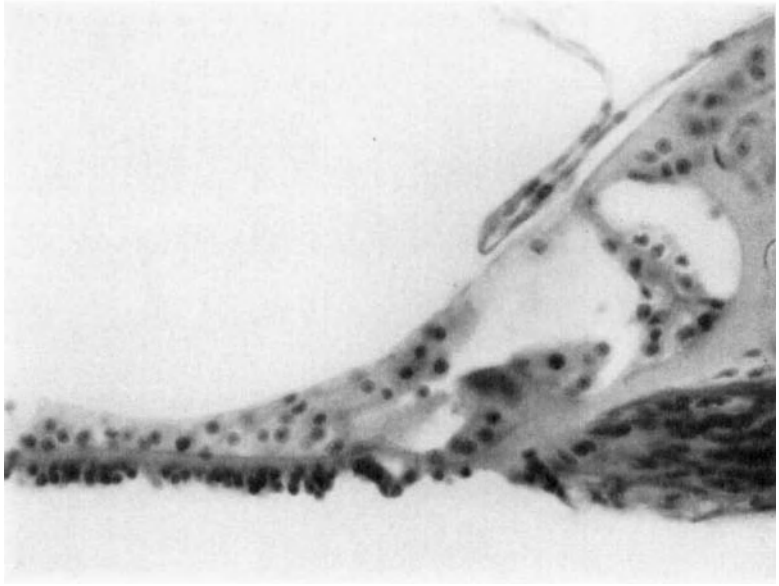

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FIG. 5. Organ of Corti in a 43-day-old deaf white cat. (*a*) Middle turn, (*b*) basal turn, showing the folding in Reissner's membrane (cf. Fig. 4). × 340. (By permission of the Royal Society.)

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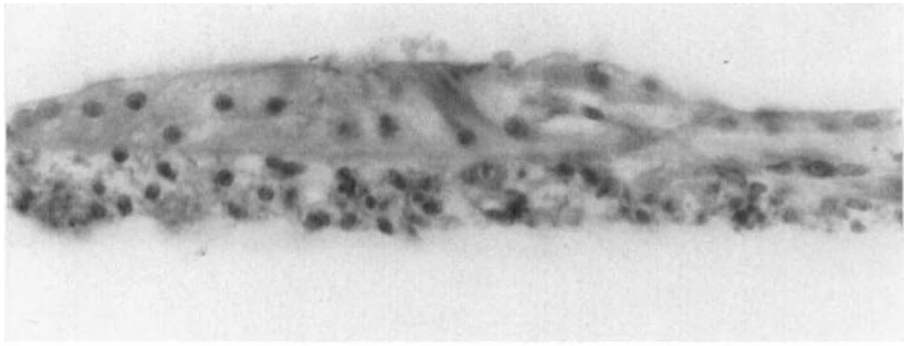

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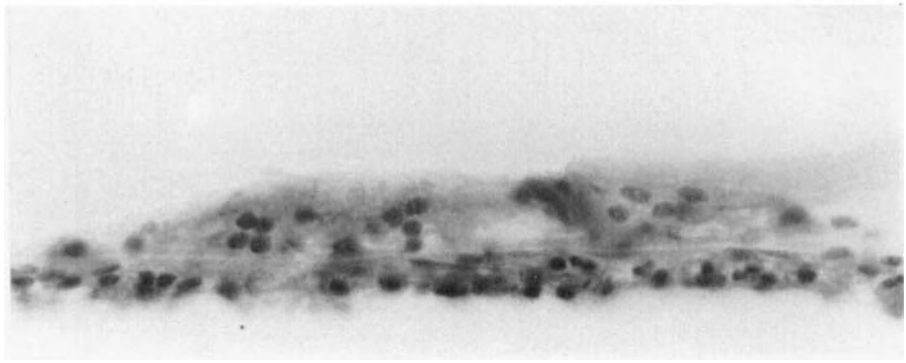
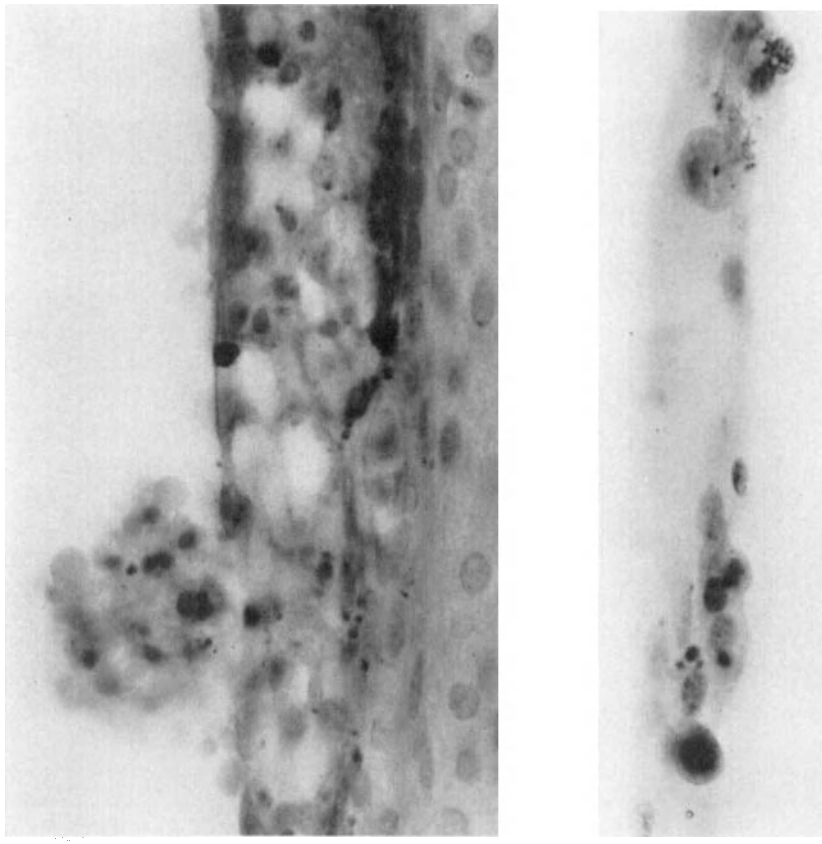


(*b*)

FIG. 7. Organ of Corti of patient with severe deafness after excessive fluid ingestion. (*a*) Left anterior middle half-turn, (*b*) right anterior apical half-turn. Remnants of the inner rods of Corti are present, but apart from these and a few scattered nuclei no other cell elements can be distinguished. ×665. (By permission of the Editor of *The Journal of Laryngology and Otology*.)



(*a*) (*b*)

FIG. 8. Stria vascularis and Reissner's membrane of patient with severe deafness after excessive fluid ingestion. (*a*) Stria vascularis, left posterior middle half-turn, showing extrusion of degenerate elements of the middle cell layer through a deficiency in the superficial cell layer. (*b*) Reissner's membrane, right posterior apical half-turn, showing gross thickening of the membrane, clumping of the nuclei and separation of the two layers. ×975. (By permission of the Editor of *The Journal of Laryngology and Otology*.)

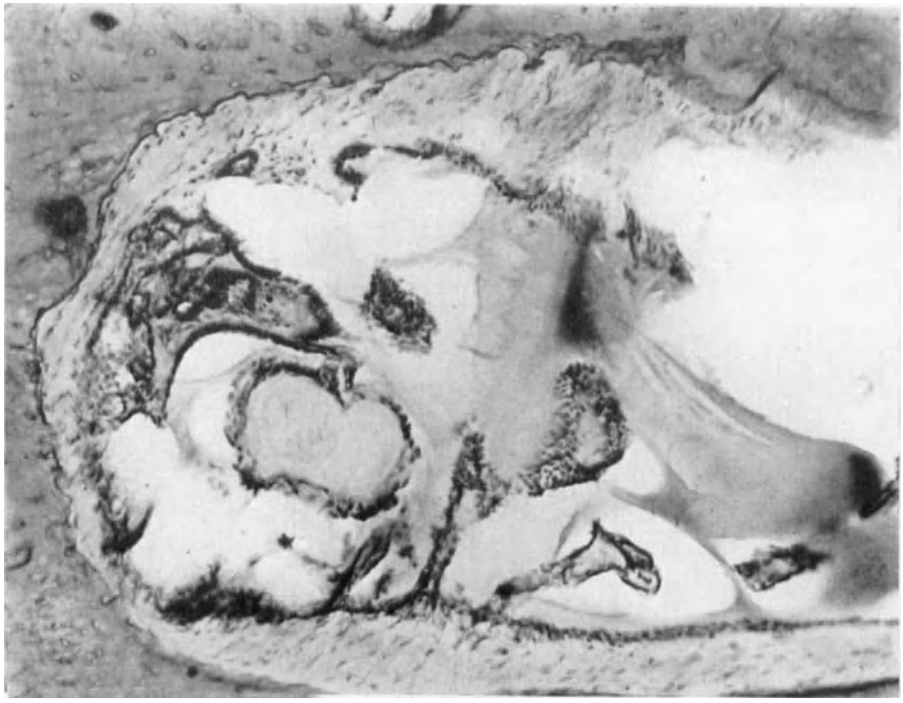


FIG. 9. Left endolymphatic sac of patient with severe deafness after excessive fluid ingestion, showing the unusually dense peri-saccal connective tissue containing a large space extending from the underlying bone to the epithelial lining, which is ruptured. × 220. (By permission of the Editor of *The Journal of Laryngology and Otology*.)

The striae vascularis, too, were grossly degenerate, especially in the right cochlea. In the left the changes principally affected the middle cell layer, which was broken up with the formation of empty spaces. The remaining cell nuclei showed irregularities of form and staining, and numerous small scattered pigmented granules were also noticeable. The superficial cell layer, although well-preserved for the most part, was broken down in places and in the neighbourhood of the resulting lacunae irregular cell masses were present which appeared to be composed of cell remnants extruded from the middle layer (Fig. 8*a*).

In Fig. 8*b* is shown a portion of Reissner's membrane at the same magnification as the stria vascularis in Fig. 8*a*. The membrane is clearly thickened and this was considered not to be an artifact resulting from tangential sectioning of the membrane, because a series of measurements made upon mid-modiolar sections gave an average value of 23·4 μm., while the corresponding figure in a series of normal subjects was 13·3 μm. In addition to this thickening, the structure of Reissner's membrane also presented certain abnormalities in both cochleae. As can be seen in Fig. 8*b*, the nuclei of both the mesothelial and endothelial cells showed a tendency to clumping, with intervening zones in which the nuclei were sparse, and the two layers of the membrane appeared in places to be separated by clear intervals.

No abnormality was visible in the vestibular labyrinth, apart from the presence of fibrin-free exudate in the sub-epithelial connective tissue of the otolith maculae and, to a lesser extent, the cupulae.

In both endolymphatic sacs, however, very marked pathological changes of unusual character were present (Fig. 9). The peri-saccal connective tissue was dense, nowhere exhibiting the loose meshwork which is characteristically present in a large proportion of normal subjects, and moreover contained large spaces extending, on the one hand, to the underlying bone and, on the other, to the epithelial lining of the sacs, which had in places been ruptured. These changes seem to suggest that fluid distension of the peri-saccal connective tissues had occurred with inward rupture of the epithelial lining.

In summary, it seemed clear that the clinical deafness, in the absence of any relevant abnormal findings in the brain stem, was attributable to these labyrinthine changes and in particular to the degeneration of Corti's organ. Of the other structures severely affected, both the stria vascularis and Reissner's membrane undoubtedly play a vital role in maintaining the special character of the endolymph. The changes in the endolymphatic sacs are perhaps more difficult to interpret but here, too, the lining epithelium and peri-saccal connective tissue almost certainly constitute an

important functional element concerned with fluid exchanges. That these three structures should be preponderantly affected would seem to indicate strongly some disturbance of endolymphatic water and electrolyte metabolism.

As regards the cause of these changes, labyrinthine reaction to meningeal infection or haemorrhage, impairment of cochlear circulation by a basilar aneurysm, atherosclerotic occlusion and uraemic neuropathy could all be excluded, and it appeared clearly evident that the deafness was related to the treatment of the renal failure.

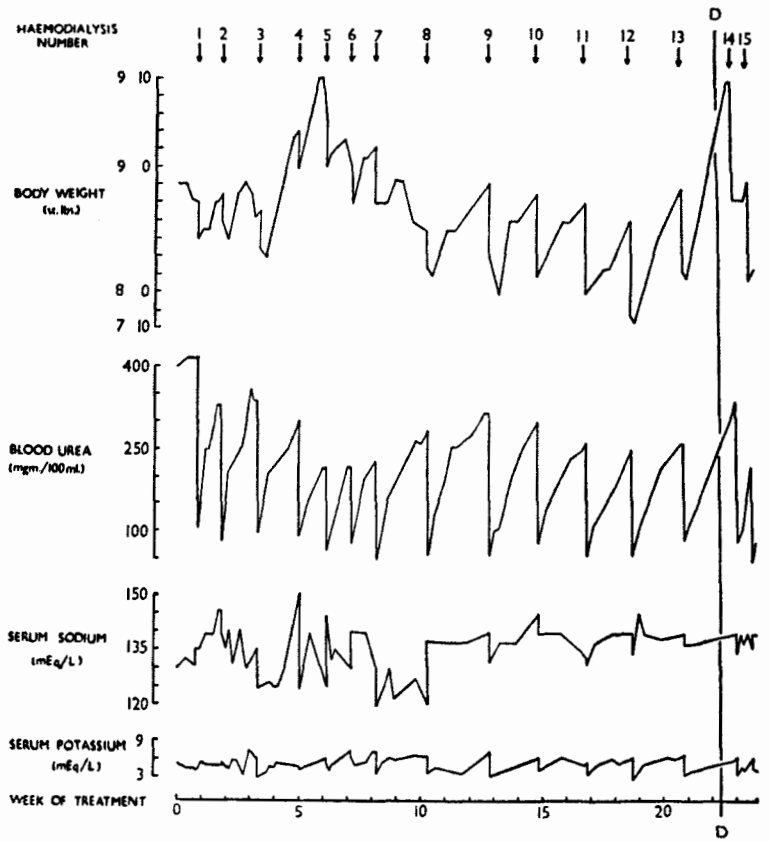


FIG. 10. Diagrammatic representation of the biochemical circumstances of the dialytic procedures. D — D indicates the time of onset of the deafness. (By permission of the Editor of *The Journal of Laryngology and Otology*.)

Thus the inner-ear changes might well be due to repeated osmotic disturbances associated with the dialytic procedures themselves. Dialysis carried out in a patient with a high blood urea will bring about a fall in the

urea content of the extracellular fluid, and the resulting imbalance between intracellular and extracellular urea levels (Shackman *et al.*, 1962) is then corrected by a diffusion process, water passing into the cells by osmosis in the initial stages. It has been argued that in the course of dialysis the abnormally severe osmotic strains to which the cells are subjected may have a serious damaging effect, and that this is the pathological basis of the so-called "dialysis disequilibrium syndrome" (Kennedy, Luke and Linton, 1964).

In these circumstances much would seem to depend upon the biochemical circumstances and frequency of the dialytic procedures. These are shown in diagrammatic form in Fig. 10, and the alternating rapid elevations and abrupt falls in the extracellular urea level are particularly striking, as are the similar changes in the volume of body fluid indicated by the body-weight curve. The associated changes in extracellular sodium and potassium do not fluctuate so widely, showing that the changes in body electrolyte concentration were much less severe. It is interesting that the patient had been subjected to 13 dialyses and, although the deafness did not commence during a dialysis, it appears possible that the unusually rapid and severe increase in body fluid volume, with which its onset was associated, might also have produced osmotic injury, finally precipitating the cochlear degeneration.

Another important aetiological factor was considered to be the ototoxic effect of the drug hexadimethrine bromide (Polybrene, Abbott). During dialysis heparin is added to the blood on its entry to the dialysing apparatus in order to prevent clotting and consequently an anti-heparin agent is added before the blood is returned to the patient. In this case hexadimethrine bromide was used for this purpose and evidence is presented in the full report of this investigation (Ransome *et al.*, 1966) that this drug when used during haemodialysis, but not in other circumstances, has an ototoxic effect. Although no histopathological data are yet available, certain of the findings within the labyrinth in the present case would seem to be explicable on this basis.

Kimura, Young and Barlow (1962) have shown that the general toxicity (indicated by the 50 per cent mortality rates in mice) of the drug, a polymeric quaternary ammonium salt, increases *pari passu* with increase in average polymer size and that in this way it resembles other macromolecular substances such as Dextran. As described by Haller and his co-workers (1962) in respect of its nephrotoxic action, the drug would seem likely to cause the obstruction of small vessels within the inner ear and so to produce anoxic degeneration of the stria vascularis with consequent derangement

of the water and electrolyte regulating mechanism of the endolymphatic system. In this situation any sudden or severe change in extracellular fluid volume or composition, occurring as a result of either the renal insufficiency or the dialytic procedures, would seem likely to cause a particularly serious disturbance of the water and electrolyte equilibrium of the endolymph and so greatly to increase the likelihood of osmotic damage to the hair cells. The reported onset of the patient's deafness in association with a period of marked increase in fluid intake thus appears particularly relevant. In this respect the changes in the endolymphatic sacs are of interest, too, suggesting as they do that the capacity of the organ to respond to sudden osmotic changes has been deranged with consequent fluid distension of the perisaccal connective tissue and rupture of the epithelial lining of the sac itself.

CONCLUSION

The results of these two investigations show particularly striking similarities. In both, deafness occurred as a result of cochlear degeneration which appeared to arise from the inability of the inner-ear fluid-regulating mechanisms to maintain the normal endolymphatic constitution in the presence of alterations in body water and electrolytes. In both, malfunction of the regulating mechanisms was present, due in the one instance to a combination of functional immaturity and some congenital hereditary enzymic defect, and in the other to a combination of the toxic effect of the drug hexadimethrine bromide and previous osmotic injury. Although in both instances the body fluid alterations were unusually severe because of renal hypofunction it will be noted that the cochlear degeneration, likewise, ran an extremely rapid and severe course, soon leading to profound deafness.

It therefore seems conceivable that the acute vertiginous attacks of Ménière's disease, in which the deafness arises from less severe, more short-lived and to some extent reversible cochlear changes, may also be precipitated by the normally occurring, less severe oscillating fluctuations in body water and electrolyte content outlined above, in the presence of some intrinsic defect in the endolymphatic homoeostatic mechanisms.

In these circumstances it could be argued that the reported varying degrees of success of dietary restriction of salt and water in the prevention of these acute attacks depended upon the varying effect this restriction had in reducing the extent of the normal body fluid fluctuations. In other words, the number of attacks has been reduced when the avoidance of excess salt and water intake has resulted in reduction of the extracellular

fluid oscillations and, similarly, the reported good effects of repeated, regular salt administration can be attributed to the same mechanism.

However, there is still a lack of detailed information about fluid and electrolyte homoeostasis in patients with Ménière's disease and there would, accordingly, appear to be a need for further comprehensive investigation to determine the precise role of dietary salt and water in the pathogenesis of the condition. It is only in this way that this aspect of its conservative management can be placed upon a firm foundation.

SUMMARY

The possibility that alterations in the body fluids may play a part in the pathogenesis of Ménière's disease seems to merit further attention, in the light of recent clinical evidence.

The dietary restriction usually practised in the treatment of the condition appears unlikely to produce an appreciable permanent reduction in total body salt and water but the normally occurring oscillating fluctuations in body fluid volume and composition, due to the surprisingly slow rate of operation of the regulatory mechanisms governing the extracellular fluid, might well play a significant role in initiating the acute vertiginous attacks.

Evidence of the possible deleterious effect of body fluid changes on the inner ear is scanty and the results of two recent investigations are therefore of interest. In the first, a histological study of the deaf white cat, the immaturity of the water and electrolyte homoeostatic mechanisms immediately after birth appeared to be one of the factors initiating the cochlear degeneration responsible for the deafness. In the second, a pathological study of a young adult with renal failure treated by periodic haemodialysis, sudden profound deafness occurred after excessive water ingestion.

Since little detailed information about water and electrolyte homoeostasis in Ménière's disease is available at present, further investigation seems desirable.

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DISCUSSION

Lowenstein: Dr. Bosher, your hopeful conclusion conflicts somewhat with your earlier more pessimistic analysis of the possibilities of influencing the various levels of salt in the body by dietary means.

Bosher: The situation, as I see it, is that the earlier studies relied merely on rather gross measurements of daily body-weight and of blood levels of sodium and potassium, but it is quite clear from the investigations of Gamble and others that this is not enough and not only must intracellular and extracellular fluid volumes be estimated but these quantities must be measured precisely if we are to obtain an intelligible picture of what is happening in the body during the acute vertiginous attacks. This has not yet been done but when it is, I am sure we shall be able to solve the problem of the role of salt and water in Ménière's disease.

Lundquist: An interesting observation was made by I. Klockhoff and U. Lindblom ([1966]. *Acta oto-lar.*, **61**, 459–462) who gave glycerol by mouth to patients in acute attacks of Ménière's disease, with acute loss of hearing. After

40 minutes hearing improves by about 15 db in the middle-frequency region and discrimination is improved. After about three hours hearing reverts to the earlier level. These findings suggest that glycerol might be altering the osmotic pressure in the endolymph.

Bosher: Here one would like to know what effect glycerol had on the body fluids. One could argue that by removing water from the body fluids it reduces the stress upon the inner ear regulative mechanisms.

Wersäll: Peroral administration of glycerol has a very efficient osmotic effect, withdrawing water from the blood. There is a rapid decrease in extracellular body fluids; but by about 30–40 minutes later the whole system is rebalanced.

Bosher: This is very interesting, but there is also the question of what happens to the electrolytes. As water is withdrawn from the extracellular fluid, is there an increase in electrolyte concentration? Glycerol may be helping in one way but making things worse in another—but of course we do not really know which is most important, fluid volume or electrolyte concentration. In the patient with renal failure that I described, the factor precipitating the deafness seemed to be an increase in fluid volume rather than some change in electrolyte concentration, as the body fluids remained iso-osmotic. It would appear that the effects brought about by glycerol in Ménière's disease may be rather complicated and so far as the inner ear is concerned, even antagonistic.

Smith: Are you suggesting that there could be electrolyte exchange without gross water movements?

Bosher: It appears possible for electrolyte exchange to occur without gross water movements, but there are many unsolved problems when one comes to consider the detailed physiology of these mechanisms. Regarding the patient we have been discussing, she drank a considerable quantity of water and we therefore expected to find marked dilution of the body fluids, but although she obviously did not consciously match her salt intake to her water input there was in fact no significant disproportion and the crucial factor seemed to be solely an increase in volume of the body fluids without any change in their composition.

Friedmann: Is an increase in fluid volume essential? I have a temporal bone from a case of chronic nephritis, treated similarly by haemodialysis, who developed deafness, but without this incident. The organ of Corti was definitely degenerated. The anti-heparin agent was hexadimethrine bromide, but I don't know of any other features which would indicate the fundamental mechanism you are suggesting.

Bosher: The increase in body-fluid volume is the feature which makes this a unique case. Deafness can certainly occur in patients with renal failure who are maintained by haemodialysis in which hexadimethrine bromide is the anti-heparin agent. The deafness does not seem to be due to the renal failure or haemodialysis alone, because when other anti-heparin agents have been used, deafness has not occurred. On the other hand, hexadimethrine bromide has been extensively used in open-heart surgery without inducing deafness. So it seems to be

the curious combination of osmotic injury due to dialysis plus some toxic effect of the drug which produces deafness. It tends to come on some time after the haemodialysis, often several weeks later when the patient has recovered from the renal failure where this has been acute. It is therefore delayed in onset; it is slowly progressive and affects preponderantly the hearing for the higher tones. The overall picture thus certainly suggests some toxic phenomenon. But in contrast, in the patient I have described the onset was quite sudden, the deafness affected the whole hearing range and progressed extremely rapidly. She drank a relatively large volume of water, ignoring her instructions, and during the day of onset developed increasing tinnitus and deafness, becoming almost completely deaf within 24 hours.

Lundquist: The very extensive changes in the endolymphatic sac of this patient are interesting. They might be due to the fact that a tremendous number of blood vessels surround the endolymphatic sac, especially in the intermediate and distal portions, and are found very close to the epithelial lining. This area might be very easily damaged by the extensive variations in the blood volume.

Hallpike: Though these changes might possibly be due to artifact, we must add that the endolymphatic sac is not at all susceptible to such artifact. Another strong argument against the possibility of artifact is that almost identical changes were present in the opposite sac. This observation certainly brings the endolymphatic sac back into focus; at this stage it ought to be possible to devise quite a number of interesting experiments, particularly in young animals where the renal deficiency makes it easier to bring about an experimental adjustment of the *milieu intérieur.*

GENERAL DISCUSSION

Henriksson: May I bring up the question of efferent control originating in one labyrinth and influencing the other labyrinth? If one "disconnects" the left labyrinth of a curarized frog and records the activity from the central part of the vestibular nerve, one will thus record efferent activity in the nerve ending. When the preparation is rotated, clear-cut spikes are obtained after clockwise rotation—that is, rotation that gives utriculopetal deviation of the cupula in the intact right labyrinth. Such deviation will cause an increase of the activity in the right vestibular nerve and this increase of activity seems to be conveyed to the vestibular nerve of the opposite side. This experiment might indicate an influence of one labyrinth on the other (Gleisner, L., and Henriksson, N. G. [1964]. *Acta oto-lar.*, Suppl. 192, 90–103).

Pompeiano: Is it possible to differentiate the action potentials coursing along the efferent vestibular fibres from the action potentials coursing antidromically along primary vestibular afferents? One might assume, in fact, that antidromic spikes can be generated by a process of depolarization of the central endings of the primary vestibular afferents, similar to that which in the spinal cord is responsible for the appearance of antidromic spikes giving the dorsal root reflexes.

Henriksson: If spontaneous activity had been recorded, as only rarely occurred, I would agree. However, there is usually no "efferent" response until one starts to rotate the preparation. So I believe it must originate from the opposite labyrinth.

Groen: This response appears to be what I would call a short-term response. That is to say, when sinusoidal oscillation is applied to the preparation, the response from the efferents has the same appearance—it also is sinusoidal. But this is not what one would expect from efferent fibres. If one provokes a strong reaction by strong stimulation one would expect that the whole level of efferent activity would either be raised or, in the other case, be lowered, but not be the exact counterpart of the stimulus.

Henriksson: In fact, we only obtained the "efferent" response from the left vestibular nerve if the preparation was turned clockwise.

Groen: True, but it is strictly correlated, and we would expect efferent fibres to have a longer-term "memory". Their response should not change immediately with the impulses.

Henriksson: But it does. However, the response differed from regular afferent activity in that the efferent threshold was much higher (5°/sec.²). Also, there was pronounced habituation; a single rotation could abolish the response for quite some time.

Gernandt: It has been demonstrated anatomically and functionally that neurones in the vestibular nuclei send commissural fibres to the contralateral vestibular nuclei. The nature of the interconnecting influences between the vestibular nuclei on each side of the brain stem has been studied (de Vito, R. V., Brusa, A., and Arduini, A. [1956]. *J. Neurophysiol.*, **19**, 241–253; Shimazu, H., and Precht, W. [1966]. *J. Neurophysiol.*, **29**, 467–492; Fredrickson, J. M., Schwarz, D., and Kornhuber, H. H. [1966]. *Acta oto-lar.*, **61**, 168–188).

Pompeiano: May I recall here the observation that you presented earlier, Professor Gernandt? The monosynaptic and polysynaptic reflexes recorded from the ventral roots were found to be reduced after section of the ipsilateral eighth nerve and they were further depressed by the subsequent section of the contralateral eighth nerve.

We (Batini, C., Moruzzi, G., and Pompeiano, O. [1957]. *Archs ital. Biol.*, **95**, 71–95) reported some time ago that the α rigidity—that is, the rigidity of the deafferentated forelimbs brought about by postbrachial transection of the spinal cord—collapses in the ipsilateral forelimb following labyrinthine deafferentation of one side, while it increases on the opposite side of the body. If the contralateral eighth nerve is now sectioned, the extensor rigidity reappears in the forelimb whose rigidity had been abolished by the first section. Both limbs are then equalized in a moderate, but clear-cut extensor hypertonus. The conclusion is that the collapse of the α rigidity in the ipsilateral limbs after section of the eighth nerve is due to the postural imbalance brought about by the unilateral interruption of the afferent inflow of labyrinthine impulses. The tonic barrage of vestibular impulses from the intact vestibular nerve not only facilitates α rigidity in the ipsilateral foreleg, but probably also exerts an inhibitory influence on the vestibular nuclei of the opposite side of the body. It is therefore surprising that the depression of the spinal reflexes following ipsilateral labyrinthine deafferentation on one side, as described by Professor Gernandt, is further accentuated by the subsequent section of the contralateral eighth nerve.

Gernandt: In our opinion, the facilitatory effect of spontaneous impulse discharge in the eighth nerve is transmitted over the reticulo-spinal and vestibulo-spinal tracts. However, an effect by the commissural fibres cannot be excluded.

Wersäll: I am not quite clear why efferent fibres to the vestibular system should not be able to react rather quickly, Professor Groen. We know that efferent fibres to the cochlea follow the stimulation very nicely and give a fast response which can be very precise.

Groen: Yes, but the response should not be so phasically related to the stimulus.

Brodal: We did not find primary vestibular fibres to the contralateral vestibular nuclei (Walberg, F., Bowsher, D., and Brodal, A. [1958]. *J. comp. Neurol.*, **110**, 391–419). As far as I know, there is only scanty evidence for the existence of fibres or collaterals of cells in one vestibular complex passing to the contralateral vestibular nuclei. We have not studied these commissural connexions ourselves, but M. B. Carpenter, F. A. Alling and D. S. Bard ([1960]. *J. comp. Neurol.*, **114**, 39–49), for example, have described them after lesions of the descending vestibular nucleus. One should be careful in drawing conclusions about the existence of fibres from physiological studies, because there are so many pathways which the impulses may take.

There is one point concerning the efferent bundle which should be mentioned. According to R. R. Gacek ([1960]. In *Neural Mechanisms of the Auditory and Vestibular Systems*, p. 353, ed. Rasmussen, G. L., and Windle, W. F. Springfield, Ill.: Thomas), in the cat this efferent vestibular bundle contains only some 200 efferent fibres, so it is a rather modest bundle.

Dohlman: I had the impression that it was generally accepted that the efferent fibres divide amply, as there are so many nerve endings assumed to be efferent at the sensory cell level but few fibres in the efferent vestibular bundle. However, from a physiological point of view it is known from investigations by Professor Smith and Dr. Henriksson that the efferents fire when the contralateral labyrinth is stimulated. If we assume that the vestibular efferents have an inhibitory function, as in the cochlea, this would mean that the action potentials from the ipsilateral labyrinth would be inhibited. As is well known, the modulation of the resting potential frequency in the corresponding ampullary nerves is always an increase in the action potential frequency in the nerve from one labyrinth and a decrease in that from the labyrinth of the opposite side. It is this difference in frequency which is coded centrally, giving the rotational sensation, eye movements, and so on. If therefore the increase in action potential frequency of the stimulated labyrinth stimulates the efferent fibres to the opposite labyrinth this would augment the physiologically produced decrease in potential frequency of that labyrinth. This seems to indicate that the feedback through the efferent system helps to increase the

important difference between the unhampered increase of the signal from one labyrinth and the signal from the opposite side, by helping to suppress the frequency of the latter. I believe that this is the same regulating principle we find everywhere in the communication system where a feedback mechanism is in operation.

Lowenstein: The efferent impulses would in fact be enlarging the contrast. Such enhancements of contrast are very common in sensory systems.

Groen: I agree with the necessity for this quick response but we have to account for long-term memories also in the inhibitory system. One may stimulate someone very strongly and four days later one can still see evidence that he had undergone strong stimulation. So there is a long-term inhibitory effect, which is probably an efferent effect, as well as the short-term effects.

Lowenstein: Quite apart from the certain existence of long-term effects of this kind, I have always postulated the necessity for short-term effects in the setting of the working level of the various epithelia.

Jansen: One might expect to find the long-term inhibitory effects higher in the central nervous system, rather than out in the sense organ.

Gernandt: The stream of vestibular impulses is progressively controlled by the influence of central commands, and the spatial and temporal pattern is remodelled at each way-station of the executive system in accordance with modulating influences converging from peripheral sensory mechanisms. In addition to looking for modulating influences from cortical, subcortical, cerebellar and spinal centres upon vestibular activity at the first synaptic level, the vestibular nuclei, it is reasonable to search for even more peripheral events in the sense organ itself. The electrophysiological analysis of the gating mechanism suppressing sensory input from the various vestibular structures has been studied and the basic facts are well established.

The old assumption that ablation of the neocortex will cause a release of tonic inhibitory control acting upon the vestibular nuclei has received some experimental and clinical support. Some proof of such an effect is shown upon the vestibulo-ocular reflex arc in the region of the vestibular nuclei. L. J. Pollock and L. Davis ([1927]. *Brain*, **50**, 277–312; [1930]. *J. comp. Neurol.*, **50**, 377–411) were able to show that another type of rigidity, produced by anaemic decerebration, was due to a release of cerebellar inhibition acting tonically upon the vestibular nuclei. The spinal cord is another source of inhibition acting upon the tonic labyrinthine reflexes. When the strength of inhibition acting upon postural tonus from these two sources, the cerebellum and the spinal cord, is compared, it becomes

evident that the cerebellar inhibition is much more powerful than that of the lumbosacral segments.

Pompeiano: May I raise a question which is relevant to the problem of the vestibular control of motor activity? During the desynchronized phase of sleep there are bursts of rapid eye movements which are due to high-frequency discharge of second-order vestibular neurones localized in the

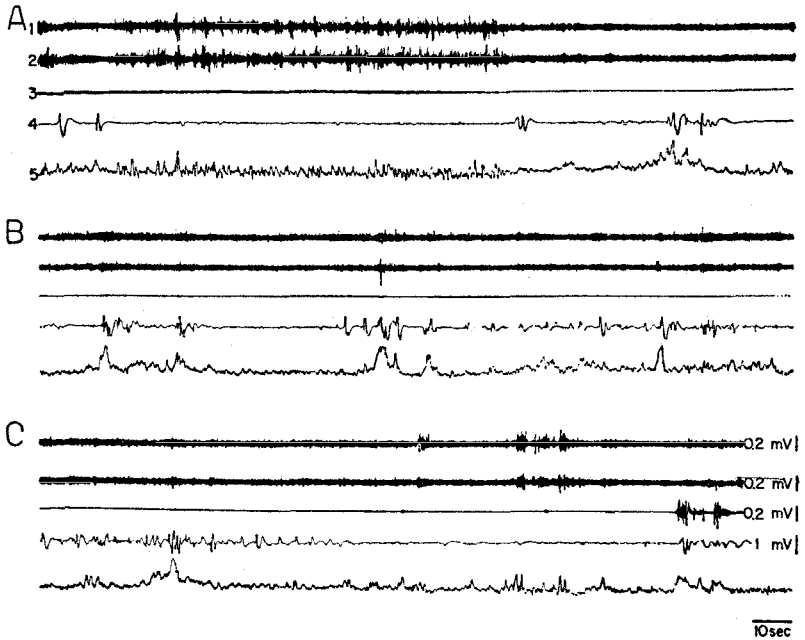

FIG. 1 (Pompeiano). Phasic increase in pyramidal discharge during the bursts of rapid eye movements occurring in desynchronized sleep.

Unrestrained, unanaesthetized cat; experiment done 4 days after operation. Bipolar records: (1) left parieto-occipital (EEG); (2) right parieto-occipital (EEG); (3) EMG of the posterior cervical muscles; (4) electro-oculogram; (5) integrated activity of the left pyramidal tract recorded at medullary level. Note modulation of the pyramidal discharge during synchronized sleep and the large phasic enhancements in the pyramidal activity during the periods of rapid eye movements of desynchronized sleep. (From Morrison and Pompeiano, 1966.)

medial and descending vestibular nuclei (Bizzi, E., Pompeiano, O., and Somogyi, I. [1964]. *Archs ital. Biol.*, **102,** 308–330). Synchronously with these trains of rapid eye movements there are phasic increases in pyramidal discharge (cf. Marchiafava, P. L., and Pompeiano, O. [1964]. *Archs ital. Biol.*, **102,** 500–529) which are associated in time with muscular contractions (Fig. 1). A complete bilateral lesion of the vestibular nuclei abolishes not only the bursts of rapid eye movements but also the related phasic

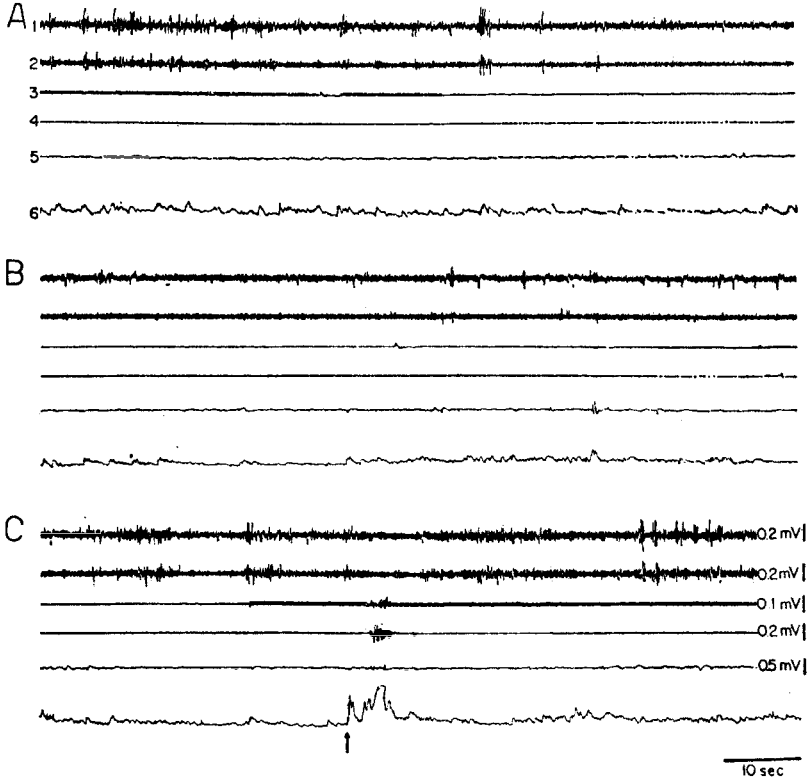

FIG. 2 (Pompeiano). Abolition of the rapid eye movements and the related phasic increases in pyramidal activity during desynchronized sleep following vestibular lesion.

Unrestrained, unanaesthetized cat; experiment done 2 days after implantation of the electrodes and complete electrolytic lesion of the medial and descending vestibular nuclei of both sides.

Bipolar records: (1) left parieto-occipital (EEG); (2) right parieto-occipital (EEG); (3) posterior cervical muscles (EMG); (4) left tibialis anterior; (5) electro-oculogram; (6) integrated activity of the right pyramidal tract recorded at mesencephalic level.

Abolition of the bursts of rapid eye movements and the related phasic enhancements of pyramidal discharge during desynchronized sleep. Throughout the episode of deep sleep the integrated pyramidal activity is flattened and stabilized to a level similar to that occurring during the inter-spindle lulls. The small peaks in the pyramidal records which appear during desynchronized sleep are similar in amplitude to those occurring during the EEG spindles of the desynchronized phase and are sometimes related to the residual, isolated ocular jerks. Note in C the phasic increase in pyramidal activity that occurs during the arousal reaction produced by a strong auditory stimulus (arrow). (From Morrison and Pompeiano, 1966.)

increases in the pyramidal discharge (Morrison, A. R., and Pompeiano, O. [1966]. *Archs ital. Biol.*, **104**, 214–230) (cf. Fig. 2). All these findings, which have been obtained in unrestrained, unanaesthetized cats, indicate that during desynchronized sleep ascending vestibular volleys are capable of triggering the pyramidal neurones, thus contributing to the appearance of motor activity.

We have tried to find out whether the transmission of somatic afferent volleys is modified during the motor activity occurring during desynchronized sleep. The main results of these experiments (cf. Pompeiano, O. [1966]. In *Muscle Afferents and Motor Control*, pp. 415–436, ed. Granit, R. Stockholm: Almquist and Wiksell; Pompeiano, O. [1967]. In *Neurophysiological Basis of Normal and Abnormal Motor Activities*, ed. Purpura, D. P., and Yahr, M. D. New York: Columbia University Press. In press) is that the transmission of afferent volleys along different sensory pathways is blocked by processes of active inhibition. In particular, both the monosynaptic and polysynaptic reflexes are phasically depressed at the time of the rapid eye movements, owing to processes of presynaptic inhibition. The orthodromic lemniscal response is also depressed at this time, due to processes of both presynaptic and postsynaptic inhibition. It is of interest that while the reduced transmission of sensory volleys along the primary afferents in the spinal cord is due to vestibulo-spinal impulses originating from the medial vestibular nucleus, the depression of somatic afferent transmission through the lemniscal pathway during the rapid eye movements is due to the efferent discharge of those pyramidal neurones whose fibres impinge upon the dorsal column nuclei and which are triggered by ascending vestibular volleys at the time of the movements. A block of transmission of somatic afferent volleys at the first relay station of a different sensory pathway therefore occurs during desynchronized sleep, particularly at the time of the rapid eye movements, when a typical motor pattern affecting not only intrinsic ocular but also spinal motoneurones occurs. It is also of interest that both these events (excitatory on the motoneurones but inhibitory on the primary afferents) are abolished by a bilateral lesion of the medial and descending vestibular nuclei. One may wonder whether some control of the transmission of somatic afferent volleys similar to that detected during sleep may be elicited by any increase in the activity of the same vestibular nuclei produced not only by central mechanisms in the sleeping preparation, but also by peripheral labyrinthine stimulation in the awake animal.

Lowenstein: Is anything known about the frequency of turning over of the subject during this period of sleep?

Pompeiano: No. I should add that the bursts of rapid eye movements as well as the related excitatory and inhibitory events do not depend upon the labyrinthine impulses, since they can still be observed after bilateral labyrinthine deafferentation.

Myotatic, Kinesthetic and Vestibular Mechanisms
Edited by A.V. S. de Reuck and Julie Knight

CHAIRMAN'S CLOSING REMARKS

PROFESSOR O. LOWENSTEIN

IT is of course impossible to attempt to sum up the enormous wealth of material that has been presented to us and discussed at this meeting, but I shall try to highlight some of the points of the symposium, however incompletely.

First of all, I feel, and others may agree, that the objective in planning this symposium of confronting the muscle and joint mechanisms and the vestibular mechanisms with one another in the persons of the exponents of the various fields of work has been, and could only be, partially successful. But I suspect that apart from the necessarily blinding effects of specialization in advanced bench work and the impossibility of any one person following closely the literature in neighbouring fields of the subject, this may be chiefly the fault of Nature herself, who has not made any overt provisions for a link-up of these two mechanisms in the form either of blatantly obvious pathways, on the morphological side, or of mutual interactions in the physiological experiments. In the symposium we have, for example, been told of the astonishing lack of vestibular influence on the so-called proprioceptor mechanisms in the posterior extremities. In the first part of the symposium our attention was drawn to the strange dimensional discrepancy between what happens in the γ loop physiologically and what an engineer would expect to happen, according to the blueprint of straightforward servo mechanisms. It became clear that there is need for further work on the influence of vestibular outflow on the muscle and joint control mechanisms.

Turning to the vestibular side, in which I am myself guilty of introducing more conundra than suggestions for their solution, those of us working primarily on this aspect have had a painful reminder of our not entirely absent-minded neglect of a very important *experimentum crucis*. We were asked to try to put a microelectrode into the hair cell and to see whether even if in doing so we destroyed the cell we could get propagated all-or-nothing potentials, because it was pointed out that this might give us a clue to what the hair cell does during its natural stimulation. Can it give rise to all-or-nothing potentials, or is whatever electric effect is found in the

hair cell in the form of an analogue-following of a mechanical event, in the shape of d.c. potential changes? I am quite sure that this experiment will now be attempted, and I am certain it will eventually succeed, and if that is so, we have justified our meeting to some extent at least!

The question of the nature of the chemical transmitter mechanism, and especially the chemical nature of the neurohumour itself, was discussed; it is of course still an open one. But, as Professor Dohlman showed us, there are ways of coming to grips with this problem, and I am sure that before long we shall see much more clearly and be able to convince those working on the myotatic side that a chemical mechanism is compatible with regularity in the end organ.

On the central side, the necessity was stressed for new ultramicroscopic work, but this can be successfully pursued only on the basis of the already existing evidence gained with classical histological methods and also by their continued application. It cannot be too strongly emphasized that no worthwhile electron microscopic work can be done without support from observations obtained with light microscopy.

We have had several contributions on the circuitry in the central nervous system, and as I listened I have become aware, perhaps more than those who have done the work in this field, of the immense complexity of the task and of the great potential sources of error in the physiological and pathological attack on such problems.

We have heard much about nystagmus, which will be with us as long as vestibular organs are discussed. One of the most interesting features is the immense progress made in the technology of recording nystagmic events; the greater precision thus permitted is sure to be the basis for new clinical insights. On the other hand, it would be a great mistake to follow the textbook too closely, because after all, as is general in living organisms, especially if one is engaged in comparative work, anything can happen!

In concluding, let me express the thanks that we owe to the Ciba Foundation and to all those who helped in the planning stages of what has turned out to be an extremely informative symposium.

INDEX OF AUTHORS*

Numbers in bold type indicate a contribution in the form of a paper; numbers in plain type refer to contributions to the discussions

* Author and subject indexes prepared by Mr William Hill.

INDEX OF SUBJECTS

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