THE ROYAL SOCIETY

doi 10.1098/rstb.2000.0732

The functions of the proprioceptors of the eye muscles

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Received 18 April 2000 *Accepted* 7 July 2000

This article sets out to present a fairly comprehensive review of our knowledge about the functions of the receptors that have been found in the extraocular muscles—the six muscles that move each eye of vertebrates in its orbit—of all the animals in which they have been sought, including Man. Since their discovery at the beginning of the 20th century these receptors have, at various times, been credited with important roles in the control of eye movement and the construction of extrapersonal space and have also been denied any function whatsoever. Experiments intended to study the actions of eye muscle receptors and, even more so, opinions (and indeed polemic) derived from these observations have been influenced by the changing fashions and beliefs about the more general question of how limb position and movement is detected by the brain and which signals contribute to those aspects of this that are perceived (kinaesthesis). But the conclusions drawn from studies on the eye have also influenced beliefs about the mechanisms of kinaesthesis and, arguably, this influence has been even larger than that in the converse direction.

Experimental evidence accumulated over rather more than a century is set out and discussed. It supports the view that, at the beginning of the 21st century, there are excellent grounds for believing that the receptors in the extraocular muscles are indeed proprioceptors, that is to say that the signals that they send into the brain are used to provide information about the position and movement of the eye in the orbit. It seems that this information is important in the control of eye movements of at least some types, and in the determination by the brain of the direction of gaze and the relationship of the organism to its environment. In addition, signals from these receptors in the eye muscles are seen to be necessary for the development of normal mechanisms of visual analysis in the mammalian visual cortex and for both the development and maintenance of normal visuomotor behaviour. Man is among those vertebrates to whose brains eye muscle proprioceptive signals provide information apparently used in normal sensorimotor functions; these include various aspects of perception, and of the control of eye movement. It is possible that abnormalities of the eye muscle proprioceptors and their signals may play a part in the genesis of some types of human squint (strabismus); conversely studies of patients with squint in the course of their surgical or pharmacological treatment have yielded much interesting evidence about the central actions of the proprioceptive signals from the extraocular muscles.

The results of experiments on the eye have played a large part in the historical controversy, now in at least its third century, about the origin of signals that inform the brain about movement of parts of the body. Some of these results, and more of the interpretations of them, now need to be critically re-examined. The re-examination in the light of recent experiments that is presented here does not support many of the conclusions confidently drawn in the past and leads to both new insights and fresh questions about the roles of information from motor signals flowing out of the brain and that from signals from the peripheral receptors flowing into it.

There remain many lacunae in our knowledge and filling some of these will, it is contended, be essential to advance our understanding further. It is argued that such understanding of eye muscle proprioception is a necessary part of the understanding of the physiology and pathophysiology of eye movement control and that it is also essential to an account of how organisms, including Man, build and maintain knowledge of their relationship to the external visual world. The eye would seem to provide a uniquely favourable system in which to study the way in which information derived within the brain about motor actions may interact with signals flowing in from peripheral receptors.

The review is constructed in relatively independent sections that deal with particular topics. It ends with a fairly brief piece in which the author sets out some personal views about what has been achieved recently and what most immediately needs to be done. It also suggests some lines of study that appear to the author to be important for the future.

Keywords: eye muscle; extraocular muscle; proprioception; receptors; oculomotor control; vision

1. FOREWORD AND NEWTON ON HYPOTHESES

It seems very appropriate, in *Philosophical Transactions*, series B, to record Isaac Newton's precepts for the investigation of Nature, for they are as relevant to the field of this article as to all other branches of experimental science. Newton's famous remark *hypotheses non fingo* made in an addition to the second (1713) edition of his *Principia* has given rise to a small industry of comment on whether this means that he thought that hypotheses are a 'bad thing' (translate *fingo* as 'frame') or whether he meant that he did not hold with conjecture (translate *fingo* as 'feign'). Since he clearly did use hypotheses himself, I follow the authorities who prefer 'feign'.[1] However, I do not think one need guess. In a much less famous passage, in a letter, Newton set out his precepts for the conduct of the investigation of Nature. The somewhat idealized position that he took is more easily understood from the context. Newton had written that the 'doctrine' of refraction and colours that he had described is simply a statement of certain properties of light and is independent of how these properties might be explained. He was defending his views against criticism from Pradies in Paris and emphasizing that the properties of light that he set out are not dependent on views of how those properties come about. The stance is more appropriate to setting ideals for presentation and the contemplation of scientific doctrine than for the process of generating it. But, since a review of a subject sets out and contemplates a field, Newton's precepts are entirely relevant. Another reason for providing some detail here is that, at least so it seems to me, the usual translation of Newton's Latin is somewhat inadequate, as well as being in part obscure to a modern reader of English. The text was published twice in *Philosophical Transactions*—in Latin in 1672 and in an English translation in 1809. The Latin text and the 19th century translation are reproduced in the endnotes.[2] In fact the Latin is quite clear and explicit. A free translation that preserves the meaning would be

> It would seem that the best and safest method of pursuing philosophy is this: first we should enquire diligently into the properties of things and then only later strive to devise hypotheses to elucidate those properties. For hypotheses must be appropriate only for elucidating the properties of things; they are not to be twisted into a means of establishing those properties, except in so far as they may suggest experiments. If one is to hold an opinion about the true nature of things solely on the grounds that a hypothesis can be constructed I do not see how certainty is to be achieved in any science, especially if it is to be permissible to add hypothesis to hypothesis each of which will be found to bring new difficulties in abundance.

In what follows I have tried to follow Newton's precepts and to separate clearly experimental evidence, hypothesis

based on evidence, and conjecture or polemic. With the latter two the field has been fairly replete. This means accepting that, more often than one would wish, the experimental results simply have to stand on their own and may not, at the moment, fit into a grand scheme.

The review is written in sections, each dealing with a topic or a range of related topics. Within each section I have followed a historical scheme. The sections themselves are also arranged mainly in rough historical order but this has not been followed slavishly because it seemed more convenient to group, for example, most of the human experimental work together rather than to divide the early experiments from the more recent ones.

I have tried to make each section fairly self-sufficient so that the reader who is interested in one topic is not forced to read about too many others. Where necessary, of course, the sections do refer to each other but I have tried to provide in each section enough background to make it comprehensible in relative isolation.

I have not provided the usual section on conclusions because the 'conclusions' are largely given in each section but, instead, I have finished with a piece that I have called 'Loose ends' in which I have tried to provide some personal comments and opinions on a few matters that I think are interesting and important for the future. I stress that these are just my opinions.

I hope that the review will be useful, at least for a time, as a source of reference for those who are interested in the proprioceptors of the eye muscles. Also, and perhaps as importantly, it should offer some attractions to anyone who is interested in visuomotor behaviour, kinaesthesis or in the construction by the brain of the 'egocentric' framework of the relationship of the individual to the environment. I also hope that it will illustrate the often transient nature of particular received opinions and cherished dogmas, the fallibility of belief in the 'obvious' and the need for continued, obstinate doubt till its final resolution by dogged experiment—if any resolution is, indeed, final.

2. INTRODUCTION

(a) *Why should one be interested in proprioception from the eye muscles?*

In the 19th century there was vigorous, and often acrimonious, debate about how Man and other animals derive the information about the position and movements of the parts of their body that seemed to be essential both for sensation and for the control of movement. It was also realized that information, perhaps from similar sources, must be necessary to define our relationship to the external world. Though there were almost as many schemes as there were authors, each differing in its details from the next, opinion divided into two broad schools—one which held that the brain relies on information derived from activity within itself related to the commands or decisions to carry out movement and the other whose opinion was that the required information is provided by mechanisms in the periphery and transmitted to the brain by influences passing along the peripheral nerves. Thus the protagonists can be broadly described as adhering to either 'outflow' or 'inflow' theories. Rather few were prepared to consider that both mechanisms might be involved and, as the debate continued, it became more heavily polarized with each side seeing little merit in the other's position.

The notion that the brain 'knows' what the limbs are doing by using central information related to motor commands in some form is fairly certainly a good deal older than the 19th century but the opinions of earlier writers are often not easy to discuss in terms that can be fitted to the real anatomy of the nervous system. Descartes' views in his *Treatise of man* (*Traité de l'homme*, 1664) form a particularly important example of this problem. What is clear, though, certainly in Descartes' writing and perhaps earlier (see Grüsser 1994), is that there was considerable emphasis on the mechanisms that give rise to knowledge of the position and movement of the eyes as a prime example of the ability of the organism to detect movements of its parts and, equally importantly, to determine its relationship to the surrounding world. This emphasis continued strongly—perhaps even more strongly—in the 19th century and persists today.

A question much debated was whether muscles are sentient and, if so, whether this involves a special sense set apart from the 'common sensation' that was believed to be subserved by cutaneous and perhaps deeper mechanisms. To overcome some of the difficulties of the debate about what, if any, sensation was peculiar to the muscles, Bastian (1880, p. 543) proposed

> '... to speak of a *sense of movement*,* as a separate endowment of a complex kind, whereby we are made acquainted with the position and movements of our limbs ... and by means of which the Brain also derives much unconscious guidance in the performance of movements generally, especially in those of the automatic type.'

*Or in one word, kinaesthesis (from κινέω, to move and αἴσθησις, sensation).

Bastian, incidentally, was fiercely opposed to the idea that kinaesthesis was related to 'the outgoing current' and believed that it depended upon 'ingoing' impressions or a revived memory of these (Bastian 1888). However, he did not believe that there is a muscular sense distinct from other senses or that kinaesthesis arises from muscles alone (see Sherrington (1900) for discussion of 19th century ideas on this). 'Kinaesthesis' has survived as a useful term. It is sometimes rendered as 'kinaesthesia' these days, perhaps by a rather unfortunate analogy with 'anaesthesia' which, unlike kinaesthesia, is a transliteration of a genuine classical Greek word (ἀναισθησία). Bastian (1880) also insisted, on the basis of good clinical observations, that kinaesthesis and cutaneous and other somatic sensations are not inextricably linked and that either can be impaired by disease independently of the other.[3] His use of kinaesthesis included conscious appreciation of limb movement and also, specifically, what he called 'unfelt' impressions that he regarded as essential for motor control. Modern usage confines the meaning to the (conscious) sensations of limb attitude and movement. That is not to say, of course, that 'unfelt' signals may not be essential for the support of kinaesthesis.

Two points are particularly striking in reading the 19th century authors: their reluctance to consider the possibility of hybrid theories involving both inflow and outflow and their failure to distinguish between afferent signals

and sensation. Really one should not be too surprised about the absence of hybrid theories since for a large part of the 20th century opinion was equally polarized. The only 19th century proponent whom I know to have held a hybrid theory abandoned it as soon as he felt able to come down on one side, as the following shows.

(b) *An early hybrid theory*

Bastian originally (1869, quoted by Bastian 1880) advocated a sort of hybrid theory of the mechanisms underlying kinaesthesis. As well as the use of afferent information from peripheral receptors he conceived the notion of involvement of centripetal feedback of information from the spinal motor neurons. He says

> '"Thus I assume it to be possible that when molecular changes are excited in certain spinal motor cells as a result of a volitional impulse, proportional recurrent impressions may be carried along certain fibres taking origin from the motor cells, and ascending in the posterior columns of the cord." In this way the brain might derive impressions of the various muscles, or sets of muscles, of a limb.'
>
> (Bastian 1880, p. 699)

This seems remarkably close to Sperry's suggestion some 70 years later of a copy of information related to the motor command being passed to a 'sensory centre' by what he called 'corollary discharge' (Sperry 1950). In Bastian's case this 'centre' would have been the Rolandic cortex, which he regarded as sensorimotor with the emphasis heavily on the sensory side, in fierce distinction to the views of Ferrier that it was purely motor (Ferrier 1886).

But Bastian later abandoned the idea of recurrent central copies when he became convinced of the invalidity of reasons that had earlier led him to believe that 'impressions' from the muscles could not be carried by the posterior columns. His final position seems to have been, in agreement with Ferrier this time, that kinaesthesis was supported entirely by information from peripheral receptors—thus he then espoused a pure 'inflow' theory.

It seems to me that the insistence on the irreconcilability of the two hypotheses, which persisted until quite recently, has been a large contributor to delaying our understanding of sensorimotor systems in general and of the actions of the eye muscle proprioceptors in particular.

(c) *The (non)equivalence of 'afferent' and 'sensory'*

The second striking attitude in the 19th century is the reluctance—usually amounting to a refusal—to contemplate the notion that inflowing impressions (afferent information in our terminology) could have any central action unless they gave rise to sensation. Again Bastian is the exception. He asserts that those impressions from the muscles that he formerly supposed arose from the spinal motor neurons but later believed to come from muscle afferents:

> '. . . may transmit to the brain those almost ever-present "unconscious" impressions which so materially guide us in the execution of all our movements'
>
> (Bastian 1880, p. 699)

This view, which we now accept without reservation, was regarded as little short of ridiculous by Ferrier (1886)—not the least eminent of Bastian's contemporaries.

There is, I think, a 20th century parallel in the way in which evidence—or putative evidence—against the existence of a conscious sense of precise eye position was included among the reasons for denying the existence or efficacy of afferent signals from the extraocular muscles. This denial, in turn, formed part of the argument that the proper concern of muscle afferents should be with motor control and not with the support of (conscious) kinaesthesis. Thus the eye, whose movement control was supposed on various grounds (constancy of its inertia was the most respectable of these) not to require muscle afferent signals, fitted the general scheme as a crowning example since it both had no (or, rather, no effective) muscle afferents and also lacked 'position sense'. The example of the eye was then used to reinforce the view that muscle afferents were not only unlikely to, but were inappropriate to, contribute to the (conscious) sense of limb movement (see Merton 1964).

The debate between the supporters of 'outflow' and of 'inflow' was sharpened by the discovery of structures that were later called muscle spindles in the skeletal muscles and the suspicion, then the demonstration, that they are sense organs (see Matthews 1972). When the presence of afferent nerve fibres in the oculomotor nerves and, later, of putative receptors in the extrinsic ocular muscles (extraocular muscles, EOM) was established, the eye and its muscles became again a particular focus for the debate. In what follows some of the history of the debate will emerge—at least so far as it relied on experiments related to the eye rather than on mere polemic.

(d) *'Outflow' in the last half of the 20th century*

In 1950, in one of those coincidences that seem to occur remarkably frequently, the notions of outflow and its interaction with afferent signals were expanded independently and along significantly different lines by Sperry (1950) and Von Holst & Mittelstaedt (1950). In the ensuing half-century the specific bases of their distinctly different views have become blurred and, indeed, largely forgotten through the indiscriminate use of the terms 'corollary discharge' and 'efference copy' as though they were equivalent.

(i) *Corollary discharge*

Sperry (1950) introduced 'corollary discharge' to explain the anarchic circling movements that are induced in fish when one eye is rotated so that its originally temporal retina lies nasally. He developed a hypothesis that involved action by a copy of the central command for motor output. This copy he called corollary discharge, saying

> 'They [the experimental results] also raise the possibility that a corollary discharge of motor patterns into the sensorium may play an important adjuster role in the visual perception of movement along with non-retinal and postural influences from the periphery.'
>
> (Sperry 1950, p. 489)

This sentence makes two statements that have often been forgotten or ignored. First, Sperry clearly supposed that corollary discharge acted via a 'sensory centre' and, at least in his original description, that it acted upon a percept (visual perception of movement) and that this

interaction might then have various consequences—including the modification of motor behaviour. Second, he specifically assumes that corollary discharge and afferent signals interact in this process. The interpretation of the implications of Sperry's hypothesis have considerable ramifications that are well discussed by McCloskey (1981).

(ii) *Efference copy*

In the same year, Von Holst & Mittelstaedt (1950) revived the outflow hypothesis along rather different and more specific lines. Their work became available to the English speaking world in the now famous paper of Von Holst (1954). A number of observations are described but the most detailed analysis is again of an experiment in which anarchic circling movements were induced, this time by rotation of the head (and thus of both eyes) of a fly. But the paper begins with a piece of insight that clarifies what had not been so clearly set out before—the different significance of afferent signals that are induced by the organism's own motor actions and those that arise as a result of changes in the external world. Von Holst's description is hard to better:

> 'In order to make myself clear, I should like first to explain a few terms. The whole of the impulses which are produced by whatever stimuli in whatever receptors I shall term *afference*, and in contradistinction to this I shall call the whole of the motor impulses *efference*. Efference can only be present when ganglion cells are active; afference, on the contrary, can have two quite different sources: first, stimuli produced by muscular activity, which I shall call *re*-afference; second, stimuli produced by external factors, which I shall call *ex*-afference. Re-afference is the necessary afferent reflexion caused by every motor impulse; ex-afference is independent of motor impulses.'
>
> (Von Holst 1954, p. 89)

Exafference and reafference are now usually written without hyphens and the term 'ganglion cells' shows its age. By it Von Holst seems to have meant any central neurons whose firing gives rise to movement (not necessarily directly) and he is particularly speaking of activity that we would now call 'motor commands' elaborated centrally and not necessarily triggered reflexly.

Exafference and reafference encapsulate concepts the importance of which it is hard to overestimate. As Von Holst also pointed out, these terms do not designate the receptors—the same receptors may be (and usually are) involved in both; they define the *circumstances* in which the afferent signal arises. The commonest example of the distinction between the two varieties of afference compares the signals that arise from eye movement and from movement of a visual target with the eye stationary. But this is not the happiest of examples because the arrays of receptors stimulated are not identical in the two cases and so the signals passing centrally are also different. Von Holst's example of the comparison between the reafferent labyrinthine signal produced by moving the head and an identical but exafferent signal that would be produced by a pitching and rolling ship is a better illustration. A question that immediately arises is how, in the absence of different signal patterns, reafference and exafference can be distinguished. This distinction is clearly necessary since reafference during movement either provides a basis for confirmation that all is going as intended or a measure of how the movement differs from that planned. To do this, however, there must be some central measure of what 'should' be happening and this realization forms the starting point for the 'efference copy' hypothesis. For completeness we note that exafference has quite different significance and will often require urgent choices to be made of the appropriate new behaviour in the light of the slings and arrows of the external world.

The 'efference copy' hypothesis (Von Holst & Mittelstaedt 1950; Von Holst 1954) proposes that the central nervous system preserves a copy of the motor signal (the 'efference') when a command is issued that leads, directly or indirectly, to movement. This copy is the 'efference copy'. The details of what then happens are critical to the hypothesis, which requires that there is a quantitative algebraic summation of reafference and efference copy that must, thus, be expressed somehow in equivalent representations or formats (again, for an admirable analysis, see McCloskey (1981)).

> 'The reafference interacts with the efference copy. The efference and its copy can be arbitrarily marked with a plus (+), whilst the reafference is marked with a minus (−). The efference copy and the reafference exactly cancel each other out. As soon as the entire afference is too large or too small, as a result of some external influence acting on the effector, either a + or a − remains as a residue . . . this residue (the exafference) is transmitted upwards, sometimes to the highest centres.'
>
> (Von Holst, quoted by McCloskey 1981, p. 1419)

Now this means that the efference copy has to exist in a form that will exactly cancel out the reafference if all has gone to plan. Thus the efference copy is not, strictly, a copy of the outflowing activity ('efference') at all—it is a (negative) copy of the expected reafference from that particular outflow. This is implied by Von Holst's description but has rarely been made explicit. As Bell (1982, 1989) points out, this means that, if for some reason the reafference produced by a particular 'efference' changes, the efference copy must also change in order to null it. At least in the electric fish studied by Bell[4] the efference copy can be built by pairing a standard efference with a particular reafference and as the reafference is modified so is the efference copy. In Bell's experiment the reafference was modified by the experimenter. In a 'truly motor' motor system (as opposed to one where the output is electric organ discharge) one might expect that the reafference for a given efference would be stereotyped over short periods. Indeed, the efference copy system would not work as a means of extracting exafference unless the reafference were stereotyped. However, any change in the peripheral plant—motor or oculomotor—will cause a different effect in the periphery for the same efference and will thus also cause a different reafference. Thus one must suppose that, if motor control systems use the efference copy mechanism, the copy must be plastic and must be altered to correspond to the results of any change in the expected reafference. When a load is added to a limb, for example, a given motor command will have a different effect from that on the unloaded limb and this will lead to a different reafferent signal in the two cases. The expectation must be adjusted accordingly. Readjustment of the afferent expectation of motor commands

must also occur to allow the interpretation of muscle spindle firing in the light of changes in fusimotor (γ-efferent) setting. None of these considerations is novel but the usual description, following Von Holst closely, of the copy being a copy of the motor command is, perhaps, less than entirely lucid since it is not the command that is relevant but the results that the command is expected to achieve. And it is this template, the expectation, against which the afference must be compared to separate the reafference from any exafferent component.

Summarizing the differences between the corollary discharge and efference copy hypotheses McCloskey (1981, p. 1419) says

> 'It must be stressed that efference copy, as envisaged by von Holst, is unlike corollary discharges in two ways. First, the efference copy is required to cancel the reafference exactly, whereas corollary discharges provide central internal adjustment of sensory centers without cancellation of reafference necessarily occurring.'

This, of course, is in cases in which the movement has gone exactly to plan.

McCloskey (1981, p. 1419) continues

> 'Second, in contrast to corollary discharges proposed specifically to deal with perceptual stability, efference copy is proposed simply as a 'mechanism for distinguishing reafference and exafference' and applies as much to centers not at all involved with perception as to higher, perceptual centers.'

These distinctions have largely been ignored by later users of 'corollary discharge' and 'efference copy' who have used the two terms synonymously and interchangeably, generally without any consideration at all of the specific premises of the hypotheses that they encapsulate. Sloppy as this may seem—and as it often is—it is also understandable because rarely do we have any idea whether a copy of a motor command acts according to one or the other, or to neither hypothesis. It is important not to forget that 'corollary discharge' and 'efference copy' are shorthand for hypotheses. Really, a general, non-committal term is needed—something like 'motor command copy' perhaps—but no such term has entered general use. So the modern reader has to accept that 'corollary discharge' and 'efference copy' do not now usually represent the specific hypotheses of their originators but rather are vague and non-committal labels for a copy of a motor command. In fact, though such copies have been widely assumed to exist, the experimental evidence for their existence was at first very weak. This has now changed and there are a number of good examples of the action of these copies (see the reviews by Gandevia 1996; Matthews 1982; McCloskey 1981), some of which we shall meet later. Since the hypotheses have undoubtedly given rise to new experiments—and these themselves have often been illuminating—these two hypotheses handsomely meet Newton's criteria.

However, of the details of the neural mechanisms that the motor command copies use we still know very little. But there is one system in which detailed physiological analysis has been possible, the central nervous system of a weakly electric fish. Here, neural discharges have been found that show the action of an adaptive signal with polarity opposite to the motor command (Bell 1981, 1982). This signal interacts with the motor command, can be retained in the central nervous system for at least 30 minutes after a motor command (Bell 1986), and seems to fulfil Von Holst's criteria for a corollary discharge.[4]

(iii) *Extension of the concept of reafference to signals of static position*

Illuminating as Von Holst & Mittelstaedt's (1950) insight into the separation of exafference and reafference is, it leaves unconsidered the question of the situation when the peripheral organ, limb or eye is at rest for some time. If the last movement went according to plan no reafference remains and, if the outside world has not changed, there is no exafference. How then is limb or eye position known, for example to allow planning of the next movement's set of motor commands? Confining our consideration to the eye we may ask if there is any need for information about static eye position, or, better, if there is any evidence that the brain is provided with such information. The answer seems to be affirmative. Not only is it difficult to see how movements could be correctly planned without this information but experiments indicate that it is, indeed, available. For example the experiment of Guthrie *et al.* (1982, 1983) showed that the monkey oculomotor system has information about eye position before a saccade. That particular experiment—discussed in more detail later (§ 16(n,o))—also shows that, under its conditions, a copy of the motor command seems to be sufficient to supply this information. But it is also clear, for example from the human experiments of Gauthier and his colleagues (Gauthier *et al.* 1990*a*), that afferent signals from the eye muscles also contribute to the signal of static 'registered' eye position. Indeed, anticipating later conclusions, we shall see that there is excellent reason to believe that both motor command copies and orbital afferent signals are involved.

Let us explore some general issues about what the use of these two signal sources of static eye position is likely to involve. If there is a signal of eye position at rest derived from motor command copies, this might involve storage of the details of the last motor command and some form of extraction from these of the eye position at the end of the last movement. Eye position in the orbit at the end of a movement is rather closely related to the firing rate of the population of ocular motor neurons—therefore monitoring the continuous motor commands required to hold the eye in its current position might, in principle, provide a measure of current eye position that did not depend on the previous history of eye movement. This is really an oversimplification, however, and it is not clear whether absolute eye position as opposed to changes in position could be extracted from the firing of ocular motor neurons (see Carpenter (1988) for references and discussion of the motor neuron properties). It is difficult to assess how good a position estimate from the oculomotor nuclei would be. It would depend on the oculomotor plant either having a very constant performance—perhaps likely in the short term—or on its frequent recalibration (which could not be by 'outflow' means alone). An additional complication may be the recently discovered effect of gravity on the eyeball the centre of gravity of which does not coincide with its centre of rotation (see Steinbach & Lerman 1990; Steinbach 1992, for discussion).

Of course, static eye position could be signalled by a continuous afferent signal from the orbit with the EOM proprioceptors as much the most likely source. Whether there is such a signal is discussed in some detail later. In brief here, there is no definite evidence that the first-order EOM proprioceptive afferents provide such a signal but the experimental evidence is not extensive and certainly does not exclude its existence. The effects of passive manipulation of eye position do, however, strongly suggest that there is a central signal of eye position that is affected by, but probably not exclusively dependent on, EOM afferents (e.g. Gauthier *et al.* 1990*a*). However, there seems to me to be another possibility. At this point one should recall that the eye is never truly stationary because of the existence of micromovements and tremor (Carpenter 1988). Setting these aside, however, since it does not seem likely that they would be large enough to be signalled with any precision by the proprioceptors, it is also the case that, in foveate animals at least and in higher primates *par excellence*, the eyes make 'ordinary' eye movements very frequently indeed. So, a signal that indicated at the end of each eye movement the position of the eye at that instant would need to be stored for only a matter of seconds at the most before it would be superseded by a new value at the end of the next movement. The oculomotor system would then always have available information, of afferent origin, about the static eye position between eye movements without there necessarily being a continuous afferent discharge signalling static eye position. Interestingly, we have recently shown (Fahy & Donaldson 1998) that, at least in the pigeon, the first-order EOM afferents seem to carry just such a signal of eye position at the end of an eye movement, though they do not seem to carry continuous discharges that would signal eye position if the eye were held stationary for periods of more than a few seconds.

One reason for setting out these speculations has been to illustrate the following: although an estimate of static eye position derived from a copy of a motor command clearly has the advantage that it is available before a movement begins, and also early in the movement before there is time for reafference to reach the brain, 'outflow' is not the only means by which the oculomotor system could be provided with eye position information at these critical times.

As a matter of convenience, in the rest of the review I have generally followed the authors being quoted in their use of 'corollary discharge' or 'efference copy' to describe a copy of the motor command or outflow signal. This is not to be taken to imply that there was necessarily any good reason that emerged from the authors' experiments to invoke the one hypothesis rather than the other. Few authors, even when they give both terms, make any distinction of meaning between them. When I have referred to a copy of the command signal myself I have preferred to call it 'corollary discharge' as implying a less precise hypothesis.

(e) *'Outflow' and 'inflow' and the eye*

The field of the study of inflow versus outflow of signals as contributors to perception or motor control is now very large. Good discussions of its recent state can be found in such sources as Jeannerod *et al.* (1979), McCloskey (1981), Matthews (1982) and Gandevia (1996). Our principal concern here is to discuss work relevant to the understanding of the actions of the inflow signals from proprioceptors in the eye muscles but we shall not be able to avoid more general matters entirely. In particular, the interpretations of experiments on the effects of displacement of the eye and of eye movement on the perception of the visual world have played a considerable part in shaping arguments about the relative roles of inflow and outflow signals in kinaesthesis, the perception of limb position and limb movement.

The broad ideas as they apply to eye position and movement are simple enough: the outflow theory contends that the effective signal of eye position and eye movement is derived by taking account of the muscular effort required to move the eye or to hold it still in the orbit and does not depend on any information entering the central nervous system from peripheral transducers such as those in the eye muscles. The inflow theory regards afferent signals from peripheral transducers as the source of information about eye position and eye movement. In their traditional forms each theory excludes the other, as we have said. However, the details of the arguments are much more complex than the simple titles suggest. Though tests of the two theories have been proposed, made and interpreted (and believed by their authors to be critical) these have turned out on several occasions to be much less critical than their confident protagonists believed. Largely as a result of these tests, supposed at the time to be critical, in the 1960s eye muscle receptors came to be regarded as incompetent to subserve sensation and also, later, as unnecessary to oculomotor control.

Some of the sand on which the edifice of the incompetence of extraocular muscle afferents was constructed has shifted with changes in fashionable interpretation—itself a fickle process. More importantly we shall see that the foundations on which the conclusions were built have been gradually eroded by the relentless waves of dogged experiment.

There are, then, good historical reasons for an interest in the way in which signals from the receptors in the EOM may act, not least since the presence and importance of such possible actions was hotly contested in the last 40 years of the 20th century. But it is far from the case that the place of EOM proprioceptive signals in the functioning of the nervous system is only, or even principally, of historical interest. It is now clear that signals from the eye muscle afferents play important parts in vision, in visuomotor and oculomotor control, and in some spatial perceptual processes. It is also apparent that we do not yet fully understand the mechanisms by which the results are achieved.

To demonstrate how important an understanding is to modern neuroscience of our present state of knowledge, and of ignorance, of the actions of signals from the eye muscle proprioceptors let us anticipate the conclusions of this account by presenting a brief list of the processes in which it now seems these signals act and for which we shall examine the experimental evidence.

The involvement of afferent signals from the proprioceptors of the extraocular muscles has been demonstrated in (i) oculomotor control of various kinds; (ii) control and

development of visuomotor behaviour; (iii) construction of the registered direction in which vision is directed and thus of the registered direction of gaze and of objects in egocentric space; (iv) development of the visual properties of neurons of the visual cortex in young animals; and (v) processing of visual information in various regions of the brain.

These signals are also probably involved in (i) effects of strabismus (squint) on visuomotor behaviour; and possibly in (ii) the genesis of some types of strabismus.

It seems that afferent signals from the eye muscles are required by vertebrates of a wide range of complexity. In the course of studying central actions of the EOM afferent signal effects have been found in a range of vertebrates from amphibia to Man.

If one can take the presence of putative proprioceptors in the eye muscles as an index, it is likely that such actions are very widely distributed indeed since the eye muscles of practically all those vertebrates in which they have been examined contain putative receptors of one kind or another (see, for example, Maier *et al*. 1974; Von Sabussov *et al*. 1964). In some higher vertebrates, at least, the extraocular muscles contain a unique receptor type, not so far found in any other muscles, the palisade or innervated neuromuscular cylinder, about whose physiology there is a good deal of speculation at the moment—so far without any experimental evidence of the nature of the signals it generates. At the moment we know that palisades are found in various mammals: Man (Lukas *et al*. 2000; Richmond *et al*. 1984), cats (Alvarado-Mallart & Pinçon-Raymond 1979; Billig *et al*. 1997), monkeys (Ruskell 1978, 1999), dogs (Ruskell 1999), and sheep (Blumer *et al*. 1998), but they may also be present in many other vertebrate species whose EOMs have not been critically examined for their presence. Spencer & Porter (1988) have gone so far as to suggest that the palisade may be the 'principal sensory apparatus' of mammalian eye muscle. All this strongly suggests that EOM afferent signals play an essential part, or more probably a number of parts, in the vertebrate nervous system.

After many years during which the existence of 'outflow' signals as a source of information used in motor control and in perception was denied if it was not ignored, such signals are again believed to be essential—but now with some good experimental support. The eye and its muscles offers a uniquely convenient system in which to study such signals and, as is only now beginning to be done, to examine the ways in which they may interact with afferent signals in underpinning such fundamental processes as the generation, maintenance and calibration of the representation of external, egocentric space within the nervous system. Since such a calibrated representation must, one supposes, underlie all our interactions, motor and perceptual, with the external world, we have every reason to examine and to try to understand all the signals which underpin it. That an afferent signal from the EOM is one of these signals is one of the theses for which this review will examine the evidence.

3. THE RECEPTORS OF THE EXTRAOCULAR MUSCLES

Towards the end of the 19th century Sherrington questioned the then received wisdom that the oculomotor nerves (the third, fourth and sixth cranial nerves) were purely motor (Sherrington 1894, 1898). In 1910, Tozer & Sherrington (1910) confirmed the presence of the putative proprioceptors at the myotendinous junction of the eye muscles that had been described by Huber (1900) and more famously by Dogiel (1906). From studies of the degeneration of these endings when the oculomotor nerves or the trigeminal nerves were sectioned, Tozer & Sherrington (1910) concluded that the primary afferent path lay through the oculomotor nerves—they thought a few fibres might pass by the trigeminal nerve, but these they regarded as insignificant. The modern view—which is rather close to the inverse of this, with the ophthalmic branch of the trigeminal nerve as the principal (and in the opinion of some the only) route—is discussed below.

After most skeletal muscles were found to contain muscle spindles these were sought in the extraocular muscles also, but at first without success. Sherrington (1894), for example, found no muscle spindles in the EOM of cats and monkeys in whose skeletal muscles they were present in abundance. The history of the search for (and eventual finding of) muscle spindles in the EOM of some, but by no means all, mammals is well described by Cooper *et al*. (1955) and more briefly by Whitteridge (1962). The comments of Matthews (1972, pp. 51–54) are also interesting.

Since the early observations, a good deal of attention has been given, if intermittently, to the questions of the morphology and distribution of putative EOM proprioceptors and there has been much speculation on their functional properties. On occasion one feels that there has been rather more speculation about likely function, or indeed lack of it, than description of experimental approaches to determine these functions. There are a number of useful reviews of receptor morphology and distribution, and not all the details they give will be repeated here. The most extensive review of the occurrence of muscle spindles in EOM is that of Maier *et al*. (1974) who also discussed the presence of other types of presumed sensory ending (relying on reports of previous observers as well as their own experiments) in 27 different species including amphibians, birds, rodents, carnivores and primates. A very useful short account is given by Spencer & Porter (1988) as part of their extensive review of the structural organization of the extrinsic eye muscles. Von Sabussov *et al*. (1964) and Montgomery & Macdonald (1980) describe the EOM receptors in various bony fish. Hayman's thesis (Hayman 1994) contains a useful table of the occurrence by species of spindles, palisades and other endings, extracted from the literature. The most recent review is that of Ruskell (1999) who discusses the morphology, distribution and some aspects of the function of EOM proprioceptors but confines himself to cats, ungulates and primates.

For convenience, current views on the occurrence and distribution of putative proprioceptors in the extrinsic eye muscles are now summarized, followed by discussion of some matters of interest and controversy in more detail.

(a) *Muscle spindles*

In skeletal muscles the predominant proprioceptor is the muscle spindle but this is not a generalization that extends to the EOM in which spindles are absent in the

majority of species (Maier *et al.* 1974; Sherrington 1894, 1898). Nevertheless they are present in the eye muscles of even-toed ungulates and higher primates including Man. This curious distribution, the significance of which is one of the unresolved problems of the field, is discussed in § 4. In those species that do have spindles these are said to be situated in the proximal and distal parts of the muscles rather than the belly and they lie at the junction of the orbital and global muscle layers (see Spencer & Porter 1988). This description is probably an oversimplification since the careful study by Lukas *et al.* (1994) strongly suggests that each of the human EOM has its own characteristic distribution of spindles. The spindles of the eye muscles tend to be simpler in structure than those of skeletal muscle (see Ruskell (1999) for details and discussion), though sheep eye muscle spindles appear similar to those in skeletal muscle (Lukas *et al.* 1994).

Human eye muscles generally have been agreed to contain spindles since their description by Cooper & Daniel (1949). According to Ruskell (1999) an early description by Buzzard (1908) was overlooked. In Man the eye muscles contain large numbers of spindles—more per unit weight than other human finely controlled muscles (Cooper *et al.* 1955), though many fewer than those of ungulates (see Lukas *et al.* (1994) for a recent study and Ruskell (1999) for detailed discussion). However, the human EOM spindles are said to show various structural peculiarities, including a lack of expansion of the equatorial zone and, in some cases, 'abnormalities' of the intrafusal fibres. These features led Ruskell (1989, 1999) to question whether they are competent to function as proprioceptors. Other morphologists, though agreeing that the spindles of the human EOM do show unusual structural features, do not question their ability to function (Lukas *et al.* 1994, 1998).

(b) *Golgi tendon organs*

Early descriptions of the receptors in the eye muscles claimed the presence of Golgi tendon organs (GTO) in a number of species but the descriptions were 'uncharacteristic of what is now accepted as the classical form of GTO' (Ruskell 1999). Ruskell later makes it clear that he believes at least some of these organs—for example those of Cooper & Daniel (1949)—to have been palisades. Recent observers like Richmond *et al.* (1984) failed to find GTO in human EOM but Ruskell (1990) did find them in sheep eye muscle tendons. Overall the morphologists seem to agree that GTO are unlikely to play much part in EOM proprioception except perhaps in sheep.

(c) *Palisade endings (myotendinous or musculotendinous cylinders)*

'The myotendinous cylinder, or palisade ending, potentially represents the principal sensory apparatus of mammalian extraocular muscle' say Spencer & Porter (1988). Dogiel (1906) called the neural structures commonly found in the musculotendinous region of EOM 'palisade endings' and he described them in the human, monkey, horse, ox, dog and cat. Tozer & Sherrington (1910) found the same types of ending in rabbit, cat and monkey and noted that they corresponded to Dogiel's description. They remarked on the large numbers of nerve fibres (250–350) entering the tendon from the fleshy part of the muscle but did not say to which species these figures apply or whether they apply to all those examined. The fine structure of the palisade has now been described in the cat (Alvarado-Mallart & Pinçon-Raymond 1979; Billig *et al.* 1997), monkey (Ruskell 1978, 1999) (Ruskell (1999) also mentions their occurrence in the dog) and, recently, in the sheep (Blumer *et al.* 1998). No endings resembling the palisade were found in the rat by Daunicht *et al.* (1985). In 1984, Richmond *et al.* (1984) described palisade endings in eye muscle specimens from human cadavers and in excised pieces of EOM from young patients with strabismus. Ruskell (1978) proposed the name 'innervated myotendinous cylinder' for these structures and, recently, the terms 'palisade ending' and 'myotendinous cylinder' have been used interchangeably by many authors. In the same paper, Ruskell confirmed that they are numerous in the monkey, his figure of 350 cylinders in a monkey medial rectus corresponding closely with Tozer & Sherrington's (1910) estimate mentioned above.

The morphology of the ending is well described by Ruskell (1978, 1999), Richmond *et al.* (1984) and Lukas *et al.* (2000). Because of the way in which the nerve terminals lie between the slips of the (split) muscle fibre with the whole organ enclosed in a fibrous cylinder, it has been suggested that the ending may be more sensitive to deformation by contraction of its parent muscle fibre than by passive elongation of the muscle (Richmond *et al.* 1984). There is no experimental evidence to test this assertion but the idea may perhaps gain a little support from observations on the structurally different GTO in skeletal muscle, for which active contraction does seem to be a more effective stimulus than passive stretch (see Henneman 1974). The evidence is reviewed by Jami (1992). The palisade ending is associated with a particular type of muscle fibre that has several motor synaptic contacts, the 'multiply innervated' fibre of the global layer of the EOM (Lukas *et al.* 2000; Spencer & Porter 1988), and each receptor seems to be associated with a single muscle fibre (Blumer *et al.* 1998; Richmond *et al.* 1984). The global multiply innervated muscle fibres give slow, graded, non-propagated responses on activation (see Spencer & Porter (1988) for references)—as do some intrafusal fibres of muscle spindles. It has been suggested that the palisade and its associated muscle fibres might form a special sensory unit—possibly, like the muscle spindle, under independent central control (Porter *et al.* 1995; J. D. Porter, personal communication; Robinson 1991). Unfortunately there is no evidence to test this intriguing notion.

(i) *Active pulleys and extraocular muscle layers*

It has been recently discovered (Miller *et al.* 1993; see also Demer *et al.* 2000) that the traditional description of the anatomy of the orbit, in which the superior oblique tendon passes through a pulley (trochlea) that redirects its line of pull but the recti are directly inserted on the globe, is incorrect. New methods of anatomical study combined with high-resolution magnetic resonance imaging show that the rectus tendons pass through pulleys before their insertion and that the pulleys change their position in the orbit with changes in gaze. Thus the

line of muscle pull is adjusted according to the direction of gaze. The recent work of Demer *et al.* (2000) also shows that the orbital layer of muscle fibres of the rectus muscles inserts into the pulley and only the global layer inserts on the globe. Thus the layers of the rectus muscles (with approximately equal numbers of muscle fibres in each layer) seem to be functionally distinct, with the orbital layer adjusting the pulley position and thus the muscle's line of pull, while the global layer provides the force that rotates the globe. For the oculomotor system the pulley arrangement may provide a simplification of one aspect of control by allowing oculomotor commands to be specified in only two dimensions but this will be at the expense of providing independent adjustment for the pulley position via the EOM fibres inserted into it. (See Demer *et al.* (2000) for details and discussion of these implications.) The 'active pulley' arrangement also poses interesting questions for EOM proprioception. As we have seen, the palisade endings are found only in the global muscle layer where they are associated with multiply innervated fibres. Muscle spindles, however, in those species that have them, usually lie in the transitional zone between the orbital and the global layers (Lukas *et al.* 1994; Spencer & Porter 1988). Thus, while the palisades are particularly well placed to signal the actual rotation of the globe (if they are primarily length receptors), or the rotating force applied tangentially (if they are primarily force transducers), the positioning of the muscle spindles seems less appropriate to these measures. Possibly the spindles are primarily concerned with the control of pulley position though there is, of course, no evidence yet that bears on this. So far, rectus pulleys have only been described in human and monkey orbits. It would be useful to know if they are to be found in other mammals—indeed in other vertebrates—and, if so, whether there is any association between the occurrence of rectus pulleys and that of muscle spindles. The active pulley arrangement also has implications, of course, for attempts to model oculomotor control and the mechanics of the oculomotor plant. For example, Quaia & Optican (1998) recently published a model of saccadic control that incorporates ocular plant with pulleys.

It has been generally accepted that the endings of palisade type found in Man by Dogiel (1906) and studied by Richmond *et al.* (1984) are similar to those of the cat as described by Alvarado-Mallart & Pinçon-Raymond (1979) and the cat ending, in turn, is considered similar in structure to that in the monkey (Ruskell 1978). The presumption, then, has been that palisades in the EOM are similar in different species and may, by implication, be expected to have similar functions. Very recent work by Lukas *et al.* (2000) confirms this presumption. In 1999, however, Ruskell made the surprising claim that the human palisade ending is not equivalent to the innervated myotendinous cylinder of the cat and monkey. More importantly, Ruskell (1999) goes on to say that he has found no endings of the palisade type in post-mortem material from human infants, though he did find some in adult material. He concludes that 'myotendinous receptors may not be present at birth in man' and 'It is unlikely that a role in proprioception can be apportioned to these late-developing, haphazardly distributed nerve endings. It has been suggested that they may represent migrated redundant sensory endings from effete muscle spindles'. These suggestions are discussed below.

(d) *Other endings*

Early accounts of EOM receptors often include descriptions of various 'free' nerve endings, some spiral in form, that were regarded as probably afferent. More recent work, however, has strongly suggested that many of the spiral endings are motor since they contribute terminals to a particular type of muscle end plate (Ruskell 1984, 1999). This has been confirmed by Billig *et al.* (1997), who found that some spirals in cat EOM are labelled by transport of marker from the oculomotor nucleus. This finding does not exclude the possibility that other spiral endings may be afferent and such a conclusion is supported by Billig *et al.*'s (1997) finding that some cat spirals are labelled from marker injection in the trigeminal ganglion. Various other types of neural ending have been described in the EOM whose status is not known.

(e) *Are the 'sensory' endings of the extraocular muscles competent to act as proprioceptors?*

Our predecessors would have thought this a foolish question but it is one about which we now need to try to be explicit since there have been suggestions, based on the details of the morphology of human EOM receptors, that these may be incompetent to provide the nervous system with signals about eye position or movement. For the early investigators the mere presence in the eye muscles of receptors that could strongly be presumed to be 'sensory' as opposed to motor would have been sufficient and there would have been no doubt of the receptors' functionality. In effect these observers were silently consenting to that ancient philosophical dictum, first found in Aristotle and repeated down the ages by Paracelsus, Thomas Brown, William Harvey and Isaac Newton—and doubtless many others—that 'Nature does nothing in vain'. It has proved a trustworthy enough guide but is, of course, no substitute for evidence of what a structure does or how this is accomplished. Nor is it safe to presume function on the basis of what seems to be a clear morphological answer to a functional need. Even Sherrington was not immune to this temptation—he clearly did not believe that the extraretinal signal, the need for which he showed (Sherrington 1918), could come other than from orbital proprioceptors. However, once the possibility of outflow as a signal source is admitted, Sherrington's arguments are not competent to decide the issue—as we shall see later (§ 16(a)). We must therefore proceed with caution.

First, we should be satisfied that there are, indeed, signals that enter the brain from EOM afferents and, preferably, that these do have central effects—better still that they have quantifiable effects that appear to make functional sense. A great deal of this review addresses instances of these questions and the sceptical reader will need to read much further to be satisfied. But let us accept—provisionally if the reader so wishes—that there are such signals. We may then try to address the question of evidence that they arise from the receptors that have been demonstrated in the EOM. The answers are not entirely satisfactory. Our knowledge of the central signals, and sometimes of their effects, is often not matched by

our knowledge of the periphery. For example, this is true of the pigeon in which we now know a good deal about the central actions of signals that arise in the EOM and pass centrally in their afferents. We know of actions at the level of single units in various central structures, at the level of the excitation of individual eye muscles and, finally, on the eye movements of the vestibulo-ocular reflex (VOR). We shall have occasion to discuss all these in detail later. Although we do know that they do not include muscle spindles (Maier *et al.* 1971), we know nothing positive about the morphology of the pigeon EOM receptors. In other species—ungulates, cats, monkeys and Man—we do know of a range of receptors that the EOM have at their disposal, so to speak. Of these, it is undoubtedly for the afferent signals from the EOM of sheep and goats that we have the best evidence to attach them to a particular receptor, the muscle spindle. Confidence that signals recorded from afferents in the orbit, when the eye muscles of sheep or goats are stretched, arise from muscle spindles rests upon the particular characteristics of the signals: slowly adapting with marked phasic activity; rapidly settling to a plateau at the end of the stretch; frequently a pause on release; and, of course, the ability to modulate the discharge by activation of efferents that do not cause an increase in muscle force and so can be claimed as gamma- or, possibly, beta-innervation (see especially Whitteridge (1959)). In the case of the pig the discharges have also been shown to be modulated at high frequency by vibration of the eye muscles (Lennerstrand & Bach-y-Rita 1974). All these characteristics we regard as diagnostic of signals from muscle spindles. This belief depends, of course, on analogy with responses recorded from limb muscles where a large body of evidence has been accumulated that such signals are, indeed, the result of activation of morphologically distinct muscle spindles rather than of other receptors. Most of this evidence is dealt with in considerable detail by Matthews (1972). It is most unfortunate that we know nothing about the central actions of the signals that we can be comfortably confident come from muscle spindles in ungulate EOM. Indeed one cannot but think that, convenient as they are for the study of eye muscle afferents, the ungulates are not particularly promising subjects for the study of eye movement.

Let us now apply analogous reasoning to the cat. It seems well established (see § 6(b,d)) that a high proportion of units recorded from cat primary afferents have slowly adapting responses with dynamic phases and often a pause on muscle release. Surely these are characteristics of spindle responses? All that is lacking is evidence of independent central control—there is none as far as I know. But, again as far as I know, it has never been sought. Doubtless this is because muscle spindles have never been observed in cat eye muscles and received wisdom is that only spindles have independent centrifugal control. But we know nothing at all about the characteristics of responses from any EOM ending other than the muscle spindle. It is not impossible that the palisade, in particular, might show independent central control. Barbas & Dubrovsky (1981*a*) found that vibration of cat superior rectus modulated the discharge of units in the frontal cortex. But this modulation did not involve following the vibration at frequencies of more than 100 Hz as do primary spindle afferents in pig EOM (Lennerstrand & Bach-y-Rita 1974). In any case, vibration of spindle-containing neck muscles by Barbas & Dubrovsky (1981*a*) also failed to give high frequency driving so one cannot conclude anything about the possible sensitivity of the cat EOM primary afferents to vibration from these effects on cortical units, beyond supposing that the receptors must be activated to some extent by vibration. As far as I know there have been no other tests of the effect of vibration on primary EOM afferents except in ungulates. So, in the cat—in which we do know something of central action of EOM afferent signals at several levels as we shall see, and, as we have seen, we know of the presence of several morphological types of receptor in the EOM—we cannot attribute the afferent signals to any particular morphological type of receptor. We might have our suspicions that some at least of the signals in the cat are likely to come from the quite common palisade endings, but there is absolutely no proof of this.

In the monkey we know nothing of central actions of the EOM afferents at the level of individual neurons and pathetically little about the first-order afferent signals, but we do know a good deal about the types of receptor present in the EOM.

In ungulates, cat, rat, monkey and pigeon we know the central primary afferent pathway and in cat, monkey and pigeon we know where the primary afferents end.

In Man the situation is somewhat different. We now know a good deal about the details of the morphology of putative receptors but our evidence about the primary afferent pathway is very indirect and doubtless incomplete. We also know, again as will be discussed in § 16, that signals from orbital receptors of some kind do have measurable effects on human perception and behaviour but most of the experiments can give no clue as to the type of receptor responsible for the signals. Two series of observations, however, might do so, if indirectly. There is good evidence that vibration applied to human eye muscles produces effects on perception (Roll & Roll 1987; Velay *et al.* 1994). In many cases the effects are similar to those seen when human neck muscles are vibrated (Biguer *et al.* 1988). In the latter case we are quite content to ascribe the effects to selective activation of muscle spindles. Likewise, the authors of the eye muscle vibration research similarly attribute their effects to activation of eye muscle spindles, in each case by analogy with the known effects of vibration on human limb muscles that are attributed to muscle spindle activation. Moreover, of course, there are muscle spindles in the human EOM so the attribution, if not certain, is certainly credible.

The second series of experiments that has attempted to attribute effects in Man to particular receptors are those of Steinbach and his colleagues (summarized in Steinbach 2000) to which there will be occasion to refer again below (§ 17). He has presented a good deal of indirect evidence that the human palisade ending provides signals that are used in the elaboration of the 'registered direction' of visual targets. This conclusion depends upon the disturbance of extraretinal signals, shown by various control experiments to be due to 'inflow' rather than 'outflow', when the musculotendinous region of human EOM is disturbed as in repeated operations for the

correction of strabismus. The evidence that the signals are due to inflow does not depend on any hypothesis about the morphology of their receptors of origin. The proposal that they arise from the palisades is based on the observations that the disturbances in visual perception of direction and in pointing to visual targets seem to be preferentially produced by damage to the musculotendinous region of the EOM, where, as we have seen, the palisades are to be found in Man as in other mammals.

Unfortunately it seems very improbable indeed that we shall be able to test the attribution of signals to particular, morphologically identified, receptors in human eye muscles and it is not unlikely that the kind of inferences about function that we can make at the moment may be the best that are possible, though there is every reason to try to devise new experiments to improve them.

What, then, should be made of Ruskell's (1989, 1999) proposals that were quoted above: first, that human palisades are not likely to provide proprioceptive signals; and second, that muscle spindles in human EOM are incompetent to act as proprioceptors? If both of these statements were true this would mean that there are no morphologically distinct proprioceptors in human EOM. Neither proposition is directly testable. The proposal that human palisades do not correspond to the musculotendinous cylinders (innervated musculotendinous cylinders, IMC) of other species is based on claimed morphological differences; If these are present is there any reason to suppose that they make the receptors incompetent? We can have no idea. As we have seen, we know nothing about the signals that myotendinous cylinders in any species send centrally if—as most of us believe they do—they send any. So arguments that human palisades are somewhat different to those in other species lead to no conclusion whatsoever. More tangibly, perhaps, Ruskell (1999) found no palisades in infant human EOM up to four years old, and so believes that those found in adults must develop postnatally and feels that such late-developing receptors are unlikely to be competent to provide proprioceptive signals. Whatever one thinks of the conclusion, the premise is refutable and has been refuted by Porter's finding of palisades in the EOM of infants under one year old (J. D. Porter, personal communication) and, very recently, by the finding by Lukas *et al.* (2000) of IMC in the eye muscles of a two-year-old child. This recent work also claims that the palisade endings of human eye muscles are also IMC that do correspond in structure to those in other animals. There seems, then, no reason to follow Ruskell in denying the likelihood of function to human palisades.

For the human eye muscle spindle the contention is that the anomalies or abnormalities seen in these organs, which lack the central expansion of classical spindles, have few nuclear bag fibres, and often show apparent degeneracy of the intrafusal fibres, are so severe that the spindles are unlikely to be able to send useful signals to the nervous system. To accept such a conclusion we would need to know in detail the quantitative effect of one morphological change or another on the efficacy of the spindle as a transducer. As far as I am aware this information does not exist. In any case, with what spindles should we compare those in the EOM? The 'classical' description of the spindle structure is based on spindles of the cat hind limb, much of it on elegant work on the tenuissimus, which is hardly a typical muscle—whatever that is—since it has rather few muscle fibres. But it is clear that not all spindles are identical in structure. For example, cat neck muscles have sets of spindles that show unusual morphological features (Richmond & Abrahams 1975). There is no conclusive evidence on whether muscle spindles in human EOM send signals centrally. However, the fact that vibration applied over the EOM sometimes, but apparently not always, leads to illusions of movement of a stationary visual target, and sometimes to contraction of the vibrated muscle (see Velay *et al.* 1997; but also Lennerstrand *et al.* 1997), together with the well-known propensity of muscle vibration to stimulate spindle afferents preferentially (see, for example, Matthews 1982), might be felt to point in the direction of EOM spindle functionality. The effects may well be due to activation of eye muscle spindles but the weakness of the argument is that we have no knowledge of the effect of vibration on other endings in the EOM and especially on palisades—indeed we know nothing of the responses of palisade endings at all. Also, the fact that vibration of cat EOM, which contain no muscle spindles but do have palisades, does seem to produce central actions (Barbas & Dubrovsky 1981*a*) emphasizes the need for great caution in drawing conclusions about the morphology of the EOM receptors involved from the observation that vibrating the human eye muscles produces effects.

Thus, though there seems no doubt that human EOM spindles do differ in some details from the classical description, at the moment we have no reason to suppose that this makes them non-functional and it seems entirely sterile to maintain this untestable assumption.

The sensible position would seem to be that of our predecessors—that nature, indeed, does nothing in vain and that, given the presence of receptors in the human EOM and that of effects due to action of proprioceptive signals from the orbit, it is reasonable to associate the two until there is good evidence to do otherwise or to attribute the effects to one or another type of receptor. To be 'good' the evidence will have to be functional and not morphological.

4. WHY DO SOME ANIMALS HAVE MUSCLE SPINDLES IN THEIR EXTRAOCULAR MUSCLES?

The EOM of most vertebrates that have been examined do not contain muscle spindles but the eye muscles of a few species do. Strangely, those that do have eye muscle spindles include not only Man and the chimpanzee (Cooper & Daniel 1949; Cooper *et al.* 1955) but also all the even-toed ungulates whose eye muscles have been examined, such as sheep, deer, cow, wild boar (Cilimbaris 1910), goat, pig (Cooper & Daniel 1949) and camel (Abuel-Atta *et al.* 1997). Naively, one might have supposed that the presence of the most sophisticated, centrally adjustable, muscle receptor would be associated with the widest range and greatest complexity of eye movement but this supposition is patently false. Certainly Man and chimpanzees have eye muscle spindles Man, at least, has them in relatively high density compared with that in skeletal muscle (for references, see Ruskell 1999).

Arguably these species have the most complex oculomotor behaviour; but the eye movements of rhesus and cynomolgus monkeys are scarcely less complex and have very few spindles, or, according to some authorities, none at all (Cooper & Daniel 1949; also see Ruskell 1999). Sheep and goats, on the other hand, have far more spindles per gram of eye muscle than any primate but it is not clear that they make many kinds of eye movement. Sheep appear to have 'correctional' eye movements on head tilt—presumably vestibularly driven (Forrester 1975)—and goats have a VOR (Whitteridge 1962) but no one seems to have looked in any quantitative way for eye movements unrelated to changes in head posture, although informal observation suggests that 'spontaneous' eye movements are not conspicuous in sheep or goats. Cats have no spindles in their EOM (Maier *et al.* 1974) but make saccades, have a VOR that has been extensively studied, and optokinetic nystagmus (OKN) and most cats show vergence also (Hughes 1972). Pigeons have saccades of eyes as well as head (Bloch *et al.* 1981; Lemeignan *et al.* 1992; I. M. L. Donaldson, unpublished data), VOR (Anastasio & Correia 1988; Gioanni 1988*a*) and OKN (Gioanni 1988*b*) and an intriguingly fast vergence to targets in the binocular field (Bloch *et al.* 1984, 1987)—their EOM contain no muscle spindles (Maier *et al.* 1971). No doubt these examples could be multiplied but they are sufficient to leave no doubt that there is no simple correlation between the possession of eye muscle spindles and complexity of oculomotor repertoire.

There is some evidence that human EOM involved in vertical eye movement, and particularly the inferior rectus (IR), contain more muscle spindles than do the horizontal muscles (Lukas *et al.* 1994) and this might be relevant to what follows.

Steinbach has proposed (1992) a particularly interesting hypothesis to explain the strange distribution of spindles among animal species. Contrary to the almost universal assumption, he showed that the centre of mass and the centre of rotation of the human eye do not coincide (Steinbach & Lerman 1990) so that gravity produces a couple that, if unresisted, would turn the eye upwards in the socket when the subject stands in the anatomical position. This he demonstrated by tilting the heads of anaesthetized, paralysed, human subjects and, by this observation, incidentally disposed of one of the traditional arguments that orbital proprioception is unnecessary. For example,

> 'There are no load changes or gravitational influences (the eye being a sphere rotating about its centre is not subject to gravity)... and a *need* for proprioceptors to inform us of the direction of gaze in the same manner as we are informed of the position of limbs, is not compelling.'
>
> (Ruskell 1999, p. 271)

Steinbach's proposal was that in animals whose eyes have such a gravitational couple the presence of spindles in the EOM might be associated with an 'antigravity' corrective reflex (Steinbach 1992). This would raise theoretical problems because such a reflex would, presumably, depend upon the stretch of a particular muscle leading to its contraction—that is, on a stretch reflex—but no satisfactory demonstration of a stretch reflex in the EOM has ever been made, and there have been several adequate experiments that confirm its general absence in these muscles (Keller & Robinson 1971; McCouch & Adler 1932; Whitteridge 1962). See also Carpenter (1988) for a useful discussion of attempts to demonstrate a stretch reflex in the EOM. Very recently, however, one piece of work has suggested that the human IR but not the lateral rectus (LR) may, just possibly, have a stretch reflex, as will appear below. Steinbach's hypothesis would predict that the eyes of animals without EOM spindles would be little affected by gravity and it therefore gained support from the demonstration (Harris *et al.* 1993) that the cat's eye is, indeed, very little affected by gravity. Cat EOM do not contain spindles. One would also predict that sheep, with a very high density of EOM spindles, would have a large gravitational rotation couple. Steinbach & Donaldson (1997) tested this in the paralysed, anaesthetized sheep but found that eye rotations due to gravity were absent or tiny and concluded that the hypothesis must therefore be reconsidered—very possibly abandoned.

There is, however, a further twist to the hypothesis that there may some antigravity stabilizing mechanism, whether connected with the occurrence specifically of muscle spindles or not. Velay *et al.* (1997) claimed that vibrating the human IR sometimes caused small eye movements downward—the direction in which contraction of this muscle moves the eye—whereas vibrating the LR never caused any eye movement. Downward is the direction of movement that would be required to counteract gravity in Man since, in a person sitting or standing with the head upright, the human eye rolls upward when the eye muscles are paralysed. Of course, this would require the existence of a conventional stretch reflex in the IR—excitation of its proprioceptors leading to shortening of the muscle. Thus the claim is interesting and Velay *et al.* (1997) also point out that many previous unsuccessful attempts to demonstrate a stretch reflex in the EOM have examined horizontal eye muscles. However, the results of Velay *et al.* (1997) were not confirmed by Lennerstrand *et al.* (1997) who found that vibration of the IR caused the other non-vibrated eye to move upwards, not downwards, and also found eye movements when the LR was vibrated. It is not clear whether these differences in results may be related to different experimental techniques, but, in any case, it is clear that more experiments are needed for us to be certain of the effects, if any, of vibration of the EOM in causing eye movement. Vibration experiments are discussed again later in a different context (§ 16(j)).

Ruskell (1999) suggests that human EOM spindles may be incapable of 'functioning as proprioceptors' but this suggestion is based purely on morphology. There has been no attempt to make any experimental test of the ability of human eye muscle spindles to provide signals of any kind and it is not easy to see how this could be tested. But, quite certainly, ungulate EOM spindles do provide centripetal signals not dissimilar to those from skeletal muscle spindles (Browne 1974, 1975; Lennerstrand & Bach-y-Rita 1974; Whitteridge 1959). Thus even taking the extreme position of deleting Man from the list of bearers of functional eye muscle spindles would not solve the conundrum of the significance of their species' distribution.

Matthews (1972), in his monumental review of muscle receptor physiology finished his commentary on extraocular muscle thus:

> 'For the time being the presence of muscle spindles in the extraocular muscles of some species and not others finds no ready explanation, but one feels that when supplemented by further evidence on differences in extraocular muscle control it might provide a clue on the general function and use made of spindles everywhere in the body'.
>
> (Matthews 1972, p. 54)

One may heartily agree with this aspiration but, so far, the hope remains unfulfilled.

5. THE PRIMARY AFFERENT PATHWAY

There has been a good deal of controversy over the details of how afferents from EOM receptors reach the central nervous system, of where the somata of the afferents lie and where their primary afferent terminals are to be found.

The primary afferent fibres leave the eye muscles in the oculomotor nerves, which are mixed (motor and afferent) within the distal orbit so, as Cooper *et al.* (1955) point out

> 'Since obvious anatomically separate sensory roots on the third, fourth and sixth cranial nerves are absent, there appear to be two alternatives: either the so-called motor roots carry the sensory impulses or such impulses go by the fifth cranial nerve.'
>
> (Cooper *et al*. 1955, p. 571)

At various times and in different species evidence has been offered for both of these routes. Present opinion, based on roughly a century's work on the question but now dominated by the results of anatomical tracing using the transport of horseradish peroxidase (HRP) from the EOM, may be summarized as follows.

Most, but perhaps not all, afferent fibres leave the mixed oculomotor nerves near the apex of the orbit or in the region of the cavernous sinus and transfer to the ophthalmic branch of the trigeminal (fifth cranial) nerve. In ungulates the connecting branches are fairly easily visible (Whitteridge 1955; Winckler 1937). In cats they are much more difficult to find but are sometimes visible (Baker *et al.* 1972). Cooper *et al.* (1955) report the presence of such connecting branches in Man, baboon and cat. Since pseudo-unipolar cells typical of primary afferent somata are filled in the ophthalmic part of the trigeminal ganglion when the EOM are injected with HRP (see § 5(a)) one presumes that transfer of EOM afferents to the trigeminal system takes place distal to the ganglion in all the species that have been examined in this way—but perhaps in places very inaccessible to dissection, as Ruskell (1999) points out. There is disagreement on whether, in addition to the pathway through the trigeminal ganglion, some afferents enter the central nervous system along the oculomotor nerves (see for discussion Porter & Donaldson 1991; Ruskell 1999; Spencer & Porter 1988). Manni *et al.* (1989*b*) have presented evidence that afferent fibres from sheep EOM running centrally in the oculomotor nerve are likely to be nociceptive and not proprioceptive and that EOM proprioceptive fibres enter the brain only via the trigeminal ganglion and root (see also Bortolami *et al*. 1991).

(a) *Somata of primary afferents*

The earliest observations suggested, on the basis of recording of unit responses believed to be driven by EOM afferents when eye muscles were stretched, that the cell bodies of the primary afferents were in the mesencephalic nucleus of the trigeminal nerve (ME5) in goats and sheep (Cooper *et al.* 1953*b*) and cat (Fillenz 1955). It was also known that muscle spindle afferent responses from the jaw muscles are found in ME5 in the cat (Corbin & Harrison 1940), which makes the interpretation of the origin of the responses seen in ME5 when the EOM are stretched open to question. This is discussed in § 6(a,b).

Modern studies in mammals using HRP transport from the EOM agree that there are somata of primary afferents from EOM, typical pseudo-unipolar cells, in the ipsilateral trigeminal ganglion; for example, lamb (Bortolami *et al.* 1987; Manni *et al.* 1966), cat (Porter & Spencer 1982) rat (Daunicht *et al.* 1985), monkey (Porter *et al.* 1983; Porter 1986), rabbit (Kashii *et al.* 1989) and guinea pig (Aigner *et al.* 2000). No tracer studies report the presence of putative somata in ME5 in ungulates (see Bortolami *et al.* 1987) but, in the cat, Alvarado-Mallart *et al.* (1975*a*,*b*) reported labelling of ME5 cells as well as of trigeminal ganglion cells. Some more recent studies in the cat (Bortolami *et al.* 1987; Buisseret-Delmas & Buisseret 1990; Buisseret-Delmas *et al.* 1990) conclude that the principal representation is in the ganglion but that a small number of primary afferent somata are to be found in ME5 also. However Porter & Spencer (1982) suggest that the labelling of ME5 cells is associated with leakage of HRP from the injected EOM to neighbouring structures, particularly to the jaw muscles, since the lateral wall of the orbit is not bony in the cat. Porter & Donaldson (1991) re-examined the question and found ME5 labelling only when there was evidence of tracer spread from the EOM with labelling of the motor nucleus of the trigeminal nerve (which supplies jaw muscles). They therefore concluded that, in the cat, as in other mammals, the trigeminal ganglion is the sole site of primary afferent somata. Physiological evidence claimed to support the view that ME5 is also involved is discussed in § 6(b).

The only non-mammal in which the pathway has been traced is the pigeon. Eden *et al.* (1982) using HRP transport from the EOM made the surprising claim that multipolar cells in the pigeon brainstem were the primary afferent somata but, significantly, they did not examine the trigeminal ganglion. However, Hayman *et al.* (1995) showed that the primary afferent somata are typical pseudo-unipolar cells lying in the ophthalmic part of the ipsilateral trigeminal ganglion and that the multipolar cells in the brainstem reported by Eden *et al.* (1982) are neurons of the accessory abducens nucleus innervating the quadratus muscle. No labelled cells were found in ME5. Thus the pigeon appears to be similar to mammals in having the primary afferent somata of its EOM proprioceptors in the trigeminal ganglion.

(b) *Primary afferent terminations in the central nervous system*

In all the (few) species examined so far central afferent terminals have been found in relation to the ipsilateral descending trigeminal system when HRP was injected into the EOM. In mammals there is general agreement

that the terminals are located in the spinal trigeminal nucleus. In the pigeon the situation is somewhat different.

(i) *Mammals*

Porter (1986) found the primary afferent terminals of the EOM proprioceptors of the monkey in the pars interpolaris of the spinal trigeminal nucleus with a second terminal zone in the pars triangularis of the cuneate nucleus where it overlapped with the region receiving primary afferent terminals from proprioceptors of the dorsal neck muscles (Edney & Porter 1986). In the cat, Ogasawara *et al.* (1987) reported that the terminals were in the pars oralis but Buisseret-Delmas & Buisseret (1990) found them in the caudal pars interpolaris of the spinal trigeminal nucleus with a considerable caudal extension to the pars caudalis. Neither reported any projection to the cuneate nucleus. In the sheep, Bortolami *et al.* (1991) illustrated an EOM afferent ending diagrammatically in the pars oralis but it is not clear what the evidence is for this attribution since there is no mention in the text, or in the previous work referred to in the figure legend, of any histological study of the brainstem. Porter & Donaldson (1991) re-examined the projection in the cat and found the afferent terminals to be confined to a discrete zone in the pars interpolaris of the spinal trigeminal nucleus in a region identical to that in which Porter found the terminals in the monkey. Again there was no projection to the cuneate nucleus. Emphasizing again the dangers of tracer spread within and beyond the orbit, Porter & Donaldson (1991) suggested that the caudal extension reported by Buisseret-Delmas & Buisseret (1990) may have been due to spread of label to orbital or periorbital nociceptors in experiments in which the orbit was widely dissected to make the HRP injections. The validity or otherwise of the claim by Buisseret-Delmas & Buisseret (1990) that central terminals of cat EOM proprioceptive fibres are distributed outside the spinal trigeminal nucleus is of some interest since, if correct, it might imply overlap between the termination zones of EOM and of neck muscle proprioceptive input in the cat—which would make it similar in this respect to the monkey (Edney & Porter 1986; Porter 1986) and perhaps the pigeon (Hayman *et al.* 1995). At the moment there is no way of deciding the issue.

In 1990, Buisseret-Delmas *et al.* (1990) made the interesting claim that cat vestibular nuclei receive a direct projection from primary afferents of EOM proprioceptors with their cell bodies in ME5. This was based on a very small number of double-labelled cells in ME5 after injections of tracer into EOM and into the vestibular nucleus. Of course this begs the question, discussed above, of whether the labelled ME5 cells were, indeed, EOM afferents. Porter & Donaldson (1991) doubt the validity of the claim on this basis, because of doubts raised by the very small number of double-labelled cells and also because the latencies of the physiological recordings of Ashton *et al.* (1985, 1988) in the cat vestibular nuclei, though they certainly showed the presence there of a signal from the EOM afferents, did not support a direct projection. Porter & Donaldson (1991), however, do not give the details of the argument on latency. These details are as follows. Batini *et al.* (1979) examined the fibre spectra of cat oculomotor nerves and give a range for the inferior oblique branch of the oculomotor nerve in the orbit of *ca.* 3–15 μm diameter with a mode *ca.* 5 μm. Taking the conventional conversion factor of six (Hursh 1939) would give a range of conduction velocities of 18–90 $m\,s^{-1}$ but there is reason to believe (see Matthews 1972) that, for smaller myelinated fibres at least, this gives too high values and that the formula of Coppin & Jack (1972) [conduction velocity $=1.5$(external fibre diameter)$^{1.5}$] gives a better estimate, in this case a range of about 8–87 $m\,s^{-1}$ with a mode *ca.* 17 $m\,s^{-1}$. These figures compare reasonably well with Batini *et al.*'s (1975) direct estimate of conduction velocity over part of the afferent path of 45–60 $m\,s^{-1}$ for the EOM afferents. Estimating the conduction distance from orbit to vestibular nuclei very generously as about 40 mm the slowest conduction time from the inferior oblique nerve in the orbit directly to the vestibular nuclei would be of the order of 5 ms and the modal value *ca* 2.5 ms. In fact it is improbable that EOM afferents would be as small as 5 μm, but, taking this value nevertheless, using the slower estimate of conduction velocity and adding a generous 1.5 ms for activation of the postsynaptic cell, one would expect latencies recorded in the vestibular nuclei to be no longer than 4 ms and most of them to be very much shorter than this. Using the lowest value of Batini *et al.* (1975) for afferent conduction gives 0.9 ms for the conduction time, which would lead to postsynaptic firing in, say, 2.5 ms. Ashton *et al.* (1988) stimulated the inferior oblique branch of the cat oculomotor nerve in the orbit and recorded responses of units in the vestibular nuclei. They present evidence that these units excited by electrical stimulation were, indeed, carrying signals from EOM proprioceptors. The shortest latency they encountered was 9 ms (range 9–80 ms with 66% of latencies 20 ms or less). Interestingly, Alvarado-Mallart *et al.* (1975*a*) found latencies of 2 ms for firing of cells in ME5 (putative first-order EOM afferents) when the abducens nerve was stimulated in the orbit. The conduction distance to ME5 is perhaps less than to vestibular nuclei but even doubling the conduction distance would give an expected latency of only 4 ms. These calculations are necessarily fairly rough but it seems difficult to believe, even taking the most favourable extreme values, that the latencies found by Ashton *et al.* (1988), the shortest of which was 9 ms with most units having latencies of at least twice this value, could represent a direct projection of EOM afferents to the vestibular nuclei. Porter & Donaldson (1991) also made a specific search of the cat vestibular nuclei for terminals in all their material from HRP injection in cat EOM and found none in preparations where there was abundant labelling in the spinal trigeminal nucleus.

(ii) *Pigeon*

In the pigeon, the only non-mammal in which the central terminations of EOM afferents have been sought, Hayman *et al.* (1995) found these in a restricted zone of the ipsilateral external cuneate nucleus with no terminals in the spinal trigeminal nucleus, though fibres of passage were observed descending in the lateral trigeminal tract. This tract—which does not seem to be present in mammals—contains fibres some of which end in the external cuneate nucleus. Interestingly it is not present in all birds but it is found in snakes that have infrared

sensitivity. Hayman *et al*. also speculate that there may be some homology in the processing of spatial information about target location between the pigeon, which depends on the visual system and its mobile eyes and head, and the almost-blind snakes which depend on infrared signals detected by the facial pits. In the cat, the external cuneate nucleus receives projections from axial neck muscles (Bakker *et al*. 1985) but the cat does not seem to have any projection from EOM primary afferents to this nucleus (see § 5(b)(i)). Whether the external cuneate receives neck muscle proprioceptive input in the pigeon is not known but the actions of EOM afferent signals on vestibularly driven neck reflexes of the pigeon, studied by Hayman and his colleagues and discussed below (§ 15), suggest that the possibility of overlap of primary afferent projections of EOM and neck muscle proprioception in the pigeon would be worth investigating.

6. THE SIGNAL CARRIED BY THE FIRST-ORDER AFFERENTS

We know much less than we would like to about the details of the information that the stretch receptors of the EOM send centrally. Yet this is the information on which all of the actions of the orbital proprioceptors depend. Our ignorance is not because the subject has been ignored; many of the 'early modern' papers in the 1950s and 1960s were devoted to study of the receptor properties by recording from their first-order afferents—real or putative. Unfortunately rather little of the information from this period is helpful in considering what one would now see as the essential questions to be asked about the afferent information—the extent to which, and the precision with which, information about the current eye position and the velocity of changes in eye position is provided to the central nervous system. There are two reasons why most of the work in the literature—interesting as it is from other points of view—is not useful in answering these questions. These converge on a similar conclusion—these were in general not the questions with which the authors were concerned. The early work on EOM afferents took place at a time when there was intense interest in the properties and physiology of the muscle spindle following Leksell's (1945) demonstration that the function of the small motor fibres of the ventral roots—themselves known for many years (Eccles & Sherrington 1930)—is to provide independent motor control to the intrafusal fibres of the muscle spindle. Matthews (1972) gives an excellent account of the history of the early work on the fusimotor system. The elegant extension of this work by Kuffler and his collaborators (for example, Hunt & Kuffler 1951; Kuffler *et al*. 1951) had shown that it is technically possible to examine the effects of the gamma system on the signalling properties of the muscle spindle. The way in which the gamma (fusimotor) system alters the transducer properties of the spindle was being pursued and one debated question was how best to measure these effects, whether by the somewhat contorted (as it now appears) calculation of gamma 'bias' (Eldred *et al*. 1953) or by some other index. Whitteridge's results (1959) on the signals from spindles in ungulate EOM are persuasive that the spindle sensitivity, that is the change in afferent firing for a given change in length, is the simple unequivocal measure from which the effect of gamma stimulation may readily be estimated. Unfortunately many workers continued the early practice of using weights to extend muscles and, when quantitative studies were made—and these were the exception in the early days—the results were usually expressed as changes in firing rate for increments in tension produced by hanging weights on the tendons (detached from the globe) of more or less isolated EOM. Not only is there no way of translating these results into sensitivity in terms of change in firing rate for unit extension but the incremental weight technique makes it almost impossible to study meaningfully the dynamic response of the receptors—their sensitivity to velocity. Finally, a point hardly ever considered, the properties of the receptors were studied by stretching individual eye muscles freed more or less completely from the globe of the eye and this is not a situation that mimics at all closely the intact muscle–globe complex, however convenient it may seem for studying receptor properties in pure culture, so to speak.

The recent results of Demer *et al*. (2000) show that the rectus muscles, in monkey and Man at least, are not simply inserted on the sclera but have pulleys, themselves variable in position. This makes even more apparent the limitations of studying the physiology of EOM receptors in eye muscles detached from the globe in a dissected orbit.

(a) *Ungulates*

In the climate of the 1950s it is easily understood that the EOM of the ungulates (in practice goats and sheep and, later, pigs) were particularly attractive for receptor study since, as we have seen, they contain very high densities of true muscle spindles. Since Cooper & Daniel (1949) had confirmed the presence of muscle spindles in human EOM, goats and sheep offered an apparently attractive model for Man. Doubts about the functional competence of human EOM spindles were then still far in the future. They also provided a rather convenient experimental preparation—after decerebration, avoiding the complicating effects of general anaesthetics on the excitability of the receptors, it was possible to record afferent spindle impulses from the ophthalmic branch of the trigeminal nerve to which Winckler (1937), confirmed by Whitteridge (1955), had shown that EOM afferents transfer from the (mixed) oculomotor nerves in the orbit. Alternatively, the mixed oculomotor nerves within the orbit could be studied more easily than in the cat since they are considerably longer. There is a further technical point to consider before the results are described. Although some of the work was carried out by recording in the periphery from mixed oculomotor nerves (Cooper *et al*. 1951; Cooper & Daniel 1957; Whitteridge 1959), many experiments in which the authors believed that they recorded first-order afferent responses were carried out on the brainstem. There Cooper *et al*. (1953*b*) recorded short-latency responses from the region of large cells within the mesencephalic nucleus of the trigeminal nerve (ME5) that they believed were the somata of first-order EOM spindle afferents. The responses were certainly typical of muscle spindles with a marked dynamic response during muscle stretch, slow adaptation and, usually, a pause on releasing the stretched eye muscle. The question is whether they arose from receptors in the

EOM. The difficulty is that sheep and goats, like cats and other non-primates, lack a complete bony orbit. Adjacent to the lateral wall lie the jaw-closing muscles and the somata of the muscle-spindle afferents of those muscles lie—and were known then to lie—in ME5 in the cat (Corbin & Harrison 1940). Cooper *et al.* (1953*b*) confirmed the presence of short-latency spindle-like discharges in the goat ME5 and took great pains to try to ensure that the units that fired in that nucleus when they stretched eye muscles were not somata of jaw spindle afferents. They argue rather convincingly from comparison of firing rates of putative EOM spindle afferents in ME5 with others, also in ME5, that they were confident were being driven by jaw muscles, that some of the central responses were most probably from EOM afferents. At the time those arguments stood. Now, however, there is perhaps more reason to doubt them because we know that the cell bodies of sheep and pig EOM proprioceptors—and presumably those of goats also, though I can find no account of this being tested—lie in the trigeminal ganglion and that cells in ME5 are not filled by transport of HRP from ungulate EOM (Bortolami *et al.* 1987). This is unlikely to be a technical failure to fill the cells because in the same series of experiments a few ME5 cells were filled when HRP was injected into cat EOM. It is most fortunate, then, that the ME5 responses of goats do not seem to differ in any way from those recorded in the mixed oculomotor nerves (Cooper *et al.* 1951; Cooper 1961; Whitteridge 1959) or the trigeminal ganglion (Lennerstrand & Bach-y-Rita 1974) (see also Bortolami *et al.* 1987; Manni & Peterossi 1976). In summary, then, ungulate EOM receptor responses include slowly adapting, 'in-parallel'-type behaviour with well-marked dynamic responses that have been confidently ascribed to the many muscle spindles known to be present in ungulate EOM (Cooper *et al.* 1955; Maier *et al.* 1974; Ruskell 1999). The afferent responses of ungulate EOM spindles can also be modulated by fusimotor activation (Whitteridge 1959) and muscle vibration (Lennerstrand & Bach-y-Rita 1974). There are also 'in-series' type responses that have been ascribed to tendon-organs—also known to be present in sheep EOM (Ruskell 1990). Without wishing necessarily to question these conclusions about the receptors responsible for the various types of response when ungulate EOM are stretched, it is worth noting that Blumer *et al.* (1998) have recently found innervated myotendinous cylinders (palisades) in sheep EOM and that, so far, we do not know what type of response these receptors give in any species.

(b) *Cat*

Though cats do not have muscle spindles in their EOM (for example, Cooper & Daniel 1949; Maier *et al.* 1974), they have been presumed for many years to have other stretch receptors (see Cooper *et al.* 1955; Cooper & Fillenz 1955; Tozer & Sherrington 1910). More recently these findings have been confirmed and it is clear that several types of receptor, including palisades but not spindles, are present (Alvarado-Mallart & Pinçon-Raymond 1979; Billig *et al.* 1997). As for goats and sheep, records have been made both peripherally in the cat orbit (Bach-y-Rita & Ito 1966; Bach-y-Rita 1971; Cooper & Fillenz 1955) from the abducens (VI) nerve near the brainstem (Bach-y-Rita & Murata 1964) and from putative somata of primary afferents in ME5 (Alvarado-Mallart *et al.* 1975*a*,*b*; Batini 1979*a*).

Recording from the inferior oblique branch of the oculomotor (III) nerve in the orbit, Cooper & Fillenz found two types of response to EOM stretch. The first were 'low threshold stretch receptors, which responded to stretch like the main sensory endings of muscle spindles' (Cooper & Fillenz 1955). They were slowly adapting with a marked pause in firing on release of muscle stretch and they reached a maximum firing rate during stretch of some 330 impulses s^{-1}, which is in the same range as the dynamic responses from true muscle spindles in ungulate EOM (Whitteridge 1959). There were also higher-threshold responses that were rapidly adapting. Bach-y-Rita & Ito (1966; the same experiments were re-described by Bach-y-Rita (1971)), in the most extensive study so far of the responses of the cat's EOM stretch receptors, reported rather similar findings that they classified as coming from 'in-parallel' type receptors (four out of 49 in their experiments), which seem to correspond to the 'low-threshold' type of Cooper & Fillenz, and rare higher-threshold 'in-series' responses (two out of 49) activated by EOM contraction, which may correspond to Cooper & Fillenz's second type. Most of Bach-y-Rita & Ito's responses, however, were of 'in-parallel' relatively slowly adapting type that showed no spontaneous activity. The finding by Bach-y-Rita & Murata (1964) of 'in-parallel' and 'in-series' responses in the abducens nerve near the brainstem would seem to indicate that some EOM afferents in the cat travel through that nerve. It is very interesting indeed that the spontaneously discharging 'in-parallel' type of response is so similar to that of limb muscle spindle primary afferents, though there seems no doubt at all that the cat EOM do not have morphologically true muscle spindles. However, Bach-y-Rita & Ito (1966) point out a number of differences between the responses of the most 'spindle-like' units—which seemed to be in the muscle belly when explored with a probe—and those of true muscle spindles. They speculated about the relationship of the cat EOM receptors to the muscle fibres. It is tempting to speculate about whether these responses, or some of them, might originate in palisade endings with which the cat EOM are well supplied but there is no evidence for this and the apparent situation of the receptors, in the muscle belly rather than the myotendinous junction, is against it. Bach-y-Rita & Ito (1966) concluded, unlike Cooper & Fillenz (1955), that there is probably only one functional type of receptor in the cat inferior oblique muscle. However, there are several morphological types of receptor in cat EOM, as recent tracer studies have confirmed (Billig *et al.* 1997) and, for the moment, there is no evidence to attribute any type of response to one or other morphological type of receptor.

For the central responses there are the same difficulties in excluding jaw muscles as the source as in the sheep, though, in the cat, there is the claim that a small number of ME5 cells are filled by HRP transport from the EOM to weight the argument. I do not believe that one can yet be certain of the status of these putative ME5 somata. The anatomical arguments are rehearsed in some detail by Porter & Donaldson (1991) and were summarized in § 5(a). If one just takes the physiological evidence on its

own merits, one's belief or disbelief turns on whether one believes it possible to be certain that manipulation of an EOM in a dissected orbit can be carried out without there being any possibility that the jaw muscles were disturbed. The various authors have been very conscious of the problem—whether one believes that they succeeded in overcoming it is likely to be coloured by one's own experience. For what it is worth, my own experience, based on many experiments on stretching individual EOM in the dissected cat orbit (Donaldson 1979; Donaldson & Dixon 1980; Donaldson & Long 1980) makes me very cautious about the claims. Anyone who has looked through the microscope at the convergence of the EOM proper, the retractor bulbi and slips of choanoid muscle in the apex of the cat orbit, and seen how any movement of one component is transmitted to others, may well feel that certainty that no disturbance is transmitted to the exquisitely sensitive spindles of the jaw muscles so close by must indeed be hard to attain. Perhaps the one exception might be stretch of the inferior oblique, which takes its origin from the bony medial orbital wall and not, as do the other EOM, from the annulus of Zinn in the orbital apex. I have recorded (I. M. L. Donaldson, unpublished data) typically spindle-like responses from cat ME5 on stretching the inferior oblique. However, the unit also responded to stretch of lateral rectus and so I could not be absolutely certain that the responses did not come from jaw muscle receptors. On the other hand, Alvarado-Mallart *et al.* (1975) recorded responses from ME5 to stimulation of the intraorbital part of the abducens nerve and these would not seem likely to have arisen from an extraorbital muscle so the question cannot be closed entirely.

Recent observations by Buisseret-Delmas *et al.* (1997) may, just possibly, add yet another twist to the question of whether responses recorded in ME5 to orbital stimuli are from EOM proprioceptors, by raising the possibility that they could be due to second-order projections from EOM afferents rather than to primary afferents. In the rat—in which no ME5 neurons appear to be filled by HRP injected into single EOM (Daunicht *et al.* 1985)—Buisseret-Delmas *et al.* (1997) found direct projections from spinal trigeminal nuclei, including the pars oralis and pars interpolaris, to ME5 whose neurons, unlike those of sensory ganglia, have synaptic contacts. This projection might provide a pathway for EOM afferent signals to ME5—albeit not a primary afferent path. However, at the moment, this possibility can only be speculative since we do not know whether EOM primary afferent fibres terminate in the spinal trigeminal nuclei in the rat as they do in the cat and monkey. It would seem well worth finding this out. The interest of this speculation is that it might explain the several well-attested records of activity in ME5 to EOM stretch or stimulation of intraorbital nerves and mean that it was no longer necessary to explain them away as caused by unrecognized activation of jaw muscle afferents. Even if the anatomy proves to be consistent with the speculation, there will remain the question of whether a pathway through the spinal trigeminal nuclei would be fast enough to explain short-latency responses in ME5. Both the questions of where primary afferent terminals from EOM proprioceptors are to be found in the rat and of whether there are responses in rat ME5 to EOM afferent activation, and at what latency, are eminently answerable and seem well worth answering. Another obvious question is whether the cat—which does have primary afferent terminals in the spinal trigeminal nuclear complex—also has a direct projection from this complex to ME5.

For the moment it is fortunate once again that the putative ME5 primary afferent responses do not seem to show any characteristics not found in units recorded in the mixed oculomotor nerves of the cat. Though it is agreed that the cat trigeminal ganglion contains most, if not all, of the somata of first-order afferents—see Porter & Spencer (1982) and discussion in Porter & Donaldson (1991)—Bortolami *et al.* (1987), who seem to be the only people who have tried, were not able to record any responses in the ophthalmic part of the ipsilateral trigeminal ganglion to stretch of cat EOM—this failure will be discussed again later (§ 6(d)).

It seems, then, that the cat EOM proprioceptors provide both slowly adapting 'spindle-like' signals to the central nervous system and also other, more rapidly adapting signals (Bach-y-Rita & Ito 1966; Fillenz 1955), but that these cannot yet be attributed to particular morphologically identified receptor types.

(c) *Monkey*

There is almost no information about the nature of signals from monkey eye muscle proprioceptors at any level. Cooper & Fillenz (1955) studied a single mangabey monkey and reported responses of two units in a slip of the inferior oblique branch of the oculomotor nerve. One of these was slowly adapting and 'spindle-like'. Cooper *et al.* (1955) mentioned responses to EOM stretch detected in the medulla of a baboon and showed a rather non-specific record. Ito & Bach-y-Rita (1969) found no dynamic response to stretch in the inferior oblique branch of the squirrel monkey's oculomotor nerve, though there were long-latency effects of sustained stretch that were abolished by adrenaline and were ascribed to vascular receptors. Ruskell (1999) rightly bemoans the lack of information about afferent signals from primate eye muscle proprioceptors, though we know the location of the primary afferent somata and the terminals of the primary afferents from the work of Porter summarized above (Porter *et al.* 1983; Porter 1986).

(d) *Quantitative information about the primary afferent signal*

Quantitative information is rather sparse.

(i) *Cat*

For the cat there is a fairly extensive study by Bach-y-Rita & Ito (1966). Changes in the response of cat primary afferent firing were recorded as the EOM were progressively stretched by hanging weights on the distal tendon after detaching it from the globe. The EOM were also stretched at various rates and with various loads. Most of Bach-y-Rita & Ito's results are expressed as firing rate change per gram of added muscle tension. However, for four slowly adapting units with no spontaneous discharge and 'in parallel', the authors quote static sensitivities calculated from the load–extension relationship, which is said to be linear for loads of less than 5 g; these

are 10.2, 4.0, 14.1 and 9.6 impulses $s^{-1} mm^{-1}$. Taking the cat's eyeball diameter as 21 mm (Henderson 1950) this corresponds to some 1.9, 0.73, 2.6 and 1.8 impulses $s^{-1} deg^{-1}$ of eye rotation. As far as I know this information, based on four units, is all that is known about the eye position sensitivity of cat EOM afferents. The static sensitivity is apparently similar to that of the true muscle spindles of sheep or goat (see below) but one must be very reluctant to draw any conclusion from measurements from a small number of afferents that also formed a very small proportion of the receptors examined (four out of 52). The other receptors had no spontaneous discharge.

(ii) *Ungulates*

In the goat and sheep, Cooper *et al.* (1951) and Whitteridge (1959) made an elegant quantitative study of the effects of gamma stimulation on the properties of spindle responses in the superior oblique muscle and compared the sensitivity of de-efferented spindles with those when the gamma system was stimulated at various rates. Cooper *et al.* (1951) estimated that in the goat the sensitivity of the afferents would be capable of detecting eye movements of less than 1.5°. They based this on the firing rate of single endings—it was the deflection required to change firing by twice the standard deviation and, to date, they appear to be the only authors who have explicitly considered the effects of the variability of primary afferent firing rates. However, it is perhaps to be expected that spatio-temporal averaging of the responses of many afferent units will form the basis of the central estimate of eye position and one might expect this to provide greater sensitivity. Though it is now known (see Browne (1975) for sources) that sheep EOM spindles are frequently beta-innervated (intrafusal fibres supplied by branches of the extrafusal motor supply rather than by independent motor gamma fibres), Whitteridge's results stand as a classical demonstration of the effect of fusimotor stimulation on spindle sensitivity. He provided measurements of the position sensitivity of the afferent responses in terms of firing rate change per change in muscle length from which, using his calibration that 1 mm of muscle stretch is equivalent to 5° of eye rotation, one can transform the sensitivities into units of angular position. He found that most de-efferented spindles had sensitivities equivalent to 0.2–1 impulses s^{-1} deg^{-1}; the maximum observed was 2 impulses s^{-1} deg^{-1}. During gamma stimulation, sensitivity increased to maxima of 3–4 impulses s^{-1} deg^{-1}. The measurements were taken 50 ms after the muscle reached its stretched length and so probably include part of the 'dynamic' response—the sensitivity of the adapted 'static' response would be less. Browne (1975) showed that sheep spindle afferents do not seem to be divisible into the primary and secondary types described classically in cat soleus (see Matthews (1972) for definitions and extensive discussion), but form a continuous population whose dynamic indices and sensitivity to vibration are related to their conduction velocities. Browne was not primarily concerned with spindle afferent sensitivity but from examination of his fig. 2 it would seem that his values for de-efferented sheep spindles are comparable (very roughly 1.5 and 2.5 impulses s^{-1} deg^{-1}) to the maximum reported by Whitteridge. From a graph in the paper of Manni *et al.* (1989) on the effects of botulinum toxin on goat and sheep afferent discharge, it is possible to estimate sensitivities for the adapted discharge as about 3.6 impulses $s^{-1} mm^{-1}$ (0.7 impulses $s^{-1} deg^{-1}$) before and 1.8 impulses $s^{-1} mm^{-1}$ (0.4 impulses $s^{-1} deg^{-1}$) after putative blocking of contraction of spindle intrafusal fibres. Both values agree with Whitteridge's range of 1–5 impulses $s^{-1} mm^{-1}$ (0.2–1.0 impulses $s^{-1} deg^{-1}$) for spindles not under gamma drive. Velocity sensitivities were not reported by Whitteridge (1959) though it is very clear from the illustrations that the spindles have marked dynamic responses. Browne (1975) however, studied the dynamic index of the sheep spindle—a measure of its velocity sensitivity—(see Matthews (1972) for definition) and concluded that its relationship to afferent conduction velocity was not dissimilar to that of the cat soleus. Overall it seems that sheep eye muscle spindles are fairly similar in their properties to those of (cat) limb muscles except that their afferents do not seem to fall into distinct populations of primary and secondary types.

(iii) *Rat*

Historically, the next quantitative observations of length and velocity sensitivity were those of Daunicht (1983) in the barbiturate-anaesthetized rat. He stretched all the EOM simultaneously using a sinusoidal length change (it is not clear to what extent the tendons were detached from the globe). The units, recorded from the trigeminal ganglion in which the primary afferent somata are found (Daunicht *et al.* 1985), seem to have been slowly adapting. He quotes 6.5 impulses $s^{-1} deg^{-1}$ as the 'sensitivity' at 1 Hz—but the sinusoidal stimulus necessarily confounds length and velocity sensitivity—and concludes that the response characteristics '...may be summarized as an intermediate behavior between position- and velocity-dependence'. However, as we have pointed out (Fahy & Donaldson 1998), the observations can equally well be described as showing dependence upon both eye position and velocity. Rat EOM do not contain muscle spindles (Daunicht *et al.* 1985; Maier *et al.* 1974) and the nature of the EOM receptors responsible for the responses is unknown.

(iv) *Pigeon*

The decerebrate pigeon has proved a fruitful preparation in which to study central effects of EOM afferent signals, as will be described later. Having shown that the somata of the pigeon's EOM proprioceptors lie in the ipsilateral trigeminal ganglion (Hayman *et al.* 1995), Fahy & Donaldson (1998) examined the responses of primary afferents by recording from their somata in the decerebrate pigeon using the same technique of imposing movement upon the eye in the intact orbit that had proved very effective in studying central actions of the signal. Though unit responses were easy to record in the ganglion, the EOM primary afferents formed a small proportion of these and seemed to be confined to a very small volume of the ganglion. If the cat ganglion is similar, this may well explain the failure of Bortolami *et al.* (1987) to record responses to muscle stretch there. Fahy & Donaldson (1998) found that most units gave sustained responses with both dynamic and static components and they found evidence of both position and velocity

sensitivity. The amplitude (position) sensitivity measured when the eye had reached its final, deflected position, ranged from 0.9 to 8 impulses $s^{-1} deg^{-1}$; these values were unaffected by the velocity with which the eye was displaced. These position sensitivities are rather similar to the range in the goat and perhaps the cat (see above) and it is interesting that the maximum sensitivity in the pigeon, which has no spindles in its EOM (Maier *et al.* 1971), is at least as great as that recorded from ungulate EOM spindles under maximum gamma drive. During the displacement, units were found to show velocity sensitivity, though this seems rather small—the maximum was 0.2 impulses $s^{-1} deg^{-1}$. The values are all based on responses from single units averaged over a number of stimulus presentations but the data collection method did not allow the variability of the responses to be calculated. Dynamic indices were also estimated and ranged from three to 52 but it is difficult to compare these to results from other muscles under very different conditions (for instance, the more extensive dynamic index study of Bach-y-Rita & Ito (1966) in the cat EOM) and their main value is to confirm that most units do have some velocity sensitivity. The pigeons were paralysed and the authors discuss the possible effects of this on the results, concluding that receptors in non-paralysed eye muscles might well show larger sensitivities (Fahy & Donaldson 1998). The units, though relatively slowly adapting, did adapt over seconds and so would not provide a continuous signal of the position of a stationary eye. It is suggested that 'they are best described as signalling position and velocity in relation to eye movements'. Since the eye is never stationary for long these characteristics seem quite appropriate to the normal requirements of the oculomotor system. Pigeon EOM do not contain muscle spindles (Maier *et al.* 1971) and it is unfortunate that we know nothing of the morphology of the pigeon EOM proprioceptors. Nevertheless, these are the only observations, as far as I know, of the behaviour of EOM proprioceptors in conditions that approximate those in the natural situation with undisturbed orbital mechanics. It is intriguing that the estimates of eye position sensitivity—even with the pigeon EOM paralysed—are very much in the same range as that apparently provided by the muscle spindles of ungulates under maximum gamma drive. From the small amount of information available, whatever other advantages having muscle spindles in the EOM may confer, it would not seem that they provide much greater sensitivity to eye position in the orbit than do other types of receptor. Unless the pigeon EOM turn out to contain palisades and only palisades, we have no information at all about the range of information that these receptors—arguably the characteristic receptor of the vertebrate EOM (see Spencer & Porter 1988)—may provide to the central nervous system. This would seem to be a fruitful field for further research if the formidable technical difficulties that are only too apparent can be overcome.

7. THE PROJECTIONS OF AFFERENT SIGNALS FROM THE EXTRAOCULAR MUSCLES TO STRUCTURES IN THE CENTRAL NERVOUS SYSTEM

In the early studies of the physiology of the EOM afferents in the 1950s, projections of their signals were found to parts of the central nervous system (Cooper *et al.* 1953*a*,*b*; Fillenz 1955) as shown by their ability to excite neurons there. Since then a considerable body of observations has accumulated, showing that the afferent signals find their way to many parts of the nervous system—significantly to areas that are concerned either with the analysis of visual information or with the control of eye movement (and sometimes of gaze), or both. Experiments have varied in their complexity and in the extent to which they have attempted to analyse the effects of the eye muscle afferent signals on neural processing in the central structures, as well as simply to document their arrival there. It has to be admitted that we know a great deal more about where the signal is to be found in the central nervous system than we do about how it gets there from the primary afferent terminals. To demonstrate just how widely the signal is distributed within the brain and over what range of species the central signals have been studied, table 1 presents a summary of our present knowledge.

8. DO EXTRAOCULAR MUSCLE AFFERENT SIGNALS PROJECT TO THE SUPERIOR COLLICULUS?

The superior colliculus was one of the first central structures in which the presence of responses to stretch of eye muscles was reported. Cooper *et al.* (1953*a*) found a few long-latency responses to stretch of goat EOM and Fillenz (1955) described a larger number of units in cat superior colliculus again activated by stretch of eye muscles, in both cases under barbiturate anaesthesia. In some experiments under chloralose anaesthesia Fillenz also noted, 'the very much greater number of responses to stretching the eye muscles than in cats under Nembutal anaesthesia and the resemblance in this respect to decerebrate preparations'. Thus the likelihood of the results of experiments on the central actions of EOM afferents being considerably affected by the particular anaesthetic used was realized early. In the 1970s, Abrahams and his colleagues (Abrahams & Rose 1975; Abrahams & Anstee 1979) studied units in cat superior colliculus activated either by electrical stimulation of neck and of eye muscle nerves or by passive rotation of the eye. Donaldson & Long (1977) and Batini & Horcholle-Bossavit (1977) independently but almost simultaneously found that visual responses in the cat superior colliculus were affected, usually inhibited, in the first case by stretch of EOM and in the second by electrical stimulation of the muscle nerves of the lateral and medial rectus in the orbit. These results were later expanded and described in detail (Batini & Horcholle-Bossavit 1979; Donaldson & Long 1980).

It is important to note that Donaldson & Long's experiments used chloralose anaesthesia, while those of Batini & Horcholle-Bossavit were carried out in the unanaesthetized *encéphale isolé* preparation. However, in 1989, Nelson *et al.* (1989), unimpressed by the apparent non-specificity of the reported responses to EOM proprioceptive afferents in the superior colliculus, carried out quite an extensive series of experiments in the cat under various anaesthetics and came to the conclusion that signals from the EOM do not reach the superior colliculus. They did find unit responses in the colliculus

Table 1. *Structures in the central nervous system shown, by electrical recording, to receive signals from extraocular muscle afferents*
(Primary, or putative primary, afferent signals are excluded.)

central structure	species	author(s)
brainstem (various areas)	goat, sheep	Cooper *et al*. 1953*a*,*b*
	cat	Fillenz 1955
	pigeon	Donaldson & Knox 1988, 1989
nucleus praepositus hypoglossi	cat	Ashton *et al*. 1988
vestibular nuclei	giant toad	Ashton *et al*. 1984*a*
	bony fish (trout)	Ashton *et al*. 1986*b*, 1989
	cat	Ashton *et al*. 1988, 1985
	pigeon	Donaldson & Knox 1988, 1993
oculomotor nuclei	cat	Tomlinson & Schwarz 1977
	bony fish (trout)	Ashton *et al*. 1986*a*, 1989
	pigeon	Donaldson & Knox 1990*b*, 1993, 1991
superior colliculus	cat	Abrahams & Anstee 1979; Abrahams & Rose 1975; Batini & Horcholle-Bossavit 1979; Donaldson & Long 1977, 1980; Nelson *et al*. 1989[a]
optic tectum	pigeon	Knox & Donaldson 1995*a*; Knox & Whalley 1997
cerebellum (vermis)	cat	Fuchs & Kornhuber 1969; Baker *et al*. 1972; Schwartz & Tomlinson 1977
	bony fish (trout)	Ashton *et al*. 1986*b*, 1989
	pigeon	I. M. L. Donaldson and P. C. Knox (unpublished data)
cerebellum (flocculo-nodular complex)	cat	Maekawa & Kimura 1980
	pigeon	F. L. Fahy and I. M. L. Donaldson (unpublished data)
pulvinar and nucleus posterior thalami	cat	Buisseret *et al*. 1983
lateral geniculate nucleus	cat	Dixon & Donaldson 1979; Donaldson & Dixon 1980; Lal & Friedlander 1990*a*,*b*
	rabbit	Molotchnikoff & Casanova 1985
visual cortex (Area 17)	cat	Buisseret & Maffei 1977; Enomoto *et al*. 1983; Ashton *et al*. 1983*a*, 1984*b*
visual cortex (Area 18)	cat	Buisseret *et al*. 1988*b*
Clare Bishop Area	cat	Donaldson 1979
frontal cortex	cat	Barbas & Dubrovsky 1981*a*,*b*

[a] These authors deny the existence of EOM proprioceptive signals in the cat superior colliculus—see discussion in text.

when eye muscles were stretched but only when chloralose was the anaesthetic or was given to cats already anaesthetized with other agents—but they dismiss these responses as being due to mechanical disturbance of periorbital tissues. Should one then accept this dismissal? Let us consider the evidence.

Nelson *et al*. (1989) imply that results under chloralose are unreliable for various reasons but similar results were obtained under barbiturate (Fillenz 1955) and, more importantly, without anaesthesia by Batini & Horcholle-Bossavit (1979) who examined not, as Nelson *et al*. (1989) said, 'small numbers' of collicular responses but 94 units using muscle nerve stimulation. Nelson *et al*. (1989) dismiss these results and the earlier observation of Abrahams & Rose (1975) on the singularly unconvincing grounds that 'it is difficult to eliminate categorically the spread of electrical current to periorbital tissues'. In fact, with the divided muscle nerves on stimulating electrodes in a pool of insulating mineral oil, it is not difficult for a competent experimenter to adjust the stimulus so that it is near threshold for the nerve fibres in contact with the electrodes when extraorbital spread is exceedingly improbable. These techniques have been used successfully and reliably since the 1950s. Interestingly, visual responses in the cat superior colliculus are critically affected by at least one anaesthetic combination. Donaldson *et al*. (1978) found that adding nitrous oxide to the oxygen inhaled by cats under chloralose anaesthesia in concentrations as low as 50% abolished or reduced the visual responses of units in the cat superior colliculus. I have also confirmed the experience of Fillenz that central activity from EOM stretch is much less marked under barbiturates than under other anaesthetics. Thus, though the anaesthetic used is not relevant to deciding the origin of the collicular responses to muscle stretch it may well be critical in deciding if any responses are found—as indeed, the work of Nelson *et al*. (1989) shows—and, very probably, may affect the details of how the central units respond. What of the claim that Nelson *et al*.'s responses arose from periorbital tissues rather than from EOM receptors? The authors failed to abolish a collicular response to stretching lateral rectus by injection of local anaesthetic near the muscle's insertion. But they do not say whether, as was apparently usually the case, the unit responded to stretch of more than one EOM. This point is dealt with specifically by Donaldson & Long (1980) who showed that it may be necessary to inject more than one EOM to block collicular responses to stretch of just one muscle. The finding of responses on stretching periorbita after failing to abolish completely the response to EOM stretch with local anaesthetic means nothing since stretching periorbita almost inevitably moves the eye muscles.

Nelson *et al.*'s (1989) further experiment on cutting oculomotor nerves, however, requires more serious consideration. They found that responses to stretch of superior, inferior and medial rectus persisted after section of the oculomotor, trochlear and abducens nerves 'in the orbit' and that after all these nerves were sectioned pulling the periorbita also caused the collicular unit to respond. It is unfortunate that insufficient details are given to allow one to decide if this is really the knock-down demonstration that it seems at first sight that the response was only from periorbital tissue. First, the unit described responded to three muscles, so to demonstrate that its origin was not from EOM proprioceptors all three muscles would need to be deafferented. Now the afferents leave the oculomotor nerves at or near the orbital apex and join the ophthalmic branch of the trigeminal nerve so either all the nerves—and all their branches—would have to be cut as they left the muscles or the trigeminal nerve would have to be cut intracranially. Cutting the oculomotor nerves in the orbit might or might not deafferent all the muscles. Nelson *et al.* (1989) were not specific enough about where the sections were made to allow one to be certain that all the muscles were deafferented. Again, stretching the periorbita and getting a response under these conditions shows nothing unless one is certain that the muscles are deafferented. However, let us suppose that the EOM were deafferented and there was a response due to receptors in periorbital tissue; Nelson *et al.* (1989) say such responses were obtained in seven of nine cells tested but they do not say if these cells were all recorded after putative deafferentation of the EOM. Donaldson & Long (1980) were very aware of the potential dangers of being misled by mechanical stimulation of receptors outside of the EOM. Their fig. 2 illustrates an experiment that gave the diametrically opposite result to that of Nelson *et al.* (1989)—it illustrates the responses of a collicular unit to four different EOM and the lack of response from this unit when the periorbital tissues, including the whole of the soft orbital floor, were stretched. The inferior oblique muscle, to which the unit responded, lies on this orbital floor. Even so there was no response to stretch of the periorbital tissue. Thus, even if one were to accept Nelson *et al.*'s (1989) contention that responses from stimulation of the periorbita might be mistaken for responses from EOM, one would also be entitled to conclude from the results of Donaldson & Long (1980) and Batini & Horcholle-Bossavit (1979) that the superior colliculus also receives signals that almost certainly do come from receptors in the eye muscles.

The criticisms of Nelson *et al.* (1989) have been analysed in detail because this illustrates some of the very considerable difficulties, technical and interpretational, that are posed by experiments using stretch of eye muscles in a dissected orbit. The topic will appear again later (§ 10) when alternative methods of inducing signals from the EOM proprioceptors are considered.

From a functional point of view the recent work of Knox (Knox & Donaldson 1995*a*; Knox & Whalley 1997) on the actions of EOM afferent signals on responses of units in the avian homologue of the superior colliculus, the optic tectum, is perhaps more interesting than the older observations on the cat superior colliculus. These experiments were carried out on decerebrate pigeons so the anaesthetic issue does not arise, the orbit was not dissected and units were found that responded in a way clearly quantitatively related to the stimulus magnitude and that were sensitive to the plane and direction in which the eye was rotated. The units' visual responses were also often modified by the proprioceptive signal. This work is discussed separately in § 11.

9. LATERAL GENICULATE NUCLEUS

The dorsal lateral geniculate nucleus of the thalamus (LGNd) receives the terminations of retinal ganglion cell axons and is the relay on the retino-geniculo-striate pathway that conveys visual information from the eye to the primary visual cortex. After the reports that EOM afferent signals reach the cat primary visual cortex (Buisseret & Maffei 1977) and other visual areas (Donaldson 1979) it was natural to seek a possible thalamic relay for these signals.

Donaldson & Dixon (1980) found units in all layers of the cat LGNd and in the overlying perigeniculate nucleus that responded to stretch of individual EOM in the anaesthetized, paralysed cat. Most (63%) of these responsive units were found in layer A1 of the LGNd ipsilateral to the eye whose muscles were stretched. This is the layer that receives visual input from the ipsilateral eye. Responsive units were also found in layer A, which receives its visual input from the contralateral eye, and in other layers. The relatively small number of responses found in layer A may reflect only the way in which the experiments were carried out since only the EOM of the ipsilateral eye were stretched and it seems probable that, if the principal EOM input goes to the same layer as the visual input (as is the case for the ipsilateral eye), layer A would receive EOM input principally from the contralateral eye whose EOM were not stretched in these experiments. All the responses were more or less phasic, that is, there were no truly tonic responses and there was no evidence of a signal of direction of eye rotation since a given geniculate unit generally responded to stretch of several EOMs, which would be activated by different directions of eye movement. Indeed, responses of the same unit to stretch of horizontal, vertical and oblique muscles are illustrated in the paper. Most (93%) of the units responding to EOM stretch also had visual responses (though the inverse was not true and only 28% of all units tested had EOM responses) and examples of sustained and transient responses with ON and OFF centre fields were found among the units that also carried the EOM afferent signal. Donaldson & Dixon (1980) did not test for interactions between visual and EOM signals, though they pointed out that these were to be expected since many units receive both signals.

In 1985, Molotchnikoff & Casanova (1985) found units responsive to stretch of individual EOM in the perigeniculate nucleus of the rabbit (but not, apparently, in LGNd) and noted excitatory and inhibitory interactions between the EOM afferent signal and the effects of a brief flash of light in the cells' visual receptive fields. The experimental arrangement was similar to that of Donaldson & Dixon (1980). The EOM of the ipsilateral eye were stretched and visual stimuli were delivered through the contralateral eye.

Donaldson & Dixon (1980) and Molotchnikoff & Casanova (1985) describe detailed control experiments that ensured that the effective signal when the EOM were stretched was not due to inadvertent visual, auditory or cutaneous stimulation. Both sets of authors also discussed the possible pathways by which the EOM afferent signal might reach the perigeniculate and geniculate nuclei and agreed that it was not possible at that time to differentiate between a putative ascending pathway and corticofugal connections from visual cortex to LGNd. In fact, by 1985, there had already been an attempt to resolve the question experimentally. In 1984, Ashton *et al.* (1984*b*) reported units in layer four of cat primary visual cortex with responses to EOM afferent signals induced by passive movement of the eye. Since the principal projections from LGNd end in cortical layer four the possibility that the EOM afferent signal might follow the same path is attractive. We therefore tried to resolve the question of an ascending versus a corticofugal projection by inactivating the primary visual cortex by cooling while recording EOM afferent responses from the LGNd. However, the experiments were not technically very satisfactory and the results were inconclusive (see note in Ashton *et al.* 1984*b*, p. 661). The question remains unresolved.

Lal & Friedlander (1990*b*) then carried out an extensive study of the effects of passive displacement of one eye of the paralysed anaesthetized cat on the responses of units in layer A of the LGNd to visual stimuli presented to the contralateral eye. In 40% of the units there was a statistically significant effect of eye position on the visual response tested while the eye was held static at a number of displaced positions temporal or nasal to the rest position. The strength of the interaction, which was more often inhibitory (69% of relevant units) than excitatory (31%), increased in many units as the eye position became more eccentric in either direction, nasal or temporal. Only eye deflections in the horizontal plane were examined. There was no effect of static eye displacement on the spontaneous activity of units and thus the effect of passive eye deflection was a modulation of the coexisting visual response. Quantitative examination of the visual response of the units allowed them to be classified as X or Y cells—members of both types showed the eye deflection effect. Control experiments eliminated visual input as a possible source for the signal producing the effect of eye deflection, which the authors argue, convincingly, was due to activation of EOM stretch receptors by the passive eye deflection. On the basis of these results, Lal & Friedlander (1990*b*) suggested that the ensemble of activity across layer A of the LGNd would differ when a visual stimulus of a given contrast was viewed with the eye in the rest position and when the eye was horizontally deflected nasally or temporally. They proposed that this ensemble of activity might encode a signal of eye position. However, as indeed the authors point out, the symmetrical effects found would not provide the basis for determination of the direction of the eye deflection but only its magnitude. In a second, rather less extensive series of experiments, the same authors (Lal & Friedlander 1990*a*) tested cat LGNd units for modulation of their visual responses in close temporal relationship to passive movement of the ipsilateral eye. Such effects, mostly facilitatory, were found. From the standpoint of the authors' theory of spatial encoding the most interesting of these was the finding of nine neurons that had directionally selective interactions between visual stimulation and passive eye movement. In view of the critical importance of the existence of a direction signal to the credibility of the hypothesis, it is curious that only 12 out of 78 neurons were tested for possible directional effects. Also, although 26 units were tested for the presence of both the passive eye deflection effect and the effect of eye movement—and four units were found to show both effects—we were not told whether any of these had directionally selective responses to eye movement. It is also both curious and unfortunate that the authors tested only eye deflection and eye movement in the horizontal plane since one would reasonably expect that a system of ensemble coding would operate in more than one plane—a good test of the hypothesis might have been to examine the extent to which signals of passive displacement in various planes were associated with visual signals directionally specific to, and within, that plane. One would also wish to know how precisely tuned the directional signal was and this cannot be determined without testing the effects of eye movement in several planes. In the absence of tests of this type it is difficult to regard the suggestion of ensemble coding of eye position within the cat LGNd based on effects of EOM afferent signals as more than a possibly interesting, but not yet critically tested, hypothesis.

Setting aside the lack of critical evidence to support it, one might enquire if the hypothesis is plausible. It is always dangerous to speculate on what might be 'sensible' arrangements for the nervous system to make in the way it encodes its signals and it may, therefore, be inappropriate to give too much credence to one's feeling that the hypothesis of Lal & Friedlander (1990*a*,*b*) is not a 'sensible' one. But it would seem strange for the nervous system to rely on what would appear to be a somewhat crude encoding system in which the magnitude of the eye deflection was encoded only by changes in the response of a population of neurons while the direction components were encoded in the responses of single units. The two signals would seem to require very different processing, the results of which would then have to be combined before any useful information was available about the eye's position in the orbit. One's doubts are increased by the observations that there do seem to be EOM afferent signals of plane of eye movement and direction of movement within that plane that are encoded at the level of single units both peripherally (Fahy & Donaldson 1998) and centrally, in the visual cortex (Ashton *et al.* 1984*b*,*c*), as well as in other central structures—for example in the cat vestibular nucleus and nucleus praepositus hypoglossi (Ashton *et al.* 1988) and pigeon optic tectum (Knox & Donaldson 1995*a*; Knox & Whalley 1997). This list is by no means exhaustive.

The results of Lal & Friedlander (1990*a*,*b*) are, however, interesting in that they contain one of the few demonstrations of a tonic effect on central units of, if not necessarily a tonic signal from, EOM afferents. In general, such tonic central effects have been conspicuous by their absence, although recently another example of a tonic effect of eye position apparently signalled by EOM proprioceptors has been uncovered in the pigeon optic

tectum (Knox & Donaldson 1995*a*; Knox & Whalley 1996). There is also a suggestion that some of the effects in the abducens nucleus may be 'tonic' (Donaldson & Knox 1991).

Over a number of years Salinger and his colleagues (see Guido *et al*. 1988) have shown that units in the cat LGNd show the effects of complex interactions between visual signals and EOM proprioceptive input. Using section of the ophthalmic branch of the trigeminal nerve to deafferent the eye muscles, and examining the effects of various combinations of visual deprivation, monocular paralysis and EOM deafferentation on the ratio of X to Y cells encountered by a recording electrode, they have found various complex binocular interactions between visual and EOM proprioceptive effects. These they describe as 'consistent with the belief that the LGNd is one site in the visual pathway where proprioceptive and visual signals from the two eyes converge' (Guido *et al*. 1988). However, they were not able to ascertain whether these binocular visuoproprioceptive interactions depend on transcortical pathways or whether they occur between signals reaching the LGNd by ascending pathways. Thus the question again remains open whether the effects are produced by signal interaction within the LGNd or whether the effects found in that nucleus are a reflection of signal processing at the cortical level. Indeed, it is not impossible that the properties of the LGNd units might depend on both putative mechanisms.

10. VISUAL CORTEX

In 1976 Maffei and his colleagues found that strabismus (squint) induced by surgical interference with extraocular muscles resulted in a decrease in the proportion of cells in the primary visual cortex that were binocularly visually activated. Since this was true both in kittens (Maffei & Bisti 1976) and in adult cats (Maffei & Fiorentini 1976) even when the animals were deprived of vision after the surgical procedure, it seemed that the asymmetry of eye movement was itself sufficient to produce a change in the behaviour of cortical units to visual input in the adult as well as in the developing cortex. Clearly eye muscle proprioceptive signals were one potential agency by which the asymmetry in eye movement might bring about these effects. In 1977, therefore, Buisseret & Maffei (1977) sought, and found, evidence for projection of signals from EOM proprioceptors to the cat primary visual cortex. Using electrical stimulation of the inferior oblique branch of the oculomotor, trochlear and abducens nerves in the orbit (where they carry EOM afferents) in cats anaesthetized with chloralose they found responses of units in both the ipsilateral and contralateral primary visual cortex. Out of 90 units recorded, 22 responded to stimulation of one or more oculomotor nerves. Under barbiturate anaesthesia they also found responsive cortical units when individual EOM were stretched and showed that these responses could be reversibly blocked by infiltration of the EOM with local anaesthetic—thus confirming that the signal source lay within the EOM. No tests were made for interaction between the effects of EOM afferent activation and visual stimulation.

Following this demonstration, work developed in three directions. First, an extensive series of experiments was made on the effects of deprivation or manipulation of the EOM proprioceptive signal on the development of the visual properties of the neurons of the cat visual cortices. This work was carried out almost exclusively by Buisseret and his colleagues and is the subject of an excellent review by Buisseret (1995). The details will not be repeated in this review but the principal findings are summarized in § 12. Second, further impetus was given to examination of the effects of eye movement and of extraocular proprioceptive signals on the development and maintenance of normal visuomotor behaviour. For background see Hein & Diamond (1983) and Jeannerod (1988) (this topic is the subject of § 16). Finally, the physiology of the EOM afferent actions in the visual cortex was studied in more detail and attempts were made to define the information carried by visual cortical units as a result of their input from EOM proprioceptors and to understand the ways in which proprioceptive and visual signals interact at the cortical level. These attempts will be considered now.

There was general surprise at the finding that the primary visual cortex appeared to receive signals from EOM proprioceptors since the current belief was that Area 17 was not likely to be concerned with either the control, or the consequences, of eye movements. However, within a short time of the appearance of Buisseret & Maffei's (1977) paper, I confirmed their findings of unit responses to stretch of individual EOM in what was undoubtedly cat primary visual cortex, Area 17, on histological examination (I. M. L. Donaldson, unpublished data). It was also apparent that EOM proprioceptive signals interacted with the effects of visual stimuli and that, to study these interactions successfully, quantitative methods of delivering the stimuli and collecting and analysing the data were going to be essential to differentiate response modulations due to the interactions of the stimuli from those due simply to variation in the cortical response to the same stimulus with time.

In the same year as Buisseret & Maffei found the responses in primary visual cortex, new information became available that suggested that other cortical visual areas might receive a signal from the orbital proprioceptors. Kennedy & Baleydier (1977), using anatomical methods, found that the intralaminar nuclei of the thalamus, already known to contain units firing in association with saccadic eye movement (Schlag *et al*. 1973, 1974), project to extrastriate visual areas including part of the suprasylvian gyrus, the Clare Bishop Area. Kennedy & Magnin (1977) then showed that units in the Clare Bishop Area of the alert cat fired in relation to spontaneous saccades and vestibularly induced fast-phase eye movements. These responses were generally directionally selective and, from the illustrations in the paper, appeared to occur only after the beginning of the eye movement. It was thus possible that they might be receiving an inflow signal from the eye muscles. I therefore recorded from the Clare Bishop Area of anaesthetized cats and found units that responded to stretch of individual EOM in the ipsilateral orbit in the absence of visual stimulation. The results were published only in summary (Donaldson 1979). Seventeen units with responses to EOM stretch were examined—16 also had visual responses. At first sight the proprioceptive

responses did not appear to be directional since units responded to more than one EOM. In fact, however, stretching individual muscles is not a satisfactory way to test for directionality in the responses of central units since more than one EOM takes part in all eye movements, so a unit responding to stretch of more than one EOM may nevertheless encode only one direction of eye movement. In effect, it is only if a central unit responds to stretch of only one EOM and all the others have been tested, and their receptors have been shown to be in working order by later recording at least one unit responsive to each muscle severally, that one can be confident about deducing directionality from responses to individual EOM. In practice these conditions are practically impossible to meet. In the Clare Bishop Area some of the latencies of response to rapid stretch of an eye muscle were very short. Donaldson (1979) reported three units with latencies of less than 10 ms 'suggesting a rather direct pathway'. In fact the shortest of these was 6 ms (I. M. L. Donaldson, unpublished data). These very short latencies are surprising—no latencies as short as this have been found in primary visual cortex—but we have really no idea what the 'rather direct pathway' to the Clare Bishop Area might be. In other unpublished experiments I also established that EOM proprioceptive signals modulate the visual response of units in the Clare Bishop Area but these interactions were not studied in detail and, as far as I know, there have been no subsequent observations on the actions of EOM afferent signals in this rather interesting visual cortical area that receives such short-latency input from the eye muscles. Its visual responses, however, have been analysed further. Toyama & Kozasa (1982) showed that neurons in the Clare Bishop Area respond to changes in visual target size and retinal disparity, suggesting that they may code movement of visual targets in three dimensions and thus that this cortical area may be important for visuospatial behaviour. That this is likely to be so is also suggested by the more extensive and comprehensive studies that have been made of neuronal responses in parts of the parietal cortex of behaving monkeys, which may be the homologues of the Clare Bishop Area. Thus the inferior parietal lobule is important for spatial perception and spatially orientated behaviour (Andersen *et al.* 1985) and contains neurons that show an interaction between eye position and the magnitude of the response from a target in the visual receptive field. It seems that gaze direction, made up from eye position and head position, modulates the gain of the visual responses in such a way that a population of neurons can provide a unique pattern of firing for each head-centred position. A number of sources of afferent information as well as, possibly, 'outflow' information from motor commands, converge in this cortical area to construct the code for the spatial locations of targets toward which movement is intended (see review by Andersen *et al.* 1997). Signals of eye position are certainly included in this synthesis but there seems to be no evidence at present to decide whether these signals come from copies of motor commands or from afferent input from the orbit or, of course, from both. My observations on cat Clare Bishop Area suggest that an EOM afferent contribution to the spatial processing in primate posterior parietal cortex might be expected but, as far as I know, it has never been sought. There is good evidence, however, as we shall see, that EOM afferent signals are involved in the accurate computation of the spatial positions of intended targets in the human primate though not of which cortical regions are involved.

Area 17 continued to be studied. Trotter *et al.* (1980), using movements imposed upon one eye rather than stretch of eye muscles to activate the EOM proprioceptors, reported that cat primary visual cortical neurons responded to only one direction of imposed eye movement in the dark. When visual stimuli were delivered to one (stationary) eye while passive eye movement was imposed upon the other (covered) eye, interactions were found, usually consisting of initial excitation followed by inhibition. The interactions were maximal when the eye movement was orthogonal to the preferred visual orientation of the neuron. This direction of eye movement corresponds, of course, to the direction of movement of the orientated visual stimulus that would excite the cell. When eye movement was parallel to the preferred visual orientation there was no interaction. This interesting work seems to have been published only as a very short abstract, which is unfortunate because there are many technical details that we do not know and so cannot compare with those of subsequent studies whose findings on the specific properties of the visual cortical neurons excited by EOM afferent signals and of the proprioceptive–visual interactions are rather different.

The next study to appear was that of Enomoto *et al.* (1983) who reported that ten out of 55 neurons recorded in cat primary visual cortex showed interactions between visual stimuli and electrical stimulation of intraorbital oculomotor nerves or stretch of individual EOM. Curiously they did not find any units activated by EOM proprioceptive signals in the dark. On the basis of examination of the responses of eight out of the ten units to stretch of individual EOM, Enomoto *et al.* (1983) concluded that cortical neurons activated by EOM stretch each receive input from only one eye muscle. However, this conclusion is certainly not justified by the evidence, as Ashton *et al.* (1984*b*, p. 659) pointed out, saying

> 'Not all the eight units were tested with stretch of all six EOM and there is really no evidence that any EOM other than the one from whose stretch the effect was recorded was "working", since no account is given of later responses (from other units) to stretch of the "unresponsive" EOM.'

It is quite difficult to keep an EOM in 'working' condition over many hours and very difficult indeed to achieve this for all six muscles. There may, of course, be some cortical units that receive input from only one EOM but the evidence adduced by Enomoto *et al.* (1983) does not demonstrate that this is true even for all the eight units they studied and their conclusion is, in fact, flatly contradicted by the much more extensive later studies of Ashton *et al.* (1984*b*,*c*).

The most extensive published study of the properties of the cat's primary visual cortical neurons to signals from the EOM proprioceptors is that of Ashton *et al.* (1984*b*) who also published a short summary of their findings on the specificity of interactions between visual and EOM afferent signals (Ashton *et al.* 1984*c*). The experiments were directed towards establishing whether cortical units

were specifically sensitive to particular directions of eye movement signalled by the EOM receptors and whether the orthogonal interrelationship between EOM and visually effective signals suggested by Trotter *et al.* (1980), and by the work which had by then appeared on the effects of EOM afferents on the development of visual cortical properties (Buisseret 1979; Buisseret & Gary-Bobo 1979, 1981), could be demonstrated in the properties of individual visual cortical neurons. By the time these experiments were begun it had become very apparent that, although stretch of individual EOM or electrical stimulation of intraorbital mixed oculomotor nerves had their uses, particularly in establishing the likely source of the afferent signals under study, they were a very poor stimulus with which to attempt to examine the specific properties of central units. Ashton *et al.* (1984*b*) discuss in some detail the reasons for preferring passive, imposed, movement of the eye in the intact, undissected, orbit as a means of imitating, albeit not perfectly, the changes in length of all the EOM that accompany natural eye movement. It is worth spending a little time discussing this since the method has been used extensively in later work. With suitable apparatus it is possible to test the effects of eye movement in various directions in such a way that they can be compared in spite of any spontaneous variation in the excitability of the cortex, using extensions of the method of interleaving of stimuli and of the collection of data that was first suggested by Henry *et al.* (1973) and which my group developed over the years (see Donaldson & Nash 1975; Donaldson & Long 1980). It was also possible to apply statistical methods to allow comparison of the size of cortical responses to different stimuli recorded almost simultaneously and so to be confident that the differences observed were unlikely to have arisen by chance, although, of course, there is no way of knowing what size of difference the central nervous system requires for it to be persuaded that two responses are 'different'. The principal disadvantages of passive eye movement as a stimulus are also shared by the earlier methods—that only one eye can be studied and that it is usually necessary to use paralysed preparations. Ashton *et al.* (1984*b*) also describe control experiments that eliminated the possibility that visual input was the effective source of signal when the eye was moved. They found responses to passive movement of the ipsilateral eye in about one-third of the units recorded in the primary visual cortex (Area 17) of anaesthetized, paralysed cats. Units that responded to passive eye movement were tested with four different interleaved passive eye movements, generally in the vertical and horizontal planes, and the sizes of the responses were compared in pairs. Units were defined as 'radially selective' if responses to movement along one radius (for example, vertically upward) exceeded significantly that along at least one other orthogonal radius (for example, horizontal–temporal). The criterion for significance of one response exceeding another was $p \leqslant 0.025$. Out of 60 units tested, 53 (88%) were 'radially selective' according to this criterion. The others showed no selectivity. Some of these radially selective units also showed additional selectivity of one of two types. In the first type the unit preferred movement in either direction (centrifugally and centripetally) along only one orbital arc—for example vertical movement up and down above the equator of the eye. These were called 'arc selective'. In the second type, in contrast, the units were preferentially sensitive to the direction of eye movement irrespective of arc—for example to horizontal movement towards the temporal side of the orbit in both the nasal and temporal halves of the orbit. These were called 'direction selective'. Out of the radially selective units nine were also arc selective and 21 were direction selective. These results are not compatible with the claim of Enomoto *et al.* (1983) that all responsive cortical cells each receive input from receptors in only one eye muscle nor with the conclusion that the results of Trotter *et al.* (1980) seemed to imply that all units have a sharply tuned directional preference when tested in the dark. All the responses were phasic—there was no evidence to suggest that the visual cortex receives a tonic signal of eye position from the EOM proprioceptors. The theoretical possibility exists that some central manipulation of the phasic signals, particularly those of direction selective cells, might be used to generate a signal of eye position but such a possibility is purely speculative. Histology confirmed that all the recording sites were in primary visual cortex, Area 17, and responses were recorded from all cortical layers II to VI, though all layers were not sampled equally frequently. There was no apparent correlation between cortical layer and particular specific properties of the units, though it is interesting that responses were found in layer IV, which receives the principal visual input from the lateral geniculate nucleus. The possible significance of this for the EOM afferent pathway was discussed earlier in § 9.

Though these results show very clearly that primary visual cortical units carry information about the arc of the orbit in which the eye is moving and about its direction of movement they do not address the questions about visuoproprioceptive interactions. My group also carried out a large number of experiments on the details of these interactions using interleaved collection of data and the same statistical techniques as above and published a summary of the results in 1984 (Ashton *et al.* 1984*c*). The following quotation from our paper (p. 19P) summarizes the findings.

> 'Responses to moving visual stimuli presented to the left eye (V), to passive movement of the right eye (PEM), and to V and PEM at various time intervals and in various combinations of visual movement and of PEM were examined [reference is made here to an earlier description of the interleaved stimuli and data collection]. In thirty units which showed interactions we found that
>
> (i) Both enhancement and reduction of the visual response occurred following PEM and the magnitude of the interactions varied with the interstimulus interval.
>
> (ii) Stretch of different combinations of EOM, produced by different directions of PEM, might excite a given unit and might also alter its visual response.
>
> (iii) At some interstimulus intervals separate responses could be identified to PEM and to V, but there was often a period, sometimes several hundred milliseconds long, during which the responses overlapped so that only the 'total' response could be measured. From these units it appears that the total response to PEM *and* visual stimulation may be much less than,

> or may greatly exceed, the sum of the responses to the individual stimuli given separately. Sometimes an interaction was found only with one direction of PEM relative to the direction of movement of the preferred visual stimulus.
>
> Interactions of these types would appear to be significant for the understanding of the processing of visual information during and after eye movements. However, our present results suggest that the interactions in different cortical units cannot be summarized by a single simple pattern. Further experiments are under way to provide more details of the patterns of stimulus arrangement which induce interactions in visual cortical units.'

These further (unpublished) experiments involving many more cortical units confirmed the results and did not add substantially to them. Thus, although units that behaved in the way described by Trotter *et al.* (1980) were certainly found, the pattern of strictly orthogonal interactions with excitation only when the eye was moved orthogonal to the preferred visual orientation was by no means the only one.

Area 18 has been much less intensively studied than Area 17, but Buisseret's group has found units in cat Area 18 that receive signals from extraocular muscle receptors. Interactions between electrical stimulation of the inferior oblique branch of the oculomotor nerve in the orbit or stretch of the lateral rectus muscle and visual stimuli were reported by Milleret *et al.* (1987) and Buisseret *et al.* (1988*b*) who describe both facilitatory and inhibitory effects of the EOM afferent signal on the visual response of units in Area 18 and say that the majority of units with interactions 'displayed an orientation selectivity approximately orthogonal to the plane of action of the muscle'. However, the diagram illustrating the proprioceptive effects in Buisseret *et al.* (1988*b*) is not easy to interpret and does not seem to give much support to the claim. The fuller account of Milleret *et al.* (1987) says that, for the cells responding to electrical stimulation of the inferior oblique branch of the oculomotor nerve, one visual orientation dominated, the orientation orthogonal to the plane of action of the muscle. However, no figures are given nor is there any comment on the preferred visual orientation of units activated by stretch of the lateral rectus muscle. It is also somewhat doubtful if the inferior oblique muscle can really be said to produce movement only in one plane. In Man, at least, it produces torsion about the visual axis as well as rotation in the orbit. As explained above, deduction of direction preference of cortical units, or indeed of other central neurons, from the effects of stretching a single EOM or, *a fortiori*, of stimulating a single intraorbital nerve, is at best uncertain. Perhaps all that one can conclude with certainty is that units in Area 18 do receive afferent signals from the eye muscle proprioceptors and that these signals have effects of various kinds on the visual responses of the neurons.

As demonstrated by recording interactions between visual and EOM afferent input in the anaesthetized cat cortex, the relationship of the properties of visual cortical units that receive EOM afferent signals to the effects of manipulation of proprioceptive afferent signals on the development of normal unit properties in visual cortex is not entirely clear. The developmental experiments seem to show that the normal development of specific visual properties such as orientation specificity depends (among other factors) on there being a particular relationship between the plane of eye movement and the orientation of visual stimuli (Buisseret *et al.* 1988*a*). What the experiments showed was that, when kitten eye movements were restricted to the horizontal or vertical plane by removal of some of the EOM, there was an overrepresentation of units in the visual cortex the visual orientation preference of which was tuned to the orthogonal plane. For example, when only vertical eye movement was permitted, there were more units that preferred horizontal stimuli than normal. Vertical eye movements, of course, will sweep horizontal contours across the retina in the optimum direction for the activation of units tuned to horizontal visual contours. However, visual factors alone do not account for the overrepresentation, as indicated by the occurrence of some overrepresentation of visual orientation orthogonal to the permitted eye movement—even when only one eye was confined to movements in one plane and that eye was closed so that it received no visual stimulation, whereas the other eye moved normally and had normal visual input. As far as I know, the distribution of preferences for particular combinations of direction of eye movement and visual orientation has not been tested in recordings from units in the cortex of kittens or cats subjected to visuoproprioceptive mismatch and compared with the distribution of such preferences in normal animals of the same age. Indeed we do not even know the distributions of such preferences in normal animals. This makes comparison between effects of manipulation of the EOM afferent signal on purely visual properties rather difficult to discuss in relation to the properties of the interactions between EOM afferent signals and visual input. A rather simple arrangement with cortical units showing enhanced responses only when these specific stimuli coexist is suggested by the results of Trotter *et al.* (1980), who found interactions in Area 17 of anaesthetized cat cortex only between the effects of imposed eye movement in a particular plane and visual stimuli orientated orthogonal to this plane, and those of Milleret *et al.* (1987) on Area 18. This would, perhaps, provide a simple explanation of the developmental effects. But the studies of Ashton *et al.* (1984*b*) showed that units in cat Area 17 did not, in general, respond to eye movement in only one plane and those of Ashton *et al.* (1984*c*) were not consistent with interactions only between orthogonal movement and orientation preference. It may be important, however, that units that did behave as described by the French workers were included among the population studied by Ashton *et al.* (1984*b*,*c*). It is unfortunate that we lack full technical details of the experiments by the French group on these interactions in Area 17 so we cannot speculate on the possible effects of differences in the details of the experiments—including the anaesthetic state—on the results. Certainly the use of muscle stretch or nerve stimulation by the French group and of passive eye movement by ours (Ashton *et al.* 1984*b*,*c*) is likely in itself to have led to rather different conclusions about preferences of central units for particular directions of eye movement. Another possibility, however, is that only a subset of the visuoproprioceptive interactions—those in which the visual orientation and preferred movement direction are

orthogonal—is particularly important for the development of cortical visual properties and that only those units appropriately connected (or potentially appropriately connected) to be activated by orthogonally arranged eye movement and orientation of visual contours are involved. The disagreement about the physiology is, of course, not about whether such units occur—they were found by both groups—but about whether the 'orthogonal' relationship is the only one or much the commonest (as Buisseret's group found) or (as our group claimed) whether it is simply one, and not a particularly common one, of many types of interaction. The matter remains unresolved.

11. AVIAN OPTIC TECTUM

In 1995, Knox & Donaldson (1995*a*) found that EOM afferent signals reach the optic tectum (OT) of the pigeon.

The avian OT has been recognized for many years as the homologue of the mammalian superior colliculus but recent work shows that it is a good deal more than this. In birds the OT is a major centre for visual processing and contains units sensitive to movement, direction and colour of visual stimuli (see review by Engelage & Bischof 1993). In the pigeon it is fairly simple to make a decerebrate preparation in which the optic tecta and their ascending connections remain intact. This preparation was used many years ago to study the retinotopic map of the visual field on the tectum by Whitteridge, from whom I learned the technique of making it (Hamdi & Whitteridge 1954). Though the forebrain, with which the OT has major connections, is absent in this preparation, the visual properties of tectal cells in the unanaesthetized decerebrate pigeon were found to be similar to those previously reported in intact pigeons either anaesthetized or alert (for details, see Knox & Whalley 1997). The bird visual pathway is completely crossed so it is possible to deliver visual stimuli to one eye, say the right, to record from the left tectum and to impose passive movement on the left eye to induce EOM afferent signals. Thus the OT of the decerebrate pigeon offers an attractive preparation for the study of interactions between visual and EOM afferent signals that might provide instructive comparison with both the mammalian superior colliculus and visual cortex. A start has been made in exploiting its possibilities in this respect but its potential has by no means been exhausted.

In the first study (Knox & Donaldson 1995*a*) EOM afferent signals induced by movements imposed on the left eye of the decerebrate, paralysed pigeon were found to reach the superficial layers of the ipsilateral (left) OT and there to interact with visual input from the right eye, usually reducing the size of the visual response. Significantly, as well as 'phasic' effects, which were often directionally selective on the visual signal during eye movement, Knox & Donaldson (1995*a*) also found that there were powerful 'tonic' effects when the eye was held deflected but stationary during presentation of the visual stimulus. Thus, when the left eye was deflected from the central position in the orbit and held stationary at the new position while a (moving) visual stimulus was presented to the right eye, there was powerful inhibition of the visual response compared with its size when the same visual stimulus was presented with the left eye at its central, rest, position. Using the same experimental arrangement with the visual stimulus given during static eye deflection of the other eye, it was also found that the magnitude of the inhibition was related, roughly linearly, to the amplitude of the static eye deflection. The effect was powerful—an eye deflection of 5° reduced the visual response to 70% and a deflection of 15% reduced it to a mere 6% of its control value. Knox & Whalley (1997), using the same methods, examined 184 units in the superficial layers of the pigeon OT and found that visual 'directional' and 'plane' specificity was commoner in the visual responses of tectal units than previous reports had suggested. 'Directional' units were defined as those that responded preferentially to a visual stimulus moving in one direction, for example horizontally headwards. These were less common (18%) than 'plane' sensitive units (78%), which responded best to movement in one plane—for example horizontal—but were indifferent to the direction of movement so that horizontal movement either headwards or tailwards gave similar responses. When the visual directional tuning through the right eye had been established, the effects of tonic deflection of the left eye in various planes and directions on the response to a visual stimulus moving in the preferred plane and direction were examined. For a given unit the visual response was modified to the greatest extent by eye deflection in a particular plane and direction 'although there was no unique relationship between the direction of visual stimulus movement to which an individual unit responded best and the direction of eye movement that caused the greatest modification of that visual response'. In a parallel series of experiments the same authors (Knox & Whalley 1996) examined the specificity of the interaction between tonic eye deflection and visual response and found most tectal units' visual responses were modified by deflections of the opposite eye of the same amplitude in any of four directions: up, down, horizontally headwards and horizontally tailwards. Some units, however, had their visual responses modified only by a single direction of eye movement—strongly suggesting that there is a quite specific, directional, signal of maintained eye position arising from activity in EOM proprioceptors available in the superficial layers of the optic tectum. The interesting work described in this preliminary report clearly needs to be extended in range and in detail.

(a) *Comparison of results in avian optic tectum with those in mammals*

Although there are reasons, explained above, to suppose that it may be justifiable to attempt these comparisons (more precisely comparing effects in pigeon OT to those in cat superior colliculus and visual cortex), such comparisons require caution not only for the obvious reason of species difference but, as we shall see, because of differences in experimental technique that may be crucial.

There is a striking similarity *prima facie* between the results on the specificity of the interactions between the EOM afferent signal and visual input in OT and in the observations of Ashton *et al.* (1984*c*) on cat primary

visual cortex. In each case there was no unique relation between the specific visual preference (direction or orientation specificity) of the units and the direction of imposed eye movement that was most effective in modifying the visual response. So the interactions in pigeon OT seem to correspond to the pattern—or rather lack of one pattern—found by Ashton *et al.* (1984*c*) rather than the strictly orthogonal arrangements reported by Trotter *et al.* (1980) in cat Area 17. In OT, however, the interactions were almost always inhibitory whereas in the cat cortex both excitatory and inhibitory effects were found. There are also other important differences. In the cat cortex there seems to be no evidence of any sustained or 'tonic' action of the EOM afferent signal, whereas 'tonic' actions are common in OT and the detailed studies of the effects on visual responses were all of such tonic effects. Again, in the cat superior colliculus none of the experiments has shown tonic effects (Batini & Horcholle-Bossavit 1979; Donaldson & Long 1980), though these experiments, relying on individual muscle stretch or electrical stimulation of afferents, were perhaps less well designed for revealing tonic effects than the more recent work. And, once again, interactions of excitatory as well as inhibitory types were found in the cat colliculus (Donaldson & Long 1980). It is possible, of course, that the absence of tonic actions in the cat cortex and colliculus simply indicates that the 'tonic' mechanism is absent in the cat. However, it is also possible that the failure to find tonic actions of the EOM afferents in cats was due to the conditions of the experiments, particularly to the fact that all the experiments on cat cortex were carried out under anaesthesia, whereas the pigeon OT was studied in the decerebrate, unanaesthetized preparation. Donaldson & Long's (1980) results were also from anaesthetized animals and, although Batini & Horcholle-Bossavit (1979) used *encéphale isolé* preparations, their electrical stimulation of afferents in the orbit would not be a satisfactory stimulus with which to seek sustained, 'tonic' actions. Thus it seems unsafe to conclude that there are no tonic actions of EOM afferents in the cat superior colliculus or visual cortex—though none have been found so far—while the evidence comes only from recordings made under general anaesthesia. This caution is encouraged by our knowledge that cat EOM primary afferents include units carrying slowly adapting signals so that a 'tonic' signal of eye position is probably available to the cat central nervous system. In passing we may note that in some Purkinje cells in the rabbit flocculus, tonic excitation by EOM afferent signals is found (Kimura & Maekawa 1981), as it is in occasional units in the trout vestibular nuclear complex (Ashton *et al.* 1989) and in the pigeon abducens nucleus (Donaldson & Knox 1991).

(b) *Does the 'tonic' signal in pigeon optic tectum arise from a position signal carried by extraocular muscle primary afferents?*

The 'tonic' effects of eye displacement on visual responses in pigeon OT are very striking. If the preliminary results of Knox & Whalley (1996) are confirmed there are not only tonic effects of eye displacement on visual processing but there is also evidence that, in some units, these effects seem to require a signal of the direction and magnitude of eye displacement to be available for at least a few seconds after the eye has become stationary in a displaced position. Does this signal simply reflect the central action of a directionally and amplitude-specific sustained signal of eye position provided by the first-order afferents from the EOM proprioceptors? It is possible, but not certain, that it does. Fahy & Donaldson (1998) found slowly adapting units among pigeon EOM first-order afferents but concluded 'The responses adapted in seconds rather than minutes so these units would not provide a continuous signal of the position of an immobile eye . . . '. Nevertheless it is not impossible that some of these signals would be adequate to explain the 'tonic' signals the effects of which were recorded in pigeon OT. There is no difficulty over directional and amplitude specificity. The primary afferents show both of these properties—it is only the rate of adaptation that poses a problem. Unfortunately, the experiments of Fahy & Donaldson did not directly examine the adaptation of units for more than a couple of seconds and adaptation times were estimated on the assumption that the units' firing showed a single exponential decay from their maximum at the end of the eye movement to its new position. Three units showed no decay during 1 s of observation time so no estimate can be made for them—they could have been very slowly adapting. Of the other units, some adapted completely within 1 s but others would have taken between 1.5 and 10 s to return to their resting firing rate. The slowest of these could certainly have provided some information about eye position over the time-intervals used by Knox & Donaldson (1995*a*) and Knox & Whalley (1997), and might even have been competent to sustain the responses of Knox & Whalley (1996) in the experiments that suggest the presence of a directionally specific eye position signal. But the accuracy of the position signal presumably must decline from a maximum immediately at the end of the eye displacement and we know neither how imprecise the signal would be after a few seconds nor what accuracy is required since the tectal experiments do not define how precisely the eye position must be maintained to produce the specific visual interaction. Finally, the population of first-order afferents studied was small—only 20 units. This was because the experiments are technically very difficult as the volume of the trigeminal ganglion that contains the afferent somata is tiny and difficult to find in a ganglion that is, itself, small. A large number of experiments is therefore needed to collect even a small sample of the afferents. Thus it is entirely possible that there are first-order EOM afferents in the pigeon that are much more slowly adapting than any yet studied. Of course, one can easily conceive mechanisms that could derive sustained information about static eye position by sampling and storing the firing rate of even rapidly adapting afferents at the end of an eye movement and resetting the stored value only after the next eye movement. However, we do not know whether such mechanisms actually exist for EOM afferents or, indeed, as a means for deriving sustained position signals from rapidly adapting afferents from the limbs.

The 'tonic' responses have been discussed at some length because one supposes that sustained information about eye position would be required both by the oculomotor system and in order to calculate the position

of visual stimuli in egocentric space. Thus the question of whether such information is available from an afferent source is clearly of considerable importance. The apparent absence in several central areas of 'tonic' effects from EOM afferent signals has been puzzling and finding such actions in the avian OT should encourage further experimental work on this preparation. It is already clear that there are questions about the precision of a sustained signal of eye position that could be answered there.

12. ACTIONS OF EXTRAOCULAR MUSCLE AFFERENT SIGNALS ON THE DEVELOPMENT OF PROPERTIES OF VISUAL NEURONS

Over the last 20 years it has been established that signals from the extraocular muscle proprioceptors are necessary for the normal development of the visual properties of neurons in the visual cortices. Most of the work on this subject has been done by Buisseret and his colleagues and collaborators, and the field was reviewed recently by Buisseret (1995). The following short summary of the principal developmental effects that have been established is included for convenience and the reader is referred to Buisseret's comprehensive article and its references for details. Where no reference is given in this section the work is that of Buisseret and his colleagues.

(a) *Orientation selectivity*

The selectivity of the responses of visual cortical cells to particular orientations of visual stimuli does not develop if young animals (kittens in these experiments) are paralysed during visual exposure nor if paralysed animals are moved passively in front of visual stimuli. However, if body movement is prevented but normal eye movements are allowed, visual orientation selectivity develops normally. Conversely, prevention of eye movement prevents its normal development. That signals from the EOM proprioceptors are required for normal development is shown by the lack of acquisition of orientation selectivity if the normally moving eyes have their EOM deafferented by bilateral section of the ophthalmic branch of the trigeminal nerve (VOphth). The conclusion is thus that both visual experience and signals from the EOM of the moving eyes are required for the normal development of cortical visual orientation selectivity.

Abnormal eye movements result in abnormal distribution of the preferred orientations of the population of cortical cells. Thus, if the eyes are allowed to move only vertically, a preponderance of units tuned to horizontal orientation is found and, if only horizontal eye movements are permitted, the predominant orientation is vertical. That these effects are not due simply to abnormal visual stimulation is shown by the finding of the same effects if one eye is deafferented (by unilateral section of VOphth) but is free to move in any direction, while the other is covered and allowed to move in only one plane but has its EOM afferents intact. These results demonstrate that the disturbance of the normal proprioceptive input from a non-seeing eye is sufficient to cause the abnormal distribution of the orientation preferences of visual cortical units.

(b) *Binocularity*

The binocular activation of cortical units is also affected by EOM afferent signals. Bilateral deafferentation of the eye muscles acts similarly to (binocular) visual deprivation and 'freezes' the cortical plasticity for ocular dominance, but previously acquired ocular dominance is not disturbed. Unilateral removal of the EOM afferent signal (like unilateral visual deprivation) causes disruption of binocular excitation of visual cortical cells. It seems that 'unbalanced' EOM proprioceptive signals are necessary to cause the disruption.

(c) *Stereoacuity*

In both kittens and adult cats binocular stereoacuity is reduced by removal of the EOM afferent signal—but in this case both binocular and monocular removal of the signal are effective in producing the disruption (see Buisseret (1995), Fiorentini *et al.* (1982, 1985, 1986) and § 16 for discussion).

13. CEREBELLUM

The cerebellum has long been known to be involved in the control of movement and cerebellar lesions produce, among many other disorders of movement, disturbances of eye movements (see Fuchs & Kornhuber (1969) and Batini (1979*b*) for references to early work). It turns out that the actions of the midline structure, the cerebellar vermis, seem to be principally on saccadic movements while the paired lateral vestibulocerebellum, and especially the flocculus, seems to be concerned mainly with vestibulo-ocular and optokinetic responses, and smooth pursuit.

Optican & Robinson (1980) found that the correction of saccadic dysmetria induced by weakening the eye muscles of one eye in monkeys is abolished by cerebellectomy. The vermis proved to be involved in the adaptive control of the pulse of motor neuron firing that deflects the eye to its new position during saccades while the flocculus was perhaps concerned in the adaptation of the sustained (step) firing that holds the eye at its new position. The latter function of the flocculus was confirmed by Zee *et al.* (1981). The flocculus was shown to be involved in the control of optokinetic responses in rabbit (Barmack & Pettorossi 1985) and monkey (Zee *et al.* 1981) but lesions there seemed to have little effect on the VOR. However, Lisberger and his group have shown that the flocculus and paraflocculus supply signals necessary for learned adaptive changes in the VOR (see, for example, Du Lac *et al.* 1995). It seems that the flocculus is also necessary for the control of smooth pursuit eye movements in the monkey (Zee *et al.* 1981). One might generalize, then, that the cerebellar vermis seems to be involved in the control of eye movements that acquire new visual targets, while the flocculus is primarily concerned with those that stabilize the image on the retina (see also Zee *et al.* 1981).

It would seem likely to be significant that EOM afferent signals reach both of these regions of the cerebellum. It will be convenient to consider the projections to each separately.

(a) *Vermis*

Following clinical observations by Kornhuber of a particular type of saccadic dysmetria in patients with

cerebellar atrophy, Fuchs & Kornhuber (1969) found surface-evoked potentials in the cat cerebellar vermis from stretch of individual eye muscles. These responses, whose latency could be as short as 4 ms, were found in Larsell's lobules V, VI and VII (Larsell 1953), an area already known to receive visual and auditory input and in which electrical stimulation induces eye movements. Fuchs & Kornhuber (1969) suggested that there might be 'a cerebellum mediated proprioceptive feedback loop for the control of saccadic eye movements'—with the feedback signal coming from the EOM afferents, of course. These results were challenged by Rahn & Zuber (1971) who ascribed them to passive volume conduction rather than conducted neural activity. Wolfe (1971), however, produced evidence and arguments that this interpretation of the evoked potentials was incorrect and, in any case, the presence of an EOM afferent input to the vermis was soon confirmed by Baker *et al*. (1972), who recorded unit responses from Purkinje cells in Larsell's lobules V to VII. They found mossy fibre input over a considerable area with additional climbing fibre responses lying laterally. The mossy fibre latencies of 5–6 ms to stimulation of the superior oblique nerve in the orbit corresponded well with Fuchs & Kornhuber's (1969) estimate but the climbing fibre responses arrived later with latencies around 18 ms. Baker *et al*. (1972) also suggested involvement of EOM proprioception in 'correction' of movements, including that of saccades prior to their execution.

Batini and her colleagues (Batini & Buisseret 1972; Batini *et al*. 1974) then examined the responses of Purkinje cells in lobules VI and VII of the cat vermis to stretch of individual EOM and to electrical stimulation of intraorbital nerves, where they carry the eye muscle afferents, and also to stimulation of other non-orbital branches of the trigeminal nerve. Both mossy and climbing fibre responses were found and responses to EOM stretch and to stimulation of the intraorbital nerves were similar. Importantly, the authors emphasize the convergent input to lobules VI and VII. Many Purkinje cells there responded to stimulation of extraorbital branches of the trigeminal nerve as well as to intraorbital stimulation of muscle nerves carrying EOM afferents. They were 'influenced by proprioceptive afferents from extrinsic eye muscles and from masticatory muscles as well as by exteroceptive afferents from the trigeminal territory'. This convergence is in addition to the 'visual, acoustic spinal and cortical inputs' that are also known to be received in vermal lobules VI and VII (Batini *et al*. 1974). The convergence of many afferent modalities necessarily complicates the search for a functional role for the EOM afferent signal in the vermis.

The properties of the vermal responses to EOM afferent signals produced by stretch of individual EOM were examined in more detail by Schwartz & Tomlinson (1977) who, in contrast to Baker *et al*. (1972), found a patchy distribution of the signal in only lobule VI. Several authors remark on the extreme sensitivity of the responses to anaesthetic conditions and one wonders whether the explanation for these patchy findings where others have found a more continuous distribution may depend on differences in anaesthetic conditions—see Batini (1979*b*), who also provides a useful figure comparing the distributions found by various authors. Most units responded to stretch of more than one EOM and Schwartz & Tomlinson (1977) found convergence that suggested that some units might be selectively activated by one particular direction of eye movement and others would be affected by movements in a particular plane. However, as the authors point out, stretching EOM with all the muscle tendons still attached to the globe is not a method well adapted to determining the direction sensitivity that units will have to natural eye movements. One cannot go beyond the conclusion that it is likely that vermal units may have some differential sensitivity to the direction or plane of eye movement. Both excitatory and inhibitory responses (that is reduction of the 'spontaneous' activity) were found. As others have also observed (see Batini 1979*b*), high velocities of muscle stretch seemed to be required to activate these units, which seemed to show a 'position' threshold but the responses of which were said not to be particularly related to the amplitude of muscle stretch. Unfortunately, Schwartz & Tomlinson (1977) made no systematic examination of the effects of either amplitude or velocity on the magnitude of the responses and Batini's (1979*b*) remark that velocity information is lost between the primary afferents and the cerebellum would seem to go beyond the experimental evidence—as, indeed, does the assumption that amplitude information from the primary afferents is preserved. The responses seem to be universally phasic (Batini 1979*b*; Schwartz & Tomlinson 1977) but, again, the stimuli applied were not adequate to test for slowly adapting responses since the hold period of the ramp stretch seems to have been less than 200 ms. It is clear that some responses were already adapting in that time so there were certainly dynamic responses, but whether some of the units also carried a tonic component cannot be ascertained. Batini's (1979*b*) paper reviewed the information about EOM afferent signals in the vermis available in 1979 and it has to be said that the succeeding 20 years have not added a great deal. Since responses to electrical stimulation of intraorbital nerves as well as to EOM stretch have been found in the vermis there can be little doubt that EOM afferent signals do arrive there. It is curious however, and a little disturbing, that authors do not mention the exquisite sensitivity of many units in Larsell's lobules V to VII to auditory input. This is particularly relevant in view of the high velocities of muscle stretch that are needed to activate the units, which are difficult to produce completely silently. Hawthorne (1977) stretched the lateral rectus to test for convergence of visual and EOM afferent input in the cat vermis and found large responses, but it was practically impossible to separate these from the effects of the (minimal) clicks made by the muscle stretcher when it was producing the very rapid stretches (up to $1000\,s^{-1}$) that he also found necessary. The best he could do was show that in some—but not all—units the response with the muscle attached to the stretcher was considerably larger than when the stretcher was operated identically with the muscle detached from it. There are a few scraps of information obtained with passive eye movement at more modest velocities at which the apparatus is silent. Ashton *et al*. (1989) found units in the vermis of the decerebrate unanaesthetized fish that responded both to natural horizontal vestibular stimulation and to passive eye movement or to electrical stimulation of the superior

oblique nerve in the orbit. Some of these units showed preferential responses to passive eye movement in one rather than another plane, sometimes with additional preference for movement in one rather than in the opposite direction. Convergence of vestibular and EOM afferent signals has been confirmed in the pigeon cerebellar vermis (I. M. L. Donaldson and P. C. Knox, unpublished data). These findings are of some interest since the vermis, unlike the flocculus, has not generally been thought to be involved in vestibularly driven eye movement. However, as Batini pointed out in 1979 (Batini 1979*b*), the effects of slow eye movement, if any, on the vermis are unknown. The possible functions that the EOM afferent signal might exercise through its influence on the cerebellar vermis remain speculative and in recent years possible actions of EOM afferents in the control of saccades have been ignored. For example, in his review of cerebellar actions specifically in saccadic control, Keller (1989) does not even mention the existence of the EOM afferent projection to the vermis though he concludes that vermal lobules including VI and VII provide a 'modulatory influence in ensuring amplitude accuracy of saccadic eye movements' both online (that is, in relation to individual saccades) and in long-term adaptation to compensate for saccadic dysmetria. The assumption, of course, is that all the information needed for these controlling actions comes from corollary discharges generated within the oculomotor system. Yet it is in exactly these sorts of processes—particularly the long-term adaptation to saccadic dysmetria produced by weakening EOM of one eye that was elegantly studied by Optican & Robinson (1980)—that one might expect EOM afferent signals to play a part. That they do play such a part is strongly suggested by the findings of Lewis *et al.* (1994) that proprioceptive deafferentation of a paretic monkey eye leads to gradual worsening of ocular alignment and saccadic accuracy. As Donaldson & Hawthorne (1979, p. 46) wrote 20 years ago:

> '. . . it is difficult not to believe that it is significant that the same cerebellar lobules (VI and VII) receive, at least in the cat, both visual and proprioceptive input and it is these lobules that affect saccades.'

Since the recent experiments of Knox (Knox *et al.* 1998, 2000) suggest that disturbance of the human EOM afferent signal, by impeding the movement of one eye, immediately alters the amplitude of saccades made by the free eye, it is surely time that the question of the action of the EOM signal in the vermis was reinvestigated.

(i) *Vergence?*

Guthrie *et al.* (1982) found that monkeys with bilateral section of the ophthalmic branches of the trigeminal nerve (and, thus, presumptive complete deafferentation of the EOM) 'performed vergence tasks poorly' with drift of the non-dominant eye after initial appropriate vergence. Lewis *et al.* (1994) later showed that EOM afferent signals are necessary for the long-term adaptive maintenance of the alignment of the optic axes. It is just possible that the projection of the EOM afferent signal to the vermis might be involved in processes of this kind. Donaldson & Hawthorne (1979) found units in lobules VI and VII of the cat vermis that greatly preferred binocular to monocular visual stimulation and some of which appeared to show tuned sensitivity to both vertical and horizontal retinal disparity—suggesting a function in the maintenance of eye alignment rather than depth detection. They suggested that the likelihood of these units being involved in the control of alignment of the optic axes or of vergence was increased since afferent signals from the eye muscles had also been found in these lobules. However, attempts to show convergence of EOM afferent signals with the visual signals in the vermis were inconclusive because of the difficulty of eliminating auditory input (see above; Hawthorne 1977). These experiments could now, with advantage, be repeated with the much better method of passive eye movement imposed via a contact lens and using modern interleaved methods of data collection.

(b) *Vestibulocerebellum* (*flocculus*)

The published studies of EOM projections to the flocculus are all on the rabbit. Maekawa & Kimura (1979, 1980) found that the firing rates of simple spikes by Purkinje cells of the flocculus were modulated by stretch of EOM or electrical stimulation of the nerve to the superior oblique (trochlear nerve) in the orbit. The responses appeared to be driven only by mossy fibre afferents and were widely distributed in the flocculus. Both 'phasic' and 'tonic' responses were reported but, since the stretch stimulus appears to have lasted only 100 ms, it is not possible to be certain to what extent these 'tonic' modulations of firing rate could faithfully signal eye position. There was no evidence of EOM afferent signal projection by climbing fibres, nor has any such projection been described since. Further study (Kimura & Maekawa 1981) using ramp stretches of EOM, or sinusoidal muscle stretching, suggested that the responses of Purkinje cells in the flocculus could be divided into three types, A, B and C. Type A cells were initially excited followed by inhibition, type B units showed both phasic and tonic excitation with no inhibition and type C responses were purely inhibitory. It seems that quite high velocities of eye muscle stretch (60–$600^\circ\,s^{-1}$) were needed to modulate Purkinje cell activity. Kimura & Maekawa (1981) proposed that the EOM afferent signal would be likely to operate 'mainly in saccadic eye movements and smooth eye movements of high velocity'. Later work, summarized by Maekawa & Kimura (1986) showed convergence of visual and EOM afferent signals onto the same Purkinje cell. However, the visual responses were evoked by electrical stimulation of the optic tract and no observations were reported on the interactions (if any) of the two signals in altering the units' behaviour. The same authors (Kimura *et al.* 1991) also examined the effect of cutting the ophthalmic branch of the trigeminal nerve (VOphth), thus deafferenting the EOM, and of kainic acid lesions of the flocculus on the gain of the vestibulo-ocular reflex (VOR) and on optokinetic responses (OKN) in the alert rabbit. Both manipulations resulted in a reduction of VOR gain, much more marked at higher frequencies, and also a reduction in OKN gain. Since cutting VOphth produced no change in the gains additional to that already resulting from a kainic acid floccular lesion, the conclusion was that the effects of deafferentation of the EOM were expressed through the

flocculus. The gain reductions in the VOR (that is, in VOR slow phase gain) were considerably greater at 0.5 Hz than at 0.1 Hz, which is consistent with the earlier indications that fairly high velocities of eye movement are required to bring the EOM afferent mechanism in the flocculus into play. From fig. 2 of Kimura *et al.* (1991) the peak velocity of the vestibular stimulus (sinusoidal oscillation) at 0.5 Hz was around $63^\circ\,s^{-1}$. The effects on OKN gain were again velocity dependent and the fast phases of OKN were somewhat reduced by VOphth section. The fast phases of the VOR do not seem to have been examined.

Miyashita (1984) attempted to estimate the contribution of the EOM afferent signal to the representation of eye velocity in the firing rates of floccular Purkinje cells. He evoked Purkinje cell responses by electrical stimulation of the optic tract of alert rabbits, identified the modulation in the ipsilateral flocculus that appeared to be related to the velocity of the eye movements induced by optic tract stimulation, and examined the effect on this modulation of retrobulbar block with local anaesthetic. He concluded that about 31% of the eye velocity signal could be attributed to the EOM afferent signal. However, the conditions of the experiment in which 'open loop' eye movements were induced by electrical stimulation of visual pathways and the assumption that Purkinje cell modulation is related only to eye velocity—and not, for example to eye position or, more probably, to a combination of velocity and position—were such that the claim to have measured the EOM afferent effect must be treated with considerable caution. It is unfortunate that no similar experiment has been done using more physiological stimuli to induce the eye movements. The conclusion, though, that deafferentation of the EOM in the alert rabbit leads to changes in the Purkinje cell firing of simple spikes related to eye movement is certainly well established.

Nagao (1988, 1989) has shown that Purkinje cells in the floccular zone concerned with horizontal eye movement (H zone) are involved in the adaptive long-term control of optokinetic responses through modulation of visually induced mossy fibre activity by retinal error signals carried through climbing fibres. Similar effects on the adaptive control of the horizontal vestibulo-ocular reflex (HVOR) were found, related to modulation of mossy-fibre-mediated responses to vestibular signals by climbing fibre input related to retinal error. Unfortunately the effects of the removal of the EOM afferent signal on this floccular control of adaptation of horizontal VOR and optokinetic eye movements do not seem to have been tested.

Care is needed, however, in extrapolation from all these results to the belief that actions of EOM afferent signals in the control of VOR or OKN take place only through the flocculus since, as we have seen, there are also vermal projections to be considered.

As with the vermis, study of the EOM afferent signal in the flocculus seems to have gone out of fashion in spite of the clear evidence that it is able to modify the responses of Purkinje cells in those floccular regions concerned with both the immediate and the long-term adaptive control of eye movement. There seem to be no published studies of the way in which EOM afferent signals interact with well-defined, physiological, visual or vestibular stimuli to modify unit responses in the flocculus. In the pigeon (I. M. L. Donaldson and F. L. Fahy, unpublished data), EOM afferent signals reach the vestibulocerebellum (flocculus) and, in the decerebrate bird, the vestibular responses to horizontal sinusoidal oscillation can be modified in a direction-selective way by EOM afferent signals induced by passive deflection of the eye. This might well be a promising preparation in which to examine interactions between the responses to natural input, visual and/or vestibular, that produces eye movements and signals from the moving eyes carried by EOM proprioceptors. This is particularly so since the work of Frost and his colleagues has provided a good deal of information about the responses of units in the pigeon vestibulocerebellum to optokinetic stimuli (for a discussion, see Frost *et al.* 1994).

14. VESTIBULAR NUCLEI AND RELATED STRUCTURES AND OCULOMOTOR NUCLEI

The reader may be inclined to feel that this section is somewhat partisan since a great deal of the work to which it refers was done by my research group. But this emphasis is the result of sheer necessity—in recent years all the work on the physiology of the EOM afferent signal as it affects the responses of single units in the vestibulo-ocular system has been carried out by our group. In contrast there have been a number of valuable contributions from several sources on behavioural effects of the EOM afferent signal on vestibularly related eye movements. These are discussed towards the end of the section.

(a) *Early observations*

There were some early observations that suggested that EOM afferents were likely to be involved in the processes controlling eye movement but these were later ignored or forgotten. As we have seen, the early writers—and this includes those working in the 1950s—did not doubt that one of the principal roles of the afferent signals from the proprioceptors of the eye muscles was to take part in oculomotor control but this they usually deduced from rather general considerations of the central sites in which they found the signal rather than from any specific effects that they observed it to have. Thus, Cooper *et al.* (1955) found projections of EOM afferent signals to the superior colliculus and suggested that these indicated an action in oculomotor control. More specifically, and intriguingly, they also wrote 'multi-unit responses [from EOM afferent activation] were heard in the eye muscle nuclei themselves'. Their discussion of the probable absence of a stretch reflex in the EOM and its significance—or lack of significance—for the possible participation of eye muscle afferents in oculomotor control is also penetrating.

The most direct pointer to the discovery of actions of the afferents on the vestibulo-oculomotor system came somewhat later. Gernandt (1968), recording in the brainstem of chloralose-anaesthetized cats, discovered that stretch of EOM or electrical stimulation of intraorbital nerves caused inhibition of brainstem responses induced by electrical stimulation of the vestibular nerve. But the

value of these interesting observations was reduced by the absence of any exact anatomical information on the recording sites of the units—though this did not prevent the somewhat rash claim that 'neither the vestibular nuclei nor the oculomotor nuclei is [*sic*] under the influence of this inhibitory mechanism'. Gernandt seems to have believed that the EOM afferent effects took place downstream from the vestibular nuclei, on the indirect pathway to the oculomotor nuclei that passes by way of the reticular formation. His results seem to have been forgotten.

Tomlinson & Schwarz (1977) found that some cat oculomotor motor neurons are affected by stretch of EOM—signals from several EOM converged on a given motor neuron with various patterns of excitation and inhibition. They discussed their results mainly in relation to the existence or otherwise of stretch reflexes in the EOM and the possibility that the slowly conducting motor neurons that received afferent signals might form part of a gamma efferent system to 'atypical muscle spindles'. Again, this work does not seem to have been pursued.

(b) *The time constant of vestibular responses in the spinal goldfish*

It was the results of experiments on the spinal goldfish by Allum & Graf (1977) that aroused my interest in the possibility that EOM afferent signals might be involved in oculomotor control specifically by way of a projection to the vestibular nuclei. Allum & Graf (1977) found that allowing the eyes to move in response to (horizontal) vestibular stimuli resulted in a lengthening of the time constant of the responses of neurons in the spinal goldfish's vestibular nuclei, compared with that found when eye movements were abolished by muscular paralysis. This effect they attributed to 'proprioceptive eye velocity feedback'. The suggestion that such proprioceptive feedback, specifically of eye velocity, might be implicated in oculomotor control was not new—it had been suggested by Fender & Nye (1961)—but the idea that such feedback might operate particularly on, or through, the vestibular nucleus was certainly novel. The suggestion was discussed at a workshop reported by Berthoz (1977) and seems to have had a mixed reception. How heavily the modelling viewpoint influenced the interpretation of the findings is indicated by the absence of any discussion in the paper or the report of the workshop of the question of evidence for the existence of a signal pathway from the EOM to the vestibular nuclei. Nor are the clear and considerable implications of the existence of such a signal path, if it were verified, discussed. These are that such a pathway would provide proprioceptive afferent signals from the eye muscles with a royal road into the oculomotor system since the vestibular nuclei project both monosynaptically and through polysynaptic pathways to the oculomotor nuclei (see Carpenter 1988; Precht 1978). Interestingly, in the light of subsequent observations, Allum & Graf's (1977) proposed mechanism of regulation of the gain of the vestibulo-ocular reflex (VOR) by modulation of the gain of the proprioceptive feedback loop would require that both excitatory and inhibitory effects of the proprioceptive signal be applied, as appropriate, to the vestibular nucleus. As a direct consequence of this work my colleagues and I set out to seek evidence for the existence of signals from the EOM proprioceptors in the vestibular nucleus and related structures.

(c) *Projection of the extraocular muscle afferent signal to the vestibular nuclei in an amphibian, a bony fish and the cat*

We began by examining an amphibian, the giant toad *Bufo marinus*, because it was clear from Precht's work (see Precht 1978) that the vestibular nerve and brainstem are relatively accessible in amphibians, which also have a rather simple eye movement repertoire, making eye movements only in response to vestibular or optokinetic stimuli (Grüsser & Grüsser-Cornehls 1978). Having shown (Ashton *et al.* 1983*b*) that the giant toad does make vestibularly evoked eye movements when it is tilted, Ashton *et al.* (1983*c*, 1984*a*) studied the effects of passive movement of one eye and of electrical stimulation of the IV nerve in the orbit on the responses of units in the vestibular nuclei, which were identified by their excitation by electrical stimulation of the vestibular nerve. Since the toad brain is small, the possibility of activation of brainstem units by direct current spread from the electrodes on the vestibular nerve, or (less probably) from those in the orbit, was considered and eliminated by the observation that, for both sites of electrical stimulation, the effects on central units could be blocked reversibly by application of a tiny quantity of local anaesthetic to the nerves on the stimulating electrodes. Out of 16 units the position of which in the vestibular nuclei was confirmed histologically, 11 (69%) received both vestibular and orbital afferent signals evoked by passive eye movement (PEM) while the remaining five units responded only to PEM. The responses to the orbital signal were phasic and excitatory. Since apparently identical responses could be evoked by electrical stimulation of the IV nerve in the orbit (and blocked by local anaesthetic so that current spread to other orbital structures was eliminated) and by PEM, it was concluded that the source of the afferent signal included, or was confined to, the stretch receptors of the EOM. 'Tendon organs' have been found in the EOM of several amphibians (Von Sabussov *et al.* 1964). When units receiving both signals were tested with vestibular stimuli and PEM at various interstimulus intervals the responses showed 'mutual inhibition', that is, the response to the second stimulus was reduced whether the vestibular stimulus followed the PEM or vice versa. Interestingly, the toad vestibular nuclear units did not respond to visual stimuli. This seems to correspond with the lack of optokinetic response of such units in frogs (Dieringer & Precht 1982) and perhaps to our finding (Ashton *et al.* 1983*b*) that the optokinetic signal that is needed for compensation for tilt in the giant toad does not seem to act on the gain of the VOR but rather on that of head and body movement. The results in the toad strongly suggested the desirability of looking for an EOM afferent signal projection to the vestibular nuclear complex in animals with more fully developed VORs than amphibians, preferably using natural vestibular stimuli rather than the quite non-physiological electrical stimulation of the vestibular nerve. Incidentally, one may note that the results in the toad were later confirmed using natural horizontal vestibular stimulation combined with PEM

(Donaldson 1986). Some principles of technique established during the work on the toad proved very valuable in later work, such as locating the origin of orbital afferent signals by comparing the results of PEM and electrical stimulation of intraorbital nerves (as, of course, others had done in studying other central projections); using interleaved collection of data to avoid being misled by 'spontaneous' changes in excitability; and, very importantly, of looking not only for responses to EOM afferent signals on their own but also studying the effect of these signals against a background of vestibular drive.

Subsequent experiments by our group showed that in the anaesthetized cat (Ashton *et al.* 1988) and the decerebrate bony fish (rainbow trout) (Ashton *et al.* 1989) the vestibular nuclei and related neighbouring structures involved in control of eye movements receive signals from EOM afferents that are able to modify their responses to vestibular stimuli—specifically to natural horizontal stimulation that would, in the intact animal, produce a horizontal vestibulo-ocular reflex (HVOR). The results in these two very different species were very similar. Those in the cat are perhaps of more interest. In the cat medial vestibular nucleus, which is principally concerned with horizontal eye movements, 58% of units responded only to (horizontal) vestibular stimulation, 21% did not carry this vestibular signal but responded to PEM (or to electrical stimulation of a branch of the oculomotor nerve in the orbit) and the same proportion (21%) carried both signals. In the nucleus praepositus hypoglossi—also known to be involved in the control of horizontal eye movement—the proportions were vestibular only 12%, EOM afferent only 31%, and 38% carried both signals, the remaining 19% carried other somaesthetic signals. Deeper in the brainstem, in the nucleus gigantocellularis of the reticular formation, there was a higher proportion of units carrying orbital afferent but not vestibular signals (58%) and only 13% carried both signals. Unfortunately, the spread of latencies of responses did not allow any conclusion about whether the signals passed through one of the nuclei to reach others. If all the units tested in the cat brainstem in and near the vestibular nuclei are lumped together, 55% of the units that received the EOM afferent but not the vestibular signal showed some degree of preference for eye movement (PEM) in one plane. For units carrying both signals, 29% showed such 'planar' specificity. The cat brainstem therefore receives signals from EOM afferents that affect some units preferentially for eye movements in, for example, the horizontal rather than the vertical plane.

(d) *Effects of the extraocular muscle afferent signal on vestibularly driven activity in the cat*

The afferent signal induced by PEM most commonly caused excitation additional to that from vestibular drive and this was often followed by a short period of inhibition of the vestibular response. In some units, however, purely inhibitory responses were found. The details of the interactions often depended on exactly when in the sinusoidal cycle of vestibular drive the eye movement was applied. It was clear that the interaction was not always a simple algebraic addition of the effects of the signals. There was also evidence that eye movement in one plane—for example, horizontal—was more effective in modulating the vestibular response than eye movement in another plane. A number of units showed this planar specificity of the effect of eye movement on the vestibularly driven responses.

It would seem that these results are consistent with the hypothesis that an afferent signal from the eye muscle proprioceptors can provide either excitatory or inhibitory influence to the vestibulo-ocular system at the brainstem level and thus could, in principle, modulate the gain of the HVOR in either direction, as Allum & Graf's (1977) hypothesis required.

The occurrence of these effects in the nucleus praepositus hypoglossi (NPH) as well as in the medial vestibular nucleus (MVN) is worthy of comment. The NPH has extensive connections with other brain structures involved in the control of eye movements (McCrea & Baker 1985) and its efferents carry activity—particularly related to horizontal eye movement—to other structures, including the oculomotor nuclei. It is believed to be the site of, or one of the structures involved in, the function of 'neural integration' to produce a signal of eye position from eye velocity (see, for example, Baker & Berthoz 1975; Cannon & Robinson 1987). It has also been suggested that NPH may distribute a corollary discharge signal that estimates eye position or velocity, derived—for example by integration—from other parts of the oculomotor system. The results just described strongly suggest that, whatever its activities may be in respect of corollary discharge, NPH could also act as a centre for distribution of afferent signals of eye position or velocity derived from EOM proprioceptors. See Ashton *et al.* (1988) for further discussion of possible relationships between afferent and corollary discharge signals.

All this, however, would depend upon the EOM afferents being able to supply appropriate signals of eye position and/or velocity, which was uncertain in 1988. Though we still have much less information on the details of the primary afferent signals than is desirable, at least in the pigeon (Fahy & Donaldson 1998) we do now know that they are able to provide signals of eye position and eye velocity for a short time after an eye movement, as we have discussed earlier in § 6.

Thus in three vertebrate species with very different repertoires of eye movement—an amphibian, a bony fish and a mammal—it had been shown that the vestibular nuclei and related structures receive a signal from the EOM proprioceptors that is able to modify the responses of units to vestibular stimulation and to modify them not in a non-specific way but according to the plane in which the eye movement takes place. This certainly suggested some role for the eye muscle afferents in oculomotor control, most probably of at least the HVOR, but there were many questions that had to be answered before the evidence could be considered stronger than just suggestive. At this stage the movements that had been imposed on the eye to evoke the proprioceptive afferent signal were rapid—in the saccadic range—and it was difficult to interpret their effects in terms of any putative specific control mechanism since the eye movements were arbitrary in size and timing and not closely related to the 'requirements' of the vestibulo-ocular system to produce stabilizing eye movement in the face of vestibular stimulation. Also, though the work on the cat had been

successful, it was clear that the results were likely to have been affected by the presence and exact state of anaesthesia as well as quite probably by the choice of agent (though the results had been similar with chloralose and ketamine). On the other hand, the decerebrate preparations of the lower vertebrates, though unanaesthetized, did not offer a large yield of responsive units—perhaps because of their lower density of cell packing than mammals—and these animals are rather far removed from the primates in their range of oculomotor behaviour.

(e) *Studies in the pigeon*

Clearly a new preparation was needed in which the signal could be studied without anaesthesia. Effectively this meant that a decerebrate animal would be needed. A well-developed repertoire of eye movements was necessary, especially those driven by vestibular stimuli. Some birds fulfil these criteria and the pigeon was chosen not only because of convenience and its previous use in visual and oculomotor work but also because afferent projections from its EOM to the brainstem had been described (Eden *et al.* 1982). It was a nice irony that these turned out not to represent EOM afferent projections at all but that, nevertheless, the pigeon does have projections from EOM afferents—in a less surprising place, the spinal trigeminal complex (Hayman *et al.* 1995). Pigeons are foveate with excellent visual acuity (Hodos *et al.* 1985) and make a variety of eye movements. They have a well-developed VOR (Anastasio & Correia 1988; Donaldson & Knox 2000; Gioanni 1988*a*) and an optokinetic system (Gioanni 1988*b*) (see also comments by Hayman & Donaldson (1997)). Finally, we knew from the work of Whitteridge, for example Hamdi & Whitteridge (1954), that a stable decerebrate preparation could be made.

Donaldson & Knox (1988, 1990*a*) found that units in the brainstem of the decerebrate unanaesthetized pigeon receive a signal induced by PEM. Control experiments eliminated visual and cutaneous sources, the responses were unaffected by local anaesthesia of the cornea and it was later possible to show that electrical stimulation of the IV nerve in the orbit produced similar central responses to those induced by PEM (Knox & Donaldson 1995*a*). There is therefore little doubt that the afferent signals originated in the eye muscles. In these experiments fast, trapezoidal eye movements at velocities similar to those during saccades were used. Large samples of units could be obtained and, of 352 units tested with natural horizontal vestibular stimulation (horizontal sinusoidal oscillation) and PEM, 40 responded to PEM only, 312 carried the vestibular signal and, of the latter, 59% (183) had their vestibular responses modified when one eye was moved passively. The EOM afferent signal produced excitatory or inhibitory effects, or both, on the vestibularly driven responses. Some units were affected only by eye movement in one plane—thus 34% (of 124 units tested) were affected only by horizontal eye movement and 6% only by vertical PEM. In a further 18%, however, horizontal eye movement had a (statistically significant) larger effect than vertical while in 2% the converse was the case. These units had, of course, been selected because of their excitation by horizontal vestibular stimulation so it was not surprising, though it was gratifying, that many of them were affected by EOM afferent signals from horizontal movement of the eye. The 'tuning' of the effects to various directions of PEM was examined and preferences for various planes and directions of eye movement were found. Some units were quite sharply tuned. Of the units with these properties some were in the medial vestibular nucleus (MVN) but many were in the reticular formation deeper in the brainstem and in the nucleus gigantocellularis (NGC)—as was the case in the cat.

The results, then, were similar to those in the cat but with the advantages of absence of anaesthesia and of being able to obtain much larger samples of unit responses to test. The existence of specificity of the effects on vestibularly driven responses for plane, and sometimes for direction, of eye movement was confirmed.

Attention then turned to the oculomotor nuclei, since, obviously, any effect on eye movement and its control must be expressed by changes in the firing of oculomotor neurons. In addition to the observations of Tomlinson & Schwartz (1977) mentioned above, a few units in the toad oculomotor nucleus and in the fish III and IV nuclei had already been shown to receive a signal from the EOM afferents (Ashton *et al.* 1989, unpublished data). The most convenient nucleus to study, however, is the abducens. It is more circumscribed than the oculomotor nucleus and has the great advantage of supplying only one muscle, the ipsilateral lateral rectus, so that the effect of changes in its responses are easier to interpret and the problem of which muscle pool has been recorded from does not arise. Responses to horizontal vestibular stimulation and to PEM were examined in the pigeon abducens nucleus by Donaldson & Knox (1991) who found that all 19 units histologically in the nucleus had their vestibular responses modified by PEM. This 100% prevalence contrasts with MVN and neighbouring nuclei where only some—very approximately one-half—of the units were affected by the EOM afferent signal. The effects were most commonly (15 out of 19, 79%) purely inhibitory and, importantly, the strength of the inhibition depended in a graded fashion on both the amplitude and the velocity of the PEM. Increasing amplitude or velocity of eye movement led to an increase in inhibition and sometimes to almost complete abolition of the vestibular response. It seemed that the inhibition was more profound when the eye was held deflected than during the deflection itself and, as far as could be judged from the fairly short deflections used, the inhibition persisted until the eye was returned from its deflected position. This behaviour contrasts with the more commonly seen purely phasic effects of PEM signals elsewhere. Incidentally, it was found that the frequency plots for gain (measured in terms of rate of cell firing), and phase of the abducens responses to sinusoidal horizontal vestibular stimulation were similar in shape to those of the overall Bode plot for the HVOR—perhaps not surprisingly.

Although the timing of the responses in relation to the cycle of sinusoidal vestibular stimulation was consistent with the records being from abducens motor neurons, there was no direct evidence that the responsive units were, or included, lateral rectus motor neurons—just conceivably all could have been intranuclear interneurons. This question was resolved by examining the

electromyogram (EMG) of individual eye muscles, including the lateral rectus (Knox & Donaldson 1991*a*). The activity of the EOM was estimated by recording EMG during horizontal sinusoidal oscillation and the effects of eye movement imposed on the eye contralateral to the recording were examined. The actions of horizontal PEM, which were inhibitory on the vestibularly driven activity, were greatest on the lateral rectus. From examination of the anatomy of the arrangement and insertions of the pigeon's eye muscles it was apparent that, during horizontal abduction of the eye, coactivation of lateral and superior rectus would be expected and this was, indeed, found to occur. Activation of lateral rectus alone, which is inserted well below the equator of the globe, would produce downward and tailward eye movement. To produce horizontal movement other muscles, particularly superior rectus, must also be active. This observation may be relevant to the rather wide tuning of the effect of PEM on abducens neurons that was noted previously, if the pigeon lateral rectus is active in movements with vertical as well as horizontal components as its arrangement in the orbit suggests. Thus it was confirmed that the EOM afferent signal does, indeed, exert effects—all of which were inhibitory in these experiments—on the vestibular drive to lateral rectus (abducens) motor neurons and, indeed, on those of other eye muscles. These experiments also tested the effects of slow eye movements and used the 'artificial VOR' method that had just been devised (Knox & Donaldson 1991*b*) and which is described below. With both fast and slow eye movements the amount of inhibition of the vestibularly driven activity was monotonically related to the amplitude of eye movement, as had been found previously for the effect of fast PEM on abducens neurons (Donaldson & Knox 1991). In the course of further experiments (Donaldson & Knox 1993) the vestibular responses of all the units recorded in the abducens nucleus and in the oculomotor nucleus were modulated by the EOM afferent signal, thus confirming and extending the previous results. Now that it has been established that the EOM afferent signal acts on the vestibular drive to lateral rectus, the finding that all the abducens neurons examined showed modulation of their vestibular responses by the proprioceptive afferent signal takes on added significance since it strongly suggests that, by the level of the final common path to the EOM, vestibular drive has been subject to the influence of EOM proprioception. Whether this influence acts at the level of the abducens nucleus itself or on the signals at earlier levels in the chain of processing (or, indeed, on both) is not yet known.

(f) *The artificial vestibulo-ocular reflex*

This experimental technique may conveniently be described here. It has been used extensively in later work. Sinusoidal horizontal oscillation in the intact and the decerebrate bird produces 'compensatory' slow horizontal eye movements—the slow phase of the HVOR. For perfect image stability the eye should move at the same instantaneous speed as the head but in the opposite direction, that is, the HVOR gain should be −1.0. In the artificial vestibulo-ocular reflex (AVOR) method one eye is moved passively during sinusoidal oscillation of the head so that the imposed sinusoidal eye movement, at the same frequency as head movement, is always in the opposite direction to that of head movement. If the amplitude of the imposed movement is arranged so that the maximum speed of the eye equals the maximum head speed, the gain of the AVOR will be −1.0 and we have a 'compensatory AVOR' during which the eye is made to move exactly as it would be moved, ideally, by the slow phase of the HVOR. If, now, the amplitude of the imposed sinusoidal movement is altered, and thus its velocity proportionally changed, eye movements can be imposed the maximum velocity of which differs from that required for compensation—that is, one can impose a series of velocity errors on the system with the error in either direction according to whether the eye moves faster or more slowly than the head. Similarly, the phase of the imposed movement can be altered and phase errors imposed on the system. The AVOR thus provides a method of inducing errors of eye movement that will be signalled by the EOM proprioceptors in a context in which vestibular drive will be evoking motor commands to the eye muscles. In contrast to the arbitrary afferent input produced by sudden 'pseudosaccadic' movements imposed on the eye at the whim of the experimenter when the oculomotor system will not, in general, be generating a command for a saccade, the errors imposed by the AVOR will give rise to afferent input that is relevant to the ongoing oculomotor commands that are themselves induced by the known vestibular stimulus. Consideration of the effects of these known and controllable errors offers the possibility of understanding some aspects of the putative actions of the EOM afferent signal in oculomotor control. The method has now been used to study effects of eye muscle proprioceptive signals on single units in the oculomotor system, on the eye muscle activity and on movements of the eye itself. The results of experiments using the AVOR and their interpretation are discussed below.

(g) *The evidence that extraocular muscle afferent signals may exert a 'corrective effect' on the slow-phase movements of the horizontal vestibulo-ocular reflex*

The first indication that errors of velocity of eye movement might lead to rather specific changes in the behaviour of the oculomotor system came from the experiments on the activity of the lateral rectus muscle during the (horizontal) AVOR (Knox & Donaldson 1991*a*). Increases in the velocity of imposed eye movement (IEM) above that appropriate for stabilization of the retinal image led to progressive reduction in the EMG activity of lateral rectus. With decreases of eye velocity below the compensatory value there were approximately corresponding increases in the muscle activity. Because the measurement of muscle activity could not be made in units that translate to eye velocity and, in any case, the absolute EMG voltages recorded from the EOM varied from experiment to experiment, it was necessary to standardize the measure of muscle activity in some way. This was done by expressing it as the ratio, for each value of IEM, of the output at that value divided by the output at the 'compensatory' eye velocity. In some later experiments the ratio was expressed relative to the output with no IEM (that is, at zero imposed eye velocity). The only

effect of this difference in the denominators of the ratios is to shift the ordinate scale—the shape of the relationship between gain ratio and imposed eye velocity is unaffected. In later experiments linear regression analysis was used to fit the best line to the relationship between the output ratio and imposed eye velocity. When the velocity imposed on one eye during the HVOR was excessive, the results of the AVOR experiments on the activity of the lateral rectus eye muscle showed that the output of the system to the other eye (judged in this case by the EMG) fell and when the imposed eye velocity was inadequate for retinal image stabilization the output increased. This immediately suggests the working hypothesis that the EOM afferent signal induces behaviour directed in a corrective sense that would, in the complete system, reduce the error in eye velocity. Suggestive as the EMG results were, it would be possible to argue that they might not be representative of the overall movement of the globe of the eye. For instance, it was possible—though it seemed most improbable—that only the activity of some small and unrepresentative sample of the lateral rectus motor units had been examined and that the behaviour of this sample would contribute insignificantly to the overall behaviour of the eye. This question was pursued by studying the movements of the globe using the AVOR. At the same time, further central recording examined the effect of the AVOR on the responses of units in brainstem structures, including the medial vestibular and abducens nuclei, in which fast eye movements had been shown to modulate vestibular responses.

(h) *Movements of the globe*

Recording horizontal eye movement using the electro-oculogram (EOG), Knox & Donaldson (1993*a*) found that some, but apparently not all, decerebrate pigeons had fast as well as slow phases in their HVOR. This was unexpected since Carpenter (1972) had found that the decerebrate cat did not show fast, nystagmic phases during the VOR. In the absence at that time of any method of removing the fast phases online, which is essential to allow the AVOR technique to be used, birds without fast phases, or in which fast phases could be made very infrequent by reducing the amplitude of the horizontal vestibular stimulus, had to be selected. It proved possible to carry out AVOR experiments in a number of decerebrate pigeons and it was found that the relationship between the amplitude ratio (for a given IEM velocity to that with no IEM) and the imposed eye velocity was similar to that seen in the EMG experiments on the lateral rectus muscle (Knox & Donaldson 1993*a*). Regression analysis showed that a linear relationship fitted the data well with a slope of about -0.01, implying that for each degree per second increase in imposed eye velocity the relative gain fell by *ca* 1%. Later work, using an electromagnetic coil method of measuring eye movement and removing fast phases online to allow estimation of slow-phase eye velocity in all, rather than just in selected, decerebrate pigeons confirmed the results obtained with the EOG method both qualitatively and quantitatively (Fahy & Donaldson 1996). By this time, the ophthalmic branch of the trigeminal nerve (VOphth) had been shown to carry the pigeon EOM afferents (Hayman *et al*. 1995). In the later experiments it was also possible to show that the section of VOphth of the eye on which movement was imposed abolished the velocity-dependent effect of the IEM. This provides additional compelling evidence that the effect is, indeed, produced by an EOM afferent signal. At about the same time, the velocity-dependent effects of IEM on the EMG activity of lateral rectus (Hayman 1994) and on the activity of neck muscles during the vestibulocervical reflex (Hayman & Donaldson 1997) were shown to be abolished by section of VOphth. It is important to notice that these velocity-dependent effects are produced by slow eye movements in the velocity range of the slow phase of the HVOR in experiments in which, as explained above, there is a vestibularly evoked motor command. All the results are consistent with the hypothesis that, when errors of eye velocity are induced during the HVOR, the system responds by modifying its output in a corrective direction.

(i) *Effects of the artificial vestibulo-ocular reflex on unit responses*

Donaldson & Knox (1993) examined responses of units in the brainstem to both rapid ('pseudosaccadic') imposed eye movements and to the AVOR. Ninety-one units whose vestibular responses were modulated by 'pseudosaccadic' eye movement were also examined using the slow IEM of the AVOR technique. For 29 of these, successful observations were made with a series of interleaved IEM during the AVOR. Definite velocity-dependent effects, in which the response diminished with increasing IEM velocity, were found in 27 (93%). The response was measured by fitting the best sinusoid (by a least-squares method) to the peri-stimulus time histograms of the unit activity to the vestibular stimulus alone, and to the same vestibular stimulus accompanied by IEM at various velocities during the AVOR. The ratio of the amplitude of the sine to that with no IEM was then plotted against IEM velocity and linear regression analysis was performed for each set of data. Analysis of covariance showed that the regression lines could be considered to form a homogeneous group with a mean slope of -0.01—exactly the same value as the mean slope for the effect of the imposed eye velocity on slow-phase eye movement. The effect of IEM velocity on the units' gain ratio was significant with ($p < 0.001$). Like the slow-phase eye movement, the units' output fell by about 1% for each degree per second increase in imposed eye velocity. The pooled regressions included results from units in various structures, including the medial and other vestibular nuclei, the abducens nucleus and reticular formation. It is interesting that the relationship of the gain ratio to the IEM velocity was closely similar in units from these different structures, all of which are involved in the control of the VOR, and was effectively the same as for the movement of the globe itself.

(j) *Effects on gain versus phase*

In all the AVOR experiments, on unit responses and on eye movement, it was found that there was a consistent effect of IEM velocity on the gain of the response but the response phase was not affected in any consistent way. Also, imposing phase errors alone (without errors in velocity) in the IEM did not lead to any consistent changes in the phase of the output but did often lead to changes in

output gain. The interpretation of the effects of imposed phase errors is complicated—see Donaldson & Knox (1993) for discussion. For example, they may lead to situations in which the IEM is in the same direction as head movement during part of the vestibular cycle rather than in the opposite direction. It does seem that when phase and velocity errors are combined the effect of the IEM may be greater than that produced by a given velocity error alone. The results of all the experiments indicate that the effects of errors, whether these are of phase or velocity, are to produce consistent effects on the gain of the responses or of the eye movements but no consistent changes in their phase. Interestingly, the effect of paralysing cat eye muscles during the VOR was dismissed many years ago as evidence for an action of EOM proprioceptors because it produced no change in the phase of the modulation of abducens neurons, although a change of some 20% in the amplitude of the response was visible (Taylor 1965).

(k) *Experiments with the artificial vestibulo-ocular reflex on intact animals*

To complement the investigations of the effect of EOM afferent signals during the AVOR on the responses of central units and on the HVOR of the decerebrate pigeon, Donaldson & Knox (2000) studied the effects on the characteristics of the HVOR of the intact, alert pigeon of velocity errors during the AVOR. In contrast to earlier measurements of the HVOR in the alert pigeon, in which the birds were sometimes (Anastasio & Correia 1988) or always (Gioanni 1988*a*) 'aroused' with amphetamine, no systemic drugs were used. The HVOR gain varied considerably between birds and in the same bird between experiments. In spite of this variability, clear effects of the EOM afferent signal during the AVOR were found in all birds, although they were not present in every experiment. When present they were consistent in character and closely resembled, qualitatively and quantitatively, the previous findings in decerebrate birds. In the intact bird an increase of one degree per second in the velocity of imposed eye movement led to a decrease of HVOR gain by *ca.* 1%, as in the decerebrate. The lack of any consistent effect on HVOR phase was also confirmed. The finding of the EOM afferent effect in only some experiments was ascribed to differences between experiments in the 'behavioural context' that were not under the experimenters' control such as alertness and attention state. Thus the effects discovered in the decerebrate pigeon are also to be found, acting in apparently closely similar fashion, in the intact alert bird.

A few pilot experiments (Knox & Donaldson 1993*b*) suggested that similar actions of the EOM afferent signal may be found on the human HVOR but these possible effects need to be studied in more detail and in more subjects before a firm conclusion is drawn.

(l) *Effects of removal of the extraocular muscle afferent signal on the vestibulo-ocular reflex and on eye stability*

As the experiments just described seem to indicate, if a signal from the EOM proprioceptors is involved in oculomotor control, one might expect that its removal would lead to disturbance of eye movement. This possibility has been considered in the past and occasional attempts were made to test it. Taylor's (1965) experiment, which seems to have been reported only in a short abstract, has already been mentioned. Presumptive removal of the EOM afferent signal by paralysis of the EOM was found not to alter the phase of abducens unit firing during the HVOR of the cat—but the amplitude of firing was reduced by some 20%, which would be expected to produce a reduction in VOR gain. Carpenter's (1972) observation is interesting—that the pattern of the EMG of the decerebrate cat during horizontal sinusoidal oscillation was not affected by whether the eye was free or was fixed. It is unfortunate that the HVOR gain of the other eye was not measured. In recent unpublished experiments on a small number of alert, intact pigeons in my laboratory, the HVOR gain of one eye was measured in the light and in darkness while the other eye was covered and held still. The gain of the HVOR slow phase of the free eye usually fell, sometimes markedly, when the other eye was held and this effect was larger when the experiment was carried out in the dark. This would, of course, be consistent with an action of the EOM afferent signal in sustaining normal HVOR gain. In any event, Carpenter's conclusion that his eye holding experiment shows that the EOM afferent signal has little or no effect on the VOR is not supported either by the experiments described in the previous section or by the effects of deafferentation of the EOM as we shall see. The effects on saccadic and pursuit eye movements of holding the human eye still or of impeding its movement are discussed later.

Fiorentini & Maffei (1977) found that section of the ophthalmic branch of the trigeminal nerve (VOphth), thus completely or largely deafferenting the EOM (according as one believes that all, or only most, of the afferents in the cat pass through this nerve), resulted in instability of the cat eye in the dark. At about the same time Maffei & Fiorentini (1977), recording vestibularly driven cat eye movements in the dark, found that the amplitude of the fast phases of the vestibular nystagmus was reduced in the deafferented eye. The reduction was not apparent in the light.

Kimura *et al.* (1981) found in rabbits that the VOR gain fell by 20–40% in both eyes on blocking the EOM afferents in one trigeminal nerve or sectioning the nerve, although the effect was greater on the deafferented eye. Both fast and slow phases were said to be affected. Eye velocity during OKN was also reduced at high velocities of visual stimulation. Later, Kashii *et al.* (1989) examined the effect of section of the rabbit VOphth (which they showed carried EOM afferents) on the EOG of the deafferented eye at rest and during the HVOR. The slow phase of the HVOR was disorganized but fast phases seemed unaltered. No measurements were made of HVOR gain. Then Kimura *et al.* (1991) confirmed that there are, indeed, gain changes with reduction in the gains of VOR and OKN after VOphth section in the rabbit and produced evidence to suggest that these are produced by way of the cerebellar flocculus.

In the decerebrate pigeon Hayman & Donaldson (1995) found that section of VOphth resulted in marked disruption of the HVOR—not only was the gain reduced but the response was disorganized—and, at rest, the deafferented eye was grossly unstable. In the pigeon the

effects were demonstrably present within minutes and the effects produced by cooling the afferents (Kimura *et al.* 1981) in the rabbit were also presumably observed within a short time. Some of the other observations on rabbits were made several days after deafferentation so it is uncertain when the effects appeared. The immediate appearance of the effect of deafferentation supports the suggestion that the EOM afferent signal takes part in moment-to-moment control of the VOR. This suggestion was made on the basis of the AVOR experiments, which clearly imply effects occurring in fractions of seconds after imposing an error of eye velocity (Donaldson & Knox 1993; Knox & Donaldson 1991*a*, 1993*a*). This of course does not exclude an additional action in the longer term. Indeed, as will appear, there is evidence for such actions also possibly operating through 'parametric' adjustment as proposed by Ludvigh (1952*a*).

15. ACTIONS OF EXTRAOCULAR MUSCLE AFFERENT SIGNALS ON NECK MUSCLES AND IN THE CONTROL OF GAZE

The direction of gaze is obviously determined by the algebraic sum of body position in space, head position on the body and eye position in the head. If we consider only egocentric gaze when the trunk is stationary in the anatomical position this reduces to the algebraic sum of the head position on the body and the eye position in the head. Vestibular stimuli in the normally behaving animal result in movements of both head and eyes (see Carpenter 1988). In the control of gaze the activation of eye and of neck muscles must, clearly, be closely coordinated. Berthoz and his group have studied the coordination of these muscles during horizontal gaze shifts (Ron & Berthoz 1991) and have also shown that signals of eye position and/or eye velocity are found in the activity of second-order units in the vestibular nuclei (Berthoz *et al.* 1981) and also in the nucleus praepositus hypoglossi (Baker & Berthoz 1975; Lopez-Barneo *et al.* 1982). These signals have often been ascribed to a corollary discharge arising from the oculomotor neural integrator (see Berthoz *et al.* (1992) for discussion). The activity of the integrator is believed to be associated with the vestibular and praepositus nuclei but these nuclei are now known also to receive signals from EOM afferents (Ashton *et al.* 1988; Donaldson & Knox 1990*a*, 1993). Thus it seems possible in principle that the EOM afferent signals could contribute to the signals of eye position or velocity in the brainstem (Berthoz *et al.* 1992) that, in turn, are concerned with the control of neck muscle activity during vestibular stimulation, for example during the vestibulocollic reflex (VCR). In fact, the work of Easton in the 1970s suggested that EOM afferent signals are involved in patterned inhibition of forelimb and neck muscles (Easton 1971) during horizontal eye movement but this suggestion seems to have been ignored. If EOM afferent signals were shown to act on the neck muscles during the VCR this would imply strongly that these signals are involved in the control of gaze via actions on the control of head position on the body as well as via their actions on the VOR.

Hayman *et al.* (1993) showed that movements imposed on one eye of the decerebrate pigeon modify the responses of several relevant neck muscles that take part in the VCR. Further background to these studies is to be found in Hayman's thesis (Hayman 1994). The experiments were then extended (Hayman & Donaldson 1997) to examine specific aspects of the relationship between the direction of the imposed eye movement and the particular neck muscle pairs involved in the VCR induced by vestibular stimulation in the horizontal plane and in the roll–tilt (ear-up–ear-down) plane. The effects of movements imposed on the left eye (IEM) on the activity of three neck muscle pairs—splenius, complexus and biventer cervicis—were studied by recording the modulation of their electromyographic activity during sinusoidal oscillation of the bird in either the horizontal or the roll–tilt (ear-up–ear-down) plane. The modulations induced by IEM appeared to be closely related to the particular functions of each muscle pair in producing head movement. Thus, biventer cervicis, which is active in nodding movements but not in head rotation, showed vestibularly induced activity during roll–tilt but not during horizontal oscillation. The response of both biventer cervicis muscles was increased when the eye was deflected upwards and decreased when it was moved downwards. The other muscle pairs are active both in head rotation and in nodding movements, although splenius has much less action in the vertical plane than does complexus. The left and right muscles showed mirror-image effects of IEM during horizontal oscillation and these effects were markedly directional. Thus, the left muscles were much more powerfully inhibited by deflection of the left eye to the right than by its movement in the opposite direction. For the right muscles the corresponding effect was maximal inhibition on deflection of the left eye to the left. The details of the interactions are set out in Hayman & Donaldson (1997) as are the various control experiments that indicated that the source of the signals during IEM was almost certainly the EOM proprioceptors. Particularly important was the observation that intracranial section of the ophthalmic branch of the trigeminal nerve (VOphth) of the eye being moved immediately and permanently abolished all the modulatory effects of IEM on the vestibularly induced modulation of neck muscle activity. Hayman *et al.* (1995) had already shown that the pathway of the pigeon EOM primary afferents is through VOphth to the trigeminal ganglion. These experiments using the VCR of the decerebrate, unanaesthetized pigeon to test the actions of EOM afferents on neck muscles strongly suggest that EOM proprioceptors are one source of a signal of eye movement that is used in the control of the activity of neck muscles and thus of head movement. This conclusion is also supported by our more recent knowledge that pigeon primary EOM afferents carry signals into the central nervous system that contain information about eye position and eye velocity and are available for at least some time after the end of each eye movement (Fahy & Donaldson 1998).

The pigeon with its small, light head probably uses head movement proportionately more in stabilizing gaze (Gioanni 1988*a*) than do animals with larger, heavier heads (for example, the cat; Peterson *et al.* 1981). However, there is no doubt of the importance of head movements in the stabilization and redirection of gaze even in Man with his proportionately very large and heavy head (see Carpenter 1988)—as one only has to

have a stiff neck to be painfully aware. If EOM afferent signals participate in the control of vestibularly induced head movement in pigeons, as the experiments above indicate, it seems likely that this will be true in mammals also. One may conclude that signals from proprioceptors in the extraocular muscles are likely to be involved in the control of gaze since there is evidence that they are concerned with the control of both vestibularly induced eye movements and head movements.

16. EFFECTS ON VISUAL PERCEPTION AND VISUOMOTOR BEHAVIOUR

Actions of signals from the eye muscle proprioceptors were observed on the visuomotor behaviour of animals before there was any systematic search for such effects in Man.

Maffei and his colleagues (Maffei & Bisti 1976; Maffei & Fiorentini 1976) found that immobilization of one eye in the adult cat, or artificial strabismus in the kitten, decreases the proportion of binocularly driven cells in the primary visual cortex even if the animals are deprived of vision. Thus, altering eye mobility is sufficient to induce the effect. Following this, and the demonstration (Maffei & Fiorentini 1977) of a projection of the EOM afferent signal to the cat primary visual cortex and of instability in the dark of an eye whose EOM were deafferented (Fiorentini & Maffei 1977), Fiorentini *et al.* (1982) tested the visually guided jumping behaviour of cats with the EOM of one or both eyes deafferented by section of VOphth, which, as we have seen, carries most if not all the EOM afferents. The unilaterally deafferented animals made consistent errors in jumping and their jumps were biased towards the side of the lesion. The errors occurred whether the cats viewed the visual target towards which they jumped binocularly or monocularly with either the normal or the deafferented eye. Bilateral deafferentation of the EOM in a single animal did not result in any bias in jumping but the cat's overall performance was less accurate than preoperatively. Thus, removal of the afferent signal resulted in deterioration in accuracy of performance, and asymmetry of the signal (when one eye was deafferented and the other was normal) added to the inaccuracy a bias towards one side of the action field. Though it was quite clear that jumping was affected by removal of the EOM afferent signal it was not apparent whether this was due to an effect on the cats' ability to detect the target direction accurately or to a disturbance of the elaboration of motor behaviour, including the direction of gaze, towards an accurately registered target position—or, of course, to a combination of the two. Later, the same observers (Fiorentini *et al.* 1985) found that deafferentation of the EOM reduced cats' ability to discriminate depth. The depth detection was judged by a jumping-stand method in which the cat had to jump towards a surface of adjustable depth so, again, it was not possible to differentiate between effects on the detection of target depth and effects on motor behaviour. In an attempt to differentiate between these possible actions, Fiorentini *et al.* (1986) estimated stereoacuity, in normal cats and in animals with unilateral section of VOphth, using an operant conditioning method in which the head and body were held still and the cat indicated stimulus detection by a change in its licking pattern rather than by jumping. Unilateral deafferentation reduced binocular stereoacuity to that of monocular viewing. The authors concluded that this indicates 'a role of oculomotor proprioception in binocular depth perception in the cat'. However, it would be better to replace 'perception' by 'detection' since there is no means of knowing the extent to which the cats may have been conscious of the depth of the target. The experiments certainly seem to exclude skeletomotor changes as the sole means of action of the deafferentation but they do not exclude the possibility that changes in vergence or in eye–head coordination might be involved in the disturbances of jumping in the earlier experiments since, presumably, it was necessary for the vergence angle as well as the relative retinal disparity to be 'known' to make the absolute depth judgements necessary to control the jump. Interestingly, as Fiorentini *et al.* (1986) point out, bilateral section of VOphth results in disturbance of vergence control in monkeys (Guthrie *et al.* 1982). The experiments using operant conditioning probably tested only the ability to judge relative depth and it is interesting that this was clearly reduced. It seems reasonable to conclude from this elegant series of experiments that an EOM proprioceptive signal is required for normal detection of visual depth by the cat and that a similar signal is involved, directly or indirectly, in the control of visuomotor behaviour.

At about the same time as these experiments were going on, Hein and his colleagues were coming to the end of a series of experiments that had lasted some 20 years on the acquisition by the young animal, and the maintenance in the adult, of visually guided behaviour. In a well-known experiment Held & Hein (1963) showed that motor action in a visible world is necessary for the normal development of visuomotor behaviour. When the only visual experience of two kittens was with one kitten towing another in a cart around a visual arena only the towing kitten developed normal visuomotor behaviour, although both had been exposed to similar visual stimulation. From this and similar observations arose a series of complicated experiments summarized by Hein & Diamond (1983). These included examination of the effects of immobilization of the eye and of deafferentation of the EOM by section of VOphth. Hein & Diamond (1983, p. 132) concluded

> 'We have provided evidence that eye movements and proprioceptive feedback from the eye muscles are fundamental to this* process. The two factors are intimately related; without inflow from the eye muscles a mobile eye is not localizable in its orbit; without eye movement any proprioceptive input that remains from the paralyzed eye seems insufficiently informative about eye posture . . . Self-produced movement, in this case eye movements, is the basis for the organism's knowledge of its environment.'
>
> *'The way spatial referents are assigned to retinal input.'

Thus, in the development of the cat's visuomotor behaviour EOM proprioceptive signals from moving eyes play an essential part.

About the same time the role of EOM afferent signals in the development of the visual properties of neurons in visual cortices began to be studied extensively with results that have been summarized above (§ 12) and are reviewed in detail by Buisseret (1995).

(a) *The need for an extraretinal signal*

In 1918, Sherrington argued that retinal signals alone are insufficient to prescribe the spatial coordinates of a stimulus in 'egocentric' visual space (Sherrington 1918). Rehearsing the experiments for the demonstration of Listing's law[5]—that on deflection of the eye from the primary position there is torsion of the eyeball—he pointed out that three points, objectively vertical on a vertical surface, are perceived as vertical both with the eye in the primary position and when they are viewed with the eye in a secondary position, although in the first case their images form a vertical line on the retina and in the second, because of torsion, they form an oblique line.

This constancy of a vertical percept, as he pointed out, could not be achieved without interaction between what we would now call signals, one of the eye position in the orbit, another of the direction of gravity (from the labyrinth) and, of course, the retinal signal itself. He clearly thought that the demonstration, by his own earlier work, of the presence of putative proprioceptors in the eye muscles and of their afferents in the oculomotor nerves was evidence of a sufficient source for the eye position signal. As to the necessity of an extraretinal signal of eye position his argument was, and remains, impeccable. But, as he says, Sherrington considered the experiments 'from the proprioceptive point of view'. In fact, as is clear from his chapter in Schäfer's *Textbook of physiology* in 1900 (Sherrington 1900) Sherrington totally rejected the earlier arguments of others—of whom Von Helmholtz was the principal author whom he discussed, though he was not the first to hold such notions (see Grüsser 1994)—that the perception of postural change was achieved as a result of a central process that depended upon activity in the motor system and not upon what would now be called peripheral proprioceptive feedback. In essence Von Helmholtz's signal was a postulated 'efference copy' or 'corollary discharge' as Von Holst & Mittelstaedt (1950) (better known in English from Von Holst (1954)) and Sperry (1950) would later call versions, differing in some essentials, of the same species of hypothetical signal (see discussion in § 2). Hypothetical, because it was not until decades after the proposals that good evidence was produced that such signals exist—although there was so-called 'evidence' in plenty. Von Helmholtz's arguments with respect to the eye were taken by Sherrington (1900) as a model to analyse and illustrate the more general issues of kinaesthesis and have been used in this way by later writers also. For perceptive comments on Sherrington's views, considered from the Helmholtzian standpoint, see Merton (1964) and for modern analyses of much more recent and decisive experimental material, see Matthews (1982) and the reviews by McCloskey (1981) and Gandevia (1996).

In fact, one could replace Sherrington's reference to EOM proprioception in his 1918 paper by references to a Helmholtzian sense of effort derived from some activity of the oculomotor system without affecting the argument for the necessary existence of an extraretinal signal of eye position in the orbit and for its interaction with retinal and vestibular signals ('labyrinthine' in the older terminology). In truth, Sherrington had no evidence that an EOM afferent signal was involved. For him, on this occasion, the existence of the appropriate receptors and peripheral path was sufficient to assume the existence and use by the brain of a proprioceptive signal, and this was clearly because he regarded the alternative as not worth serious consideration. One can hardly blame him. The presumption that muscle afferents must support kinaesthesis must have been well-nigh irresistible compared to the very vague and unsatisfactory notions of 'sense of innervation', 'sense of will to action' and so on. The short step from the proven existence of suitable receptors to the assumption that this guaranteed their seemingly obvious function must have given rise to no doubts at all. By now, Helmholtzians (believers in 'outflow alone') reading this may be in a state of agitated fury—'Has he never heard of the evidence that Von Helmholtz adduced?' Patience—he has, and will discuss it anon.

(b) *Is eye position perceived?*

Though it is not entirely explicit in either Von Helmholtz's or Sherrington's accounts, there is, I think, in both cases an implied belief that the extraretinal signal of eye position, whatever its source, is not only 'known' to the oculomotor system—in the sense that the system uses its information—but is also 'known' in a more particular sense to the individual. In short, the individual is believed to have a perception of eye position which is not derived solely from the retina but also requires the extraretinal signal. Thus a perception of eye position in the dark should exist. Some 20 years earlier Sherrington had also reported briefly (Sherrington 1898) that he had shown that the eyes can be directed accurately in the dark and he promised a more detailed publication of the experiments. This, unfortunately, he never seems to have made.

Much later, Brindley & Merton (1960) moved the topically anaesthetized eye with forceps and reported that, in the dark, a subject could neither tell whether the eye had been moved nor whether an attempt at voluntary movement had succeeded. Merton (1964) discussed this experiment among other results and theoretical considerations that he felt established that muscle afferents (principally spindle afferents) were incompetent to take part in kinaesthesis and, indeed, did not so take part. Once again one of the arguments used the eye as a model for a more general analysis of the skeletal system. For a decade or more the issues were hotly contested but in the 1970s they were settled to the satisfaction of (almost) everyone by the unequivocal demonstration by Matthews and his colleagues of the veracity of Sherrington's views on the necessity for muscle spindle signals to support skeletal kinaesthesis and the incompetence of 'outflow signals' (efference copies or corollary discharges) to support position sense. These critical experiments, based on muscle vibration to activate spindle afferents and selective anaesthesia of joints and of limb segments, are summarized by those who carried them out (see Matthews 1982; McCloskey 1981). One should note that the experiments demonstrate that muscle-spindle afferents are required for normal kinaesthesis and that outflow signals alone are insufficient to sustain kinaesthesis. These experiments do not deny to outflow any influence upon normal kinaesthesis nor demonstrate that spindles are the exclusive providers of the afferent signal in kinaesthesis. Indeed it is quite clear that knowledge of 'outflow' through the gamma-efferent system must be essential for the nervous

system to decode spindle afferent signals into information on absolute limb position (see Matthews 1982, 1988). Interestingly it was this very requirement, for what was thought to be an unduly onerous and quite inappropriate task for the brain, that had been one of the arguments against the likelihood of spindle afferents contributing to kinaesthesis. For example,

> 'The muscle spindles respond to changes in muscle length i.e. measure relative length, but with their contractile ends they would obviously be unsuitable instruments for making absolute length measurements.'
>
> (Merton 1964, p. 387)

But we now know that that is precisely one of the things that they do.

However, none of these experiments on kinaesthesis tested whether there is position sense in the eye.

There are at least two situations to consider: What happens when a subject moves his/her eyes? What happens when a subject's eye is moved passively? In fact things are more complicated than this and some experiments examine mixtures of these conditions. At its simplest, demonstration of a perception of passive eye movement would suggest a proprioceptive source for the signal, whereas a sense of eye position on actively moving the eyes might include, or be entirely dependent on, some outflow information. It would not seem to be difficult to devise experiments to choose between the alternatives but, in fact, this has proved very troublesome.

Ludvigh (1952*b*) found that deflections of at least 6° were needed for subjects to give *ca.* 75% correct responses to the question of whether their eyes were directed to the left or the right when they moved their eyes to view a visual target that appeared at random to the right or left of straight ahead in the dark. This, of course, represents very crude 'position sense' indeed. The experiments do not have anything to say about the source of the eye position signal, although Ludvigh seems to believe that it was proprioceptive since he writes

> 'The conclusion ... is that the muscle spindles in the extraocular muscles give rise to little, if any, acceptable information concerning the position of the eyes.'
>
> (Ludvigh 1952*b*, p. 440)

What is meant by 'acceptable' is obscure.

Acceptance that, apparently, the sense of ocular direction in the dark is crude does not lead Ludvigh to doubt that EOM proprioceptive information may be used in oculomotor control. He says 'The question then arises as to how ocular movements are controlled, considering the degree of speed and precision that they exhibit. In a subsequent paper, the hypothesis is advanced with supporting evidence that the chief function of the muscle spindles may be to provide a parametric feedback that alters the response of the muscle to motor stimulation.' The subsequent paper to which he refers is Ludvigh (1952*a*).

As we have seen, Brindley & Merton (1960) found no evidence of even crude sensation of eye position in the dark when the topically anaesthetized eye was moved passively. So in the 1960s it was generally accepted that there is either no extraretinal signal of eye position or its change that gives rise to perception, whether the eye is moved actively or passively—or, possibly, that there is a crude signal that is evoked only when the eye is moved actively.

In 1970, Skavenski & Steinman (1970) recording the position of one eye found that the eye can be held in a relatively stable orientation in the dark for long periods by voluntary effort. Topical anaesthesia of the cornea and eyelids did not affect the stability but did alter the subject's perception of his performance so that he felt that he had been unable to keep his eye steady when, in fact, he had achieved this. It seemed almost certain that an extraretinal signal was involved in keeping the eye steady—the only alternative would have been for the eye position to be set and then uncontrolled and this alternative was made unlikely by the observation that there were eye movements during the holding of a relatively stable eye direction. That an extraretinal signal must be involved was made even more probable by the later finding (Skavenski 1971) that these movements were largely corrective, tending to return the eye towards the 'set' direction. Subjects were also found to be able to 'remember' a given eye direction held in the dark, that is, they could reproduce it, again in the dark, after a period when they had made ordinary eye movements, with an accuracy of some 4° of arc over 15 min. Skavenski and his colleagues (Skavenski *et al.* 1972) then applied loads to one eye during fixation of a solitary visual target in the dark and found that this altered the perceived direction of the target, although it did not alter eye position since the target remained fixated. The conclusion was, therefore, that a change in an outflow signal,[6] related to the increased drive to eye muscles required to resist the applied load, was the cause of the change in perceived visual direction. At this point one might feel that the relevant question had now been asked—that of perceived visual direction and not of perceived eye position—and that the latter might not be a very sensible question to which to expect an answer. In a somewhat parallel situation, Matthews & Simmonds (1974) found that pulling on a tendon at the wrist induced no sensation of muscle lengthening but did produce a sensation of movement at the relevant joint and thus of change in posture of a limb segment (see also discussion of tendon pulling in Matthews 1982). One might then expect that, as we are unconscious of the lengths of our muscles, we might be unconscious of the posture of our eyeballs, although in each case the unperceived parameter can be closely controlled and disturbing forces resisted. However, perhaps surprisingly, Skavenski (1972) also found that inflow signals from the orbit, presumably from the EOM proprioceptors, can, after all, give rise to perception of a kind since trained subjects could, on most occasions, choose correctly whether or not an eye had been deflected and correctly name the direction in which their eyes had been passively deflected in the dark. However, this does not mean that human subjects normally have any precise percept of where their eyes are pointing in the dark. In terms of the requirements for oculomotor control of eye position the deflections detected by Skavenski's subjects were large. It is also not clear that they were perceived as being changes in eye position even though the subject could usually choose the correct direction of deflection from the alternative wrong one. With cornea and conjunctiva locally anaesthetized I can confirm that neither I nor two other subjects could feel an eye being passively deflected by an opaque suction contact lens, nor could we

detect in which of a number of trials the eye was moved nor whether the eye was moved through larger or smaller angles. In fact we had no sensation from the eye about whether any change had taken place but, since this was not the purpose of the experiments, we did not use any psychophysical procedure (like forced choice) to find out whether our nervous systems had detected any such change, unknown to us.

It is difficult to avoid two conclusions about sense of eye position in the dark. First, that under some conditions there can be some reportable experience more or less accurately related to fairly large, passively produced changes in eye position—though whether this should be called perception of eye position is not entirely clear—and that this is supported by an inflow signal almost certainly from the EOM proprioceptors.

Second, that such a perception—if such it is (perhaps one should say detection)—of eye position in the dark is crude compared to the precision of control of eye position. As Carpenter (1988) says, it seems unlikely that 'such a function could be of any great utility in normal life'. For the avoidance of all doubt: it is the perception of the effects of the afferent signal as a change in eye position that is unlikely to be of much significance not the afferent signal itself. It is tempting to say, with Gilbert, that perhaps 'This particularly rapid, incomprehensible patter isn't usually heard, and if it is it doesn't matter' (W. S. Gilbert, 1887, *Ruddigore*, Act 2).

(c) *The perception of visual direction and related matters*

If we have little sense of the angular position of our eyes in their orbits we certainly have a clear and generally fairly precise sense of visual direction, that is, of the vector joining our eyes to an object fixated in the external world. In normal binocular viewing the vector runs from the position of the 'cyclopean eye'. In those with two functional eyes this point is on the forehead midway between the eyes but, after the loss of one eye, its position may shift towards the remaining functional eye (Moidell *et al*. 1988).

It has long been realized that an extraretinal signal is required to allow the elaboration of visual direction in combination with information from the retina though, of course, the early writers do not put it in these terms. According to Grüsser (1994), Aguilonius in 1613 realized that a signal of eye position is needed: 'Consequently an internal faculty also records the movement of the eyes'. Grüsser (1994) interpreted this as indicating an early concept of efference copy.

(d) *The 'eye-press' experiment*

The 'eye-press' experiment is very well known and easy to repeat. Close one eye and with the other fixate a stationary object. Now, press against the lateral canthus of the fixating eye (or pinch the skin there and pull). The visual world and the fixated object are seen to move during the press or pull and to remain deflected as long as the external force is applied. If the lateral canthus of the right eye is pressed the visual world moves to the right and if it is pulled the image moves to the left, that is, the visual world moves against the direction of the applied force. If both eyes are open, double images will be seen with variable separation that can be manipulated by adjusting the eye-press. If, however, an after-image is formed in the eye, that image does not displace when the eye is pressed but does move on each voluntary eye movement.

Though modern writers usually refer to Von Helmholtz (1867, 1925) as the source of description and analysis of this famous experiment it is very clearly illustrated by a figure and rather briefly described by Descartes in 1664 in the *Traité de l'homme*.[7] Descartes illustrates the experiment as it is usually performed, with a press on the lateral canthus. Von Helmholtz describes pulling the skin at the lateral canthus but this produces similar effects, though opposite in direction from a press, and whether pull or press is used does not affect the analysis of the results or the arguments that arise from these. Descartes does not discuss the eye-press experiment in very much detail but he does describe the displacement of the fixated object against the direction of the applied force and its false location and implies the occurrence of diplopia since he says that the object is perceived as different from that viewed by the other eye. It is not clear from his brief description how he believes that what we would call 'the signal of eye position' is derived. From his immediately preceding discussion of what happens when the hand touches an object and on the effects of obstructing a movement of the finger, it seems likely that he believed in a kind of muscle sense mediated by central patterns of the flow of animal spirits within the cerebral ventricles and into the (motor) nerves rather than of afferent signals from the periphery.

In other sections of the *Traité*, Descartes clearly requires that some influence ascends from the periphery to cause changes in the flow of the spirits into some, rather than other, 'efferent' nerve channels—an afferent signal, putting it in our terms, is envisaged.[8] But he discusses this 'afferent signal' only in relation to what we would now call exteroception via the special senses and the skin. Although he says that the nerves end peripherally in 'skin and flesh' there does not seem to be anything that indicates that he believed that muscles send 'afferent signals' to the brain. So it does seem most probable that for Descartes the signal of eye position did depend on a mechanism somewhat analogous to outflow, since it involved changes in the patterns of flow of the animal spirits moving within the cerebral ventricles and into the efferent pathway as he conceived it—the fine tubules that he believed made up the motor part of the nerves. This, certainly, is Hall's (1972) opinion.

For Von Helmholtz (1867, 1925) and his school, however, there was no doubt at all that the eye-press experiment was a demonstration that the signal of eye position arises from a 'sense of innervation'. Indeed, this experiment, and accounts of phenomena said to arise when patients try to move an eye in the direction of pull of a paralysed eye muscle (of which there is more below), form the bedrock of the basis for belief in 'outflow' rather than 'inflow' as the source of the extraretinal signal of eye position.

The interpretation in terms of outflow seemed straightforward enough at the time. Von Helmholtz (1925, p. 244) says

> 'When the eyeball is rolled outwards thus as a result of an external pull, of course, the internal rectus muscle will be

> elongated, and the external rectus contracted just as much as if the rolling of the eye had been produced by muscular action. For even in equilibrium the muscles are elastic bands that always contract as far as their points of attachment will allow.
>
> Thus, our judgement as to the direction of the visual axis is not formed either by the actual position of the eyeball or by the actual elongation or contraction of the ocular muscles that is the result of this position.'

He then describes the effects reported by clinicians of attempts by patients to move an eye in the direction of the pull of a paralysed eye muscle—in brief, the visual world and fixated objects are seen to move in the direction of action of the paralysed muscle. The situation is simplest if the sound eye is closed to avoid diplopia. For example, if the right lateral rectus is paralysed, objects are seen as stationary in their normal positions except when the right eye attempts, unsuccessfully, to move to the right when the visual world is seen to move and be displaced towards the right.

Moving the hand towards the object with the eyes deflected in the direction of the paralysed muscle results in errors and the target may be missed.

After describing these effects Von Helmholtz (1925, p. 245) adds:

> 'These phenomena prove conclusively that our judgements as to the direction of the visual axes are simply the result of the effort of will involved in trying to alter the adjustment of the eyes'.

As we have seen in passing, Sherrington (1918) found these arguments unconvincing and he dismisses them in his chapter 'The muscular sense' in Schäfer's *Textbook of physiology* in 1900 (Sherrington 1900).

As Merton (1964) points out, Sherrington's dismissal is based largely on William James's (1890) arguments that failing to consider what happens to the normal non-fixating eye of the patient with ocular motor paresis is fatal to the outflow argument. James quotes Hering to argue that the normal eye continues to rotate when the paralysed eye has stopped moving and that inflow information will then be available from the normal eye that will conflict with the extent of displacement of the retinal image of the paralysed eye and so produce 'the erroneous conviction that the eyes are moving'. He quotes von Graefe as actually observing that the normal eye moves and that when the patient points to the target the 'line of sight [of the normal eye] and the line of direction of the pointing finger agree'. Merton (1964) quotes observations by Jackson & Paton (1909) as establishing that what happens to the normal eye is irrelevant. This does seem to be the conclusion of the authors but their observations, based on patients with a variety of oculomotor palsies, often involving several EOM and in some cases clearly supranuclear, are difficult to interpret in any clear way. The results do suggest that 'outflow' is likely to be involved in the mislocations but they certainly do not critically distinguish between outflow and inflow as the sole signal source. Interestingly, neither James nor Sherrington discussed the eye-press experiment but, as we shall see, failure to consider what happens to the covered, non-fixating eye is fatal to the conclusion that the eye-press experiment differentiates between outflow and inflow as sole sources, although interestingly it is not fatal at all to the belief that either source may participate in the elaboration of the signal of eye position.

Recent experiments strongly suggest that the eye-press experiment and its interpretation are far from simple. The two new observations are that what the covered, non-fixating eye does is, indeed, critical and that the assumption that pressing on the outer canthus causes rotation of the eyeball is not necessarily correct. Ilg *et al.* (1989) and Bridgeman & Stark (1991), revisiting the experiment with the pressed eye fixating a point target, found that pressing the lateral canthus often does not cause rotation but rather displacement of the eyeball. Since the target remains fixated the displacement must have been resisted by increased 'innervation' (motor drive to some of the EOM) and this will have altered the 'efference copy' signal—presuming such a signal to exist—to the pressed eye. Proprioception from the pressed eye was assumed not to change since the eye did not rotate. One might wonder, however, whether stretch of some of the EOM might result from the displacement and there remains the question of whether spindle afferent firing might change with increased drive to the EOM due to alpha–gamma coactivation. Thus it seems a little doubtful that one can legitimately assume that there was no change at all in proprioception from the pressed eye. The other occluded eye does indeed move when the open, fixating eye is pressed—as Hering's law predicts—so its proprioceptive signal will certainly have changed, as well as its 'efference copy', since the drive to its EOM has also changed. So the eye-press will produce a quite complex change in both inflow and outflow, and certainly cannot be used to ascribe the visual effects to outflow alone. Pressing the covered, non-fixating eye (while the open eye continues to fixate the target) does not cause any movement of the fixating eye and should not alter the occluded eye's efference copy since the oculomotor drive to it does not change, but the occluded eye does rotate and so its inflow, proprioceptive, signal will alter. Bridgeman & Stark (1991) found that eye-presses of either the fixating or the occluded eye alter the perceived direction of the visual target and that there are shifts in pointing direction when the subject points to the target with the unseen hand during the eye-press. Thus they confirm that signals related to both eyes are used in the determination of target direction even during monocular viewing—as James (1890) had maintained. Examining the effects of pressing the fixating, then the occluded, eye and making various assumptions—in particular that the proprioceptive signal from a single eye can be counted as one-half of the normal signal to be expected from the two eyes and that the signals are additive—they come to the following conclusions. 'Efference copy' yields larger effects on perceived direction and pointing than does extraocular proprioception. Expressed as gains they estimated efference copy as giving 0.61 and proprioception 0.26. This leaves a gain deficit of 0.13 that they believed to be accounted for by errors in location of eccentric targets under normal conditions. They quote from previous work a value of 0.13 for this factor and thus neatly account for a total gain of unity when the three signal sources are added.

Recent experiments by Lewald & Ehrenstein (2000) confirm earlier observations that retinal eccentricity seems to be overestimated with respect to the fovea by a constant factor (about 2.6° in the recent experiments). Although one may feel considerable doubt about the validity of the assumptions on which the apparently very precise partitioning is made by Bridgeman & Stark, their experiments do seem to demonstrate that both outflow and inflow signals act in the determination of the final value of the extraretinal signal used in the elaboration of visual direction. Gauthier (1990*a*) reached the same conclusion on the basis of quite different experiments where he passively deflected one eye, as will be described later. He also attributed about one-quarter of the total signal to proprioception.

The latest reworking of this somewhat worn experiment was by Rine & Skavenski (1997) who found the effects of eye-press to be both complex and variable. They did confirm that the extraretinal signal from an eye-press does affect perception of visual direction in both monocular and binocular vision. They also discovered that, in binocular viewing, both version and vergence change when one eye is pressed and that registered visual direction is affected by these changes. However, the results were variable, complex and difficult to interpret. Rine & Skavenski (1997), unlike Bridgeman & Stark (1991), conclude that eye-press is not a reliable means of manipulating the extraretinal signal of eye position.

Perhaps the eye-press should now be laid to rest as doubtful of precise interpretation and certainly incapable of providing a critical test by which to choose between outflow and inflow as sole provider of the extraretinal signal. It can no longer stand, as it did in many minds for many years, as the 'knock-down' demonstration of the effectiveness of outflow, and the impotence of inflow signals in registering eye position. The suggestion from recent eye-press experiments that both types of signal are involved is supported by other experimental results, as we shall see.

(e) *The paralysed eye*

As we have seen, reported movement of the visual world when movement of an eye in the direction of a paralysed eye muscle is attempted was one of the experimental results on which Von Helmholtz based his belief in what one may now call 'outflow' as the provider of the extraretinal signal of eye position. When eye muscles are weakened but not completely paralysed it seems that such movements of the visual world are regularly reported (for references, see Brindley *et al.* 1976; Stevens *et al.* 1976). However, the outflow theory also predicts that with complete paralysis, so that no movement of the globe takes place, the visual world should still seem to move. This contention, sometimes seen as a critical test of outflow versus inflow, has not proved easy to test conclusively. Whether it is a critical test is also open to some doubt if one accepts that signals from, or related to, both eyes may be involved in what is perceived when one eye is prevented from moving. Presumably the test would be critical if all the EOM of both eyes were paralysed, including the intrafusal fibres of the muscle spindles.[9] It would not be easy to be sure that the last part of this condition had been met.

Brindley *et al.* (1976, pp. 65–66P), using retrobulbar block with local anaesthetic with or without added muscle relaxant (and blocking one eye only), reported

> 'we see no displacement of the environment with a wholly unsuccessful movement of a paralysed eye, even when it is only those muscles actually needed for the attempted movement that are completely paralysed.'

There were also no pointing errors with complete paralysis but there was past pointing with incomplete paralysis. The overall conclusions of the experiments are best given in the authors' own words:

> 'The stationariness of the seen world during attempted movement of a totally paralysed eye strongly suggests that proprioceptive information can be used for correcting eye movement; but the argument is not compelling. We think that the argument would be more compelling if, with one eye paralysed, after-images formed in the non-paralysed eye moved with all eye movements, but those formed in the paralysed eye failed to move with attempted movement in the totally blocked direction. J.K.K. clearly found just this in all relevant observations (all his last three sessions). G.S.B., from many observations in the second of his two sessions, thinks it almost certainly true for him. It is difficult to recruit more subjects.'

As far as I know these experiments have never been repeated.

In the same year, Stevens *et al.* (1976) reported a heroic series of experiments using subparalytic doses of 'curare' (presumably tubocurarine) to produce weakness of all somatic muscles, including the EOM, in three awake subjects. In one subject, complete paralysis necessitating artificial ventilation was achieved using suxamethonium.[10] The results of attempting eye movements when partially paralysed included displacement of the visual world in the direction of a successful eye movement. With complete paralysis the results were difficult to describe precisely. In the first experiment the completely paralysed subject reported no displacement or movement of the visual world during attempted (but unsuccessful) saccades. In the second experiment there was some impression of a displacement but this was 'not necessarily visual in nature' and was difficult to describe. In the third experiment the results were similar but the subject emphasized that the apparent change in spatial localization 'was not visual'. In the end, it seems that the authors believed that there was no perceived displacement with complete paralysis since Matin *et al.* (1983) quote the earlier paper on their work to that effect. Though these experiments are not entirely conclusive they do suggest rather strongly that outflow alone is not competent to produce the perceived displacements and so, by implication, that a proprioceptive signal from the orbit is required for them to appear.

The position is further complicated by the findings by Matin and his colleagues (summarized in Matin *et al.* 1983) that visual context is also critical in deciding the nature of percepts during partial paralysis. This is not the place to discuss the fascinating series of illusions that Matin and his colleagues have discovered (initially during partial paralysis), and studied, that throw light on various actions of the extraretinal signal of eye position

(for further information, see Li & Matin 1998; Matin & Li 1995).

Once again what was regarded as a critical experiment turns out to be less simple in its interpretation than might have been hoped for. This in addition to requiring procedures that are unlikely to attract many willing subjects. Perhaps the safest tentative interpretation is that some eye movement—that is physical rotation of the eye—is essential for the visual world to be seen displaced during attempted eye movement when the eye muscles are weakened. Since there seems to be no visual displacement in complete paralysis, the 'outflow' signal when acting alone must be incompetent to produce the illusion. The experiments do not exclude the participation of an outflow signal in, for example, affecting the magnitude of the illusion when the presence of a change in inflow permits such an illusion to occur and *a fortiori* in the normal signalling of eye position.

(f) *A hybrid signal of eye position?*

The eye-press experiments and, to a lesser extent, those with EOM paralysis seem to be taking us towards the conclusion that both inflow (from EOM proprioceptors) and outflow (from efference copy or corollary discharge related to motor innervation) may be involved in signalling eye position. If this is so one would expect them to interact.

In 1976, Matin (1976) argued that the paralysed eye experiments could be reinterpreted by suggesting that a hybrid mechanism containing both outflow and inflow signals might explain the results. His proposal was that changes in the gamma-efferent signal to EOM spindles might determine whether or not an inflow signal was produced. At the time this was unexceptionable but now begs the question of whether human EOM spindles are used in signalling eye position (see § 3(e) and § 18(a)). Matin adduced no new evidence but his thoughtful discussion is valuable.

In 1992, however, Li & Matin (1992) revisited the subject and presented evidence in favour of a hybrid inflow–outflow signal determining visual direction during voluntary human saccades. Subjects made horizontal saccades towards a visual target 10° eccentric to initial fixation. When the eye reached 2.5° from the target the display disappeared, to be replaced by a single new target displaced to the right or left of the original fixation target by amounts of up to 4° in 0.5° steps. In some trials the new and old fixation targets were coincident. The subject had to report whether the new target lay to the right or left of the original one. From psychometric functions derived from very large numbers of observations the perceived locations of the new target were estimated and plotted against the physical length of the saccade and the best fitting lines were calculated. An 'inflow only' theory predicts a slope of zero, that is, eye position is known accurately at all times and so the target is always perceived to lie in its physical location. An 'outflow only' theory predicts a slope of unity, that is, the target is always seen in the direction in which the eye has been commanded to point and so in the visual direction corresponding to where the saccade actually ended. The results are interesting. The slopes are small, between 0.13 and 0.29—much nearer zero than unity. This is interpreted as indicating that most (about 80%) of the eye direction signal contributing to 'registered eye position' during (more strictly at the end of) saccades is derived from inflow, with outflow contributing about 20%. It would be very interesting to know if these results could be confirmed by other experiments.

(g) *The proprioceptive contribution to the eye position signal in Man*

Three methods have been used in Man to manipulate the putative proprioceptive component contributed by EOM proprioceptors and, thus, to provide evidence that the receptors of the eye muscles do, indeed, contribute an afferent signal that affects registered eye position. Thus, passive deflections have been imposed upon an eye, the eye muscles have been vibrated and studies have been made of patients with definite or likely deafferentation of the EOM. In addition, studies on strabismic patients, especially in relation to surgical or chemical procedures to correct the squints, have been revealing. Experiments using all these methods have shown effects on the localization of visual targets, and/or on 'open loop' pointing (pointing with the unseen hand) towards them. These support the contention that EOM proprioception provides one component (though not the only component) of the eye position signal used for the elaboration of perceived visual direction and for action towards visual targets.

(h) *Passive deflection of the eye*

Gauthier *et al.* (1986, 1987) were among those who found that some patients with uncorrected or corrected strabismus mislocated visual targets viewed monocularly by either the normal or the squinting eye. They therefore tried the effect of introducing an artificial squint by deflecting one eye passively using a suction contact lens (Gauthier *et al.* 1990*a*,*b*). One eye was deflected horizontally and temporally by a predetermined amount, such as 30°, while a point target was fixated monocularly in darkness by the undeflected eye. The subjects, pointing with the unseen hand to the target position, made errors in location, always mislocating the target in the direction of the deflected eye. However, the size of the angular error was much less than the angle of deflection of the non-viewing eye—for example, errors of 4–6° for an eye deflection of 30°. The size of the error was related to, though always much smaller than, the amount of passive deflection. When the perceived position of the subjects' midline was tested by a method not requiring pointing, the midline was also mislocated in the direction of eye deflection. There were no illusions of target movement or displacement either during the deflection of the non-viewing eye or while it was held deflected (up to 20 min) and there were no systematic movements of the (fixating) viewing eye. Errors were greatest immediately after eye deflection. As time passed the size of the errors diminished but the variability of pointing increased. Why these changes occurred with time is not clear. The conclusion was that both outflow and proprioceptive inflow were involved in explaining the pointing errors. Outflow and inflow were presumably normal for the fixating eye, indicating 'straight ahead'. For the deflected eye inflow would indicate temporal deflection and outflow would indicate

straight ahead. The argument that outflow cannot have changed is that any change in oculomotor drive would have affected the fixating eye also and this eye is known not to have moved. Had outflow been the only signal, there should, presumably, have been no error. Had inflow been the only signal, the inflow from the deflected eye should have resulted in an error similar to the deflection if the signal from each eye were evaluated separately—or, presumably, to an error of about half the deflection if each provided a signal and these were summed to give the total inflow signal. In the event the maximum errors were only about 16% of the angle of deflection. The authors conclude that signals from both eyes are likely to be equally involved and suggest that the total inflow signal might be *ca.* 32% of the overall signal with the rest being supplied by outflow. As with the results of Bridgeman & Stark (1991) discussed above—who came to a similar figure for the proprioceptive contribution—one may be a little doubtful about the justification for assuming that the signals behave in this simple additive fashion but there seems no reason to doubt the conclusion that the results require contributions to the signal of registered eye position from both inflow and outflow. The fact that the midline was also mislocated suggests that the manipulated proprioceptive signal acted on the central representation of visual direction and not simply on the motor mechanisms responsible for pointing. It is interesting that there were no changes in the perception of the target direction—the target neither moved nor was it seen as displaced in position.

(i) *Abnormal active deviation of an eye*

A most interesting paper by Lewis & Zee (1993) describes the effect of deviation of an eye brought about by contraction of the medial rectus muscle under the influence, not of a normal oculomotor command but occurring when the subject commanded and achieved a quite different motor act, deviation of the jaw. The subject was a patient with a congenital abnormality of innervation of her left medial rectus muscle, which received its principal motor supply from a branch of the motor part of the trigeminal nerve so that, when she deviated her jaw to one side, the left eye adducted powerfully, that is, it turned to the right (the right eye was unaffected by jaw movement). When the patient fixated a target light with either eye and deviated her jaw she had an illusion of target movement to the left. When she fixated a target with the normal eye with the abnormal eye covered, she made errors in pointing to the target when she deviated her jaw and caused adduction of the left eye. Arguments similar to those rehearsed above are convincing that a proprioceptive signal from the abnormally deviating eye must have been involved in these mislocations. However, a striking difference between the mislocation in this patient and that in normal subjects with passive eye deviation is that in the patient the deviations were in the opposite direction to the eye rotation, whereas passive deviation in normal subjects results in errors in the direction of eye rotation. It would have been very interesting to have known whether passive deviation of the patient's abnormal eye to the right gave errors in the same direction as for a normal subject since this finding would have raised a strong presumption that the patient's central processing of the EOM afferent signal was not abnormal; but no doubt circumstances made it impossible for the authors to test passive deflection in the patient.

To explain the difference in the direction of the errors, Lewis & Zee (1993) advanced an ingenious hypothesis. After reviewing the evidence that receptors at the EOM musculotendinous junctions (probably palisade endings) are involved in the elaboration of the proprioceptive signal of eye position (this evidence, which is circumstantial though rather persuasive, is discussed in § 17), they repeat the suggestion previously made by Richmond *et al.* (1984) that these endings are preferentially activated by active muscle contraction and not, or much less so, by passive eye deflection. If this is accepted, their argument is also acceptable that the active deflection of the eye by contraction of medial rectus would produce a different proprioceptive signal—in effect an opposite one—from passive deflection of the eye in the same direction (since in the former case the principal activity would be from the palisades but in the latter from muscle spindles). This suggestion would be a satisfactory explanation of the results then, if, first, the palisades are involved in contributing to the EOM afferent signal in these circumstances and second, if they behave in this differential fashion to active contraction of EOM and to passive eye deflection. That palisades contribute seems likely if not absolutely certain. That they behave differently on active contraction and passive stretching is much less certain. Unfortunately there is no experimental evidence that palisades do behave in this way though there is evidence that Golgi tendon organs—which are fairly certainly absent from human EOM (see Ruskell 1999)—do give much larger signals on active shortening than on passive stretch of muscle (Henneman 1974; Jami 1992). But the palisade structure differs from that of the Golgi tendon organ and, much more importantly and unlike Golgi tendon organs, no one has recorded in any species from primary afferent fibres known to come from palisade endings.

If one continues to speculate in spite of this, it would be well to remember the particular relationship between the palisade and the single global multiply innervated muscle fibre with which each palisade seems to be associated. If, as has been suggested by Porter (Porter *et al.* 1995; J. D. Porter, personal communication) and Robinson (1991), and discussed in § 3(c), this fibre and its palisade constitute a functional unit somewhat analogous to the muscle spindle receptors and their intrafusal fibres, it would not be safe to assume that the palisade is a simple, passive, transducer in series with the muscle motor. Continuing this speculative digression one should remember that although cat eye muscles contain no muscle spindles, some of their EOM first-order afferents show responses of spindle-like type, strongly suggesting that they come from end organs that are functionally in parallel with, and not in series with, the muscle motor (Bach-y-Rita & Ito 1966; Bach-y-Rita 1971). Rather similar responses are found among pigeon first-order afferents, although pigeons also have no spindles in their EOM (Fahy & Donaldson 1998). In the cat at least there are also other responses that are of the in-series type. Cat EOM have simple spiral endings that are probably afferent but they also have large numbers of palisades (see

Billig *et al.* 1997; Ruskell 1999). Man has large numbers of palisades, as we have seen.

In sum, when Lewis & Zee refer to 'sensory organs at the musculotendinous junction, which are differentially activated by active muscle contraction and passive displacement' this is just speculation—perhaps reasonable, and certainly attractive, speculation, since it sustains an ingenious theory, but speculation nevertheless. One of the pieces of information most urgently needed for better understanding of the origin of the EOM afferent signal is a quantitative physiological study of the characteristics of the afferent signals from palisade endings. Unfortunately, the technical difficulties in the way of providing this information are rather formidable. Thus, for the moment, one must regard as an attractive, ingenious, but untested hypothesis the attribution of the difference between the results of passive eye deflection in normal subjects, and those of active deflection in the patient with abnormal EOM innervation, to a difference in activation of EOM musculotendinous receptors. The results of the experiment certainly should not be considered to provide evidence for a differential behaviour of palisade endings during active contraction and passive stretch. The experiment, though, does provide yet another good piece of evidence that EOM proprioception contributes to the signal of registered eye position in Man.

(j) *Vibration of eye muscles*

By analogy with the effects of vibration upon the muscle spindle afferents of human skeletal muscles (see, for example, Matthews 1982) it might be possible to modify the signals from eye muscle proprioceptors by vibrating the EOM in humans. This possibility depends, of course, on either there being functional muscle spindles in the human EOM or on the presence there of other muscle proprioceptors the afferent signals of which can be influenced by vibration. As we have seen, central effects have been produced by vibration of the EOM of cats (Barbas & Dubrovsky 1981*a*) whose eye muscles do not contain muscle spindles (Maier *et al.* 1974) though, perhaps significantly, they do contain palisade endings (Alvarado-Mallart & Pinçon-Raymond 1979; Billig *et al.* 1997). Thus, while it is possible—perhaps even probable—that effects of vibrating human EOM might, indeed, be due to activation of muscle spindle afferents, it cannot be assumed that this is necessarily the case.

Roll & Roll (1987) found that vibration applied to the human skin around the eye and to the eyelids, with the vibrating tip pressed firmly against the tissues, produced illusions of head, trunk or body movement according to the postural context. These effects were, reasonably, presumed to be the result of stimulation of EOM proprioceptors. They also found that vibration induced a perceived displacement of a visual target. These visual illusions were very similar to those reported by Biguer *et al.* (1986, 1988) when human posterior neck muscles are vibrated. In the case of the neck muscles there is little difficulty in ascribing the illusions to actions on muscle spindle afferents and it has been presumed widely that this is the case for the EOM also. In any case it seems safe to attribute the effects to EOM proprioceptors if not necessarily to spindles. A little later, Roll *et al.* (1991) reported that similar visual illusions and effects on pointing at a visual target with the unseen hand were found when either neck or eye muscles were vibrated. For example, vibration of the inferior rectus induced an apparent upward movement of a solitary visual target viewed in darkness and pointing was disturbed in the same direction. In further experiments, Velay *et al.* (1994) found that vibrating human EOM produced no illusions of eye movement but did produce illusions of target displacement that were explicable if the nervous system interpreted the effect of vibration as a signal of lengthening of the EOM over which the vibrator was placed. Thus, vibration of the right lateral rectus gave an illusion of target movement to the left and when inferior rectus was vibrated the illusory movement was upwards. Lengthening of the right lateral rectus normally only occurs when the right eye moves to the left so an image objectively stationary on the retina was interpreted as a shift of the target in the direction in which the eye would move if the manipulated signal from lateral rectus were veridical. Effects were found when viewing with either eye when one eye was vibrated, although the most powerful illusions were produced when the dominant eye both viewed and was vibrated. Thus, again, it seems that manipulation of the proprioceptive inflow from one eye altered the signal used to elaborate the registered position of the cyclopean eye (the registered eye-in-head component of gaze). Pointing errors also occurred as before. Velay *et al.* also found that the presence of a structured visual environment abolished the illusions, as Biguer *et al.* (1988) had found for the visual illusions produced by neck muscle vibration. So the stability of a structured visual environment was once again found to override an (erroneous) extraretinal signal. But it is important not to forget that, in these vibration experiments, only one or perhaps two EOM are giving false signals of eye position. The other ten or 11 are presumably signalling, truthfully, that there has been no change in the eye position. All these interpretations of the effects of EOM vibration assume that the retinal image of the visual target does not, in fact, move, that is, that there is no eye movement induced by EOM vibration. Notice that the presence of eye movement need not necessarily invalidate the conclusion that vibration of the EOM induces a proprioceptive signal that affects the registered eye position (see the discussion on the eye-press experiment, § 16(d)) but it would certainly complicate it.

In 1997, Velay *et al.* (1997) specifically sought evidence of whether the eye (or eyes) move when EOM are vibrated. In the same year, Lennerstrand *et al.* (1997) also looked for eye movement with EOM vibration. The results are rather puzzling. Velay *et al.* (1997) did sometimes detect what seemed to be small downward movements of the vibrated eye when inferior rectus was vibrated but vibrating lateral rectus produced no eye movement. The non-vibrated eye did not appear to move. However, when there were eye movements, these were not always accompanied by a visual illusion and the illusion sometimes occurred when there was no eye movement—and of course when lateral rectus was vibrated the illusion was always unaccompanied by eye movement. Another puzzling finding was of postvibration illusions that lasted for minutes and were in the same direction as the illusion during vibration; these the authors also found

inexplicable. Postvibration illusions are common when neck muscles are vibrated but these are very short lived (perhaps 1 or at most 2 s) and are always in the opposite direction to the illusion during vibration (Biguer *et al.* 1988). The results of Lennerstrand *et al.* (1997) can only be said to contradict many of those of Velay *et al.* (1997). Lennerstrand *et al.* (1997) vibrated the EOM of the dominant, fixating eye of normal subjects and strabismics and measured the position of the other non-dominant, non-fixating covered eye. In normal subjects vibration of inferior rectus sometimes caused upward movement of the non-vibrated eye and vibration of lateral rectus induced abduction (temporal movement) of the non-vibrated eye. Movements of the fixating eye were not measured, unfortunately. Thus, Lennerstrand *et al.* (1997) found movement of the non-vibrated eye, which never moved significantly in Velay *et al.*'s (1997) experiments, and also found this with lateral rectus vibration, which never produced movement of either eye in the other set of experiments. In addition, vibration of the inferior rectus caused downward movement of the vibrated eye in the experiments of Velay *et al.* (1997) but upward movement of the non-vibrated eye in those of Lennerstrand *et al.* (1997). It is difficult to avoid the conclusion that there is considerable uncertainty about whether there is eye movement and, if so, of which eye or eyes and in which direction when the EOM of one eye are vibrated. The lack of correlation found by Velay *et al.* (1997) between the presence of eye movements and the occurrence of the visual illusion does suggest that the illusions may not be simply the result of the (variable) eye movements and that EOM vibration may modify the proprioceptive component of the eye position signal that other experiments strongly suggest is present, as we have seen. If, however, eye movements do accompany the illusion, or when eye movements accompany the illusion, one must suppose that an outflow signal related to the oculomotor drive to the EOM may also be involved in the genesis of the illusion. The same arguments would apply to the pointing errors. At the moment, though they are clearly interesting and are an attractive potential means of modifying the EOM afferent signal, experiments in which human eye muscles are vibrated are somewhat equivocal of interpretation. (See also discussion above, in § 4.)

(k) *Removal or reduction of the proprioceptive signal from the human eye muscles*

As Ruskell (1999) has rightly pointed out we have no certain information on the pathway followed by EOM afferents from the human orbit to the central nervous system. As in other animals there are no separate afferent branches from the eye muscles in the orbit but cross-communications have been reported between the trochlear and abducens nerves and the trigeminal nerve in the region of the human cavernous sinus (for references, see Ruskell 1999). However, pathological or surgical lesions of the ophthalmic division of the trigeminal nerve (VOphth) have produced effects that strongly suggest that VOphth carries EOM proprioceptive afferents in Man and that damage to their signals affects registered eye position.

Campos *et al.* (1986) found that five out of six patients with unilateral damage to VOphth caused by viral infection (herpes zoster ophthalmicus) made errors in pointing with the unseen hand to a monocularly fixated target in darkness. These errors varied with the eccentricity of the visual target. The author noted absence of diplopia but does not say whether this was during normal binocular viewing of a structured visual scene or whether it was during binocular viewing of the isolated target in the dark—or in both conditions. Two months later, after clinical recovery, there were no pointing errors. Campos ascribed this to some kind of adaptation because the damaged nerve fibres are said not to recover—but there is really no evidence to decide between peripheral recovery and central adaptation in these patients.

Ventre-Dominey *et al.* (1996) were able to perform a rather more sophisticated study in the more controllable situation of patients undergoing unilateral surgical transcutaneous destruction of VOphth for the treatment of trigeminal neuralgia. In their experiments it was possible to test each patient before and after surgery. Patients fixated visual targets with the affected eye in darkness and pointed with the unseen hand to their position. After the operation they were divided into two groups according to whether or not they had corneal anaesthesia on the operated side. Those with corneal anaesthesia were regarded as having unilateral destruction of VOphth. Shifts in pointing direction, calculated as the differences between postoperative and preoperative pointing to targets at the same eccentricity, were found only in the group with destruction of VOphth. These shifts were towards the lesioned side and were predominantly found in pointing in hemispace on the lesioned side. The conclusion was that asymmetry of an EOM proprioceptive signal was the cause of the shifts. It would have been interesting to know whether there were shifts in pointing when the normal eye viewed the target monocularly and with binocular viewing and if the patients experienced any difficulties in normal life—such as in reaching for objects. It seems a pity that pointing tests were carried out only once postoperatively (at three days) so it is not known if the pointing errors persisted.

The effects of damage to, or destruction of, VOphth are consistent with the conclusions from passive deflection of the eye, although the observations are necessarily more limited. It would be very interesting to know whether patients with ophthalmic branch damage show the differences one would expect between the effects of stimuli that manipulate the EOM proprioceptive signal applied to the normal and to the denervated eyes. Since corneal anaesthesia accompanies damage to VOphth and renders the patient particularly susceptible to corneal damage it would seem quite unjustifiable to attempt what seems the most reliable means of manipulating the signal—imposed passive deflection using a suction contact lens. Vibration of the EOM might be considered safe, however, and, in spite of the present uncertainties in its interpretation until the question of the presence of eye movements is definitely settled, would seem to be well worth considering in future studies.

(l) *The extraocular muscle afferent signal and the control of eye position and eye movement in monkeys and Man*

As we have already seen there have been a number of experiments in which the effects of manipulation of, or

removal of, the inflow signal from EOM proprioceptors upon the oculomotor system have been examined. The studies so far described have been concerned with changes in the activities of single units in the oculomotor system or of effects on oculomotor behaviour of non-primate species. In recent years there have also been a number of attempts to determine whether the EOM afferent signal acts on the oculomotor system of Man and of awake, behaving monkeys. In some cases a number of different types of oculomotor behaviour have been examined in the same series of experiments but, for convenience, we shall consider the information under headings of types of eye movement.

(m) *Horizontal vestibulo-ocular reflex*

As we have seen the EOM afferent signal has been found to affect the horizontal vestibulo-ocular reflex (HVOR) gain of pigeons (see Donaldson & Knox 2000) and rabbits (Kashii *et al.* 1989). It has also been found to modify the adaptation of HVOR gain in rats (Gauthier *et al.* 1995). In primates, however, the only observations seem to be the pilot study of Knox & Donaldson (1993*b*) in Man, in which there were indications of modification of HVOR gain of one eye by passive movement imposed on the other with results similar to those in pigeons. These experiments need to be repeated with more subjects and more sophisticated control of the imposed eye movement and of the recording of eye position before any firm conclusions can be drawn on whether EOM afferent signals take part in the control of the human HVOR.

(n) *Saccades and postsaccadic drift*

The well-known experiment by Guthrie *et al.* (1982, 1983) showed that monkeys with deafferentation of the EOM by bilateral section of VOphth were still able to make accurate saccades to remembered visual targets when the eyes were driven to a new position by electrical stimulation of the superior colliculus just before the saccade. The conclusion was that an outflow signal was sufficient to sustain the behaviour. These results have also been regarded by some as proof that an inflow signal is not involved in oculomotor control, or, more modestly, not in control of saccadic eye movements (see, for example, Van Gisbergen & Van Opstal 1989). Experimental evidence is now appearing, however, that suggests that, in Man at least, inflow signals from the EOM proprioceptors may influence saccadic control and that, in the monkey, they affect the adaptation of postsaccadic drift that follows eye muscle paresis.

The first results, however, seemed to support the contention that the inflow signals did not affect saccades. Gauthier & Vercher (1992) measured the amplitude of human horizontal saccades to various target positions left and right of straight ahead with monocular fixation and the non-fixating eye covered. The observations were then repeated with the non-fixating eye deflected to 20° left or right of the primary position and held immobile there while the free eye made the required saccades. No differences were found between the amplitudes of the saccades with the non-viewing eye free or held in an eccentric position.

In contrast, Knox and his colleagues (Knox *et al.* 1998, 2000), using a very similar method but with movement of the non-viewing eye impeded near the primary position, found a consistent decrease of some 20% in the amplitude of the horizontal saccades made by the free eye when the covered eye was prevented from moving normally. The effect was apparent within seconds of holding the covered eye still—indeed, the first saccade made with the covered eye held was reduced. Saccadic dynamics seemed to be normal for the sizes of saccade that were achieved. There are no obvious technical differences that might account for the difference between these results and those of Gauthier & Vercher (1992). It is difficult to believe that the deflected position of the eye in one set of experiments and its centred position in the other is a satisfactory explanation. As Knox *et al.* (2000) point out, their finding of reduced saccadic amplitudes is rather surprising; they suggest it may represent an attempt by the saccadic control system to maintain conjugacy. Although this is just speculation, perhaps their results uncover a mechanism that would normally make small adjustments to the amplitude of movements of one eye during saccades, for instance to maintain conjugacy. The reductions seen when the covered eye is largely prevented from moving may represent the maximum adjustment available to the system. In any case it would be very interesting for each group to repeat the experiments exactly as carried out by the other. Whatever the explanation of the functional significance of the amplitude reduction, if it can be replicated it must indicate that an inflow signal, almost certainly from EOM proprioceptors, is able to influence the control of human saccades.

Allin *et al.* (1996) vibrated the inferior rectus muscle of the dominant viewing eye of human subjects just before they made saccades either to the remembered position of a visual target or to a continuously visible target. After the disappearance of the target to be remembered, the subjects tracked a fixation target that moved either up or down or stayed still and, while they were tracking, the inferior rectus was vibrated in one set of trials but not in the other. They found no effect of the vibration on the trajectories of saccades to continuously visible targets, but the trajectories of saccades to the remembered target position were modified in the vibration trials. The eye consistently landed below the position of the remembered target and below the position reached when the eye muscle was not vibrated. Since vibration of the inferior rectus causes an illusion of a visual target moving upwards, interpreted as indicating an erroneous inflow signal of downward eye movement (see discussion earlier), the results are consistent with the explanation that the modified inflow signal caused reprogramming of the saccadic trajectory to correspond to the wrongly registered starting position of the eye. The lack of effect when the target was continuously visible is explained by the suggestion that the inflow signal is used only when an extraretinal signal is essential for correct saccadic programming and it is argued that such a signal would not be essential when the target was continuously illuminated since all the necessary information would be available from the retinal input. Once again, whether this explanation is entirely satisfactory or not, there seems no doubt that an inflow signal, almost certainly from EOM proprioceptors, is able to influence the control of at least some human saccades—those to remembered targets.

Interestingly, it was this very class of saccades in the monkey that were apparently correctly performed without an inflow signal in the experiments of Guthrie *et al*. (1982, 1983). Allin *et al*. (1986) comment that they cannot account for this difference in results other than by pointing out that the conditions of the two experiments were very different. However, apart from any possible doubt about whether the monkey EOM were completely deafferented (I think it likely that they were), the experiment of Guthrie *et al*. (1983) does not exclude the possibility that inflow signals are normally used in programming such saccades—rather it indicates that they are not essential in their experimental conditions. It may also be, perhaps, that an abnormal inflow signal of eye instability just before the saccade (as in Allin *et al*.'s experiment) has a much larger effect on the control system than the absence of any inflow information about what the eye is doing (as in Guthrie *et al*.'s (1983) case). All depends on the details of how the inflow signal interacts with the corollary discharge, or other outflow signals that there is very good reason to believe are also acting—these details, at the moment, we do not know.

These effects are immediate on the saccadic system when EOM are vibrated or an eye is prevented from moving. They take place within seconds of the signal being manipulated.

Lewis *et al*. (1999) described a rather different type of action of eye muscle proprioception on the saccadic control system. When the saccadic control system operates on the EOM the innervation pulse that drives the eye to its new position is followed by a decaying drive, the 'slide', that is believed to adjust for relaxation of viscoelastic forces in the orbit and, finally, by the 'step', the tonic drive that maintains the eye at its new position against the restoring orbital forces. These drives must be correctly adjusted and matched to the characteristics of the oculomotor plant—including the EOM. Damage to the plant, such as paresis of an EOM, alters the matching requirements for the drives and the consequent mismatch may result in postsaccadic drift of the eye. In principle this drift could be detected by visual means (a retinal slip signal) or by signals from the EOM proprioceptors (see Lewis *et al*. (1999) for a fuller account and for references). Compensation for postsaccadic drift develops over time and adjustment is required to each eye separately (disconjugate adaptation). Lewis *et al*. (1999) produced postsaccadic drift in monkeys by unilateral surgical paralysis of a vertical eye muscle. The effects of various viewing regimes and of deafferentation of the paretic eye on the development of compensation were then studied in an elaborate series of experiments. The findings indicated that disconjugate adaptation could be visually driven and did not require binocular fusion. Proprioception from EOM also modified the adaptation in a way that suggested that the 'step' and 'slide' oculomotor drive were affected. However, deafferentation did not prevent visually driven adaptation. The changes that deafferentation induced were not consistent and could not be explained by a proprioceptive eye position or velocity signal simply modifying the corresponding parameters of the neural activity driving the drift. The effect was complex and the interpretation of the mechanisms is not entirely clear—but the results do suggest that the EOM afferent signal, as judged by the effect of its removal, produced its effects gradually over a period of days and weeks by bringing about changes in the characteristics of the oculomotor drive. As we shall see this is the latest of a number of demonstrations of long-term slowly acting modulations of the oculomotor system by afferent signals from eye muscle proprioceptors. These types of action seem to be concerned particularly with altering or bringing about adaptive changes in the oculomotor system to adjust to changing circumstances.

(o) *Control of eye alignment and version*

When Guthrie *et al*. (1982, p. 156) deafferented the EOM of both of a monkey's eyes they found

> 'Deafferented monkeys performed vergence tasks badly. Although an appropriate initial vergence response was made to stimuli with crossed or uncrossed disparity, the resultant vergence angle was not maintained due to the medial 'drift' of the non-dominant eye.'

This result, strongly suggesting that EOM afferent signals are important in the control of eye alignment, has received much less attention than their other observations on the competence of outflow signals in saccadic control that were described in a longer paper the following year (Guthrie *et al*. 1983), in which the effects on vergence are not mentioned.

Lewis *et al*. (Lewis & Zee 1992; Lewis *et al*. 1994) examined the effect of proprioceptive deafferentation of the paretic eye of monkeys with a surgically induced unilateral palsy of a vertical eye muscle. They reported that

> 'Following deafferentation, ocular alignment and saccade conjugacy gradually worsened over several weeks. In contrast, disconjugate adaptation induced by habitual binocular viewing with a prism (disparity-mediated adaptation) occurred normally after deafferentation.'
>
> (Lewis *et al*. 1994, p. 1028)

The suggestion is that an EOM afferent signal takes part in long-term calibration of ocular alignment so that removal of this signal leads to a gradual deterioration of alignment over days and weeks because of a reduction in the ability to make appropriate adaptive changes to misalignment caused by changes in the oculomotor plant. The authors point out the possible relationship of such a mechanism to the development of strabismus. The finding that the disconjugate adaptation driven by binocular fixation was unaffected by the removal of the EOM afferent signal from the paretic eye suggests, as the authors point out, that the paired congruent visual and proprioceptive signals that seem to be necessary for normal development of visual cortical properties (see Buisseret 1995) are not required in disconjugate adaptation. Clearly, though, the mismatch between outflow and inflow signals induced by the deafferentation may well be significant to the adaptation.

Gauthier *et al*. (1994) applied the method of modification of EOM afferent input by passive deflection of one eye using a suction lens to the question of whether orbital proprioceptive signals affect ocular alignment in Man. They used an ingenious method, in which each eye could be made to view independently, that employed red and green filters and red and green target lights so that each target was visible to one eye only, or yellow targets that

could be seen by both eyes simultaneously. Passive deflection of one eye by 30° for 6–10 min was found to alter the relative position of one eye to the other, that is ocular alignment, by some 2–4° . This was true whether tested by monocular viewing, saccadic movements to step changes in target position or pointing to the target with the unseen hand. The alignment change lasted 5–10 min if binocular viewing was not allowed but disappeared very rapidly after even a few seconds of binocular viewing. The pointing experiments showed large deviations when the target was viewed with either the eye that had been deflected or the undeflected eye showing that deflection of one eye for a period alters the visual direction registered through both the eye the proprioceptive input of which was modified and the other normal eye. The authors emphasize the sustained nature of the changes in alignment produced, without the intervention of any retinal disparity cues, by passive eye deflection. They speak of long-lasting changes, but the duration of the effects, though substantial if considered in relation to moment-to-moment control of eye movement, are not of the same order as those found in the disconjugate adaptation of postsaccadic drift in the monkey or of those found in human strabismic subjects when an EOM is weakened with botulinum toxin (Dengis *et al.* 1998, discussed below (§ 17(a)).

(p) *Smooth pursuit*

The ability to maintain fixation of an object moving against a stationary background is found only in foveate animals and is particularly well developed in Man (see Carpenter 1988). Though smooth pursuit is normally controlled continuously by feedback of the retinal slip signal, which is used to adjust the tracking velocity, it has been shown that adaptation of the system is possible when a patient with an eye muscle weakness views monocularly with the weak eye for several days (Optican *et al.* 1985). Another method of inducing adaptation is to add to the target velocity a portion of the recorded eye movement signal from the pursuing eye. This results in increased pursuit responses to subsequent brief test target motions.

Van Donkelaar *et al.* (1997) tested the effect of preventing movement of one eye on the characteristics of adaptation of smooth pursuit by exposure to target motion enhanced by addition to the motion of 75% of the signal recorded from the pursuing eye. Pursuit by the free (left) eye was measured before and after adaptation to the enhanced target motion with the right eye either covered but free to move or covered and prevented from moving. The increase in pursuit velocity produced by the adaptation procedure was reduced when the non-tracking eye was prevented from moving compared to its value when the non-tracking eye was free to move. Similar effects were found, although the tracking gains were smaller than with eye pursuit when the subjects tracked the moving visual target with the unseen hand and there was again reduction in manual tracking gain when the non-fixating eye was prevented from moving. Interestingly, the changes induced by manipulation of the proprioceptive signal during adaptation to enhanced target motion were greater than those found when the covered eye was held still during visual pursuit of a normally moving target (without enhanced motion), suggesting that the EOM proprioceptive signals are particularly effective at times when the oculomotor system is required to respond to abnormal demands. Since both eye and hand movement were affected, the EOM afferent signal seems to have influenced the processing of information about both eye motion and target motion. Van Donkelaar *et al.* (1997) also point to possible parallels between the effects of passive eye movement upon unit responses to visual or vestibular stimuli in the pigeon (Donaldson & Knox 1991, 1993; Knox & Donaldson 1995*b*) in their interpretation of the modulation of adaptation of smooth pursuit by EOM afferent signals in these human experiments. The analogy is interesting and may, indeed, be important in understanding the human results but it does not seem possible to press the details further at the moment.

(i) *Effect of obstructing eye movement on pursuit with the other eye*

In recent experiments, Knox and his colleagues have found (P. C. Knox, personal communication) that obstructing movement of one eye leads to reduction of the initial acceleration and velocity with which the other (free) eye pursues a visual target. Since these effects are immediate and do not build up over a series of trials they suggest that EOM afferent signals may supply information used in controlling the initiation and maintenance of smooth pursuit. These results, taken together with the earlier findings of Van Donkelaar *et al.* (1997), suggest that EOM afferent signals may have two types of action on the control of smooth pursuit. There would seem to be both an immediate 'online' action on individual pursuit movements before visual feedback is available and a longer-term action that adjusts adaptive processes in the pursuit mechanism.

17. EXTRAOCULAR MUSCLE PROPRIOCEPTION AND STRABISMUS

Study of registered visual direction in strabismic patients has, as we have already seen, inspired illuminating experiments using the 'artificial strabismus' produced by passive deflection of one eye. But, even earlier, the examination of the effects of treatment of the squint had also been of great value in providing evidence of a proprioceptive contribution to the signal of registered eye position. Most of this work is due to Steinbach and his colleagues. Conversely, information about likely defects in the putative sources of the inflow signal from the EOM has important potential implications for the treatment of strabismus.

Steinbach & Smith (1981) tested pointing with the unseen hand towards a visual target in strabismic patients before corrective surgical manipulation of an eye muscle and again after the operation as soon as the operated eye was uncovered and before the patient had any postoperative visual experience with it. In patients being operated upon for the first time, pointing shifts were found but the size of these amounted to only about one-quarter of the eye rotation produced by the operation. Thus, following the same line of reasoning described earlier for the passive eye rotation experiments, an inflow signal must have operated in conjunction with outflow to determine visual direction. In some patients a pointing shift was

found when viewing with the non-operated eye showing that the inflow signal from one eye affected visual direction as judged by each eye viewing monocularly. These conclusions about the actions of the inflow signal, now familiar from later experiments, were first suggested by Steinbach's work on strabismic patients. A second group of patients, tested after a second or subsequent operation for correction, did not show evidence of an inflow signal from the operated eye—rather there were large shifts in pointing with the treated eye as would be predicted from a pure 'outflow' theory. Steinbach & Smith (1981) suggested that this, at first sight puzzling, difference might be due to destruction by repeated operations of proprioceptors in the musculotendinous region of the EOM—the region disturbed by the surgical procedures.

Prompted by these results, Steinbach and his colleagues (Richmond *et al.* 1984) searched the musculotendinous region of human EOM and found there palisade endings, as we discussed § 3(c), but not the Golgi tendon organs that they had originally suspected of being at the origin of the inflow signal in the strabismic patients.

Bock & Kommerell (1986) failed to replicate Steinbach & Smith's (1981) findings and concluded that there was no evidence for an inflow signal. It is not clear why the results of these superficially similar experiments should be different but it may be related to important differences in technique including the use of retrobulbar block by Kommerell rather than the general anaesthesia used by Smith (Steinbach 1987). It seems possible that the orbital oedema produced by the local block might have disturbed the proprioceptors for a considerable time after the operation, thus preventing any evidence of an inflow signal being found when the patients were tested within a few hours of the operation.

As a test of the hypothesis that palisade endings are necessary for the inflow signal of eye position, Steinbach *et al.* (1987) compared the effects of two types of procedure: marginal myotomy in which a portion of the musculotendinous region of an EOM was resected; and recession in which only the distal tendon was cut and the musculotendinous region was relatively unaffected. The results showed that disruption of the musculotendinous region by marginal myotomy resulted in a reduced proprioceptive signal from the operated eye that explained both the larger pointing shifts found with the operated eye but also, because there was little contribution from the operated eye to the total inflow signal, the smaller pointing shifts that occurred with the non-operated eye. The patients with recession showed shifts similar to those in the 1981 study. Since the region damaged by the myotomy contains the palisade receptors, Steinbach *et al.* (1987) suggested that these endings were the effective source of an EOM proprioceptive signal of eye position in their experiments. Although this evidence is necessarily circumstantial, it is persuasive that palisades are likely to be at least one of the important sources of EOM proprioception in humans.

Support for the idea that proprioceptors at the musculotendinous junction of human EOM may be important also in the genesis of strabismus comes from the observations of Corsi *et al.* (1990) of abnormalities of receptor structures in the musculotendinous regions of specimens of EOM from patients with congenital strabismus. It is not entirely clear from their description whether the structures were abnormal palisades or not. However, it does seem more probable that they were palisades, which are known to occur in these parts of the EOM, than that they were Golgi tendon organs as the group's earlier description had suggested (Salvi *et al.* 1986). This work needs to be repeated. Of course, even if the presence of abnormal receptors is confirmed this will not show that this abnormality is causative, but it should prompt further work trying to relate the presence and, if possible, the normality or abnormality of the EOM input signal's effects to the presence or absence of normal palisade endings.

(a) *Botulinum toxin*

Botulinum toxin, which produces paralysis of striated muscle by blocking acetylcholine release from the presynaptic motor terminals, is sometimes used to treat strabismic patients by selectively weakening particular eye muscles (see Steinbach 2000). Manni *et al.* (1989), in an interesting experiment, examined the effect of botulinum toxin on the firing rate of muscle spindle afferents from ungulate EOM. Some 10 min after injection of the toxin into the EOM muscle belly, the firing rate of spindle afferents began to fall and by 45 min it had fallen by up to 35% of the control rate. At the same time the sensitivity of the spindle afferents to static muscle stretch also fell. From fig. 4 of Manni *et al.* (1989*a*), for the responses of the one ending illustrated, one can estimate that the sensitivity fell from *ca.* 3.6 impulses $s^{-1} mm^{-1}$ before, to *ca.* 1.8 impulses $s^{-1} mm^{-1}$ after toxin injection. Both values are within the range found by Whitteridge (1959) for (normal) ungulate spindles without gamma efferent stimulation. Over the 45 min of observation there was no change in the overall length–tension curve of the whole EOM. The authors' suggestion that the botulinum toxin affected the spindle intrafusal fibres before there was any detectable effect on the extrafusal fibres and so altered spindle firing is consistent with their results, although better evidence of such an effect would have been a change in the effects of particular rates of gamma drive on the spindle firing rate at constant length or, better still, on its length and velocity sensitivity. This would have required a (more difficult) experiment that would have been, effectively, a repetition, with the addition of botulinum toxin, of the work of Whitteridge (1959). It is strange that Manni *et al.* (1989) did not refer to this pioneering, and definitive, study of ungulate EOM spindle responses.

It seems, then, that botulinum toxin produces an effect on ungulate EOM spindle firing within a few minutes. To what extent this result is transferable to Man is uncertain given the structural differences between ungulate and human EOM spindles (see Lukas *et al.* 1994; Ruskell 1999).

The possible actions of botulinum toxin on human EOM afferent signals were studied by Dengis *et al.* (1998) who examined registered eye position in human strabismic patients before and after injection of an EOM with botulinum toxin to treat their squint. The injections were made under local anaesthesia and control by electromyography. A group of normal subjects was also tested over the same time-course as the patients. The normal

subjects and the patients before, and for 45 min after toxin injection, showed no shifts in pointing to visual targets with the unseen hand. One patient who was followed for 7 h after the injection developed no pointing shifts during this time. Thus one concludes that botulinum toxin had no immediate effect on the input signal from the EOM. Dengis *et al.* (1998) then carried out a long-term study in which patients were tested by examining both open-loop pointing as before and measuring the position of the occluded normal eye while the treated eye fixated the targets used in the pointing test. These measures were carried out before, and a few minutes after, injection of botulinum toxin and were then repeated daily for three to four weeks with a few tests made after 14 weeks. All the patients showed significant correction of their strabismus. The patients were divided into three groups: esotropes with no previous injections, exotropes with no previous injections and exotropes who had had injections previously. Normal subjects formed a fourth group. The differences between the measured eye position and the pointing response were calculated and compared. They were statistically significantly different across the groups. The esotropes' results also differed from those of the other groups. In esotropes with no previous injections there was evidence of a change in the EOM afferent signal developing over days and weeks. Exotropes showed similar, but smaller, effects. Larger effects were produced when the medial rectus was injected (in esotropes) than with injection of the lateral rectus. Whether patients had had surgery to the EOM did not affect the results but those with previous botulinum injection showed no change in the proprioceptive signal. The normal subjects showed no changes and the patients tested at 14 weeks no longer had pointing errors.

Dengis *et al.* (1998) point out the differences between ungulate and human EOM spindles in their discussion of the absence of an effect of botulinum toxin injection in human EOM on the proprioceptive signal over the time-course during which Manni *et al.* (1989) found changes in spindle firing from ungulate eye muscles. They argue for an effect on human palisade endings as the explanation for their results, suggesting that in the short term only outflow information is used in registering eye position but that over the long term 'baseline' information about eye position registered by palisades alters and that this 'overrides the eye position information from efference'. The lack of effect in the previously injected patients is explained by postulating a threshold of eye rotation below which EOM proprioception has no effect. The previously injected patients had small eye deviations and the change produced by botulinum injection was perhaps insufficient to trigger the proprioceptive effect. There is some evidence for such a threshold for the action of the EOM proprioceptive signal from the work of Gauthier *et al.* (1990*a*) who put it at about 10° of eye deflection and Lewis & Zee (1993) whose estimate is about 15°. There is no doubt that the results of Dengis *et al.* (1998) demonstrate a change in the inflow signal that appears after a delay of days and lasts for several weeks. However, in view of the evidence from passive deflection, and from the eye-press experiment that both outflow and inflow signals contribute to the signal of registered eye position within seconds or minutes of manipulating the system, it seems unlikely that, even in the short term, outflow alone is used to determine registered eye position. The attribution of the botulinum effect to human palisades is based on the lack of a short-term effect over a time-course comparable with that found for the action of the toxin on ungulate spindles together with the evidence from Steinbach's group, discussed above, that palisades are likely to be involved in the modulations of the input signal that result from operations on the EOM. Though this attribution must necessarily be provisional it does seem probable—see Steinbach (2000) for a cogent discussion of the role of palisade endings as proprioceptors in the eye muscles.

(b) *Are there differences in the action of extraocular muscle proprioceptive signals between strabismic patients and normal subjects?*

Some years ago, Mitsui (see Mitsui (1986) for an extensive account) found that, in some strabismic patients, adduction of the straight ('master' in his terminology) eye, produced by pulling the anaesthetized conjunctiva medially with forceps when the eye was in the primary position, resulted in rotation of the other ('slave') eye to the straight primary position. This 'magician's forceps phenomenon' was present only in the light but persisted under general anaesthesia. Mitsui provisionally attributed the effect to a 'proprioceptive reflex' induced by the adduction that cancelled an abnormal proprioceptive drive to the lateral rectus of the 'slave' eye, which was the cause of the exodeviation of the 'slave' eye and thus of the strabismus. Though the presence of the 'magician's forceps phenomenon' was confirmed by Lennerstrand *et al.* (1997) among others, the mechanism and significance of the effect remain obscure.

Lennerstrand *et al.* (1997) vibrated the inferior and lateral recti of normal subjects, as we have seen previously, and of patients with exotropia. There was no difference between the effects of vibration of the inferior rectus in the two groups. However, vibration of the lateral rectus of the dominant eye in exotropes was followed by adduction (nasal deviation) of the other, covered, non-dominant eye, whereas in normal subjects the non-dominant eye moved in the opposite, temporal, direction (abduction). If the proprioceptive signal produced by vibration of the lateral rectus is interpreted by the oculomotor system as lengthening of the vibrated muscle, one would expect the other eye to abduct (if it moved at all) to maintain conjugacy. Thus the results suggest that the EOM proprioceptive signal in exotropes is either different or is processed differently than in normal subjects. On the subject of possible sources for the EOM proprioceptive signal in experiments using vibration of human eye muscles and the question of whether muscle spindles are involved, see the apposite comments on Lennerstrand *et al.*'s (1997) article by Lukas *et al.* (1998). As has been pointed out already there are conflicts in the results reported when human EOM were vibrated by Lennerstrand *et al.* (1997) and those of Velay *et al.* (1997) so more experimental work is needed to clarify the situation.

Perhaps all one can say at the moment is that, in one kind of strabismus, there are some results that suggest the possibility that either proprioceptive signals from the EOM may be abnormal or that they may be processed

abnormally by the brain. This would seem to be a fruitful field for work—of which there has been rather little so far—on the pathophysiology of EOM proprioception in strabismus.

18. LOOSE ENDS

(a) *The supposed incompetence of human eye muscle proprioceptors*

I hope that the evidence set out above, and the interpretations of this evidence that I have suggested, are sufficient to lay to rest speculation, based on morphology, about the incompetence of the muscle spindles and palisade endings of human eye muscles to act as proprioceptors. There is, of course, nothing wrong with speculation on function on the basis of relevant and critical evidence. Evidence about details of receptor structure is certainly likely to be relevant to function but, in my belief, it cannot be critical to competence in the present state of our ignorance since to be critical it would have to be a reliable guide to the presence or absence of certain aspects of function. Thus if we were in a position in which the evidence could be critical we would know the details of the receptor function and, were that so, the question of incompetence or otherwise would cease to exist since it would have been answered. It would then be possible to enquire why the structure–function relationships were such and such, but that is not a question that can arise at the moment.

(b) *Palisades and their signals*

Although the work of Cooper and her colleagues and then of Whitteridge in the 1950s laid the foundations for the modern study of the physiology of the receptors of the eye muscles, it is an unfortunate curiosity that we know so little about the details of the first-order afferent signal. Undoubtedly the most pressing problem is to discover the characteristics of the palisade as a receptor since this structure seems both to be unique to EOM and, arguably, to be the characteristic receptor of the vertebrate EOM (see Spencer & Porter 1988). It is also present in the EOM of species both with and without eye muscle spindles. Thus, as well as needing information about the physiology of the palisade, we need to know much more about the extent of its distribution in the EOM of vertebrates. For the transducer function of the muscle spindle we have a great deal of information—some of it from the eye muscle spindles though not, of course, from those in human EOM. About the signals that the palisade may send centrally in its afferents we know nothing at all. Among the questions to which we need answers are: Do the palisades supply signals principally related to muscle length and its derivatives or to muscle 'tension'? If the former, do they supply information about both muscle length and its rate of change, and are the position signals slowly adapting and able to provide information about eye position when the eye is as stationary as the eye ever is? Do they react differently to passive length change and to active contraction of the eye muscle? How are their responses related to the state of activity of the multiply innervated muscle fibres with which they seem to have an exclusive association? Is there any evidence that these multiply innervated fibres are controlled separately from the rest of the motor units of the eye muscle so that they might act as a centrally adjustable device analogous to the muscle spindle, as has been suggested? What are the implications of the recent discovery that the orbital fibres, some of which carry the palisades, pass through adjustable pulleys? This would be a demanding list of questions for any receptor—it took many decades to provide answers to similar questions for the fairly accessible muscle spindle. For the palisade ending it represents a formidable set of tasks indeed—the more so because, ideally, one would like the answers from receptors in the eye muscles in their normal state in an undissected, undisturbed orbit. Even with a working preparation of a relatively isolated eye muscle in a species known to have palisades it is very difficult to see how one could identify a particular response as coming from a palisade rather than from some other receptor. This is a chicken and egg problem since identification of the receptor is usually made by the characteristics of the signal and until these characteristics are known this is, obviously, impossible. Recalling how this problem was solved for the muscle spindle is instructive and might, I think, just possibly provide a key to a solution. B. H. C. Matthews in 1931 (Matthews 1931*a*) made the first study of a receptor identified histologically as a muscle spindle by recording from the muscle nerve of a tiny toe muscle of the frog that he showed contained only one receptor, a muscle spindle. With the same preparation he then showed the effect on spindle firing of muscle contraction (Matthews 1931*b*). If one could find an animal whose only EOM receptors were palisades our questions would immediately become answerable—perhaps with greater ease than was the case for the muscle spindle since we already have means of moving the eye in the orbit precisely, although the difficulties of recording the first-order afferents in the trigeminal ganglion remain quite considerable—we suppose that we have shown our hypothetical vertebrate to have its primary afferent somata in the ganglion. Of course we do not yet know whether Nature has provided an animal of this description. Failing an animal with a pure culture of palisades, we would want—as very much a second best—one with palisades and perhaps one other type of ending. As the number of additional ending types increases, the difficulties of identifying the palisade response increase enormously. What is needed then, in the first place, is a painstaking survey of the vertebrates for our 'pure palisade' animal—and this will be a task that may not be popular since there is no certainty of success. Cats are not a good starting point since they have several types of ending in addition to palisades (see Billig *et al.* 1997), though at least they have no spindles. Perhaps the pigeon might be a good first subject—it has no spindles but does have receptor responses that can be characterized by recording from the ganglion (Fahy & Donaldson 1998), but we do not yet know if it has palisades. It would seem to be worth finding out.

(c) *An important observation about first-order afferent signals from the eye muscles*

One of the most surprising things to emerge from comparison of the results of our study of pigeon first-order afferents (Fahy & Donaldson 1998) with those of previous work (Bach-y-Rita & Ito 1966; Manni *et al.*

1989*a*; Whitteridge 1959) is the evidence—set out for the first time, to my knowledge, in this review—that the sensitivity of afferents from eye muscles with no muscle spindles is of the same order as (and possibly even a little greater than) that provided by the most complex and 'typical' muscle spindles found in any eye muscles. Even more striking is that this is true for pigeon afferents recorded with the eye muscles paralysed as compared to ungulate spindle afferents recorded while the spindles were under considerable gamma drive and thus much above their baseline sensitivity with the spindle passive. Surely this should cast considerable doubt on the notion that the eye muscle afferent apparatus of the great majority of animals who lack spindles in their eye muscles must, of necessity, be inferior in its capability to that of the eccentric few species who have spindles.

(d) *The interpretation of the action of extraocular muscle afferent signals on the horizontal vestibulo-ocular reflex*

The results of the experiments on the action of the EOM afferent signal on the pigeon HVOR seem very clear. Whether measured at different levels as a firing rate of neurons in the brainstem or on the output of the system, it is striking that the relationship between the effect and the movement of the eye itself is so similar. In each case the relationship between the magnitude of the output and the velocity of the imposed eye movement is more or less linear with a slope of −0.01 and this is true both in decerebrate and in awake intact birds. This similarity gives one some confidence that one is looking at a fairly stable effect that is not modified much in magnitude as it passes through the control system. The interpretation of the results in terms of a mechanism for stabilizing or adjusting the HVOR is less easy. We now know (see Donaldson & Knox 2000) that the HVOR gain of awake unmedicated pigeons with their heads held is rarely −1.0. The experiments were originally devised on the basis that the 'desired' gain set by the motor command was −1.0. As far as the regression goes the fact that the 'desired' gain seems rarely to be unity is not very important—it just shifts the ordinate. But our ignorance of the fluctuating target gain at any moment makes it very difficult to judge how effective the apparently corrective action of the signal from the EOM proprioceptors might be in adjusting the gain of the HVOR towards the target value.

The artificial vestibulo-ocular reflex technique (AVOR) suffers from the disadvantage that only one eye is manipulated to induce the error in eye velocity to be signalled by the EOM receptors whose effect is, in the HVOR experiments, estimated by the behaviour of the other eye. It would probably be possible, though difficult, to impose the error on both eyes and to examine effects on the behaviour of single brainstem neurons but there seems no way of imposing errors on both eyes and having a means of estimating the effect on the output of the HVOR unless one were to be content with examining the firing of oculomotor neurons as a measure of this. Perhaps that would be worth doing.

(i) *Effects on gain and phase*

The effects of the imposed error are consistently on the HVOR gain and not on its phase and it is not immediately obvious why this should be so unless the drive signal—derived from the semicircular canals—is more robust in the accuracy of its phase than of its amplitude. For stabilization of the retinal image—supposing the head to be stationary relative to the body—the necessary condition is that the eye moves at the same speed but in the opposite direction to the whole bird and this would require accurate control of both gain and phase. But even when the HVOR gain is considerably less than −1.0, as it often is (see Donaldson & Knox 2000), the phase remains close to 180° so it seems that the phase is, indeed, less unstable than the gain, supposing always that the 'aim' of the system is image stabilization. Why this should be so is obscure but it is at least consistent with the finding that errors in eye velocity affect the output gain but do not alter its phase. All this is, of course, based on experiments on pigeons with almost all the observations made at a single frequency (0.4 Hz) and the only (fairly tenuous) indication that it might apply to other animals is the old observation of Taylor (1965) that eliminating eye movement by paralysing the EOM of the anaesthetized cat during horizontal oscillation did not change the phase of abducens neuron firing but did reduce its amplitude modulation. The effects of errors in imposed eye velocity on the gain and phase of the human HVOR would, in principle, be testable by systematic experiments along the lines of our pilot work (Knox & Donaldson 1993*b*).

(e) *Fast (immediate) and slow (long-term) effects of the afferent signal*

Some recent work has emphasized the 'long-term' effects of the removal or manipulation of the EOM afferent signal both in Man (effects of botulinum toxin; Dengis *et al*. 1998) and monkey (eye alignment and post-saccadic drift; Lewis *et al*. 1994, 1999). The significance of effects of this kind, developing over days and persisting for weeks, seems clear in the adjustment of oculomotor behaviour to take account of changes in the 'plant' produced by disease or by artificial insults to its integrity. Gauthier *et al*.'s (1995*a*) findings on the modification of the adaptation of the rat VOR by orbital afferent signals also fall into this class and demonstrate yet another facet of the adaptability of this piece of oculomotor behaviour, which itself has often been used as a model for the study of some aspects of motor learning (see, for example, du Lac *et al*. 1995). I have suggested in § 13 how manipulation of the EOM afferent signal might be used to try to elucidate some of the adaptive processes taking place in the cerebellar flocculus.

But there is also clear evidence, as we have seen, that EOM afferent signals can, and do, exert actions that are manifest certainly within seconds—and probably in fractions of a second—and others that come on in a short time (minutes or less) and last for minutes. In the most rapid group are the actions on the HVOR gain that occur in less than a second and the effects of impeding the movement of one eye that are apparent within seconds in changes in the amplitude of saccades made by the free eye and in the characteristics of pursuit movements. The effects on registered eye position of deflecting an eye are also apparent within a short time (less than a minute) as are those of vibrating eye muscles.

The notion that EOM afferent actions may take place by adjustment of settings within the oculomotor control system ('parametric adjustment') was introduced by Ludvigh (1952*a*) and is discussed by Carpenter (1988). Recently it seems to have been invoked mainly in relation to the slow or 'long-term' effects—perhaps the idea of a gradual reshaping of a facet of oculomotor performance by serial adjustment of 'control knobs' in the oculomotor system has a certain attraction. But there is no reason at all why a 'parameter' should not be changeable very quickly if by 'parameter' one means something like, for example, gain. That the EOM afferent modulation of gain occurs very quickly in the AVOR experiments is indubitable. The experiments are done with interleaving of the stimuli so that the imposed error changes in a pseudorandom way from one tested sinusoidal cycle to another. Under these conditions each cycle shows a different output amplitude, and thus a changed gain, demonstrating that the gain 'parameter' can be adjusted in both directions very rapidly by the EOM afferent signal. I wonder, then, how useful it is to make a distinction between 'parametric control' and 'control', plain and simple? What is puzzling is why, when the mismatch conditions that produce the 'long-term' effects are applied, there is a delay of days in the onset of the effect. That delay does seem to argue for a different mechanism, but I am uncertain whether 'parametric adjustment' carries this imputation of mechanism. The long duration of the effect seems less puzzling since the mismatch that induced it generally continues.

In any case there seems no need for disquiet that the EOM afferent signal can produce both immediate and long-term effects. If the signal is essential to the economy of the oculomotor system this is exactly what we should expect that it, or the changes that it produces centrally, would do. The combination of results from experiments in which the afferent signal is manipulated by changes in the oculomotor environment—or by mendacious indication that there have been such changes (imposed errors)—and those in which the signal is 'simply' removed without otherwise changing the environment, strongly suggests that the afferent signal is concerned with the control of ongoing processes from moment-to-moment as well as in the response to overt change. It is interesting that these ongoing processes seem to include both perceptions (as evidenced by the induction of illusions and so on) and motor processes, and that these can be of a relatively simple kind like the control of saccades or the VOR, or of a high order of complexity such as visual reaching. That the signal acts at what we may call (for the want of a better name) by the horrid title of the 'sensory–motor interface' is clear from its effects both on the 'registered eye position' and on pointing to targets with the unseen hand.

Two types of action of the EOM afferent signal

From what has gone before it seems that we may conclude that the EOM afferent signal has at least two types of action on the oculomotor control systems—and that these actions are broadly on the 'gain' of the control systems. We may summarize the experimental results thus:

(i) The EOM afferent signal from each eye affects both eyes, although the effect may be greater on the eye from which the signal originates.

(ii) There is a continuous or background action of the afferent signal since:

deafferenting the EOM of one eye results in an apparently permanent fall in the gain of the VOR and of optokinetic nystagmus;

deafferentation of one eye leads to reduction in the capacity of the oculomotor system to adapt to changes imposed on it, for example by changes to the oculomotor plant.

(iii) There is a dynamic action of the afferent signal from moment to moment since:

imposing movements on one eye during a commanded movement (the AVOR experiment) produces corrective action on the movement of the free eye. The experiment is such that one can be sure this action occurs within fractions of a second.

(iv) The following might be regarded as evidence of either a continuous or a dynamic signal:

holding one eye and thus reducing or abolishing EOM signals related to movement of that eye results in

reduction of the VOR gain of the free eye;
reduction of saccadic 'gain' of the free eye;
reduction of initial pursuit velocity and acceleration of the free eye;

these effects persist as long as the eye is held or its movement obstructed. They then disappear effectively at once.

All the above is just restatement of experimental results (not all from the same species) that have already been discussed in detail. What follows is speculative.

The corrective action of the afferent signal during the AVOR experiment (see (iii) above) is likely to be due to interaction of a copy of a motor command signal (from the command driving the VOR in response to the vestibular input) and a reafferent signal from the EOM. This reafferent signal is presumably derived from both eyes but that from the manipulated eye is erroneous because of the movements externally imposed on that eye. The 'corrective' action is consistent with an interaction between a command copy (or more precisely an expectation of reafference constructed from the motor command) and the reafference from the EOM. The result of the interaction can have either sign since the gain of the AVOR shifts up or down accordingly as the eye velocity 'required' is less than or greater than that required for compensation. The evidence is certainly consistent with this general scheme, although there are difficulties with pursuing the details of this process further with the experimental evidence we have at the moment (because the 'set' gain is not always -1.0 and errors are imposed on one eye only so the arrangement is, in a sense, analogous to interfering with the ocular plant of one eye). Interestingly, what seems to be similar 'corrective' behaviour to that adjusting the eye movement is seen in the responses of single units in at least two levels of the oculomotor system (vestibular nuclear complex and oculomotor nuclei). In sum, then, the dynamic EOM afferent input seems to have an opposite sign to the motor command copy or reafferent expectation and the result of the interaction can move the gain up or down.

However, the continuous or background signal would seem always to act to increase or maintain the gain and never to reduce it since the effect of removing the 'background' EOM signal is always to cause a reduction in the output of the system. For this reason it seems simplest to think of the effects of holding the eye or obstructing its movement (see (iv) above) as being examples of the 'background' signal, since the effect of reducing the EOM input by reducing eye movement is always to cause a fall in the gain or the output. It is possible that this signal is present even when an eye movement is not being commanded—but this might not be the case if the reafferent expectation, derived from the motor command, 'expected' a very rapid and considerable EOM afferent input that would be reduced if one eye were held. If this were so, the expected input would be effectively positive feedback since without it the gain resulting from the command is too small. On the whole I find it easier to suppose that there is some kind of tonic action from a more or less continuously acting EOM afferent signal that acts to keep the gain of the oculomotor systems set to a relatively high level. There is no experimental evidence at the moment to choose between these alternatives. It is clear, though, that this signal does not have 'corrective' interaction with the command copy, at least in the short term.

If we accept the idea of a 'background' EOM afferent signal that keeps the oculomotor gains up, where does this come from? The possibilities have been touched on in previous sections. Though there is only a little evidence of a 'continuous' signal of eye position in the recorded actions on central units, there are, at least in some species, potential sources for such a signal in the EOM proprioceptors—supposing these to be competent as we have already discussed. But it seems to me there is also another quite interesting possibility. In the pigeon at least, we know that there is a signal of eye position available at the end of each eye movement and that this signal seems to represent absolute eye position in the orbit and not just the amplitude of the last eye movement. Suppose these signals were retained centrally, either by some kind of sample and hold device or integrator. Since the eye moves very frequently there would be a quasi-continuous signal of eye position available to the oculomotor system, one of whose actions, I suggest, would be to keep the gains of various subsystems 'turned up'. The storage system would seem to be quite leaky since stopping the succession of position pulses by obstructing movement of one eye very soon (within seconds probably) leads to reduction in the background signal and so in the gains. The putative background signal would be a likely candidate for the signal acting on the adaptive properties of oculomotor subsystems.

It seems probable that the background and dynamic actions on gain would interact, perhaps simply by algebraic summation.

The actions of the signal from the eye muscle proprioceptors that have been shown on the development of the visual cortex (see the section on the development of properties of visual neurons (§ 12); see the review by Buisseret 1995) are, presumably, 'long term' or 'background', of course, as are those on the development and maintenance of visuomotor behaviour (see § 16). The existence of these effects underlines the importance of signals from the orbital proprioceptors in the general postnatal development of the organism.

(f) *Cyclopean eyes and hybrid theories*

Recent human experiments seem to leave no doubt that EOM afferent signals from both eyes affect analysis of visual information received through either eye even when the eye views monocularly (Bridgeman & Stark 1991; Dengis *et al.* 1998; Gauthier *et al.* 1990*a*, 1994). Thus, what happens to the non-viewing eye is critical in interpreting the effects of manipulation of the viewing eye. This vindicates the criticism of James (1890) adopted by Sherrington (1900) of the interpretation of the 'paralysed eye' experiment of Von Helmholtz (1867, 1925) and others. It also dethrones the 'eye-press' observations long regarded as a cornerstone of the demonstration of the impotence of ocular proprioceptive inflow and the efficacy of outflow acting alone. But, together with this confirmation by experiment of the criticism of the interpretations of the Von Helmholtz school—that were in reality, until recently, no more based upon critical evidence than were the views they attacked—we should place the demonstration by the modern experiments that 'inflow' and 'outflow' are not rival pretenders for monarchy over the eye (nor equally over kinaesthesis and general motor control) but are interacting, and surely cooperative, mechanisms in an oligarchy, that is, in a multifactorial control system. While this conclusion could have been reached some time ago on a balance of arguments—though it was not (see Matin (1976) for a perceptive and luminous exposition that predates the critical experiments)—experiment has now shown that the observations cannot be explained by either 'outflow' or 'inflow' acting alone and that some kind of 'hybrid' explanation is necessary in which both are involved.

One of the great challenges for the future is to try to define how the two systems interact and this should require quantitative analysis. If, as I have said earlier, I am not entirely convinced by the results of attempts to partition the total amount of information about the registered position of the eye quantitatively between 'inflow' and 'outflow' sources, I most heartily applaud the attempts themselves. At the moment it seems puzzling that one set of experiments (Bridgeman & Stark 1991; Gauthier *et al.* 1990*a*) partitions the total signal about 70:30 in favour of outflow and the other (Li & Matin 1992) finds a similar ratio but this time with inflow giving 80%. The results of Dengis *et al.* (1998) show convincingly that registered eye position uses both signal sources from both eyes but does not partition the compound signal quantitatively. It is unclear whether all this means that, under different circumstances, the two signals do indeed contribute very different proportions of the signal of registered eye position, or whether the differences are to be explained by the different methods used to attack the question, or even by some technical fault. Further experiment is clearly required.

One would wish also to have quantitative estimates of the interaction in the generation of the signals of eye position and velocity used in motor control—because it now seems, to me at least (and I hope to those who have read thus far), that it is undeniable that the EOM afferent signal is competent to take part in this. But dissecting the

interaction between 'inflow' and 'outflow' signals in oculomotor control seems both conceptually and technically more difficult than for their interaction in perception and visually guided pointing. The crux of the experimental problem is to have simultaneous measures of both the motor command (and thus of its presumptive corollary discharge and expected reafference) and of the proprioceptive signal at the same time as measuring the behaviour that results from the motor command. With apologies for writing again of our own work I point out that we have begun, in a very limited way, to try to meet these requirements using the AVOR method. The idea was that this would allow us to manipulate the inflow (EOM proprioceptive signal) while the oculomotor system was producing a known oculomotor drive accompanied by its corollary discharge. We began with the rather naive belief that the goal of the oculomotor system as it responded to horizontal sinusoidal oscillation of the animal (bird) with the head fixed in relation to the body would be to produce minimal retinal image slip—thus an HVOR slow-phase gain of about −1.0. But it seems that, in the pigeon at least, under these conditions the system is not particularly interested in producing a gain of unity. I say interested because it clearly can, and occasionally does, produce unity gain but most of the time the gain is a good deal less. As I have pointed out earlier this means that we cannot know the system's goal in terms of gain at any moment so that, while we can show that the EOM afferent signal modulates the gain and we can measure (because we determine it) the error in movement of one eye, we cannot calculate what error the oculomotor system 'sees' and thus estimate the power of the inflow signal in modifying the motor output. Still, the very close similarity in the relationship between the relative gain (the ratio of the movement of the free eye when an error is imposed on the other eye to its movement in an arbitrary standard condition) and the magnitude of the manipulation of the inflow signal on the one hand, and the relative gain measured in terms of unit firing in the brainstem on the other, and, again, the close similarity of the relationship in different nuclei involved in the HVOR, encourages one to believe that at least a start has been made. Progress might follow an attempt to elaborate the experiments of Knox *et al*. (2000) and Gauthier and his colleagues (Gauthier & Vercher 1992; Gauthier *et al*. 1995*b*; Van Donkelaar *et al*. 1997) by using dynamic stimuli—that is, using imposed eye movements rather than impeding 'natural' eye movement to study saccadic and pursuit eye movements in humans.

(g) *The question of a universal model for the actions of the extraocular muscle proprioceptive signal*

For me one of the most annoying criticisms of reports of experimental work on eye muscle afferents and their signals is that of 'failure to provide a model'. Referees' reports on our own manuscripts have not infrequently included comments of this sort. By 'model' they seem to mean a mathematical model of the type favoured by many who study eye movement. Our own group has consistently resisted trying to produce such a 'model' to 'explain' our experimental findings because, in short, we do not believe the time is yet ripe. I am very conscious of the force of Cornford's (1908) comment on the dangers of 'the principle of unripe time' as an argument for avoiding action. As he said 'Time, by the way, is like the medlar; it has a trick of going rotten before it is ripe.' But, for the time to be ripe for modelling even the actions on one system—oculomotor control for example—we would have to have much more knowledge than we have now of the way in which signals interact at the various levels of the system at which, as we have seen, the afferent information from the eye muscles exerts effects.[11]

We also have no particular reason to believe that a model of action in one system would necessarily apply—or even that it would be particularly likely to apply—to other systems within the brain upon which experimental evidence clearly shows that the afferent signal acts. At least, so it seems to me.

Interestingly, and perhaps reassuringly, almost all the other groups who work on the signals from the eye muscles have also resisted the temptation to construct models. It would be quite possible, no doubt, in many cases to produce some kind of model, provided that one did not mind introducing untested conjecture. And it might be useful to do this if, as a result, one gained an insight that led to new experiment. However, if one reflects that a mathematical model is—or at least should be—a hypothesis, in addition to, and more importantly than, being simply a set of procedures that reproduce the numerical results of the experiment, then that hypothesis, in my view, should be admitted only if it follows those precepts set out by Newton with which this review began. We must hope that it will not be too long before it is possible to construct models that meet these criteria. A collection of untested—and perhaps untestable—assumptions and conjectures is not a hypothesis nor a model worthy of the name even if it reproduces the input–output relationships that the experiments reveal. For the moment I think it speaks well for the field that it is not burdened with a collection of such models to take on lives of their own and, as Newton foresaw, to be added to and modified to explain—or explain away—each new piece of evidence.

I am most grateful to The Leverhulme Trust for the award of a Research Fellowship for the period during which I wrote this review. To my collaborators over the last 20 years I owe a great deal for their ideas and their patience, skill and diligence in many long experiments. But most of all, without the help, patience, forbearance and meticulous work of my wife over 30 years, in collaborating in countless experiments in the past and more recently in searching the shelves of libraries, checking sources and, especially, in reading drafts, this review would probably not have been begun and would certainly not have been completed. *Scire aevi meritum, non numerare decet.*

ENDNOTES

[1] In fact Newton was not entirely consistent in his views on the use of hypotheses and, indeed, in his own use of them. The topic is complex and controversial, see T. S. Kuhn in Cohen (1958, pp. 27–45) and Koyré (1965, especially pp. 25–52). On 'frame' versus 'feign' see Koyré (1965, p. 35) and Gjertsen (1986, p. 266).

[2] The passage is from Newton's second letter to Pradies in Paris replying to comments about his original publication of his prism experiments and to a second letter from Pradies raising further objections. Having said that his observations of certain properties of light do not depend on any particular explanation of how the properties come about, Newton continues, generalizing:

> *'Optimus enim et tutissimus philosophandi modus videtur, ut imprimis rerum proprietates diligenter inquiramus et per experimenta stabiliamus ; ac dein tardius contendamus ad Hypotheses pro earum explicatione. Nam HYPOTHESES ad explicandas rerum proprietates tantum accommodari debent, et non ad determinandas usurpari, nisi quatenus experimenta subministrare possint. Et siquis ex sola HYPOTHESIUM possibilitate de veritate rerum conjecturam faciat, non video quo pacto quicquam certi in ulla scientia determinare possit ; siquidem alias atque alias Hypotheses semper liceat excogitare, quae novas difficultates suppeditare videbuntur.'*
> (Isaac Newton, reproduced in Cohen (1958). Originally published in *Philosophical Transactions* in July 1672, p. 5014, wrongly numbered 4014.)

The 1809 translation from the *Transactions* runs:

> 'For the best and safest method of philosophising seems to be, first to enquire diligently into the properties of things, and establishing these properties by experiments and then to proceed more slowly to hypotheses for explanations of them. For hypotheses should be subservient only in explaining the properties of things, but not answered in determining them; unless so far as they may furnish experiments. For if the possibility of hypotheses is to be the test of the truth and reality of things, I see not how certainty can be obtained in any science; since numerous hypotheses may be devised, which shall seem to overcome new difficulties.'

Not all of this makes much sense in the 2lst century. Also, one must suppose that Newton chose his words and constructed the passage with care. The 1809 version fails somewhat in its emphases. In particular it loses the force of Newton's antithesis, which is clear in the Latin, between the improper use of hypotheses as a means of establishing properties and their exceptional, proper, use in suggesting further experiments. I am most grateful to John Richardson, Professor of Classics in the University of Edinburgh, for his advice on, and for a luminous discussion of, the weights of the Latin phrases.

My translation is in § 1.

[3] He also objected strongly to the ideas of Ferrier and Hughlings Jackson on the exclusively 'motor' nature of the electrically excitable cortex around the central fissure. His paper in *Brain* in 1888 (Bastian 1888), delivered as a lecture in 1887, is followed by a lengthy account of the comments of Ferrier, Hughlings Jackson and others and Bastian's reply. The arguments are still of some interest.

[4] The motor command in question is the drive to the electric organ of a weakly electric mormyrid fish, which has an electric organ insufficiently powerful to be used as a weapon but which is used for electrolocation and for communication. Since the electric organ is, effectively, a battery of motor end-plates it can be paralysed with a neuromuscular blocker such as curare so that there is no electrical discharge into the water, while leaving the motor volley unaffected and recordable by an electrode over the electric organ. This discharge is the command signal (Bell 1981, 1982, 1986). Recordings from neurons in the central nervous system to simulated electric organ discharges are modified when they are temporally associated with the command. These neurons are able to respond differently to electric fields that are surface positive (with respect to the fish) and those that are surface negative. What is studied is the result of the interaction of the response of the central cells to the electroceptor afferent signals when the experimenter applies an electric field, and the copy of the motor command to the electric organ. The motor command occurs spontaneously and triggers the electric field stimulus. This interaction between command copy and afferent response allows the deduction that the motor command copy is always opposite in sign to the response of the afferent input from the electroceptors and so probably serves to reduce the central effect of electrical signals picked up by the fish's electroceptors when its own electric organ discharges. These effects are, of course, reafferent in Von Holst's terms since they are induced by the animal's own activity. However, this activity is not motor in the ordinary sense since it evokes an electrical discharge and not movement and, as Bell points out, the command signal is a stereotyped synchronous motor neuron discharge to the electric organ and not a graded and temporally variable discharge to muscle motor units. How good a model this fascinating system may be for actions of motor commands in 'true' motor control is uncertain but it does confirm that the type of interaction of a 'motor' command copy and the consequent reafference that was postulated by Von Holst & Mittelstaedt (1950) does exist in Nature. More recently Bell (1989), in a most interesting review, has described results—many of them his own—that show that there is more than one type of motor command copy in the mormyrid fish. As well as the plastic 'corollary discharge' there is at least one other type with fixed properties (not alterable by pairing electric organ command and afferent input) that appears to act to switch off or disable the response of central units to the fish's own electric organ discharge and thus prevent it being deafened, so to speak, by the sound of its own voice as it listens for electrical signals coming from the environment. Bell's article also offers an interesting comparison of the electric organ command copy system with effects ascribed to command copies in motor systems in other species.

[5] See Merton (1964) for references to Von Helmholtz's demonstrations of Listing's law and some comments.

[6] Note, though, that presuming human EOM spindles are competent as proprioceptors, increased drive to the eye muscles is likely to alter proprioceptive feedback from them by the action of an associated increase in gamma drive to spindle intrafusal fibres. An inflow component is therefore not definitely excluded.

[7] Descartes' *Traité de l'homme*, written in French, was published posthumously in an incomplete Latin version in 1662 and in a complete French version edited by Descartes' literary executor Clerselier in 1664 (Hall 1972). See Hall (1972) for a facsimile of the text of the first French edition with an English translation and notes.

[8] Descartes conceived the nerves as taking origin from the brain, in the tissue forming the walls of the ventricles, and as consisting of tubes within which were very fine filaments that occupied only a little of the volume of the tube leaving plenty of room for the animal spirits to flow from the brain to the periphery. The fine filaments mechanically transmitted 'signals' from the periphery to the ventricles there altering the disposition of the mouths of the nerve tubes and so adjusting the flow of spirits into them. The sections on the effects of fire close to the foot on pp. 27–28 of Clerselier's 1664 edition and on the formation of visual impressions (p. 71) make this mechanism explicit. Elsewhere it is explained that these mechanically transmitted

'signals' would, in an organism equipped by God with a sentient soul, also cause sensation as a result of their alteration of the flow of the animal spirits. All this is well explained and discussed by Hall (1972).

[9] Mammalian static, but not dynamic, fusimotor neuromuscular junctions are more resistant to neuromuscular blockers (gallamine) than are skeletomotor junctions (Yamamoto *et al.* 1994).

[10] Because of its short action it is understandable that suxamethonium was used but it is particularly unfortunate since suxamethonium is known to cause tonic contraction of intrafusal muscle fibres (see Browne 1975) and of multiply innervated extrafusal fibres of the EOM, some of which carry palisade endings (Porter *et al.* 1995). Thus, as well as producing paralysis of the EOM, changes in proprioceptive signals may have been induced unrelated to the fact that the eyes were stationary. There is evidence from one experiment that spindle activity evoked by fusimotor stimulation alone (during whole body paralysis) leads to illusions of joint movement (see Proske *et al.* 2000) so it seems possible that similar activity from EOM spindles evoked by suxamethonium might also lead to illusions.

[11] Of course, much depends on just what one means by 'modelling'. For example, most models of oculomotor control have not included signals from the EOM proprioceptors but one which does is that of Kettner *et al.* (1997) who made a network model of cerebellar control of pursuit eye movement. This model contains feedback of eye position and eye velocity to cerebellar mossy fibres apparently from an 'efference copy' from the brainstem and from EOM proprioceptors. However, though these signals are shown separately in the block diagram of the model, they are not treated separately by the model itself, which uses only one set of position and one set of velocity inputs. The model is indifferent to the source of this input and the labels 'efference copy' and 'proprioceptive feedback' only indicate that the authors suggest that signals might come from one or both of these sources. So, excellent as it may be for other purposes, this model cannot be used to study the effects of EOM afferent signals and quite clearly its authors had no such purpose in mind. It would not be difficult to add a new label saying 'proprioceptive input' to the eye position or velocity feedback in many of the well-known models of oculomotor control but this would achieve nothing beyond an admission that the EOM proprioceptors are a possible signal source. To be useful, a model of EOM afferent action would need to contain a signal from the EOM proprioceptors that could be manipulated independently of, as well as in concert with, the other components of the model so that its effect on the system could be studied as it varied and co-varied with other signals.

REFERENCES

Abrahams, V. C. & Anstee, G. 1979 Unit activity in the superior colliculus of the cat following passive eye movements. *Can. J. Physiol. Pharmacol.* **57**, 359–368.

Abrahams, V. C. & Rose, P. K. 1975 Projections of extraocular, neck muscle and retinal afferents to superior colliculus in the cat: their connections to cells of origin of tectospinal tract. *J. Neurophysiol.* **38**, 10–18.

Abuel-Atta, A. A., DeSantis, M. & Wong, A. 1997 Encapsulated sensory receptors within intraorbital skeletal muscles of a camel. *Anat. Rec.* **247**, 189–198.

Aigner, M., Lukas, J. R., Denk, M., Ziya-Ghazvini, F., Kaider, A. & Mayr, R. 2000 Somatotopic organization of primary afferent perikarya of the guinea-pig extraocular muscles in the trigeminal ganglion: a post-mortem DiI-tracing study. *Exp. Eye Res.* **70**, 411–418.

Allin, F., Velay, J. L. & Bouquerel, A. 1996 Shift in saccadic direction induced in humans by proprioceptive manipulation: a comparison between memory-guided and visually guided saccades. *Exp. Brain Res.* **110**, 473–481.

Allum, J. H. J. & Graf, W. 1977 Time constants of vestibular nuclei neurons in the goldfish: a model with ocular proprioception. *Biol. Cybern.* **28**, 95–99.

Alvarado-Mallart, R.-M. & Pinçon-Raymond, M. 1979 The palisade endings of cat extraocular muscles: a light and electron microscope study. *Tissue Cell* **11**, 567–584.

Alvarado-Mallart, R.-M., Batini, C., Buisseret, C., Guéritaud, J. P. & Horcholle-Bossavit, G. 1975*a* Mesencephalic projections of the rectus lateralis muscle afferents in the cat. *Arch. Ital. Biol.* **113**, 1–20.

Alvarado-Mallart, R.-M., Buisseret-Delmas, C., Guéritaud, J. F. & Horcholle-Bossavit, G. 1975*b* Primary mesencephalic projections of the rectus lateralis muscle afferents in cat: physiological and anatomical evidence. In *Basic mechanisms of ocular motility and their clinical implications* (ed. G. Lennerstrand & J. McLure), pp. 465–468. Oxford, UK: Pergamon.

Anastasio, T. J. & Correia, M. J. 1988 A frequency and time domain study of the horizontal and vertical vestibuloocular reflex in the pigeon. *J. Neurophysiol.* **59**, 1143–1161.

Andersen, R. A., Essick, G. K. & Siegel, R. M. 1985 Encoding of spatial location by posterior parietal neurons. *Science* **230**, 456–458.

Andersen, R. A., Snyder, L. H., Bradley, D. C. & Xing, J. 1997 Multimodal representation of space in the posterior parietal cortex and its use in planning movements. *A. Rev. Neurosci.* **20**, 303–330.

Ashton, J. A., Boddy, A. & Donaldson, I. M. L. 1983*a* Units in cat visual cortex with preferential responses to particular directions of passive eye movement. *J. Physiol.* **345**, 120P.

Ashton, J. A., Boddy, A. & Donaldson, I. M. L. 1983*b* Stabilization of gaze after body tilt requires an optokinetic signal in the giant toad. *J. Physiol.* **346**, 28P.

Ashton, J. A., Boddy, A. & Donaldson, I. M. L. 1983*c* Input from orbital proprioceptors to vestibular nuclear neurones in the giant toad, *Bufo marinus*. *J. Physiol.* **334**, 24P–25P.

Ashton, J. A., Boddy, A. & Donaldson, I. M. L. 1984*a* Input from proprioceptors in the extrinsic ocular muscles to the vestibular nuclei in the giant toad, *Bufo marinus*. *Exp. Brain Res.* **53**, 409–419.

Ashton, J. A., Boddy, A. & Donaldson, I. M. L. 1984*b* Directional selectivity in the responses of units in cat primary visual cortex to passive eye movement. *Neuroscience* **13**, 653–662.

Ashton, J. A., Boddy, A. & Donaldson, I. M. L. 1984*c* Interactions, in cat Area 17, between visual and orbital proprioceptive signals. *J. Physiol.* **348**, 19P.

Ashton, J. A., Boddy, A., Donaldson, I. M. L. & Milleret, C. 1985 Input from extraocular muscle afferents to the vestibular nuclear complex and the medullary reticular formation of the cat. *J. Physiol.* **369**, 46P.

Ashton, J. A., Donaldson, I. M. L. & Milleret, C. 1986*a* Input from extraocular muscle afferents to oculomotor nuclei in the trout. *J. Physiol.* **382**, 74P.

Ashton, J. A., Donaldson, I. M. L. & Milleret, C. 1986*b* Afferent signals from the extraocular muscles reach the vestibular nuclei and cerebellum in the trout. *J. Physiol.* **376**, 56P.

Ashton, J. A., Boddy, A., Dean, S. R., Milleret, C. & Donaldson, I. M. L. 1988 Afferent signals from cat extraocular muscles in the medial vestibular nucleus, the nucleus praepositus hypoglossi and adjacent brainstem structures. *Neuroscience* **26**, 131–145.

Ashton, J. A., Milleret, C. & Donaldson, I. M. L. 1989 Effects of afferent signals from the extraocular muscles upon units in the cerebellum, vestibular nuclear complex and oculomotor nucleus of the trout. *Neuroscience* **31**, 529–541.

Bach-y-Rita, P. 1971 Neurophysiology of eye movements. In *The control of eye movements* (ed. P. Bach-y-Rita, C. C. Collins & J. E. Hyde), pp. 7–45. New York: Academic Press.

Bach-y-Rita, P. & Ito, F. 1966 Properties of stretch receptors in cat extraocular muscles. *J. Physiol.* **186**, 663–688.

Bach-y-Rita, P. & Murata, K. 1964 Extraocular proprioceptive responses in the VI nerve of the cat. *Q. J. Exp. Physiol.* **49**, 408–416.

Baker, R. & Berthoz, A. 1975 Is the praepositus hypoglossi nucleus the source of another vestibuloocular pathway? *Brain Res.* **86**, 121–127.

Baker, R., Precht, W. & Llinas, R. 1972 Mossy and climbing fiber projections of extraocular muscle afferents to the cerebellum. *Brain Res.* **38**, 440–445.

Bakker, D. A., Richmond, F. J. R., Abrahams, V. C. & Courville, J. 1985 Patterns of primary afferent termination in the external cuneate nucleus from cervical axial muscles in the cat. *J. Comp. Neurol.* **241**, 467–479.

Barbas, H. & Dubrovsky, B. 1981*a* Central and peripheral effects of tonic vibratory stimuli to dorsal neck and extraocular muscles in the cat. *Exp. Neurol.* **74**, 67–85.

Barbas, H. & Dubrovsky, B. 1981*b* Excitatory and inhibitory interactions of extraocular and dorsal neck muscle afferents in the cat frontal cortex. *Exp. Neurol.* **74**, 51–66.

Barmack, N. H. & Pettorossi, V. E. 1985 Effects of unilateral lesions of the flocculus on optokinetic and vestibuloocular reflexes of the rabbit. *J. Neurophysiol.* **53**, 481–496.

Bastian, H. C. 1880 *The brain as an organ of mind*. London: C. Kegan Paul.

Bastian, H. C. 1888 The 'muscular sense'; its nature and cortical localisation. *Brain* **10**, 1–137.

Batini, C. 1979*a* Properties of the receptors of the extraocular muscles. *Prog. Brain Res.* **50**, 301–314.

Batini, C. 1979*b* Extraocular muscle input to the cerebellar cortex. *Prog. Brain Res.* **50**, 315–324.

Batini, C. & Buisseret, P. 1972 Projections cérébelleuses et trajet périphérique de la proprioception extra-oculaire. *C. R. Acad. Sci. Paris* D **275**, 2711–2713.

Batini, C. & Horcholle-Bossavit, G. 1977 Interaction entre activation visuelle et activation proprioceptive au niveau des neurones du colliculus supérieur. *C. R. Acad. Sci. Paris* D **285**, 1491–1493.

Batini, C. & Horcholle-Bossavit, G. 1979 Extraocular muscle afferents and visual input interactions in the superior colliculus of the cat. *Prog. Brain Res.* **50**, 335–344.

Batini, C., Buisseret, P. & Kado, R. T. 1974 Extraocular proprioceptive and trigeminal projections to the Purkinje cells of the cerebellar cortex. *Arch. Ital. Biol.* **112**, 1–17.

Batini, C., Buisseret, P. & Buisseret-Delmas, C. 1975 Trigeminal pathway of the extrinsic eye muscle afferents in cat. *Brain Res.* **85**, 74–78.

Batini, C., Buisseret-Delmas, C. & Kado, R. T. 1979 On the fibers of the III, IV and VI cranial nerves of the cat. *Arch. Ital. Biol.* **117**, 111–122.

Bell, C. C. 1981 An efference copy which is modified by reafferent input. *Science* **214**, 450–453.

Bell, C. C. 1982 Properties of a modifiable efference copy in an electric fish. *J. Neurophysiol.* **47**, 1043–1056.

Bell, C. C. 1986 Duration of plastic change in a modifiable efference copy. *Brain Res.* **369**, 29–36.

Bell, C. C. 1989 Sensory coding and corollary discharge effects in mormyrid electric fish. *J. Exp. Biol.* **146**, 229–253.

Berthoz, A. 1977 Role of the vestibular and reticular nuclei in the control of gaze. A. Vestibular nuclei. In *Control of gaze by brain stem neurons* (ed. R. Baker & A. Berthoz), pp. 279–289. Amsterdam: Elsevier and North-Holland Biomedical Press.

Berthoz, A., Yoshida, K. & Vidal, P. P. 1981 Horizontal eye movement signals in second order vestibular nuclei neurons in the cat. *Annls NY Acad. Sci.* **374**, 144–156.

Berthoz, A., Grantyn, A. & Olivier, E. 1992 The origin of horizontal gaze signals in neck muscles during orienting. In *Muscle afferents and the spinal control of movement* (ed. L. Jami, E. Pierrot-Deseilligny & D. Zytnicki), pp. 259–270. Oxford, UK: Pergamon.

Biguer, B., Donaldson, I. M. L., Hein, A. & Jeannerod, M. 1986 La vibration des muscles de la nuque modifie la position apparente d'une cible visuelle. *C. R. Acad. Sci. Paris* (*Série III*) **303**, 43–48.

Biguer, B., Donaldson, I. M. L., Hein, A. & Jeannerod, M. 1988 Neck muscle vibration modifies the representation of visual motion and direction in man. *Brain* **111**, 1405–1424.

Billig, J., Buisseret-Delmas, C. & Buisseret, P. 1997 Identification of nerve endings in cat extraocular muscles. *Anat. Rec.* **248**, 566–575.

Bloch, S., Martinoya, C. & Rivaud, S. 1981 Eye movements in pigeons: participation in binocular fixation and visual pursuit. *J. Physiol.* **320**, 20P–21P.

Bloch, S., Rivaud, S. & Martinoya, C. 1984 Comparing frontal and lateral viewing in the pigeon. III. Different patterns of eye movements for binocular and monocular fixation. *Behav. Brain Res.* **13**, 173–182.

Bloch, S., Lemeignan, M. & Martinoya, C. 1987 Coordinated vergence for frontal fixation, but independent eye movements for lateral viewing in the pigeon. In *Eye movements: from physiology to cognition* (ed. J. K. O'Regan & A. Levy-Schoen), pp. 47–57. Amsterdam: Elsevier Science.

Blumer, R., Lukas, J.-R., Wasicky, R. & Mayr, R. 1998 Presence and structure of innervated myotendinous cylinders in sheep extraocular muscle. *Neurosci. Lett.* **248**, 49–52.

Bock, O. & Kommerell, G. 1986 Visual localization after strabismus surgery is compatible with the 'outflow' theory. *Vision Res.* **26**, 1825–1829.

Bortolami, R., Lucchi, M. L., Pettorossi, V. E., Callegari, E. & Manni, E. 1987 Localization and somotopy of sensory cells innervating the extraocular muscles of lamb, pig and cat. Histochemical and electrophysiological investigation. *Arch. Ital. Biol.* **125**, 1–15.

Bortolami, R., Calzà, L., Lucchi, M. L., Giardino, L., Callegari, E., Manni, E., Pettorossi, V. E., Barazzoni, A. M. & Lalatta Costerbosa, G. 1991 Peripheral territory and neuropeptides of the trigeminal ganglion neurons centrally projecting through the oculomotor nerve demonstrated by fluorescent retrograde double-labeling combined with immunocytochemistry. *Brain Res.* **547**, 82–88.

Bridgeman, B. & Stark, L. 1991 Ocular proprioception and efference copy in registering visual direction. *Vision Res.* **31**, 1903–1913.

Brindley, G. S. & Merton, P. A. 1960 The absence of position sense in the human eye. *J. Physiol.* **153**, 127–130.

Brindley, G., Goodwin, G. M., Kulikowski, J. J. & Leighton, D. 1976 Stability of vision with a paralysed eye. *J. Physiol.* **258**, 65P–66P.

Browne, J. S. 1974 The response of de-efferented muscle spindles in sheep extraocular muscles to stretch and vibration. *J. Physiol.* **242**, 60P–62P.

Browne, J. S. 1975 The responses of muscle spindles in sheep extraocular muscles. *J. Physiol.* **251**, 483–496.

Buisseret, P. 1979 Does extraocular proprioception influence the development of visual processes and the oculomotor system? *Prog. Brain Res.* **50**, 346–352.

Buisseret, P. 1995 Influence of extraocular muscle proprioception on vision. *Physiol. Rev.* **75**, 323–338.

Buisseret, P. & Gary-Bobo, E. 1979 Development of visual cortical orientation specificity after dark-rearing: role of extraocular proprioception. *Neurosci. Lett.* **13**, 259–263.

Buisseret, P. & Gary-Bobo, E. 1981 L'orientation codée par un neurone visuel cortical dépend-elle de la direction des

mouvements oculaires as cours du développement? *J. Physiol. (Paris)* A **77**, 50–51.

Buisseret, P. & Maffei, L. 1977 Extraocular proprioceptive projections to the visual cortex. *Exp. Brain Res.* **28**, 421–425.

Buisseret, P., Gary-Bobo, E. & Milleret, C. 1983 Responses in cat pulvinar-lateralis posterior to stimulation of proprioceptive afferents from extraocular muscles. *J. Physiol.* **345**, 160P.

Buisseret, P., Gary-Bobo, E. & Milleret, C. 1988*a* Development of the kitten visual cortex depends on the relationship between the plane of eye movements and visual inputs. *Exp. Brain Res.* **72**, 83–94.

Buisseret, P., Gary-Bobo, E. & Milleret, C. 1988*b* Visuoproprioceptive interactions in area 18 neurones of the anaesthetized cat. *J. Physiol.* **406**, 25P.

Buisseret-Delmas, C. & Buisseret, P. 1990 Central projections of extraocular muscle afferents in cat. *Neurosci. Lett.* **109**, 48–53.

Buisseret-Delmas, C., Epelbaum, M. & Buisseret, P. 1990 The vestibular nuclei of the cat receive a primary afferent projection from receptors in extraocular muscles. *Exp. Brain Res.* **81**, 654–658.

Buisseret-Delmas, C., Pinganaud, G., Compoint, C. & Buisseret, P. 1997 Projection from trigeminal nuclei to neurons of mesencephalic trigeminal nucleus in rat. *Neurosci. Lett.* **229**, 189–192.

Buzzard, E. F. 1908 The occurrence of muscle spindles in human ocular muscles. *Proc. R. Soc. Med.* **1**, 83–87.

Campos, E. C., Chiesi, C. & Bolzani, R. 1986 Abnormal spatial localization in patients with herpes zoster ophthalmicus. *Arch. Ophthalmol.* **104**, 1176–1177.

Cannon, S. C. & Robinson, D. A. 1987 Loss of the neural integrator of the oculomotor system from brain stem lesions in monkey. *J. Neurophysiol.* **57**, 1383–1409.

Carpenter, R. H. S. 1972 Cerebellectomy and the transfer-function of the vestibulo-ocular reflex in the decerebrate cat. *Proc. R. Soc. Lond.* B **181**, 353–374.

Carpenter, R. H. S. 1988 *Movements of the eyes*, 2nd edn. London: Pion.

Cilimbaris, P. A. 1910 Histologische Untersuchungen über die Muskelspindeln der Augenmuskeln. *Arch. Mikr. Anat.* **75**, 692–747.

Cohen, I. B. 1958 *Sir Isaac Newton's papers and letters on natural philosophy.* Cambridge University Press.

Cooper, S. 1961 The responses of the primary and secondary endings of muscle spindles with intact motor innervation during applied stretch. *Q. J. Exp. Physiol.* **46**, 389–398.

Cooper, S. & Daniel, P. M. 1949 Muscle spindles in human extrinsic eye muscles. *Brain* **72**, 1–24.

Cooper, S. & Daniel, P. M. 1957 Responses from the stretch receptors of the goat's extrinsic eye muscles with an intact motor innervation. *Q. J. Exp. Physiol.* **42**, 222–231.

Cooper, S. & Fillenz, M. 1955 Afferent discharges in response to stretch from the extraocular muscles of the cat and monkey and the innervation of these muscles. *J. Physiol.* **127**, 400–413.

Cooper, S., Daniel, P. M. & Whitteridge, D. 1951 Afferent impulses in the oculomotor nerve, from the extrinsic eye muscles. *J. Physiol.* **113**, 463–474.

Cooper, S., Daniel, P. M. & Whitteridge, D. 1953*a* Nerve impulses in the brainstem of the goat. Responses with long latencies obtained by stretching the extrinsic eye muscles. *J. Physiol.* **120**, 491–513.

Cooper, S., Daniel, P. M. & Whitteridge, D. 1953*b* Nerve impulses in the brainstem of the goat. Short latency responses obtained by stretching the extrinsic eye muscles and the jaw muscles. *J. Physiol.* **120**, 471–490.

Cooper, S., Daniel, P. M. & Whitteridge, D. 1955 Muscle spindles and other sensory endings in the extrinsic eye muscles: the physiology and anatomy of these receptors and of their connexions with the brain-stem. *Brain* **78**, 564–583.

Coppin, C. M. L. & Jack, J. J. B. 1972 Internodal length and conduction velocity of cat muscle afferent nerve fibres. *J. Physiol.* **222**, 91P–93P.

Corbin, K. B. & Harrison, F. 1940 Function of mesencephalic root of fifth cranial nerve. *J. Neurophysiol.* **3**, 423–435.

Cornford, F. M. 1908 *Microcosmographia academica* (tenth impression, 1978). Cambridge, UK: Bowes & Bowes.

Corsi, M., Sodi, A., Salvi, G. & Faussone-Pelligrini, M. S. 1990 Morphological study of extraocular muscle proprioceptor alterations in congenital strabismus. *Ophthalmologica* **200**, 154–163.

Daunicht, W. 1983 Proprioception in extraocular muscles of the rat. *Brain Res.* **278**, 291–294.

Daunicht, W., Jaworski, E. & Eckmiller, R. 1985 Afferent innervation of extraocular muscles in the rat studied by retrograde and anterograde horseradish peroxidase transport. *Neurosci. Lett.* **56**, 143–148.

Demer, J. L., Oh, S. Y. & Poukens, V. 2000 Evidence for active control of rectus extraocular muscle pulleys. *Invest. Ophthalmol. Vis. Sci.* **41**, 1280–1290.

Dengis, C. A., Steinbach, M. J. & Kraft, S. P. 1998 Registered eye position: short- and long-term effects of botulinum toxin injected into eye muscle. *Exp. Brain Res.* **119**, 475–482.

Descartes, R. 1664 *L'homme de René Descartes: Et un traitté De la formation du foetus du mesme auteur: Avec les remarques de Louis de La Forge, docteur en médecine, demeurant à La Flèche, sur le traitté De l'homme de René Descartes et sur les figures par luy inventées* (ed. C. Clerselier). Paris: Charles Angot.

Dieringer, N. & Precht, W. 1982 Dynamics of compensatory vestibular reflexes in the grassfrog, *Rana temporia*. In *Physiological and pathological aspects of eye movements* (ed. A. Roucoux & M. Crommelinck), pp. 417–423. The Hague, The Netherlands: Dr W. Junk Publishers.

Dixon, R. & Donaldson, I. M. L. 1979 Unit responses to stretch of extrinsic ocular muscles in the lateral geniculate and perigeniculate nuclei of the cat. *J. Physiol.* **292**, 28P.

Dogiel, A. S. 1906 Die Endigungen der sensiblen Nerven in den Augenmuskeln und deren Sehnen beim Menschen und den Säugetieren. *Arch. Mikrosk. Anat.* **68**, 501–526.

Donaldson, I. M. L. 1979 Responses in cat suprasylvian cortex (Clare Bishop Area) to stretch of extraocular muscles. *J. Physiol.* **296**, 60P–61P.

Donaldson, I. M. L. 1986 The vestibulo-ocular system receives proprioceptive signals from the extraocular muscles. In *International workshop on proprioception of the ocular muscles* (ed. O. Tamura & J. Tsutsui), pp. 53–62. Hakone-Matsuyama, Japan: Ehime University Press.

Donaldson, I. M. L. & Dixon, R. A. 1980 Excitation of units in the lateral geniculate and contiguous nuclei of the cat by stretch of extrinsic ocular muscles. *Exp. Brain Res.* **38**, 245–255.

Donaldson, I. M. L. & Hawthorne, M. E. 1979 Coding of visual information by units in the cat cerebellar vermis. *Exp. Brain Res.* **34**, 27–48.

Donaldson, I. M. L. & Knox, P. C. 1988 Units in pigeon brainstem whose vestibular responses are modulated by passive eye movement. *J. Physiol.* **398**, 35P.

Donaldson, I. M. L. & Knox, P. C. 1989 Interaction between the effects of vestibular stimuli and those of passive eye movements on units in the brain stem of the pigeon. *J. Physiol.* **420**, 5P.

Donaldson, I. M. L. & Knox, P. C. 1990*a* Directionally-specific effects of afferent signals from the extraocular muscles upon responses in the pigeon brainstem to horizontal vestibular stimulation. *Neuroscience* **38**, 145–151.

Donaldson, I. M. L. & Knox, P. C. 1990*b* Afferent signals from the extraocular muscles affect vestibular responses in oculomotor nuclei of the pigeon. *J. Physiol.* **420**, 106P.

Donaldson, I. M. L. & Knox, P. C. 1991 Afferent signals from pigeon extraocular muscles modify the vestibular responses of units in the abducens nucleus. *Proc. R. Soc. Lond.* B **244**, 233–239.

Donaldson, I. M. L. & Knox, P. C. 1993 Evidence for corrective effects of afferent signals from the extraocular muscles on single units in the pigeon vestibulo-ocular system. *Exp. Brain Res.* **95**, 240–250.

Donaldson, I. M. L. & Knox, P. C. 2000 Afferent signals from the extraocular muscles affect the gain of the horizontal vestibulo-ocular reflex in the alert pigeon. *Vision Res.* **40**, 1001–1011.

Donaldson, I. M. L. & Long, A. C. 1977 Suppression of visual responses in the cat superior colliculus following stretch of extraocular muscles. *J. Physiol.* **272**, 94P–95P.

Donaldson, I. M. L. & Long, A. C. 1980 Interactions between extraocular proprioceptive and visual signals in the superior colliculus of the cat. *J. Physiol.* **298**, 85–110.

Donaldson, I. M. L. & Nash, J. R. G. 1975 Variability of the relative preference for stimulus orientation and direction of movement in some units of the cat visual cortex (areas 17 and 18). *J. Physiol.* **245**, 305–324.

Donaldson, I. M. L., Long, A. C. & Tasker, T. C. G. 1978 Suppression by nitrous oxide of visual responses in the cerebellar vermis and superior colliculus of cats anaesthetized with chloralose. *Brain Res.* **148**, 526–529.

du Lac, S., Raymond, J. L., Sejnowski, T. J. & Lisberger, S. G. 1995 Learning and memory in the vestibulo-ocular reflex. *A. Rev. Neurosci.* **18**, 409–441.

Easton, T. A. 1971 Patterned inhibition from horizontal eye movement in cat. *Exp. Neurol.* **31**, 419–430.

Eccles, J. C. & Sherrington, C. S. 1930 Numbers and contraction values of individual motor units examined in some muscles of the limb. *Proc. R. Soc. Lond.* B **106**, 326–357.

Eden, A. R., Correia, M. J. & Steinkuller, P. G. 1982 Medullary proprioceptive neurons from extraocular muscles in the pigeon identified with horseradish peroxidase. *Brain Res.* **217**, 15–21.

Edney, D. P. & Porter, J. D. 1986 Neck muscle afferent projections to the brainstem of the monkey: implications for the neural control of gaze. *J. Comp. Neurol.* **250**, 389–398.

Eldred, E., Granit, R. & Merton, P. A. 1953 Supraspinal control of the muscle spindles and its significance. *J. Physiol.* **122**, 498–523.

Engelage, J. & Bischof, H.-J. 1993 The organization of the tectofugal pathway in birds: a comparative review. In *Vision, brain and behavior in birds* (ed. H. P. Zeigler & H.-J. Bischof), pp. 137–158. Cambridge, MA: MIT Press.

Enomoto, H., Matsumara, M. & Tsutsui, J. 1983 Projections of extraocular muscle afferents to the visual cortex of the cat. *Neuro-Ophthalmol.* **3**, 49–57.

Fahy, F. L. & Donaldson, I. M. L. 1996 Extraocular muscle proprioception and the vestibulo-ocular reflex (VOR) in the pigeon. *J. Physiol.* **495**, 149P.

Fahy, F. L. & Donaldson, I. M. L. 1998 Signals of eye position and velocity in the first-order afferents from pigeon extraocular muscles. *Vision Res.* **38**, 1705–1804.

Fender, D. H. & Nye, P. W. 1961 An investigation of the mechanisms of eye movement control. *Kybernetik* **1**, 81–88.

Ferrier, D. 1886 *The functions of the brain*, 2nd edn. London: Smith, Elder & Co.

Fillenz, M. 1955 Responses in the brainstem of the cat to stretch of extrinsic ocular muscles. *J. Physiol.* **128**, 182–199.

Fiorentini, A. & Maffei, L. 1977 Instability of the eye in the dark and proprioception. *Nature* **269**, 330–331.

Fiorentini, A., Maffei, L. & Berardi, N. 1982 Role of extraocular proprioception in the orienting behaviour of cats. *Exp. Brain Res.* **48**, 113–120.

Fiorentini, A., Maffei, L., Cenni, M. C. & Tacchi, A. 1985 Deafferentation of oculomotor proprioception affects discrimination in adult cats. *Exp. Brain Res.* **59**, 296–301.

Fiorentini, A., Cenni, M. C. & Maffei, L. 1986 Impairment of stereoacuity in cats with oculomotor proprioceptive deafferentation. *Exp. Brain Res.* **63**, 364–368.

Forrester, J. M. 1975 Rolling movements of the sheep's eye. *J. Physiol.* **244**, 72P–73P.

Frost, B. J., Wylie, D. R. & Wang, Y. C. 1994 The analysis of motion in the visual system of birds. In *Perception and motor control in birds* (ed. M. N. O. Davies & P. R. Green), pp. 248–269. Berlin/Heidelberg, Germany: Springer.

Fuchs, A. F. & Kornhuber, H. H. 1969 Extraocular muscle afferents to the cerebellum of the cat. *J. Physiol.* **200**, 713–722.

Gandevia, S. C. 1996 Kinesthesia: roles for afferent signals and motor commands. In *Handbook of physiology. XII. Exercise: regulation and integration of multiple systems* (ed. L. B. Rowell & J. T. Shepherd), pp. 128–172. New York: Oxford University Press for the American Physiological Society.

Gauthier, G. M. & Vercher, J.-L. 1992 Ocular muscle proprioception and ocular motor control. In *Muscle afferents and spinal control of movement* (ed. L. Jami, E. Pierrot-Deseilligny & D. Zytnicki), pp. 277–285. Oxford, UK: Pergamon.

Gauthier, G. M., Berard, P. V., Deransard, J., Semmlow, J. L. & Vercher, J.-L. 1986 Adaptation processes resulting from surgical correction of strabismus. In *Adaptive processes in visual and oculomotor systems* (ed. E. L. Keller & D. S. Zee), pp. 185–189. Oxford, UK: Pergamon.

Gauthier, G. M., Berard, P. V., Deransard, J., Semmlow, J. L. & Vercher, J.-L. 1987 Adaptive phenomena resulting from surgical correction of strabismus. In *Eye movements from physiology to cognition* (ed. J. K. O'Regan & A. Levy-Schoen), pp. 219–226. Amsterdam: Elsevier Science.

Gauthier, G. M., Nommay, D. & Vercher, J.-L. 1990*a* Ocular muscle proprioception and visual localization of targets in man. *Brain* **113**, 1857–1871.

Gauthier, G. M., Nommay, D. & Vercher, J.-L. 1990*b* The role of ocular muscle proprioception in visual localization of targets. *Science* **249**, 58–61.

Gauthier, G. M., Vercher, J.-L. & Zee, D. S. 1994 Changes in ocular alignment and pointing accuracy after sustained passive rotation of one eye. *Vision Res.* **34**, 2613–2627.

Gauthier, G. M., de'Sperati, C., Tempia, F., Marchetti, E. & Strata, P. 1995*a* Influence of eye motion on adaptive modifications of the vestibuloocular reflex in the rat. *Exp. Brain Res.* **103**, 393–401.

Gauthier, G. M., Vercher, J.-L. & Blouin, J. 1995*b* Egocentric visual target position and velocity coding: role of ocular muscle proprioception. *Annls Biomed. Eng.* **23**, 423–433.

Gernandt, B. E. 1968 Interactions between extraocular myotactic and ascending vestibular activities. *Exp. Neurol.* **20**, 120–134.

Gioanni, H. 1988*a* Stabilizing gaze reflexes in the pigeon (*Columba livia*). II. Vestibulo-ocular (VOR) and vestibulo-collic (closed loop VCR) reflexes. *Exp. Brain Res.* **69**, 583–593.

Gioanni, H. 1988*b* Stabilizing gaze reflexes in the pigeon (*Columba livia*). I. Horizontal and vertical optokinetic eye (OKN) and head (OCR) reflexes. *Exp. Brain Res.* **69**, 567–582.

Gjertsen, D. 1986 *The Newton handbook*. London: Routledge & Kegan Paul.

Grüsser, O.-J. 1994 Early concepts on efference copy and reafference. *Behav. Brain Sci.* **17**, 262–265.

Grüsser, O.-J. & Grüsser-Cornehls, U. 1978 Neurophysiology of the anuran visual system. In *Frog neurobiology* (ed. R. Llinas & W. Precht), pp. 297–385. Berlin, Germany: Springer.

Guido, W., Salinger, W. L. & Schroeder, C. E. 1988 Binocular interactions in the dorsal lateral geniculate nucleus of monocularly paralyzed cats: extraretinal and retinal influences. *Exp. Brain Res.* **70**, 417–428.

Guthrie, B. L., Porter, J. D. & Sparks, D. L. 1982 Role of extraocular muscle proprioception in eye movements studied by chronic deafferentation of intra-orbital structures. *Soc. Neurosci. Abstr.* **8**, 156.

Guthrie, B. L., Porter, J. D. & Sparks, D. L. 1983 Corollary discharge provides accurate eye position information to the oculomotor system. *Science* **221**, 1193–1195.

Hall, T. S. 1972 *Treatise of man* (René Descartes). Cambridge, MA: Harvard University Press. [French text with translation and commentary.]

Hamdi, F. A. & Whitteridge, D. 1954 The representation of the retina on the optic tectum of the pigeon. *Q. J. Exp. Physiol.* **39**, 111–119.

Harris, L. R., Goltz, H. C. & Steinbach, M. J. 1993 The effect of gravity on the resting position of the cat's eye. *Exp. Brain Res.* **96**, 107–116.

Hawthorne, M. E. 1977 *Quantitative analysis of visual responses of units in the cerebellar vermis.* MSc thesis, University of Oxford, UK.

Hayman, M. R. 1994 *Anatomical and physiological evidence for the role of extraocular muscle proprioception in the control of gaze.* PhD thesis, University of Edinburgh, UK.

Hayman, M. R. & Donaldson, I. M. L. 1995 Deafferentation of pigeon extraocular muscles disrupts eye movements. *Proc. R. Soc. Lond.* B **261**, 105–110.

Hayman, M. R. & Donaldson, I. M. L. 1997 Changes in dorsal neck muscle activity related to imposed eye movement in the decerebrate pigeon. *Neuroscience* **79**, 943–956.

Hayman, M. R., Dutia, M. B. & Donaldson, I. M. L. 1993 Afferent signals from pigeon extraocular muscles modify the activity of neck muscles during the vestibulocollic reflex. *Proc. R. Soc. Lond.* B **254**, 115–122.

Hayman, M. R., Donaldson, J. P. & Donaldson, I. M. L. 1995 The primary afferent pathway of extraocular muscle proprioception in the pigeon. *Neuroscience* **69**, 671–683.

Hein, A. & Diamond, R. 1983 Contribution of eye movement to the representation of space. In *Spatially oriented behavior* (ed. A. Hein & M. Jeannerod), pp. 119–133. New York: Springer.

Held, R. & Hein, A. 1963 Movement-produced stimulation in the development of visually guided behaviour. *J. Comp. Physiol. Psychol.* **56**, 872–876.

Henderson, T. 1950 *Principles of ophthalmology.* London: William Heinemann.

Henneman, E. 1974 Peripheral mechanisms involved in the control of muscle. In *Medical physiology*, 13th edn, vol. 1 (ed. V. B. Mountcastle), pp. 617–635. St Louis, MO: C. V. Mosby Co.

Henry, G. H., Bishop, P. O., Tupper, R. H. & Dreher, B. 1973 Orientation specificity and response variability of cells in the striate cortex. *Vision Res.* **13**, 1771–1779.

Hodos, W., Bessette, B. B., Macko, K. A. & Weiss, S. R. B. 1985 Normative data for pigeon vision. *Vision Res.* **25**, 1525–1527.

Huber, G. C. 1900 Sensory nerve terminations in the tendons of the extrinsic eye-muscles of the cat. *J. Comp. Neurol.* **10**, 152–158.

Hughes, A. 1972 Vergence in the cat. *Vision Res.* **12**, 1961–1994.

Hunt, C. C. & Kuffler, S. W. 1951 Further study of efferent small nerve fibres to mammalian muscle spindles. Muscle spindle innervation and activity during contraction. *J. Physiol.* **113**, 283–297.

Hursh, J. B. 1939 Conduction velocity and diameter of nerve fibers. *Am. J. Physiol.* **127**, 131–139.

Ilg, U. J., Bridgeman, B. & Hoffman, K. P. 1989 Influence of mechanical disturbance on oculomotor behavior. *Vision Res.* **29**, 545–551.

Ito, F. & Bach-y-Rita, P. 1969 Afferent discharges from extraocular muscle in the squirrel monkey. *Am. J. Physiol.* **217**, 332–335.

Jackson, J. H. & Paton, L. 1909 On some abnormalities of ocular movements. *Lancet* **1**, 900–905.

James, W. 1890 *The principles of psychology.* London: Macmillan.

Jami, L. 1992 Golgi tendon organs in mammalian skeletal muscle: functional properties and central actions. *Physiol. Rev.* **72**, 623–666.

Jeannerod, M. 1988 Directional coding of reaching. In *The neural and behavioural organization of goal-directed movements*, pp. 132–170. Oxford, UK: Clarendon Press.

Jeannerod, M., Kennedy, H. & Magnin, M. 1979 Corollary discharge: its possible implications in visual and oculomotor interactions. *Neuropsychologia* **17**, 241–258.

Kashii, S., Matsui, Y., Honda, Y., Ito, J., Sasa, M. & Takaori, S. 1989 The role of extraocular proprioception in vestibulo-ocular reflex of rabbits. *Invest. Ophthalmol. Vis. Sc.* **30**, 2258–2264.

Keller, E. L. 1989 The cerebellum. In *The neurobiology of saccadic eye movements* (ed. R. H. Wurtz & M. E. Goldberg). *III. Reviews of oculomotor research* (series ed. D. A. Robinson & H. Collewijn), pp. 391–411. Amsterdam: Elsevier Science.

Keller, E. L. & Robinson, D. A. 1971 Absence of a stretch reflex in extraocular muscles of the monkey. *J. Neurophysiol.* **34**, 908–919.

Kennedy, H. & Baleydier, C. 1977 Direct projections from thalamic intralaminar nuclei to extra-striate visual cortex in the cat traced with horseradish peroxidase. *Exp. Brain Res.* **28**, 133–139.

Kennedy, H. & Magnin, M. 1977 Saccadic influences on single neuron activity in the medial bank of the cat's suprasylvian sulcus (Clare Bishop Area). *Exp. Brain Res.* **27**, 315–317.

Kettner, R. E., Mahamud, S., Leung, H. C., Sitkoff, N., Houk, J. C., Peterson, B. W. & Barto, A. G. 1997 Prediction of complex two-dimensional trajectories by a cerebellar model of smooth pursuit eye movement. *J. Neurophysiol.* **77**, 2115–2130.

Kimura, M. & Maekawa, K. 1981 Activity of flocculus Purkinje cells during passive eye movements. *J. Neurophysiol.* **46**, 1004–1017.

Kimura, M., Takeda, T. & Maekawa, K. 1981 Functional role of extraocular muscle afferents in the control of eye movements in rabbits. *J. Physiol. Soc. Jap.* **43**, 317.

Kimura, M., Takeda, T. & Maekawa, K. 1991 Contribution of eye muscle proprioception to velocity-response characteristics of eye movements: involvement of the cerebellar flocculus. *Neurosci. Res.* **12**, 160–168.

Knox, P. C. & Donaldson, I. M. L. 1991*a* Afferent signals from the extraocular muscles of the pigeon modify the electromyogram of these muscles during the vestibulo-ocular reflex. *Proc. R. Soc. Lond.* B **246**, 243–250.

Knox, P. C. & Donaldson, I. M. L. 1991*b* Effects of extraocular muscle afferent signals on units in pigeon brainstem during an artificial vestibulo-ocular reflex. *J. Physiol.* **438**, 163P.

Knox, P. C. & Donaldson, I. M. L. 1993*a* Afferent signals from the extraocular muscles of the pigeon modify the vestibulo-ocular reflex. *Proc. R. Soc. Lond.* B **253**, 77–82.

Knox, P. C. & Donaldson, I. M. L. 1993*b* Do extraocular muscle afferent signals play a part in the human vestibulo-ocular reflex? *Soc. Neurosci. Abstr.* **19**, 858.

Knox, P. C. & Donaldson, I. M. L. 1995*a* The effect of afferent signals from extraocular muscles on visual responses of cells in the optic tectum of the pigeon. *Proc. R. Soc. Lond.* B **259**, 285–291.

Knox, P. C. & Donaldson, I. M. L. 1995*b* Modification of vestibulo-ocular reflex gain by extraocular muscle afferent signals. *Jpn. J. Physiol.* **45**, S330–S331.

Knox, P. C. & Whalley, H. C. 1996 The effect of eye position on the visual responses of single units in the pigeon optic tectum. *Soc. Neurosci. Abstr.* **22**, 663.

Knox, P. C. & Whalley, H. C. 1997 The directional effects of passive eye movement on the directional visual responses of

single units in the pigeon optic tectum. *Exp. Brain Res.* **116**, 510–518.

Knox, P. C., Murphy, P. J. & Weir, C. 1998 Impeding the movement of one eye modifies the saccadic amplitudes of the other eye. *Soc. Neurosci. Abstr.* **24**, 1742.

Knox, P. C., Weir, C. R. & Murphy, P. J. 2000 Modification of visually guided saccades by a non-visual afferent feedback signal. *Invest. Ophthalmol. Vis. Sci.* **41**, 2561–2565.

Koyré, A. 1965 *Newtonian studies.* London: Chapman & Hall.

Kuffler, S. W., Hunt, C. C. & Quilliam, J. P. 1951 Function of medullated small nerve fibres in mammalian ventral roots: efferent muscle spindle innervation. *J. Neurophysiol.* **14**, 29–54.

Lal, R. & Friedlander, M. J. 1990*a* Effect of passive eye movement on retinogeniculate transmission in the cat. *J. Neurophysiol.* **63**, 523–538.

Lal, R. & Friedlander, M. J. 1990*b* Effect of passive eye position changes on retinogeniculate transmission in the cat. *J. Neurophysiol.* **63**, 502–522.

Larsell, O. 1953 The cerebellum of the cat and the monkey. *J. Comp. Neurol.* **99**, 135–199.

Leksell, L. 1945 The action potentials and excitatory effects of the small ventral roots to skeletal muscle. *Acta Physiol. Scand.* **10**(Suppl. 31), 1–84.

Lemeignan, M., Sansonetti, A. & Gioanni, H. 1992 Spontaneous saccades under different visual conditions in the pigeon. *NeuroReport* **3**, 17–20.

Lennerstrand, G. & Bach-y-Rita, P. 1974 Spindle responses in pig eye muscles. *Acta Physiol. Scand.* **90**, 795–797.

Lennerstrand, G., Tian, S. & Han, Y. 1997 Effects of eye muscle proprioceptive activation on eye position in normal and exotropic subjects. *Graefe's Arch. Clin. Exp. Ophthalmol.* **235**, 63–69.

Lewald, J. & Ehrenstein, W. H. 2000 Visual and proprioceptive shifts in perceived egocentric direction induced by eye-position. *Vision Res.* **40**, 539–547.

Lewis, R. F. & Zee, D. S. 1992 The role of ocular proprioception in disconjugate ocular motor adaptation. *Soc. Neurosci. Abstr.* **18**, 215.

Lewis, R. F. & Zee, D. S. 1993 Abnormal spatial localization with trigeminal-oculomotor synkinesis. *Brain* **116**, 1105–1118.

Lewis, R. F., Zee, D. S., Gaymard, B. M. & Guthrie, B. L. 1994 Extraocular muscle proprioception functions in the control of ocular alignment and eye movement conjugacy. *J. Neurophysiol.* **72**, 1028–1031.

Lewis, R. F., Zee, D. S., Goldstein, H. P. & Guthrie, B. L. 1999 Proprioceptive and retinal afference modify postsaccadic ocular drift. *J. Neurophysiol.* **82**, 551–653.

Li, W. & Matin, L. 1992 Visual direction is corrected by a hybrid extraretinal eye position signal. *Annls NY Acad. Sci.* **656**, 865–867.

Li, W. & Matin, L. 1998 Change in visually perceived eye level without change in perceived pitch. *Perception* **27**, 553–572.

Lopez-Barneo, J., Darlot, C., Berthoz, A. & Baker, R. 1982 Neuronal activity in prepositus nucleus correlated with eye movement in the alert cat. *J. Neurophysiol.* **47**, 329–352.

Ludvigh, E. 1952*a* Control of ocular movements and visual interpretation of environment. *Arch. Ophthalmol.* **48**, 442–448.

Ludvigh, E. 1952*b* Possible role of proprioception in the extraocular muscles. *Arch. Ophthalmol.* **48**, 436–441.

Lukas, J.-R., Aigner, M., Blumer, R., Heinzl, H. & Mayr, R. 1994 Number and distribution of neuromuscular spindles in human extraocular muscles. *Invest. Ophthalmol. Vis. Sci.* **35**, 4317–4327.

Lukas, J.-R., Blumer, R., Aigner, M., Denk, M. & Mayr, R. 1998 Effects of eye muscle proprioceptive activation: morphological particularities of human extraocular muscle spindles. *Graefe's Arch. Clin. Exp. Ophthalmol.* **236**, 238–239.

Lukas, J.-R., Blumer, R., Denk, M., Baumgartner, I., Neuhuber, W. & Mayr, R. 2000 Innervated myotendinous cylinders in human extraocular muscles. *Invest. Ophthalmol. Vis. Sci.* **41**, 2422–2431.

McCloskey, D. I. 1981 Corollary discharges: motor commands and perception. In *Handbook of physiology. II. Nervous system* (ed. V. B. Brooks), pp. 1415–1447. Baltimore, MD: Williams & Wilkins.

McCouch, G. P. & Adler, F. H. 1932 Extraocular reflexes. *Am. J. Physiol.* **100**, 78–88.

McCrea, R. A. & Baker, R. 1985 Anatomical connections of the nucleus prepositus of the cat. *J. Comp. Neurol.* **237**, 377–407.

Maekawa, K. & Kimura, M. 1979 Mossy fiber responses in cerebellar flocculus evoked from extraocular muscle stretches. *Neurosci. Lett.* (Suppl. 2), S32.

Maekawa, K. & Kimura, M. 1980 Mossy fiber projections to the cerebellar flocculus from the extraocular muscle afferents. *Brain Res.* **191**, 313–325.

Maekawa, K. & Kimura, M. 1986 Control of eye movements by proprioceptive afferents from extraocular muscles through the cerebellar flocculus. In *International workshop on proprioception of the ocular muscles* (ed. O. Tamura & J. Tsutsui), pp. 107–122. Hakone-Matsuyama, Japan: Ehime University Press.

Maffei, L. & Bisti, S. 1976 Binocular interaction in strabismic kittens deprived of vision. *Science* **191**, 579–580.

Maffei, L. & Fiorentini, A. 1976 Asymmetry of motility of the eyes and change of binocular properties of cortical cells in adult cats. *Brain Res.* **105**, 73–78.

Maffei, L. & Fiorentini, A. 1977 Oculomotor proprioception in the cat. In *Control of gaze by brain stem neurons* (ed. R. Baker & A. Berthoz), pp. 477–481. Amsterdam: Elsevier and North-Holland Biomedical Press.

Maier, A., DeSantis, M. & Eldred, E. 1971 Absence of muscle spindles in avian extraocular muscle. *Exp. Eye Res.* **12**, 251–253.

Maier, A., DeSantis, M. & Eldred, E. 1974 The occurrence of muscle spindles in extraocular muscles of various vertebrates. *J. Morph.* **143**, 397–408.

Manni, E. & Peterossi, V. E. 1976 Somatotopic localization of the eye muscle afferents in the semilunar ganglion. *Arch. Ital. Biol.* **114**, 178–187.

Manni, E., Bortolami, R. & Desole, C. 1966 Eye muscle proprioception and the semilunar ganglion. *Exp. Neurol.* **16**, 226–236.

Manni, E., Bagolini, B., Pettorossi, V. E. & Errico, P. 1989*a* Effect of botulinum toxin on extraocular muscle proprioception. *Documenta Ophthalmologica* **72**, 189–198.

Manni, E., Draicchio, F., Pettorossi, V. E., Carobi, C., Grassi, S., Bortolami, R. & Lucchi, M. L. 1989*b* On the nature of the afferent fibers of oculomotor nerve. *Arch. Ital. Biol.* **127**, 99–108.

Matin, L. 1976 A possible hybrid mechanism for modification of visual direction associated with eye movements—the paralysed-eye experiment reconsidered. *Perception* **5**, 233–239.

Matin, L. & Li, W. 1995 Multimodal basis for egocentric spatial localization and orientation. *J. Vestib. Res.* **5**, 499–518.

Matin, L., Stevens, J. K. & Picoult, E. 1983 Perceptual consequences of experimental extraocular muscle paralysis. In *Spatially oriented behavior* (ed. A. Hein & M. Jeannerod), pp. 243–262. New York: Springer.

Matthews, B. H. C. 1931*a* The response of a single end organ. *J. Physiol.* **71**, 64–110.

Matthews, B. H. C. 1931*b* The response of a muscle spindle during active contraction of a muscle. *J. Physiol.* **72**, 153–174.

Matthews, P. B. C. 1972 *Mammalian muscle receptors and their central actions.* London: Edward Arnold.

Matthews, P. B. C. 1982 Where does Sherrington's 'muscular sense' originate? Muscles, joints, corollary discharges? *A. Rev. Neurosci.* **5**, 189–218.

Matthews, P. B. C. 1988 Proprioceptors and their contribution to somatosensory mapping: complex messages require complex processing. *Can. J. Physiol. Pharmacol.* **66**, 430–438.

Matthews, P. B. C. & Simmonds, A. 1974 Sensations of finger movement elicited by pulling upon flexor tendons in man. *J. Physiol.* **239**, 27P.

Merton, P. A. 1964 Human position sense and sense of effort. *Symp. Soc. Exp. Biol.* **18**, 387–400.

Miller, J. M., Demer, J. L. & Rosenbaum, A. L. 1993 Effect of transposition surgery on rectus muscle paths by magnetic resonance imaging. *Ophthalmology* **100**, 475–487.

Milleret, C., Gary-Bobo, E. & Buisseret, P. 1987 Réponses des neurones du cortex visual (Aire 18) aux stimulations proprioceptives extraoculaires: évolution chez le chat normal ou élevé à l'obscurité et interactions avec l'activité visuelle. *C. R. Acad. Sci. Paris* (*Série III*) **305**, 531–536.

Mitsui, Y. 1986 *Strabismus and the sensorimotor reflex*. Tokyo: Excerpta Medica.

Miyashita, Y. 1984 Eye velocity responsiveness and its proprioceptive component in the floccular Purkinje cells of the alert pigmented rabbit. *Exp. Brain Res.* **55**, 81–90.

Moidell, B., Steinbach, M. J. & Ono, H. 1988 Egocenter location in children enucleated at an early age. *Invest. Ophthalmol. Vis. Sci.* **29**, 1348–1351.

Molotchnikoff, S. & Casanova, C. 1985 Reactions of the geniculate cells to extraocular proprioceptive activation in rabbits. *J. Neurosci. Res.* **14**, 105–115.

Montgomery, J. C. & Macdonald, J. A. 1980 Stretch receptors in the eye muscles of a teleost fish. *Experientia* **36**, 1176–1177.

Nagao, S. 1988 Behaviour of floccular Purkinje cells correlated with adaptation of horizontal optokinetic eye movement response in pigmented rabbits. *Exp. Brain Res.* **73**, 489–497.

Nagao, S. 1989 Behaviour of floccular Purkinje cells correlated with adaptation of vestibulo-ocular reflex in pigmented rabbits. *Exp. Brain Res.* **77**, 531–540.

Nelson, J. S., Meredith, M. A. & Stein, B. E. 1989 Does an extraocular proprioceptive signal reach the superior colliculus? *J. Neurophysiol.* **62**, 1360–1374.

Ogasawara, K., Onodera, S., Shiwa, T., Ninomiya, S. & Tazawa, Y. 1987 Projections of extraocular muscle primary afferent neurones to the trigeminal sensory complex in the cat as studied with the transganglionic transport of horseradish peroxidase. *Neurosci. Lett.* **73**, 242–246.

Optican, L. M. & Robinson, D. A. 1980 Cerebellar-dependent adaptive control of primate saccadic system. *J. Neurophysiol.* **44**, 1059–1076.

Optican, L. M., Zee, D. S. & Chu, F. C. 1985 Adaptive response to ocular muscle weakness in human pursuit and saccadic eye movements. *J. Neurophysiol.* **54**, 110–122.

Peterson, B. W., Bilotto, G., Goldberg, J. & Wilson, V. J. 1981 Dynamics of vestibulo-ocular, vestibulocollic and cervicocollic reflexes. *Annls NY Acad. Sci.* **374**, 395–402.

Porter, J. D. 1986 Brainstem terminations of extraocular muscle primary afferent neurons in the monkey. *J. Comp. Neurol.* **247**, 133–143.

Porter, J. D. & Donaldson, I. M. L. 1991 The anatomical substrate of cat extraocular muscle proprioception. *Neuroscience* **43**, 473–481.

Porter, J. D. & Spencer, R. F. 1982 Localization and morphology of cat extraocular muscle afferent neurones identified by retrograde transport of horseradish peroxidase. *J. Comp. Neurol.* **204**, 56–64.

Porter, J. D., Guthrie, B. L. & Sparks, D. L. 1983 Innervation of monkey extraocular muscles: localization of sensory and motor neurons by retrograde transport of horseradish peroxidase. *J. Comp. Neurol.* **218**, 208–219.

Porter, J. D., Baker, R. S., Ragusa, R. J. & Brueckner, J. K. 1995 Extraocular muscles: basic and clinical aspects of structure and function. *Surv. Ophthalmol.* **39**, 451–484.

Precht, W. 1978 *Neuronal operations in the vestibular system*. Berlin: Springer.

Proske, U., Wise, A. K. & Gregory, J. E. 2000 The role of muscle receptors in the detection of movements. *Prog. Neurobiol.* **60**, 85–96.

Quaia, C. & Optican, L. M. 1998 Commutative saccadic generator is sufficient to control a 3-D ocular plant with pulleys. *J. Neurophysiol.* **79**, 3197–3215.

Rahn, A. C. & Zuber, B. L. 1971 Cerebellar evoked potentials resulting from extraocular muscle stretch: evidence against a cerebellar origin. *Exp. Neurol.* **31**, 230–238.

Richmond, F. J. R. & Abrahams, V. C. 1975 Morphology and distribution of muscle spindles in dorsal muscles of the cat neck. *J. Neurophysiol.* **38**, 1322–1339.

Richmond, F. J. R., Johnston, W. S. W., Baker, R. S. & Steinbach, M. J. 1984 Palisade endings in human extraocular muscles. *Invest. Ophthalmol. Vis. Sci.* **25**, 471–476.

Rine, R. M. & Skavenski, A. A. 1997 Extraretinal eye position signals determine perceived target location when they conflict with visual cues. *Vision Res.* **37**, 775–787.

Robinson, D. A. 1991 Overview. In *Eye movements* (ed. R. H. S. Carpenter). *XIII. Vision and visual dysfunction* (series ed. J. R. Cronly-Dillon), pp. 320–331. London: Macmillan.

Roll, J. P. & Roll, R. 1987 Kinaesthetic and motor effects of extraocular muscle vibration in man. In *Eye movements: from physiology to cognition* (ed. J. K. O'Regan & A. Levy-Schoen), pp. 57–68. Amsterdam: Elsevier Science.

Roll, R., Velay, J. L. & Roll, J. P. 1991 Eye and neck proprioceptive messages contribute to the spatial coding of retinal input in visually oriented activities. *Exp. Brain Res.* **85**, 423–431.

Ron, S. & Berthoz, A. 1991 Eye and head coupled and dissociated movements during orientation to a double step visual target displacement. *Exp. Brain Res.* **85**, 196–207.

Ruskell, G. L. 1978 The fine structure of innervated myotendinous cylinders in extraocular muscles of rhesus monkeys. *J. Neurocytol.* **7**, 693–708.

Ruskell, G. L. 1984 Spiral nerve endings in human extraocular muscles terminate in motor end plates. *J. Anat.* **139**, 33–43.

Ruskell, G. L. 1989 The fine structure of human extraocular muscle spindles and their potential proprioceptive capacity. *J. Anat.* **167**, 199–214.

Ruskell, G. L. 1990 Golgi tendon organs in the proximal tendon of sheep extraocular muscles. *Anat. Rec.* **227**, 25–31.

Ruskell, G. L. 1999 Extraocular muscle proprioceptors and proprioception. *Prog. Ret. Eye Res.* **18**, 269–291.

Salvi, G., Frosni, R., Corsi, M. & Sodi, A. 1986 Examination by means of optic and electron microscopy of proprioceptive organs of the extraocular muscles. In *International workshop on proprioception of the ocular muscles* (ed. O. Tamura & J. Tsutsui), pp. 123–138. Hakone-Matsuyama, Japan: Ehime University Press.

Schlag, J., Lehtinen, I. & Schlag-Rey, M. 1973 Neuronal activity correlated with eye movements in 'nonspecific' thalamic nuclei. *Brain Res.* **62**, 268–272.

Schlag, J., Lehtinen, I. & Schlag-Rey, M. 1974 Neuronal activity before and during eye movements in thalamic internal medullary lamina of the cat. *J. Neurophysiol.* **37**, 982–995.

Schwartz, D. W. F. & Tomlinson, R. D. 1977 Neuronal responses to eye muscle stretch in cerebellar lobule VI of the cat. *Exp. Brain Res.* **27**, 101–111.

Sherrington, C. S. 1894 On the anatomical constitution of the nerves of muscles. *J. Physiol.* **17**, XIX–XX.

Sherrington, C. S. 1898 Further note on the sensory nerves of the eye muscles. *Proc. R. Soc. Lond.* B **64**, 120–121.

Sherrington, C. S. 1900 The muscular sense. In *Textbook of physiology*, vol. 2 (ed. E. A. Schäfer), pp. 1002–1025. Edinburgh, UK: Pentland.

Sherrington, C. S. 1918 Observations on the sensual role of the proprioceptive nerve-supply of the extrinsic ocular muscles. *Brain* **41**, 332–343.

Skavenski, A. A. 1971 Extraretinal correction and memory for target position. *Vision Res.* **11**, 743–745.

Skavenski, A. A. 1972 Inflow as a source of extraretinal eye position information. *Vision Res.* **12**, 221–229.

Skavenski, A. A. & Steinman, R. M. 1970 Control of eye position in the dark. *Vision Res.* **10**, 193–203.

Skavenski, A. A., Haddad, G. & Steinman, R. M. 1972 The extraretinal signal for the visual perception of direction. *Percept. Psychophys.* **11**, 287–290.

Spencer, R. F. & Porter, J. D. 1988 Structural organization of extraocular muscles. In *Neuroanatomy of the oculomotor system* (ed. J. A. Büttner-Ennever). *II. Reviews of oculomotor research* (series ed. D. A. Robinson & H. Collewijn), pp. 33–79. Amsterdam: Elsevier Science.

Sperry, R. W. 1950 Neural basis of the spontaneous optokinetic response produced by visual inversion. *J. Comp. Physiol. Psychol.* **43**, 482–489.

Steinbach, M. J. 1987 Proprioceptive knowledge of eye position. *Vision Res.* **27**, 1737–1744.

Steinbach, M. J. 1992 The need for eye muscle proprioception. In *Muscle afferents and the spinal control of movement* (ed. L. Jami, E. Pierrot-Deseilligny & D. Zytnicki), pp. 239–244. Oxford, UK: Pergamon.

Steinbach, M. J. 2000 The palisade ending: an afferent source for eye position information in humans. In *Advances in strabismus research: basic and clinical aspects* (ed. G. Lennerstrand & J. Ygge), pp. 33–42. London: Portland Press.

Steinbach, M. J. & Donaldson, I. M. L. 1997 Minimal effect of gravity on the paralysed anesthetized sheep's eye. *Invest. Ophthalmol. Vis. Sci.* **38**, S227.

Steinbach, M. J. & Lerman, J. 1990 Gravity affects resting eye position in humans. *Arch. Ophthalmol. Vis. Sci.* (Suppl. 31), 553.

Steinbach, M. J. & Smith, D. R. 1981 Spatial localization after strabismus surgery: evidence for inflow. *Science* **213**, 1407–1409.

Steinbach, M. J., Kirshner, E. L. & Arstikaitis, M. J. 1987 Recession vs. marginal myotomy surgery for strabismus: effects on spatial localization. *Invest. Ophthalmol. Vis. Sci.* **28**, 1870–1872.

Stevens, J. K., Emerson, R. C., Gerstein, G. L., Kallos, T., Neufeld, G. R., Nichols, C. W. & Rosenquist, A. C. 1976 Paralysis of the awake human: visual perceptions. *Vision Res.* **16**, 93–98.

Taylor, A. 1965 The role of sensory feedback in the vestibulo-ocular response in cats. *J. Physiol.* **179**, 76P–77P.

Tomlinson, R. D. & Schwarz, D. W. F. 1977 Response of oculomotor neurons to eye muscle stretch. *Can. J. Physiol. Pharmacol.* **55**, 568–573.

Toyama, K. & Kozasa, T. 1982 Responses of Clare-Bishop neurones to three dimensional movement of a light stimulus. *Vision Res.* **22**, 571–574.

Tozer, F. M. & Sherrington, C. S. 1910 Receptors and afferents of the third, fourth and sixth cranial nerves. *Proc. R. Soc. Lond.* B **82**, 450–457.

Trotter, Y., Maffei, L. & Buisseret, P. 1980 Effets de mouvements oculaires passifs sur l'activité des neurones visuels corticaux chez le chat. *J. Physiol.* (*Paris*) **76**, 62A.

Van Donkelaar, P., Gauthier, G. M., Blouin, J. & Vercher, J.-L. 1997 The role of ocular muscle proprioception during modifications in smooth pursuit output. *Vision Res.* **27**, 769–774.

Van Gisbergen, J. A. M. & Van Opstal, A. J. 1989 Models. In *The neurobiology of saccadic eye movements* (ed. R. W. Wurtz & M. Goldberg). *III. Reviews of oculomotor research* (series ed. D. A. Robinson & H. Collewijn), pp. 69–101. Amsterdam: Elsevier Science.

Velay, J. L., Roll, R., Lennerstrand, G. & Roll, J. P. 1994 Eye proprioception and visual localization in humans: influence of ocular dominance and visual context. *Vision Res.* **34**, 2169–2176.

Velay, J. L., Allin, F. & Bouquerel, A. 1997 Motor and perceptual responses to horizontal and vertical eye vibration in humans. *Vision Res.* **37**, 2631–2638.

Ventre-Dominey, J., Dominey, P. F. & Sindou, M. 1996 Extraocular proprioception is required for spatial localization in man. *NeuroReport* **7**, 1531–1535.

Von Helmholtz, H. 1867 *Handbuch der physiologischen Optik*. Leipzig, Germany: Voss.

Von Helmholtz, H. 1925 *Treatise on physiological optics*, vol. 3. Menasha, WI: The Optical Society of America. [Translation by J. P. C. Southall of third German edition.]

Von Holst, E. 1954 Relations between the central nervous system and the peripheral organs. *Brit. J. Anim. Behav.* **2**, 89–94.

Von Holst, E. & Mittelstaedt, H. 1950 Das Reafferenzprinzip (Wechselwirkungen zwischen Zentralnervensystem und Peripherie). *Naturwissenschaften* **37**, 464–476.

Von Sabussov, G. H., Maslow, A. P. & Burnaschewa, D. W. 1964 Vergleichend-morphologische und einige histochemische Beobachtungen an besonderen Rezeptoren der Augenmuskeln bei Wirbeltiern. *Anat. Anz.* **114**, S27–S37.

Whitteridge, D. 1955 A separate afferent nerve supply from the extra-ocular muscles of goats. *Q. J. Exp. Physiol.* **40**, 331–336.

Whitteridge, D. 1959 The effect of stimulation of intrafusal muscle fibres on sensitivity to stretch of extraocular muscle spindles. *Q. J. Exp. Physiol.* **44**, 385–393.

Whitteridge, D. 1962 Afferent mechanisms in the initiation and control of eye movement. *Proc. Int. Union Physiol. Sci.* 509–512.

Winckler, G. 1937 L'innervation sensitive et motrice des muscles extrinsèques de l'oeil chez quelques ongulés. *Arch. Anat. Strasbourg* **23**, 219–234.

Wolfe, J. W. 1971 Cerebellar evoked potentials related to extraocular muscle stretch. *Exp. Neurol.* **33**, 693–697.

Yamamoto, T., Morgan, D. L., Gregory, J. E. & Proske, U. 1994 Blockade of intrafusal neuromuscular junctions of cat muscle spindles with gallamine. *Exp. Physiol.* **79**, 365–376.

Zee, D. S., Yamazaki, A., Butler, P. H. & Gücer, G. 1981 Effects of ablation of flocculus and paraflocculus on eye movements in primate. *J. Neurophysiol.* **46**, 878–899.