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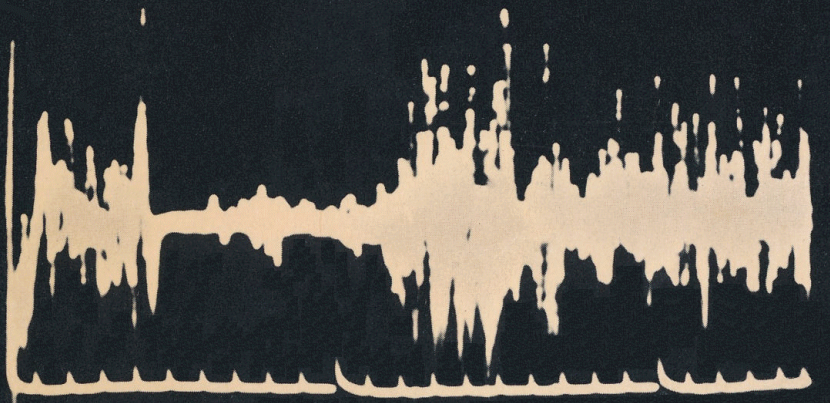

RECEPTORS AND SENSORY PERCEPTION

Based on the Silliman Lectures delivered at Yale University

RECEPTORS AND SENSORY PERCEPTION

A Discussion of Aims, Means, and Results of Electrophysiological Research into the Process of Reception

BY RAGNAR GRANIT

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Preface

THE title and with it the theme of these lectures was suggested by my friend and colleague John Fulton and tempted me immediately because I thought it might be of interest at this particular moment to comment on the achievements of a quarter century of work by electronic methods on the special senses. It was clear that there was no need for an annual-review type of book, or for one expanded to deal with the results text-book fashion. Again, a complete general physiology of the special senses, apart from the danger of being too pretentious for the present age, might easily turn out to be too general for the specialist, yet too special for the general scientific reader.

Thus I felt I had good excuse for following my natural inclination to go into detail only in the fields where I felt I had mastered the details, to extract general principles from them, and to look for applications in adjacent fields. It seemed to me also that what we as experimenters individually pay a price for is laboratory experience and that therefore my innumerable omissions might be more generously forgiven if, as a counterpoise, I inserted chapters based on first-hand knowledge acquired by experimentation. The sections on the eye, on the muscle receptors with their reflexes, and on centrifugal control of sense organs serve this purpose.

My major omissions concern audition, which as a subject of electrophysiological research has been so beautifully developed by several workers in the United States. I try to follow the work on the ear but am not expert enough in the field to include a separate chapter on it.

Now, why is this an appropriate moment for commenting on the aims, means, and results of research by electrical methods on various aspects of perception? Clearly, the main reason is that we have actually arrived at principles which ought to be formulated and held to a mirror in order to prevent them from becoming immersed in the steady stream of annual contributions from many different points of view. Such principles concern, among others, "receptive fields," "generator potentials," "centrifugal control," "specific and unspecific afferents," and "organization of the frequency code." These and many others will be dealt with below.

Much as I speak about results obtained by electrical methods, my

secret plea between the lines—I emphasize it now—is really for this kind of work *combined* with adequate stimulation of sense organs. I see no other way to a real understanding of the principles of organization of the central nervous system. This, in a different way, was emphasized very long ago by John Locke (see below, introductory quotation). The brain, after all, is the great interpreter of the senses.

While preparing these lectures I occasionally felt some apprehension that the time required was being spent less profitably than for laboratory work. I then derived some solace from the thought that the generation of postgraduate students about to enter this field may find the book useful as an introduction to the principles involved. At other times, in other moods, I have greatly enjoyed both the excuse for writing and the writing itself, feeling stimulated by the hope of, perhaps, gathering something of what, with Walter B. Cannon, one might refer to as the "durable results of the perishable years."

In the preparation of the manuscript my secretary, Gunvor Larsson, has given freely of her spare hours in order to make it possible to finish the book in time for the lectures. Evi Reigo and Anne-Marie Bengtson took charge of the illustrations and legends. At Yale John F. Fulton and Mary P. Wheeler devoted a great deal of unselfish care and labor to the perusal of the manuscript, suggesting improvements and corrections. The book and its author owe a great deal to these collaborators.

Several members of the staff of the Nobel Institute for Neurophysiology, as well as guest workers, have read parts of the manuscript and made valuable suggestions. Friends in Stockholm, London, and Cambridge have read sections of the book and given me the benefit of their criticism. Many more in different parts of the world have liberally lent me originals of illustrations from their papers and given me access to data in the course of publication. Though no one is specifically mentioned, none is forgotten, and I thank them all.

It is seldom that one has an opportunity of expressing one's gratitude to the foundations which have supported the Nobel Institute and made its work possible. This seems such an occasion, and I therefore wish to put on record my great indebtedness to the Knut och Alice Wallenbergs Stiftelse, the Royal Caroline Institute, the Nobel Foundation, the Rockefeller Foundation, and the Swedish Medical Research Council. Originally my Institute was set up in 1940 by a generous combined gift from the Wallenberg and the Rockefeller Foundations.

Finally, to the officers of Yale University and the members of the Silliman Committee I wish to convey my sincere thanks for the invitation to deliver the Silliman Lectures. The great care taken by the Yale University Press in publishing this book is gratefully acknowledged.

Contents

If it shall be demanded, then, when a man begins to have any ideas? I think, the true answer is, When he first has any sensation. For since there appear not to be any ideas in the mind before the senses have conveyed any in, I conceive that ideas in the understanding are coeval with sensation; which is such an impression or motion made in some part of the body as produces some perception in the understanding. It is about these impressions made on our senses by outward objects, that the mind seems first to employ itself in such operations as we call "perception, remembering, consideration, reasoning," &c.

John Locke, *An Essay concerning Human Understanding*

Chapter 1

Historical Background. The Electrophysiological Approach to Primary Processes

1. Introduction

At the time when the psychophysical era of sensory research was beginning to feel the impact of electrophysiological analysis J. von Kries in his Allgemeine Sinnesphysiologie (1923) gave a masterly presentation of the main principles discovered in the last epoch of research, as well as the psychological and epistemological background. To show how ripe the time was for Adrian's discovery of the frequency variation in single sensory afferents, I offer this translated quotation from Von Kries' book (pp. 51–2):

> For skeletal muscle we now regard the rhythmic nature of the motor innervation as certain. We see in this one of its most important distinctive features, and the frequency of this rhythm has been the subject of much research. It is a question of fundamental importance whether in a similar way the activity in the sensory nerves is rhythmical, but on this question it is not yet possible to pass definite judgement. Fröhlich has observed action potentials of very regular rhythms in certain sensory nerves of cephalopods. In afferent nerves of higher animals corresponding phenomena have not yet been established. Nevertheless, Fröhlich is inclined to accept the rhythmical nature of activity for all sensory nerves, and he assumes that it has escaped notice in higher animals because the frequency is relatively high, so that the string galvanometer fails to record it.

Von Kries goes on to discuss the all-or-none law of the nerve impulse and concludes, "If we transfer these notions—which, at least for motor nerves, seem probable—to sensory nerves, we have to assume that stronger stimuli give a more frequent, weaker stimuli a rarer, reiteration of the same process" [viz. the action current].

Having made the distinction—somewhat artificial, like all such distinctions—between the mainly psychophysical epoch of sensory research and the present era dominated by electrophysiology, I feel obliged to consider briefly the background of the latter in order to indicate its legitimate claim to a title of its own. In a recent lecture Adrian (1953) captured something of the atmosphere of the early twenties when he said:

> No one in those days who was interested in electrophysiology could have failed to realise what it might mean to his own work when the initial difficulties were overcome, and then came the papers of ALEXANDER FORBES and of GASSER & NEWCOMER * to show that the difficulties were already yielding. The technique they were using was clearly not to be undertaken lightly; it involved all sorts of unfamiliar components, high tension batteries, condensers and resistances—electrical gear which now overflows our store cupboards but then had all to be made by hand in the laboratory. But the technique could be used for physiological purposes. It was a practical method for magnifying the very small electrical changes which had been beyond the reach of our recording instruments. It promised direct information about events which formerly we had only been able to study by inference.
>
> Reading some of the early papers of that time one cannot help remembering what a pleasure it was to find that most of the inferences had been correct. Impulses arising in sense organs or nerve cells were accompanied by action potentials like those in a nerve trunk stimulated electrically. They followed the all-or-nothing rule inferred from KEITH LUCAS'S † work on the frog's dorso-cutaneous muscle. They appeared where and when we had reason to expect them, in sensory and in motor nerves. In fact there was no need to revise the accepted theories of the nature of nervous communication. It was carried out by impulses of the familiar type.

Having myself from the beginning been interested in the special senses and consequently in psychophysics, I can well remember how deeply stirred I was when Adrian's first contributions began to appear (1926, 1926–27; see also his summaries of 1928 and 1932b). It suddenly became clear that both sense organs and neurones (cf. Denny-Brown, 1929) delivered a message of repeated brief, electrical impulses, so-called spikes, all of which were of the same size but increased in frequency when the stimulus was made more intense. Such spikes are shown in Fig. 1 in response to touch (*A*) and a painful stimulus (*B*). The message in the individual nerve fibers thus had the character of a simple frequency code! And it was all made more exciting by the fact that one could listen through the loudspeaker (Adrian and Bronk, 1928) to the code of the nervous message in the act of being delivered. An immense field was opened up for research. The code itself had to be studied in various sense organs. The retina and the

* The papers intended I take to be Forbes and Thacher (1920) and Gasser and Newcomer (1921). For these and all other references see pp. 303 ff.

† See Lucas (1917) in References.

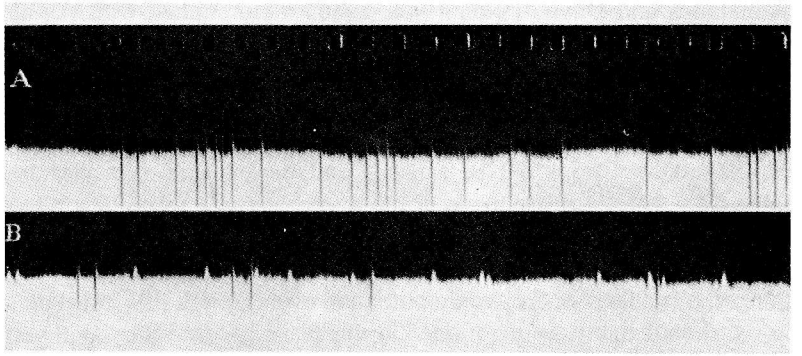

Fig. 1. Discharges in dorsal cutaneous nerves of frog. *A* shows large rapid impulses due to touching skin; *B*, slow impulses produced by 2% acetic acid on skin. (Adrian, The mechanism of nervous action, Oxford University Press, London, 1932b.)

organ of Corti seemed particularly fascinating. For these organs there was available an enormous body of psychophysical information to direct further research by the new method. Adrian immediately showed that impulse frequency diminished during continuous stimulation and so put sensory adaptation to the stimulus on a firm basis. It was obvious, too, that with such a definite measure available as spike frequency many new sense organs would be discovered. This expectation has been fulfilled. So far the only serious disappointment of this technique has been with the very thin nerves from some insect sense organs, which even expert technicians have attacked in vain (Hartline, Waterman, in personal communications).

Another source of inspiration around the same period was Erlanger and Gasser's work (see e.g. their summary, 1937). This provided a clear picture of the properties of the nerve impulse in terms of fiber size and conduction rate and thus laid the basis for the precise analysis

of electrical events which plays such a great role in contemporary work. In the physiology of the special senses its general significance has been obvious in the study of primary mechanisms, impulse generation, and sensory discrimination.

Forbes and his collaborators (1937) introduced the microelectrode technique for the study of neurone responses.* This method (cf. Buchthal, 1934) became an important supplement to nerve dissection (see Adrian, 1928) which technically had culminated in Hartline's (1938a) work on single fibers in the frog retina. First the retina (for a summary see Granit, 1947, 1950b) and then the organ of Corti (Galambos and Davis, 1943, 1944, 1948) were studied with the aid of microelectrode records, and a vast amount of new information was obtained. Perhaps the main advantage of the technique at this stage was that it made the mammalian eye and ear, as well as several nervous centers, available for analysis. Most of our detailed information about the elementary properties of sensory end organs and neurones has come from later improvements of the microelectrode technique, about which a great deal more will be said below.

The discovery by Wever and Bray (1930) of what is nowadays called the cochlear microphonic potential, even though first not understood, should rightly be mentioned in this place because it created very great interest at the time and served as a starting point for much important work.

Berger's rediscovery of the electrical potentials of the brain, popularly called "brain waves," his early fundamental results, subsequent scepticism as to the value of such mass analysis, and the final justification of this mode of approach, also had repercussions in the sensory field (1929; for a good historical review in English see Gibbs and Gibbs, 1948). These will be dealt with below when sensory projections and specific and unspecific relays are discussed. Adrian in England, Bremer in Belgium, and Bard and Fulton in the United States took up the study of sensory and motor projections and thus pioneered the large amount of important work that is being carried out today. It is well known that modern psychosurgery, which began as frontal lobotomy, owes its origin to experimental work carried out at Yale University by Jacobsen and Fulton (for a review see Fulton, 1949a,b; 1951).

* A number of reports of the new method were published; but the most complete description of it was given by Renshaw, Forbes, and Morison (1940). In this paper will be found a full account of the physical principles involved in recording with microelectrodes from a volume conductor. As early as 1934 Buchthal had used microelectrodes for electrophysiological work on single muscle fibers.

I recall these events in passing as memoirs of a sense-organ man, because it may be of some historical interest to put such impressions on record. In retrospect they seem to me formative influences. At that time the electrophysiology of the sense organs did not as a field enjoy the popularity that has fallen to its lot today. One of the reasons for the revival of interest seems to be the appeal of the microelectrode technique, with its emphasis upon general principles of cellular behavior. This puts a premium on easily accessible reactive structures wherever such structures may be found. It is particularly convenient to use sense organs because they are accessible to both adequate and electrical stimulation.

May I also venture to suggest that the general importance of receptors has been emphasized by such discoveries as that by Heymans and Heymans (1927) of chemoreceptive regulation of respiration from glomus caroticum; by Verney (1947) of osmosensitive structures in the brain stem; by Ranson (see e.g. 1940) of heat-sensitive structures in the hypothalamus; followed more recently by C. von Euler's and Söderberg's (1952a,b) demonstration that the region in the medulla which is sensitive to carbon dioxide has in every respect properties of receptors such as those to be described below. It has been realized for a century to be sure, that the body contains a considerable number of internal measuring instruments—Sherrington (1906) used to speak of interoceptors as opposed to exteroceptors—but electrical methods have invited close analysis of their effects and made it imperative for both general physiologists and neurophysiologists to cross the boundaries of their own limited territories and invade each other's domains of research. For instance, the heart specialist must know something about receptors because study of cardiac afferent impulses, important for reflex self-regulation within the vascular system, has again attracted a large body of workers. (See e.g. Amann and Schaefer, 1943; Jarisch and Zotterman, 1948; Whitteridge, 1948; Dickinson, 1950; Schaefer, 1950; Paintal, 1953b.) The recent pioneer work in this field was begun by Jarisch (1940, 1941), who took up the well-known problem of the Bezold reflex.

2. *Scope of the study*

The sense organs are our "private" measuring instruments and, like other instruments, they have properties such as sensitivity, range, speed,

and power of resolution. The study of these is common to both psychophysics and electrophysiology. A great deal of experimental work has gone into determining the limitations of the senses as interpreters of the external world in terms of perception. The analysis by electrical methods of primary processes in sense organs is part of this study but at the same time is also part of general neurophysiology.

At this point it is appropriate to remember that in the course of evolution the sense organs have developed by being in intimate contact with movement to or from external objects. This principle of organization is preserved in the reflex arcs of man and all animals. Indeed, highly important receptors, e.g. the vestibular ones, adjust balance by reflex postural contractions—according to most authors—without ever entering the world of perception. Many sense organs have pathways which do and others which do not evoke that particular conscious state which is called perception or sensation. We are not aware of our pupillomotor reflexes; yet their afferent path is that of light. All this is significant because the electronic era of work on sense organs has made some of its greatest contributions to the understanding of first principles by analyzing receptors lacking psychological equivalents in perception. It is not untrue perhaps to state that by comparison the previous era was one of great psychophysical discoveries.

In vision I can think of only one major psychophysical discovery from the same period, the "directional effect" (Stiles and Crawford, 1933; Stiles, 1939), which implies that the effect of light falling on the cones depends upon its angle of incidence. Of course there has been brilliant work done in sensory physiology with methods involving little or no electronics. I should like to mention the discovery of the "supersonic radar" of bats in flight (Griffin and Galambos, 1941; Galambos and Griffin, 1942; Galambos, 1942) suggested by Hartridge's early experiments (1920); Von Frisch's (1946, 1949, 1950) beautiful results on the orientation of bees; Waterman's (1950) precise analysis of the polarizing properties of the eye of *Limulus;* and Dethier's (1953) study of taste receptors on the legs of flies. Several others will be mentioned below when the subjects are discussed.

In many instances it is exceedingly difficult to translate electrophysiological results into sensory equivalents at the psychological level. I shall return to this point in Chapter 8 and when discussing microdissection and microelectrode techniques, which set problems that cannot be translated into perceptual terms. I do not mean problems which by definition are purely physicochemical propositions, e.g. ion transfer in impulse generation, but problems concerning the organiza-

are often difficult to approach in terms of perception. It is fortunate that in higher animals inhibition of motor performance is organized entirely within the central nervous system, not, as in some arthropods, by additional inhibitory mechanisms in the muscles themselves (Biedermann, 1895; Marmont and Wiersma, 1938; Kuffler and Katz, 1946; Fatt and Katz, 1952b), because it means that impulses in the efferent branch of a reflex to a muscle, or movement in the latter itself, can be used as an index to gain insight into central inhibitory mechanisms. It is well known that fine adjustment on the motor side involves an interplay of inhibition and excitation. The same is true for many acts of sensory discrimination, and inhibition by light has actually been discovered in the retina (for a summary see e.g. Granit, 1952b), but often the motor act is easier to understand by analysis than is the perceptual effect.

For many purposes, e.g. physicochemical studies of primary events, we can neglect the teleological aspects of the sensory message and the general problem of central decoding of the code of spikes, but I want to emphasize that research into special senses differs from many other recognized branches of physiology in presupposing and accepting the fact that understanding of biological purpose is part of its aim, be it movement or perception. To close one's eyes to this aspect of sensory physiology is to neglect the biological, psychological, and philosophical implications of a branch of natural science which actually is capable of giving some meaning to "meaning."

3. The psychophysical approach and the Fechner integration

In studying our "private" measuring instruments, the sense organs, we use "public" measuring instruments, "meters" of various kinds which disregard the limitations of our sensory experiences. Weighing, for instance, can be performed only within a limited range with the aid of our sensations of touch, weight, and pressure; but the principle, once applied, can be extended to an enormous range. It suffices to draw attention to the notion of wave length or frequency in optics to realize how much we have expanded the very limited perceptual range of our eye and what amount of insight we have achieved by measuring based on this notion. Adaptation in the sense organs tends to make our private measuring instruments fraudulent (to be sure, for a very good biological purpose), but, having developed units for measuring, we have also become capable of exposing the fraud and creating concepts

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such as that of a constant stimulus or any other constant event for that matter (see Chapter 8).

It is perhaps surprising that we should have succeeded in creating the idea of constancy in the face of sensory adaptation. Coal reflects more light in bright sunshine than snow in the evening and yet coal is always perceived as black and snow as white (Hering, summary, 1925). Wherever I move within a lecture theater (for example) you will *see* me as a person of constant size, yet the retinal image changes with the distance of the observer, as the renaissance inventors of the perspective truly realized. Similarly, movement, color, and form of objects remain constant within considerable limits of physical variation. Thus we may say that the unconscious processes of sensory integration (to which I shall return in Chapter 8) have dropped us a good hint of the possibility of things constant in a changing world. If these had not been designed that way, would we ever have succeeded in creating the idea of constancy? The reply is that all possible worlds are within us; they are our present and inherited responses to information from sense organs laid down with reasonable phylogenetic constancy (cf. Lawrence, 1949; Hilgard, 1951).

Relatively late in the history of civilization systematic investigation of our private measuring instruments with the aid of public measuring instruments began in earnest. The new science which ultimately was called psychophysics (Fechner, 1862) consisted of the application of the system of conventions known as the c.g.s. units (centimeter, gram, second) to sensation. It was forced to jump the intermediate links (which are the subject of these lectures) when it defined sensation in terms of the c.g.s. units, so-called stimuli. It seems like a vicious circle, first to derive c.g.s. units from sensory experiences and then to study these experiences by means of the same units. However, definition of stimuli in this fashion is no more "vicious" than any other application of the same or other conventional sets of rules to establish a system of relations. Science is pragmatic, as should be well known in the country of Peirce and James. It has rules for what is done and what isn't done, and just as in society its norm is a convention that must not be broken. The reward is prediction of behavior.

Psychophysics, for instance, predicts that most people see yellow when the stimulus is defined as 5800 units of Ångström. This, by hypothesis, is ascribed to certain events which are assumed to be absent or otherwise abnormal if people fail to see as predicted. Several great deductions were made in psychophysics on this general basis. They were stimulated by discoveries which in turn stimulated new discov-

eries, perhaps the most famous ones dealing with vision and hearing. I need not now enumerate the achievements of Thomas Young, Von Helmholtz, Maxwell, Hering, and many others. However, as an introduction to the study of impulse generation in sense organs, Fechner's classical integration should not be forgotten. I will try to explain what it means and how it has fared when confronted with electrophysiology.

Exactly 121 years ago E. H. Weber published some experiments in which he tried to measure the difference threshold for weights, tones, and the appreciation of length. The experiments with weights were carried out in two ways. In some of them he used what he held to be sense of pressure alone, the hand lying flat on the table while different weights were applied. He concluded that one weight felt heavier than another when they were related as 29:30. In the other set of experiments the muscle sense was also involved because the weights, covered in cloth, were actually lifted. The difference threshold was then 39:40 (description from Weber, 1846).

Fechner (1862) drew the conclusion that the increment threshold ΔR of the stimulus R was constant, and he carried out several series of experiments to establish the validity of this generalization $\Delta R/R =$ constant. The constant itself he regarded as a minute sensory unit ΔS. He then defined as Weber's law or the fundamental law (*Fundamentalformel*):

1. $\Delta R/R = \mathrm{k} \cdot \Delta S$, (in which k is a factor of proportionality).

His next daring step was to suggest that ΔR and ΔS were true limiting values dR and dS, such as required by the definitions of calculus, and that one therefore could rewrite (1) as an elementary differential equation, here rearranged as

2. $dS/dR = 1/kR$,

from which by integration one obtains

3. $S = a \log R + b$,

in which the constant a also includes the coefficient for transformation into decadic logarithms and b is an integration constant.

This, then, is Fechner's law (*Massformel*), which he also derived in other ways. It states that something in sensation that one might call its quantity S is proportional to the logarithm of the stimulus R.

There is an enormous literature dealing with Fechner's law: tests of its validity, criticism of the assumptions—which as mathematical propositions are indeed open to criticism—attempts to replace it with better expressions, epistemological difficulties, etc. (cf. Von Kries, 1923). If one scrutinizes Fechner's own data, these, too, must be taken with a grain of salt because there are often systematic variations of the Weber fraction. Many other tests reveal weaknesses. Nevertheless, despite the validity of much of the criticism directed against it, Fechner's law has survived every attack. The psychophysicists of today still keep it in their arsenal as a convenient rule of thumb to be taken down from the shelf whenever difference thresholds are discussed.

It would show lack of historical sense to look upon Fechner's famous integration as a mathematical treatment that could not be improved upon. The real question again is pragmatic: did he or did he not hit upon something important? His law shows that when stimulus strength R increases in geometric progression, something in sensation that we call its quantity S increases in arithmetical progression. Has this law been useful in the same way as other concepts of limited validity, such as the well-known elementary relation between volume and pressure? Very few laws, if any, have eternal validity and many useful laws are restricted in range.

This brings us back to the present day of electronics because if Fechner served psychophysics well, he must also be said to have raised a number of valid problems for the electrophysiology of the special senses.

4. *Stimulus strength, generator potential, and impulse frequency*

We admit to a property of "quantity" in sensations. We speak of tones of different loudness, light of different brightness, pain more or less intense. When Adrian (1926) showed that nerve impulses from the sense organs registered stimulus intensity by a frequency variation, there arose an opportunity of testing Fechner's generalization. The curve in Fig. 2 was recorded by Matthews (1931a) in Adrian's laboratory and refers, indeed, to the muscle sense (cf. Leeuwen, 1949), but in this case to a single end organ in the small muscle on the upper, outer side of the middle toe of the frog, a toe extensor. The logarithm of the load in grams is plotted against impulse frequency per second, one second after loading. We see that impulse frequency is proportional to the logarithm of the stimulus as implied by Fechner's law.

To be sure, it is not very easy to define the stimulus of a muscle receptor with great precision. Ultimately it must be in the nature of a mechanical deformation set up by stretch, and it is possible to argue

that length rather than load is the decisive factor. According to Hooke's law length would be proportional to tension, but muscle does not obey this law strictly (Buchthal, 1942; Hill, 1953).

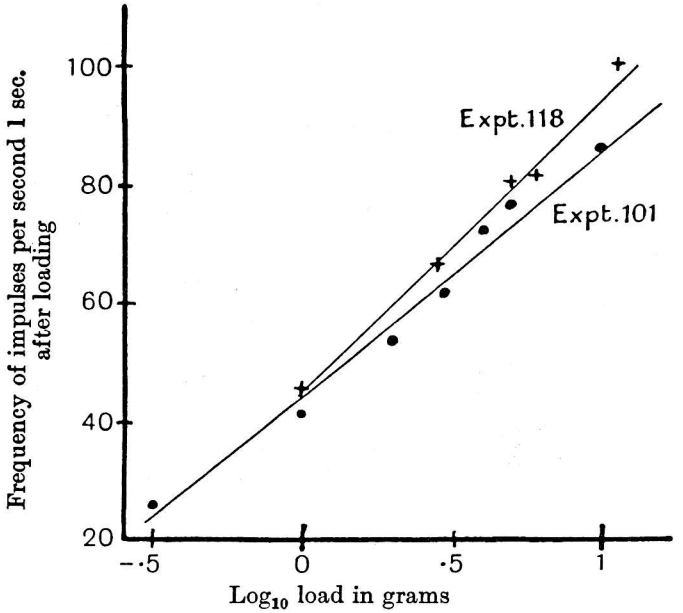


Fig. 2. Discharge of frog muscle spindle under different loads. Graphs showing the relationship of the frequency 1 second after loading to the logarithm of the load. Temperature 15°C. (Matthews, *J. Physiol., 71,* 64. 1931a.)

A better example is the visual end organ of the horseshoe crab (*Limulus polyphemus*) for which the stimulus can be defined with greater precision. This eye consists of ommatidia or sensory units; and one big nerve fiber, held to be coming from a definite isolated structure—the so-called excentric cell (Hartline, Wagner, and MacNichol, 1952)—can easily be isolated. Hartline and Graham (1932) have recorded the curve illustrated in Fig. 3. Again spike frequency is proportional to the logarithm of the stimulus intensity. Such examples could be multiplied (cf. e.g., single auditory fibers, Galambos and Davis, 1943).

It seems reasonable to conclude that Fechner did arrive at a sound generalization and that its basis is laid down somewhere in the receptor mechanism.

The next question is therefore: if this is so, where does the logarithm

come in? There must obviously be some generator mechanism starting the discharge of impulses in the nerve, apparently preceded by at least one mechanism that provides the specific sensitivity of the end organ to its adequate stimulus. This question immediately raises the whole problem of impulse generation in sense organs (cf. Granit, 1947). We have some information about the generative mechanism, but the specific ones are not very well known, except in some instances. Their

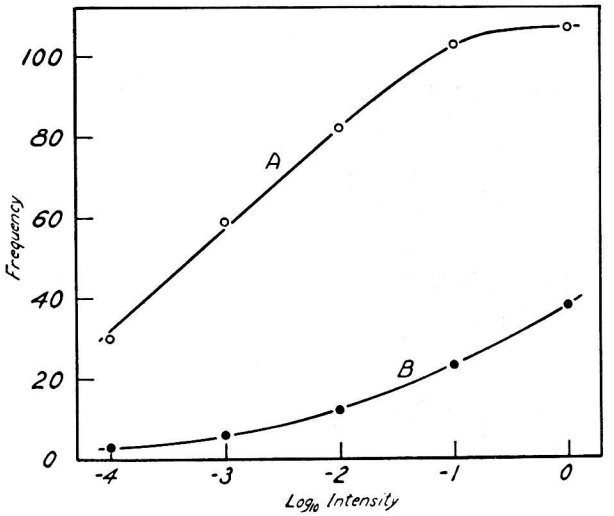


Fig. 3. The relation between frequency of impulses (number per sec.) and log. of the intensity of stimulating light. Intensity in arbitrary units (1 unit = 630,000 meter candles). Curve A shows frequency of the initial maximal discharge; curve *B,* frequency of discharge 3.5 sec. after onset of illumination. (Hartline and Graham, *J. Cell. Comp. Physiol., 1,* 277. 1932.)

very specificity suggests that they are different for different receptors, while the generative mechanism, faced everywhere with the same problem of initiating impulses at nerve endings, is likely to be run on similar principles throughout the whole gamut of receptors. Furthermore, these principles are likely to be familiar from work on peripheral nerves. Keeping this in mind and considering the fact that the work on simple eyes—i.e. eyes uncomplicated by the presence of ganglionic structures at the precise level of the retina, such as those of cephalopods studied by Fröhlich (1914, 1921)—presented evidence for maintained depolarization potentials in the sense cells during illumination, one may say it is likely that the impulse discharge is initiated and kept up by a generator potential of depolarization which either directly or

by electrotonic transfer along the fine nerve terminals depolarizes the nerve and sets up impulses. For a review of these arguments, see Granit (1947). It is hardly necessary to repeat them, beyond mentioning that depolarization potentials from simple visual receptors such as those of cephalopods and some arthropods have been recorded from the beginning of the electrophysiology of vision. Fröhlich's (1921) classical picture of depolarization in the visual cells of the cephalopod eye is shown in Fig. 4. Autrum and his collaborators (1951, 1952) have systematically studied receptor depolarizations in insect eyes of

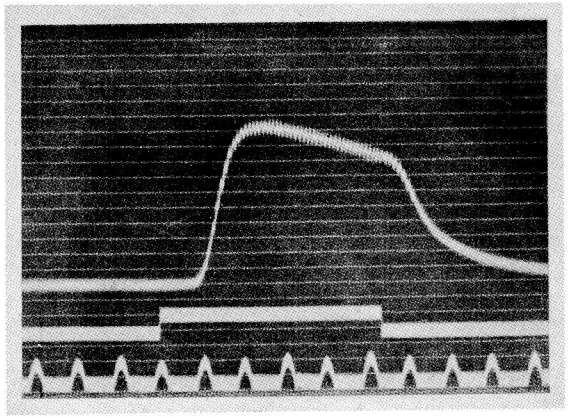


Fig. 4. Electroretinogram of *Eledone moschata.* Time marking: 1/5 sec. (Fröhlich, *Grundzüge einer Lehre vom Licht- und Farbensinn,* Fischer, Jena, 1921.)

the type in which receptors and neural layers are far apart. Dewar and McKendrick (1873a,b) were the first to observe the electrical response of the invertebrate eye to illumination. They were followed by Chatin (1880), Beck (1899), Piper (1904), and Fröhlich (1914, 1921). Hartline (1928) later studied a number of insect eyes, some of which were complex and gave complicated responses, and then in *Limulus* found the relatively simple preparation mentioned. I shall return to it below.

The arguments concerning the Fechner integration having been developed on the basis of muscle receptors, it is of some interest to continue along this line. Recently Katz (1949, 1950a,b) recorded the electrical changes in afferent nerve terminals of the extensor digiti IV muscle of the frog which appear when the muscle is subjected to stretch. Fig. 5 presents a photomicrograph of this preparation, in which I want to draw special attention (in *B*) to the splitting up of

the single afferent fiber into a number of fine terminals. Such branching seems to be characteristic of most sensory nerve fibers, and we shall have reason to consider its physiological significance below.

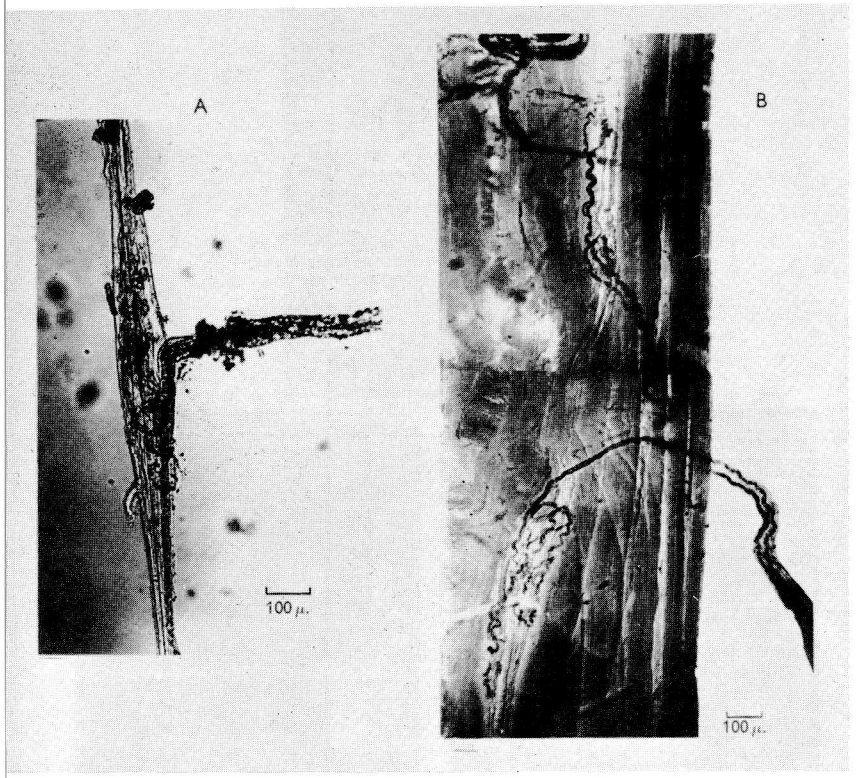


Fig. 5. Photomicrographs of frog muscle spindles. *A:* isolated living spindle immersed in Ringer solution, showing capsule, intrafusal muscle fibers, and nerve supply. The nerve contained a sensory and a motor axon which was cut. *B:* stained preparation (osmic acid). Muscle with two sensory axons, one of which was cut. The muscle was flattened between slides before fixation. (Katz, *J. Physiol., 111,* 248. 1950.)

In Figs. 6a and 6b the muscle with its sensory organs (spindles) had been subjected to stretch. In record A1 there is a spontaneous discharge at rest but in 2–4 a stretch of increasing intensity is seen to have elicited not only impulses, the fast deflections, but also a slow potential change shifting the baseline downward. On the right (*B*) are similar records made monophasic by crushing the central portion of the axon. The slow potential change has apparently originated

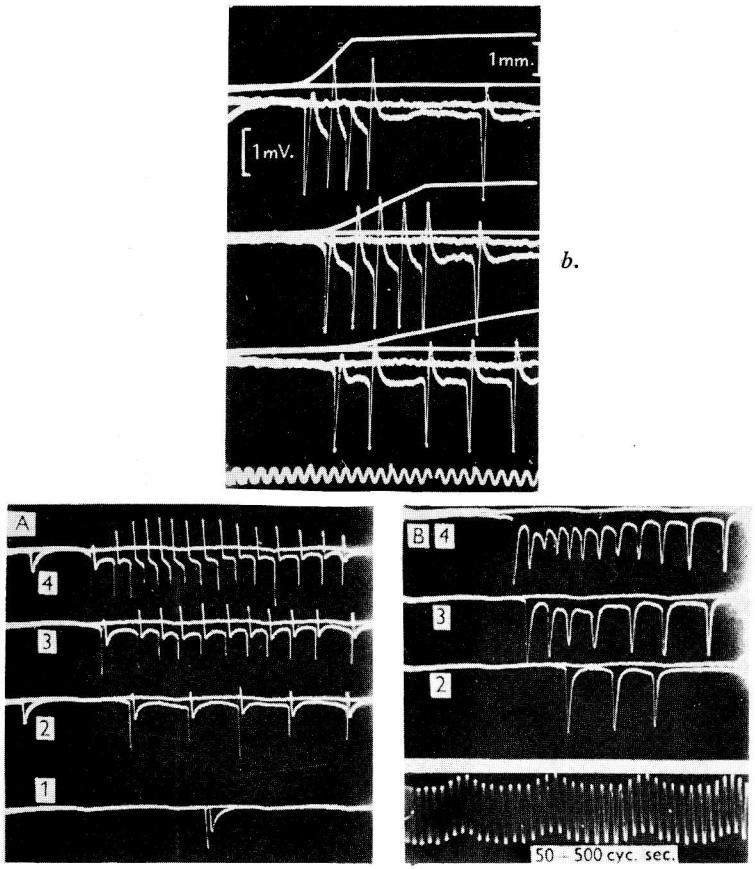


Fig. 6a. Potential changes in a sensory axon when the muscle is subjected to a transient stretch. The stretch was applied by a sartorius muscle contracting against the M. extensor dig. IV. All records read from left to right and show "spindle negativity" (i.e. a positive potential difference between electrodes) as a downward deflection. *A:* usual recording from uninjured axon—1, at "rest"; 2–4, with increasing intensity of stretching. *B:* the records have been made monophasic by crushing the central portion of the axon. (Note: in this preparation the axon divided into two branches before entering the muscle.) Occasional alternations in spike size (e.g. record *A*2) are probably to be attributed to impulses starting along alternate branches of the axon. (Katz, *J. Physiol., 111,* 261. 1950.)

Fig. 6b. Electric responses (lower trace of each pair) during three mechanical stretches at different rates (upper traces). The response consists of spikes and of a slow local depolarization which depends upon rate and amplitude of stretching. Time signal: 500 cyc./sec. (Katz, *J. Physiol., 109,* 9P. 1949.)

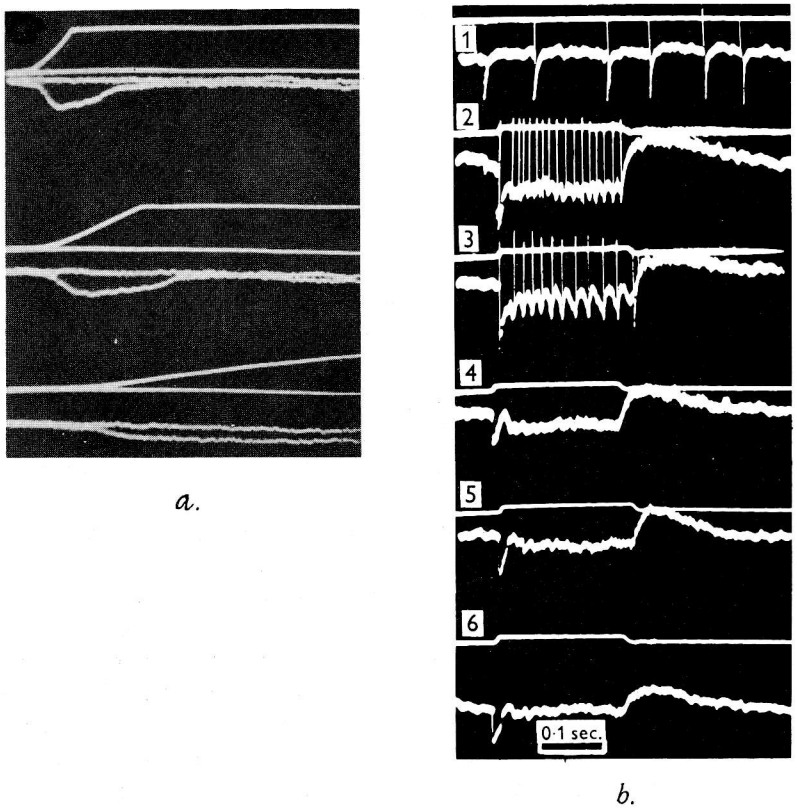


Fig. 7a. Like Fig. 6b, but the impulses have been removed by application of 0.5% procaine, so that the slow potential change alone remains. (Katz, *J. Physiol., 111,* 261. 1950.)

Fig. 7b. "Off-effect" at the end of a period of stretching. Initial length 15–16 mm. In records 2–6 a 1.8 mm. stretch was applied. Records 1–3: normal preparation, initial length being slightly less in 3 than in 1 and 2. Record 1 shows "resting" discharge. Records 4 and 5: after application of 0.15% procaine; record 6, after 0.3% procaine. In records 4 and 5 an initial spike was present but is not visible in the reproduction. (Katz, *J. Physiol., 111,* 261. 1950.)

within the sensory end organ itself and been conducted electrotonically along the nerve terminals to the recording electrodes.* During intense

* Kuffler (*J. Neurophysiol.,* in course of publication) has since obtained direct records from the *receptor* end of a muscle spindle in the dorsal tail muscles of the crayfish. Katz's results, obtained by recording from the nerve terminals, are confirmed in every aspect as reviewed in this chapter.

depolarization by stretch (Fig. 6a, record *B*4) the size of the spike is diminished. This is due to the local depolarization and not to conduction in the refractory period, because in the diphasic record (*A*4) the effect is absent, meaning that a few millimeters away, in a region outside the reach of electrotonic spread from the terminals, the impulses have recovered their full size. The spikes and the terminal depolarization potentials are shown in Fig. 6b as a function of rate of stretch.

After application of procaine the impulses disappear but the slow potential change remains and can thus be studied in isolation. Fig. 7a shows this effect for stretch at different rates (recorded upward). There is an initial rapid swing, which Katz calls the dynamic effect, followed by a maintained static effect. A dynamic overswing in the opposite *positive* direction, a hyperpolarization, follows at cessation of stretch, as shown in Fig. 7b, and it is clear that the afferent axon is silent during this time.

Before considering the slow potential changes accompanying excitation in the terminals, it is of interest to study Fig. 8, which represents the relation between impulse frequency and the maintained local depolarization in millivolts. This relationship is one of direct proportionality. In Fig. 2 it was shown that the impulse frequency of the frog's muscle spindle is proportional to the logarithm of the load, and we raised the question of where in the receptive mechanism the logarithmic relation came in: clearly not between the generator potential and the discharge of impulses, because the size of the generator potential determines frequency directly. It must arise earlier in the chain of events, but Katz's experiments do not provide any evidence of how the energy of mechanical stretch is converted into a local depolarization.

At the moment it is probably too early to make too much out of the differentiation of the depolarization potential into a dynamic and static component. The positive overswing of hyperpolarization of the membrane potential at cessation of stimulation seems, however, a singularly interesting observation and may well be a general phenomenon because, as we shall see below, there is evidence for a postexcitatory depression of afferent impulse frequency in many sense organs other than the frog muscle spindle.

Katz has not plotted his data so as to allow direct comparison with those of Fig. 2, illustrating the relation between spike frequency and the logarithm of the load. I therefore return to the visual cells of eyes in which their response can be recorded, if not pure yet without admixture of ganglionic potentials from nervous centers in close contact with the receptor layer. One's expectation is to find the generator potentials roughly proportional to the logarithm of stimulus intensity, and Fig. 9a shows that for the cephalopod eye this is the case. For comparison I have added to this figure a curve (9b) referring to the

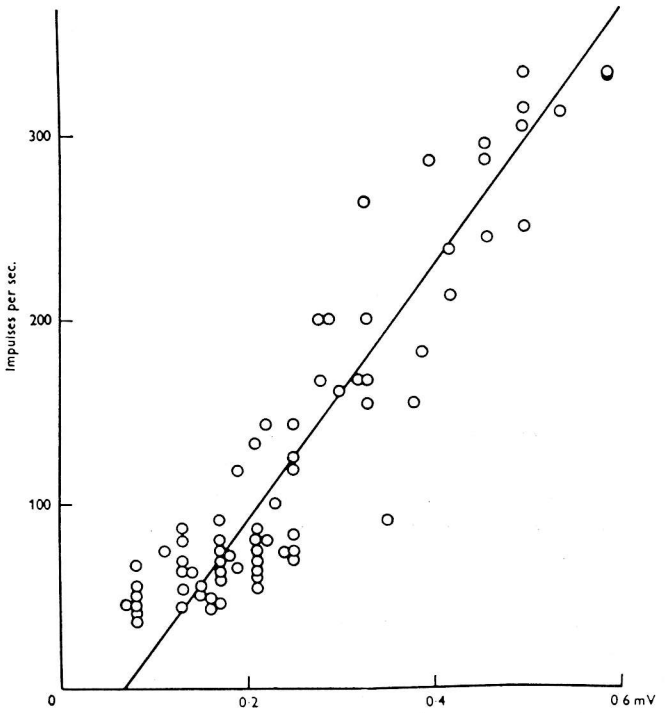
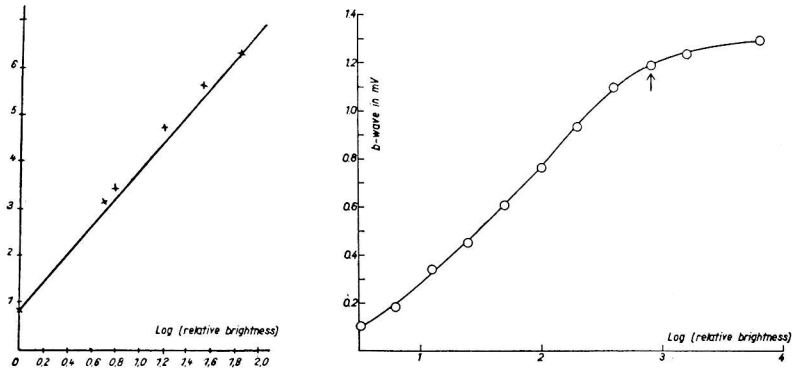


Fig. 8. Frog muscle spindle. Relation between local depolarization (abscissae) and frequency of impulses (ordinates). A regression line has been drawn through the results obtained from 91 pairs of observations. (Katz, *J. Physiol., 111,* 261. 1950.)

initial phase of the electrical response of a complex eye such as that of the cat, to be discussed in Chapter 5. (Cf. in Granit, 1947, the critical remarks on pp. 109–19.) In view of all these results we have some reason for stating that despite the many objections raised against Fechner's generalization, he did succeed in getting hold of something fundamental. The maintained generator potential is logarithmically related to stimulus intensity, though, as I said, when full-range results from various single end organs become available, other formulas prob-

ably will be found which fit better. The curves in general tend to be *S*-shaped. I have taken up this question against the background of the classical law because in the end one must be grateful for work which has left as its inheritance such keen insight into problems.



a. *b.*

Fig. 9a. Size of electrical response to illumination in cephalopod eye. Ordinates: millivolts. Abscissae: log. relative intensity of illumination. (Fröhlich, Grundzüge einer Lehre vom Licht- und Farbensinn, Fischer, Jena, 1921.)

Fig. 9b. Same for dark-adapted cat in terms of size of b-wave. At arrow, when curve approaches asymptote, the rate of rise of the b-wave continues to increase for higher intensities (cf. Fig. 69, p. 155).

Further expansion of this line of work on the generator potential should profit a great deal from the technique of the internal capillary microelectrode in the form developed particularly by Graham and Gerard (1946) and Ling and Gerard (1949). Their electrodes are fine micropipettes which can be inserted into single cells.

Microelectrodes were pushed into giant nerve fibers of squids from the cut end by Hodgkin and Huxley (1939) and Curtis and Cole (1940) in order to measure the membrane potential directly, both in rest and during activity, which led among other things to the important discovery that the spike of the action potential exceeds the membrane potential. These microelectrodes did not have to be very fine because the giant nerve fibers are of the order of half a millimeter in diameter. The capillary micropipettes of Gerard, Graham, and Ling are below 0.5μ in diameter at the tip, and when they are inserted into the cell its membrane tends to seal around the capillary, thereby preventing free ionic exchange through the

opening. They can be left in the cell for a considerable time. Important work on ventral horn cells has been carried out with this technique by Brock, Coombs, and Eccles (1951, 1952).

Hartline and his collaborators have recently published some preliminary results obtained by this technique on the isolated ommatidium of the *Limulus* eye (Hartline, Wagner, and MacNichol, 1952). The uppermost record of Fig. 10, introduced for comparison, is obtained from a single ommatidium *and* its nerve fiber in the ordinary way by enclosing both structures within the leads. It shows that the impulses arise on the rising phase of the ommatidial depolarization potential, the frequency decreasing when the electrical response of the ommatidium decreases. The relation between size of potential and spike frequency was not, however, as simple as at the nerve terminals of the frog muscle spindle. They suspect that there are at least two potential sources, the ommatidium as well as the nerve strand. To quote:

> The nerve strand itself appears to contribute significantly to the potential gradients thus recorded. This contribution can be seen directly in some preparations, especially in those that have been slightly damaged so that the repetitive discharge of nerve impulses no longer takes place. When these slow potential changes [partly electrotonic ones, comparable with those measured by Katz] in the nerve strand can be observed, their time course is very similar to the rise and fall of frequency of impulses discharged from undamaged preparations . . . although no exact quantitative comparisons have yet been made [p. 135].

The notion that the electrotonic spread is the stimulus for the nerve terminals was part of the theory of "generator potentials" (see Granit, 1947). Electrotonic potentials in the frog's optic nerve were described by Granit and Therman (1938) and measured in our laboratory by Bernhard (1942) on *Dytiscus*. Electrotonic spread into the optic nerve of *Limulus* can be seen also in the early records of Hartline and Graham (1932).

In the lower part of Fig. 10 the upper record has been obtained with a micropipette. Since these experiments are not yet published in full, I shall report them in the authors' own words (Hartline, Wagner and MacNichol, 1952):

> Many probings by the pipette were necessary before the responses illustrated were obtained, even though the group of retinula cells

always comprises a sizable fraction of the volume of the ommatidium. This would seem to support our belief that it is the eccentric cell that is responsible for the discharge of nerve impulses. In the experiment [from which Fig. 10 is taken] . . . the final successful probing resulted in a sudden change in the potential of the micro-

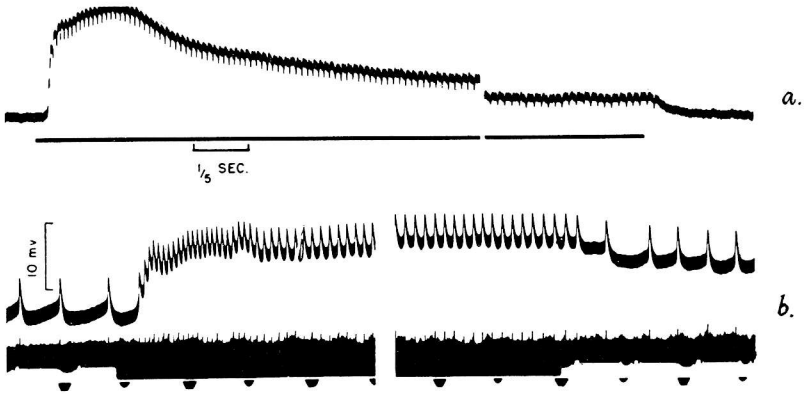


Fig. 10a. Action potential of isolated ommatidium (*Limulus* eye) and its nerve strand in response to prolonged steady illumination. Deflection upward indicates increasing negativity of cornea with respect to cut end of nerve strand. DC amplification. Black line above time scale signals period of illumination (record interrupted for approximately 8 sec.).

Fig. 10b. Simultaneous records of the potentials arising within an ommatidium (upper trace) and from the nerve bundle attached to the ommatidium (lower trace) in response to prolonged illumination. The black band under the lower trace indicates the duration of illumination. The activity of the ommatidium was recorded between a micropipette (tip diameter 1μ) inserted into it and an indifferent electrode in the solution covering the eye. DC amplification was used, the resting potential having been canceled by means of a potentiometer. Wick electrodes and a capacitance-coupled amplifier were used for recording the potentials from the nerve. Interval between time marks = 1/5 sec. (Hartline, Wagner, and MacNichol, *Cold Spr. Harb. Symp. Quant. Biol., 17,* 125. 1952.)

pipette, the electrode becoming more negative with respect to an indifferent lead by at least 50 mv. At the same time, the nerve bundle from the ommatidium suddenly began to discharge impulses spontaneously, and, synchronously with each nerve impulse, spike-like positive deflections were recorded by the micropipette [as shown by Fig. 10]. . . . The higher the intensity of the stimulating light, the greater was the elevation of potential of the micro-electrode, and the greater was the increase in the frequency of the discharge of impulses [pp. 136–137].

The authors conclude: "Our experience with this type of preparation is too limited to permit us to discuss the relation between the potential level and the frequency of nerve discharge, or to relate the potential changes recorded by means of the micropipette to the slow action potentials recorded with external electrodes [Fig. 10a] on the ommatidium or its nerve bundle" (p. 137). No doubt further experience with this preparation will soon supply the missing links.* With the vertebrate retina a corresponding degree of clarity has not yet been reached. This I shall discuss in Chapter 5.

Recently, two research groups (Alvarez-Buylla and Ramirez de Arellano, 1953; Gray and Sato, 1953a,b) have succeeded in recording the generator potential of the Pacini body (for the histology of this organ, see below, p. 38), thus supporting with one more example the theory of stimulation by generator potentials. Its application to the ear has been discussed by Davis, Tasaki, and Goldstein (1952) and Tasaki and Fernandez (1952). In brilliant work with an internal vibrating microelectrode Von Békésy (1952b) showed that the cochlear microphonic potential probably arises in the sensory hair cells riding on the basilar membrane. Thus, after having once been relegated to the role of an epiphenomenon, the cochlear microphonics are now again held to be the generator potentials of the mechanoreceptors in the ear. Eleven years ago Zotterman (1943) studied the distribution of the microphonic potential over the large sacculus of the pike with the aid of one of my platinum microelectrodes and a micromanipulator, as used for the retina. It was quite evident that the microphonic potential was generated over the sensitive macular region of this organ. Leads from the nerve showed that the spikes arose on top of the microphonic wave. Ever since I had the pleasure of seeing those experiments performed I have been waiting for the moment when the ear physiologists would return to the notion that the cochlear microphonics might serve as generator potentials in the organ of Corti. The work of Von Békésy (1952a,b) also contains an important analysis with microelectrodes in this organ of the distribution of AC and DC potentials.

All these results with generator potentials do not, of course, exclude the possibility that some end organs may be driven by chemical mechanisms with little or no generator potentials as intermediaries.

* Since this was written Hartline and his collaborators (in personal communication) have actually shown that, just as in muscle spindles, the impulse frequency is directly proportional to the semistationary (static) phase of the generator potential recorded across the ommatidium alone. This potential is logarithmically related to light intensity.

5. *Sensory adaptation. Accommodation*

The best known electrophysiological equivalent of sensory adaptation is the decline in the frequency of discharge of a single afferent coming from an end organ which is being subjected to continuous stimulation. This has been well illustrated in many of the records already shown. Since Adrian's early work (1928) it has been known that there are slowly and rapidly adapting end organs. The fast touch receptors and the slowly adapting muscle spindles (to be discussed in Chapter 6) may be taken as prototypes of these two categories. A relatively full discussion of adaptation from the standpoint that sense organs act by setting up generator potentials which stimulate the nerve terminals is found in my book of 1947. At that time it was still necessary to refer to analogies with results of stimulation of peripheral nerves with slowly rising constant currents. The last section has shown that the generator potentials today are being analyzed directly with microelectrodes at the site of spike generation. This clearly is the road of future progress. The notion of generator potentials as intermediates in the production of a sensory discharge—whatever its ultimate fate—has proved a useful theory, directing further research into the actual mechanism of impulse generation.

An end-organ consists of at least two intimately associated mechanisms: one responsible for its specific sensitivity, e.g. a photochemical substance in the case of the eye, and another, e.g. the generator potential, responsible for the transformation of the specific change into a form of energy capable of discharging the nerve terminals. Both may adapt to the stimulus, but inasmuch as the generator potential is the one responsible for the discharge, it would also, by its fall, indicate adaptation of the former. The primary approach to the problem of adaptation is therefore identical with a study of the generator potential and its relation to the spike frequency (cf. above). The motoneurone is a good model. Brock, Coombs, and Eccles (1951, 1952) have inserted a microelectrode into the motoneurones and directly recorded its generator potential, a characteristic depolarization of the cell which they assume is dependent upon a chemical mediator. In the eye the photosensitive substances may be regarded as the best candidates for the role of chemical mediators. At the motor end plates in the muscle the end-plate potential, first seen by Göpfert and Schaefer (1938), has been shown by Eccles and O'Connor (1939), Eccles, Katz, and Kuffler (1941), and Kuffler (1942, 1949) to be a generator potential. Finally, Fatt and Katz (1951) by intracellular recording have shown

in a model fashion how release of acetylcholine elicits this end-plate potential and the latter the discharge, thus integrating Dale's (1952) classical acetylcholine theory into the electrical mechanism.

This raises the general problem of whether chemical mediators also play a part in translating, e.g., mechanical deformation of touch and stretch receptors into generator potentials. Brown and Gray (1948) and Douglas and Gray (1953) have recorded sensory discharges from skin and mesentery in response to arterial injections of acetylcholine. Dodt, Skouby, and Zotterman (1953) report similar results with afferents from thermoreceptors (cf. psychophysical tests by Bing and Skouby, 1950). It does not necessarily follow that this substance plays a role in normal transmission, nor is this assumed by the authors cited. Indeed, Brown, Douglas, and Gray present evidence against this view. Hunt (1952b) has reported that acetylcholine fires the large nuclear bag (annulospiral) afferents of the muscle spindle, but his evidence indicates that the effect is indirect and caused by the depolarizing action of this substance on the motor end plates of the efferent gamma fibers which contract the muscle spindle (see Chapter 6). With respect to acetylcholine the gamma end plates behave like ordinary motor or alpha end plates. Granit, Skoglund, and Thesleff (1953) find that the same spindle afferents are fired by very small doses of succinylcholine, but in their case there is also some evidence for a direct effect on the sensory organ itself. Similarly, succinylcholine discharges the chemoreceptors of the glomus caroticum (Landgren, Liljestrand, and Zotterman, 1952), which lack the complications of a muscular apparatus attached to the sense organ. This gives an indication of how matters stand at the moment.* Clearly work at the microlevel would be needed for the elucidation of these problems. As such, chemical mediation seems unnecessary for mechanoreceptors (cf. Gray and Malcolm, 1950; Douglas and Gray, 1953). Mechanical stimulation of nerve was demonstrated and studied by Tigerstedt as early as 1880. In the mechanoreceptors of the ear the latent period seems too short for anything but direct mechanical stimulation—in fact, 0.15 msec. with strong stimuli (Davis, Tasaki, and Goldstein, 1952).

At the nerve end of the receptor's generator potential nerve accommodation may be a contributing factor to adaptation, though on the other hand it is well known from the early work of Adrian, Cattell, and Hoagland (1931) and Cattell and Hoagland (1931) that skin receptors can be adapted to zero excitability without firing a single

* G. Liljestrand has recently reviewed the problem of chemical transmission, with especial reference to chemoreceptors (*Pharmacol. Rev., 6,* 73–8. 1954).

impulse. Therefore nerve accommodation alone can never fully explain receptor adaptation.

Now, what is accommodation? At present it is still a purely formal description of the fact that each impulse in the nerve is succeeded by a process of restitution which counteracts the setting up of a fresh impulse. Some of the best known mathematical treatments of this problem have been given by A. M. Monnier (1934), Hill (1935–36), and Katz (1939). A discussion of sense organs is found in Granit (1947). Accommodation has not yet been given its final place in modern physicochemical excitation theories, though suggestions based on experiments have been made by Hodgkin and Huxley (1952). For the present purpose it suffices to realize that nerve excitation is counteracted by opposing processes which we call "accommodation," and it is therefore necessary to consider whether such processes can also be shown to counteract maintained stimulation by a generator potential in the receptors. If so, they would contribute to adaptation as defined by the decline in spike frequency during maintained stimulation.

The classical method of measuring accommodation was introduced by Von Kries (1884) and consists in stimulating the nerve with a slowly rising current. The question then arises of whether the nerve can still respond when the current rises very slowly, so that the accommodative counterprocesses are given full scope. Lucas (1907) found that there is a "minimal current gradient" or critical slope below which the current simply fails to excite. This is the *pente limite* of the French school (see e.g. A. M. Monnier, 1934). Pente limite is a sign of accommodation and can be used to measure it. Present-day techniques require that this be established with a single fiber and with a single Ranvier node stimulated by the outwardly directed current. The adjacent nodes have to be cocainized. With these strict criteria the experiment has been repeated by Tasaki (1950, 1953a) and by Frankenhaeuser (1952), both of whom are in perfect agreement: for frog nerve there is a minimal current gradient below which it does not excite. Frankenhaeuser, however, states that repetitive firing may be obtained if the next Ranvier node is uncocainized, so that the excitatory disturbance can spread to it.

Does this mean, then, that a generator potential in the receptors only can cause repetitive firing by virtue of its electrotonic spread on to a number of nodes? Is this how we have to understand that stretch receptors fire continuously, as shown by Fig. 8, at a rate proportional to the amount of generator potential, or that a single vertebrate sensory fiber behaves in much the same way when stimulated with a slowly

rising current, maintained at different levels of strength, whatever its rate of rise (e.g. Granit and Skoglund, 1943; Katsuki and Yoshino, 1952)? There is a considerable literature on repetitive firing in nerve. See e.g. Biedermann (1895), Fessard (1936), Skoglund (1942, with references), Kugelberg (1944), Laget and Lundberg (1949), and Sato (1952), to which especially French authors (see below) have contributed.

My answer to the question raised is simply that we do not yet possess the necessary information for a final explanation of how generator potentials in sense organs can maintain stimulation of their nerve fiber in the face of accommodation. Fig. 116 (below, p. 246) shows a single stretch receptor in the leg extensor of a decerebrate cat firing for a considerable time at a rate as high as 300 impulses per second. The innervation of the muscle was intact, stimulus was stretch, and only a thin filament in a dorsal root was taken out for recording. Conditions were thus perfectly physiological. How is such long-lasting intense firing possible?

Some alternative explanations, not necessarily mutually exclusive, may be suggested:

(1) It is known that rhythmic firing with disappearance of accommodation can be induced in highly accommodating nerve fibers by, for instance, decalcifying agents (see e.g. Fessard, 1936; Solandt, 1935–36; Brink and Bronk, 1937; Monnier and Coppée, 1939). Many sensory nerves may be normally in a state on the verge of firing and show what L. and M. Lapicque (1937, 1938) used to call autorhythmicity (also "climalyse"), a property which Monnier and Coppée (1939) have characterized by specific resonance phenomena. A. M. Monnier (1952) has given a summary of his later generalizations on resonance in nerves. The role of resonance phenomena in specific afferent fibers is still unknown and, to become significant in this connection, would have to be studied with reference to generator potentials, spike frequencies, and adaptation.

(2) It is particularly likely that the fine unmyelinated nerve terminals which are a characteristic feature of most sense organs (see Fig. 5, *B*) are specially adapted to be a relatively nonaccommodating point of attack for receptor potentials. Thus, Katz (1950a,b) has shown that the fine terminals of the muscle spindle, even in the absence of definite provocation by a stimulus, may generate small nonpropagated spike potentials which mature into a conducted spike when several of them at the same time reach the confluence point of the undivided fiber (see also Buller, Nicholls, and Ström, 1953). Spontaneous im-

pulse generation of this kind is almost conclusive evidence against the presence of accommodation. I shall discuss these experiments in considerable detail when dealing with the mechanism of generation of spontaneous impulse discharges from sense organs (Chapter 3). Even if there were some accommodation in the individual nerve terminals, their great number ensures stimulation on a statistical basis of simultaneous invasion of their common junctional point. This theory has the further advantage of making a very characteristic morphological feature of sense organs intelligible. If I have understood Katsuki *et al.* (1951) correctly, their views run along similar lines of thinking.

(3) Finally, electrotonic spread of the receptor potential may counteract accommodation.

The amount of accommodation at the receptor end of any fiber, as pointed out by Granit and Skoglund (1943), is likely to be adjusted to the needs of the sense organ. Gray and Matthews (1951) have compared accommodation to linearly increasing *mechanical* stimuli of individual Pacinian corpuscles in the cat's mesentery with accommodation to linearly rising *electrical* currents in their afferent fibers. The two critical slopes for stimulation (pentes limites) were very similar, suggesting some connection between adaptation and accommodation. The recent work on the generator potential of the Pacini body (Alvarez-Buylla *et al.,* 1953; Gray and Sato, 1953) also shows this to have a fast exponential decay with a time constant of the order of 2 msec. In the Pacini organ, however, the nerve fiber's terminal portion is of a rare type, a formation reminiscent of a stalk with a club at the end residing within a number of concentric pouches (see below, p. 38). Therefore its rapid accommodation to linearly rising stimuli does not contradict apparent absence of accommodation in an organ like the stretch receptor, with the common, typical, split-up nerve terminals (Fig. 5, *B*) seen also in Golgi tendon organs, muscle spindles, Ruffini's "cylindre terminal," Krause end bulbs, unorganized beaded terminals subserving pain, nerve nets encircling hair stalks, and retinal cones—to mention only structures with which I shall deal below.

6. *Sensory hyperpolarizations*

In discussing adaptation of sense organs I have so far not considered the possibility that in some end organs depolarizing generator potentials at cessation of stimulation might be cut short by an opposite process of hyperpolarization which would act to prevent afterdischarge. In the retina I found it necessary to postulate a process of postexcitatory inhibition to account for results such as those of Fig. 11, obtained with single elements picked up by a microelectrode in the eye of the guinea pig. In *a, b,* and *c* the duration of stimulation is lengthened, the last record showing merely the end of an illumination lasting for 5 seconds. The pause in the spike discharge after cessation

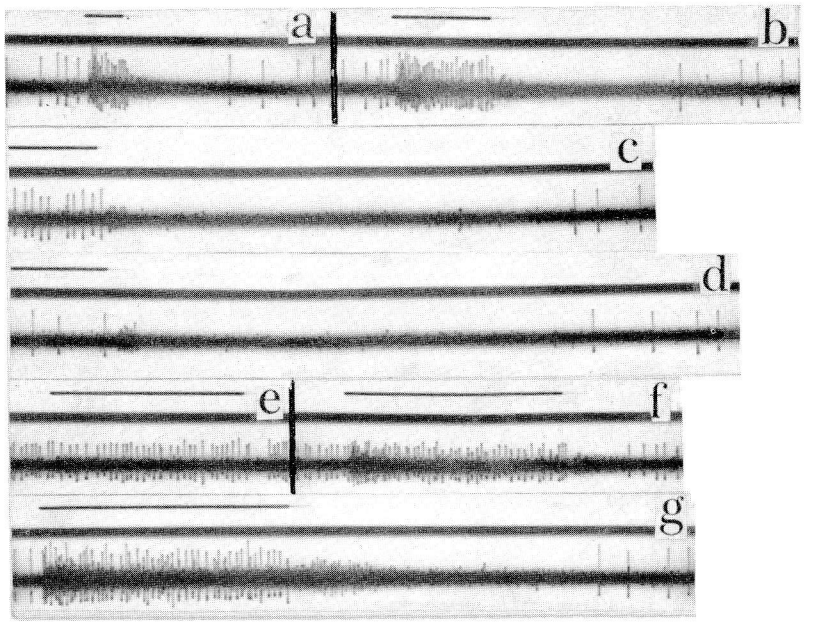


Fig. 11. Postexcitatory inhibition in eye of guinea pig. Microelectrode. Records *a–d* show effect of duration of stimulus of 600 m.c.: *a,* about 0.5 sec.; *b,* 1 sec.; *c,* end of exposure of 5 sec.; *d,* end of exposure of 20 sec. Records *e–g* show effect of stimulus intensity: *e,* 20 m.c.; *f,* 150 m.c.; *g,* 500 m.c. (Granit, *Vet. akad. ark. f. zool.,* A *36,* No. 11. 1945a.)

of illumination increases in length when stimulus duration is lengthened. Similarly, *e, f,* and *g* show that an increase of stimulus intensity lengthens the pause. These are elements of the type discharging merely to onset of illumination (cf. Chapter 2), very common in the rod eye of this animal.

These microelectrode records from the retina refer to the third neurone, but similar postexcitatory inhibitions have been described in many simple sense organs, e.g. the thermoreceptors (Hensel and Zotterman, 1951a–c; Dodt, 1952a,b).

Matthews (1933) described cessation of the discharge of muscle spindles after stretch, illustrated in Chapter 7 (Fig. 113, *A, B,* p. 241). In this case, as pointed out by him, part of the effect must probably be ascribed to the viscoelastic forces in the muscle, the spindles being unloaded for a while during readjustment of tension to length. This, however, cannot be the whole truth because Katz's records from the terminals of frog muscle spindles, shown above in Fig. 7b, very clearly demonstrate a terminal hyperpolarization potential after stretch, and during this time the muscle spindle was silenced. It remains to be seen whether further work at the microlevel will succeed in demonstrating similar postexcitatory or *secondary* hyperpolarizations in other sense organs to account for the very common phenomenon of postexcitatory depression.

Have we any evidence for *primary* hyperpolarization in sense organs adequately stimulated? The earliest evidence obtained again refers to the retina. This, as we shall see below, is a complex organ which is inverted in vertebrates so that the conventional signs of the potentials in the electroretinogram recorded in the standard leads, cornea to back of the eye, probably refer to events of opposite sign within the structure itself. Fig. 12 shows what happens in the frog's eye during illumination with a single flash (Granit and Therman, 1938). Four ways of leading off (I, II, III, and IV) have been used, of which I is the standard way in which electroretinograms are recorded. The upper electrode in this figure is always positive and thus in the standard lead (I) also cornea-positive. In this lead the normal retinogram is initiated with a negative-positive response at onset of light and completed with a positive off-effect at cessation of illumination (column marked normal response, lead I). The cornea-negative response is the so-called a-wave, the positive the b-wave. A drop of a potassium solution into the bulb first emphasizes the initial negative a-phase of the negative-positive complex (soon after potassium, lead I) and ultimately this response (for some time) without change of latency continues as a wholly negative retinogram (later after potassium). Potassium is a well-known depolarizing agent, and so the remaining negative response to illumination cannot be a depolarization by light. In view of the inversion of the vertebrate retina its sign, which in the standard lead is cornea-negative, would actually be cornea-positive with regard to the orientation of the retinal structures. The conventional nomenclature will, however, be used everywhere in these lectures.

The other leads show two further events, the electrotonic spread into the optic nerve superimposed upon the retinogram in II and the

volleys in the optic nerve isolated in IV. Potassium immediately removed these signs of activity, and so leads I and II after potassium merely record mirror images of the electroretinogram. I shall discuss recent developments of electroretinography in Chapter 5 and now merely reiterate the conclusion that a process of hyperpolarization is found in the vertebrate retina and that it can be isolated with a depolarizing agent which removes the (cornea-positive) depolarization potential. The latter is upward in lead I (normal response). A full discussion of these results is given in Granit (1947, 1952b).

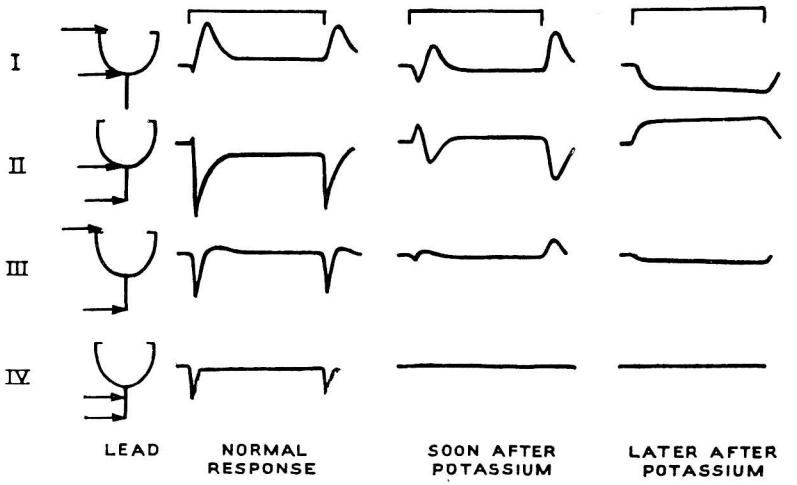


Fig. 12. The effect of potassium chloride on the frog electroretinogram in different leads. Upper electrode positive plotted upward. (Granit and Therman, *J. Physiol., 93,* 9P. 1938.)

Evidence for primary hyperpolarization in a sense organ comes from the clear-cut results of Parry (1947) on the single ocellus of a locust, probably the simplest visual receptor. This organ responds to illumination by increased polarization. This membrane change can be recorded from the raised-up ocellar nerve as a positive electrotonic potential in the way Katz (see above, p. 15) recorded the hyperpolarization potential from the stretch-receptor afferents at cessation of stimulation. But in Parry's work, as shown in Fig. 13, the only response to illumination was this positive effect. At cessation of illumination the response was reversed; the ocellus now became depolarized with an overswing toward the negative side. The negative depolarization potential was thus an off-effect. Neither change caused any discharge in the optic nerve, which in this animal is quite large (25μ) but only

1 mm. in length. However, when the negative electrotonic change reached the next station, the cells of the circumoesophageal ganglion, they were found to discharge to the negative swing at "off," behaving therefore like other cells when depolarized. Here then is a mechanism for an off-discharge by potential changes similar to the one that originally was postulated for the vertebrate retina (Granit, 1933, 1947, 1952b). So far this is the only *single* sensory cell which unequivocally has been shown to be hyperpolarized instead of depolarized by light. The eye of *Limulus,* as we have seen, is merely depolarized by light,

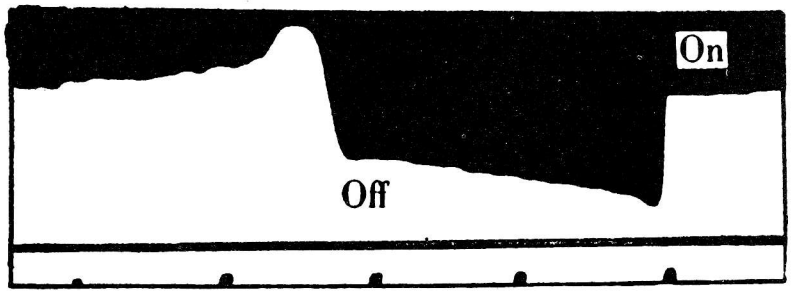


Fig. 13. Electrical response of ocellus recorded electrotonically in the ocellar nerve. Light on and off as marked. See explanation in text. Records read from right to left; on-response is 0.27 mV. Time marks every 1/10 sec. (Parry, *J. Exp. Biol., 24,* 211. 1947.)

and so are all the simple visual receptors mentioned above (sec. 4), provided that the ganglion layers are absent or have been removed. Svaetichin (1954a), on the basis of microelectrode work with the fish retina, states that fish cones discharge to hyperpolarization, but his evidence seems to me inconclusive. It will be discussed in Chapter 5. As such, records showing opposite potentials in the retina have been a feature of electroretinography from 1865 to the present day (Granit, 1947). However, as mentioned above, from ventral horn cells Brock, Coombs, and Eccles (1951, 1952), using inside microelectrodes, have found membrane depolarization to excitation and hyperpolarization to inhibition of the cell. These results are unequivocal in demonstrating a correlation between excitation and depolarization, and between hyperpolarization and inhibition. It is therefore impossible to accept the idea that hyperpolarization causes a discharge until it is backed by extremely clear-cut and definite evidence.

7. *The on/off system*

A brief presentation of this feature of sensory organization should perhaps be given at this stage because it is part of both the visual and the auditory responses and thus must be highly important. The simplest on/off system known is that of the clam *Pecten* (Hartline, 1938b), in the eye of which there are two layers of visual receptors, the one discharging to onset of light, the other to cessation of light. Work with internal microelectrodes on these two types of cells is urgently needed. Something might also be done with polarizing currents of opposite orientation, because in the vertebrate retina these tend to have opposite effects on the retinal elements according to whether they respond chiefly to onset or to cessation of light (Gernandt and Granit, 1947).

In the eye of *Limulus* there is no off-effect proper unless individual fibers are isolated on the central side of the optic ganglion (Wilska and Hartline, 1941), and the same holds good for the mammalian ear, in which off-effects do not occur until the discharge has reached the medial geniculate body (Galambos, 1952). Actually it was first picked up in the auditory path by Ek and C. von Euler (1943) in frogs and by Bremer (1943) in the cortex of cats. Evidently, then, off-discharges, like so-called reflex rebound (Sherrington, 1906), can be produced by central interaction between structures with mutually antagonistic effects on the same neurone. There is no reason why the mechanism of interaction necessarily need be different in peripheral and central structures. Depolarization and hyperpolarization occur in both. The only common denominator for on/off systems hitherto found is the presence of two antagonistic processes. Since the ommatidium of *Limulus* generates only a depolarization potential, there is no reason why there should be an off-effect in it. But if, for the sake of argument, one takes Hartline's ommatidium and combines it with Parry's ocellus —the former depolarized, the latter hyperpolarized, by light—into an imaginary double-cell eye, then the outcome might easily be a design such as the on/off retina of *Pecten* or the highly complex vertebrate eye. There would be two potentials of opposite orientation, the one generating excitation, the other inhibition to illumination, and their combined effect might produce an on-discharge, an off-discharge, or even an on/off discharge—in other words, an eye such as the vertebrate retina.

Actually, this—put in a form easy to understand—is the way thinking and experimentation concerned with the vertebrate retina has pro-

ceeded (see Granit, 1947, 1952b). The deflections to "on" and "off" of its electroretinogram, as illustrated in Fig. 12 above, have been known from the beginning of electroretinography. Adrian and R. Matthews (1927a,b, 1928) were the first to pick up the corresponding discharges in the optic nerve by modern methods (for earlier attempts see historical section of Granit, 1947). On the basis of an analysis of the mammalian electroretinogram (Granit, 1933) I postulated inhibition in the retina to account for the off-discharge and with Therman

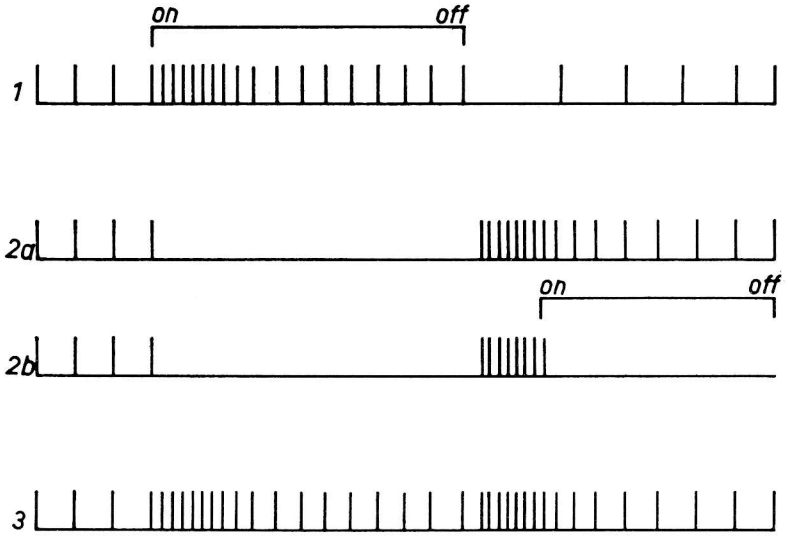


Fig. 14. Diagram illustrating three fibers in the optic nerve firing spontaneously and their responses to illumination, as described in text.

(1934, 1935) demonstrated its actual existence. Then followed Hartline's (1935, 1938a) well-known microdissection of the frog optic nerve fibers, which proved that there were fibers responding either to onset or to cessation of light as well as fibers responding both to onset and cessation of light, now commonly spoken of as on-, off- or on/off fibers or elements, even though it is realized that these distinctions represent some oversimplification. His results were soon confirmed by the microelectrode technique (see Granit, 1947). The inhibition to light that we had found had been an inhibition of the massed off-discharge during reillumination. With his single-fiber preparation Hartline proved that reillumination quenches the off-discharge of individual off-elements, which thus were silenced by light and, as it were, set free by darkness.

All these results may be conveniently summarized in a diagram such as the one of Fig. 14. There are three fibers which, characteristically, are firing spontaneously. This activity serves as a background for the inhibitory effects as well as for the postexcitatory inhibition of Fig. 11, which without it could not be demonstrated. It was described very much later (Granit, 1945a). Element 1 discharges to onset of illumination and is silenced at "off." Element 2, as illustrated in 2*a*, is inhibited by light and discharges at cessation of illumination. In 2*b* the same element is supposed to suffer reillumination during its off-discharge and so again is inhibited. Element 3 is introduced merely to show how with one particular combination of excitation and inhibition there would be both an on- and an off-discharge. Such elements, in fact, tend to be the most common ones. All response types in this diagram have been seen in actual experiments with retinal elements.

There is, however, a hypothetical component in this brief presentation of the on/off system. This is the notion that inasmuch as purity of type could be definitely established, the pure on-element *always* would be excited at "on" and inhibited at "off," the pure off-element *always* inhibited at "on" and excited at "off." Actually the pattern of opposite retinal potentials, from which the search for inhibition started, fitted into this scheme, at least as well as could be expected with such complex structures. Production of inhibition in its purest possible state by reillumination on top of the off-effect coincided with the onset of the cornea-negative change of Fig. 12 (Granit and Therman, 1935; Granit and Helme, 1939), while excitation was found to depend on the cornea-positive potential (Granit, 1947, 1952b; cf. Noell, 1953). This, at the time, was the earliest evidence for the view that sensory excitation and inhibition was characterized by opposite changes of potential. It has been fully discussed in Granit (1947, 1952b).

Chapter 2

Peripheral Principles of Organization Discovered in Skin Organs and Retina. Fiber Size. Receptive Fields. Receptors Re-represented in the Brain

1. Introduction. Background of electrophysiological work

THE body turns a large sentient surface toward the external world, and this great primitive sense organ has in the course of evolution evolved focalized structures for specific tasks. To these also belong several organs for space analysis, e.g. the "glorified heat spots" of the retina (Sherrington's term, 1941), reaching to astronomical distances, the vibrissae of certain carnivora—studied by Fitzgerald (1940)—for displacing touch a little further away from the surface than can be done by hairs of ordinary length, or the temperature receptors which in certain snakes have developed into a special kind of eye for the reception of infrared radiation. The impulses from this heat-sensitive structure have recently been studied by Bullock and his collaborators (1952, 1953).

The principle of focalization combined with specialization received great attention in classical psychophysics because of the discovery by Blix of Lund (1882–83, partly translated into German 1884) of the punctate representation of cold, warmth, and pressure. Investigation of touch spots, pain spots, etc. has ever since been a recognized part of skin physiology, just as the Von Frey hairs and algesimeters of different types have been part of the standard equipment in most physiological class rooms. To Von Frey (1895) we owe the notion that the Krause (1860) end-organs are the cold receptors and that the Ruffini (1891–92, 1894) cylinder terminal might be the warmth receptor. Many other end-organs have been identified with specific

sensory experiences but it serves no obvious purpose to repeat here what may be found in every textbook dealing with the sensory apparatus of the skin (see also the classical papers by Von Frey, 1894a,b, 1895, 1910). I mention heat and cold because they will be chosen as models in the following discussion of the problem of specificity of skin sensations and of the difficulties in identification. Today the zest for identification of sensory spots with structure is abating. The reasons for this illustrate present trends of development and therefore deserve some comment.

The difficulties of identification began to be noticeable at an early date. At that time "sensation" was often regarded as something simple and different from "perception," which was held to be more of an elaboration of the primary data from sense organs. There may be some foundation for distinctions along such lines in that sensory experiences can be more or less elaborated depending upon the significance for the organism of the information delivered. On the whole, however, the distinction between sensation and perception has lost its validity (cf. Graham, 1951), and by the last chapter of this book, if not before, it should be clear that a sensation is an exceedingly complex affair. For this reason the age-old question of what structure corresponds to what sensation may often be irrelevant, except when raised for highly specialized structures or in a very general fashion.

Bazett and his collaborators (Bazett *et al.*, 1932) tried to determine as completely as possible the number of sensory experiences obtainable from a piece of skin (prepuce) that afterward was sacrificed for histological study. They could not record more than four types of sensation—heat, cold, touch, pain—but the piece contained seven clearly differentiated types of ending. As early as 1905 Ruffini wrote:

> De 1891 à aujourd'hui, par l'application des méthodes plus électives au chlorure d'or et au bleu de méthylène, le nombre des formes connues s'est énormément accru, sie bien que ne croyons pas exagérer en disant que la peau, tant en surface qu'en épaisseur, est littéralement remplie d'expansions nerveuses. Et tandis qu'avant cette époque les fonctions étaient beaucoup plus nombreuses que les formes, aujourd'hui, par contre, cettes-ci ont pris leur revanche sur les premières [p. 422].

This is one of the many situations in biology in which the extreme rationalist might have had expectations other than those of the empiricist. The former might have referred to Occam's razor: *entia non sunt multiplicanda praeter necessitatem.* But the biologist's attitude

should be humbler. His duty is to admit that he does not know nature well enough to understand its requirements or "necessities." This is why he experiments. Some of the histological "entities" may be there to facilitate discrimination by providing a greater variability of pattern; some touch receptors may adapt quickly, as those originally described by Adrian and Zotterman (1926b), others very slowly, as those found by Frankenhaeuser (1949), which are unorganized endings in the rabbit's skin. Some may be there for purposes not necessarily connected with what we call perception (which is a psychological term). Many of these difficulties are clearly of a conceptual nature and do not in the same way taint electrophysiological work.

When the electrophysiologist finds an isolated pacinian corpuscle, which is easy enough in the flexor aspect of tendons (Adrian and Umrath, 1929) and particularly in the mesentery, where they can be seen as small translucent ovals embedded in a still more transparent medium, he can also demonstrate that it is fired by light touch or pull. Gammon and Bronk (1935) found these rapidly adapting organs to be sensitive enough to discharge to the pulsations of the mesenterial vessels (cf. Gernandt and Zotterman, 1946), much as do the slowly adapting pressoreceptors in the carotid sinus wall (Bronk and Stella, 1932, 1935; U. S. von Euler, Liljestrand, and Zotterman, 1941).

The pacinian corpuscles are visible to the naked eye, their long axis being 2 mm., and the organ consists of concentric lamellae around a stalk with a terminal expansion, thus admirably suited to perceive localized pressure changes. Their impulses, as elicited by pressure, were first recorded by Adrian and Umrath (1929) from the nerve to the plantar fascia of the cat's hind foot (for later work on their generator potentials see Chapter 1, sec. 3). From such experiments one may infer that these structures, wherever they may be found, have a similar specificity, as envisaged for the Pacini organ by e.g. Rauber (1867), Von Schumacher (1911), and Sherrington (1900b), the last of whom stated: "The ordinary Pacini, embedded in muscle, is admirably placed for being compressed, especially when, as sometimes, seated in the retiring angle between a septum or aponeurosis and obliquely inserted muscle bundles" (p. 1010). Von Schumacher, who demonstrated that the basal pole of the Pacini organ was vascularized, also pointed out that they were so intimately joined to the mesenterial vessels that they were bound to respond to variations of blood pressure (cf. Sheehan, 1933). A review of the old literature on the pacinian corpuscles and their discovery has been given by Gray and Malcolm (1950).

Some further difficulties in identification might be mentioned. Sensation as a measurable entity is defined psychophysically in c.g.s. units, the precise values of which are difficult to assess with organs hidden within the skin. Sensations as well as impulses in response to touch and pressure arise from skin deformations with unknown distribution of the forces around the organs. Heat and cold have extension and gradients in all three space coordinates. Definition of the sensation in c.g.s. units may therefore prove deceptive. The punctiform mode of stimulation may often be an abstraction. Also, some sensory qualities may not be as fundamental as commonly stated.* I, for one, feel that there is no difference between the modalities of "touch" and "pressure" other than one of quantity (strength). They are not so distinctly different experiences as the two qualities "red" and "green." Itching or tickling seems to me more genuine as a quality and yet, on reasonably good evidence, electrophysiological (Zotterman, 1939) as well as clinical (cf. Pritchard, 1932; Walshe, 1948), it is held to be a combination of messages from touch and pain organs, possibly only from pain organs feebly stimulated.

Specificity, as defined by electrophysiological means, may have its limitations—it cannot deal with itching—but, when one does define any given peripheral afferent fiber as belonging to a sensory "thermometer," "tactometer," etc., the appropriate adequate stimulus has been picked up by the "meter" with one of those particular properties independently of whether specificity resides in form as seen under a microscope or in something else. It is not difficult to find examples of sensitivities to specific agents which are properties of nervous tissues. The papers on chemical stimulation of nerve fibers are legion. Mechanical stimulation is also well known (Tigerstedt 1880). In our laboratory we have devoted considerable attention to the fact that nerve fibers themselves are quite sensitive to temperature changes (Bernhard and Granit, 1946; C. von Euler, 1947; Granit and Lundberg, 1947; Lundberg, 1948). C. von Euler found that small afferent fibers discharge specifically to heat of only a few degrees above normal, while large fibers fire to cooling. These effects are extremely selective and the turning point from heat to cold discharge is around a fiber diameter of 5–6μ. Small efferents cannot be thermally stimulated (C. von Euler). More recently Dodt (1953) has found that the cold fibers (below 5–6μ) also respond to cooling but not to heat. Other valuable observations on thermosensitivity of nerve fibers were reported in his paper. Here,

* One speaks of "modalities" such as hearing, sight, pain, temperature, and touch, within each of which are distinguished "qualities" such as color, tone, etc.

then, is a kind of specificity, perhaps primitive from the point of view of sense organs but obvious enough to make one realize that very little improvement of this property in either direction would be needed to provide us with two temperature end-organs neither of which need be like a Krause end-organ or a Ruffini terminal cylinder in appearance.

At the opposite extreme there are the glorified heat spots of the retina which perceive light of the order of a few quanta at the absolute threshold (Von Kries and Eyster, 1907; Hecht, Shlaer, and Pirenne, 1942; Bouman and Van der Velden, 1947; Baumgardt, 1950; Pirenne, 1953), and the no less glorified mechanoreceptors in the organ of Corti that are held to respond to vibration of an amplitude of the order of a fraction of the diameter of the hydrogen atom (Von Békésy and Rosenblith, 1951). With these structures specificity is such a unique achievement that they must also be (structurally) unique.

Lesser degrees of specificity may well be found in unorganized endings. Weddell and his colleagues (Hagen *et al.,* 1953; Sinclair *et al.,* 1952) recorded the number of touch, pain, cold, and warm spots per unit area in the ear for comparison with similar measurements on forearm and finger tips (right ring finger). There were only minor differences in the number of such spots in the places chosen and the four sensory experiences were everywhere the same. The skin of the ear was found to be well innervated but there were no organized endings such as the organs of Krause, Ruffini, or Meissner (tactile corpuscles). Yet cold, heat, and pressure were perceived. The cartilage did not contain any nervous tissue apart from the fibers accompanying the blood vessels. The finger tip was found to contain both free and organized endings. They write about the latter:

> We cannot detect any distinct varieties of the fine arborizing terminal and in the organized group there appears to be an unbroken and graded series of end organs from the simplest to the most complicated, from superficial, loosely encapsulated whorls to the thickly capsulated highly complex dermal corpuscles. If we can rid our minds of the desirability of fitting each observed ending into a rigid classification, we are forced to admit that no such classification can justifiably be made. One type of ending insensibly merges into another, and intermediate forms occur in profusion. Our histological findings, therefore, do but confirm the much neglected statements made by Ruffini,* who noted the existence of intermediate forms and the futility of rigid classification.

* Ruffini (1905).

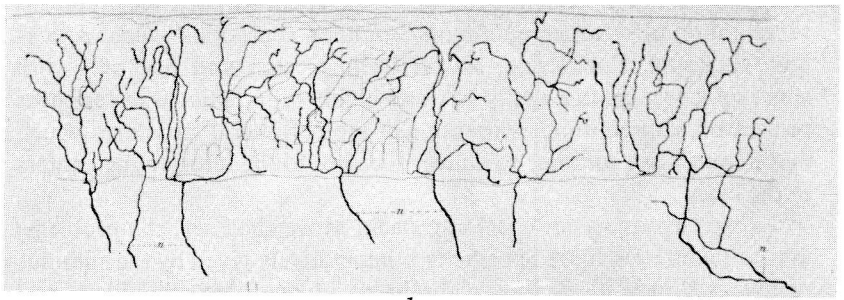
It might be added that many other histologists (see e.g. Stöhr, 1928) and also psychologists (Nafe, 1942; Morgan, 1951; Jenkins, 1951) have taken similar standpoints.

Fifty years ago Sherrington (1900a) spent twenty pages of his presentation of skin perception on "common sensations" such as tickling, shivering, shuddering, sexual feelings, etc., and one may with some right assume that many of those highly differentiated experiences project back upon minor variations in the peripheral structures which in different ways combine to deliver the cues to the interpreting centers in the brain.

To the electrophysiological approach, as we shall see, the problems appear in different light. Specificity is immediately given by the stimulus of lowest threshold eliciting a discharge in one particular fiber, and identification of the specific end-organ has for its ultimate goal analysis of its physicochemical properties by microtechniques (which so far, however, have not been applied to skin organs). Since the afferent nerves must terminate somehow, it seems only natural that the skin should be "punctuated" by various types of receptors, as was admirably elucidated by a previous generation of workers despite the many difficulties alluded to above. The histology of skin innervation is the natural starting point for electrophysiological research. There are the curious plexus formations looking like skeins and described by the early workers (and by nobody of that period better than by Retzius, 1892) and also the organized endings whenever they can be localized. In more recent times Woollard, by the introduction of his methylene blue *intra vitam* stain (1935–40), again drew attention to the plexus formations, and since Woollard's death his work has been continued by his former collaborator Weddell (see his summary, 1945). The advantage of this method is that both the fiber and its endings can be traced. It must be admitted that at the moment histology still is far in advance of physiology, and the electron microscope is likely to add a few hundred years to this lead.

It appears from Woollard's and Weddell's work (see Fig. 15b) that the cutaneous nerve plexus consists of two layers of dichotomized nerve fibers forming a meshwork from which fibers run as beaded terminals to the epidermis as well as to the hairs. Some of Retzius' drawings are given as Fig. 15a. The network from any one fiber is interlocked with that of neighboring fibers, a single fiber innervating an area the size of which presumably depends upon the region in which it has been found. Two networks were known also at the time of Von Frey, who wrote (1894b): "What this double innervation

means from the physiological point of view, if the lower network serves pressure and the other possibly pain . . . cannot at the moment be decided" (p. 296). Waterston (1933), confirmed by Woollard (1936–



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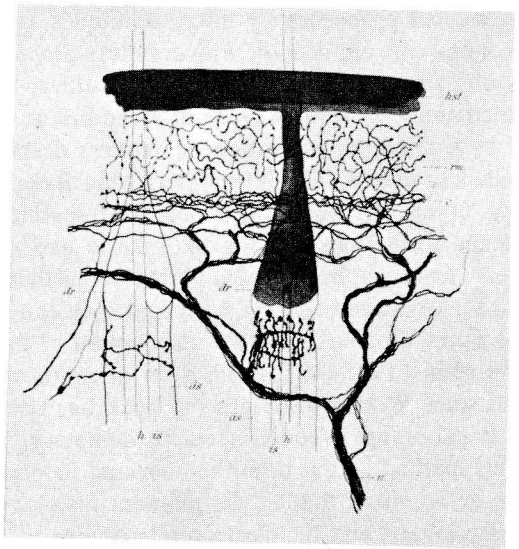

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Fig. 15a. Skin innervation. a1: vertical section through epithelium of soft palate of human foetus showing nerves (*n*) ending in free beaded terminals. a2: Mouse. Innervation of hair roots from cheek. (Retzius, *Biologische Untersuchungen, 4,* 1892.)

1937), showed that the epithelium with its nerve endings could be sliced away without causing sensations other than touch. Woollard stated that these epidermal endings are rare in man and may be regarded as an accessory organ of touch. The subepidermal nerve net, on good evidence, is held to subserve pain (Woollard, Weddell, and

Harpman, 1940). There is definitely branching of one fiber to several end-organs of a single type as well as multiple (overlapping) innervation of hairs. Thus, for instance, the number of hair follicle groups supplied by branches from one fiber was

> in the neighbourhood of 300, and a group of hair-follicles may contain up to 10 hairs. The terminal ramifications of every main fibre,

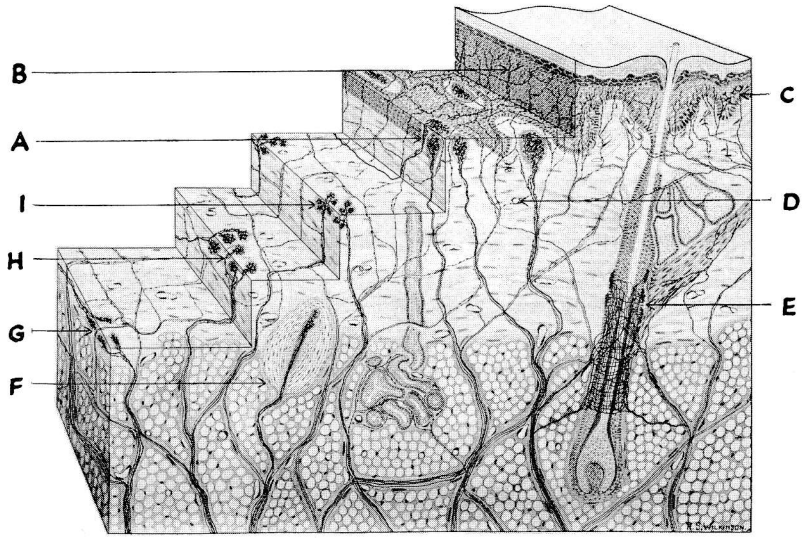

Fig. 15b. Weddell's conception of cutaneous innervation, based on the studies described in his article. *A:* groups of Meissner's corpuscles subserving the sensation of touch. *B:* beaded nerve nets subserving pain (probably fast pain). *C:* Merkel's discs subserving touch. *D:* beaded nerve fibers derived from nerve nets subserving pain and associated with blood vessels (probably slow pain). *E:* nerve terminals around the sheath of a hair subserving touch. *F:* a pacinian corpuscle subserving pressure. *G:* a group of Ruffini endings subserving warmth. *H, I:* groups of Krause's end-bulbs subserving cold (these lie at somewhat variable depths beneath the skin surface). Note: The organized endings are accompanied in every instance by fine-beaded nerve fibers subserving pain. (Weddell, *Brit. Med. Bull., 3,* 167. 1945.)

> when traced, were found to remain independent from those of other fibres, but it was noted that each hair-follicle group was supplied by branches from *at least two main nerve-fibres.* This also applies to individual hairs . . . so that a single hair may be innervated by as many as 15 terminal ramifications [Weddell, 1945, p 170].

It is interesting to note that Von Frey (1894a) found up to 15 pressure-sensitive points around the hair stalk.

The encapsulated or otherwise organized endings also tend to occur in groups (Meissner, Pacini, and Merkel tactile corpuscles). Multiple innervation is established only with hairs, but several adjacent encapsulated endings of the same type may be innervated individually or by branching from one fiber. Evidence has been obtained in favor of associating the Meissner corpuscles with touch and the Krause end-organs, when they occur, with cold (see the summary by Hensel, 1952). An interesting point is that the well-known innervation of the hairs and encapsulated endings by an accessory fiber, to which so many authors (for references see Woollard, Weddell, and Harpman, 1940) have drawn attention, is ascribed to the nerve nets subserving pain. As has been pointed out by Woollard (1936), Weddell (1945), and Le Gros Clark (1947), this would provide a simple explanation of the observation (Von Frey, 1894a) that any specific stimulus if sufficiently intense will cause pain. While the threshold to pressure (touch) is around 2–3 gr/mm.^{2}, it is necessary to use 200 gr/mm.^{2} to elicit pain from touch spots (Von Frey, 1894a).

From the electrophysiological point of view the problems of skin innervation canalize themselves into four main channels of approach, all of which recur with other sense organs. (1) The study of specific responses to adequate stimuli (touch, pressure, temperature, etc.); the description and analysis of the sensory endings down to the final stage of microscopic identification with microtechniques. (2) The responses should be analyzed from the point of view of principles of organization. One of the leading principles deals with the organization of receptors of the same type into receptive fields. (3) A fundamental problem concerns the significance of fiber size. (4) Finally, the role of the accessory fibers should be elucidated by electrophysiological means.

2. *General experiences with skin afferents*

In a sufficiently thin branch of a mixed nerve the impulses running in medullated fibers of different size stand out by their differences in spike height. It has been found (cf., for the early work, Erlanger and Gasser, 1937; for later work, Gasser and Grundfest, 1939) that the relative size of the spikes in A-fibers of different diameter is proportional to conduction rate, which in its turn is proportional to fiber diameter (Hursh, 1939a,b; Tasaki, 1953). Rushton (1951) has recently integrated all the observations of Gasser, Erlanger, their coworkers, and others on conduction velocity and fiber diameter in a theoretical interpretation based on internodal length, to which reference may be made. For the present purpose it is enough to realize that in very thin strands of nerve it is generally possible to conclude from differences in spike height that the spikes observed are from individual afferents conducting at different velocities (for exceptions, see Paintal, 1953). Thus, some identification is possible without actually splitting the nerve strand into single units, provided that the nerve itself contains fibers of different size. A cross section of a skin nerve, presented in Fig. 16, shows the latter postulate to be true. Spike heights and

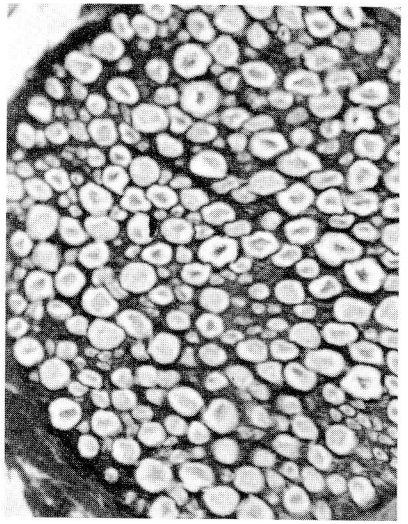

Fig. 16. Cross section of part of cat's saphenous nerve, stained by Alzheimer-Mann method.

conduction velocities, both referable to fiber diameter, have therefore become important landmarks in the identification of specific sensitivities and as such will be continuously referred to in these lectures. Erlanger (1927) was the first to demonstrate that specific sensitivities often were represented in afferent fibers of different size.

In 1934 Gasser gave a summary of older and newer attempts to refer specific sensations from the skin and other receptors of the limbs to different fibers on the basis of (1) compression experiments, which act by pressure and asphyxia (cf. Frankenhaeuser, 1949), and (2) on local anesthesia. At the time he could make out a good case for the view that differentiation by compression first attacked large fibers, while local anesthesia suppressed small fibers before large ones (because of the experiments on electrical identification of fiber size under

such conditions: Gasser and Erlanger, 1929). There were, however, considerable discrepancies between the results of various observers, and we have since had the experiments by Frankenhaeuser (1949), in which it was proved that rapidly and slowly adapting fibers in the rabbit's skin had the same range of conduction velocity, yet the former survived compression a great deal better than the latter. While this does not invalidate the general differentiation by compression in the sense that large fibers suffer before small ones, it is clear that the method never can be very critical. There were already at that time many electrophysiological observations on single fiber preparations from receptors with different specificities, and their number has since increased. A very complete tabulation of available data has been made by Hensel (1952). I shall mention actual figures below, as I proceed with the description of skin afferents. These have supported Gasser's conclusion, reiterated in 1943, "that the fibers belonging to different modalities must be widely distributed throughout the various fiber sizes."

This statement should not be interpreted to mean that there is a complete random distribution of skin sensations over the fiber spectrum. Cold and warmth, as we shall see below, have been found represented only in small fibers, wholly overlapping with pain. Paintal (1953a), in a study of vagus afferents, found the mean conduction rate of fibers from slowly adapting pulmonary stretch receptors to be 36 m/sec., from rapidly adapting ones 25 m/sec., from depressor receptors 33 m/sec., from right atrial types of receptors 20 m/sec., from chemoreceptors 10 m/sec., and from receptors firing on injection of phenyl diguanide 6 m/sec. For other receptors see Hensel's table (1952).

Gasser's (1943) summary of the status of pain is still valid today, eleven years later: barring the objection that the study on animals has to be carried out by observing reflexes or spikes aroused by supposedly painful stimuli (burning, scraping, crushing), it seems perfectly clear that the large majority of pain fibers are to be found among the unmyelinated smallest fibers of all, conducting at rates below 2 m/sec. These give the characteristic massive sensation of burning, lasting pain or "second pain," while a faster group conducting at 15–20 m/sec. or more seems responsible for the initial pain or "first pain" (pin prick) which is experienced too early for the unmyelinated ones to be involved. There is nothing to add to Gasser's clear presentation of this problem, but some papers may be recommended as leading references for a study of the relevant evidence (Ranson and Billingsley, 1916; Adrian, 1931a; Zotterman, 1933; Heinbecker, Bishop, and O'Leary, 1933; Heinbecker, O'Leary, and Bishop, 1934; Clark, Hughes, and Gasser, 1935; Zotterman, 1936, 1939; Woollard, Weddell, and Harpman, 1940; Gernandt and Zotterman, 1946; Maruhashi *et al.,* 1952). The early experiments by Ranson and Billingsley, carried out in the pre-electronic era of research, were particularly interesting. Making use of the fact that in the cat the small fibers enter separately in the lateral portion of the root, they succeeded in cutting them selectively by a small incision into the spinal cord. Reflexes characteristic of pain then disappeared. Unfortunately this arrangement is not found in man. It is only in the trigeminal region that the small fibers can be separated from the rest. Sjöqvist's (1938) operation, the section of the bulbospinal tract of the trigeminus nerve, is based on this fact and leads to complete loss of pain in the face, thus vindicating the conclusions of electrophysiology (cf. Zotterman, 1933, 1936).

Tactile fibers seem to be distributed over a particularly large range of the spectrum, the fastest conducting at 90 m/sec. and the slowest at 2–20 m/sec. Considering that tactile fibers arise from such widely different structures as the terminals around the hairs and encapsulated endings such as those of Meissner, Pacini, and Merkel (see e.g. Woollard, 1936; Weddell, 1945), this also should be expected. Localized microrecording would be needed to develop this problem in detail. (For references see Adrian and Zotterman, 1926b; Adrian, 1928, 1932b; Zotterman, 1939; Maruhashi *et al.,* 1952; Hensel, 1952.) Most of the early work following Adrian was carried out on frog skin (Dun and Finley, 1938; Adrian, Cattell, and Hoagland, 1931; Cattell and Hoagland, 1931; Talaat, 1933; Hogg, 1935; Echlin and Propper, 1937; Fessard and Segers, 1943).

The ambition of the experimenters was generally directed toward isolating single fibers. However, from the point of view of sensation as well as the understanding of what a simple stimulus really can do, it is of equal interest to follow the events in a thin strand of nerve fibers from a given region in the skin. This was done by Zotterman (1939), from whose work Fig. 17 is taken. It illustrates the frequency distribution of rates of conduction of impulses in response to the stimuli characterized in its legend. The values were sometimes measured directly but were also calculated from the spike height.

Light stroke of the cat's fur (*A*) activated both slow and fast fibers; very light touch (*C* and *G*) activated fibers conducting as slowly as around 2 m/sec., thus overlapping with pain fibers. At least in man Waterston's (1933) results show that light touch is likely to be con-

ducted in very thin fibers. It should be noted that the spikes of the smallest unmyelinated fibers tend to be occluded in multifiber records. Zotterman had good evidence that pain (burning) elicited activity in such fibers. It will further be noticed that responses in the very small-

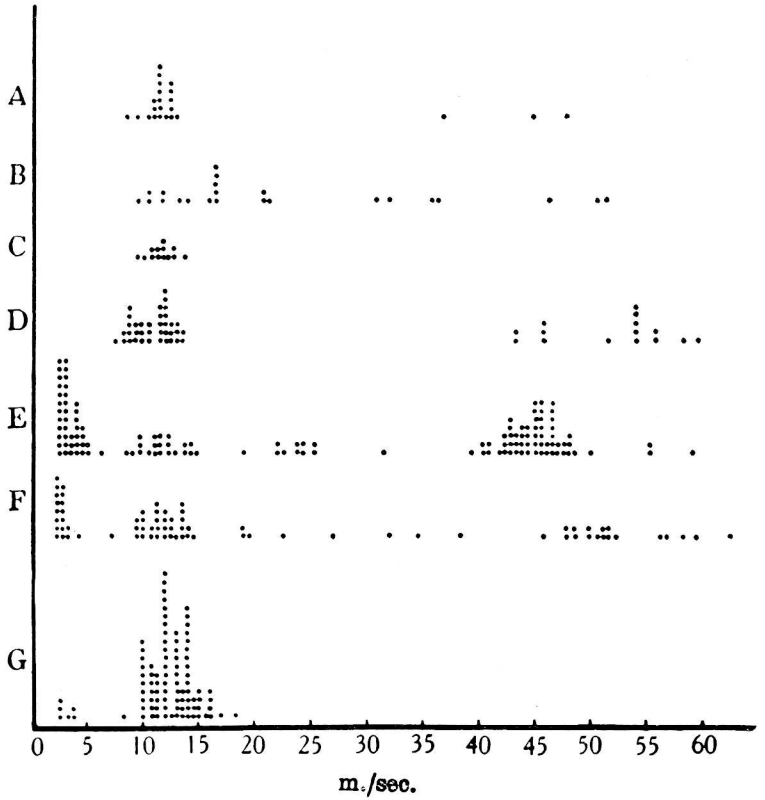

Fig. 17. The frequency distribution of rates of conduction of axon potentials recorded in response to: *A*, light stroke; *B*, pulling a few hairs; *C*, very light touch; *D*, very light stroke. The three lower diagrams give the distribution of the axon potentials according to spike height: *E*, needle prick; *F*, hard stroke; *G*, very light touch. Diagrams *B*, *C*, *E*, *F*, and *G* all come from the same nerve preparation. (Zotterman, *J. Physiol., 95,* 1. 1939.)

est myelinated (and very likely also unmyelinated) fibers appeared with stimuli as widely different as hard stroke (*F*) and very light touch. The actual records showed them to be late and usually appearing as an afterdischarge when stimulation was over, even though only a few hairs had been moved. Zotterman associated this discharge with

tickling or itching, as he found these sensations to be absent in the face of patients who had undergone Sjöqvist's operation. Tickling would therefore be a combination of touch and pain. The existence of accessory pain fibers to the hairs, alluded to above, may also be adduced in support of his view. Alternatively we may have to assume the existence of double specificity (see below), touch combined with pain, or else interaction between the two in the nerve nets below the epidermis. Inasmuch as interlacing of touch with pain fibers may occur in this network, interaction is quite possible under pressure (Granit, Leksell, and Skoglund, 1944), perhaps even without it (Arvanitaki, 1940). Again we conclude that there is room for investigation of skin receptors and skin afferents with microstimulation. Whatever the causes of the rich fullness of response in Zotterman's experiment, it shows that simple stimuli activate complicated response patterns and emphasizes the necessity of going beyond single fiber analysis in the study of sensation. This was also pointed out by Adrian in his early summary (1928).

So far we have implicitly accepted the idea of single specificities as the basis of interpretation. This is nothing but Mueller's well-known law of "specific energies" in the modern version, namely that end-organ specificity is matched by specificity within a central interpreting structure. Have we any electrophysiological reasons for criticizing this law? Recently Hensel and Zotterman (1951b) were able to locate in the cat's tongue two types of pressure afferents, the large "ordinary" pressure spike conducted in fibers of 12–15μ in diameter and a smaller one in fibers of 8–10μ. The latter is also excited by cooling, but whereas the specific cold receptors (in still smaller fibers) go on discharging permanently to a certain temperature, the cold-sensitive pressure receptors do so only for a few seconds. The effect of direct cooling of the nerve fibers seems excluded by satisfactory controls as well as by the results of Dodt's (1953) later study of thermosensitivity in nerve. The large pressure spike could be excited only by cold sufficient to stimulate its nerve fiber directly. It thus differed from the small pressure spike in being specifically sensitive to pressure alone. The high cold sensitivity of some afferents may well reside in the finest nerve terminals rather than in the end-organ itself.

Recently it has been reported by Bullock and Faulstick (1953) that single afferents from the facial pit organ of the rattlesnake, which is specifically sensitive to infrared radiation, also subserve touch. Zotterman and Hensel did not question Mueller's law. They suggested that the combined cold-pressure receptor has what I have called double

specificity because of some common basic principle in the function of thermo- and mechanoreceptors. Other alternatives were mentioned above. One might also consider release of excitatory substances in the nerve net (Echlin and Propper, 1937; Feng, 1933; Hogg, 1935) as very convincingly demonstrated by Habgood (1950).

At present, however, double specificities in the sense that two "meters" have relatively low thresholds seem to be exceptions, and the rule is that an afferent is connected to one or several receptors which respond to one particular, so-called adequate, stimulus with greater facility than to any other, i.e. with the lowest threshold. Therefore, relative spike size (conduction velocity) in combination with determination of the adequate stimulus are in actual practice still the two means used for electrophysiological identification.

What role can we ascribe to fiber size from the point of view of central interpretation of the frequency code? Gasser (1943) has pointed out that faster rate of conduction means that impulses in larger fibers can initiate or facilitate effects which impulses in slower fibers then go on to elaborate. He has also drawn attention to the longer duration of the impulse in small fibers. Certain central systems may therefore require spikes of long duration to become activated. Much of Gasser's work (see e.g. in Erlanger and Gasser, 1937) has gone to show that in fibers of different type there are considerable differences in the slow so-called afterpotentials following upon an impulse. It is not known whether these differences play a significant role in the fine terminals at the point of destination of the spike. Gasser himself has chiefly stressed the element of timing. "The more one sees of the exquisite precision with which events take place in the central nervous system the more one is impressed by it. The more the idea of timing grows in meaning content the more it becomes a directive for future exploration. Differential axonal velocities must play their part in the mechanism. Be this their only contribution to integration, it is still a large one" (Gasser, 1946, p. 141).

To this one might add the surmise that fiber size must mean something also in terms of the receiving station in different parts of the brain. Why, for instance, is the number of small fibers so very much greater in the ipsilateral than in the contralateral optic tract (P. O. Bishop, Jeremy, and Lance, 1953, confirmed by myself)? The sense organs, as we shall see, have other projection areas than the well-known specific ones.

3. Specificity illustrated by thermoreceptors. Re-representation in centers

Among the skin perceptions the temperature sense is particularly interesting. This is partly because the psychophysical theories (recently reviewed again by Hensel, 1952) have exceeded in number and complexity what the subject could afford in view of the relative ease with which they could be tested by spike recording, partly also because of the analogies with direct thermal stimulation of peripheral nerve. The rule is that cold and warmth receptors are highly specific

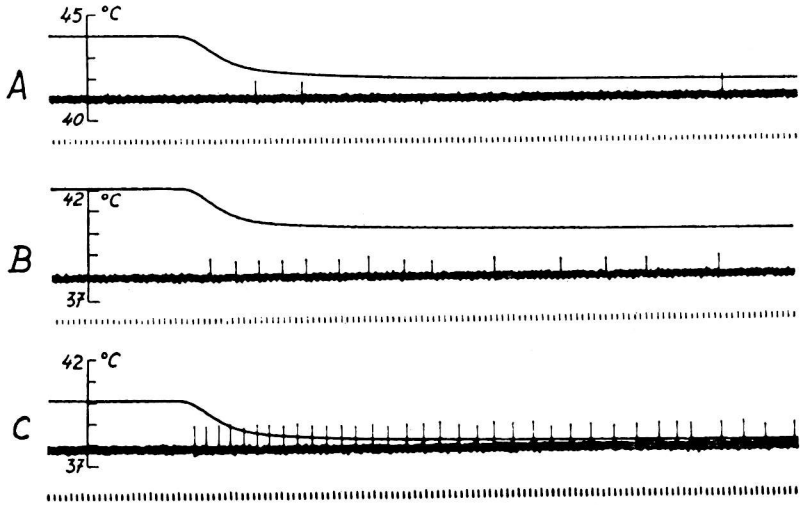

Fig. 18. Impulses in single cold afferents from the lingual nerve of the cat in response to sudden temperature drops of 2°, as recorded above the spikes: *A*, 44 to 42°; *B*, 42 to 40°; *C*, 40 to 38°. Time in 1/50 sec. (Hensel and Zotterman, *Acta physiol. scand., 23,* 291. 1951a.)

(Zotterman, 1935, 1936), both effects being transmitted in relatively thin fibers (4–6μ). In the cat's tongue the warmth fibers give larger spikes than the cold fibers, as again confirmed by Dodt and Zotterman (1952a). Thanks to the psychophysical experiments of Hensel (1952), who developed excellent stimulating devices, and the electrophysiological ones of Hensel and Zotterman and Dodt and Zotterman, we are now better informed about temperature receptors than about any other type of skin organ, and for this reason, too, their results deserve to be singled out for a presentation of the problem of specificity as it appears in the light of two well-analyzed skin organs.

These organs, not unexpectedly, turned out to behave like other relatively nonadapting receptors: to sudden stimulation they responded with a discharge characterized by a high-frequency onset, gradually petering out into a low-frequency constant discharge. This is well illustrated by Fig. 18 for temperature drops of 2° starting from three different levels, 44°, 42°, and 38°. Very clearly the drops of 2° of cooling were most effective at 38°. The slow rate of firing goes on indefinitely at sufficiently low temperatures and in this sense every cold receptor behaves like a thermometer capable of delivering information about the actual temperature of its surroundings. Some visual receptors and stretch receptors behave in the same way with respect to their adequate stimuli. With them and most other end-organs (Adrian and Zotterman, 1926a,b), the cold receptors also share the property of responding to the gradient stimulus intensity/time. Quick cooling causes a faster initial discharge than slow cooling. Both these aspects of behavior have been recognized in the psychophysical work of an earlier epoch (see Hensel's summary, 1952), but the clarity of the electrophysiological analysis makes further comments unnecessary.

Turning now to assemblies of cold receptors, I think that the existence of an optimum of sensitivity, so clearly shown by Fig. 18, is the most interesting feature in the design of the receptors for cold. In Fig. 19 a number of cold receptors have been analyzed from this point of view. The frequency of the final constant discharge plotted against temperature has optima at different temperatures for different receptors. Sensitivities at the optima are of the order of 2 spikes/sec. for 1° or 20% of the maximum frequency. Considered as organs for responding to disturbances of chemical equilibria set up by temperature changes, the specialization of the receptors upon specific temperature ranges is clearly a more elaborate solution of the problem of specificity than the design of one single organ equally sensitive to the full range needed. There is such an organ in some fish, the Lorenzinian ampullae, which respond to heat by acceleration, to cold by deceleration, of the spontaneous discharge (Sand, 1938). The rattlesnake's heat-sensitive facial pit also belongs to this type (Bullock *et al.*, 1953). Mammals apparently have greater differentiation. Again, Occam's razor does not apply. Inasmuch as the end-organs of Krause are responsible for the sensation of cold, these too vary a great deal in appearance, as shown by Belonoschkin (1933) in preparations from the human mamilla, where they are particularly dense and cold sensitivity also is high. When the many differentially cold-sensitive end-organs act together, they actually cover the range from 40° to 20° by an approximately linear increase of the *total* discharge frequency. It is tempting to suggest that the fractional subdivision of this range also is there for some purpose of its own. It may, for instance, have some significance in the thermoregulation, perhaps in the sense that the receptors with maxima of sensitivity at low temperatures might be more active than the others in eliciting certain compensatory reflexes of thermoregulation. This, however, at the moment remains a conjecture, based on the general notion that thermoregulation is far more important in mammals than in, say, the poikilotherm fish.

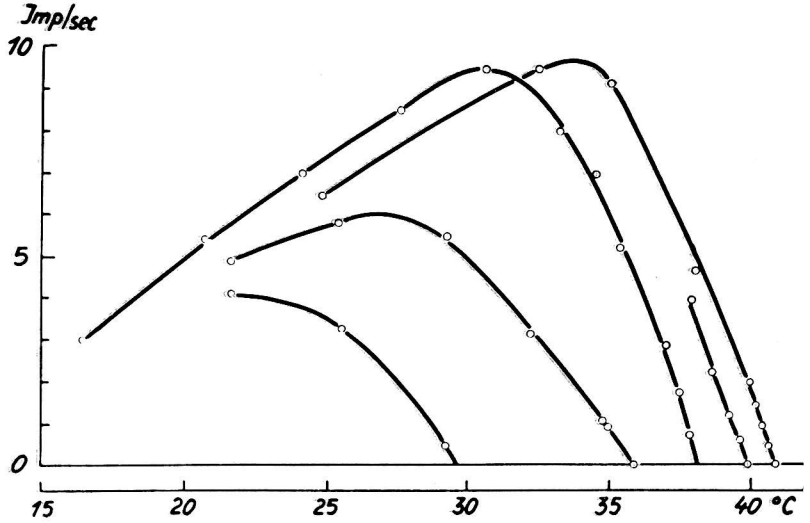

Fig. 19. The steady discharge of different isolated cold afferents in the lingual nerve of the cat as a function of temperature of the tongue. (Hensel and Zotterman, *Acta physiol. scand., 23,* 291. 1951a.)

Hensel and Zotterman (1951c; Hensel, L. Ström, and Zotterman, 1951), with thermodes on both sides of the cat's tongue, measured the temperature gradients and spike latencies and could actually localize the depth of the cold receptors with considerable accuracy (to 0.2 mm.). Yet they did not from their histological control (Palmgren silver stain) attempt any further identification than to state that the cold receptors were situated subepithelially partly in the papillas, particularly at their base or just beneath them. However, the tongue is richly supplied with Krause end-organs (Krause, 1860, pp. 112–39; Gairns, 1953).

The warmth receptors (Dodt and Zotterman, 1952a) respond to

heating just as do the cold receptors to cooling, and their range is shown in Fig. 20. There is a similar differentiation among the warmth receptors with respect to their optima, but in the diagram the whole assembly, compared with that of Fig. 19, is shifted to the right. Nevertheless, the overlap is sufficient to make it seem a difficult task for the center to distinguish steady warmth from steady cold in the same skin region without the aid of secondary cues. Actually there are such cues. The cold receptors fire at a steady rate, the warmth receptors in an irregular spluttering fashion and also at considerably lower frequencies

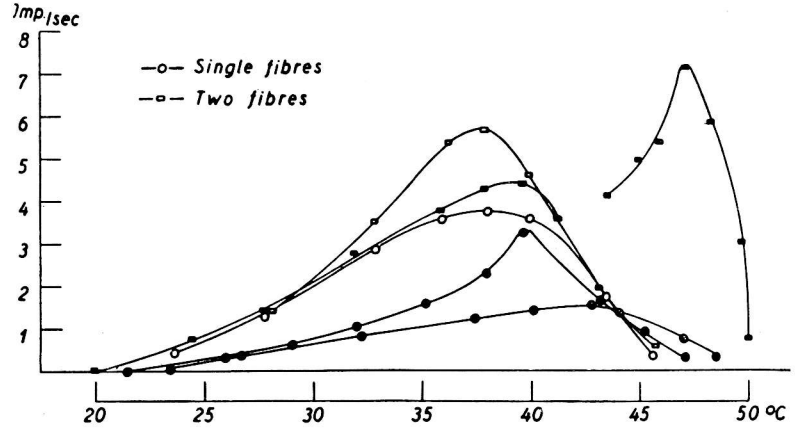

Fig. 20. Graphs showing the frequency of the steady discharge of different single and dual warm fiber preparations as a function of the temperature of the tongue. (Dodt and Zotterman, *Acta physiol. scand., 26,* 345. 1952a.)

than the cold receptors. Fiber size provides an additional cue. Also, when sensory discrimination is concerned, the leading principle, as we shall see, is always one of differentiation by pattern as a cue, and this seems achieved by the statistical sensitivity distributions of the individual receptive units (Figs. 19 and 20).

The degree of specificity of the cold receptors is actually considerable. This is perhaps best illustrated by the well-known sensation of paradoxical cold, discovered independently by Lehmann (1892) and Von Frey (1895, 1910). This is a feeling of cold to stimulation with heat from 45° upward. Dodt and Zotterman (1952b) have succeeded in demonstrating that there is a corresponding discharge of the cold receptors at high temperatures, as illustrated by the secondary rise of the curve for the cold receptor at high temperatures in Fig. 21. The curve for a typical warmth receptor has been inserted for com-

parison (Dodt and Zotterman, 1952a). Pain fibers will also be stimulated at this temperature (Zotterman, 1939) and, as the sensory threshold for pain in response to heat is around 47–48° (Skouby, 1952), admixture of pain may explain the curiously biting character of the sensation of paradoxical cold (cf. Zotterman, 1953). The behavior of cold and warmth receptors at extreme temperatures have been further elucidated by Dodt (1952b). Cold fibers have also been studied in isolation by Maruhashi, Mizuguchi, and Tasaki (1952). These fibers were from abdominal skin nerves and the plantar nerves (cat) and were found to be between 1.5 and 3μ in diameter, hence the smallest among the myelinated fibers.

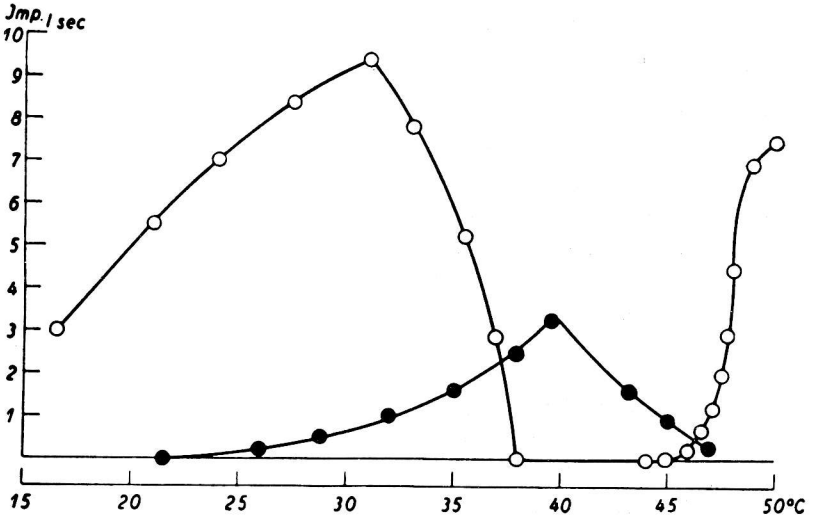

Fig. 21. Graphs showing to the left the steady discharge of a typical single cold fiber (*open circles*), in the middle a typical single warm fiber (*filled circles*), and to the right the paradoxical cold fiber discharge (*open circles*) as a function of the temperature. (Dodt and Zotterman, *Acta physiol. scand., 26,* 345. 1952a.)

A theoretical physicochemical explanation of the high degree of specificity of the temperature receptors is still lacking. The observations on heat and cold sensitivity of nerve fibers (cf. in particular the papers by C. von Euler, 1947; Lundberg, 1948; and Dodt, 1953) suggest an interesting indirect approach by way of analyzing membrane potentials in nerve fibers as influenced by temperature changes.

The observations on temperature receptors have disclosed that they will discharge permanently within the whole range of temperatures to

which the body is likely to be subjected. This seems particularly important in view of their role in thermoregulation, which requires continuous information from receptors. In this task the receptors cooperate with the thermoregulatory center in the hypothalamus known and studied for a number of years in several laboratories. References may be made to summaries by Thauer (1939), Ranson and Magoun (1939), Ranson (1940), Stoll (1943), Grant (1951), Hensel (1952), and Zotterman (1953). Lately a number of fresh experimental contributions have been published by Uvnäs and his collaborators, G. Ström and Folkow (Folkow, Ström, and Uvnäs, 1949a,b; Ström, 1950a–c), who used vasodilatation as an indicator. From our point of view the central issue concerns the existence of thermoreceptors in the brain itself. In agreement with the original observations of Ranson's school (Magoun *et al.*, 1938; Beaton *et al.*, 1941, and Hemingway *et al.*, 1940), Folkow, Uvnäs, and Ström (see in particular the paper by Ström, 1950a) also find that the anterior hypothalamus is sensitive to local heating with a diathermic needle point, but not to cooling.

Another fresh approach is that of C. von Euler (1950), who noted that heating in this fashion of the hypothalamic region sets up a local slow potential obtainable only within a highly circumscribed region in the anterior hypothalamus. This slow potential is shown in Fig. 22. It correlates well with thermoregulatory reflexes to heat and is the most sensitive index of the effect hitherto found. Hence, this central response is exceedingly specific. Actually, in the best cases, Von Euler obtained a change of potential of 1 mV. per 0.1°. No similar effect to cooling could be found anywhere in the brain. Von Euler suggests that these "heat" potentials serve as generator potentials for the regulatory reflexes panting, sweating, vasodilatation, etc. The hypothalamic local response to heating would therefore mean that the warmth receptors are re-represented in the brain.

These warmth receptors in the hypothalamus are of particular importance because of the relative scarcity of peripheral warmth receptors in relation to cold receptors (cf. König, 1943, 1944). The reflex effects of the latter might easily lead to an overproduction of heat combined with heat stagnation because of contracted skin vessels. The warmth receptors in the brain which respond to blood temperature will prevent this from happening. They are therefore likely to fulfill the role of brakes in a mechanism of self-regulation in the service of homeostasis.

This conclusion that a sense organ might be re-represented in the brain in order to improve certain types of self-regulation in the body

seems pregnant with possibilities, particularly for chemoreceptors. Von Euler and Söderberg (1952a,b) followed it up by demonstrating that the respiratory center in the medulla, which is known to respond to the arterial pCO_2 (see e.g. Heymans and Bouckaert, 1939), also sets up a slow change of potential to an increase of CO_2 in the inspired

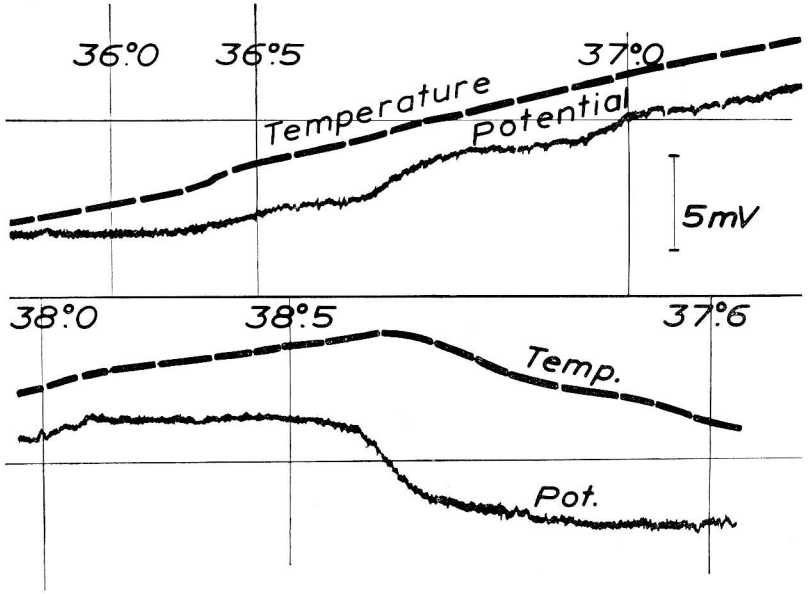

Fig. 22. From cat under urethane anesthesia. Temperature of the brain stem and temperature potential from a point 0.3 mm. in front of the anterior edge of the chiasma, 0.5 mm. lateral of ventr. III and 1.5 mm. dorsal of the ventral boundary of the brain, recorded simultaneously. Upper and lower halves of picture in direct succession. From this electrode site no potential changes could be obtained, owing to changes in blood pressure or respiration. The temperature potential follows the temperature only within a limited region. Records interrupted every 30 seconds. Retouched. (Von Euler. *J. Cell. Comp. Physiol., 36,* 333. 1950.)

gas. The effect was highly specific for CO_2 and was obtainable only within that region of the brain stem from which Comroe (1943) succeeded in eliciting respiratory responses by injections of a few μl. of buffered carbonate solution. Von Euler and Söderberg found the effect also in a completely denervated respiratory center, and it was associated with the production of a discharge in nerves to respiratory muscles. Thus, these structures had all the attributes of receptors: specific chemosensitivity, generator potential, discharge.

As is well known, Verney (1947) came to the conclusion that within the central area of distribution of the internal branch of the common carotid there were receptors specifically sensitive to osmotic changes. An injection of hypertonic salt solution inhibited diuresis by an effect on the antidiuretic hormone of the posterior lobe of the hypophysis. Andersson (1952, 1953) succeeded in eliciting copious thirst in goats by injecting the paraventricular nuclei with 1.5–2% NaCl solution in doses of 0.1 cc. C. von Euler (1953), in a preliminary report, has from this general region obtained slow local changes of potential of the order of 1 mV. by injections into the carotids in the manner of Verney. All these observations on receptors in the brain indicate the opening of a new and important field of research in sensory physiology. It would not be surprising if many other blood constituents influenced receptors for hypophyseal control.

4. *Receptive fields. Other organizations of skin receptors*

As originally defined by Adrian and his collaborators with reference to skin receptors in the frog (Adrian, Cattell, and Hoagland, 1931; Adrian, 1932), a "receptive field" is the surface innervated by a single afferent fiber. Thus, at least in this animal, the receptive field is not only a physiological or functional unit but also an anatomical constant. The anatomical criterion is not merely a tautological definition. We shall see below that the far more complex receptive fields of the vertebrate eye, though anatomically constant, are variable in size because of the variable amount of interaction of opposite effects within them. Tactile fields, as determined by moving the jet of an air nozzle over the skin, proved to be of exceedingly variable size, from 4 to 100 sq. mm., and overlapped in the manner shown by Fig. 23, from the work of Adrian *et al.* (1931). Both these principles, overlap and variation in size, also occur with the eye and the ear (see below). The overlap is due to branching of one or several afferents within the same skin field. It is clear and was fully realized by Adrian that all these features are integral factors in a mechanism of discrimination planned for a particular kind of receiver, the central nervous system. In Adrian's work on receptive fields in the cat's paw and with cutaneous fields in the guinea pig it appeared also that adjacent receptive fields might be further differentiated in their central projections because their messages were being delivered in fibers of strikingly different size (Adrian, 1931a, 1932b). Tower (1940) measured the receptive fields

in the cornea and found them to extend over very large areas varying from 50 to 200 sq. mm. It is perhaps not quite clear whether these receptors subserve pain alone or pain and touch combined, as another instance of double specificity. Most authors (e.g. Von Frey, 1894a,b; Nafe and Wagoner, 1937) hold that the cornea feels only pain (see discussion by Tower, 1940; recent reports on touch in cornea by Jalavisto, Orma and Tawast, 1951). The free terminals in the cornea branch widely, as shown in the recent experiments of Rexed and Rexed (1951, with references). Tower found the receptive fields to be most sensitive in the middle. In the eye this particular property of the fields has taken on interesting fresh aspects (cf. below).

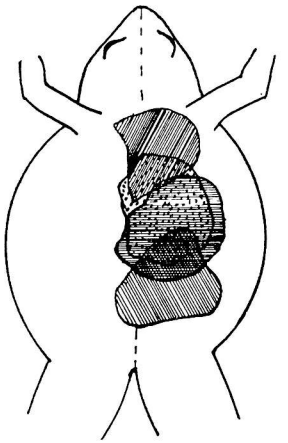

Fig. 23. Areas supplied with tactile endings by different cutaneous nerve trunks in the frog, showing the great overlap in peripheral distribution. (Adrian, Cattell, and Hoagland, 1931; Adrian, *The mechanism of nervous action,* Oxford University Press, London, 1932a.)

Tasaki and his group (Maruhashi *et al.,* 1952) found the receptive fields for various skin receptors to be punctiform for pressure fibers (1 to 2 sq. mm.); the nociceptive fields in the plantar cushion of the toe pad (cat) were small—up to 3 × 3 mm. in area; while those in the hairy regions were about 10 times larger. Most interesting is their finding of special fibers with excessively large receptive fields up to 50 × 90 mm. Their afferents responded to light touch, and the nerve fibers had a diameter between 2 and 5μ. They were abundant in all the skin nerves examined. A special study was made of the receptive fields, of afferents coming from the hair roots. Within their fields, 20 × 25 mm. in area, a response could be elicited by bending every

individual hair or even by touching the hair tips. Afferents that seemed to be specifically sensitive to scratch only were also noted.

Summarizing these facts, I conclude that the sentient skin surface which may be regarded as the prototype of all sense organs well illustrates a number of elementary principles in the peripheral organization of the sensory message. The stimuli called touch, pressure, and pain deliver both general and localized messages. The general piece of information is based on very large receptive fields, the localized on smaller receptive fields down to punctiform ones. There is considerable overlap of receptive fields. These principles will recur in other organs, such as the eye and the ear, which are built up as sentient surfaces. There may well be an inverse ratio between the degree of specificity of end-organs and the amount of branching of the sensory nerve.

Discrimination on this basis and general principles concerning the decoding of the frequency code will be discussed in Chapter 8.

Much has been written about aspects of skin innervation which are familiar to most physiologists and neurologists under the headings "protopathic" and "epicritic" sensations (Head, Rivers, and Sherren, 1905; Rivers and Head, 1908). There is, however, little to add to the judicious criticism by Walshe (1948).

Receptors may be joined functionally on the basis of principles other than those concerned with receptive fields. In vision, for instance, the perception of space and distance brings corresponding points in the two retinae into an integration which has been studied a great deal by psychophysical methods but not at all by electrophysiological ones. In the skin the receptive fields of most sense organs from one and the same region contribute to a similarly unique integration of locality. At this stage I shall take but one example of such integrations referring to the skin, chosen because, to the best of my knowledge, this is the only one that has been properly analyzed by electrophysiological means (Hagbarth, 1952). Historically it is a development of Sherrington's (1906, 1910) notion of the receptive field of a reflex. Sherrington, of course, used the term "receptive field" in a different and wider sense to signify the skin area from which a certain type of reflex response could be elicited. The specific reflex effect is thus an exponent of "local sign."

It is well known that the easiest ipsilateral reflexes to elicit from any nerve are the flexor reflexes, of which there is both a nociceptive and a postural variety (Sherrington, 1910), the latter generally being neglected in semipopular accounts in which the reflex of ipsilateral

flexion is often presented as wholly nociceptive. Submerged below the general flexor activity may also be found extensor contractions (e.g. Sherrington and Sowton, 1910–1911). The concealed extensor reflex, so difficult to elicit and study, was called by Denny-Brown (in Creed *et al.,* 1932) the "residual ipsilateral extension." Hagbarth (1952) brought clarity into this field by proving that there was a defi-

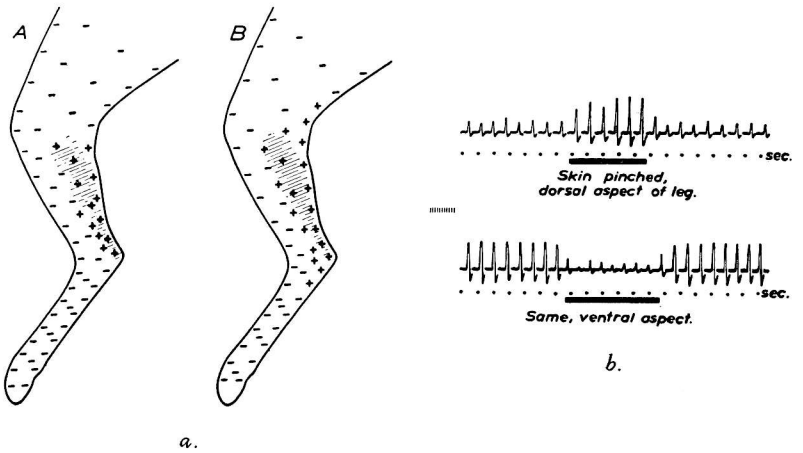

Fig. 24a. Diagrams showing the extent of inhibitory and excitatory skin areas for the extensor muscles of the ankle. Results obtained from two spinal cats. In one (*A*) the excitatory region was unusually small, in the other (*B*) it was relatively large. The shadow indicates the localization of the extensor muscles investigated. The strength of the responses is approximately indicated by the density of the signs.

Fig. 24b. Decerebrated cat. Records from the ventral root S_1. Monosynaptic test volleys obtained from the nerve of the ankle extensors. By pinching the skin of the limb the excitability of the motoneurones is influenced, and the effect is changed by varying the localization of the skin stimulus. Time in msec.; on the left. (Hagbarth, *Acta physiol. scand., 26,* Suppl. 94. 1952.)

nite functional connection between a muscle and the portion of skin that covers it. Hagbarth's rule is quite simple: skin and muscle are functionally integrated, so that the muscle is excited by stimuli within its own skin area. Adjacent portions of the skin may be inhibitory. This is true for both flexors and extensors, and so, by his approach, it proved easy to find the formerly elusive ipsilateral extensor reflexes.

The excitatory and inhibitory skin areas for the ankle extensors are shown in Fig. 24a; 24b shows the outcome of a test by pinching the skin over these regions. Testing is carried out monosynaptically (the

technique is described in detail in Chapter 6) and to understand the result depicted in Fig. 24b all that is necessary is to realize that the monosynaptic test volley increases in size during facilitation (upper curve) and decreases during inhibition (lower curve). The same result may be obtained by electromyography and by recording the muscle contraction (myography), but the monosynaptic test, carried out with de-efferented animals, demonstrated that the effects are direct and not secondary to events set up by a reflex loop from the afferents of the recorded muscle or its antagonist.

Thus the skin has established "local signs" for reflex action also, and not only for conscious perception, as, indeed, has been well known practically from the beginning of reflexology.

5. *Receptive fields of the vertebrate retina*

The principle of discrimination by overlapping fields of different size must indeed be an important one or else it would hardly have reached its pitch of perfection in an organ such as the retina, which is the most complex sensory apparatus in the vertebrates and apparently in many invertebrates. One might have expected, once organs of such minute size as the rods and cones had been developed, that this fineness of grain, just as in the photographic plate, might have had for its sole reason reproduction of detail and as a consequence a 1:1 ratio of sense cells to nerve fibers right up to the center. However, this cannot be the case, because exceedingly slender elongated rods are found in deep-sea fishes (Bayliss, Lythgoe, and Tansley, 1936) in combination with a particularly high ratio of rods to optic nerve fibers. In general, the cones, the organs for visual acuity and daylight vision, tend to be somewhat thicker than the rods, which integrate light over large convergence units with up to hundreds or thousands of receptors per nerve fiber. It is only in the relatively few species with a well-developed *fovea centralis* that the foveal cones become slender and rodlike in appearance. If we assume that the photochemically sensitive visual purples are located at the surface of the receptors (Granit, Holmberg, and Zewi, 1938; Lythgoe, 1940), it is likely that fineness of grain has for one of its reasons expansion of surface (Bayliss *et al.*, 1936). On the other hand, it cannot be denied that, by analogy to photographic emulsions, reproduction of detail requires discrete units (grain) below a certain minimum size, ultimately determined by the perfection of the optical parts (lens, cornea) as well.

To the old controversy between Helmholtz and Hering is attributed this story (to which in 1922 the late Professor A. Gelb of Frankfurt a/M first drew my attention): Helmholtz, who had stated that if an optician delivered to him as bad a lens as that of the eye he would return it, received from Hering the reply that he might perhaps have kept it after all if he had realized what marvellous compensatory arrangements there were for perfection of the image (contrast in the first instance). Since that time lenses and photographic emulsions have improved but the eye with its faulty optics remains the same, performing better over a range from dusk to brightest sunlight than any instrument designed to imitate it.

The idea that good reproduction also requires fineness of grain is certainly supported by comparative studies of the number of optic nerve fibers in different species. Despite its very much smaller eye, the pigeon, dominated by cones, has much the same number of optic nerve fibers as man. Bruesch and Arey (1942) give 1,010,000 for man, 988,000 for the pigeon, but only 119,000 for a predominantly rod animal such as the cat. Polyak's (1941) figure for man is "800,000 to more than 1,100,000." The optic nerve fibers in the cat are particularly large, the eye not very much smaller than our own. Grain size, in order to mean something in our analogy with photographic emulsions, should, of course, be defined by the size of the receptive field of a single optic nerve fiber.

It is concluded, then, that though the average convergence of receptors on optic nerve fibers is very great, say of the order of 100:1, the retinal surface is nevertheless capable of good discrimination on the same basic principle as is the skin, i.e. by using overlapping receptive fields of different sizes, from very large to very small, the latter likely to be multiplied in cone eyes which have good visual acuity. The presence of an outgrowth of cells from the central nervous system in two layers below the receptors entails further elaboration of the message before it is concentrated into the optic nerve fibers. This makes the retina particularly interesting as a model for what might happen within central projections elsewhere. Thus it seems that restriction of receptive fields to a limited number of pathways transmitting a code of spikes (optic nerve fibers) need not necessarily mean deterioration of the information, provided that the message itself is sufficiently elaborated and that a sufficient number of small fields are included to modulate it. Visual perception, after all, is a dynamic act maintained by a continuous frequency variation and not by a static image on a photographic plate.

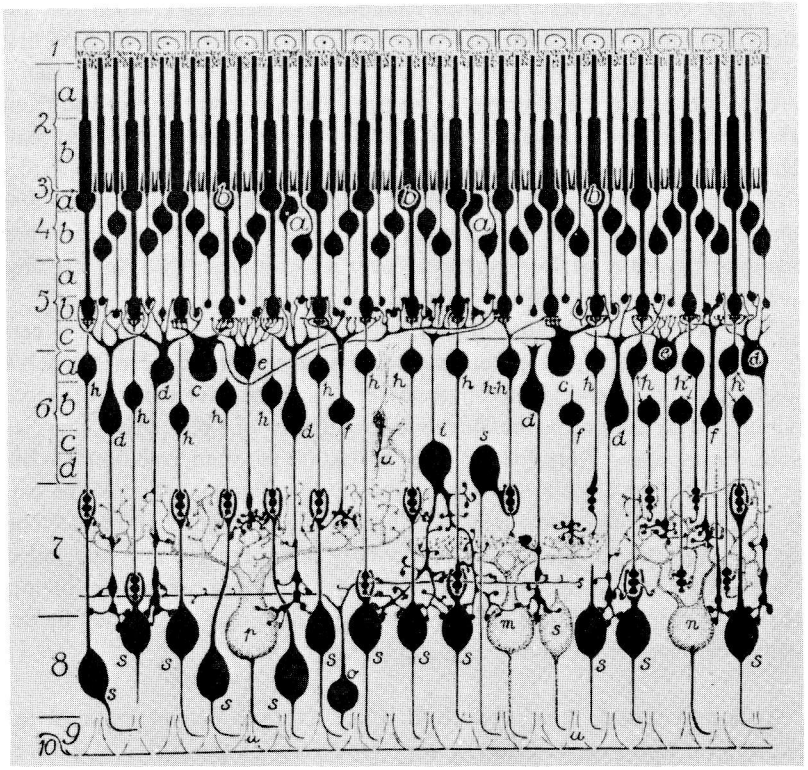

Fig. 25. Scheme of the structures of the primate retina as revealed by the method of Golgi. The designation of the layers and the zones: (1) pigment layer, (2, *a*) outer zone, (2, *b*) inner zone of the rod and cone layer, (3) outer limiting membrane, (4, *a*) outer zone, (4, *b*) inner zone of the outer nuclear layer, (5, *a*) outer zone, (5, *b*) middle zone, (5, *c*) inner zone of the outer plexiform layer, (6) inner nuclear layer with its four zones, (7) inner plexiform layer, (8) layer of the ganglion cells, (9) layer of the optic nerve fibers, (10) inner limiting membrane.

The designation of the nerve cells: (*a*) rods, (*b*) cones, (*c*) horizontal cells, (*d, e, f, h*) bipolar cells, (*i, l*) so-called "amacrine cells," (*m, n, o, p, s*) ganglion cells, (*u*) "radial fibers" of Müller.

In this scheme the nervous elements are reduced to their essentials, with, however, the characteristic features of each variety preserved—the location of the bodies, the size, the shape, and the spreading of the dendrites and the axis cylinders—and with the synaptic contacts presented accurately. (Polyak, The retina, University of Chicago Press, Chicago, 1941.)

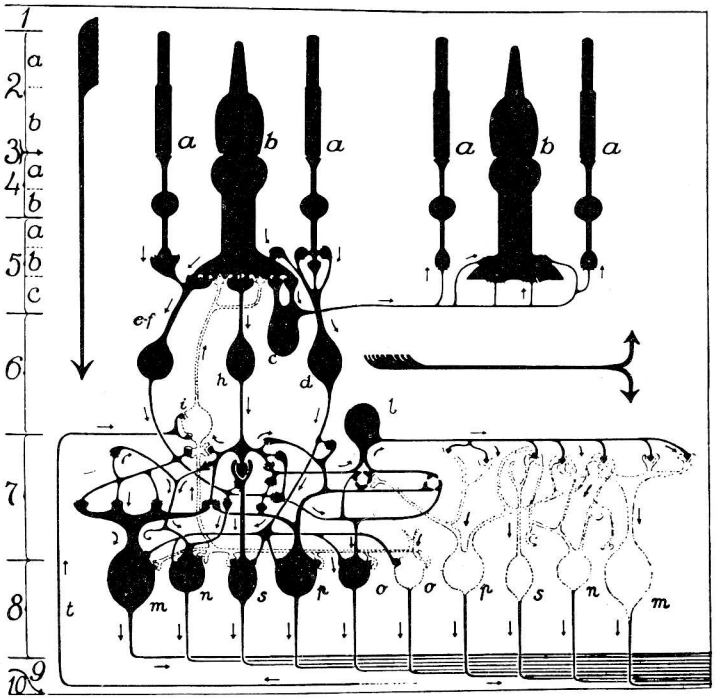

Fig. 26. The structure of the primate retina reduced to its essentials, including the synopsis of the propagation of the retinal impulses from the photoreceptors to other parts of the retina, to the brain, and from the brain back to the retina (direction indicated by the arrows). The marking of the layers and the zones is the same as in Fig. 11.

Labeling of the cells: (*a, b*) rods and cones, or the photoreceptors where the nervous impulses are generated by physical "light" (in the scheme only the left group of the photoreceptors is assumed to be stimulated by light); (*c*) horizontal cells, by means of which the impulses are transmitted to the surrounding rods and cones; (*d, e, f, h*) centripetal bipolar cells of the mop, brush, flat, and midget varieties, which transmit the impulses from the photoreceptors to the ganglion cells, the bipolars serving as analyzers; (*i*) centrifugal bipolar cell, a variety of the amacrine cells, which probably receives the impulses from the centripetal bipolars, from the ganglion cells, and also from the brain, by way of the centrifugal or efferent fibers (*t*) and transmits them back upon the photoreceptors (*a, b*); (*l*) an amacrine cell which possibly intercepts a part of the bipolar impulses and spreads them over the surrounding territory; (*m, n, o, p, s*) ganglion cells which receive impulses from the centripetal bipolars and transmit them to the brain along their axons, called "optic nerve fibers." (Polyak, The retina, University of Chicago Press, Chicago, 1941.)

Figs. 25 and 26, from Polyak's great work on the primate retina, illustrate the two additional neurones below the receptors, called bipolars, and ganglion cells, as well as the lateral connections, one by the horizontal cells along the feet of the rods and cones, the other by amacrines above the ganglion cells. There are also centrifugal components of which little is known functionally (see Chapter 3, sec. 5).

If the physiological analysis of the messages from the optic nerve with microdissection (Hartline, 1935, 1938a, 1940a,b,c; Thomson, 1953) or microelectrodes (see my summaries, 1947, 1950b; later work by Rushton, 1949, 1953; Barlow, 1953a,b; Kuffler, 1952, 1953) had been able to provide an equivalent interpretation in terms of the circuits and slow potential changes present, it would have been of interest to describe the histology in greater detail with the aid of Cajal's and Polyak's diagrams. As it is, an interpretation has not so far become possible in anything but outlines. And yet, looking back upon what we knew two decades ago, I think that all the painstaking work on single fibers has not been in vain. We do not know enough but we do know a great deal about the workings of the retinal switchboard and can formulate the problems with greater clarity than was formerly the case. It is perhaps true, too, that even if there are simpler structures than the retina available for the study of synaptic excitation and inhibition, the understanding of the principles of central organization and transmission of sensory information is never likely to be very much in advance of our understanding of the principles governing the form and delivery of the retinal messages.

The retina is organized on the general basis of two successive layers of superimposed receptive fields: the receptors converge onto the bipolars, the latter converge onto the ganglion cells, from which our information with microtechniques in terms of spike frequencies is derived. At least in primates and birds there are midget bipolars (*h* in Figs. 25 and 26) which potentially are capable of delivering a punctate message on a 1:1 basis (from a single cone down to the optic nerve fiber of the ganglion cell), but this message, too, is at the mercy of interaction from adjacent structures, as contemplation of Fig. 25 will show. The overlap of receptive fields is clearly shown by the histological pictures, and functional analysis tells the same story (Hartline, 1938a, 1940a,b). The possibilities for interaction are legion. Functionally true interaction was first demonstrated by Adrian and R. Matthews (1928). The overlapping receptive fields thus collaborate in a more complex fashion than in the skin, for which the inhibitory processes come in at about the level of the spinal cord.

As stated in Chapter 1, sec. 7, Hartline (1938a) first demonstrated that the characteristic discharges to onset and cessation of light (on-discharge, off-discharge) are differentially distributed over the afferents in the optic nerve. There are on-elements (on-fibers), off-elements and on/off elements, the term "element" standing for the single fiber or ganglion cell from which recording takes place. A diagrammatic representation was given in Fig. 14. Some characteristic discharges are shown in original records in Figs. 27 and 28. The fibers discharging at cessation of illumination are inhibited by light (see Chapter 1). In the types of eye so far studied the elements that discharge to both onset and cessation of illumination are in the majority. As far as the large fibers are concerned, the guinea pig's rod eye is an exception. It contains mostly on-elements (Granit, 1942a,b).

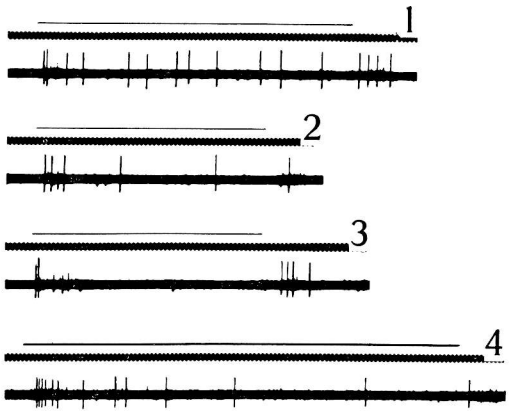

Fig. 27. Effect of different types of stimulus on the form of the response of a single retinal element of the cat: (1) response to a stimulus of relative energy 6.3 and wave length 6200 Å; (2) response to the same wave length at a relative energy of 2.3; (3) response to a stimulus of relative energy 2.5 and wave length 4600 Å; (4) response to a wave length of 5,000 Å from another experiment. Time marking: 1/50 sec. (Granit, *Acta physiol. scand., 5,* 219. 1943c.)

In our evaluation of these features of organization of the retinal elements some change has gradually taken place (see Granit, 1950b). Fifteen years ago one used to think of the types of discharge as relatively stable in the sense that the individual afferents had specialized upon the delivery of a certain type of response. This may still be true for certain types of retinae such as that of the frog and the pigeon (Donner, 1953). In the cat's retina there is, however, an extreme variability of the on/off ratio of the elements (calculated on thresh-

olds or frequencies) with respect to level of intensity, wave length, and state of adaptation (Granit, 1944; Granit and Tansley, 1948; Gernandt, 1948b). This led to the conclusion that the balance of discharge between onset and cessation of illumination was one of the main exponents of interaction in the retina, as further emphasized by studies with polarizing currents (results summarized by Granit, 1950b). It was actually possible to suppress or emphasize either the on- or the

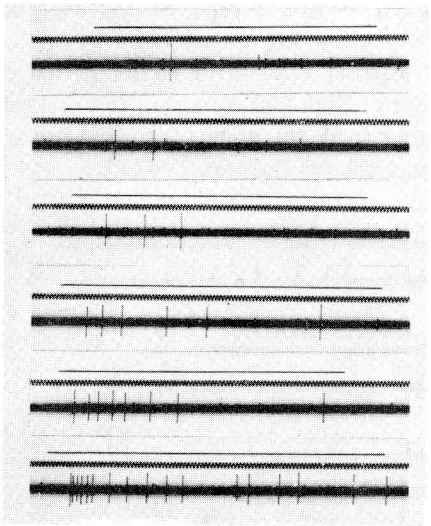

Fig. 28. Effect of increasing the intensity of the stimulus on the response of an isolated retinal element of the guinea pig. Relative energy values of stimuli (from above downward): 1 (threshold), 1.3, 1.48, 2.22, 3.91, 9.31. Wave length of stimulus: 5300 Å. Time markings: 1/50 sec. (Granit, *Acta physiol. scand., 3,* 137. 1942a.)

off-discharge to a constant stimulus by maintaining weak polarization across the retina (Granit, 1948). Finally it was shown by Kuffler (1952) with punctiform stimuli and the cat's eye that within the receptive field of a single afferent some spots gave off-responses, others on-responses, and that mixtures of these in different on/off ratios could be obtained by combining two stimuli from different spots. It is probable, therefore, that most elements are on/off elements merely because this is the most likely state of balance of on- and off-components. On/off discharges are also dominant in the cat's retina if one tries to evade the large single spikes and uses the massed discharge of small spikes as index (Bohm and Gernandt, 1950). Interaction

means plasticity of response, and one of the main variables expressing plasticity is the on/off ratio.

A further step—at least in my own interpretation of retinal organizations—came from our general observation with the cat's eye that the on- and off-components of the discharge tended to be mutually exclusive (Fig. 29), so that when stimulus intensity was varied, the

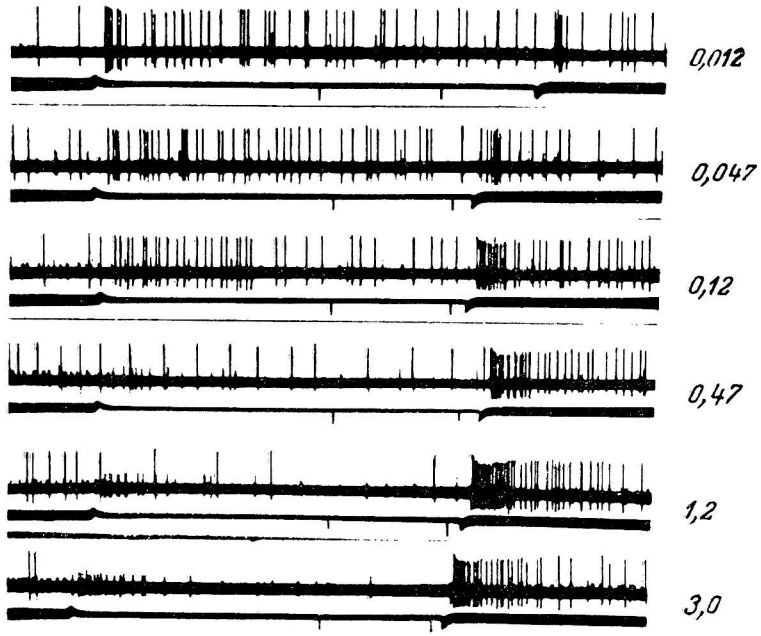

Fig. 29. The large and small spike of Fig. 31, elicited by illumination with wave length 4600 Å at the relative intensities indicated beside the records. Period of illumination marked by photocell and amplifier connected to second beam of cathode ray below the one recorded from. This beam also records the 50-period AC of the mains but, at this film speed, so compressed that the duration of 1 sec. has been indicated by separate marks below it. (Granit, *J. Neurophysiol., 11,* 239. 1948.)

off-discharge often diminished while the on-discharge increased, or vice versa (Granit, 1944). This is well shown also in Fig. 30, from the measurements by Donner and Willmer (1950). Was there perhaps an antagonistic relationship between the two? This problem was first systematically approached by the technique of polarization of the retina by a weak electric current through external electrodes on

either side of the eye bulb. To understand these results it is necessary to realize that although the on/off ratio is variable, it is possible, even in the mammalian retina, to distinguish Hartline's categories of response types when a large enough number of elements are studied under similar conditions, in our case dark-adapted animals and illumination of the whole retina. Thus, some elements are found which act as pure on-elements, others as pure off-elements, though the majority of them respond to both onset and cessation of light.

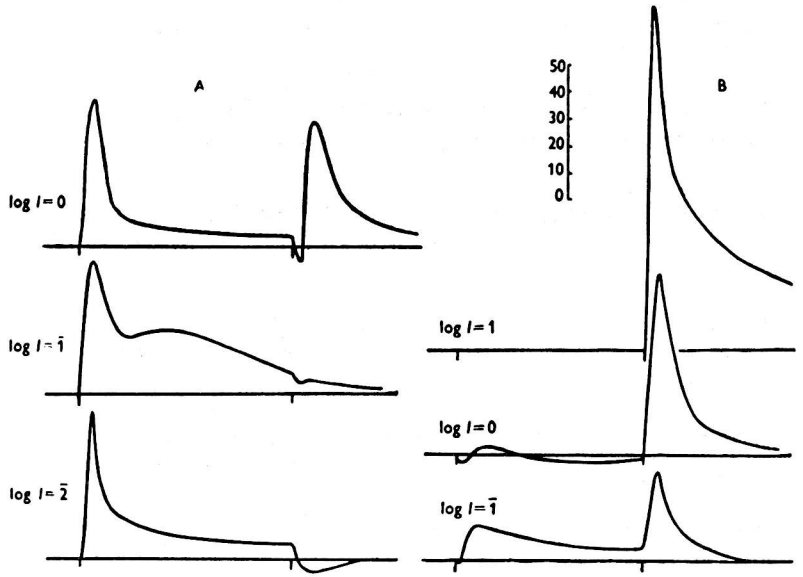

Fig. 30. *A:* discharge of an element which changes from the "on" type to the "on/off" type as the intensity of the stimulus is raised. *B:* discharge of an element which changes from the "on/off" type to the "off" type as the intensity of the stimulus is raised. Ordinates: impulses per sec. Abscissae: time, the duration of the stimulus being 3 sec. (Donner and Willmer, *J. Physiol., 111,* 160. 1950.)

To sudden polarization with the electric current the isolated elements respond either with excitation or inhibition at the threshold. Reversal of the current reverses the response. The polarizing electrodes in such experiments are in the temporal and nasal cavities, the microelectrode on the inside opposite the nasal electrode. Also, by this technique of measuring the threshold effects of polarizing currents, the antagonism between the on- and off-components of an element came to light in that the pure on-elements tended to discharge to the cathode, the pure off-elements to the anode (Gernandt and Granit,

1947). The same result may also be stated differently: the on-elements tended to be inhibited by the anode, the off-elements by the cathode. A third way of stating this generalization is that light and the cathode tended to act in the same way: the on-elements, excited by light, were excited by the cathode, the off-elements, inhibited by light and discharging at cessation of illumination, were inhibited by the cathode. The mixed on/off elements were of either type, cathodal or anodal, as defined by the excitatory effect. This antagonism between "on" and "off" is not due to a shift in the leading-off point relative to the distribution of the polarizing current. In Fig. 31 the same microelectrode is

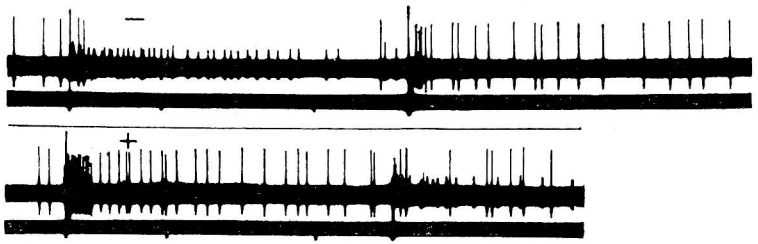

Fig. 31. A large and a small spike isolated by the same microelectrode. Stimulation between the two clearly visible shock artifacts with nasal electrode cathode (above) and anode (below). One second marked on lower line in the middle of each period of stimulation. Note opposite responses of small and large spike during and after polarization. These spikes are shown in Fig. 29 also. (Granit, *J. Neurophysiol., 11,* 239. 1948.)

picking up from two fibers. These adjacent on/off elements are clearly of opposite polarity. The illustration of the mutually antagonistic behavior of the two elements in Fig. 29 with respect to light at different intensities is from the same experiment with the same spikes.

Perhaps the simplest way in which to demonstrate that the on- and the off-components are mutually exclusive is to shorten step by step the duration of stimulation (Granit, 1951). The discharges are long-lasting events compared with the flash, and so the on- and the off-discharge will sooner or later collide. In this situation "on" and "off" do not add their effect upon the ganglion cell, but the one that has the shorter latency or is otherwise stronger impresses its frequency upon the cell, and the effect of the other one is inhibited. The same effect is very marked in an on/off flicker response to intermittent light at frequencies of stimulation for which the two components clash (Enroth, 1952). This antagonism of the on- and off-components is of considerable interest in color reception (Granit, 1949).

The receptive fields of the retina, to which we now are prepared to turn our attention, thus contain two antagonistic systems, the one discharging to onset, the other to cessation of illumination. Whatever notions one entertains about the origin of on- and off-discharges, it is clear from what has been said that inasmuch as these two discharge-provoking systems converge upon the same ganglion cell, they cannot both activate it at the same moment. The one inhibits the other. Thus the two systems have confluence points somewhere in the retinal switchboard above the level of the ganglion cells. When the on-path is active it places the off-path to the same ganglion cell under inhibition and, vice versa, during the activity of the off-path there is blockage of the on-path at some confluence point.

As stated above, the off-discharges are inhibited by illumination. It is possible, of course, to regard this inhibition as but one aspect of the antagonism of on- and off-components just described. I hesitate to subscribe to this identification. A very essential feature of pure off-elements is that they in silence, as it were, pile up excitation during illumination (see also Hartline, 1938a, 1940b,c), afterward to release it in the form of a vigorous discharge the moment the light is turned off. For some time (Granit, 1933, 1947, 1950b, 1952b) I have held the view that the off-discharge is a release from inhibition produced by a positive potential change, which upon its return swings to the negative side and excites at "off." I find this view supported by Parry's (1947) results (see Chapter 1, sec. 6). The total balance of evidence (see e.g. Granit, 1952b) seems to me to support the idea of a primary mechanism for the production of off-discharges as well as a primary excitatory mechanism for the production of on-discharges. However, since these primary mechanisms themselves are antagonistic, the whole point of this organization would be missed if at the ganglionic level on- and off-discharges were mixed indiscriminately. The synaptic arrangements in the retinal switchboard must be organized to preserve the on/off distinction, and this is done by the mechanism of synaptic antagonism leading to the inhibition. It will be shown in Chapter 5 that complex electrical feedback mechanisms operate in the retina, suggesting a definite reason for the arrangement of receptors in combination with synaptic layers. It will be some time before these facts are fully understood.

It seems to me that Kuffler's recent work (1952, 1953) shows that the mutual exclusiveness of "on" and "off" within the receptive field of the ganglion cell is organized in such a delicate fashion (see below) that it is easier to understand it in terms of synaptic arrangements similar to those responsible for the organization of reciprocal reflex effects in the spinal cord. This also appears to be Kuffler's view (1952). Admitting that these problems of retinal inhibition are exceedingly difficult to penetrate, at the moment I would, nevertheless, think it the simplest explanation of all the available facts to assume that primary "on" and "off" mechanisms are taken care of secondarily by a retinal organization of reciprocal innervation in secondary neurones.

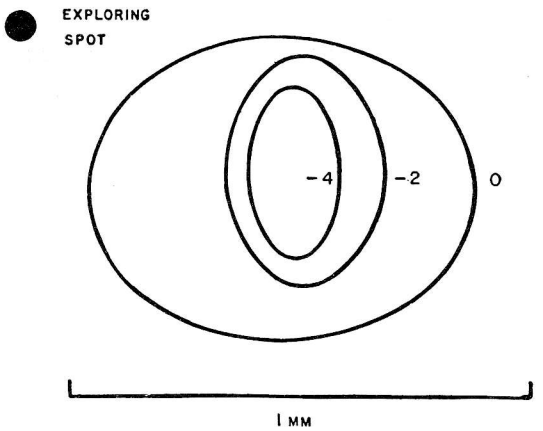

Fig. 32. Chart of the receptive field of a single optic nerve fiber of the frog. Each line encloses a retinal region within which the exploring spot light (relative size shown above, left)—of an intensity the log. of which is given on the line—produced a response from the fiber. On each line the indicated intensity was the threshold; the set of curves constitutes a contour map of the distribution of the retinal sensitivity to light with reference to this particular fiber. (Hartline, *J. Opt. Soc. Amer., 30,* 239. 1940.)

The size of the receptive field was found by Adrian and Matthews (1927a,b, 1928) to be of the order of 1 mm. in diameter in the eye of the Conger eel. The result was based on discharges from the whole nerve. By exploring the frog's retina with a minute light spot, 0.55 mm. in diameter, Hartline (1940a,c) studied the receptive field from which the single spike could be elicited. He arrived at much the same figure. Hartline's chart is shown in Fig. 32. The receptive field is very sensitive in the middle, less so toward its edge. The curve of Fig. 33, from Thomson's work, confirms Hartline's result and is recorded from the rabbit with the spike seen in the record, isolated by a microelectrode stuck into the optic nerve itself. Barlow (1953a,b), with the microelectrode technique used as in our laboratory on the inside

of the opened bulb (frog), added the significant observation that around the on/off elements the roughly circular receptive field was surrounded by a ring of inhibition. When this ring was illuminated separately, a discharge to light elicited from the middle of the receptive field was inhibited, even though the ring illuminated by itself failed to give a discharge and thus seemed to be outside the zone projected onto the single fiber. If we assume the receptive field to be the

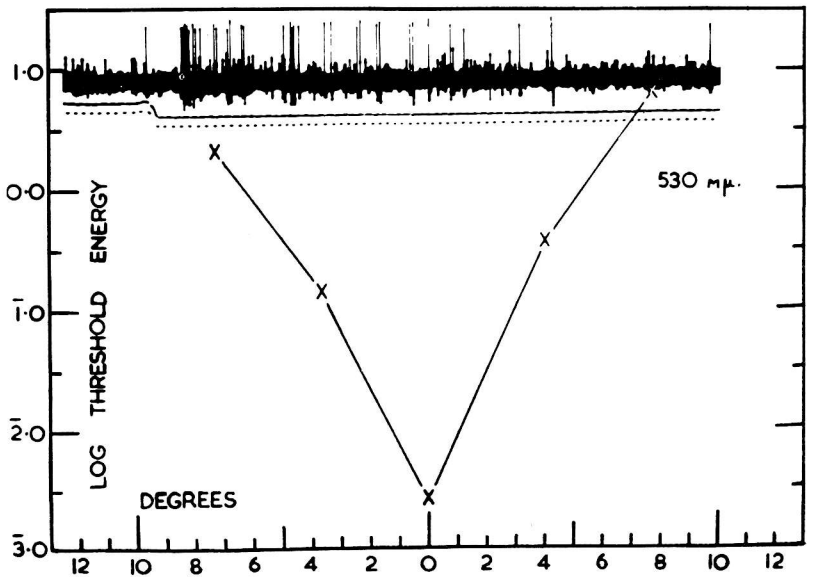

Fig. 33. The receptive field demonstrated by measuring the threshold energy for wave length 5300 Å. The logarithm of the threshold energy is plotted on the ordinate. The degrees through which the stimulating spot has been moved are shown on the abscissae. Time trace of insert recording: 10 msec. (Thomson, *J. Physiol., 119,* 191. 1953.)

sum total of converging receptors and bipolars, this means that the surrounding inhibition may have been carried by internuncial neurones for lateral spread (amacrines, as originally suggested by Graham and Granit, 1931). At any rate, an organized inhibition of the type found by Barlow is very difficult to understand on any other basis than that it is organized by the neural network, probably to constitute a basis for simultaneous contrast. This was Hartline's (1940a) view also, based on the fact that within a receptive field there was inhibitory summation as well as excitatory summation. At the background of this is Sherrington's experience that reflex excitation and inhibition in the

spinal cord have the same properties but with opposite algebraic sign.

Barlow's experiment raises the question of what to define as a receptive field. In the absence of proofs to the contrary the discharge pattern of an element may be assumed to be affected by events so far away from it that it may seem worth while, for the time being, to preserve the distinction between *element* and *receptive field,* concepts which otherwise would be undistinguishable. Thus, for instance, Gallego (1953) has recently demonstrated in the cat's retina a quite specific widespread plexiform layer which may well serve to integrate vast areas into a diffuse discharge in the dark. Kuffler (1952) in the same animal actually has found receptive fields up to 4 mm. across in the dark but is worried by spread of light, which is known to be considerable. He therefore always uses some background illumination and then obtains values of the order found by other workers on other animals. However, when scatter is wholly excluded, as by Wirth and Zetterström's (1954) method of studying the electroretinogram elicited by light passing through blackened Perspex cones applied directly onto the retina (see Chapter 5, sec. 1), 4–5 mm. of diameter is also necessary to obtain all the features of the normal high-intensity type of electroretinogram. The question of what to include in a receptive field therefore embodies a real experimental problem and not dialectics. I shall return to it below in connection with the question of receptive fields as a function of state of adaptation.

Hartline (personal communication) found both large and small receptive fields in the frog's eye, apart from proving that the field increased as much as double its size when stimulus intensities 100–1000 times the threshold were used. These are still modest intensities for an eye. Within the receptive field, as stated, there is summation of excitatory effects in on-elements and summation of inhibitory effects in off-elements (Hartline, 1940a).

An interesting feature of Kuffler's (1952, 1953) recent study of the receptive fields in the cat's eye is the preservation of an intact eye by inserting the electrode through a small opening in the sclera. By using two small light spots he was able to demonstrate in a particularly elegant way the above-mentioned antagonism between the on- and off-components of an element that I had seen when using the simple expedient of making on- and off-discharges clash by shortening the time of exposure (Granit, 1951; Enroth, 1952, with flicker). Kuffler's most important new findings concern the minute organization that is characteristic of the receptive fields. Thus, in Fig. 34 it is seen that the center of the field gives on-effects only, in an intermediate zone

on/off discharges are obtained, and the surroundings produce pure off-discharges. There were other fields designed in an opposite fashion: the center producing off-discharges, the periphery on-discharges. Since the center, in agreement with all previous work, is the most sensitive part of the field, its characteristics will be emphasized by properly choosing stimulus strength and background illumination. All these

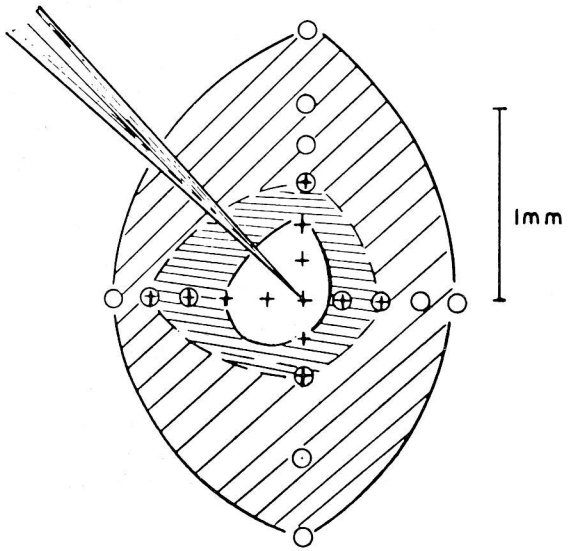

Fig. 34. Cat retina. Distribution of discharge patterns within receptive field of ganglion cell (located at tip of electrode). Exploring spot was 0.2 mm. in diameter, about 100 times threshold at center of field. Background illumination approximately 25 m.c. In central region (*crosses*) "on" discharges were found, while in diagonally hatched part only "off" discharges occurred (*circles*). In intermediary zone (*horizontally hatched*) discharges were "on/off." Note that change in conditions of illumination (background, etc.) altered discharge pattern distribution. (Kuffler, *J. Neurophysiol., 16,* 37. 1953.)

factors, including area of stimulus and position, were studied one by one and found to be capable of altering the type of discharge from the field. By these experiments Kuffler also considerably deepened our understanding of why the on/off ratio of the cat's eye is so variable, as we always have found it to be. It is very likely that rod-cone antagonism in an eye with a large number of rods complicates this issue.

To illustrate the fundamental antagonism between the on- and the off-components within a single receptive field I am reproducing as Fig. 35 an experiment from Kuffler's work. One of the exploring spots

(A), 0.2 mm. in diameter, was placed near the tip of the recording electrode in the center of the receptive field and proved to give a high frequency on-discharge to light. The other spot (B) was placed within that part of the field which gave off-discharges only. Each vertical row of records shows first A and then B by itself as control, then the

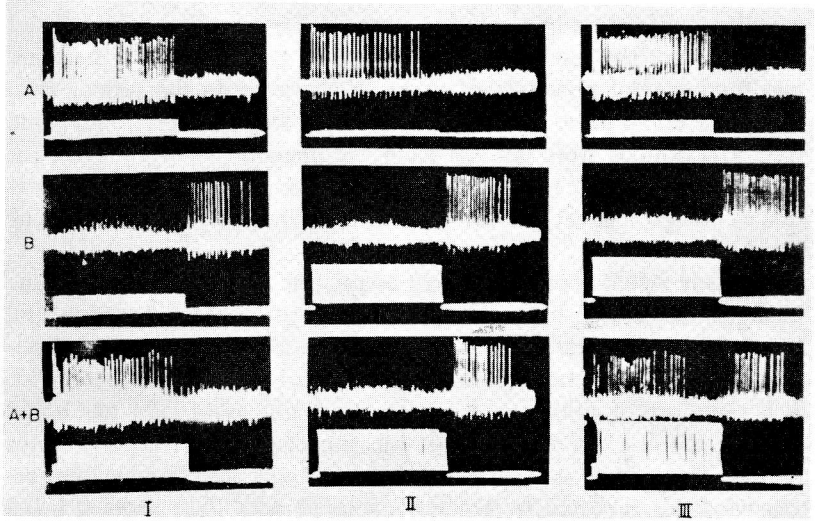

Fig. 35. Cat retina. Interaction of two separate light spots. Single ganglion cell discharge during background illumination of 20 m.c. Spot A, 0.1 mm. in radius, was placed in center of receptive field at tip of recording electrode. Spot B, 0.2 mm. in radius, was 0.6 mm. away in surroundings. Flashed separately, they set up "on" (A) and "off" (B) responses. With a simultaneous flash, $A + B$ in col. I, "off" response is suppressed and at same time number of "on" discharges in $A + B$ is slightly reduced as compared with A. In col. II intensity of spot A was reduced, while spot B was increased (note flash strength indication on second beam). As a consequence B suppressed "on" discharge of A. In col. III, both spots were "strong." When flashed together ($A + B$) they reduced each other's discharges. Flash duration was 0.33 sec.; potentials were 0.3 mV. (Kuffler, *J. Neurophysiol., 16,* 37. 1953.)

effect of making them clash ($A + B$). In the first vertical row when A is strong B is suppressed by collision with A. In the second row A is weakened and B increased in strength. When they clash, A is suppressed. In the third row both A and B are strong and both have lost in effectiveness by the collision. Enroth's (1952) flicker studies with single elements gave similar results, though not in terms of receptive fields.

This antagonism of the on- and off-system in the retina seems to me

of fundamental importance for another reason: it is maintained over such a broad range of phenomena. First of all, the on-discharge is excited by light and stops in the dark, while the off-discharge is inhibited by light and excited by darkness (Fig. 14). Second, the two seem to be closely associated with opposite slow potentials in the retina. Finally, they are mutually exclusive when they clash on the ganglion cell. One might say, too, that all these results are a belated vindication of the essential truth of Hering's contention that there are two fundamental processes of opposite character in the retina, even though he could never have foreseen in what way his idea would come true. His notions were derived from the phenomena of contrast, for which no doubt the antagonism described is of fundamental importance, though a great deal of painstaking work will go into showing just how.

In many visual phenomena light adaptation and illumination of the background tend to have an equivalent effect (see e.g. Lythgoe and Tansley's work on perceived flicker, 1929; Craik and Vernon's demonstration that the summation area shrinks in light adaptation, 1941). It is therefore of considerable interest that Kuffler (1952) has found that as the background illumination increases, the receptive fields shrink. This effect was noted with all types of fields. The smallest receptive fields reported by Kuffler, explored with light spots 0.1–0.2 mm. in diameter, were themselves not larger than 0.5 mm. in diameter, yet they responded with on/off discharges. This suggests that the high flicker frequency noted in light-adapted animals with strong stimuli (Dodt, 1951a; Dodt and Enroth, 1953; Dodt and Wirth, 1953) and consequent light adaptation is a flicker with a small receptive field. Since the pigeon's eye under such conditions runs up to fusion frequencies of around 140 flashes per second (Dodt and Wirth, 1953), its cone-retina is probably characterized by particularly small receptive fields, as suggested by Dodt and Wirth on the basis of the pigeon's large number of optic nerve fibers, nearly 10 times greater than in the cat (Bruesch and Arey, 1942).

Kuffler (private communication) in work with Barlow has recently found that at the threshold (heavy background activity) the receptive fields in the dark-adapted cat's eye tend to be uniform, i.e. give over its whole area the response which is characteristic of the center during light adaptation. At the same time area summation occurs over the whole field, while in light this happens only over the small central or surrounding areas respectively. This again suggests a physiological role for Gallego's widespread plexiform layer, mentioned above.

6. *Limitations of the technique of single fiber analysis*

It remains to discuss what limitations should be imposed upon the interpretation of all these experiments with single fibers or single ganglion cells in the retina from the point of view of the technique itself. The experimenter, inasmuch as he wants to perform long-lasting analyses, tends to go in for large spikes which are delivered by large ganglion cells (Rushton, 1949, 1953). These in the cat are likely to have large receptive fields (Cajal, summary, 1933; Polyak, 1941). In my early work on color reception I did not follow this line of procedure alone but often measured the threshold of the spike most sensitive to a given narrow spectral region and was not too particular about isolation. Some of these spikes were just as likely to come from optic nerve fibers as from ganglion cells because, as pointed out at the time (Granit, 1941a), when microillumination was used (Granit and Svaetichin, 1939), there was often a considerable distance between the spike and the microilluminated spot. Donner (1953) too, in his recent work on color reception in pigeons, measures the discharge from isolated *small* spikes. Gernandt (1948a) studied the spikes more closely and found two kinds in the cat's eye which since have been clearly differentiated by Kuffler (1952) in the same eye and by Barlow (1953a,b) in the frog eye, the one coming from optic nerve fibers, the other from ganglion cells. This difference would be of little significance for analyses in terms of spike frequencies had it not become customary to go in for rather large spikes in order not to lose them in long-lasting experiments.

Receptive fields have not been systematically studied with small spikes but it is well known that these, too, give on/off discharges (Bohm and Gernandt, 1950, with the cat's eye; Donner, 1953, with the pigeon's eye; Barlow, 1953a,b, with the frog's eye). Also, some of the fields studied by Kuffler, as we have seen, were quite small, yet gave on/off discharges. One further line of evidence suggests that the difference between large and small spikes should not be exaggerated: provided stimulus strength is high enough, the large spike in the cat's eye can be made to follow flicker up to the highest frequencies known for the human eye under similar conditions (70–80 flashes per second), as proved by Dodt and Enroth (1953). The rod eye of the guinea pig cannot follow equally fast rates of intermittency (Dodt and Wirth, 1953). Thus, the large spikes are capable of perfect dis-

crimination of the flashes in flicker. We shall return to flicker in connection with the general problem of discrimination. Again, the assumption that the small spikes do not possess off-discharges is not only contrary to first-hand experience but also very unlikely when one considers that the off-discharge is the only retinal phenomenon capable of furnishing a peripheral cue for successive contrast which reaches its climax in color vision.

While it is highly desirable to have more work carried out with small spikes, I cannot share the surmise of Rushton (1953) that the small spikes may have very different response patterns. Even in the fovea of primates the private 1:1 path over the midget bipolar has other connections which make it potentially subject to influences from adjacent paths. It may well act in isolation in one context and together with adjacent receptors in another. Animals without fovea see well enough to make it a problem how they can do it. Also, it seems very unlikely that the principles discovered by the work on relatively large spikes would suddenly have been sacrificed at the very late stage of phylogenetic development (primates among mammals, birds) when a fovea occurs. To enumerate these principles briefly, they are: (1) the existence of two systems antagonistic throughout—the on- and the off-systems; (2) an organization similar to the one in the sentient skin and consisting of overlapping receptive fields of very different sizes; (3) a minute organization of these fields, which serves to emphasize the properties of the center of the field, either "on" or "off," at the expense of the periphery; (4) means of expansion or contraction of the receptive field with variations in state of adaptation.

In the absence of studies of the fovea we can, for the time being, well disregard it and be content with the fact that the retina is a good organ for discrimination, even in animals without a fovea. If we fail to make sense of its properties as known at the moment, we are not likely to succeed very much better when the foveal records become available (see Chapter 8, dealing with discrimination).

Chapter 3

Spontaneous Activity in Sense Organs and Its Functional Significance. The Principle of Centrifugal Control

1. Introduction. The peripheral mechanism

THE ideas we entertain today about spontaneous activity in sense organs are entirely a product of the electronic era of sensory research which made it possible to observe the impulse. This does not mean that these problems are wholly without a history in psychophysical research. Do we have spontaneous sensations? To be sure, most sense organs are held to possess in the normal state an absolute zero-point of no sensation, but of old the eye has been regarded as an exception, since something is always perceived, even under closed lids in the dark. This to Helmholtz (1867) was the *Eigenlicht* produced by internal excitation and to Hering (1925) the autogenetic gray (das *Eigengrau*). These great opponents also disagreed about the sensation of "black." With Helmholtz's acceptance of Young's color theory went the notion that white is the sum of all colors and black the absence of sensation, while to Hering "absence of sensation" was something that one *saw* with one's back, and deep black, as perceived, was just as positive a sensation as white, besides being obtainable only by contrast against white. According to Hering's theory black and white were the opposite poles of his two antagonistic processes, assimilation and dissimilation; and the autogenetic gray, just as any other gray, was some intermediate point.

If the calculations of Bruesch and Arey (1942) to the effect that 38% of all the sensory input in man is delivered through his one million optic nerve fibers are correct, there need not be much spontaneous activity in these fibers to produce a sensation of gray. We are exceptionally visual animals.

With the advent of electronics into the study of sense organs spon-

taneous activity arrived—at first as a mild surprise to Adrian and his collaborators (e.g. Adrian and Zotterman, 1926a), because there was always a chance of injury or internal stresses in the early muscle and skin preparations. However, Adrian and R. Matthews (1927a,b; 1928) saw spontaneous discharges very markedly also in the eel's optic nerve, and, again, Adrian (1932a, 1937) in the optic ganglion of the water beetle (*Dytiscus marginalis*). Matthews (1931a) confirmed Adrian and Zotterman's observation that the end-organs in frog muscle sometimes may discharge in the absence of any external tension but held it to be due to slight deformation consequent upon some internal strain despite absence of external tension. The advent of the mammalian preparation contributed to establishing the reality of spontaneous activity because, as a rule, rates of resting discharge are higher in mammals than in cold-blooded animals. However, we shall see below that there are sense organs which discharge spontaneously in all types of animal as if this form of activity were part of their normal pattern of behavior.

Gradually, therefore, the idea of spontaneous activity as an integral part of the performance of the sensory instruments has grown upon us. My own experience derives from two such highly active sense organs as the retina and the mammalian muscle spindle, in both of which the existence of a spontaneous discharge is pregnant with meaning. Apparently because the subject in this way gradually has wheedled itself into our attention, spontaneous activity has never, to the best of my knowledge, received the recognition it deserves in the form of a review of its own which treats it synthetically. This omission is what I now, belatedly, shall try to rectify.

I have already mentioned (Chapter 1, sec. 3) Katz's experiments in which he studied the electrical activity of the afferent terminals of muscle spindle end-organs in the frog (Chapter 1, sec. 4, Fig. 5). When the state of tension of the spindle was very low, a random discharge of impulses was observed, but it was quite clear that a considerable number of them never were propagated up the axon but remained in the abortive state as prepotentials incapable of maturing into a discharged spike. These abortive impulses at a given ending occurred in discrete quantal sizes and were not subject to continuous gradation. They were probably therefore real impulses, but limited to the fine terminal branches of the end-organ failing to propagate individually because of the low safety factor for propagation at the site of expansion of the fiber. Only when several such impulses arrived

simultaneously could they set up the current density necessary for evoking a propagated impulse in the common fiber into which they fed. As to the cause of the random discharge at very low tension Katz suggested that there are considerable fluctuations in the excitatory state of the stretch receptor which possibly are due to molecular agitation in the mechanical receptor substance or ionic noise in the terminal nerve membrane. This view has been experimentally elaborated by Buller, Nicholls, and G. Ström (1953). They found in Katz's type of preparation the mean value of the standard deviation from a regular firing frequency to be of the order of 3.0–3.5 impulses per second. This, they calculated, would correspond to a fluctuation of membrane potential of the order of $\pm$ 0.7 mV. in S.D. which may well occur in terminals below 0.1μ (Fatt and Katz, 1952a). Thermal agitation could therefore be one permanent source for this "biological noise."

Fatt and Katz (1951, 1952a), using internal microelectrodes, found a random succession of miniature potentials also in the motor end plate, their amplitude being of the order of 1/100 of the normal end plate potential. While admitting that unknown causes may contribute to this spontaneous activity (cf. Buller *et al.*, 1953), they were inclined to ascribe the phenomenon to thermal agitation of ions within the membrane. Brock, Coombs, and Eccles, by the same technique (1952), found similar random fluctuations across the membrane of the ventral horn cell but those may, partly at least, arise from impulses arriving into individual synaptic knobs. Analysis of the spontaneous discharge in the lateral line organ of fish, performed by Katsuki *et al.* (1950), also showed a random distribution in addition to a periodic fluctuation.

Katz's observations on muscle spindles provide another role for the characteristic fine divisions of sensory nerve terminals in the periphery which I have already considered as a possible factor favoring repetitive firing in many sense organs. Even specialized organs such as the retinal cones have dendritic terminals connected with a single bipolar. The rods which end in round knobs have solved this problem by converging in large numbers upon a single bipolar. They would therefore be expected to possess a particularly high capacity for spontaneous impulse generation, as this, on Katz's results, would be a function of the number of terminals (rods) impinging upon the fiber (bipolar). This assumption is borne out by experimentation (see next section).

2. *Role of spontaneous activity illustrated by retina. The arousal reaction from reticular centers*

In the retina we may also have other sources of spontaneous activity, it being, as we have seen, a layer of receptors lined by two layers of neurones. In most of the preparations on which I have made my observations the optic nerve has been cut (decerebrate cats) or else excised eyes have been used so that the discharge in the optic nerve under all circumstances has arrived only from the periphery. It is therefore from the present points of view immaterial whether the spontaneous activity is ascribed to instability in the transition from receptors to bipolars alone, in the neural structures alone, or in both.

Adrian and Matthews (1928) made the first observations on spontaneous rhythms in a retina. They recorded from the whole nerve of the eel's eye and often found that the spontaneous activity became synchronized into large beats when the entire eye was illuminated. Regular massed rhythms are not seen in the more normal vertebrate retina unless the animal is given strychnine (Granit, 1945a). It is likely to be an abnormality also in the excised eye, as suggested by Adrian (1937) himself in connection with later work on the optic ganglion of the water-beetle (*Dytiscus*). The microelectrode technique, however, will do very little damage to an eye if the electrode is carefully applied to the retina. The lens and cornea may be removed, as in our laboratory (Granit, 1947), or the electrode may be stuck in through a small hole in the bulb, as is being done by Kuffler (1952, 1953). The result is the same. A large number, perhaps most, of the ganglion cells maintain a spontaneous discharge which fluctuates somewhat but in general tends to increase a great deal in dark adaptation (see Granit, 1947, pp. 95–6). This I have seen in both frogs and cats, and Kuffler (1953) in cats. In frog eyes the massed discharge tends to be considerable in the dark and is small during illumination or even some time after cessation of illumination (when the off-discharge proper has disappeared). However, it is never absent and is found also in pure cone eyes (tortoise, snake). Spontaneous activity in the auditory nerve fibers and inhibition of it by noise was described by Galambos and Davis (1944). On the whole, eye and ear present a series of striking similarities in terms of spike patterns and their behavior. A recent important addition to the list of organs with marked

spontaneous activity is the temperature organ (Hensel, 1952; Zotterman, 1953).

In the retina there will be corresponding changes of slow potential because in this organ, as elsewhere, each impulse is preceded by a prepotential (Kuffler, 1953; Best, 1953b). One might say that this little "brain" in the periphery, which is attached to the visual receptors, behaves like the rest of the brain in that it generates small "brain waves." This has recently been emphasized also by Barlow (1953a,b).

In studying the spontaneous activity of the retina with microelectrodes I made the curious observation (Granit, 1941a) that, apart from the spontaneously active cells that could be influenced by light in the ordinary way, there were others which acted with great independence. The strongest illumination I had at the time was 2400 meter candles at the opened eye. Yet, when this light was switched on, there were spikes which remained uninfluenced. There was no reason to suspect that mechanical stimulation by the microelectrode had activated the cell. When slowly screwing the microelectrode into position, looking at it all the time in the microscope (that was placed above the excised cone eye of the tortoise used in the experiment of Fig. 36), one often heard first the rhythm of the discharge in the loudspeaker as a faint distant noise which gradually increased in strength as the point of the electrode approached the active unit from above. Recently Kuffler (1953) also has reported on spontaneously active light-resistant elements with his preparation, the unopened eye of the cat. This need not necessarily mean that such units always are, as it were, shut off from the influence of the receptor layer.

It is far more common, however, to find light to excite or inhibit the discharge, according to stimulus strength and the nature of the element, with an over-all effect of considerable depression of the rate of spontaneous firing in the light-adapted state. In light adaptation fewer elements seem to be spontaneously active than in dark adaptation.

The spontaneous activity, so lively in the mammalian retina, is thus the background against which effects of stimulation are displayed. It would provide a natural explanation of Hering's autogenetic gray. What functions can be ascribed to it on the basis of electrophysiological research?

With regard to the spikes influenced by light in the ordinary way, it seems clear that the fluctuating state of excitability expressed by spontaneous activity must permit some rotation of activity between individual units. This is evident when intermittent stimulation is com-

bined with observations of several units at sufficiently high rates of flicker. Some rotation then takes place, as is shown by Fig. 36.

Further, the increase of the spontaneous firing in the dark may serve to compensate for the drop in excitability that would be a likely consequence for the visual central projections when they are deprived of their sensory input. Without the spontaneous rhythm darkness would be a kind of de-afferentation by natural means of most important sections of the brain. Some years ago, when the only visual projections considered were those through the lateral geniculate bodies to the occipital field in the striate area, permanent cortical facilitation did not suggest the problems it does today.

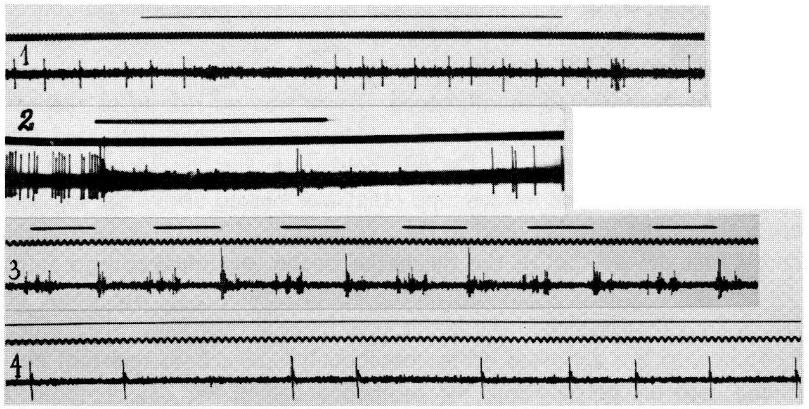

Fig. 36. Microelectrode records. 1. Spontaneous activity in dark-adapted retina of tortoise inhibited by illumination. 2. Same in retina of rat. 3. Response to intermittent light in retina of frog. Several units and some rotation of activity. 4. Spontaneous activity in retina of tortoise, not influenced by illumination. Light signal and time in 1/50 sec. above each record. (Granit, *Acta physiol. scand., 1,* 370. 1941a; *Vet. akad. arkiv f. zool.,* A *36,* No. 11. 1945a.)

On account of the recent electroencephalographical work on facilitatory centers for the cortex situated in the brain stem (see below), the whole problem of the level of activity of the brain centers has taken on a new aspect. For the eye, however, there was early evidence in Bremer's laboratory by Claes (1939) to the effect that the retina is of considerable importance for the maintenance of a normal electroencephalogram had we but understood its significance. Her results have been explained by our microelectrode records of spontaneous activity in the cat's retina.

Claes used Bremer's preparation *encéphale isolé* (Bremer, 1936b).

The atlanto-occipital membrane of a cat is opened under narcosis and the medulla cross-sectioned. The animal is then maintained on artificial respiration without narcosis. In this preparation the brain is active compared with that of ordinary anesthetized animals. As a most characteristic sign of this state of activity the electroencephalogram from the striate area is characterized by an incessant low-voltage high-frequency discharge interrupted by large bursts similar to those seen under barbiturate anesthesia but somewhat faster and often not quite as large. Claes studied this electroencephalogram *before* and *after* (a) enucleation of the two bulbs, (b) retrobulbar severance of the optic

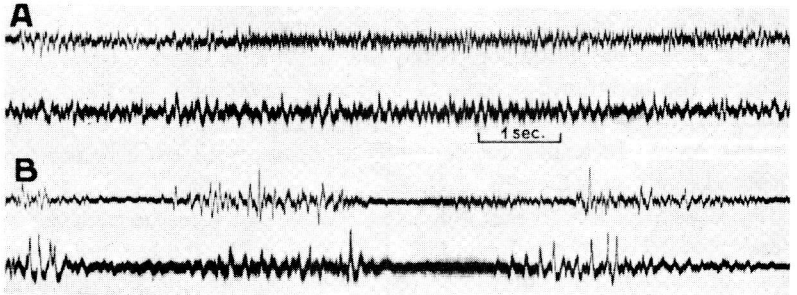

Fig. 37. Cat, *encéphale isolé.* Electroencephalograms. *A:* simultaneous records from the two striate areas before bilateral enucleation of the eye bulbs. *B:* same after enucleation. Note groups of slow waves separated by almost total inactivity. (Claes, *Arch. Int. Physiol., 48,* 181. 1939.)

nerves without enucleation and (in one case) (c) cauterization of the papilla of the optic nerve. The result of those operative procedures in most animals was that there appeared long periods of almost complete central inactivity lasting from ten to fifteen seconds, which interrupted groups of activity of higher voltage but lower frequency than before, a change in the direction of the one occurring in sleep. Electroencephalograms from the striate area before and after bilateral enucleation of the bulbs are shown in Fig. 37. I have confirmed her results on one similar preparation. Ingvar (1954) has since confirmed them on several animals with instantaneous severance of both optic nerves behind the eye bulb. Large scale chronical experiments are still lacking.

This change, Claes observes, is never seen merely in the absence of stimulation with light, even if darkness be maintained indefinitely. She concluded that the retina, also in the complete absence of visual stimuli, exercises a tonic influence upon the level of spontaneous activity in the brain. This effect is primarily noted in the striate area

but some influence can also be detected as a repercussation in other regions—for instance, in the auditory area.

The electroencephalographic results seem capable of explaining the general biological significance of the striking spontaneous activity that I at the same time found in the dark-adapted mammalian retina. It also seems possible that some retinal ganglion cells, as Kuffler and I have found, actually—while subthreshold—devote themselves chiefly to the role of "energizers" maintaining the level of excitability of the centers and for this reason keep up their firing rate with relative disregard of stimulation by light. From the point of view of vision they would probably be high-threshold units requiring a very great amount of illumination to alter their firing frequency. I find it difficult to believe that they would be completely inaccessible to illumination. However, if the spontaneous activity is partly maintained by the neural elements, the system may well be temporarily independent of the receptor input. It would be valuable to have more experimentation devoted to all these aspects of vision.

Now what is this "tonic influence"? How can sense organs act as "energizers"? Can we formulate this idea with greater precision? Spontaneous activity may well be a very important physiological phenomenon. To this end we have to turn to current notions about sleep and wakefulness.

Ranson's group (see e.g. Ranson, 1939; Ranson and Magoun, 1939), in the large-scale work with the Horsley-Clarke instrument carried out at Northwestern University in Chicago, came to the conclusion that the essential problem in sleep, far from being one of generalized inhibition, had to be turned upside down. Thus, what had to be accounted for was not in the first instance somnolence but the state of activity and awareness. Ranson's view was that the hypothalamus contained a "waking center" to take care of these functions. When this was destroyed, the animals fell asleep. Other aspects of the problem of sleep need not concern us in this connection except that it is necessary to realize that opposing systems in the lamina medullaris interna of the thalamus induce sleep (see e.g. Hess, 1944a,b; Hunter and Jasper, 1949), including the electroencephalographic signs of sleep (Akert, Koella, and Hess, 1952). Bremer (1935, 1936a), in developing his preparation *cerveau isolé,* had followed a similar line of thinking, believing the electroencephalographic signs of somnolence that he observed in his animals were due to section of the specific sensory lemniscal paths running through the thalamic regions to activate the sensory projections in the cerebrum, a view at the time widely accepted.

Bremer's transection for this preparation was at a higher level than Claes', through the mesencephalon, and instead of the active brain of the encéphale isolé by a bulbar section, he now encountered a brain, the cerveau isolé, with all the electroencephalographic signs of sleep or of barbiturate anesthesia. Visual and olfactory paths remain, but if these also are removed by destroying the basal parts of the diencephalon, inactivity becomes profound (Bremer, 1938; Lindsley, Bowden, and Magoun, 1949).

The work of Magoun and his collaborators Niemer and Rhines, which will be discussed in connection with the activation of the muscle spindles (Chapter 7), had led to the elaboration of the concept of

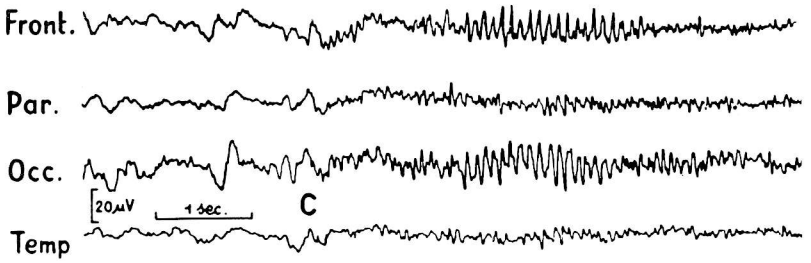

Fig. 38. Awakening of a sleeper. Normal adult male. At the beginning of the records the E.E.G. shows the irregular slow waves which characterize light sleep; at *C,* awakening by a call. Note the succession of a slow reaction wave synchronous in the four leads, a burst of alpha waves, and finally the fast low-voltage activity of the waking state. The monopolar leads, all on the same left hemisphere, were frontal, parietal, occipital, and temporal. Calibrations: 20 microvolts, 1 second. (Bremer, Some problems in neurophysiology, Athlone Press, London, 1953.)

excitatory and inhibitory regions of generalized action in the brain stem and medulla, serving to induce respectively hyperactivity and hyporeflexia, with lack of tonus in the periphery, without much discrimination between individual muscle groups. Adding electroencephalography to their methods of research, Moruzzi and Magoun (1949) and Moruzzi (1949) identified a cephalically directed brain-stem system, apparently consisting of reticular relays ascending to the basal diencephalon and further to the cortex, where it was found to desynchronize the high-voltage slow waves and create a pattern of low-voltage high-frequency activity, the so-called arousal reaction (see for a summary, e.g., Bremer, 1953; Magoun, 1950, 1952). Fig. 38, from Bremer's work, illustrates this change during awakening in man. Magoun and his collaborators found that basal mesencephalic and

diencephalic lesions which abolished the electroencephalographic arousal reaction had spared the specific sensory relay nuclei which therefore could hardly be held responsible for the maintenance of the state of awareness as defined electroencephalographically. Bremer (1953) fully accepted these conclusions and thus subscribed to the view that the reticular activating system rather than the specific relay nuclei, which he first had thought of, were the ones setting up the arousal reaction.

Several other lines of research by electroencephalographic methods, carried out practically during the same period, converged toward establishing and giving precision to the idea of "waking centers" in the mesencephalic and diencephalic reticular system. Thus, Morison and his collaborators (Dempsey and Morison, 1942; Morison and Dempsey, 1942) originated a very prolific line of experimentation by showing that thalamic stimulation at a slow rate activated a recruiting response of waves similar to the barbiturate spindles. This was found in widespread areas of both hemispheres. Stimulation at fast rates, however, suppressed barbiturate bursts (Dempsey and Morison, 1943; Morison, Finley, and Lothrop, 1943). The latter observations were explained by Murphy and Gellhorn (1945), who found that hypothalamic stimulation which suppressed such bursts also dispersed synchronized strychnine spikes and induced the high-frequency low-voltage response which characterizes awakening or arousal. Jasper and his group (summary by Jasper, 1949; cf. Hanbery and Jasper, 1953) pointed out that arousal reactions were obtained from stimulation with high frequencies of certain portions of the thalamus and the posterior hypothalamus. He regards what he calls the *thalamic reticular system* as a more highly organized portion with diffuse central projections capable also of more restricted cortical action and of setting up the recruiting response types first described by Morison and Dempsey. In this respect it differs from the mesencephalic reticular system, the desynchronizing action of which normally will keep the thalamic neurones under control (see e.g. Jasper, Ajmone-Marsan, and Stoll, 1952). He agrees, however, with Magoun as to the strongly desynchronizing action of the mesencephalic reticular system. The projections of this system upon the thalamic nuclei have been studied by Starzl, Taylor, and Magoun (1951a).

From the present point of view it seems particularly important that the system of ascending reticular relays recently has been found to receive "a hitherto unsuspected wealth of afferent connections" (Magoun, 1952; cf. Dell, 1952). By the technique of evoked potentials

Starzl, Taylor, and Magoun (1951b) have found in it responses to somatic and auditory stimuli. French, Van Amerongen, and Magoun (1952) have also demonstrated visual projections in this area. Simultaneous records from cortex and reticular system show the reticular afferent response to be accompanied by the characteristic arousal reaction at the higher levels, as obtained by direct electrical stimulation of the same region. Since decerebellation or decortication did not remove the reticular response to afferent stimulation, it was concluded

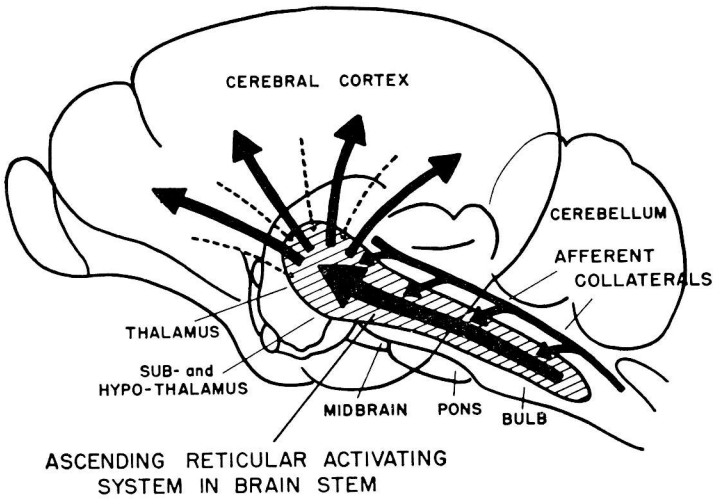

Fig. 39. Outline of brain of cat, showing distribution of afferent collaterals to ascending reticular activating system in brain stem. (Starzl, Taylor and Magoun, *J. Neurophysiol., 14,* 479. 1951b.)

that the effects did not as such depend upon corticofugal paths. Taken in conjunction with the fact, mentioned above, that destruction of the specific lemniscal pathways of the sensory impulses did not by itself suffice to reduce the activity of the brain to somnolence, as defined electroencephalographically, all this work seems to support the notion that the sense organs actually possess another route of relays through the reticular portion of mesencephalon and diencephalon which is essential in maintaining a state of wakefulness or alertness. Fig. 39 summarizes these conclusions.

Returning, after this excursion, to the question of spontaneous activity in sense organs, it seems that our "private measuring instruments" must play a great role also in keeping us alert and active. Spontaneous activity now emerges as something vastly more significant

than a random noise in itself might have been held to be. It is incorporated in the functional plan upon which the body is organized for action and reaction. We can now better understand how sense organs can serve as "energizers." A good example on a simpler scale is the olfactory bulb, which shows continuous fast activity in light anesthesia but can be induced to rest by intravenous injection of barbiturates or other anesthetics (Adrian, 1950). In such cases

> the intrinsic activity may return after a time as the effect of the anaesthetic wears off, but before it has returned spontaneously it can often be started up again by a short period of olfactory stimulation. The sudden resumption of activity is an example of a reaction which occurs in many other collections of unstable nerve cells and is best described as the awakening reaction. . . . [This] may be regarded as little more than the development of a prolonged after activity in a structure which tends to oscillate when it is disturbed. In some conditions and in some structures the oscillations die out in a short time, in others they continue indefinitely. [Adrian, 1950, pp. 381–2.]

In thinking of the spontaneous activity from sense organs in such terms it is necessary to recall that some sense organs are provided with centrifugal fibers which may "set" their permanent output frequency to any desired level. I shall take up this question in sec. 6 below.

In their capacity as "energizers" the sense organs may well be supported by other structures. I am thinking in particular of the cerebellum, in which Brookhart, Moruzzi, and Snider (1950), using the microelectrode technique, have found very high firing frequencies in individual Purkinje or granular cells. It is difficult to see any other obvious reason for spontaneous firing at average rates of from 70 to 80 impulses per second in a cerebellum deprived of its connections with the cerebrum. The cerebellum also receives a very large number of afferent sensory projections, particularly from the skin and the muscles and projects to the reticular substance (Snider, McCulloch, and Magoun, 1949; Whiteside and Snider, 1953). Excellent anatomical reviews are given by Brodal (1943, 1949). Recently Jansen and Brodal have summarized the extensive work of the Oslo school. This should not be interpreted to mean that the cerebellum serves this purpose alone. One of the more important advances from the last decade is, indeed, our increasing knowledge about the existence of highly specific projections on the cerebellar cortex and other functional subdivisions (Dow, 1939; Adrian, 1943b; Fulton, 1949a; Snider, 1950; Moruzzi, 1950; Woolsey, 1950; Chambers and Sprague, 1951, 1952; Sprague and Chambers, 1953).

To hold the view that sense organs, and in this particular connection the retina, energize certain systems and individual cells by way of a maintained spontaneous activity is to provide a new role for peripheral inhibition in sense organs, whatever its cause. If all optic nerve fibers were silent, unless stimulated, an effect of inhibition around the edges of illuminated patches projected onto the silent retina would be negligible because it would never be transmitted to the perceiving cortex. But if the sense organ normally is spontaneously active, the suppression of the inherent activity will be notified to the cortex which, as is well known (see e.g. Fulton, 1949b), reproduces the peripheral sentient surface on a striate map of its own. The edges around the projected patches on the cortical map may now appear as regions of correspondingly altered excitability. There is also a gradation on the perceptual side in quantity from "black" to "white," and intense black is perceived only by contrast against white. These facts presuppose notification on the part of the periphery, by some kind of "cue" to the center, that there is complete cessation of impulse activity. The center may well provide further elaboration, but it is difficult to see how it could do so except against a background of suppressed discharge.

In studying the optic nerve discharge of a retinal element in dark-adapted cats, very commonly one finds that inhibition precedes excitation, particularly at high intensities of stimulation (Granit, 1944). If there is a spontaneous rhythm, it need not be immediately accelerated. The acceleration may come after an initial inhibition, suggesting that for some unknown reason the spontaneous discharge is cleared away before the excitatory message is allowed to reach the brain.

We do not yet fully understand the specific sensory significance of the maintained spontaneous activity of the retina as distinct from its general role in activation of the higher centers. The suggestions put forth have served to emphasize possibilities all of which have one feature in common: that a background of spontaneous discharge will enhance the significance of peripheral inhibition. We shall find this generalization vindicated below by evidence from other sense organs. The general advantage accruing from this arrangement is the same as that of a galvanometer with its needle at the midpoint of the scale instead of at the end.

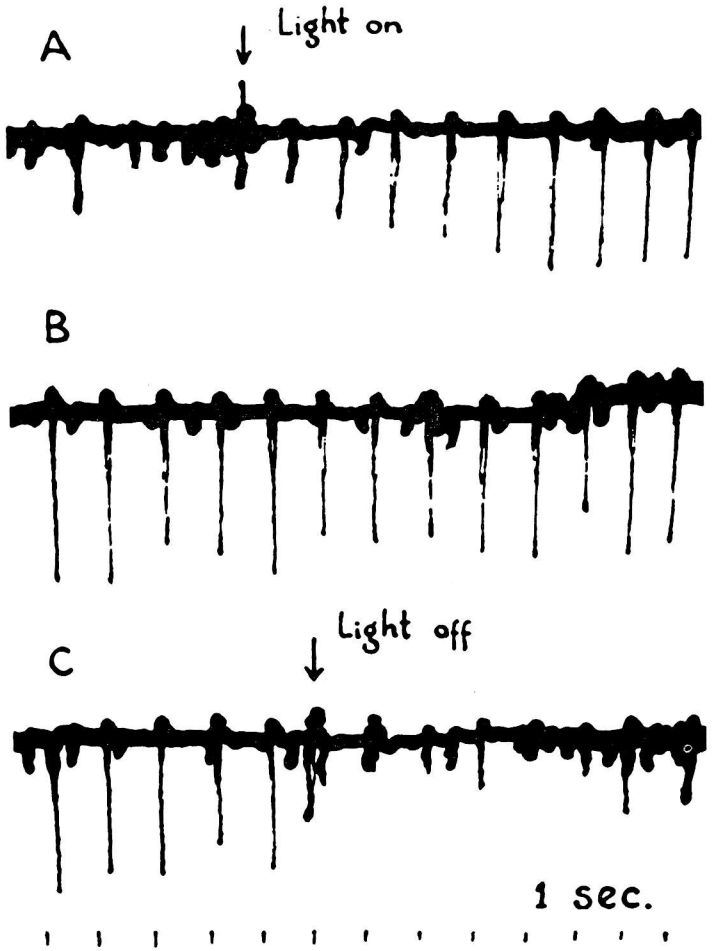

Fig. 40. Cortical responses to the stimulation of the lateral geniculate body as recorded by an electrode inserted into the cortex at a depth about 1.5 mm. beneath the surface. *A:* in dark. *B:* during retinal illumination. Note the increase in size of the three radiation potentials in *B*. (Chang, *Res. Publ. Ass. Nerv. Ment. Dis., 30,* 430. 1952.)

To this section also belong some observations by Chang (1950a,b). He was using cats and recorded the response to light from the lateral geniculate body which is the first synapse on the path of the optic nerve. Fig. 40 illustrates that the response to a slowly repeated electrical test shock applied to the optic nerve is small in the dark but gradually increases in size when the light is allowed to shine for some

time. The effect is slow but of a remarkable order of magnitude. It develops within 5 seconds. Light, as it were, potentiates itself! This effect is also reflected in the striate area and spreads to the auditory area, proving in a way different from that in the work previously mentioned that the discharge through the optic nerve has a great influence on the general level of activity of the brain. Chang holds that the effect is caused by excitatory impulses, and he may well be right in this view. If so, it should occur also at cessation of illumination (off-discharge).

3. Spontaneous activity in certain mechanoreceptors

Highly sensitive mechanoreceptors like those in the vestibular organ and in the lateral line of fishes operate on the principle of microlevers in the shape of hairs standing in fluid. The principle that flow of the fluid in one direction will excite a discharge and in the other direction will depress the spontaneous rhythm was established by the work of

Fig. 41. Records showing the effect of perfusing the hyomandibular loop of a roach on the activity of a number of lateral line receptors. The white line is the perfusion signal. Its upward displacement signals tailward perfusion, its downward displacement signals headward perfusion. Time signal in seconds. Perfusion at 10 cm. water pressure. Further explanation in text. (Sand, *Proc. Roy. Soc. of Lond.,* B *123,* 472. 1937.)

Löwenstein and Sand (1936, 1940) on the semicircular canals of elasmobranchs. The significance of this result is perhaps easier to understand if I first consider the lateral line organ of fishes, with which the vestibular organs are morphologically homologous. It is, in fact, a bilateral tube containing hairs in endolymph and placed on the surface of the body. Katsuki, Mizuhira, and Yoshino (1951), in the relatively wide canal of the Japanese sea eel, found groups of sensory hair cells covered by a thin transparent cupula.

Hoagland in a series of papers (1933a,b, 1933–34a,b) described the spontaneous activity in the nerve of this organ (cf. Katsuki *et al.*, 1950). Hoagland and independently of him Schriever (1935) found them to be mechanoreceptors, but it remained for the late Alexander Sand (1937), who developed a technique for perfusion of the hyomandibular loop of the canal, to show that flow in one direction excited some receptors, flow in the other direction inhibited them. This is shown in Fig. 41. Actually there are two types of end-organs which have opposite responses, as shown in Table 1.

TABLE 1 *

	Group I		Group II	
	During Perfusion	*After-Effect*	*During Perfusion*	*After-Effect*
Headward	strong response	silent period	inhibition	accelerated rhythm
Tailward	inhibition	accelerated rhythm	response	silent period

* Sand. *Proc. Roy. Soc. of Lond.*, B *123*, 481. 1937.

Perhaps one should remark, too, that the lateral line organ obeys Fechner's law, the spike frequency being proportional to the logarithm of the rate of flow. A rate of flow of 16 mm/sec. was a maximal stimulus for these receptors, and the threshold was so low that it could not be exactly determined. Actually the gentlest tapping on the table or footsteps on the floor of the laboratory stimulated the preparation, effects which, before they were eliminated, proved to be embarrassing sources of error. This being so, one might think that the marked spontaneous activity of the lateral line receptors would be mechanical artifacts or else due to ciliary movements of the hairs (Hoagland). But Sand mentions that when he injected the canal with a suspension of particles of methylene blue, he could not, through a binocular, see any motion in them during more than an hour of observation. Yet, though the particles remained motionless, the nerve of the canal showed a vigorous persistent discharge. As to artifacts, he had his preparation well under control. In this connection Sand made the following very good remark: "If it is thought that ciliary activity of the hair cells is in some way more intelligible than an inherent rhythmicity of a purely nervous peripheral mechanism, it is only because we are familiar with such autonomous peripheral effectors, while the

conception of an unprovoked peripheral nervous rhythm is new" (p. 490). The marked spontaneous rhythm of the retina and many other sense organs, and Katz's evidence on the muscle spindle, reviewed above, rather tend to lay the burden of proof on those who deny the existence of true spontaneous impulse generation. Conceptually, one should perhaps make a distinction between a true resting discharge and one maintained by a stimulus such as slight tension on a muscle spindle or mechanical stress influencing receptors around the hair stalks. For the present problem this distinction is of little importance but in the last section I will show at what stage in the argument it really matters.

On the whole I feel inclined to stress that we move on firmer ground when we tentatively ascribe the close similarities in the principles of action of various sense organs to the operation of analogous mechanisms, rather than when we proceed to hypothecate a large number of special mechanisms. Actually, the types of response from receptors fall into a relatively limited number of categories. When, as shown by Table 1, in the lateral line organ excitation is followed by inhibition to flow in one direction, inhibition by excitation to flow in the other direction, it is likely that these effects in the last instance are due to depolarization and hyperpolarization of a membrane of the kind previously discussed (Chapter 1, sec. 4). Another question, then, is how the movements of the hair succeed in bringing about depolarization and hyperpolarization. It is perhaps most reasonable to assume two kinds of hair cells in which the hairs are slightly bent or mechanically so fixed that flow in one direction augments the stress on them, flow in the other direction releases it. This problem is unsolved. It recurs with several other mechanoreceptors of the same type, such as the vestibular ampullae for which Löwenstein (1953) recently has obtained evidence in favor of an electrical depolarization potential being responsible for impulse generation.*

In this place one should perhaps mention the vibrissae of the cat. They have far more elaborate endings around their stalks than do ordinary hairs. These endings are surrounded by sensory structures enclosed in bags, which may provide the mechanical forces necessary for their directional sensitivity described by Fitzgerald (1940). The spontaneous discharge is enhanced when the vibrissa is moved in one

* The prediction that depolarization and hyperpolarization will occur in such organs and depend upon the direction of current flow has since been verified by Y. Katsuki, H. Uchiyama and G. Totsuka (*Proc. Jap. Acad., 30,* 248–55. 1954).

direction, suppressed when it is moved in another direction. This organ is always under the influence of gravity, and so tensile stress on the endings around the stalk is probably always maintained.

With regard to the significance of spontaneous activity, the experiments on the lateral line organ are deficient in that the reflex effects of the receptors are unknown. Thus, it is merely by hypothesis that we can ascribe to their spontaneous rhythms an activating function of the type proved to exist for the mammalian retina. This hypothesis was, in fact, proposed by Hoagland. However, for other homologous structures the reflexes are known, and it seems reasonably certain, therefore, that the inhibitory and excitatory modifications of the spontaneous activity, also in the lateral line organs, constitute an important mechanism for setting up differentiated responses. They are not likely to be an exception to the general rule that spontaneous rhythms, apart from activating higher centers, play an important role wherever the peripheral mechanism of excitation is developed so as to include peripheral inhibition.

This conclusion is again emphasized by the behavior of the receptors in the semicircular canals, which also interpret movement in space, differing from the lateral line in that the fluid is enclosed in a tube, put in motion by acceleration, and thus bending the large gelatinous "cupula" which is seen in Fig. 42 to ride upon hair cells. The actual swing-door movement of the cupula within the canal has been observed on fishes in beautiful experiments by Steinhausen (1931, 1933) and Dohlman (1935, 1941). These semicircular tubes in the labyrinth of the ear are well known to every student of biology to be oriented in the three space coordinates—in fact three space organs in one—and so to be capable of recording acceleration in all directions (see e.g. the book by Camis, 1930). They are also known to initiate a large number of compensatory reflexes upon the eye muscles, the body, and the limbs—elucidated in brilliant experiments by Flourens (1830a,b), Ewald (1887), Breuer (1889), Magnus (1924), and others.

The vestibular nerves have been studied by several workers (Ross, 1936; Löwenstein and Sand, 1940; Adrian, 1943a; Gernandt, 1949; Boenninghaus, Henatsch, and Vilmar, 1952), all of whom have noticed the marked spontaneous resting discharge. In describing the dynamic responses to acceleration I follow the paper by Löwenstein and Sand on the thornback ray (*Raja clavata*). In this animal the piece of cartilage containing the labyrinth can be removed, studied in isolation, and thus conveniently rotated in all directions. Their work

is therefore singularly complete and, as far as any specific aspect of it is concerned, the results are in essential agreement with those obtained on other animals, including mammals (Adrian, Gernandt).

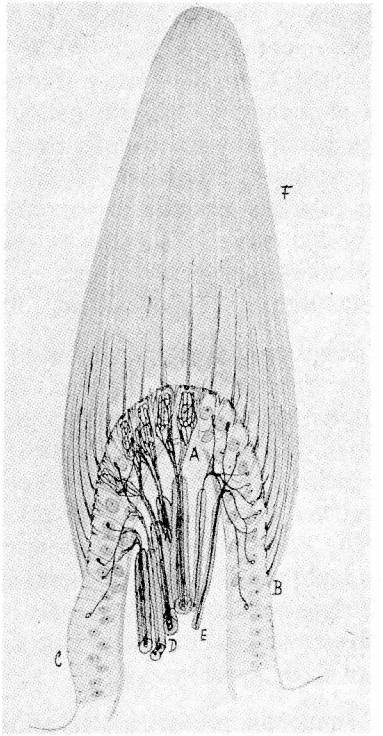

Fig. 42. Diagrammatic sketch of a crista. On the surface of the crista are the ciliated cells *A*, between which are seen the supporting cells *B*. Toward the base of the crista are the undifferentiated epithelial cells *C*. *D* indicates large nerve fibers, the endings of which are connected with the intracellular network. *E* are fine nerve fibers in the lateral parts of the crista, with free intercellular endings. *F* is the cupula; the hair-processes of the sensory cells are seen penetrating the canals of the cupula. (Kolmer, *Ergebn. Physiol., 11,* 372. 1911.)

Löwenstein and Sand made the fundamental observation to which I have already alluded, namely that for each canal there were two opposite reactions: rotation one way increased the spontaneous discharge, rotation in the opposite direction suppressed it. Consider now that there are six such canals, three in each ear, and it will be apparent that the presence of a spontaneous rhythm that can be accelerated or decelerated makes for a discrimination which, unless utilized by the

brain, would be wholly meaningless. Table 2 summarizes the actually observed responses of the semicircular canals to rotation about three primary axes.

This table repays close study. The way it resolves space into a number of permutations makes one feel grateful for having the appropriate compensatory movement in the muscles wholly performed by automatic reflex adjustments! There is no more instructive demonstration of the significance of pattern for discrimination. The fact that we do not discriminate vestibular impressions by perception, i.e. consciously (according to most authorities), is not a serious argument when one considers that this message is correctly interpreted by the lower centers for the eye muscles. There is no reason to regard consciousness as more than a fringe on the pattern.

An interesting detail is that, to quote Löwenstein and Sand,

> the four vertical canals are functionally grouped in pairs, the grouping differing in the three types of rotation. Thus, during rotation about the longitudinal axis (tilting sideways) they may be described as *laterally synergic,* during rotation about the transverse axis (tilting forward and backward) they are *transversely synergic,* and during rotation about the vertical axis (turn-table rotation) they are *diagonally synergic.* For example: tilting towards the right excites the right anterior and posterior canals (lateral synergy), tilting forwards excites the right and left anterior canals (transverse synergy) and clockwise turn-table rotation excites the left anterior and the right posterior canal (diagonal synergy).

Löwenstein and Sand also present a scheme of correlations with actual eye muscle movements, but it is not practicable to take it up in this context. My purpose has been to point out the significance for discrimination of spontaneous rhythms in receptors. From this point of view the semicircular canals are a model organ because only one clearly definable task in space orientation is involved: by their response to acceleration they must create means for discriminating one direction of movement from another in order to be capable of directing reflex orientation the way they do. They have, as do other sense organs, only the frequency code at their disposal, grafted, however, upon a magnificent space-sensitive instrument, the tubes for the spatial coordinates containing the fluid moving the swing-door cupula. Acceleration and deceleration of the spontaneous rhythm of discharge creates an interpretable pattern. One of our major aims as sensory physiologists is to attempt to identify peripheral "cues" for sensory discrimination

TABLE 2 *

Responses of the Six Semicircular Canals to Angular Displacements about the Three Primary Axes. ● excited; ⊗ inhibited; O unaffected. ant. vert. = anterior vertical; post. vert. = posterior vertical

Semicircular Canal	Rotation about the					
	Longitudinal Axis		Transverse Axis		Vertical Axis	
	Right	*Left*	*Forward*	*Backward*	*Clockwise*	*Anticlockwise*
Right ant. vert.	●	⊗	●	⊗	⊗	●
Left ant. vert.	⊗	●	●	⊗	●	⊗
Right post. vert.	●	⊗	⊗	●	●	⊗
Left post. vert.	⊗	●	⊗	●	⊗	●
Right horizontal	O	O	O	O	●	⊗
Left horizontal	O	O	O	O	⊗	●

* Löwenstein and Sand, *J. Physiol., 99,* 96. 1940.

in terms of the frequency code. In this, Löwenstein and Sand have been successful.

Spontaneous rhythms from the vestibular organs also serve to "energize" specific structures, such as the ventral horn cells responsible for the motor part of the tonic or postural reflexes of the body. Long ago, Fulton, Liddell, and Rioch (1930) showed that destruction of the vestibular nuclei of animals in the state of decerebrate rigidity made them atonic, and this experiment has more recently been repeated and confirmed by Bach and Magoun (1947). Apparently, however, this is not the sole source of tonic impulses from this region (Sprague and Chambers, 1953). We shall return to this problem in Chapter 7, which deals with the control of tonus.

4. *Spontaneous discharge in certain chemoreceptors*

The spontaneous activity of the chemoreceptors of *glomus caroticum,* which were discovered by Heymans and Heymans (1927), is an interesting case because for these receptors there is an excellent reflex index of the effect in the animal's respiration. They respond to lack of oxygen in the blood. Their impulses were recorded by Von Euler, Liljestrand, and Zotterman (1939), who found them to be spontaneously active also in eupneic breathing. Later Bjurstedt (1946), by cooling the sinus afferents, made systematic observations on removal of the permanent stimulus from the carotid body to the respiratory center. Even in the eupneic state, cooling of the sinus nerves diminished respiration, showing that the reflex drive kept up by spontaneous activity was of importance for the normal excitability of the respiratory center.

5. *General significance of spontaneous activity*

By piecing together evidence from different sources it has proved possible to reach a number of conclusions about the spontaneous activity that has been observed in various sense organs. When it was first seen, one was naturally suspicious. The preparation might have been abnormal; it may have been impossible to avoid some stimulation. Ultimately, however, the existence of spontaneous firing from sense organs became acknowledged, and now it has been picked up practically at birth. In several cases it has been shown that it is most

important for the maintenance of general excitability of the nervous centers and that, in addition, it has an important function in discrimination, particularly for sense organs possessing peripheral inhibition. Thus it supplies the need for private measuring instruments with indicators pointing both ways. We have evidence also for the belief that the spontaneous activity of the sense organs makes them one of the brain's most important "energizers."

As a young medical student I was told of Strümpell's (1877) famous case, which was a curious one of successive loss of the use of the sense organs. Ultimately only two channels, one eye and one ear were left. When these two input sources were excluded, the patient regularly fell asleep, within 2 to 3 minutes. Bremer very much later found that the electroencephalogram of cats with the brain sectioned at the level of mesencephalon characteristically changed in the direction of an electroencephalogram during sleep and inferred that the specific sensory pathways carried impulses necessary for the state of wakefulness. Chang, for the visual centers, arrived at the same conclusion from his experiments (1952) and, indeed, drew attention to Strümpell's case. New light has been cast upon these observations by the recent disclosure (Magoun, 1952) of an unspecific mesencephalic reticular system which receives branches from various sensory afferents in their passage upward, and which is engaged in transforming this sensory input into an activating discharge destined for large portions of the cerebral cortex. It is now very likely that these unspecific paths rather than the specific sensory afferents are responsible for the task of energization.

6. *Centrifugal control of sensory messages*

Sense organs may have a practically fixed or a variable sensitivity determined by their design. In addition most of them possess some sort of regulatory control. Well-known mechanisms of this type are the pupillary reflexes and those governing the state of contraction of the two muscles, *tensor tympani* and *stapedius,* of the middle ear. A most elaborate system for self-regulation is built up around the limb muscles. There are inhibitory reflexes arising in the tendons of the muscles which prevent the latter from reaching dangerous states of tension. Other organs, the mammalian muscle spindles, which reside in a special kind of "intrafusal" muscular tissue, have preserved a high degree of freedom from the necessity of passively following variations in length of the ordinary muscle fibers. They owe this independence

partly to the anatomical arrangement of the intrafusal fibers, partly to a special kind of spinal centrifugal nerve elements which adjust the length of these fibers. In recent years we have made great progress in the understanding of centrifugal control of the spindles and other sense organs in the muscle. I shall discuss these problems in considerable detail in Chapters 6 and 7.

What concerns us here is the general principle of control exercised by centrifugal nerve fibers, because if, as is the case, relatively slowly adapting and therefore spontaneously active sense organs really are controlled from nervous centers in the brain, it is clear that spontaneous activity in the intact organism is not wholly at the mercy of "biological noise." In other words, the spontaneous discharge in sense organs connected with the rest of the body is no longer wholly spontaneous. The organism itself can adjust the level of permanent firing to its needs. How this is arranged with the muscle spindles will be demonstrated with many examples in Chapters 6 and 7. It suffices here to point out that the spindle discharge is very effectively controlled from the mesencephalic reticular activating system (Granit and Kaada, 1952), which receives an important part of the unspecific sensory input. The spontaneous discharge from the retina appears to be similarly controlled from the same system (Granit, 1953, and below).

It therefore seems as if there were all requirements present for large self-exciting loops, e.g. a circuit comprising brain stem → muscle spindles → brain stem. Such loops may well be of great importance. In pathological cases they may acquire the character of vicious circles and help to maintain a state of nervous tension. I shall not elaborate these notions further. There is nothing in them that cannot be approached experimentally, and ten years hence we shall know a great deal more about these problems. But a certain amount of—as I hope—constructive speculation may not at the moment be out of place. The problems are of the kind that need some guidance by theory if they are not to fall flat altogether from lack of perspective.

What is, for instance, the role of the centrifugal fibers in the eye and the ear? What are the elementary facts? Held (1893), recently confirmed by Rasmussen (1946, 1950), described the centrifugal fibers of the ear. Nothing, however, is known about their function. Cajal (1894, 1933) and Dogiel (1895) found the centrifugal fibers of the retina (cf. Arey, 1916). Polyak (1941), summarizing the literature, pointed out that these fibers have not yet been convincingly demonstrated in the optic nerve with degeneration methods. Some of them may therefore be recurrent axon collaterals of the type found in the

ventral horn cells and thus provide inhibitory or excitatory feedbacks to the retinal neurones. The inhibitory feedback of the ventral horn cells will be discussed in Chapter 6.

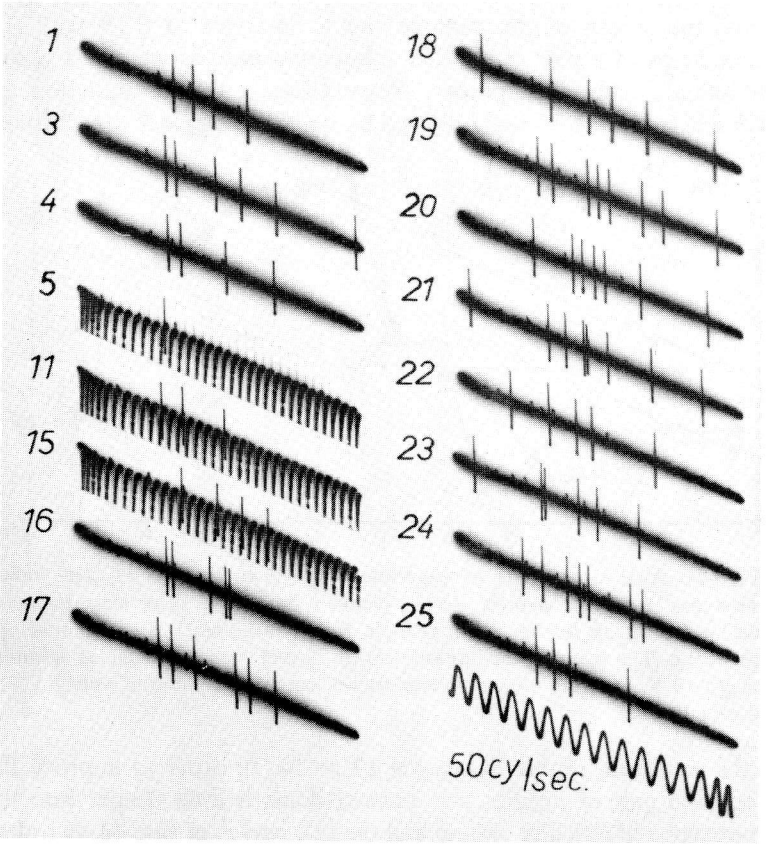

Fig. 43. Encéphale isolé cat. Curarized. Each sweep represents test with flash of 2.7 lux. Sweep interval 0.75 sec.; 1–4: controls. 5–15: samples during stimulation of superficial portion of reticular formation at pretectal level. Stimulus frequency 107/sec. Shock artifacts downward. 16–25: successive sweeps after stimulation.

On the other hand, with regard to the retina I have recently (1953) succeeded in demonstrating centrifugal effects from the mesencephalic reticular activating system, some of which are difficult to understand unless the centrifugal fibers really exist and can be activated from structures in this region. The new results have been obtained by recording with microelectrodes from the (curarized) cat's retina and stimulat-

ing with frequencies from 50 to 200 per second through needles inserted into the mesencephalic reticular substance by means of the Horsley-Clarke stereotaxic orienting instrument.

Fig. 43 illustrates the test response (1–4) to a flash of 2.7 lux swept across the screen of the cathode ray at intervals of 0.75 sec. The isolated tips of a pair of parallel stimulating needles were just above the reticular substance proper. Nevertheless, tetanic stimulation for 11.3 sec. from 5 to 15 was followed by a definite increase of sensitivity

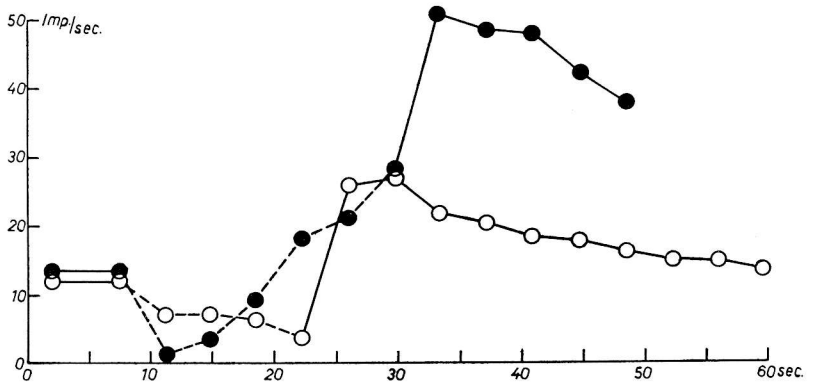

Fig. 44. Analysis of type of experiment as shown in Fig. 43. The values plotted per 5 sweeps *before, during* (broken line), and *after* stimulation of reticular formation further down than in Fig. 43 (see text). Same animal and experiment. The greater facilitation (upper curve) was obtained at stimulus strength 10 V. and rate 49/sec. Lower curve: same, with stimulus strength 5 V. and rate 107/sec.

to the test flash, visible in records 17 to 24. In order to improve the effect, the pair of needles was pushed down a little deeper into the mesencephalic reticular system and the two curves of Fig. 44 recorded. Every point on these curves is an average of the values of five sweeps, each lasting 284 msec. at sweep intervals of 750 msec. The ordinates are given in impulses per second, the test response being an on-discharge to 2.7 lux. Tetanization of the reticular structures (during broken line) was followed by very great facilitation of the test response. In Chapter 7 similar effects on the muscle spindles will be described. In the present case, however, it is a phenomenon wholly within the central nervous system to which the neural layers of the retina belong. Yet in general outline the two phenomena look very much alike. In both cases the reticular substance has to be stimulated for a while, responds slowly, and remains active for a considerable time after

cessation of stimulation. The "arousal" response of the cortex, mentioned above, behaves in the same way. We might speak of an arousal of the retina or of the muscle spindles. However, while the electroencephalographic arousal of the cortex still must be regarded as imperfectly understood as an electrophysiological event, the present effect, defined in terms of the sensitivity to light of a single retinal ganglion cell, is perfectly definite: it is a slow semistationary rise or fall (see below) of the sensitivity of the retina's own nervous center. If the retina is spontaneously active, as most good preparations are, reticular stimulation is followed by a very great increase of the spontaneous rhythm. When light is used for testing, the effect consists partly in an increase of impulse frequency, but just as dominant, sometimes more so, is the extended duration of the discharge. In very active preparations the whole response pattern changes into a drawn-out semipermanent discharge within which "on" and "off" appear as a temporary increase of the spike frequency. In fact, if the reticular effect is strong, it may often be difficult to detect a clear differentiation of the response into "on" and "off" discharges. The results presented are so recent that it would be premature at this stage to try to theorize widely about their significance even though a large number of tempting consequences readily suggest themselves. However, as a tribute to Cajal's acumen, I would like to quote: "Nosotros habiamos admitido que las fibras centrífugas traían del cerebro alguna acción indispensable para el fisiologismo retiniano, algo así como tensión ó energía necesaria á la buena transmisión" (Cajal, 1904, p. 644). What he postulated was thus some kind of arousal reaction!

The subject raised ramifies rather widely into different theoretical and experimental problems of general neurophysiological interest. It is necessary to dwell upon one more aspect of it in order to explain why some caution should be exercised in discussing brain control of the retina. With the aid of the Horsley-Clarke stereotaxic instrument it is possible to shift the stimulating needles to the pretectal and collicular areas and locate places within which the optic nerve fibers sweep round from the lateral geniculate body to penetrate into these structures. A relatively small number of optic nerve fibers can thus be located on the margin between pretectum and the superior colliculus and, as shown in Fig. 45(I), it is possible to pick up the corresponding spike in a single retinal ganglion cell. Records *C* are two control responses to light preceded by a shock to this region, demonstrating that the spike is driven from above. Identification in such cases is obtained by making the driven spike collide with the natural one

elicited by light. Fig. 45(I) shows that a spike, driven in this fashion at a high frequency for some 7 seconds (between records 1 and 6), sets up a strong posttetanic facilitation, like the one illustrated in Fig. 43. In this case, however, in order to obtain an effect it is actually necessary to be able to drive the spike. If the electrodes are pushed up or down until driving ceases, there will be a small effect or no post-tetanic potentiation whatever unless the encéphale isolé preparation be used and the needle enters the reticular substance. For stimulation of the latter very much stronger shocks are required. It should be emphasized that reticular effects such as those of Figs. 43 and 44 take place *without* any driving of the ganglion cell, nor need any adjacent cells be driven by the stimulus.

In Fig. 45(II) the first fast record *D* again shows that the spike is driven from above. End of "on" and beginning of "off" have been visualized on the screen (controls). In this case the effect of tetanization is a very strong transient inhibition. Finally in Fig. 45(III) an inhibition has been obtained by stimulating inside the superior colliculus at a fairly slow rate. It is easily seen that in this case there was no driving.

The records presented show all main types of effect hitherto obtained from the retina upon tetanic stimulation of mesencephalic portions of the brain, including the end branches of the optic nerve fibers in this region. Those of Fig. 45 demonstrate that very little could be gained by performing this kind of analysis at the optic-tract or optic-nerve level. Both excitation and inhibition are present and the greater the cross-section of fibers stimulated, the more complex the sum total of opposite effects. It is also possible that there are specific after-effects of "driving," and for this reason, too, the optic tract is unsuitable for an analysis of what happens. I have had facilitations of the kind described from the optic tract, but inhibition so far has been more common. There is also a curious inhibition of slow onset that may well be of vascular origin. The vascular effects are being studied at the moment.* The effects of facilitation after driving turn up so forcefully at threshold strengths and, in the best cases, are of such an order of magnitude that some are likely to be neural. Even *during* stimulation the isolated spike may then break through the stimulus rhythm with

* Vascular effects upon reticular stimulation have been described by Ingvar (1954), who studied the cortical vessels under a microscope. They have since been seen by him, in our laboratory, in the retina. Part of the arousal effect may therefore be vascular arousal.

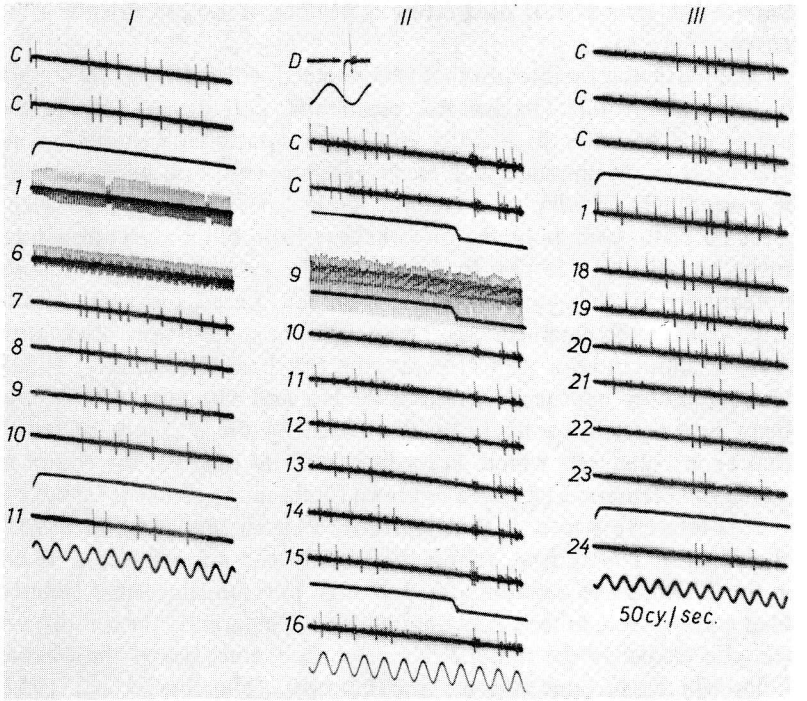

Fig. 45. I. Chloralose-dial cat. Horsley-Clarke stimulation. The two uppermost records (*C*) are controls. Single antidromic shock to surface of contralateral colliculus elicits retinal spike picked up by microelectrode. Shock coincides with flash of 40 lux, to which same spike responds. It is then driven at rate 333/sec. for 6 sweeps (about 6.6 sec.) of which the first (1) and last (6) are shown. 7–11: tests with same light at intervals of 1.1 sec. show increased excitability (post-tetanic potentiation), which on account of the narcosis is of short duration. Photocell deflection in this and the other records indicates light upward, darkness downward. Sweep in these records interrupted before flash is over.

II. Pentobarbitone cat. Curarized. Stimulation as above. *D:* faster sweep to demonstrate driving. *C:* controls with test light 500 lux, end of *on* and beginning of *off* shown. 9: last sweep after driving spike at rate 270/sec. for about 10 sec. 10–16, tests with same light proceeding at intervals of 1.1 sec. The effect is an inhibition which in this case was present despite driving, and required the high frequency used. Typical effect of driving in these records as well as in those above (I) is diminution of spike height.

III. Encéphale isolé cat. Curarized. Stimulating electrode now inside colliculus sup. at 2 mm. above Horsley-Clarke zero. *C:* controls with test light 3 lux, on-discharge. 1: stimulation at 47/sec. begins. 18–20: three last sweeps of 22 sec. period of stimulation. No driving in this case. 21–24: tests with same light proceeding at intervals of 1.1 sec. The effect is inhibition. Time for all records 50 cy/sec.

bursts of its own and, if stimulation is prolonged too far, intense firing ensues.

The particular facilitation that is connected with "driving" is technically an antidromic (backward) posttetanic potentiation, but at the outset one hesitates to identify it with the posttetanic potentiations known. It is not obtained with every ganglion cell, but, when present, is exceedingly regular and definite. Only orthodromic or normally directed posttetanic potentiation is known from other structures. Larrabee and Bronk (1947), in describing the *ortho*dromic posttetanic potentiation of the sympathetic ganglion cell, found suppression only after *anti*dromic tetanization. There is also suppression after antidromic stimulation of ventral horn cells (cf. Eccles' summary, 1953) or oculomotor neurones (Lorente de Nó and Graham, 1938), but these experiments are likely to be vitiated by the presence of recurrent axon collaterals which, according to Cajal (1899), are found in all nervous centers. They have not been found in the retina (cf. above).

It is interesting to note that Hartline, Wagner, and Tomita (1953; cf. Hartline, 1949) have found that antidromic stimulation of fibers in the *Limulus* eye can inhibit a discharge in a nonstimulated isolated fiber coming from an adjacent ommatidium. Apparently the antidromic stimulus activates the inhibitory cross-connections below the ommatidia, which Hartline and his collaborators (Hartline *et al.,* 1952, 1953) have found to transmit the effect from one illuminated ommatidium on to an adjacent one. The retinal ganglion cells are not homologous with the *Limulus* ommatidia, but the inhibitory mechanism may, nevertheless, be run on the same pattern. Dogiel (1895) actually described two types of centrifugal fibers in the retina. Cajal (1904) denied the existence of Dogiel's second type but described different types of ramification. However, some work must still be done in this field before vascular effects are finally excluded. The inhibitory effect in Fig. 45(II) is fast and certainly looks genuine. The reticular excitatory effects which do not require driving are best obtained in good encéphale isolé preparations at stimulus strengths of from 5 to 10 V. Facilitation upon driving, the antidromic posttetanic potentiation, can be obtained, despite some anesthesia, at threshold strengths (1–3 V.).

From time to time it has been suggested that the afferent message within the central nervous system also might be under regulatory control (e.g. Head and Holmes, 1911; Brouwer, 1933, Peele, 1942). Brouwer, for instance, stated that "several descending systems influence the reflex arcs in its sensory part and many terminate in centers which are of a pure sensory character" (p. 626). Dusser de Barenne

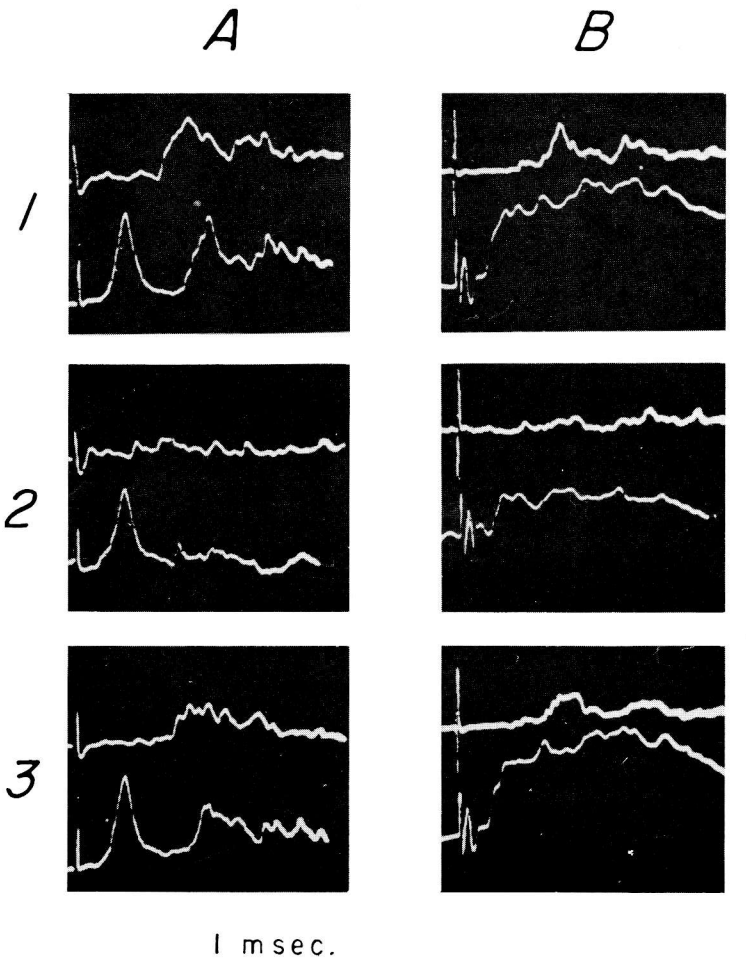

Fig. 46. Encéphale isolé cat, curarized. Single test shocks were applied to the right dorsal root L_7 to elicit direct wave followed by relayed wave. Tip of recording needle placed in right dorsal column a few tenths of a mm. below the surface and about 9 cm. above the zone of entrance of the stimulated dorsal root, part of which was split for simultaneous recording of so-called dorsal root reflex.

A: dorsal root reflex (upper beam), dorsal column response (lower beam) before (1), during (2), and after (3); repetitive stimulation at rate 100/sec. in the bulbar reticular formation.

B: dorsal root reflex (upper beam) and the negative intermediary potential (lower beam) recorded from the cord surface at the dorsal root zone before, during, and after stimulating the same area of the bulbar reticular formation, (Hagbarth and Kerr, *J. Neurophysiol., 17,* 295. 1954.)

with several collaborators (see e.g. Dusser de Barenne, 1934; Dusser de Barenne and McCulloch, 1938) established corticothalamic control. Recently Hagbarth and Kerr (1953, 1954) have succeeded in devising experiments which have carried the approach to these problems to the spinal cord level and thus represent a significant advance. They stimulated the dorsal root L7 in cats with rectangular shocks and recorded from the dorsal columns or from part of the stimulated dorsal root. In the dorsal columns one obtains in response to each shock a spikelike action potential which is followed by a more prolonged relayed discharge, as described by Hursh (1940). The relayed response has a peripheral counterpart in the so-called dorsal root reflex (Barron and Matthews, 1935; Toennies, 1938; Barron, 1940). Both the dorsal column relayed response and the root reflex could be depressed by stimulating regions such as the bulbar and midbrain reticular formation, the ventro-medial part of the anterior vermis, the precentral motor cortex, the primary sensory cortex and the so-called secondary somatic sensory area. This is illustrated in Fig. 46(*A*). Stimulus frequencies of around 100 per second were used. As clearly shown by the figure, the primary spikelike wave remains uninfluenced. The cord's slow so-called intermediary potential, described by Hughes and Gasser (1934), was also depressed by stimulation in this manner (Fig. 46, *B*).

The examples presented should suffice to emphasize that questions concerning feedback mechanisms and direct neural control of the sensory input from stations in the brain are now clamoring for attention. The best known of these mechanisms, the centrifugal control of the muscle spindles, will be dealt with in detail in Chapters 6 and 7. The present examples have been added to indicate the scope of these problems and the necessity of considering them in the light of what has been set forth above about spontaneous activity and the arousal reaction. There are, of course, several other aspects to the general problem of centrifugal control (see Chapter 7), but we do not yet possess enough evidence for dealing with them, except in the case of the muscle spindles.

Chapter 4

Present State of Dominator-Modulator Theory. Photochemical Parallels

1. First principles. Scotopic and photopic dominators

THE retina may contain one or several photosensitive substances with absorption maxima in different wave lengths. Since only that light which is absorbed can be effective in initiating a stimulus, the absorption spectra of these photosensitive substances are close approximations to the spectral sensitivities of the mechanisms concerned. It has been shown that the receptive fields are complex. Taking man as an example, there are not less than 4 million cones, nearly 7 million according to some estimates, and 125,000,000 rods as against only 800,000–1,000,000 optic nerve fibers (figures from Polyak, 1941). Evidently a very minor number of receptors can afford to keep a private path and in view of the way sensory messages are organized elsewhere (Chapter 2) the problem of color reception must be solved by central interpretation of information over a complex frequency code which also expresses interaction (see Chapter 8). Even if one knew every photosensitive substance in a retina, the question of how they are represented in the messages transmitted by the frequency code would remain a problem in its own right.

Howsoever color reception is approached, whether in terms of sensory brightness, receptor potential, or spike frequency, the principle always is the same, and it is easily understood from a schematic presentation. The following is somewhat inaccurate, but I shall add a photochemical derivation below. Let the effect of light (sensory brightness, size of potential, spike frequency) at any wave length be L_λ. This will be proportional to the amount of energy E_λ and the specific sensitivity S_λ for this particular wave length. S_λ is the retinal sensitivity factor. With $L_\lambda = E_\lambda \cdot S_\lambda$ our problem is to obtain a measure of S_λ. It is clear that $S_\lambda = L_\lambda / E_\lambda$. If one proceeds to make L_λ constant (constant bright-

ness, or receptor potential in mV., constant spike frequency, constant threshold or threshold fusion frequency of flicker), the sensitivity in every wave length is directly measured by $1/E_\lambda$. The curves to be described below have been obtained by recording energy reciprocals for a constant effect in the wave lengths tested.

Many photochemical studies have been carried out on substances extracted from the eye. The absorption spectra of solutions of these substances are obtained from spectrophotometric measurements. If I is the intensity of light incident on the optical cell containing the solution and I_t is the light transmitted, the absorption coefficient (for wave-length λ) is proportional to the density $D_\lambda = \log I_\lambda/I_t$. The amount absorbed is $I_a = I_\lambda - I_t$, or the difference between light incident and light transmitted. From the above definition of density (D_λ) it follows that I_a, the amount absorbed, also may be given as $I_\lambda\ (1 - 10^{-D_\lambda})$. "For small values of D_λ, such as occur in retinas, this expression approximates $I_\lambda \cdot D_\lambda$. In the determination of spectral sensitivities the values of I_λ are recorded which elicit a response of constant magnitude. Constancy of response requires constancy of $I_\lambda \cdot D_\lambda$, the light absorbed, no matter how complex the relations between them may be. For any invariant value of $I_\lambda D_\lambda$ throughout the spectrum, I_λ will be an inverse measure of D_λ and hence $1/I_\lambda$ will reproduce the absorption spectrum of the visual pigment." (Dartnall, 1953a, p. 30).

In view of these considerations it was a great event in the history of psychophysics when the frog's visual purple, discovered by Boll (1876, 1877), was for the first time found by König * (collected papers, 1903) to possess an absorption curve which fairly closely corresponded to the brightness distribution of the dark-adapted or scotopic human eye. This work, which was soon confirmed by his pupils, Köttgen and Abelsdorff (1896), has since been several times repeated with the improved methods introduced by Lythgoe (1937) and Saito (1938). Fig. 47 illustrates measurements of frog and human visual purple by Crescitelli and Dartnall (1953a), compared with a scotopic brightness distribution averaged by Crawford (1949) from values obtained with fifty observers. Ludvigh and McCarthy's (1938) corrections for absorption in preretinal media have been applied to Crawford's values. It can be seen that while frog visual purple has its maximum at 5020 Å, the human visual pigment has it at 4970 Å. From their results Crescitelli and Dartnall calculated that the retinal density of human visual purple *in situ* was as low as 0.016 (at its

* This paper was presented in the Berlin Academy of Sciences by Von Helmholtz in June, 1894.

maximum 4970 Å), corresponding to 3.5 per cent absorption. Hecht, Shlaer, and Pirenne (1942), in their work on the number of light quanta necessary for the scotopic threshold, assumed an upper limit of 20 per cent absorption.

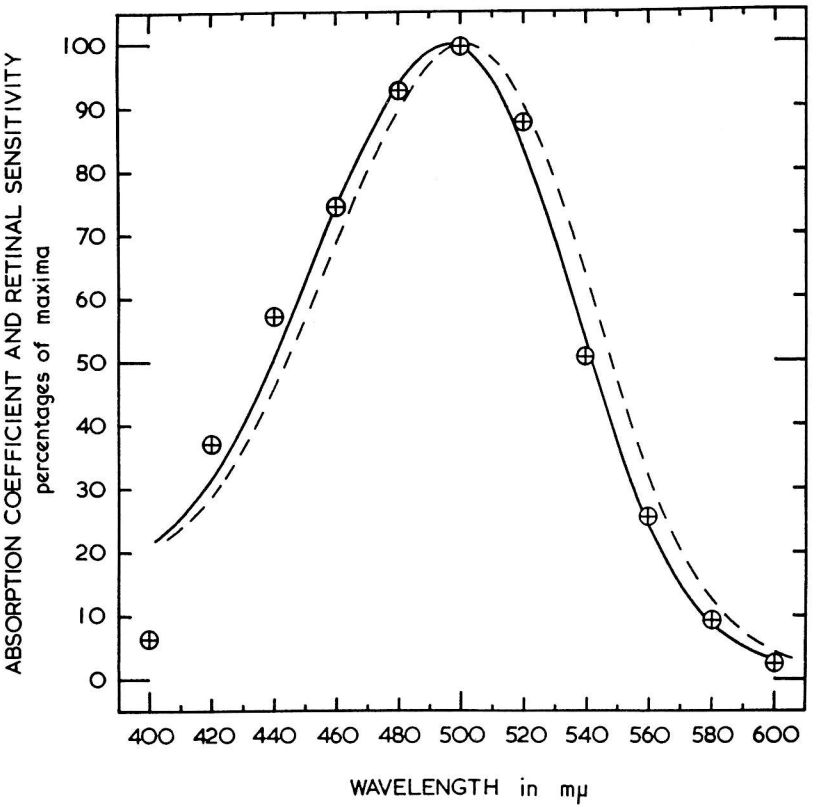

Fig. 47. Comparison of the human retinal scotopic sensitivities (*crossed circles*) with the absorption spectra of visual pigment 497 from man (*solid line*) and visual pigment 502 from the frog (*broken line*). Both pigments are varieties of visual purple. (Crescitelli and Dartnall, *Nature, 172,* 195. 1953a.)

Averaging on the basis of perception, one thus (Fig. 47) obtains a very close replica of the spectral distribution of visual purple photosensitivity, transmitted in terms of the frequency code. Yet the optic nerve fibers may well have carried a more complex message. The perceived brightness is not based on events in one fiber. In order to study how transmission takes place it is necessary to establish a set of correlations for an animal such as, for instance, the cat, in which the inter-

mediate link is accessible to measurement. The cat's visual purple is probably identical with that of the human eye rather than with that of the frog.

Several methods are available for obtaining average scotopic sensitivity distributions from this animal. (1) The most difficult method was the first to be used (see Granit, 1943a, 1947). It measures optic nerve frequencies of individual elements with the threshold frequency as the constant index and averages the results obtained with several single fibers. This gave good agreement with the visual purple curve. (2) Behavioristic tests may be applied on trained animals. This method was used by Gunter (1952), who found agreement with the average scotopic distribution curve of man, as determined by Stiles and Smith (1944), as well as with my results (after correction for selective absorption in preretinal media according to measurements on the bovine eye by Roggenbau and Wetthauer, 1927). (3) The electroretinogram also is an average. This function was studied by Wirth (1953), who found good agreement with the other measurements. The average spectral sensitivity of the dark-adapted eye may also be measured by recording with the aid of electrical resonance a constant electroretinographic response in terms of flicker at a fixed rate or flicker fusion. The principle of this method (Granit and Wirth, 1953) is to adjust a resonance meter (a tuned amplifier) by varying the energy in each wave length in the spectrum to give a fixed reading to a flickering electroretinogram (fusion, if used, being fixed at zero reading). The flickering electroretinogram is amplified in the usual way (see Chapter 5) and the amplifier is connected to the resonance meter. The result is shown in Fig. 48 and is compared with the human scotopic sensitivity distribution (the so-called scotopic luminosity curve) of Stiles and Smith (1944). There is perhaps a slight shift toward the short wave lengths with this method, emphasized in some animals at certain frequencies of flicker.

So far, then, all is according to expectation, and the cat responds electroretinographically and acts (by behavioristic tests) as if it had succeeded in averaging perceptually the information from the retina when the latter is activated by visual purple.

However, in Granit and Wirth's, in Wirth's, and probably also in Gunter's experiments intensities considerably above those needed to activate visual purple were used. Either this animal must possess visual purple alone or has means of disregarding other types of information. In order to investigate this question it is necessary (1) to study the frequency reports from individual retinal elements at the threshold

with the greatest possible accuracy, as well as (2) to find out whether other photosensitive substances contribute to the discharge from such elements.

With some care individual retinal elements can be kept under the microelectrode for several hours, and it is thus possible to measure with sufficient accuracy their threshold distribution of photosensitivity

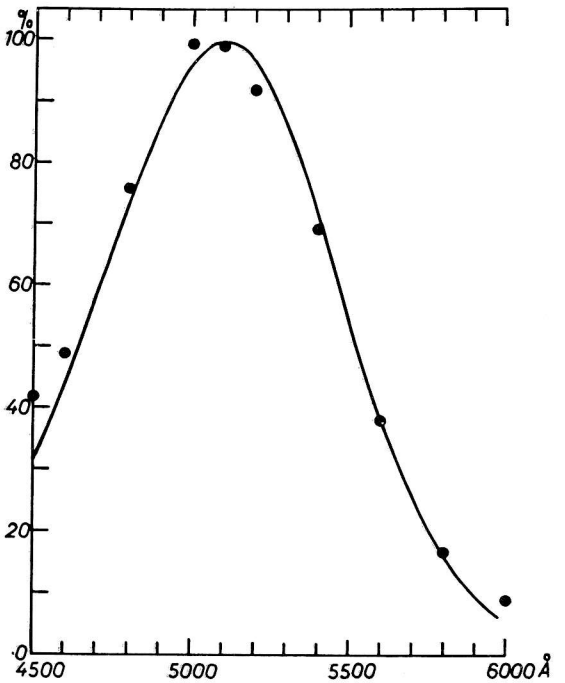

Fig. 48. Human scotopic sensitivity curve of Stiles and Smith (1944). *Filled circles* are averages from experiments on four dark-adapted cats, the values being determined by measuring flicker resonance electrically, as described in text. (After Granit and Wirth, *J. Physiol., 122,* 386. 1953.)

in the dark. Donner and Granit (1949) did this and found a considerable number of curves which did not agree with visual purple absorption. Two examples are shown in Figs. 49 and 50. The maxima were in the right place and broad-band curves were obtained, but the curves show very definitely that substances other than visual purple have influenced them. Fig. 51 illustrates that slight light adaptation sufficed to bring about specific distortions. There was no more light adaptation than is consistent with "scotopic" behavior on the part of

the animal (cf. below, sec. 6). It is necessary, in fact, to use a great deal more light adaptation to bring about further shifts of the curve. The conclusion is that in acting as if the information had been based wholly on visual purple absorption, the animal itself had done the averaging that the experimenter with the aid of elementary mathematics could produce from a sufficient number of individual curves referring to single fibers. In Chapter 8 I shall give further instances

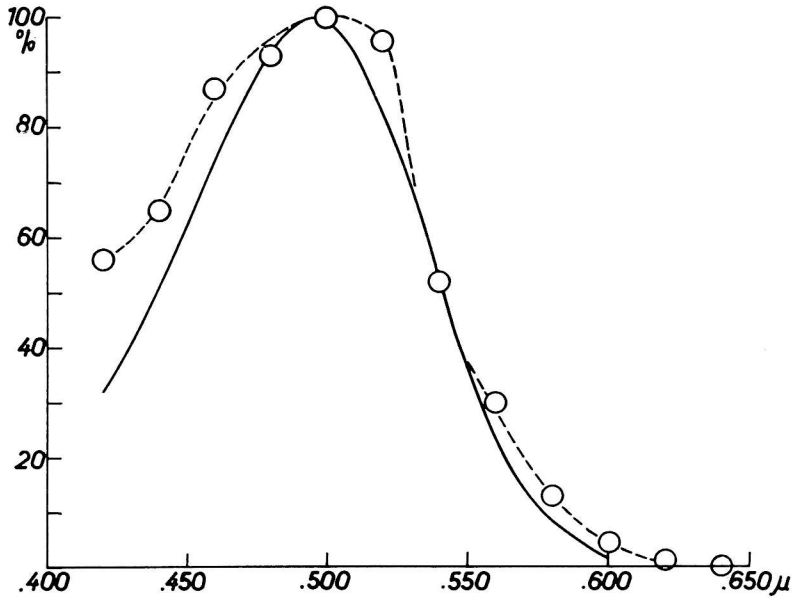

Fig. 49. Absorption in Dartnall's (1953a) pigment 497 (*solid line*) compared with Donner and Granit's (1949) scotopic dominators from cat (*open circles*).

of how perceived brightness is averaged. I shall also discuss experiments in which the sensory evaluation of the peripheral message has been completely transformed by various procedures to the extent of leaving long-lasting after effects when the observer returned to normal conditions of observation. I refer to this evidence here merely in order to raise the point—rarely mentioned in visual psychophysics—that the largely unknown laws of central integration cannot be neglected in psychophysical experimentation. It is, for instance, hardly possible to expect that the effects obtained with *individual* retinal elements represent psychophysical functions based on large averages without considering what averaging implies.

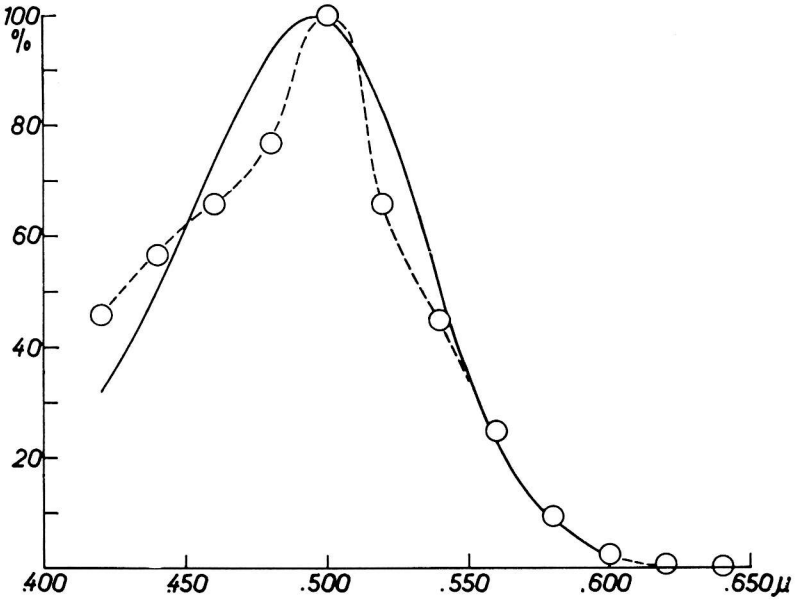

Fig. 50. Same as Fig. 49.

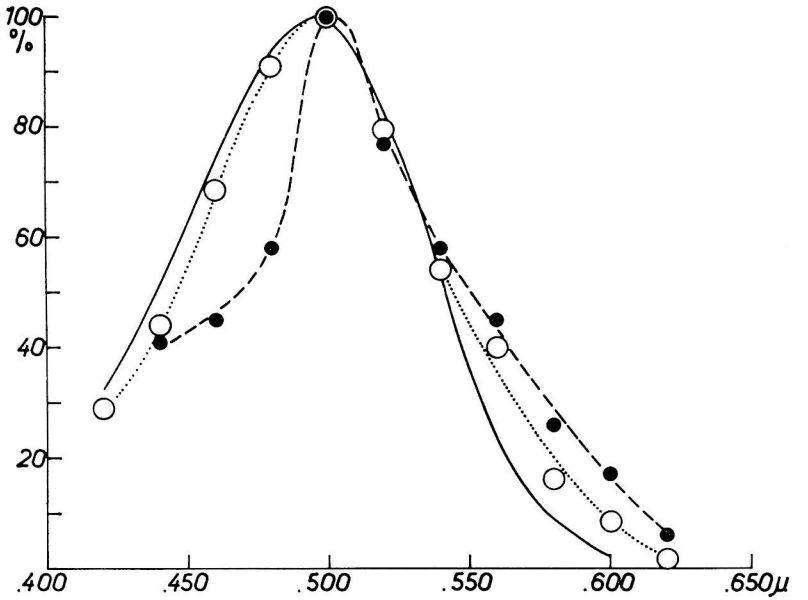

Fig. 51. Same as Fig. 49. The *black dots* show the change of the original curve (*open circles*) after moderate light adaptation.

From both psychophysics and classical electrophysiological work on animals it is well known that vision, after light adaptation, is taken over by cones and that their over-all spectral distribution of sensitivity is different from that of the rods in the dark, based on visual purple. Neglecting for the moment differences due to absorption in the pre-retinal media, we may observe that the curve shifts bodily in light

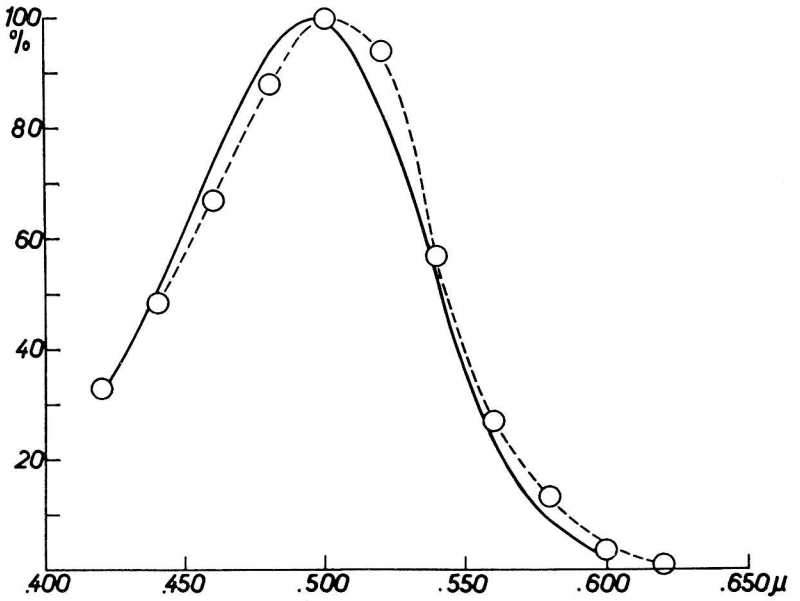

Fig. 52. Absorption in Dartnall's (1953a) pigment 497 compared with cat's scotopic dominator from Donner and Granit (1949).

adaptation to around 5600 Å (see e.g. Granit, 1947). This is the Purkinje shift, named after its original discoverer. There are thus two fundamental curves, differing by about 600 Å. These are the scotopic (dark-adapted) and photopic (light-adapted) distributions of spectral sensitivity.

Now, are there any cones in the cat's eye? "Fabulous though the cat's ability may be for 'seeing in the dark', she has a very respectable number of cones—about a third as many as we ourselves" (Walls, 1942, p. 215). Piper (1905) failed to find a Purkinje shift in this animal by electroretinography, but the microelectrode is a more sensitive device and I found the shift in some 36% of the spikes studied in the photopic state, having previously found it regularly in eyes

from various other animals possessing a relatively greater number of cones (Granit, 1945b, 1947, for summaries). Fig. 52 shows a relatively pure scotopic curve obtained with a single element. Fig. 53 shows photopic curves from four averaged sets of measurements. The hump at 6,000 Å is of some interest because similar phenomena are also found in man (see e.g. Sloan, 1928; Wright, 1946; Thomson,

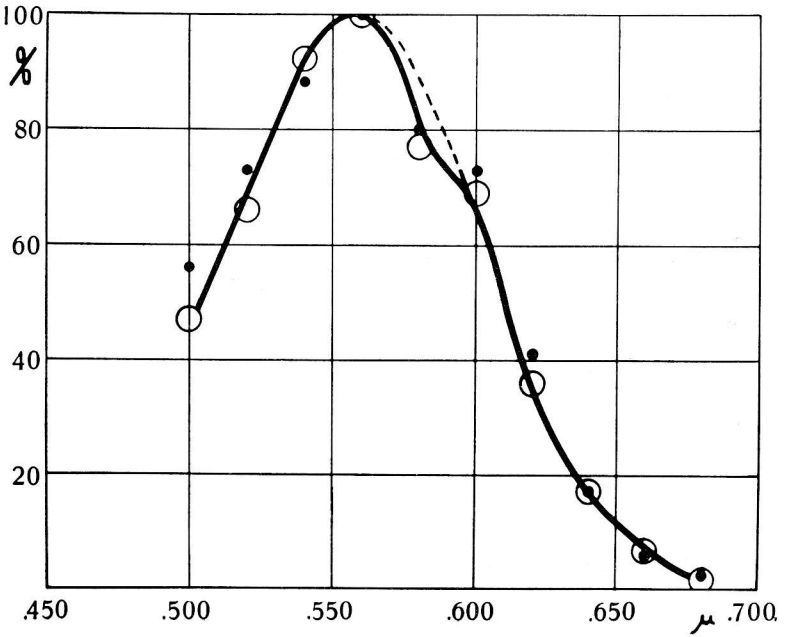

Fig. 53. Photopic dominator curve of cat. *Open circles:* averaged results of 4 series in which suppression of dark adaptation was particularly successful. *Black dots:* averaged results in 12 series with prominent dominator activity. Incipient dark adaptation can be seen in the increase of sensitivity of *black dots* over *open circles* at 5,000 Å. The average dominator curve (completed along the dotted line) is similar to that of the frog. Equal quantum intensity spectrum. (Granit, *Acta physiol. scand., 5,* 219. 1943c.)

1949; Hsia and Graham, 1952; Armington, 1952). These two curves were called the scotopic and photopic dominators and recurred in all animals studied in which the visual mechanism in the dark was based on the type of visual purple known as rhodopsin, provided that the animals had a sufficient number of cones. Photopic dominators could not be found in eyes of guinea pigs and rats. This need not mean more than that the cones are so few in these animals that there is little

chance of detecting them. The two curves of Figs. 52 and 53 illustrate the Purkinje shift from scotopic (Fig. 52) to photopic (Fig. 53) vision, practically identical in cat and man. Thus, the dominators may be called the carriers of the Purkinje shift.

Rushton (1952) has recently developed a method of measuring visual purple in animal eyes directly by measuring the different amounts of light reflected in dark and light adaptation from the same parts of

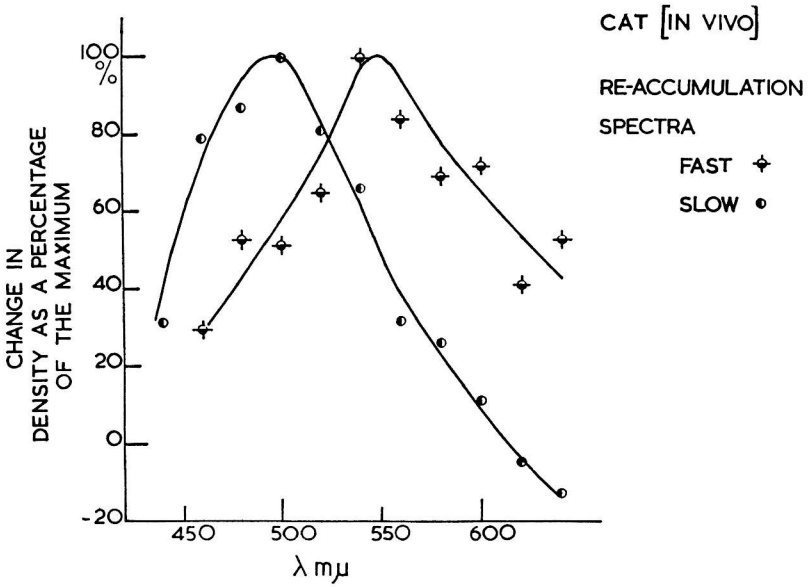

Fig. 54. The spectral distribution of fast and slow regeneration in the living cat's retina, measured by reflection, after 5 min. of bleaching to 228,000 foot lamberts. (By courtesy of R. A. Weale, Institute of Ophthalmology, London.)

the retina. In applying a similar method to the cat's eye, Weale (1953b) has found the absorption curves of two substances, one slowly regenerating and in good agreement with the absorption of visual purple, another rapidly regenerating and suggesting the photopic dominator. Exceedingly bright light was used for bleaching the visual purple. From the regeneration or re-accumulation data Weale has since (personal communication) plotted the two curves of Fig. 54.

Owing to the convergence of several receptors on a single optic nerve fiber, this fiber may respond as a scotopic dominator in the dark-adapted eye and as a photopic dominator after light adaptation. In

the experiments on the cat's eye large fibers were used, and so it may well be asked whether these run to the striate area in the occipital cortex. The minimal latency of response in the visual cortex for optic nerve stimulation is well known to be of the order of 1.6–2.0 msec. (G. Bishop and O'Leary, 1940; Bartley and Bishop, 1940; Marshall, Talbot, and Ades, 1943; Chang and Kaada, 1950), a fact easily confirmed, and so the message must have been conducted in the largest

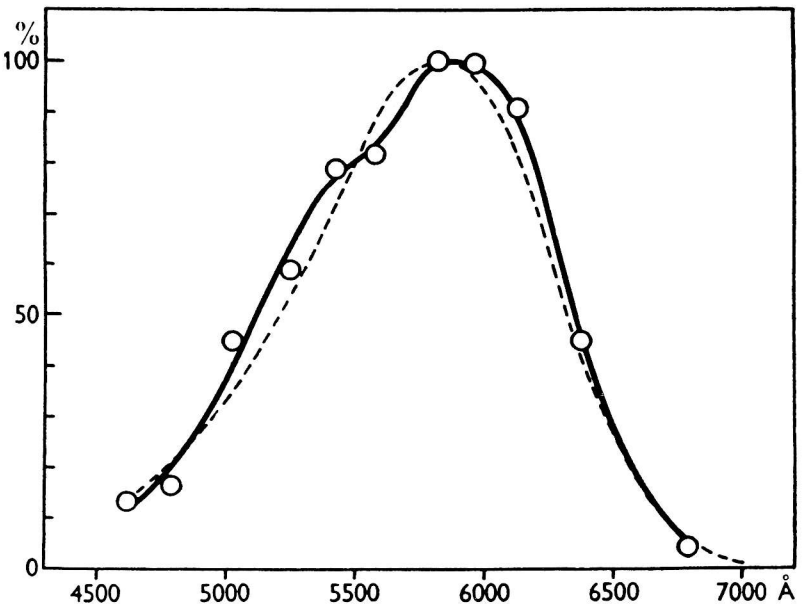

Fig. 55. Average of three elements giving the photopic dominator response (*solid line and circles*) as compared with the averaged curve for pigeons determined by Granit (1942c) (*broken line*). Equal energy spectrum. (Donner, *J. Physiol., 122,* 524. 1953.)

and fastest fibers available (average conduction velocity 34 m/sec., maximum 70 m/sec., according to P. O. Bishop *et al.,* 1953). This raises an interesting problem. Since scotopic and photopic dominators are represented in the same fiber, in proportions depending upon stimulus strength and state of adaptation, these fibers must deal with the general brightness distribution, as shown also by the fact that such elements are the only ones known to reproduce scotopic and photopic brightness. Independently of whether they act as scotopic or photopic dominators, they serve as a basis for achromatic vision and can hardly

represent wave length discrimination (color) except by frequency modulation (see Donner, 1950, and Chapter 8, p. 289).

My technique at the time proved too coarse for the pigeon's eye, which contains a million optic nerve fibers as against 150,000 in the cat (Bruesh and Arey, 1942). Nevertheless, the average spectral sensitivity of the optic nerve fibers in this eye, in which the cones are in the majority, could be studied in light adaptation. The averaged curve should give the averages of the dominator types of response, and so, indeed, it was found to do, but—curiously enough for an eye based on the rhodopsin system—with its spectrum shifted to 5800 Å. This further shift from 5600 Å was ascribed to absorption by the well-known colored oil globules (Granit, 1942c). Recently Donner (1953) has studied the pigeon's eye with finer microelectrodes and has succeeded in isolating its photopic dominator response, illustrated in Fig. 55. As will be shown below, there is evidence for ascribing the shift from 5600 to 5800 Å in the pigeon to colored oil globules. In the eyes of certain fishes and tortoises the two dominator curves are found to be shifted toward the red end of the spectrum (see below).

In the work on animals with microelectrodes on the retina there also occurred narrow bands, the so-called modulators, centered in three spectral regions, for which some photochemical equivalents recently have been found. But this is perhaps easier to understand if I first deal with some general questions referring to methods of extraction, broad and narrow absorption bands, and photochemical nomenclature.

2. *The photochemical approach. Nomenclature*

Visual purple is the term that Kühne's (1879) great work made classical. He also called this substance rhodopsin. Elsewhere I have given a full account of the historical development of our knowledge in this field (Granit, 1947). Fig. 47 has already shown that the frog visual purple has its maximum at 5020 Å, the human at 4970 Å. Bliss (1948) described visual purple in the squid with a maximum at 4950 Å, placed by Wald (1953) at 4900 Å. The maximum of cattle rhodopsin was given by Krause and Sidwell (1938) at 4950 Å, by Collins and Morton (1950a) at 5,000 Å. The maximum of rat rhodopsin they placed at 4980 Å. This is probably the human and rat visual purple of Crescitelli and Dartnall (1953a) with maximum at 4970 Å (Fig. 47). These visual purples or rhodopsins about which—despite minor discrepancies—there seems to be general agreement, thus vary at least between 4900 and 5020 Å. Kühne and Sewall (1879–80),

confirmed by Köttgen and Abelsdorff (1896), described another type of visual purple in fish with maximum in 5400 Å, according to the latter authors. This they called visual violet,* now better purified and defined. As will be shown below, there are also variations in its maximum to be considered.

Two of the leading research groups, that of Wald and his collaborators at Harvard and Dartnall and his colleagues at the Institute of Ophthalmology in London, are agreed in their desire to drop the old nomenclature based on color of the pigments which, of course, in the long run is unsuitable for the simple reason that the photochemically active (i.e. absorbed) light is not the one transmitted and seen. "Visual purple," however, is too well established by tradition to be eradicable by decree. Wald (see e.g. his summary, 1953) uses the terms rhodopsin and porphyropsin for visual purple and visual violet respectively, prefixed by the name of the animal from which it is extracted, while Dartnall (1952a, 1953a) characterizes all pigments by their absorption maxima in mμ, e.g. frog pigment 502 (for frog visual purple with maximum in 5020 in Ångström units). Considering that there are visual purples, or rhodopsins in Wald's terminology, with maximum varying between 4900 and 5020 Å, I think it clarifying to name them also by their absorption maxima. Behind this disagreement in terminology is also more profound disagreement as to the number and spectral location of the broad absorption bands concerned.

In this discussion the final decision does not rest with the photochemists alone. Considering how well the averaged dominators, when known, reproduce the broad absorption bands, it is painstaking experimentation along electrophysiological lines which ultimately will have to settle the question of whether an absorption band of an extracted substance is likely to be physiologically significant or not. If a substance is easily extracted chemically but cannot be demonstrated electrophysiologically, it is likely to be an artifact or to contain impurities. Many substances absorb light but few are photosensitive. In this field we can well afford to wait and see.

A common feature of present chemical work with the retina is that, following Lythgoe (1937) and Saito (1938), the earlier use of detergents on the detached retina itself has been supplanted by separation of the outer rod segments in a suspension to which the detergent (digitonin, bile salts) later is added. Thus, purer solutions are ob-

* Wald (1953) erroneously ascribes the invention of the term "visual violet" to me. I have used it for historical reasons as a tribute to the discoverers of this substance.

tained. Within the London group Arden (1953) rightly has raised the question of whether the method might not be selective and favor substances with broad absorption bands at the expense of pigments with narrow ones. For this reason, as will be shown below, he has introduced direct measurement of absorption in the suspensions of receptors.

Without entering into further detail in a discussion which cannot deal with photochemistry except as it touches electrophysiology, let me briefly summarize the position. In addition to the photopigments mentioned—490 (or 495), 497, 502—Dartnall (1952a) describes a pigment 467 found in the retina of the tench, a pigment 510 Dartnall (1952b) in the bleak (*Alburnus lucidus*), and a pigment 519 in the clawed toad (*Xenopus laevis*) (Dartnall, personal communication). Crescitelli and Dartnall (1953b) have found a pigment 523 in the carp (*Cyprinus carpio*). Wald, Brown, and Smith (1953) have synthesized a cone pigment cyanopsin (see below), which reproduces my photopic dominator in the cone eye of the tortoise (and the light-adapted tench, Granit, 1941b,d), thus at 6200 Å. Wald (1937) and Bliss (1946) have extracted a cone pigment corresponding to the other photopic dominator, that of man, mammals, frog, etc. (Fig. 53) with maximum around 5600 Å. A similar pigment has since been synthesized (see below) by Wald, Brown, and Smith (1952). Synthesis of visual pigments is the most important advance of recent research with biochemical methods (see below).

Hubbard and Wald (1952) disagree with Dartnall about the pigment 467, which they regard as an artifact. Further disagreement concerns the position of fish visual violet, Wald's porphyropsin. Collins and Morton (1950a) place it at 5250 Å, Kampa (1953) at 5200 Å, Wald (1953) at 5220 Å, and Dartnall (1952a) at 5330 Å except in the carp, where it is found at 5230 Å. The major argument in Hubbard and Wald's criticism of Dartnall's pigment 467 is that it is a product of isomerization, which is an early step in regeneration. If so, why is it absent in pike extracts? Spectral shifts in regeneration is an idea traceable to an early result of Lythgoe's, according to which regeneration from the bleached state does not reproduce the original photoproduct. This work was interrupted by Lythgoe's premature death, but Collins and Morton (1950b) reinvestigated the problem and found, indeed, that bleached rhodopsin regenerated into a new substance, called *iso*rhodopsin, with its spectrum slightly shifted toward the short wave lengths. Hubbard and Wald found the new maximum

to be at 4870 Å, Collins and Morton at 4920 Å. Dartnall's technique (described in detail, Dartnall, 1952a) is based on difference spectra, a method which he has elaborated with great care, and his opinion (Dartnall, 1953, personal communication) is that the homogeneity of Wald's porphyropsin has not been established.

It has been emphasized by Dartnall (1953a) that all these spectra of the broad type are remarkably similar, merely being displaced along the abscissa, if plotted in terms of frequency instead of wave length. He has therefore calculated a nomogram from which it is possible to plot any absorption curve of the broad type provided its maximum be known.

Investigation of narrow-band visual pigments is just beginning. As stated above, it is premature to assume from the facts emerging from one kind of technique—such as extraction by detergents—that no photochemically active substances are found in the retina other than the broad-band absorption curves. Destruction of the cell membrane may well favor broad bands at the expense of narrow ones. The possibility of narrow-band pigments based on the chromophore of visual purples was first envisaged by Ball, Collins, Morton, and Stubbs (1948), whose work developed Morton and Goodwin's fundamental discovery that Wald's carotenoid retinene (see his summaries, Wald, 1951, 1953) actually was vitamin A aldehyde (cf. Ball *et al.*, 1946, 1948). With the light-sensitive chromophore of the molecule thus chemically identified, several new possibilities with which I need not deal in this connection were opened up for the chemical line of attack (cf. in particular the syntheses by Wald and his collaborators). Prior to this discovery by the Liverpool group (around Morton), all work, including Wald's discovery of retinene, was based merely on colorimetric reactions. Wald (1953) and his colleagues have since made a number of important contributions to the chemistry of the visual pigments. Ball *et al.* showed that retinene treated with strong acids produced a variety of narrow-band pigments. This method clearly was unphysiological but had the merit of showing that narrow-band pigments were within the realm of possibilities. Dartnall (1950) next found a narrow band in extracts from the eye of the tench, the maximum being between 6050 and 6100 Å. This is illustrated in Fig. 56. Arden's (1953) narrow-band pigment in the frog's retina with maximum around 5300–5400 Å will be discussed below (Fig. 66). Finally, Dartnall (1953b) has recently mentioned a third narrow-band pigment 565 in the eye of the clawed toad (*Xenopus*), the absorption spectrum

of which suggests a hump in this region found in Denton and Pirenne's (1954) behavioristic data for the spectral sensitivity of this animal.

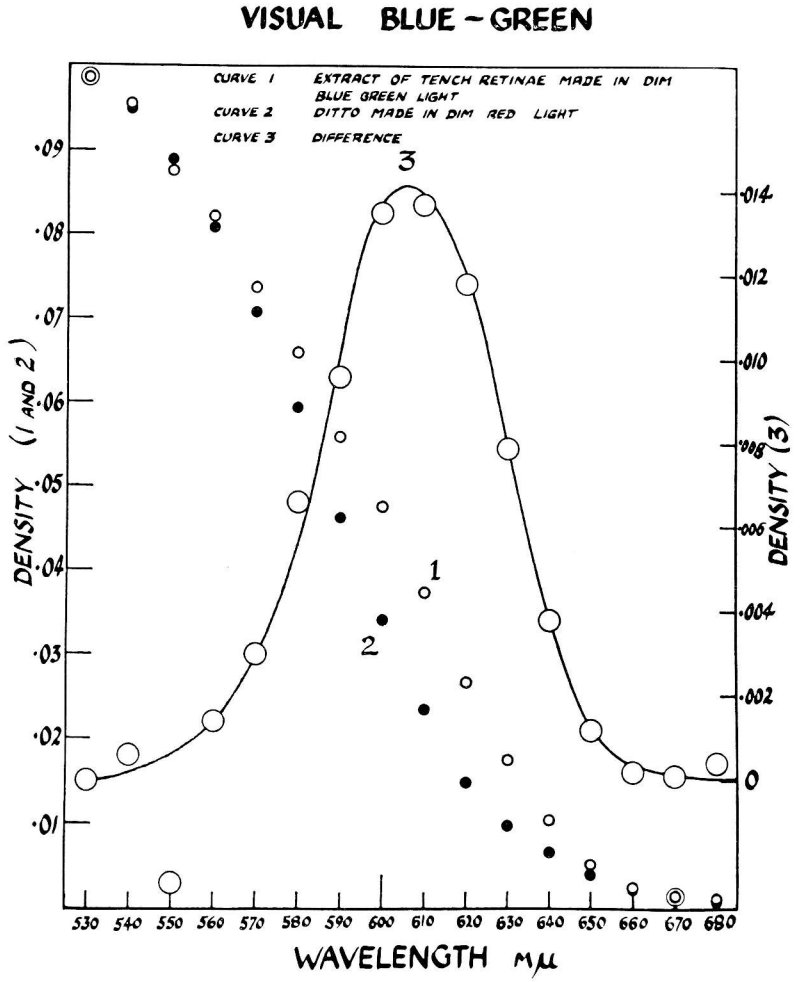

Fig. 56. Evidence for a pigment (in tench retinae) normally destroyed by extraction in red light. Curve 1: extract of tench retinae made in dim blue-green light. Curve 2: the same, made in dim red light (curve 2 scaled to agree with curve 1 at 530 mμ. Curve 3: Difference between curve 1 and 2. (By courtesy of H. J. A. Dartnall, Institute of Ophthalmology, London.)

It should be emphasized that two main photochemical systems are known in the retina (for a historical review see Granit, 1941d, 1947; Wald, 1953), one based on Wald's retinene$_1$ which is retinaldehyde$_1$ or vitamin A_1 aldehyde (Morton and Goodwin, 1944; Ball *et al.*, 1948), the other based on Wald's retinene$_2$ which is retinaldehyde$_2$ or vitamin A_2 aldehyde (Morton, Salah, and Stubbs, 1947). I have so far chosen my examples chiefly from the former system (visual purple and photopic dominator of mammals, frog, snake). The latter is found in some fish and in tortoises (visual violet and cone or photopic dominator of these animals). Isomers of retinene have been found and discussed by Wald (1953) and his collaborators. They cannot be taken up in this connection without devoting a great deal more space to biochemical points of view.

After this brief presentation of the photochemical situation, let us proceed to compare the photochemical data with the electrophysiological, inasmuch as the latter refer to the same animals.

3. *Some further comparisons with broad-band absorption curves*

Dartnall (1953a) has made a comparison between broad-band absorption curves from his nomogram with my data for frog and tench respectively as representatives of the two main types of scotopic dominators. To this end it is necessary to know the concentration of the photosensitive pigment in the retina itself in terms of its optical density, as defined above. Only for the frog is this figure available from Dartnall's work. It was calculated to be 0.25 for visual purple (recently confirmed by Arden, 1954d), thus a much higher concentration than in the human retina (cf. above). Fig. 57, from Dartnall's work, compares averaged scotopic dominators in frog and tench with the nomogram curves for pigments 502 and 533 respectively. With the frog the fit is as good as can be expected; the scotopic dominator of the tench has an expansion in the short wave lengths which may be due to fluorescence or to some substance not known (e.g. Dartnall's pigment 467). However, riboflavin, which is fluorescent, is a characteristic component of fish retinae (H. von Euler and Adler, 1933).

Fig. 58 illustrates Dartnall's (1953a) comparison with the photopic dominators of the same animals, assuming (1) that the cone pigments have maxima in respectively 5600 and 6100 Å and (2) that their absorption bands agree with the broad-band nomogram template curves based on scotopic substances. The near fit of the right-hand limbs of the curves is, of course, a consequence of the assumptions made concerning the maxima of these absorption bands. Wald's (see below) cone substances corresponding to the photopic domi-

nators of the two systems actually have their maxima in 5620 and 6200 Å respectively. What seems significant in Figs. 57 and 58 is that the cone or photopic dominators average out to be narrower than the nomogram curve. Dartnall's final explanation of the discrepancy between the dominators and his so-called "template curve" is that the

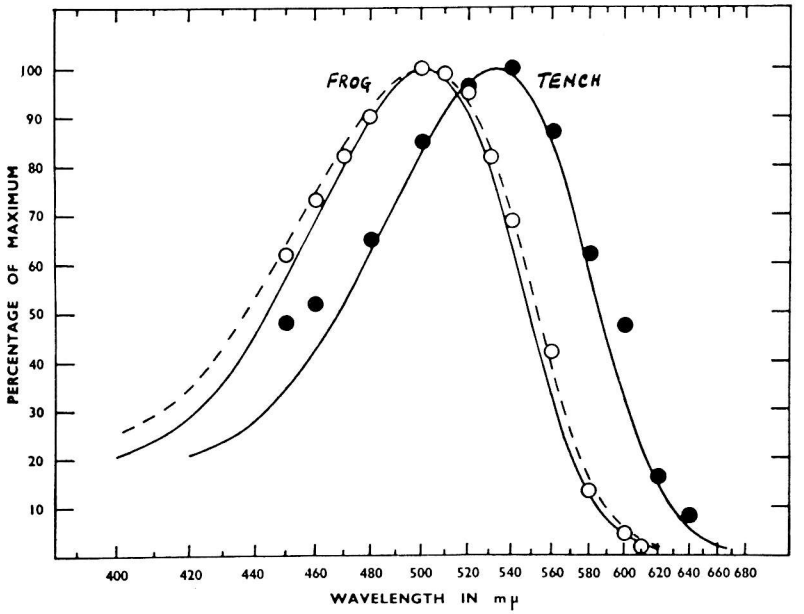

Fig. 57. Comparison of scotopic dominator data with nomogram curves for visual pigments 502 and 533. Frog: *open circles* show Granit's scotopic sensitivity data; *solid line:* the absorption spectrum of visual pigment 502 (on which Dartnall's nomogram is based); *broken line:* the spectral variation of light absorbed by visual pigment 502 at an optical density of 0.25. Tench: *filled circles* show Granit's scotopic sensitivity data (Granit, 1941d); *solid line:* the absorption spectrum of visual pigment 533 calculated from Dartnall's nomogram. (Dartnall, *Brit. Med. Bull., 9,* 24. 1953a.)

photopic dominators cannot be interpreted in terms of a single visual pigment, and he cites my evidence to the effect that it is possible, by selective adaptation, to split dominators (cf. Granit, 1945c, 1947), as has also been done since by Weale (see below), using the method of reflection from the living eye.

However, Dartnall's template curves, if plotted on a basis of wave length and not against frequency (as in Figs. 57 and 58), expand toward the long wave lengths; yet the two main photopic dominators

cover substantially the same spectral area for all animals: cat, frog, snake, tortoise, tench. They merely fall into two groups, one with maximum around 5600 Å (cat, frog, snake) for the system based on vitamin A_1 aldehyde, the other (tortoise, tench) with maximum around 6200 Å, for the system based on vitamin A_2 aldehyde as

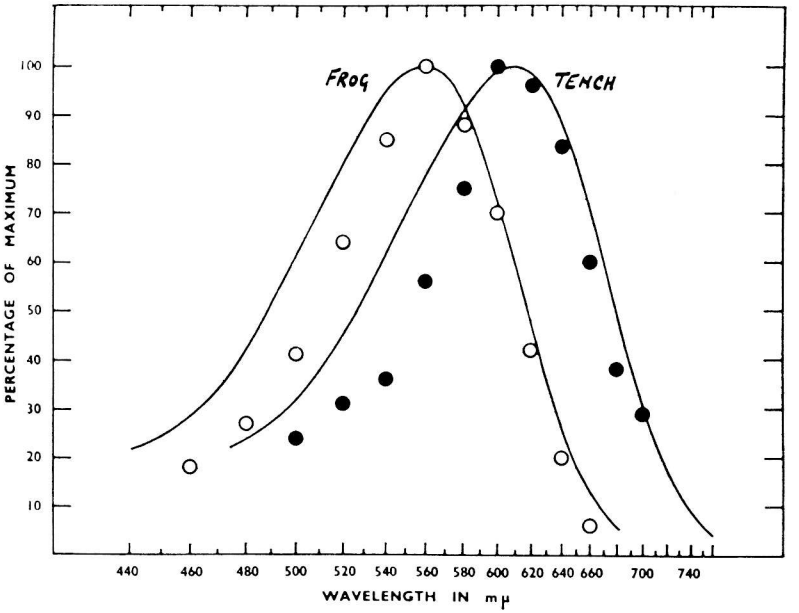

Fig. 58. Comparison of photopic dominator data with nomogram curves for hypothetical visual pigments 560 and 610. Frog: *open circles* show Granit's photopic sensitivity data (Granit, 1942a); *solid line:* the absorption spectrum (calculated from Dartnall's nomogram of a hypothetical visual pigment with λ max = 560 mμ. Tench: *filled circles* show Granit's photopic sensitivity data (Granit, 1941d); *solid line:* the absorption spectrum (calculated from Dartnall's nomogram) of a hypothetical visual pigment with λ max = 610 mμ. (Dartnall, *Brit. Med. Bull., 9,* 24. 1953a.)

chromophore. A substance corresponding to the latter type of dominator has recently been synthesized by Wald, Brown, and Smith (1953) from cone protein and retinene$_2$ (retinaldehyde$_2$). Their values (black dots) are compared with my curve for the tortoise's pure cone eye, drawn through the open circles, in Fig. 59a. The crossed circles refer to my measurements with the light-adapted tench. The fit is as good as can be expected. This substance has not yet been extracted. However, iodopsin has been both extracted and synthesized from cone

protein and retinene$_1$ (cf. above, Wald, Brown, and Smith, 1952). It corresponds to the photopic dominator based on vitamin A_1 aldehyde (man, cat, frog, etc.). Fig. 59b illustrates comparisons between broad-band chicken pigments and scotopic and photopic dominators of the pigeon. The photopic dominator curve is shifted to the right in the

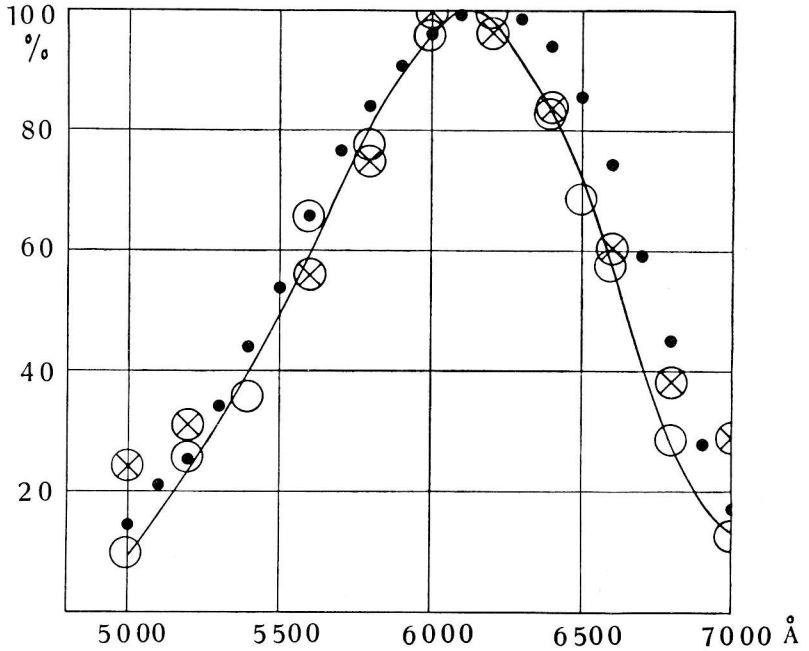

Fig. 59a. Comparison of dominator of tortoise's cone eye and photopic dominator of tench with Wald's cyanopsin (*Science, 118,* 505. 1953). *Open circles* with curve drawn through them: dominator of tortoise. *Crossed circles:* photopic dominator of tench (Granit, *Acta physiol. scand., 2,* 334. 1941). *Black dots:* Wald's cyanopsin. (By courtesy of G. Wald, Biological Laboratories, Harvard.)

spectrum by comparison with the photopigments. The probable explanation of this discrepancy—as stated—is the existence of absorbing oil globules in the cones of the pigeon. The template curve of Fig. 58 would be a great deal wider than the ones presented in Fig. 59. Extraction, synthesis, and electrophysiological measurements thus show the photopic cone dominators to be narrower than the scotopic ones. The reason for this discrepancy may be the one suggested—that extracts, synthetic substances, and dominators are complex curves; but

it is just as likely that all three curves represent as pure substances as those responsible for scotopic dominators. The latter, of course, agree with Dartnall's template as well as with absorption in the extracts from which the template curve was derived. Wald's (1953) results seem to presuppose that the dominators actually represent pure sub-

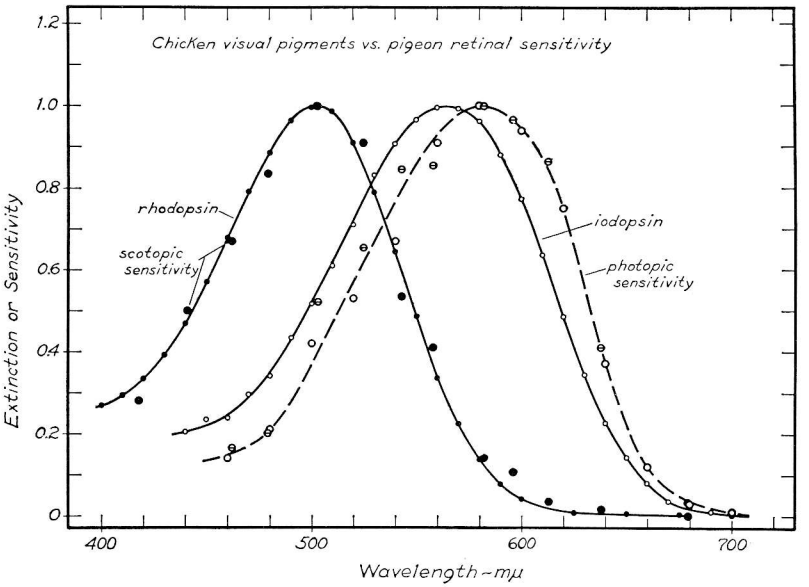

Fig. 59b. Scotopic and photopic sensitivities of the pigeon, compared with the absorption spectra of chicken rhodopsin and iodopsin in digitonin solution. The absorption spectra are from Wald, Brown, and Smith (1954–55). The spectral sensitivities were measured electrophysiologically and are plotted in terms of the reciprocals of the numbers of quanta needed to produce a constant response. The scotopic luminosity data are from Donner (*J. Physiol., 122,* 524. 1953); the photopic data from the same source (*barred circles*) and from Granit (*open circles; Acta physiol. scand., 4,* 118. 1942). (From Wald, Brown, and Smith, *J. Gen. Physiol.* 1954–55. In press. By courtesy of G. Wald, Biological Laboratories, Harvard.)

stances. If so, there are narrower absorption bands than the visual purples. The photopic dominators thus would be a step in the direction toward narrow-band photopigments responsible for modulators, though still falling within the category of broad-band spectra. All four dominators—two in each system—have now been synthesized.

4. *The modulators*

In working with the electroretinogram of the frog's eye Granit and Wrede (1937) and Granit (published in Wright and Granit, 1938) showed that it was impossible to account for all the changes in the response to variations of wave length by merely two substances, one for the rods and one for the cones. Both in the blue and the red regions of the spectrum sensitivity changes occurred which were independent of the two main types of rod and cone response separated by the Purkinje shift. The general electroretinographic approach has been developed in a new way by Forbes and Burleigh (1952), who have tried to discover whether it is possible to shift instantaneously from one wave length to another without eliciting an electroretinogram. As a preliminary they proved that shifting from white to another white could actually be accomplished without any response whatever from the retina. However, in cone eyes such as those of turtles it was impossible to shift from one wave length to another, whatever their intensity relationship, without producing a fresh electroretinogram. Their photopic sensitivity cannot therefore be based on the properties of one substance only. The same held good for the light-adapted retina of the frog.

Some narrow-band curves were first found in the light-adapted eye of the frog by Granit and Svaetichin (1939), recording with microelectrodes from single and grouped retinal optic nerve fibers and ganglion cells using microillumination from a spectrum. A very large number of animals (Granit, 1941–45) were then studied in a series of papers most of which were reviewed in 1947 (cf. 1945b). This extensive work gradually led to the conclusion that there were two main types of responses from single elements, dominators and modulators, the former relatively broad, the latter narrow with respect to the spectral area enclosed. The modulators were chiefly found in three regions of predilection widely apart in the spectrum. In my Thomas Young Oration (1945b) I therefore concluded that Young's (1801, 1855) main ideas were "fundamentally correct":

> The mechanism of colour reception is organized by the peripheral visual apparatus, the number of colour-sensitive elements is relatively limited, and these elements represent widely different regions in the spectrum. Those were Young's three fundamental assumptions. He was right even in assuming three main types of colour-receiving apparatus. These are the three preferential regions within which modulators are found. The electrophysiological work may, indeed, be said to have confirmed the view he gave of the framework of the mechanism of colour reception. Its finished picture looks somewhat different, but the old framework was solid enough and shines through [pp. 462–3].

This view was restated in 1947 (Granit, 1947, p. 317). It was pointed out that the number of modulators within these areas of predilection may well be greater than three and that the fundamental response curves of the trichromatic theory may be mathematical concepts (averages). At an early stage (Granit, 1942a) I raised the question of whether it would be necessary to suggest a polychromatic theory. My reply was: "Statistical averages of the 'modulator' groups actually have three preferential regions, and on this basis it is possible to suggest a trichromatic theory instead of a polychromatic one" (Granit, 1942a, p. 148). I see no reason to depart from this view. Later Hartridge (1950) developed the notion of polychromatism (cf. Motokawa and Ebe, 1953).

It is often stated (cf. Wald, 1953) that all of my records were from a specific type of isolated giant ganglion cell. This is erroneous. To begin with, it was clearly pointed out that I did "not rely merely on experiments with isolated elements. Strict adherence to this criterion may, for instance, lead to the conclusion that blue elements are exceedingly rare whereas often the influence of the blue-sensitive substance can be traced in a less restricted type of response" (Granit, 1942a, p. 139, paper on frog retina). Records of grouped units were presented in this paper and a "blue" modulator plotted from a grouped discharge was shown on p. 144. It is clear that the threshold method which was used favored the most sensitive elements of the group or else that specific color receptors occurred in clusters (Hartridge, 1950). It is also well known today that microelectrode records from frog eyes, unless specifically isolated to contain large spikes only, contain both fiber and ganglion cell responses (Barlow, 1953a,b). As early as 1941 (Granit, 1941a) I pointed out that when microillumination was used, there was often a distance of several millimeters between the microilluminated spot and the place from which the microelectrode picks up the response. It was only in the later work with the mammalian eye that the technique of recording from large units was systematically explored. With the large spikes dominators were obtained—with very few exceptions—and it was necessary to use indirect methods to split the response into narrower bands. The later work

with indirect methods was summarized in 1950 (Granit, 1950b). I shall not deal with its details here. Other indirect methods have been used by Motokawa, Iwama, and Tukahara (1951) and Tukahara (1951), confirming the modulator concept.

One of my indirect methods (Granit, 1945c) based on the microelectrode technique, consisted in selective adaptation of the dark-adapted cat's retina with red, blue, and green light. These experiments are of considerable interest today because Weale (personal communi-

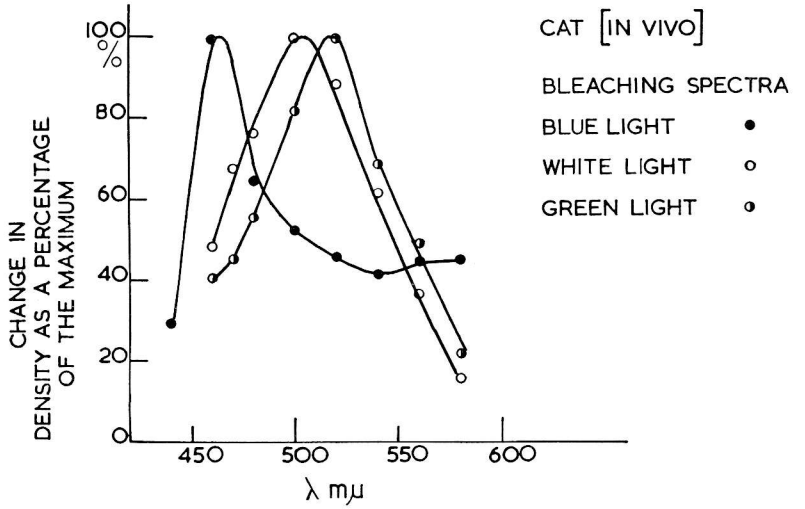

Fig. 60. The method of reflection (as in Fig. 54) applied together with selective adaptation for the analysis of the spectral sensitivity of the cat's eye. (By courtesy of R. A. Weale, Institute of Ophthalmology, London.)

cation) has recently, with the aid of Rushton's (1952) method of measuring retinal absorption directly in the living eye by reflection, tried selective adaptation on the same species. It was found impossible to account for the bleaching spectra in the medium and short wave lengths on the basis of visual purple alone. The fast adaptation in the long wave lengths made work at that end very difficult. Weale's results are shown in Fig. 60, mine in Fig. 61. His narrow-band curve at the blue end of the spectrum is strongly reminiscent of my blue modulator, as isolated in the frog's eye by the direct technique and in the cat's eye by indirect methods.

This is work in its beginning, by a new method of approach, and it is still capable of being developed and improved. In itself it is a

welcome addition to the extraction techniques based on a detergent which may or may not be selective (cf. Arden, 1953).

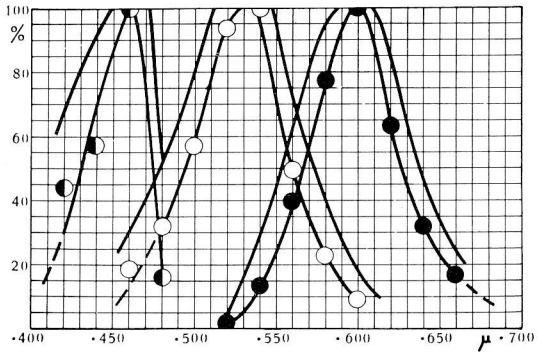

Fig. 61. Averages of individual modulators as obtained by selective adaptation. *Filled circles:* red modulators; *open circles:* green modulators; *half-filled circles:* blue modulators. Outer contours indicate dispersion. (Granit, *J. Neurophysiol., 8,* 195. 1945c.)

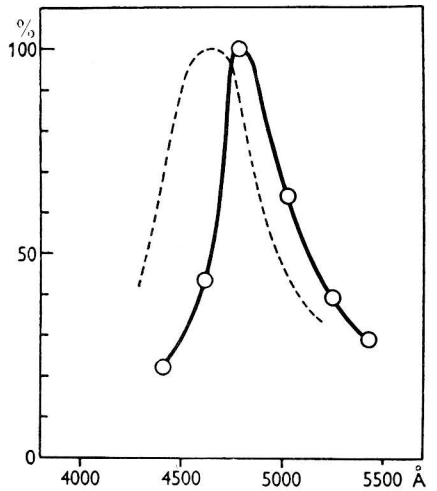

Fig. 62. *Solid line:* averaged curve for blue modulator. Four elements. *Broken line,* here and in Figs. 63 and 64, indicates modulator curves of frog (Granit, 1942b). Equal quantum intensity spectrum. (Donner, *J. Physiol., 122,* 524. 1953.)

Recently, Donner (1953) with his improved microelectrodes has measured the sensitivity distribution of individual elements in the pigeon's eye, where cone areas are easily found. In addition to the dominator broad-band sensitivity curves (Fig. 55), he found the

modulator narrow-band curves illustrated in Figs. 62, 63, and 64. He has also included frog modulators from my work (Granit, 1942a), from which the response curves of the pigeon differ in being still narrower and shifted slightly toward the red end of the spectrum. He ascribes this shift to colored oil globules. Most interesting is the extreme narrowness of these curves, which illustrate the message as transmitted through the optic nerve upward. The pigeon's is an eye at least as good as and probably better than our own—at any rate very much better

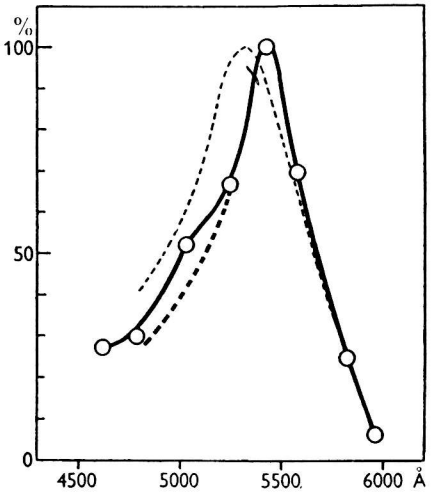

Fig. 63. *Solid line:* averaged curve for green modulator. Six elements. Equal quantum intensity spectrum. (Donner, *J. Physiol., 122,* 524. 1953.)

provided with cones—and thus it seems that improvement in cone vision, far from expanding the individual color bands over wider and wider spectral areas, actually tends rather to take the opposite course of narrowing them still further.

The cone eye of the snake (*Tropidonotus*) was used in my experiments (Granit, 1943b), and in this eye, too, it was easy to obtain red and green modulators. For the blue end of the spectrum the energy available in the instrument (Hilger-Tutton monochromator) was probably too low, or else blue modulators are few. Fig. 65 shows pure red modulators and a red coupled with a hump in the green. Green modulators tended to occur connected with the red one. The red modulator with maximum around 6,000 Å proved to be the easiest to isolate and was found in a large variety of animals belonging to the retinaldehyde,

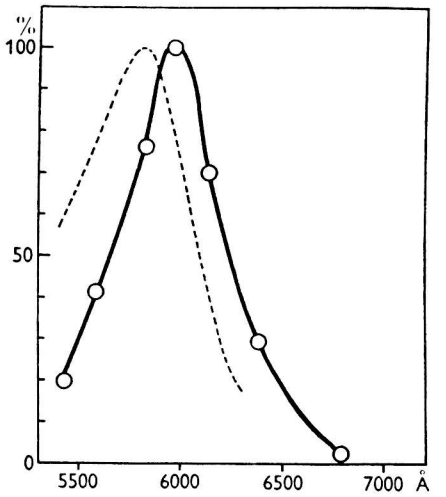

Fig. 64. *Solid line:* averaged curve for yellow modulator. Three elements. Equal quantum intensity spectrum. (Donner, *J. Physiol., 122,* 524. 1953.)

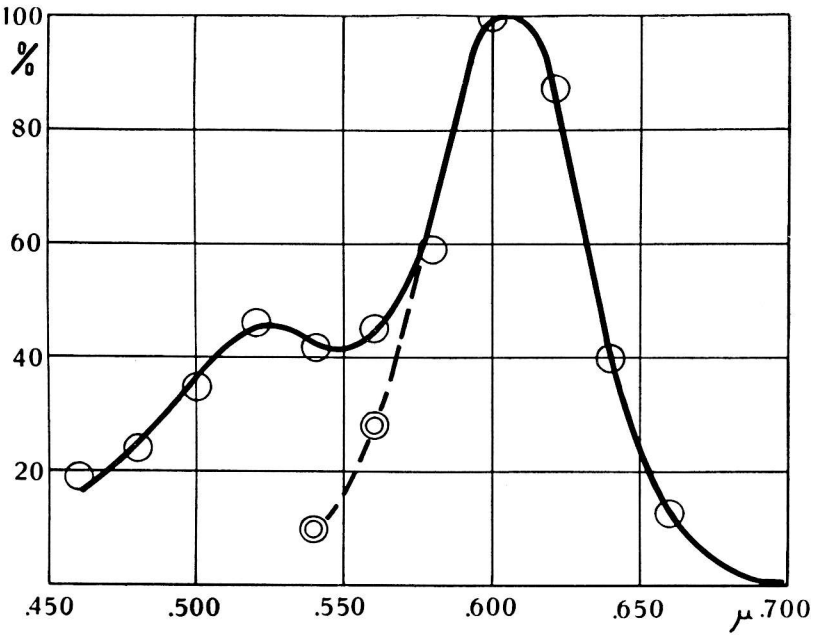

Fig. 65. Red modulator of snake's cone eye. *Open circles:* averaged results of 7 series; *circles on broken line:* averaged results in 2 series in which there was little or no hump in the green. (Granit, *Acta physiol. scand., 5,* 108. 1943.)

system with scotopic dominator around 5,000 Å and photopic dominator around 5600 Å.

In fish eyes (retinaldehyde$_2$), with the spectrum shifted toward the long wave lengths, a red modulator was found so far out as to be around 6500 Å (Granit, 1941d). As was pointed out above, human vision is based on the former type of photochemical system (see also Granit, 1947; Wald, 1953; Ball *et al.*, 1946, 1948; Morton *et al.*, 1947, for a discussion of vitamin A1 and A2 aldehyde as the respective chromophoric groups of these two systems).

Recently, Svaetichin (1954a,b) has inserted microelectrodes into the receptor layer of fish and in some preliminary experiments found color discrimination reminiscent of my results with fishes and tortoises. His contention that single cones have been obtained can hardly be said to be based on convincing evidence. Undoubtedly, however, the recording is from relatively restricted areas. Unfortunately, the curves were not recorded in terms of the photochemical function $1/E$. Microelectrodes within the retina have also been used by Tomita *et al.* (1953) for color work on the frog's retina. Evidence in favor of color discrimination was obtained, but again in terms which at the moment are difficult to evaluate for comparisons with photochemical results.

It should be clearly realized that the concepts "dominators" and "modulators" refer to the kind of information that is delivered by optic nerve fibers to the higher stations in the brain and that the analysis was carried out at the optic nerve level. These generalizations are therefore as such independent of the nature of the mechanism—photochemical alone or photochemical *plus* neural—which makes the message assume this particular form. It simply *has* this form and for this reason it is necessary to consider modulators and dominators as a device by means of which nature has chosen to deliver a particular kind of information to the brain.

However, considering that the message, as recorded, actually has traversed the retina, it is extremely interesting to see how relatively well it is reproduced in the case of the scotopic and photopic dominators of two such different systems as that of fish and cat, provided that a number of single fiber responses are averaged. Together with several other lines of evidence (see Chapter 8), this suggests that averaging is an important mode of sensory interpretation. With regard to the photochemical equivalents of the modulators a great deal of work still remains to be done. "When it is certain that the absorption curves of such [i.e. cone] extracts represent reasonably pure substances . . .

then, and not before, is it time to suggest other explanations [i.e. than photochemical ones] of discrepancies between photochemical and electrophysiological results" (Granit, 1947, p. 309). Since this was written, it has become possible to make further comparisons between

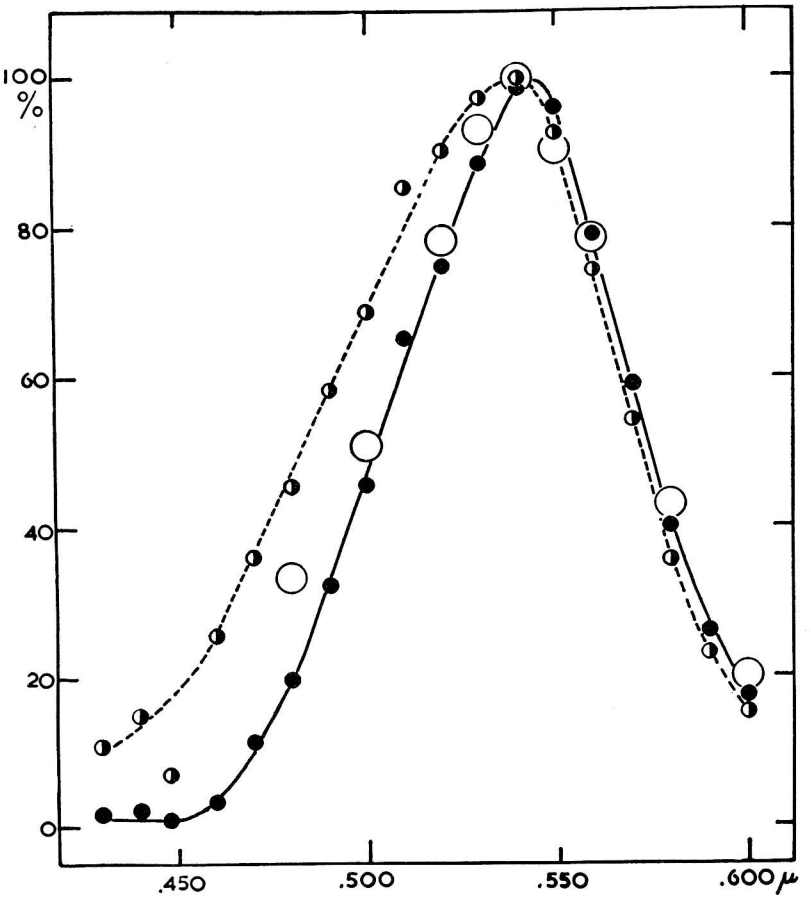

Fig. 66. Arden's (*J. Physiol., 122,* 13P. 1953) narrow-band photosensitive substance from frog's eye compared with Granit's (*Acta physiol. scand., 3,* 137. 1942) averaged green modulators as described in text. (By courtesy of G. B. Arden, Institute of Ophthalmology, London.)

dominators and photochemical absorption curves (cf. above). The only detailed comparison yet made between a modulator and an absorption curve comes from Arden's (1953) work * on suspensions

* A complete account of Arden's work (1954 a–c) has just been published.

of frog receptors in sucrose. This avoids the use of detergents. In Fig. 66 the line drawn in full is Arden's curve, the large circles the averages of my three green modulators from the frog's eye. The dotted line is obtained by assuming that the receptor segment absorbs some light at 4600 Å, but Arden himself is inclined to hold the line drawn in full to be the correct one.

The other aspect of the question, the neural one, theoretically developed by Jahn (1946a), was attacked by myself (Granit, 1949) with the cat's retina for which, indeed, it was possible to prove that red and green stimuli interact on the same element. This, however, is a demonstration of a possible situation. To conclude immediately (as does Wald, 1953) that all modulators under all circumstances owe their narrowness merely to neural interaction would be premature and, today, does not even seem likely. When more cone substances become available, it should not provide any difficulties, with the much improved microtechniques of today, to return to the problem of neural interaction. For some time it was maintained that there were only two photochemical substances in the eyes of the species discussed above. This view can be entertained no longer. What is required is simply more work.

5. *Some theoretical implications*

As for the color-theoretical implications of the dominator-modulator concept, I can but reiterate my views, as stated in 1947:

> The dominator-modulator theory, as such, is only concerned with a number of facts relating to the reception of and discrimination between wave-lengths, facts which have been accumulated by means of the application of the electrophysiological technique to the eye, as well as with their relation to what we know about the photochemistry and anatomy of the retina. The question as to whether or no any given experimental animal is capable of utilizing its retinal mechanism of wave-length discrimination is, therefore, not of immediate interest. Still less it is claimed that the theory can give any information as to whether, or to what extent, an animal may possess *colour vision* [Granit, 1947, p. 298].

This does not mean that one should wholly abstain from interpretation of the physiological cues, as has been so successfully done in many cases presented above. Nothing can be gained by refusing to consider evidence obtained with methods other than psychological ones. The

task of physiology is to detect cues for behavior based on our "internal measuring instruments" and to do so at all levels where such cues might be had.

From this point of view it seems that the dominators, as stated, can hardly be responsible for anything but the average spectral distribution of scotopic and photopic brightness and that the modulators provide the cues for discrimination of wave length. This was my standpoint, as presented in 1947, when I mentioned some relevant psychophysical data. It is substantially the same today. The dominators were described as the carriers of the Purkinje shift and there is no reason whatever to depart from this view either. Nor has, to the best of my knowledge, any other physiological evidence regarding the nature of the cues for wave length ever been presented. The recent valuable work by Jung and his collaborators (Jung *et al.,* 1952) with microelectrodes in the optical cortex of the cat has not yet been extended to color reception. It is not intended to discuss physiological optics from the psychophysical point of view.

A very complete and instructive text book has recently been published by Yves le Grand (1952). It is at the moment the best survey of the whole field. Somewhat more popular is a book by Linksz (1952). Color vision from the standpoint of the trichromatic theory has been discussed in considerable detail by Wright (1946), but a great deal has since been added. Thus, for instance, Stiles (1953) at the Madrid conference on physiological optics presented important new results on experimental subdivision of color sensitivity curves in the short wave lengths. Hartridge (1950) has given an account of his polychromatic theory.

6. *Mode of action of visual purple*

There is probably no aspect of visual physiology in which premature generalizations from apparently simple and incontestable assumptions have proved more deceptive than in this question of the mode of action of visual purple on the rod cell. It used to be held that since light bleached visual purple and regeneration took place in the dark, this was the basis of its photochemical action. It all began with Kühne's (1877–78) highly seductive optograms. He projected the window of his laboratory on the retina of the frog's eye and found it reproduced like a photographic image, the optogram, in the bleaching pattern of the photopigment. Then followed the quantitative psychophysical analysis of the increase of light sensitivity of an originally light-adapted

observer in the dark as introduced by Aubert (1865). Kohlrausch (summary, 1931b) was the first to show that dark adaptation in terms of the logarithm of the threshold sensitivity traced the curve of Fig. 67. There is an initial fast portion and a slower extended phase of increase in sensitivity (drop of threshold). Hecht (see summary, 1937) repeated the work and expanded these observations in different ways, agreeing essentially with Kohlrausch about the necessity of ascribing

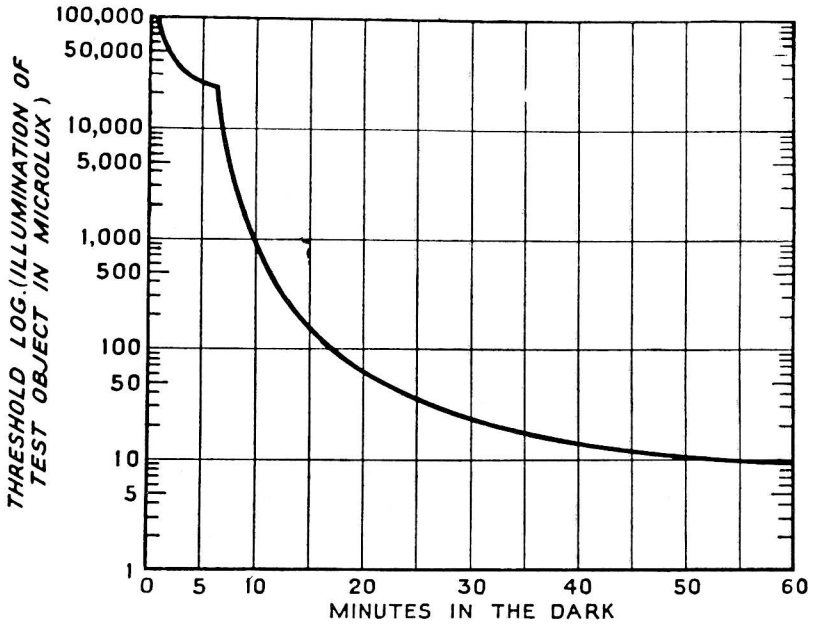

Fig. 67. Course of dark adaptation in the human eye. Dieter's data from Kohlrausch (*Handb. Norm. Path. Physiol., 1,* 394. 1931), replotted by Wright and Granit (*Brit. J. Ophthal.,* Suppl. 9. 1938).

the first portion of the curve to the cones, the second (after the kink) to the rods. The second phase of the curve was held to indicate that sensitivity was a simple function of the amount of regenerated visual purple available at each moment in the dark. The same curve may be traced in the mixed eye of the frog by electroretinographic methods (Riggs, 1937), as well as by impulse recording (Granit, 1942a). There can be no doubt about the fact that—in a general way—the first portion of the curve can be ascribed to the cones, the second to the rods. In fact, fast and slow regeneration has since been described by Weale (1953b) in his direct measurements of the light reflected from the retina, mentioned above. Regeneration of visual purple in the eye of

the rat (Tansley, 1931) and the frog (Zewi, 1939) has been followed quantitatively and seemed to be in reasonably good agreement with expectation from the general theory which has been well stated by Lythgoe (1940, p. 26) in a paper devoted to criticism of it:

> by photochemical reasoning we can say that, in order to produce a minimal stimulus, a constant amount of visual purple must be broken down, and the more visual purple there is, the less will be the illumination necessary to produce this amount of breakdown. This simple theory can be stated thus: For a threshold stimulus, *Illumination* $\times$ *Concentration of Visual Purple* $=$ *A Constant,* provided the density of visual purple is small.

Around 1937 I began to suspect that all this needed to be reconsidered. We (Granit, Holmberg, and Zewi, 1938) therefore made direct comparisons between the size of the initial so-called b-potential (Chapter 5) or b-wave of the frog's electroretinogram and the amount of visual purple that could be extracted. The size of an electrical test response to wave length 5,000 Å in a Hilger-Tutton monochromator was first established. Then a filter of density 1.3 was temporarily removed from the beam of the eye, light adapted to one of a number of wave lengths in the equal energy spectrum for 5 minutes (Granit, Therman, and Wrede, 1938). There was a very large drop in the size of the b-wave elicited by the test stimulus when the filter had been reinserted. The amount of reduction depended upon wave length of adaptation. Recovery was followed for 6 minutes. The same experiment was then repeated with a number of animals in which, after 5 minutes exposure to the adapting light, the retina was removed and put in digitonin for extraction of its visual purple. I am giving a set of readings referring to the reduction in the size of the b-wave in different wave-lengths 75 seconds after cessation of bleaching. This additional delay corresponds to some regeneration during the time necessary for removing the retina and placing it in digitonin. It is convenient to give the theoretically expected concentrations of visual purple, as derived by calculation from the drop in the b-wave:

TABLE 3

Reduction in Concentration of Visual Purple 75 Seconds after Cessation of Adaptation, as It Should Be if Calculated from the Reduction in Size of the b-Wave of the Electrical Response

Wave lengths in Å	5850	5600	5400	5000	4700	4500	4300
Percentage reduction	74	69	77	59	56	35	27

These are considerable reductions, and if sensitivity, as expressed by the size of the b-wave (a very good index, as will be shown in Chapter 5), actually is dependent upon the concentration of visual purple, this drop is of an order of magnitude that should make it easy to detect. We recall (Chapter 1) that the b-wave is roughly proportional to log. intensity and, since the sensitivity is proportional to the reciprocal of intensity, the table means that we are dealing with very large drops of sensitivity, of the order of 100–1,000fold.

The experiment was next repeated in the following way: The one eye of the animal was kept as dark-adapted control, the other one subjected to adaptation exactly as in the electrical tests. Controls showed that with a sufficient number of animals the concentration of visual purple in two dark-adapted left and right eyes did not differ by more than 1%. When the fifteen dark-adapted controls (one eye) were compared with fifteen bleached retinae (the other eye) the values were identical within 1% and the individual samples varied between −4% and +6%. Thus, the adaptation to the weak monochromatic light led to no definitely measurable reduction of the concentration of visual purple despite the large reduction in the b-wave. (Incidentally, it is of considerable interest to note in Table 3 that the short wave lengths were relatively less efficient in reducing the size of the b-wave than were the long wave lengths; see e.g. Granit, 1947).

It proved easy to check these results by placing the visual purple solutions themselves in the spectrum adjusted for adaptation in the same manner as with the frog's eye. Even though the absorption trough (length 20 mm.) containing the solution was kept in the optimal wave length for visual purple absorption (5,000 Å) for 10 minutes, there was only a reduction of maximally 2–3%. This has recently been confirmed by Hagins and Rushton (1953), who used Rushton's direct method of measuring visual purple absorption in the living eye. Light of strength 100,000 times the human threshold had no effect on the rhodopsin density. Rushton (personal communication), in studying visual purple in solution, found a few parts in 1,000 bleached by light, causing a fiftyfold change in threshold.*

Lythgoe (1940) immediately understood and accepted our early results and himself added a number of arguments from psychophysical experiments, in addition to suggesting that the findings should be accounted for by neural factors. Our view had been that most of the visual purple was a store in the sense that it had not taken part in the photochemical reaction leading to a response. There is clearly "an enormous discrepancy between the brightness needed to bleach the retina and that which would abolish the electroretinogram," to put it the way Rushton and Cohen (1954) have stated our findings. Actually, Baumgardt (1950) has since calculated that very little visual purple is needed for stimulation and that very little of it would be broken down unless strong lights were used. Noell's (1953) results (to be reported in Chapter 5) show that the greater part of the outer limb of the rod (which is the structure containing the visual purple) to all appearances can be degenerated without much diminution in the size of the b-wave (rabbit eyes).

* Wald (*Science,* 1954, vol. 119, pp. 887–892) has since taken up the same problem and calculates that exposure of an eye for 5 sec. to 10 millilamberts (= 100 lux) bleaches at most 1,200 of the 18 million rhodopsin molecules of one rod. This, however, would raise the threshold 8.5 times.

Lythgoe (1940), as stated, pointed out several discrepancies between light sensitivity, determined by psychophysical methods during dark adaptation and the visual purple concentration which was known from work on animals. A particularly lucid experimental criticism of the old view has recently been given by Rushton and Cohen (1954): they light adapted their own eyes for 3 minutes to 30 ft. lamb. and calculating from the quantum efficiency of visual purple in solution (Dartnall, Goodeve, and Lythgoe, 1936), concluded that only 0.3 per cent of the photopigment could have been bleached. Hagins and Rushton had found, using Rushton's direct method on rabbits and cats, that the bleaching rate in the periphery of the living eye was about the same as in solution or a bit slower (unpublished measurements). Sensitivity, however, was greatly diminished, and its course of recovery was followed alternately with two flashes, one lasting half a second and occupying a field of 2°, the other 7 msec. with a field of only 3′. The two curves obtained are illustrated in Fig. 68, the upper referring to the threshold of the large field, the lower to that of the small. To what is the vastly superior dark adaptation of the upper curve due?

Since pupil area was constant and the light was focused upon the center of the pupil, the fraction of light incident and absorbed must have been constant. But the larger flash represented both a longer summation time and a larger summation area, which according to Craik and Vernon (1941) will favor dark adaptation (cf. Lythgoe, 1940; Kuffler, 1953—see Chapter 2, p. 78; and Pirenne and Denton, 1952). The index of sensitivity was the threshold, namely the minimum number of light quanta N needed. The larger the area and the longer the time of exposure, the greater the likelihood that N quanta will be caught and thus lead up to a discharge along the optic nerve. Since, in

the lower curve, the stimulus area was small and the flash duration brief, it remains to ask why in this case quantum sensitivity, which is the inverse of N, has decreased because of light adaptation, despite the virtual absence of bleaching of visual purple.

Rushton and Cohen conclude that the change in quantum sensitivity is greatly influenced by events in the nervous network of the retina (of the kind with which we have become familiar in Chapter 2). Thus their results showed that quantum sensitivity has decreased in light

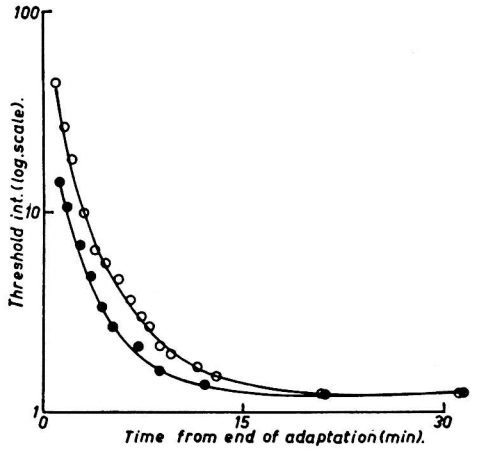

Fig. 68. Threshold intensity of a just visible flash plotted against time from end of light adaptation (300 ft. L. for 20 sec.) *Open circles:* 2° field, ½ sec. flash. *Filled circles:* 3′ field, 7 msec. flash. Adjusted to coincide at full adaptation. (Rushton and Cohen, *Nature, 173,* 301. 1954.)

adaptation and increased in dark adaptation, perhaps owing to retinal interaction. Chapter 5 will give further instances of interaction studied by electrophysiological methods (see also Granit, 1947, chapters 11 and 13). It is also possible that centrifugal action with consequent variations of retinal sensitivity (Chapter 3, sec. 6) might be dependent upon area and state of adaptation.

As long as modest light adaptation is used, it is unlikely that the bleaching of visual purple plays any significant role in determining the course of dark adaptation. If rhodopsin is removed by bleaching in strong light, it is reasonable to expect that the substance must be regenerated in order to be present at all. It is easy enough for any reader of this section to pick up a number of papers and summaries on dark adaptation in which most riddles in this field are presented as solved in terms of the old notion of visual purple concentration, and

so it is perhaps of some interest to continue to point out difficulties and obscure points (cf. Jahn, 1946b), all of which must be understood before it can be said that we know how the rods are excited by their photopigment.

There is, for instance, a serious discrepancy between on the one hand the fact that most of the outer limb of the rod can be destroyed without significant effect on the electroretinogram (Noell, 1953) and on the other hand the necessity for a high concentration of visual purple in order to obtain maximal electrical responses (Granit, Munsterhjelm, and Zewi, 1939). It is also well known that after adaptation to strong light the recovery of log. sensitivity increases parallel, roughly, with the increase of visual purple (see e.g. Tansley, 1931; Karpe and Tansley, 1947; Johnson and Riggs, 1951; Best, 1953a) and that it also requires much the same time as the regeneration of the photopigment. But sensitivity is defined by the inverse value of energy and not by the logarithm of the threshold. There are probably also conelike rods (Granit, 1947) that may contain a relatively stable variety of rhodopsin.

Bleaching and regeneration play no role in the eye of the horseshoe crab *Limulus* (Hartline and McDonald, 1947); yet in several respects the behavior of this eye when it is left to recover in the dark after light adaptation is strikingly similar to that of the rods in cat and man. These similarities have been pointed out by Hartline and McDonald.

Turning to visual purple in solution in order to learn something about the photochemical effect itself, one may note that the observation that first pointed out the road to a deeper understanding was Lythgoe's (1937) discovery of transient orange. He found that if the solutions were kept cold, light transformed visual purple into an orange colored substance that disappeared when the test tube was warmed. This is the photochemical process; later changes are thermal. Lythgoe and Quilliam (1938) then proceeded to establish the absorption curve of transient orange (cf. Dartnall, Goodeve, and Lythgoe, 1938) while Broda and Goodeve (1941) introduced the technique of studying visual purple in glycerol-water solutions at several degrees below zero. Thus they succeeded in isolating better than before the photochemical effect, which is independent of temperature, from the thermal reactions transforming the original photoproduct transient orange. This line of work has been continued by Wald and his collaborators (see e.g. Wald, 1953), who are in agreement with the British workers that finding in solution a very small shift toward the short wave lengths is the only effect induced by light, actually a shift of the

order of merely 50 Å. Wald, however, uses a different terminology and has split the later thermal reactions into several components.

For the present purpose the important point is that the actual photochemical change (in the retina as well) may consist of the minor shift of the absorption spectrum toward the short wave lengths. This is not likely to be measurable in the living eye. However, its relation to bleaching and regeneration can and must be analyzed so as to bridge the gap between photochemistry and the slow chemical processes of bleaching and regeneration which now, to a superficial view, seem so meaningless for the visual processes after having been in the foreground for almost a hundred years. At the moment we will have to assume that bleaching of visual purple serves merely to remove it from harm's reach when the cones take over the act of vision. This brings us back to the questions concerning light sensitivity and visual purple concentrations, discussed above. The late A. F. Bliss (1948) found the reddish photopigment in the eye of cephalopods, which he called cephalopsin, to be an unbleachable rhodopsin and yet very definitely to be the substance mediating the photochemical response to light. In this animal, which has a homogeneous receptor population, there seems to be no need for having one kind of photopigment removed when another takes over. Its photopigment has since been studied by St. George, Goldstone, and Wald (1952).

As to the process of excitation itself, Dartnall (1948b) suggested that activation of a visual purple chromophore by a light quantum may be "succeeded by a chemical process resulting in an electron transfer down the conjugated chain to the protein base and thence, *in vivo,* to the retinal end organ to which, in all probability, the visual purple molecules are attached." Wald and Brown (1952) ascribe to the —SH group a role in eliciting the electrical generator potential. At the moment this, however, is a consequence more of their method of analysis than of their evidence. It is of some interest in this connection to recall the lamellar structure of the rods, as found by Schmidt (1938) and studied by Sjöstrand (1949, 1953a,b) with the electron microscope. If the outer limb of the rods consists of superimposed discs the way Sjöstrand pictures them, then considering Noell's results mentioned above (and in Chapter 5, p. 184), it seems appropriate to ask how many discs are necessary for excitation—and to answer, possibly only the innermost ones. This brings us back to the original suggestion by Granit, Holmberg, and Zewi (1938) that under such circumstances the excess visual purple actually may be regarded as a "store."

Chapter 5

The Electroretinogram

1. Introduction

AN electrophysiology of the retina was recognized at a time when only the muscle and nerve action potentials were known and for the history of this subject I can refer to my book of 1947. It is of some interest to recall that the retinal electrical response to light was discovered independently in Sweden (Upsala) by Frithiof Holmgren (1865–66, 1870–71) and in Scotland (Edinburgh) by Dewar and M'Kendrick (1873a,b), because they converged toward the same result from very different assumptions. The Scottish authors imagined that the newly discovered photoelectric action of light might be the means of activation of the eye and Holmgren, following Du Bois Reymond (1849), wanted to study what was regarded as a natural cross-section of the optic nerve, where it might be possible to observe the resting potential as influenced by an impulse without killing the end of the nerve. He was surprised to find in the fish eyes which were used a deflection of his galvanometer to onset and cessation of illumination. These he first misinterpreted, believing them to be the nerve action potentials he was looking for. Later on (1870–71) Holmgren studied the distribution of the resting potential around the eye and from these results concluded that the electrical responses to onset and cessation of illumination had arisen in the retina itself.

Owing largely to the monumental histological work of Ramón y Cajal (1933), it soon became generally understood what a complex organ the vertebrate retina really is, but it was not until the electronic era of sensory research that this knowledge became part of any relevant physiological stock of ideas. This new era of research was heralded by the pioneer contributions of Adrian and R. Matthews (1927a,b, 1928) on the optic nerve response of the Conger eel. A summary of the achievements up to 1945 was given in my Sensory mechanisms of the retina (1947), and a later summary dealing with the organization of the retinal elements was published in 1950

(Granit, 1950b). I now intend to consider the subject in bird's-eye perspective in order to indicate briefly what recent advances have been made in the study of the electroretinogram but also and chiefly to point out some general trends of thinking in the problems in this field. It is not intended to review the field monographically with complete references. However, in the presentation of leading ideas a sufficient number of papers will be quoted in order to make it easy for the reader to trace them back to their original sources and to locate the growing number of research centers devoting themselves to electroretinography.

Figs. 25 and 26 in Chapter 2 (pp. 64, 65) have already drawn attention to the fact that behind the layer of receptors in the retina there are two additional neurones, the bipolar cell and the ganglion cell, and that the axon of the latter is what we conventionally call an optic nerve fiber, though, strictly speaking, it is what elsewhere in the central nervous system would be called a tract fiber. In addition there are lateral connections formed by horizontal and amacrine cells. The centrifugal or efferent paths were discussed in Chapter 3, sec. 6. Polyak's (1941) scholarly book on the histology of the retina deserves careful study by anyone interested in this field.

2. *The electroretinogram, a mass response*

It should be realized at the outset that the electroretinogram recorded in the standard way *in situ* with one electrode on the cornea and the other on the animal's body is a mass effect dependent upon the favorable orientation of some retinal structures capable of conducting currents in one direction. Such oriented structures are the rows of receptors and bipolar cells. There are also two membranes, *m. limitans externa* and *m. limitans interna,* the former at the base of the receptors, the latter below the ganglion cells. However, according to Sjöstrand's (1949, 1953a,b) analysis by electron microscopy, m. limitans externa is not a membrane at all but consists of independent and isolated rings around each receptor cell. These "membranes" may nevertheless possess relatively high resistances and so play a significant role in determining the distribution of the current between the two recording electrodes. It is clear from what we know about the behavior of nerve cells elsewhere that all cell types must be the seat of potential changes when activated, but for the reasons mentioned only receptors and bipolars have been seriously considered as significant for the currents recorded as electroretinograms. The large receptor potentials observed in the retinae of animals having the neural layers at some distance from the receptors were mentioned in Chapter 1, secs. 3, 4, and 7.

The so-called indifferent electrode on the animal's body is not wholly indifferent. Some authors use the other eye, kept in the dark, as the site of the indifferent electrode but, at least in cats, the "dark" eye may record the potential of the illuminated eye with inverted sign and so cannot be neutral. Such effects, inasmuch as consensual pupil reactions have been excluded, may lead to the conclusion (actually drawn) that centrifugal fibers have carried an effect reflexly from an illuminated eye onto the nonilluminated eye, but so far there is no evidence for this conclusion.* The centrifugal effects have been discussed in Chapter 3. The consensual pupil contractions have been analyzed by Karpe (1945) and Dodt (1951b). In small animals the indifferent electrode may also pick up the cortical visual response if placed near the head. In unoperated cats the indifferent electrode is best placed in either nasal orifice. The dominating part of the response is cornea-positive. The initial positivity which at high intensities is preceded by a small negative a-wave, is called the b-wave (see Figs. 69 and 70).

The large eye of the cat can be used to clarify one of the essential complications in electroretinography. This is that the eyes of most laboratory animals, including man, are dominated by rods. Hence they are very light sensitive when properly dark adapted, so that a relatively weak stimulus, if spread over a sufficiently large area, elicits an electroretinogram of considerable magnitude. In fact, the stray light spread diffusely by the different optical media will stimulate the eye, as is most conclusively shown in clinical electroretinography. Thus, Karpe (1945) found that large scotomata were perfectly compatible with a scotopic retinogram of normal size. This problem of light scatter has aroused considerable interest. Fry and Bartley (1935) and Bartley (1941) held the view that the electroretinogram is caused wholly by stray light. Granit, Rubinstein, and Therman (1935) did not think their evidence conclusive. Later Asher (1951) showed that an electroretinogram could be elicited by stimulation of the blind spot, and Boynton and Riggs (1951) on similar and other evidence again

* Recently Müller-Limmroth (*Zt. Biol., 107,* 216–40. 1954) has found that the slow potential change noted in one eye after illumination of the other actually disappears after severance of the optic nerve (guinea pigs, urethane narcosis). So far I have failed to find any corresponding effect on retinal elements in cats (encéphale isolé, spike recording).

concluded that the retinogram is produced by stray light (cf. Boynton, 1953). My own standpoint (see Granit, 1947, p. 174, where the earlier phase of the discussion is reviewed) was that "though it is certain that scattered light excites receptors outside the area of stimulation, particularly when the stimulus is strong," there are nevertheless unsettled objections to the view that "area" is of no significance. I need not now enter upon these objections but will limit myself to the description of a recent experiment in our laboratory (Wirth and Zetterström, 1954) in which, for the first time, the effect of area of stimulation upon the electroretinogram has been recorded in the absence of stray light. These experiments demonstrate the influence of "area" in an unequivocal manner. The idea was to illuminate through Perspex cones blackened on the outside and apply them directly onto the retina of the opened eye after removel of lens and cornea, while the electroretinogram was recorded in the standard way.

Fig. 69 illustrates some results taken with a condenser-coupled amplifier which has a sufficiently long time constant to reproduce the fast initial phases correctly. These are the ones generally measured. On an average it was found that a surface not less than 5 mm. in diameter had to be illuminated to give a full-size electroretinogram. Most animals gave only a small, slow response with an area 2 mm. in diameter, some none at all. In the best cases it was just possible to notice a small response with the 1.5 mm. cone. Clearly, therefore, the contention by M. Monnier and Boehm (1947) that perimetry would be possible by electroretinography can mean only that there are general differences between central and peripheral responses because of the variations in the relative number of rods and cones.

It has been stated from the beginning of electroretinography that area and intensity are interchangeable in determining the size of the electroretinogram (for references see Granit, 1947), but the experiments illustrated in Fig. 69 which exclude stray light show that it is impossible to obtain a full-size and high-intensity type of electroretinogram by any reasonable intensity if the area goes below a minimum of the order of 10 sq. mm.—to make a very generous estimate. In most cats 20 sq. mm. will be needed. Now, since the diameter of the rods is of the order of 0.002 mm., a truly enormous number of receptors is required for a full-size and high-intensity type of electroretinogram. The most significant result of Fig. 69 is that the responses to small areas and high intensities never look like high-intensity responses but in every respect are identical with low-intensity electroretinograms obtained with large areas, rising, like those, slowly

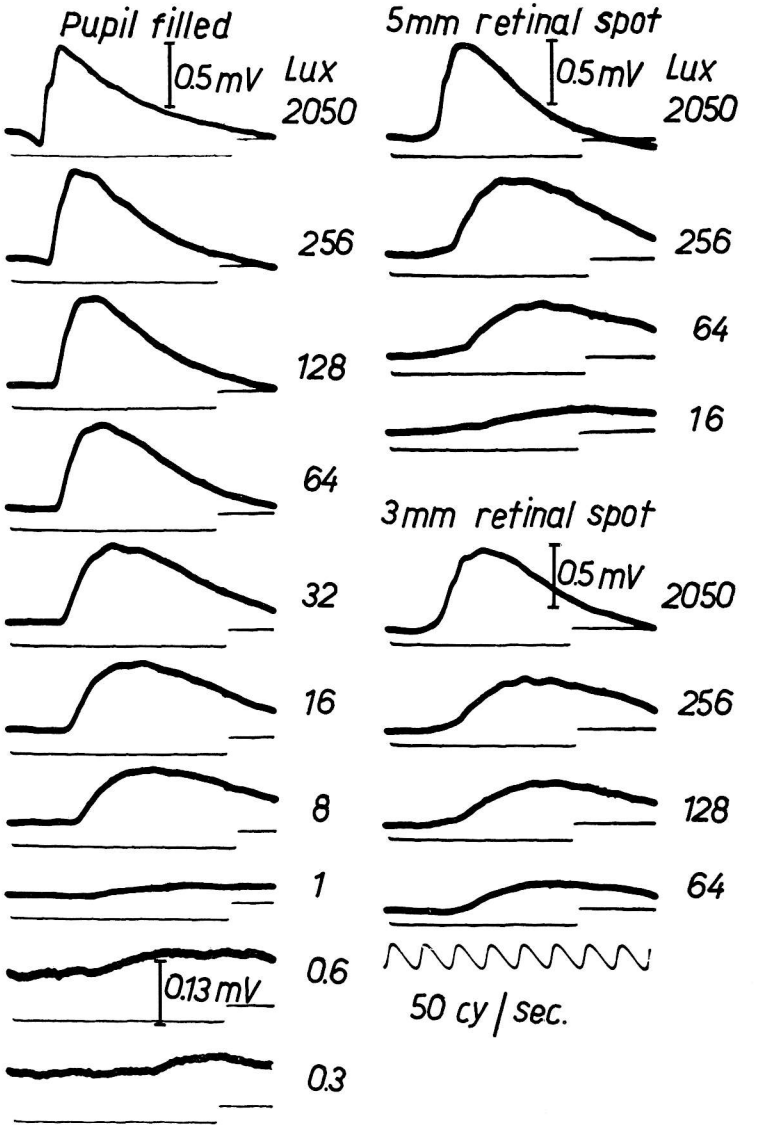

Fig. 69. Initial phases of electroretinogram of dark-adapted cat. Note change of calibration for lowest intensities on the left. *Left column:* pupil filled. *Right column:* Perspex cones of 5 and 3 mm. respectively, applied directly onto retina, as described in text. Note that at high intensities b-wave does not increase in size, only in rate of rise, and a-wave occurs. Oscillations on the records. Cf., e.g., 64 lux under different conditions. (Wirth and Zetterström, *Brit. J. Ophthalm., 38,* 257. 1954.)

toward their maxima and reaching low amplitudes only. True high-intensity responses (to the left in Fig. 69) are initiated by a small negative a-wave and have a very fast rate of rise. In fact, as with large areas, when the high-intensity range is reached, the electroretinogram does not alter very much in size but chiefly in rate of rise of the positive b-wave (cf. Granit, 1947, fig. 78, p. 149; Bornschein, 1952). This effect of rate of rise may account for the fact that in the experiments with different Perspex cones, flicker frequency proved to be a function of area and intensity, just as in Granit and Harper's (1930) experiments on area with perceived flicker (cf. Berger, 1953). The oscillations on top of the high-intensity responses should also be noted. This phenomenon has recently attracted the attention of several workers (Cobb, below; Müller-Limmroth and Andrée, 1953a; Tomita, 1950; Ottoson and Svaetichin, 1952; Dodt and Wirth, 1953). Some of the oscillations are due to nerve impulses, some to b-waves of different rates of rise in individual elements (Granit, 1947), but as yet unknown factors cannot be excluded.

Now, what is the explanation of this effect of area? In Chapter 2 it was pointed out that the receptive fields of a single optic nerve fiber can be of considerable size; in cats actually a maximum of 4 mm. has been given by Kuffler (1953). If the retinogram were due, partly at least, to an integration within the receptive field and thus to summation in synaptic networks, the effect of area could be simply explained but the natural consequence of this view would be that the electrical response would have to be influenced by structures activated in the chain of events later than the outer portion of the receptors, the first site of neural interaction being at the synapses with the bipolars. This problem was first raised by Adrian and Matthews (1927a), who on the one hand found area and intensity interchangeable with respect to the latency of the discharge in the optic nerve, on the other hand found the retinal-nerve interval to be constant when counted from the beginning of the a-wave. These two facts were held to require the spatial effect to express interaction by convergence, alternatively physical or chemical direct interaction in the receptors. In both cases the summative process would have to be at a point somewhere before the retinogram had arisen or at this very site—at any rate, not between it and the spike discharge. Adrian and Matthews assumed the a-wave of the electroretinogram to be localized in the receptors themselves and interaction consequently to be due to physical or chemical direct forces between the receptors. They did not express any opinion on the localization of the b-wave. I shall return below to this question of the localization of the electroretinogram.

An alternative view to interaction in Wirth and Zetterström's experiments would be that the receptors, even within the rod range, have widely different thresholds, and so the effect of area would be to add up charges or "batteries," much as in the *Limulus* eye (Graham, 1932), where the retinal response is dependent merely upon the number of ommatidia activated. On this view the effect of area on the latent period would have to be ascribed to the greater probability for the inclusion of a sufficient number of brief-latency, quickly responding high-threshold receptors in a response from a larger area. However, the interaction in the synaptic layers, demonstrated by a very large number of perfectly clear-cut experiments (see e.g. the summary by Granit, 1950b, and papers by Adrian and R. Matthews, 1927a,b, 1928; Hartline, 1938a, 1940a–c; Barlow, 1953a,b; Kuffler, 1953), would then leave the electroretinogram untouched and the specific features by which high-intensity electroretinograms of large areas differ from high-intensity responses of small ones would be wholly accounted for by the increasing number of high-threshold receptors (cones). As such, the number of receptors activated must, of course, be a factor of primary importance. One need but imagine the likelihood that a single receptor is capable of producing a recordable retinogram, despite retinal and extra-retinal shunts, in order to realize that the number of oriented elements is significant.

This should suffice as a first presentation of one of the main problems of electroretinography. Is it possible definitely to assign the electroretinograms to one specific structure and to assert that the electrical events in that structure are independent of electrical events in adjacent or proximal structures in the path to the optic nerve? I shall return to this question below. In 1947 I found it necessary to ascribe the origin of the electroretinogram to both receptors and neural layers.

3. Rod and cone electroretinograms

Summarizing the knowledge on the electroretinogram (see Fig. 70) in 1947, I came to the conclusion, based largely on the work of Piper (1911) and ourselves, that there were two main types of response, those of E- and I-retinae, which often were represented or "mixed" in the same eye in such a fashion that it seemed likely that they were the electroretinograms of the rod- and the cone-systems respectively.

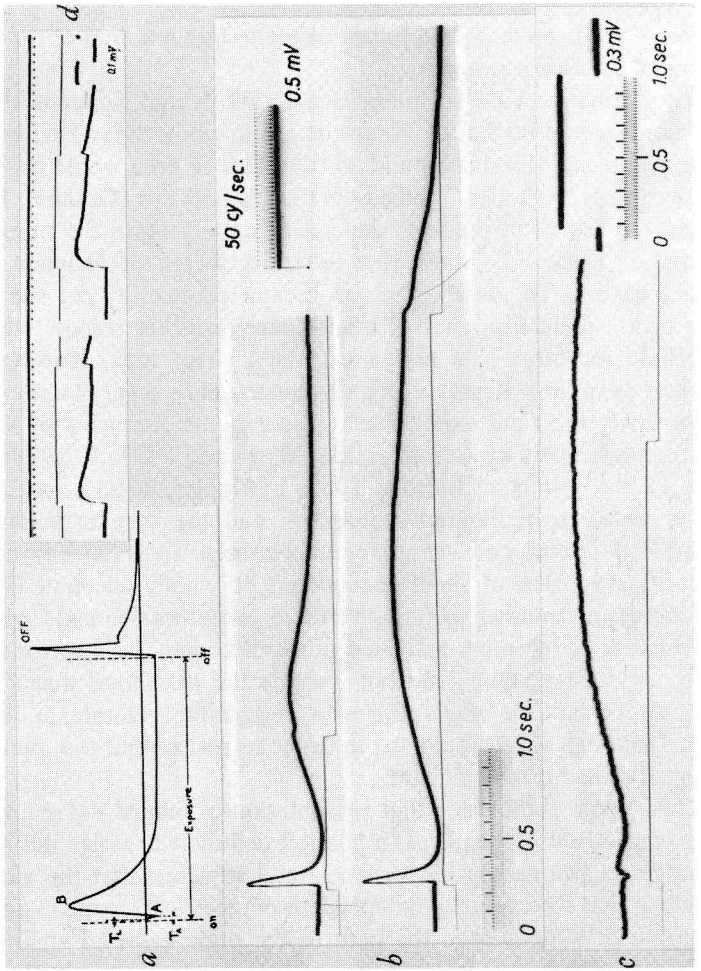

Fig. 70. Electroretinograms.

a. Cone retina of horned toad, *Phyronosoma.* (Chaffee and Sutcliffe, *Amer. J. Physiol., 95,* 250. 1930.)

b. Cat, dark adapted. Two flash durations. Intensity about 700 m.c. Note a-wave just visible, b-wave with fast oscillation, drop below baseline before c-wave begins, and d-wave or off-effect as a retardation of fall of response at cessation of illumination.

c. Guinea pig, dark adapted. Intensity about 900 lux. Definite a-wave, indication of double b-wave. In this eye the c-wave or secondary rise tends to be the most prominent phase of the response. Light signal below retinogram in this and in *b.*

d. Gecko. Intensity 1250 m.c. First record is 3.8 sec. illumination after 1 min. in the dark, second record 2.8 sec. illumination after 2 min. in the dark. Time marks 0.2 apart. (Dodt and Heck, *Pflüg. Arch. ges. Physiol., 259,* 226. 1954. By courtesy of E. Dodt, Physiological Institute, Freiburg in Bresgau.)

At the time, however, it was felt necessary (Granit, 1947, p. 165) to insert some words of caution against unqualified acceptance of this view. It was largely based on anatomical considerations and on our evidence to the effect that mixed retinae underwent a transition from E- to I-type in light adaptation, provided they had a sufficient number of cones. This question must now be re-examined in the light of later evidence.

Let us begin with an eye, such as that of the frog, in which rods and cones occur in about equal proportions. It is actually possible to put this animal or its opened eye (if one uses freshly caught autumn frogs) in the window and expose it for an hour to bright sunshine and still, immediately afterward, record a typical electroretinogram, provided a sufficiently strong light be used. Some changes, to be sure, have taken place: the slow, so-called c-wave, ascribed to component PI (see below, Fig. 71), has disappeared, as have also the slow components of the b-wave and the off-effect; the electroretinogram has decreased in size and often the negative phases have become more prominent. As shown by Fig. 70, *a,* negative phases are more prominent in cone eyes (Granit, 1947; cf. Noell, 1951; Müller-Limmroth and Andrée, 1953a). This is beautifully illustrated also in Schubert and Bornschein's (1952) record of the electroretinogram of a congenitally rod-blind observer, in which the b-wave rises from a negative level of potential. In general, however, it may be said that the electroretinogram of the light-adapted frog eye is complete in that it has an initial negative a-wave, a b-wave, and an off-effect or d-wave. Its spectral distribution of sensitivity is that of the cones with maximum shifted from 5,000 Å to 5600 Å (Granit and Wrede, 1937). The pure cone electroretinogram is perhaps best illustrated by a diagram based on records from the cone retina of the horned toad (Fig. 70, *a*) obtained by Chaffee and Sutcliffe (1930). No drastic light adaptation has been necessary for this record. Recently Noell (1951) and Forbes and Burleigh (1952) have recorded electroretinograms from pure cone retinae of turtles and in them, too, they find all the phases described.

As a counterpart to the cone electroretinogram we have in Fig. 70, *b,* the electroretinogram in the dark-adapted state of a rod-dominated animal such as that of the cat, which nevertheless has a sufficient number of cones to be able to give in light adaptation the cone spectrum of the photopic dominator (Granit, 1943c with microelectrodes—cf. ch. 4—and Gunter, 1954) and a flicker fusion frequency as fast as that of the human eye, with both spikes and electroretinogram, provided that the stimulus intensity is made very high (Dodt and Enroth,

1953). The off-effect is small. Fig. 70, *c,* shows the rod electroretinogram of the guinea pig. This eye has so few cones (O'Day, 1947) that it has been impossible to obtain the photopic dominator—so characteristic for cones—by the microelectrode technique (Granit, 1942b), and its flicker fusion frequency is also low, even at very high intensities of stimulation (Dodt and Wirth, 1953). Sometimes one finds a small off-effect. Guinea pig electroretinograms have also been published by Adrian (1946), Boehm, Sigg, and Monnier (1944), and others. Finally, Fig. 70, *d,* shows two electroretinograms (Dodt and Heck, 1954a) from the pure rod eye of the Gecko. It should be noted that there is an a-wave, a b-wave, and an off-effect, the last small compared with that of the horned toad.

By compressing the time scale and using dark-adapted frogs, it would be possible to make the frog high-intensity electroretinogram look more like the cat electroretinogram of Fig. 70, *b.* There would be only a more prominent off-effect in the former, but even this difference could be made less conspicuous by comparing them at shorter exposures. In cats and rabbits the electroretinogram sometimes swings toward the negative side after the b-wave, as in the case of Fig. 70, *b,* in which the c-wave was small; it does so more regularly in the albino rat (Charpentier, 1936), in the guinea pig (Boehm, Sigg, and Monnier, 1944), in rabbits (Noell, 1953), and particularly in the dog (Piper, 1905; Parry, Tansley, and Thomson, 1953). Below, I shall discuss separately slow negative and positive responses. The positive secondary rise is well known to be a characteristic of the dark-adapted state. It is sensitive to ether and for this reason may be absent in the Gecko which has been anesthetized with ether (for an alternative explanation see below, p. 182). There were some doubts of whether the dark-adapted human eye has a secondary rise, but these have been dispelled by Dodt (1951b) and Wirth (1951). It should be realized that I am speaking of high-intensity electroretinograms capable of displaying all the features of the response.

In conclusion it may be stated that with the exception of the c-wave or secondary rise all principal features seen in rod (E) electroretinograms are also found in cone (I) electroretinograms, but the latter tend to have a far more conspicuous off-effect or d-wave. There is nothing wholly new in this conclusion. It was also emphasized in the general component analyses of the electroretinogram, illustrated in Fig. 71 for the frog eye (for the cat retina see Granit, 1933), in which long ago our laboratory expanded and developed experimentally the old work of Piper (1911) and Einthoven and Jolly (1908) in the belief

that some such skeleton of an analysis was necessary for directing further work. These components do exist and for many purposes the analysis is still serviceable (Müller-Limmroth and Andrée, 1953a). It generally seems to have been overlooked that in the light-adapted frog the whole off-effect could not be accounted for unless an overswing

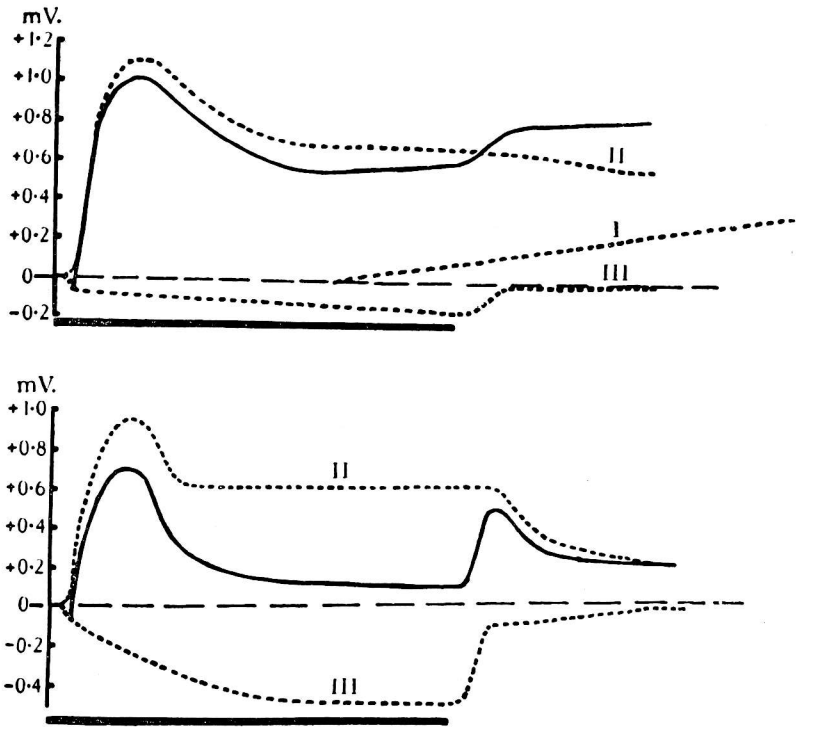

Fig. 71. Analysis of the I-electroretinogram. Upper: dark adapted. Lower: light adapted. Duration of stimulus: 2 sec. (Granit and Riddell, *J. Physiol., 81,* 1. 1934.)

to the positive side of the component labeled PIII or renewed activation of PII was assumed to take place, as was experimentally found by Granit and Therman (1937). This is in agreement with Parry's work discussed in Chapter 1, sec. 6 (cf. also Fig. 13) and has recently been emphasized again by Tomita (1950).

A consequence of this general theory of the electroretinogram, which after twenty years, no doubt, is ripe for improvement, is that both rod and cone systems possess the same components but that their relative size may vary a great deal from animal to animal. In particular the

negative component PIII was found to be relatively larger in cone electroretinograms. This, by some authors, has since been taken to mean that it is specific for cone eyes but it was clearly pointed out that "of course, both processes [i.e. PII and PIII] are present in all types of retina" (Granit, 1947, p. 135; cf. Best, 1953a; Noell, 1953; Dodt and Heck, 1954a). One of the most definite early arguments that PIII was also present in rod retinae came from Therman's (1938) work with the isolated PIII, in which this component was found to reproduce the visual purple spectrum in dark adaptation (Granit, 1947, p. 125). To this, Armington, Johnson, and Riggs (1952) and, independently, Bornschein (1952) and Best (1953a) have since added emphasis by demonstrating that in man the initial a-wave which (on the analysis of Fig. 71) is the initial part of PIII, if proper precautions be taken, can also be isolated as a rod phenomenon. Finally, Dodt and Heck (1954a) for the first time have recorded the electroretinogram of a pure rod eye (the Gecko, Fig. 71, *d*) which does not differ fundamentally from that of the pure cone eye (Fig. 71, *a*). There was a definite a-wave which increased in the dark.

In view of these facts Ottoson and Svaetichin's statement (1952; reiterated by Svaetichin, 1954a,b) that the negative component of the electroretinogram is a pure cone component and that cones do not contribute to the b-wave cannot be upheld. It is also well known that the b-wave is a good index of both cone and rod activity—indeed, it is capable of giving the Purkinje shift (cf. Chapter 4) between the two states of adaptation. Pure cone eyes are also well known to have positive b-waves (see Fig. 71, *a*, and Noell, 1951; Forbes and Burleigh, 1952). Their phasic components tend to be faster than in rod eyes (Meservey and Chaffee, 1927).

Now, why is the off-effect absent or less conspicuous in the electroretinogram of rod eyes? Is it because elements capable of giving off-discharges are absent or rare in them? With an Adrian-Bronk needle electrode in the optic nerve I found very marked off-discharges in the cat's eye (Granit, 1933). This was confirmed by Bartley and Bishop (1940)—who used the rabbit's eye, which likewise is lacking a good off-effect in its electroretinogram—and by Adrian (1946) with other retinae of the E-type. Later, using the microelectrode technique, I found (Granit, 1942b) that pure on-elements were far more common in the guinea pig's eye than in any eye containing a greater number of cones. However, off-discharges were by no means absent, as has been since confirmed by Adrian (1946), who employed the massed discharge from the optic nerve of the guinea pig as an index. Apparently we are dealing with differences of degree rather than of kind. The differences between rods and cones should not be exaggerated. Many facts have, indeed, made it necessary to assume that there are cone-like rods (Granit, 1947). However, considering the very large number of pure off-elements in the frog's eye (Hartline, 1938a), it seemed to me (1947) that the organization responsible for the off-effect might well be better developed in cone eyes (see Fig. 71, *a*). In the eyes of cats and guinea pigs *pure* off-elements are rare, possibly absent, "purity" being partly a matter of definition.

If this view is correct—that the off-mechanism is less developed in rod eyes, and, when present, possesses slower time constants (Granit and Munsterhjelm, 1937)—it is clear that at cessation of illumination the algebraical interference of the components may easily lead to obliteration of the off-effect in the electroretinogram. Cessation of illumination is also characterized by postexcitatory inhibition, particularly easy to demonstrate in the retinal elements of guinea pigs (Granit, 1945a). If the latter is opposed by a less active off-mechanism than in cone eyes it may well dominate the electroretinogram. Sometimes the electroretinogram actually becomes negative at "off," as in record *C*, Fig. 72, and in some of Noell's (1953) and Ottoson and Svaetichin's (1954) records. It was shown in Chapter 2, sec. 6, that receptor potentials may change polarity at cessation of stimulation (the hyperpolarization of Katz).

The eyes of most laboratory mammals and that of man are dominated by rods, and so, normally, their electroretinograms would tend to bring out the interference picture characteristic of the rod system. Pigeons have been used to some extent in recent work for representative cone eyes. However, they do not lack rods. Their electroretinograms show marked off-effects (Piper, 1910, 1911; Granit, 1935; Adrian, 1946; Dodt and Wirth, 1953).

From what has been mentioned above it should be perfectly clear that in mammals cone electroretinograms will in general be covered by rod electroretinograms. This is well known to be the case in man (Adrian, 1945; Karpe, 1945; Karpe and Tansley, 1947; Johnson and Riggs, 1951). Some evidence clearly indicates active suppression of the cones by the rods (Granit, 1947; Dodt, 1952a; Dodt and Heck, 1954b). This being so, it is necessary to look for means of "uncovering" the cones. This general problem, together with clinical applications of electroretinography, has been very much in the foreground in recent work on the electroretinogram. The three chief methods applied, singly

or in combination, have been to use (1) light adaptation to suppress rods, (2) differences in color sensitivity between rods and cones (see Chapter 4), and (3) flicker and fusion frequency. All require strong light sources. In human electroretinography, which is clinically important (cf. e.g. Karpe, 1945) and of theoretical interest because of its bearing upon psychophysical interpretations, much experimentation has lately been devoted to methods of uncovering cones. It is regrettable that with few exceptions most workers have neglected the off-effect and restricted their analysis to the initial phases alone. The cone-component is just as important at "off." I shall therefore begin with the analysis of "flicker," which has thrown some light on the off-effect.

It should be realized that the human electroretinogram cannot be expected to give a picture of the average sensory events in which our visual perceptions are directed by the cones of the fovea with their (relative to the peripheral rods) enormous sensory projection area. We can *see* well with the cones at modest intensities, beginning at about a tenth of a meter candle, when rod dominance in the electroretinogram still would be practically complete. Roughly speaking, the sizes of the peripheral and central parts of the field of vision in primates are inversely represented in retina and the cortical striate area. The cortex of the cat is likely to be better interpretable in terms of this animal's electroretinogram than our own cortex (or that of a monkey) in terms of our retinal response. The cat has no fovea, only an *area centralis* with a greater number of cones than elsewhere (Zürn, 1902). This is not rodfree like the primate fovea.

The most striking differences between the electroretinograms of E- and I-type are seen in flicker, or the response to intermittent illumination. The vertical line in Fig. 72 marks cessation of illumination. In the eyes (*A, B, C*) which have a good off-effect, resumption of illumination elicits a negative a-wave followed by a b-wave; however, in the cat's rod-dominated eye (*D*) the first effect of reillumination is a pure b-wave. In accordance with this, flicker in the electroretinogram of cone eyes is generally a succession a-b-a-b, while in rod eyes it tends to be b-b-b-b. This is well known (see Granit, 1947) and has recently again been confirmed by Müller-Limmroth and Andrée (1953b) and Dodt and Heck (1954b). With *mixed* eyes, using dark adaptation and low intensities, to keep well within the rod range, the flicker sequence of wavelets is b-b-b; with strong lights, which cause some light adaptation, the response changes into a-b-a-b (Granit and Riddell, 1934). At the same time the fusion frequency increases in accordance with the

likewise well-known fact that cones follow faster rates of flicker than rods.

Until recently it was thought that eyes dominated by rods could not flicker at the fast rates required by the presence of a limited number of cones, the notion being that the cone response in such eyes could not be traced below the dominating rod response. Thus, the perceived flicker of the human eye, mediated by cones, was known to run up to

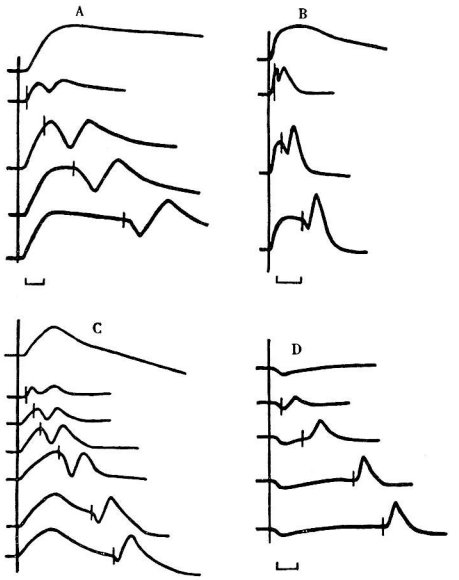

Fig. 72. Effect of increasing the interval between two stimuli on the electroretinogram of different types of retina. *A:* frog, *B:* pigeon, *C:* owl, *D:* cat. Uppermost curve of each series shows the uninterrupted off-effect; short vertical lines indicate the beginning of the second stimulus. Time marking: 1/10 sec. (Granit, *J. Physiol., 85,* 421. 1935.)

values around 70 flashes per second, while the electroretinographically determined flicker fusion stopped at around 25 flashes per second, a maximum characteristic of rods. Dodt (1951a; 1952a), however, succeeded in showing that if sufficiently strong lights were used, the electroretinographically determined flicker fusion could be driven up to the value of the cones. The stimuli naturally had to be very much stronger than those necessary for perceived flicker, in accordance with the fact that because of the large central projection area for the fovea, perception responds in terms of cone vision while the electroretinogram tends

to reproduce rod behavior based on the numerical preponderance of the rods in the periphery. Fig. 73 is from Dodt's paper and shows a slowly increasing high-intensity flicker in man, for whom the electroretinogram is well known to be of the E- or, as we henceforth would like to say, rod-type. This response begins as a monophasic b-b-b-flicker, but from the third flash it changes type and continues as a diphasic a-b-a-flicker. Between the tops of the later b-waves one notices a definite positive swing, the off-effect. This is very difficult to demonstrate with a single stimulus. The a-waves in flicker are thus very much larger

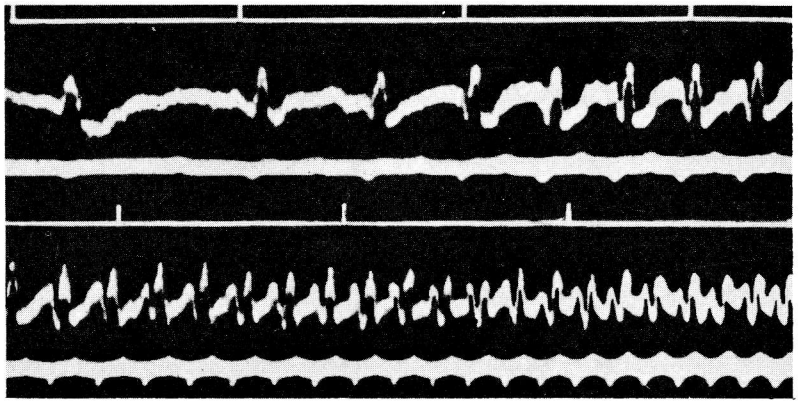

Fig. 73. Flicker in high intensity human electroretinogram. Lower curve in direct continuation of upper curve. Time in 2 sec. Stimulus duration marked below record. Onset of light downward, cessation upward. (Dodt, *Von Graefes Arch. Ophthal., 153,* 152. 1952a.)

than with nonflickering stimuli. Here, then, flicker with strong light serves to "uncover" the off-effect and emphasize the a-wave. These two phenomena seem to belong together. Very large a-waves are seen on top of off-effects, larger than against zero activity.

This is well illustrated by record *C* of Fig. 72, in which reillumination during the off-effect has taken place in the owl's eye. It is seen that in eyes with off-effects the a-waves (in response to flashes timed to fall into different phases of the off-effect) run through a maximum on top of the latter.

Why is it that flicker can uncover an off-effect and, together with it, a larger a-wave than would be normal for a single flash at this intensity (see the first flash of Fig. 73) and thus change the rod electroretinogram of the human eye into a cone electroretinogram? Part of the answer is undoubtedly that the high-intensity flickering electroretinogram is

recorded against a background of permanent illumination carried over, as it were, from one flash to the next. It is in reality one light superimposed upon another. In this way the normal rod electroretinogram can be sufficiently suppressed to release the cone electroretinogram. Long ago the same change was shown to take place in another mixed eye, that of the frog (Granit and Riddell, 1934).

The fast cone-flicker at high intensities may fuse as an a-b-flicker or a b-b-flicker. What actually happens is difficult to determine with the small deflections at the limiting point for fusion. Besides, it is a general effect of light adaptation to make the phasic components of the electroretinogram faster. Thus, in Fig. 74 the frog's eye has been stimulated with 1,800 meter candles. There is the initial a-wave, the b-wave, and the off-effect or d-wave. The same stimulus is repeated as a brief

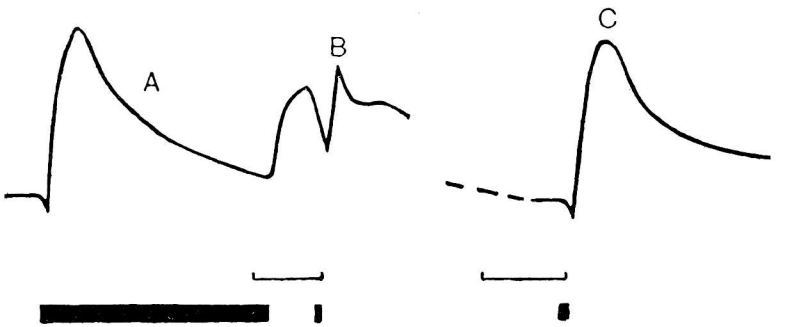

Fig. 74. Effect of a short dark interval on the b-wave produced by reillumination in the frog. *A:* original electroretinogram. *B:* b-wave produced by a flash superimposed on the off-effect. *C:* b-wave produced by the same flash 10 sec. after the end of the off-effect. Time marking: ½ sec. (Granit and Riddell, *J. Physiol., 81,* 1. 1934.)

flash on top of the off-effect as *B* and now produces a quick diphasic response a-b. The eye was left in the dark for ten seconds and then stimulation with the brief flash was repeated as *C*. The effects *B* and *C* of the same flash are vastly different; *B* is fast and the a- and b-phases of much the same relative height as compared with *C,* in which the response again has gone more monophasic and become slow. Similar changes take place in the human eye, to judge by Dodt's records of Fig. 73. But in this eye they develop on a very much faster time scale, so that in order to see the a-b-flicker and the off-effect one has to use fast high-intensity intermittent stimulation. It is possible to produce b-b-flicker and suppress the off-effect in the dark-adapted frog's eye, also, by stimulating at a very slow rate with brief flashes.

It helps to clarify matters if one considers the responses to flicker of individual elements isolated by the microelectrode technique. These have been studied by Enroth (1952). The retinal elements flicker with the off-component, if that is dominating, or with the on-component if that happens to be dominating. If one has isolated an on/off element, it flickers with both on- and off-bursts until the rate has become so fast that the on- and the off-discharges clash. If the rate of flicker is further increased, either component takes the lead and flicker goes to its final fusion point as a pure on-flicker or as a pure off-flicker. Fig. 75 is from Dodt and Enroth's (1953) later work with light-adapted cats. At slow rates of intermittent stimulation there are responses at both "on" and "off," but as the rate increases the "stronger" off-discharge takes the lead and at the point of fusion, which is as high as 60.8 flashes per second, flicker has for some time been a pure off-flicker. (By calling the off-component "stronger" or "dominating" I mean that its discharge frequency is higher and latent period shorter.) Similarly, if the on-component has been dominating, flicker will have fused as on-flicker. Both on- and off-flicker can run up to the same maximum values of fusion. It all depends upon the nature of the element. Fundamentally, both can flicker and fuse at equally fast rates. On the notion that fast flicker is cone flicker, for which more evidence will be given below, the result means that both "on" and "off" are represented in the cone system and that both become faster in light adaptation, provided that sufficiently high intensities be used. The determining factor, as shown by Enroth (1952) and confirmed by Dodt and Enroth (1953), is the impulse frequency in the individual flashes. Fusion frequency is actually directly proportional to impulse frequency, a remarkable and important generalization considering that fusion frequency, as perceived, is a measure of brightness. I shall discuss this problem in Chapter 8.

Returning now to high-intensity flicker in the electroretinogram of the light-adapted cat's eye, we may note that it rarely if ever changes into a definite a-b-flicker, as does flicker in the human eye with its greater number of cones, but generally continues up to maximal values as a b-b-flicker. Occasionally it is possible to detect true positive off-effects (cf. Dodt and Heck, 1954b). Fig. 76, from Dodt and Enroth's work, shows a flickering electroretinogram in the cat's eye running up to 50 flashes per second at fusion. Differences in the shape of the flickering wavelets of rod and cone flicker in the cat have since been studied by Dodt and Heck (1954b).

In order to show that the fast flicker actually is cone flicker, comparisons may also be made between pigeons (dominated by cones),

cats (definitely possessing cones capable of giving the cone spectrum after light adaptation), and guinea pigs (incapable of doing so). Fusion

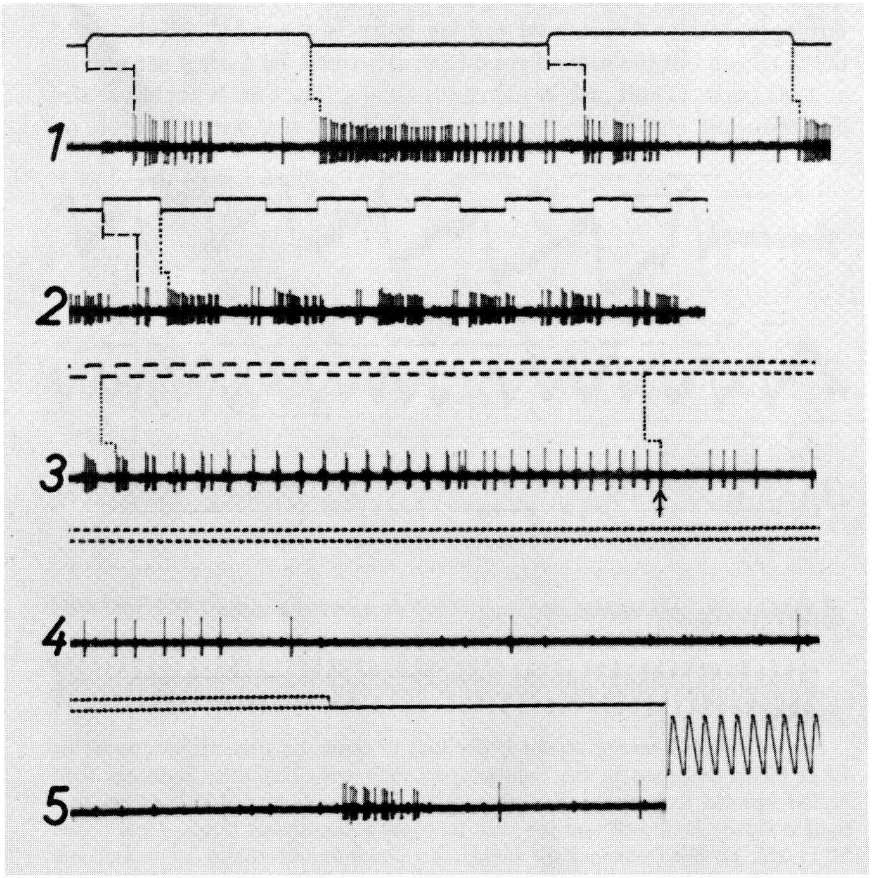

Fig. 75. Flicker response of an on/off discharge of a retinal ganglion cell during increasing frequency of intermittent stimulation. Top trace indicates light period upward and dark period downward. The off-discharge is much stronger than the on-discharge and can be traced to frequencies higher than those at which the two components clash. Fusion frequency 60.8 flashes/sec. Light intensity 7,000 lux. Time trace: 50 cy/sec. On-latency marked by *broken line,* off-latency by *dotted line,* fusion by *arrow.* (Dodt and Enroth, *Acta physiol. scand., 30,* 375. 1953.)

frequency is plotted against light intensity for these eyes in Fig. 77. The pigeon's eye is the fastest, running up to values around 140 flashes per second; the cat's curve definitely has two branches and the turning point is around 500 meter candles at the animal's eye; the guinea pig

has a very small second branch, the turning point being around 4,000–5,000 meter candles. It is quite possible that conelike rods are responsible for the second branch in the guinea pig's curve. For man the electroretinographically determined turning point is around 5–20 m.c. and the maximum of the second cone branch around 70 flashes per second at 1,000 m.c. (Dodt and Wadensten, 1954). The two branches of the flicker-fusion curve have been well known, from sensory work on

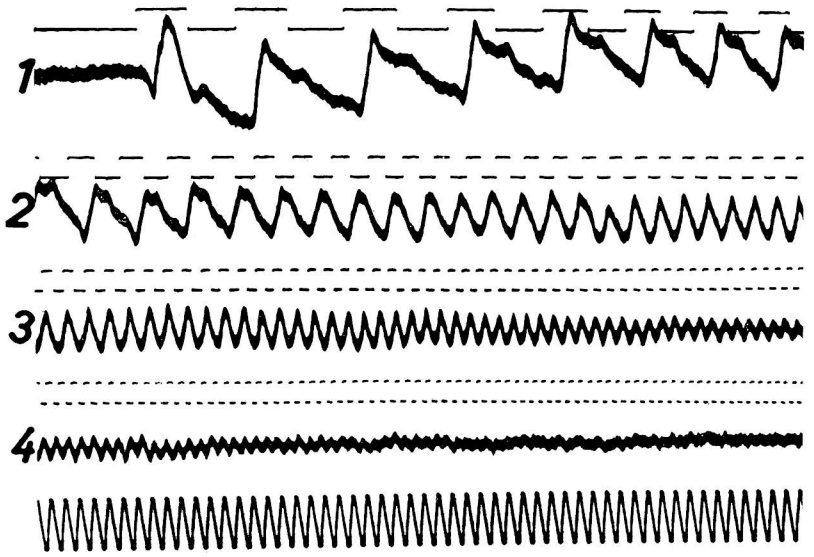

Fig. 76. High intensity record (5260 lux) to show the general features of an ERG flicker response in the light-adapted cat's eye. Top trace indicates light period upward and dark period downward. The frequency of the intermittent light is slowly increased and the records form a continuous series. Time trace: 50 cy/sec. Fusion frequency 69 flashes/sec. Urethane-chloralose cat. (Dodt and Enroth, *Acta physiol. scand., 30,* 375. 1953.)

flicker, ever since the first observations by Porter (1902). The two branches of Porter's curve, since repeatedly observed in many laboratories, were ascribed respectively to rods and cones by Von Kries as early as 1903; he supported this conclusion by experiments on a totally color-blind (cone-blind) observer. A similar observer has been studied by Dodt and Wadensten (1954) electroretinographically. Not only was the second portion after the kink in the curve missing, but at intensities above 60 m.c., when a maximum of 18 flashes per second had been reached, the fusion frequency again fell at higher intensities. In the recent work by Dodt and Heck (1954a) on the pure rod eye of the

Gecko the maximal fusion frequency was also around 20 flashes per second. The turning point of the mixed human eye in sensory flicker is, of course, much lower than in the flickering electroretinogram. Ives (1912) found it to be around 0.25 m.c., Porter around 0.1 m.c.

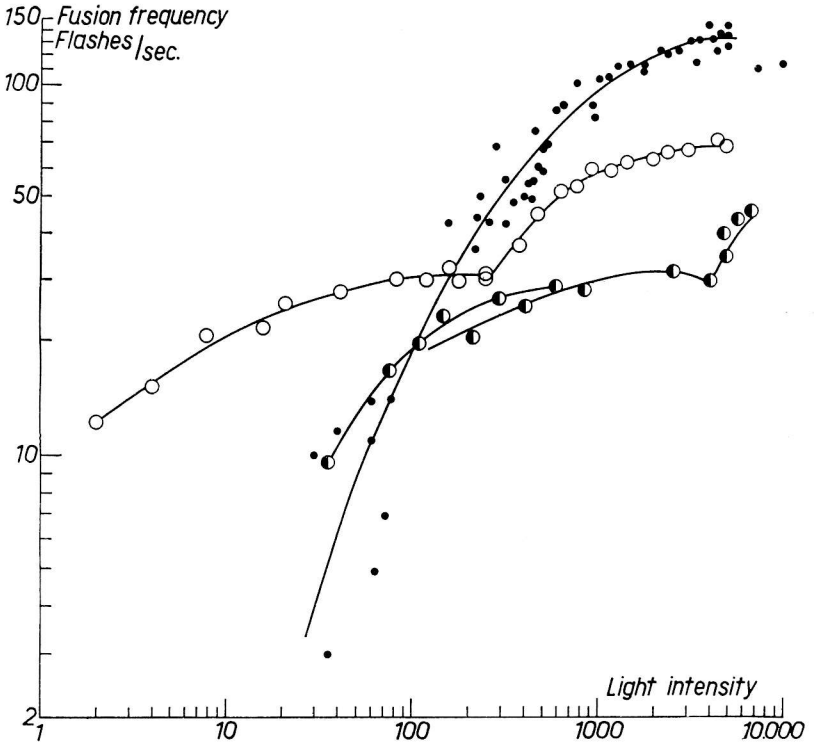

Fig. 77. Double logarithmic plot of fusion frequency of the electroretinogram against stimulus intensity in meter candles. *Open circles:* cat; *half-filled circles:* guinea pig (2 animals); *black dots:* pigeon. Replotted from data of Dodt and Wirth (*Acta physiol. scand., 30,* 80. 1953) and Dodt and Enroth (*Acta physiol. scand., 30,* 375. 1953.)

It is clear from all this evidence that the study of flicker fusion provides an excellent approach to human cone electroretinography. The electrical resonance method (Granit and Wirth, 1953) should prove useful in this work.

In the belief that intermittent stimulation is in many respects one of the best ways to establish a cone electroretinography with most mammals—including man, in which rod dominance is the normal state of affairs—I have discussed this method of "uncovering" the cones in

considerable detail. The traditional methods are of course light adaptation and determination of spectral sensitivity, by means of which, as stated above, it is perfectly easy to show that the frog's cone electroretinogram after adaptation to bright sunshine does not differ fundamentally from its rod electroretinogram in the dark. Its spectral sensitivity has, of course, shifted toward the red side. This is the well-known Purkinje shift (cf. Chapter 4) from visual purple vision with maximum sensitivity of around 5,000–5,100 Å (depending upon corneal absorption) to around 5,600 Å.

Man apparently has a sufficient number of cones to give an indication of a Purkinje shift of the spectral sensitivity to single flashes in light adaptation, as was found by Motokawa and Mita (1943, 1945). It can never become very marked because of the rod dominance in our eye (cf. Bornschein, 1952; Armington, 1953). In cats no Purkinje shift can be demonstrated by ordinary electroretinography (Piper, 1905). The electroretinogram in this animal approaches the vanishing point after light adaptation. However, the microelectrode technique brings out the shift in a certain number of elements (Granit, 1943c), and so do Weale's (1954) measurements by direct reflection from the living eye, as is shown by Fig. 54 in Chapter 4. Flicker has not yet been tried in combination with a sufficiently intense spectrum, but in view of the identity of the maximal critical frequencies in cat and man it is more than likely that the cone b-wave could be uncovered in this way also.

In man Motokawa and Mita (1942) actually found an early and fast positive wave, shown in Fig. 78, ascribed as coming from cones and labeled by them the x-wave. Later work by Armington (1952, 1953) and by Schubert and Bornschein (1952) has identified this wave with the early b-wave seen by Adrian (1945) and by him definitely proved to be due to cones. Adrian showed that the initial phases of the electroretinogram tended to be slow and monophasic in the short wave lengths (blue) and fast and diphasic in the long ones (red). In between, b-waves made up of a slow and a fast component were noted in man, pigeon, and monkey (Adrian, 1946) but not in cat, rabbit, and guinea pig, which have a smaller number of cones. This then established a method of uncovering cones (at onset of illumination) and was also in complete agreement with the early work on the electroretinogram which with different eyes had shown that a- and b-waves occurred in both cone and rod retinae and were faster in the former. The only question that remained uncertain was whether the small a-waves that were always seen in eyes with rod dominance if the stimuli were strong enough were or were not a sign of cone activity. It has already been

pointed out above that the isolated cornea-negative component PIII, of which the a-wave is the initial part, gave the rod spectrum in the dark. Later work on the human electroretinogram by Armington, Johnson, and Riggs (1952), Bornschein (1953), and Best (1953a) succeeded in demonstrating beyond doubt that the a-wave, like the b-wave, could be split up in a slower rod- and a faster cone-component. The rod a-wave has since been also confirmed with the pure rod eye of the Gecko (Dodt and Heck, 1954a). Thus, inasmuch as the initial a-b sequence of events is concerned, we can now be certain that it occurs in both rods and cones and that these events generally are faster in the latter. Further progress, no doubt, can be expected from the use of the

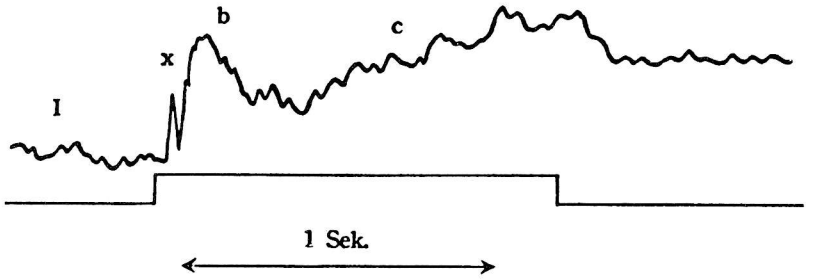

Fig. 78. The fast initial positive response (*x*) of the human electroretinogram. Red light, b-wave, and c-wave marked on record. (Motokawa and Mita, *Tohoku J. Exp. Med., 42,* 114. 1942.)

flicker method at high stimulus intensities, especially with bright spectra. There is a considerable early literature on the differences between rod and cone electroretinograms in various animals, including man (cf. Kohlrausch, 1918, 1931a; Gröppel, Haas, and Kohlrausch, 1938), of which a fairly complete review is given in my summary of 1947.

Motokawa and Mita's x-wave * was obtained with the electrode on the bridge of the nose (Motokawa and Mita, 1942), which may have recorded from both eyes, and so some workers, including myself, were uncertain of its significance, even though I was aware of Adrian's results, referred to above; and Munsterhjelm and I (1937), using a spectrum, described multiple b-waves in the frog's eye as well as slow and fast off-effects. However, Schubert and Bornschein (1952), with the contact glass electrode, set out to investigate this question and soon found that the x-wave could be obtained in the normal, hemeralopic (rod-blind) and deuteranopic eye but not in the protanopic eye. This was very definite evidence in favor of its being due to cones. Moto-

* This work did not become available until after the war.

kawa and Mita (1942) stated that their x-wave was equally definite in protanopes and deuteranopes. Armington (1952) emphasized the fast b-wave (x-wave) by using a fast coupling condenser in his amplifier and by this means found an expansion of sensitivity to red light when determining the spectral distribution of the b-potential in man. This was absent in the protanopic eye. He also (1953) found the electroretinograms of two night-blind observers to be less sensitive to blue light. Taken as a whole, these observations suggest that the fast b-wave is merely one of several cone components—possibly red cones only—and that the eye of man, like that of the frog, is capable of responding with component b-waves of different rates of rise and spectral sensitivity, but that those produced by blue-sensitive and visual purple receptors are the largest of all and therefore normally dominant. Elsewhere I have reviewed the evidence for the connection between blue sensitivity and visual purple sensitivity (1947; cf. Riggs, Berry, and Wayner, 1949).

Recently Best (1953b) has developed an interesting technique of recording with the same microelectrode—applied to the cat's retina—the spikes and the electroretinogram simultaneously. The light was projected *through* the microelectrode, and thus an area of less than 0.1 mm. was illuminated. From different places very different types of electroretinogram were obtained. In most records a definite a-wave was seen, and the spikes appeared to coincide with the rise of the b-wave.

4. *The components of the electroretinogram*

The components PI, PII, and PIII were presented in Fig. 71 for the frog's eye. This interference construction shows the cornea-negative a-wave to be the early onset of PIII, interrupted by the rise of the cornea-positive PII responsible for the b-wave. The slow PI responsible for the c-wave has been greatly clarified by Noell (1953). Inasmuch as different latencies and rates of rise are represented among the responding structures, e.g. the differences mentioned above due to rods and cones, the fast components PII and PIII of opposite sign will be split up in a corresponding fashion, since the evidence available shows them to be associated with, respectively, excitation and inhibition (see Granit, 1947, 1952b; Noell, 1953). The multiple b-waves and off-effects of the frog's eye were well known in 1937 (cf. above), yet I did not consider it necessary to include them in the general diagram of the analysis. The latter was meant to raise the general question of whether

such components represent homogeneous events in the sense that they can (1) be referred to definite structures and (2) ultimately be physicochemically explained.

My view in 1947 was that PI and PII probably were such homogeneous events or processes but that PIII apparently represented two separate events of the same electrical polarity, two components in one. The difficulties were pointed out in detail, with a full discussion of alternative localizations and all arguments pro and con the unitary view of PIII (pp. 109–19), some of which since have been summarized by Cobb and Morton (1952). It was explicitly pointed out (Granit, 1947, p. 113) that we did not know the final answer to the complicated questions raised.

The most systematic recent attempt to throw fresh light upon the components of the electroretinogram, as recorded with standard leads, is that of Noell (1951, 1952a,b, summarized, 1953), which in many respects has deepened our understanding of the complicated problems involved. The work has been carried out (under histological control) with three substances, sodium azide (NaN_3), iodoacetate, and sodium iodate, generally injected intravenously into rabbits.

1. *Iodoacetic acid* (IAA) abolishes vision and the discharge in the optic nerve within a few minutes after an injection and, if the spontaneous elimination of the substance is delayed by a second injection, the effect becomes irreversible. Histological examination of the eyes several weeks after the injection shows widespread disappearance of the visual cells, while the inner layers generally are well preserved.

2. *Sodium iodate* produces a severe reduction of vision, developing within hours or days. Its first and strongest effect is on the pigment cells. Histologically, there is widespread deterioration of the pigment epithelium and degeneration of the outer limbs of the receptors.

3. *Sodium azide* injected in as small a dose as from 10 to 20 mg. produces a slow potential rise of the type and sign of the c-wave, reaching maximum values as high as 20 mV. The threshold dose is only 0.005 mg. While judiciously combining the effects of these fairly selective poisons, Noell followed the retinogram, optic nerve response, and histological changes.

The principles of the analysis are easiest to comprehend if a beginning is made with its contribution to the understanding of the generation of PI, the slow component responsible for the c-wave, which Therman (1938) showed could be activated by adrenaline. In 1947 a number of facts were held to favor the view "that PI appears early

in the chain of events initiated by stimulation of rod receptors" (Granit, 1947, p. 112). This component did not seem to be directly associated with excitation or inhibition of the impulses in the optic nerve.

Fig. 79, fully explained in its legend, illustrates stepwise injections of azide while tests with illumination at two intensities are repeated. The effects on the initial a- and b-waves are of a minor order in comparison with the enormous increase of the slow cornea-positive c-wave. Azide, as stated, almost instantaneously raises the slow d.c. potential of the eye, and this effect is independent of whether the receptors have been previously degenerated with IAA or still are present. Azide cannot therefore act by creating a direct current change referable to the receptors. Since, however, the c-wave of the retinogram can be tested only by illumination, it is impossible to use eyes without receptors for this particular type of test, but iodate can be injected to destroy the pigment epithelium and, if this is done, azide injections cease to be effective. Simultaneously, the c-wave disappears. The inference is that the latter (PI) is dependent on the pigment epithelium, thus on a structure peripherally relative to the receptors and not likely to be of immediate significance for the discharge, except indirectly by the polarizing currents set up by this comparatively large potential change (Noell, 1953). It may, however, be of considerable significance for the visual purple mechanism. As such the pigment epithelium can hardly be the actual seat of PI, because a microelectrode within the pigment layer does not record any response (Tomita, 1950).

Iodate, in addition, acts on the outer limbs of the receptors, but this effect is slow. In Fig. 80 the left vertical column shows the initial a- and b-waves taken at fast sweep speeds, the middle column the full retinograms at slower sweep speeds, and the right column the effect of injections of azide. Under the gradual influence of iodate the c-wave disappears and is replaced by a large cornea-negative slow potential while, as the right column (bottom) shows, the retina has become insensitive to azide. The changes in the initial a-b-complex during the same time are of a much smaller order. This azide-insensitive cornea-negative potential in response to illumination is apparently present from the beginning (see below) and revealed by the effects of iodate on the pigment epithelium. Previous degeneration of the ganglion cells by optic nerve section has no influence on any retinal potential, as is also suggested by the failure of my many attempts (see Granit, 1947) to influence the retinogram by antidromic stimulation of the optic nerve as well as by clinical experience (Karpe, 1945) with optic nerve diseases (see also references in Noell, 1953).

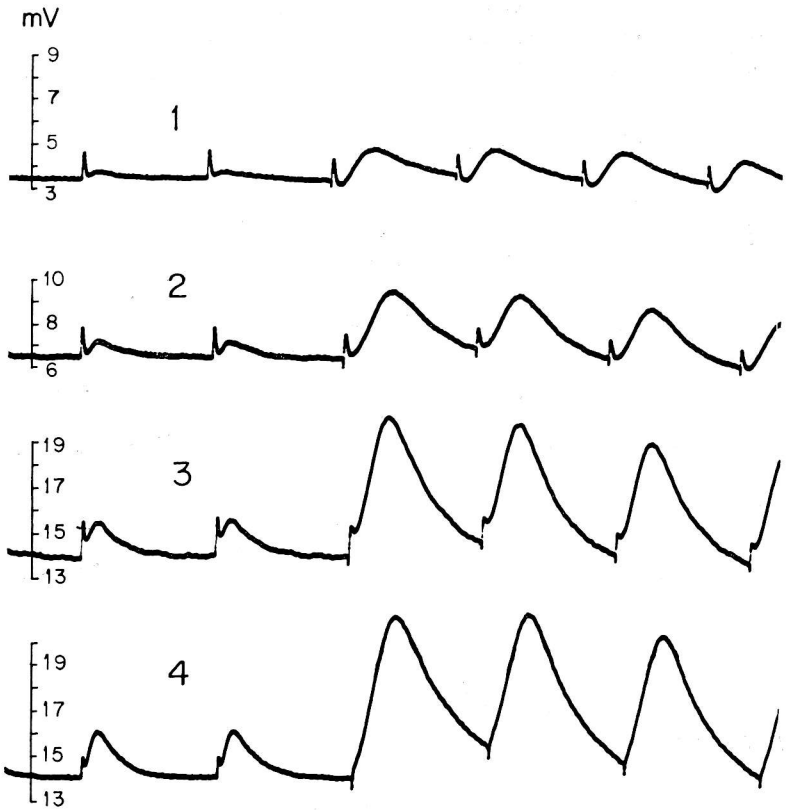

Fig. 79. Effect of azide on the a-, b-, and c-waves. Rabbit. The potential across the eye is recorded by DC amplifier. The eye is exposed to low intensity flashes (I-1/100), once every 4 sec. At the illustrated periods the intensity of the flash is transiently increased 100 times (the two left-side responses are with I-1/100, the following with I-1). Azide is administered intermittently throughout the experiment, resulting in stepwise increases of the DC level. Tracing 1 is recorded after the DC potential has been increased by 1.3 mV. from control value in response to 2.5 mg. NaN_3; tracing 2 is recorded 26 minutes later after a total of 10 mg. has been injected since start of the experiment; 3 is recorded 59 minutes after 1, when the total amount of the injected azide has reached 55 mg.; 4 is recorded 17 minutes later after additional administration of 30 mg. in 3 injections. Note the additional increase of the c-wave in 4 while DC responsiveness has diminished and the b-wave has been reduced. The animal is anesthetized by urethane and artificially ventilated under curarization. (Noell, Studies on the electrophysiology and the metabolism of the retina. USAF School of Aviation Medicine, Randolph Field, Texas. 1953.)

It was pointed out above (cf. Figs. 70 and 80) that the electroretinogram often swings toward the cornea-negative side after the b-wave. In some animals the state of balance between the cornea-

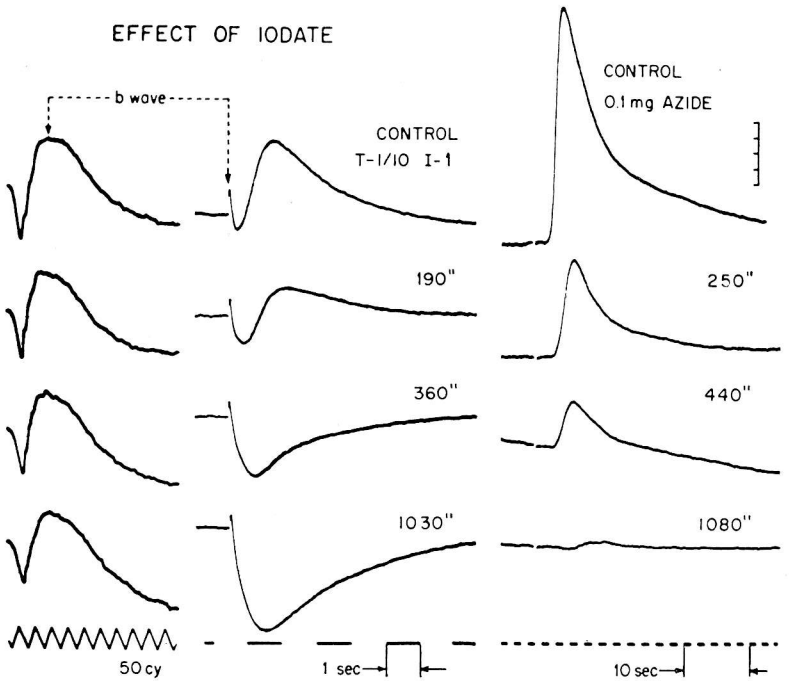

Fig. 80. Effect of iodate on c-wave and azide response. Rabbit, right eye; electrodes across eye-bulb, DC amplifier. Left column shows on single sweep the a- and b-waves of the ERGs of the middle column. The light stimulus has a duration of 130 msec. Amplification of left column is higher than middle column. Right column presents the responses to 0.1 mg. NaN_3 in 2 cc., injected rapidly into leg vein; the interruption in the baseline marks the time of azide injection. Amplification is the same in middle and right columns; the time base differs. After the control tracings, 3 cc. of a 5% iodate solution were administered intravenously. The numbers beside the tracings give the time in seconds after iodate. Vertical scale is 0.1 mV. units. (Noell, Studies on the electrophysiology and the metabolism of the retina. USAF School of Aviation Medicine, Randolph Field, Texas. 1953.)

positive PI and the cornea-negative azide-insensitive potential seems to be displaced in favor of the latter. Fig. 81, from Parry, Tansley, and Thomson's (1953) paper, compares dog and rabbit. These authors also came to the conclusion that their large negative change was not identical with the one responsible for the a-wave. It is evident, however, that

both a-wave negativity and the azide-insensitive potential fall into the category of PIII, which therefore would be made up of a fast and a slow cornea-negative component, just as the opposite cornea-positive potentials are made up of a fast (PII, b-wave) and a slow (PI, c-wave) component.

Turning now for a moment to the old evidence suggesting two components in PIII, we find interesting parallels that should be worked out by further experimentation. PIII was produced by asphyxia or potassium chloride, and in both cases it was often found to linger on after illumination and return more slowly to the base line than a receptor

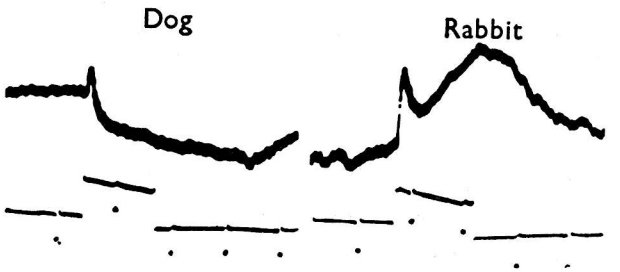

Fig. 81. A comparison of the electroretinogram of red Irish setter and rabbit. The upper tracing in each record gives the electroretinogram, and the lower, the time mark. The light is "on" when the time tracing is displaced upward. The record shows that the normal positive c-wave of rabbits is replaced by a negative potential in dogs. Time mark: 0.5 sec. Calibration: 50 μV. (Parry, Tansley, and Thomson, *J. Physiol., 120,* 28. 1953.)

potential might be expected to do. This was called "remnant negativity" (Granit, 1947, pp. 55, 132). The many available records of pure receptor potentials, as e.g., Fröhlich's of the cephalopod eye and Hartline's (1928) of *Limulus* (see Chapter 1), showed a relatively fast return to the baseline after illumination and the receptor potentials did not increase during illumination, as did PIII. Also, PIII had the property of practically no adaptation, being easily re-established by re-illumination. At the time, however, our interest was directed toward those changes of potential which showed some correlation with excitation or inhibition in the optic nerve, and so the very slow phenomena were neglected, particularly in potassium-treated retinae, in which there was no impulse activity left to correlate them with. However, Fig. 82 (Granit, 1938) shows the slow course of "remnant negativity" in one of the experiments by Granit and Therman, in which the fast negative dips of reillumination during the cornea-positive off-effect are super-

imposed upon a slow negative change. The experiment refers to the potassium-treated frog's eye stimulated with monochromatic green light at maximum strength of our Hilger-Tutton monochromator.

Noell's (1953) observations also show that the c-wave has little if any direct effect on the optic nerve discharge, and his slow azide-insensitive negative potential does not seem to be directly concerned

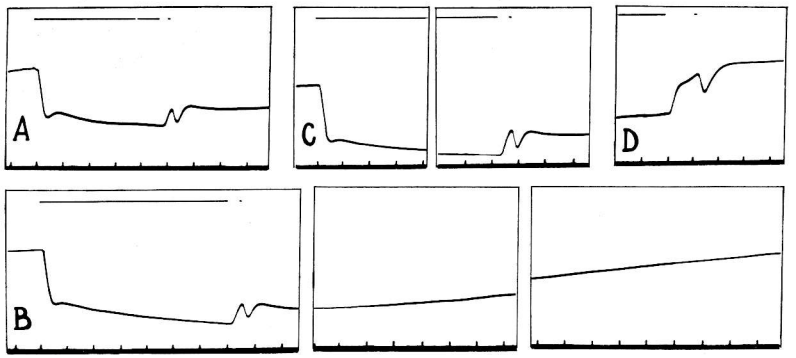

Fig. 82. Original photograph (cathode ray oscillograph) of electrical responses of frog's retina after treatment with potassium. *A:* exposure of about 4.8 sec.; *B:* 7.2 sec.; *C:* about 12 sec.; *D:* off-effect alone after exposure of 60 sec. Rate of recovery followed in *B,* in which two intervals of 5 sec. each have been cut away from the film. From film *C,* likewise, part of the electrical response is cut out. Time in seconds below. Upper line is photograph of stimulus.

Note: In record *A* small positive deflection is clearly visible. Off-effect increases with length of exposure. In each case a flash on top of it causes a large negative deflection ("negative notch") which does not reach the maximal level of negativity of PIII. Early in the same experiment it did reach it. (Granit, *Docum. Ophthal., 1,* 7. 1938.)

with it. For this reason, in addition to others mentioned above, these slow changes, which in relation to the fast ones are bigger by a factor of from 3 to 5, can hardly be ascribed to any system placed on the route of the excitatory or inhibitory disturbance down to the nerve. Noell locates both in the pigment epithelium, which is in contact with the outer limbs. These changes play a great role for the resting potential across the retina.

Differentiation of PIII into an early and a late component with different time constants is also suggested by the effect of IAA, the substance destroying the receptors. IAA is combined with iodate in Fig. 83, in which 1 is the control before iodate, 2 the response after iodate which has removed PI (c-wave) and laid bare the azide-insensitive,

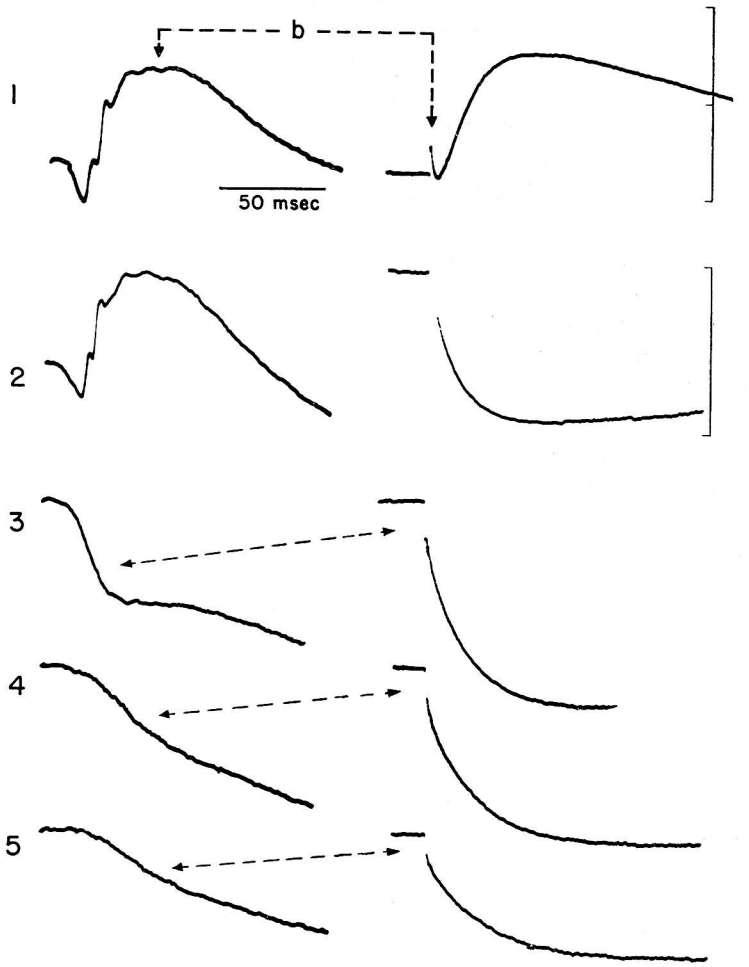

Fig. 83. Effect of IAA on the isolated, slow, azide-insensitive potential. Left column presents the a- and b-waves of the ERGs of the right column. Both tracings are obtained with DC coupled amplifiers; the a- and b-waves are recorded with higher oscilloscope gain than the ERG of right column. 1: control 12 minutes before administration of 3 cc. of a 5% iodate solution; the DC level is 2.2 mV.; 2: 15 minutes after iodate and 3 minutes prior to the administration of 20 mg/kg. of IAA; the DC level is 2.5 mV. 3: 5 minutes after IAA; DC level is 2.9 mV.; a small fraction of the b-wave has survived. 4: 9 minutes after IAA; DC level 2.8 mV.; the b-wave has disappeared; a-deflection and slow cornea-negative wave are preserved. 5: 15 minutes after IAA; DC level 2.7 mV.; a-deflection and slow negative wave are reduced in amplitude. Vertical scales: 1 mV. units. (Noell, Studies on the electrophysiology and the metabolism of the retina. USAF School of Aviation Medicine, Randolph Field, Texas. 1953.)

slow, negative component. At this stage the fast initial changes are hardly affected at all. Injection of IAA quickly removes the b-wave (PII) and with it excitation through the retina into the optic nerve, but the fast and slow negative changes to illumination are present for some time. The progressive lengthening of the latent period suggests interference with the fast component. The dose was not large enough for instantaneous removal of any change other than PII.

PI or the c-wave is held by Noell to be the expression of a process of *active* ion transport across the pigment epithelium, which thus is of great importance for the retinal resting potentials (recently studied also by Wulff, 1948, and Müller-Limmroth and Lemaitre, 1953). Its allocation to the pigment layer depends upon the experiments and arguments reviewed, in particular upon the inverse correlation between effects of the azide injections and the amount of epithelial destruction by iodate. The azide-insensitive, cornea-negative component is assumed to be a *passive* ionic transfer, emphasized when a specific "membrane" function of the epithelium has been destroyed. It is impossible to go into further details of Noell's theoretical interpretations. Clearly most important metabolic processes are involved, which probably also take part in the synthesis of the photosensitive substances in the outer limbs.

Light adaptation is known to remove PI, but this may now be interpreted as—partly at least—due to a shift in the state of balance between it and the azide-insensitive, slow, negative change. Long ago (1933) I found that PI in cats could be selectively removed by ether. This could only be demonstrated by high-intensity responses and at a stage of anesthesia in which low intensity responses still were normal and wholly uninfluenced. Accordingly, in this species PI must be a high-intensity response. The c-wave is also known to require flashes of long duration (see e.g. Dodt, 1951b; Noell, 1953). These simple modes of approach, consisting of variations of stimulus intensity and flash duration, which require no drugs, have not yet been sufficiently utilized for removing slow components. For instance, it is unknown to what extent the slow negative component in this respect behaves like the slow positive one.

Cobb and Morton (1952) and, independently, Rendahl (1952) have done some work along these lines on man. Very strong brief flashes have been used, and these emphasize the initial negative a-wave. Cobb and Morton report a latency as short as from 4 to 7 msec. for the a-wave (cf. also Einthoven and Jolly, 1908). A set of their records is shown in Fig. 84 for different intensities, illustrating clearly that the

large negative response may very well consist of two components. "Notching of the first three phases is considered to be evidence of the dual nature of PIII suggested by Granit" (Cobb and Morton, 1952). This method would seem to be the ideal approach to separation of fast and slow PIII.

The description of the slow components of the electroretinogram would be incomplete if it were not pointed out that Noell (1953) also

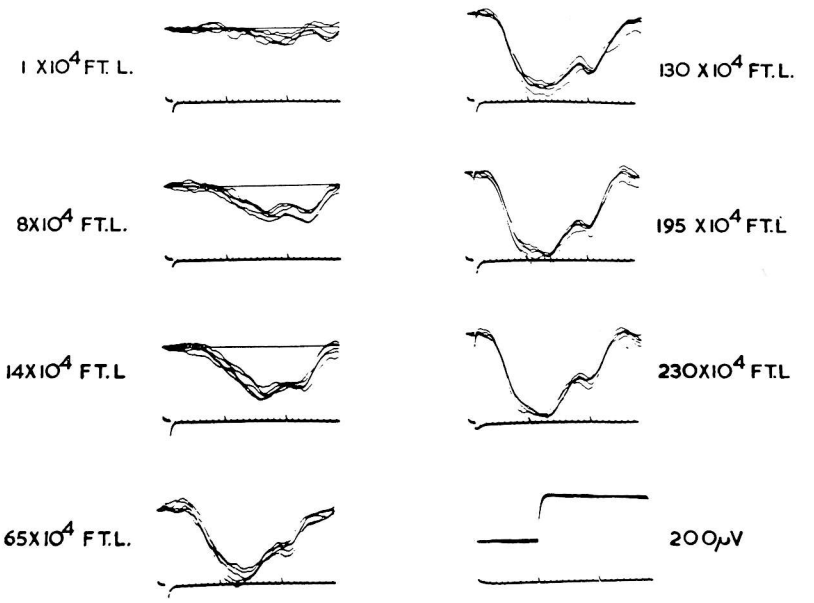

Fig. 84. Electroretinogram of human eye to photoflash at the intensities marked beside records. (By courtesy of W. Cobb, National Hospital, London.)

has found slow reversals of these changes at cessation of illumination, but for these the reader is referred to the original paper. It is impossible to take up here the whole of Noell's extensive work, which is richly documented and charged with perspectives for future experimentation, particularly with regard to retinal metabolism and mechanisms of ion transfer in relation to changes of potential.

It is, however, of some interest in view of the connection between the fast positive and negative potentials with excitation and inhibition, to consider his evidence for allocation of the a- and the b-deflections, PIII and PII (in Noell's sense), to specific structures. Noell identifies

his two opposite "fast" potentials with PII and PIII, and distinguishes them from his two opposite "slow" potentials, one of which is PI. Removal of the fast negative and positive components by IAA, which destroys the visual cells, is perhaps not so easy to interpret because absence of receptors means that stimulation by light is impossible. Iodate influences the receptors more slowly and selects the outer limbs, which in the histological pictures appear degenerated. In Fig. 85 (bottom) are presented the normal controls of the a-b-complex together with the same responses four days after the injection of iodate. *A* and *B* (above) are the histological controls of the eyes of the iodate-treated animals, from which the responses *A* and *B* (bottom, on the right) were obtained just before removal of the bulbs on the 4th day. Noell rightly draws attention to the "surprising discrepancy between the maintenance of the electrical reaction in response to illumination and the severity of the rod damage" in the eye of an animal such as the rabbit, for which the response actually is dominated by rods. We have seen above that a very large number of receptors is necessary for the recording of an electroretinogram. The whole literature on visual purple in the retina (summarized, Granit, 1947) goes to show that this light-sensitive pigment is found only in the outer limbs. The records and slides of Fig. 85 would be wholly unintelligible if any mechanism responsible for PII were a membrane potential across boundaries in the outer limbs of the receptors. Indeed, it is difficult enough to understand how visual purple can exercise its effect on what is left of the receptor, but it may well be that very little of this extremely light-sensitive substance is required for stimulation with supramaximal stimuli. After all, only a few quanta are needed for a threshold effect (see above, Chapter 4, sec. 6).

In one monkey Noell (1953) also destroyed the central ophthalmic artery aseptically, so that the vessels collapsed and immediate blanching of the retina occurred. Three weeks later the electroretinograms of both eyes were recorded and the injured eye removed. Both a- and b-waves were present, the latter reduced to a third or a quarter of its original size, the former very much less reduced but slower. The sections showed reduction of the bipolar nuclei and degeneration of the ganglion cells. The visual cells were entirely normal, the outer nuclear layer had normal width. Fundamentally, this retina was capable of giving fast PII and PIII, the latter much better preserved, which fact, together with the evidence of Fig. 85, limits the generation of PII to the outer plexiform layer and, at the other end, to the *inner* limb of the receptors, while PIII in accordance with earlier evidence and Noell's

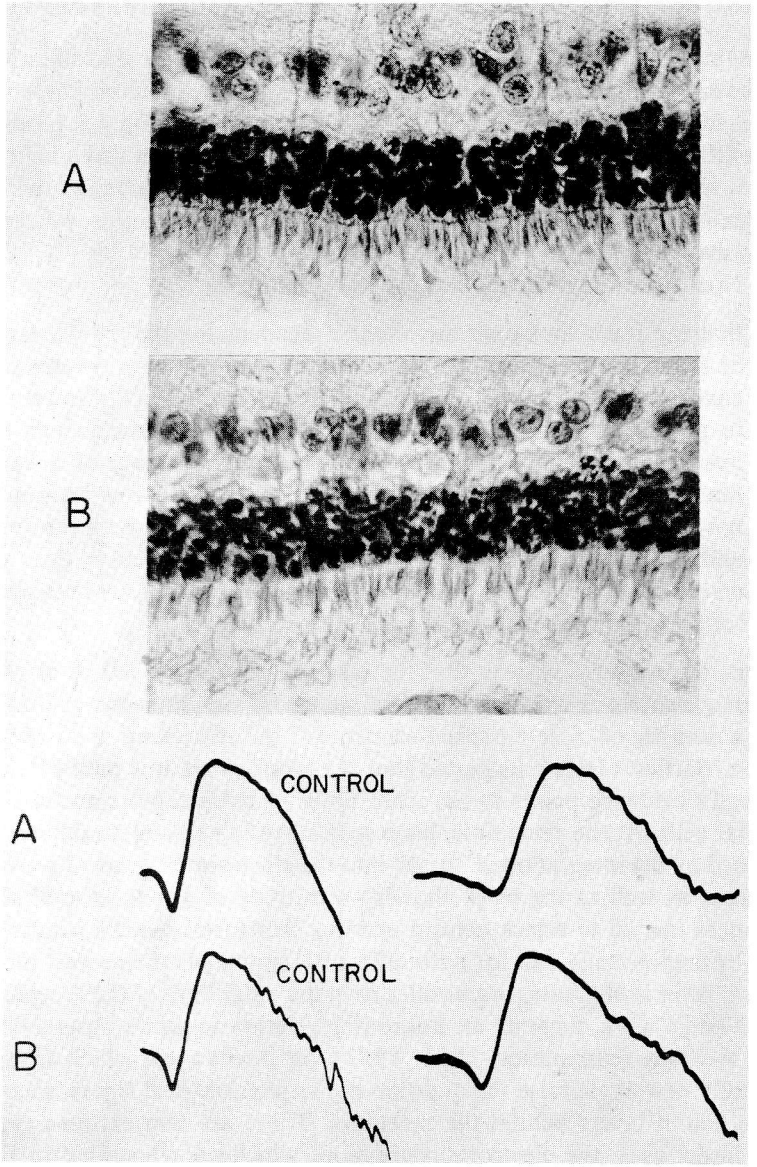

Fig. 85. The two reproductions of retinal sections (*A, B*) show visual cells and ERG from two animals on the 4th day after iodate administration, the control electroretinograms of which are *A* and *B*. *Hematoxylin-eosin* × 770.

ERG was recorded by cotton thread electrodes from the cocainized cornea. The animal is unanesthetized. The right column gives the ERG tracing on the 4th day just before enucleation. Same amplification and sweep speed as in the control. (Noell, Studies on the electrophysiology and the metabolism of the retina. USAF School of Aviation Medicine, Randolph Field, Texas. 1953.)

results probably is located further toward the receptor end than PII. The most striking result, however, is the fact that the intact visual receptors in this experiment, to be compared with the one of Fig. 85, produce so little PII. In Noell's own words: "It is unequivocal in revealing that the sensory organelles—isolated from functional processes within proximal portions of the pathway—are unable to generate a normal b-wave potential."

Noell accordingly concludes that his assumption

> that the inner limbs are an essential element for the manifestation of a- and b-waves must take into consideration that physico-chemical changes in the vicinity of the inner limbs seem equally important in producing these electrical reactions and that consequently the inner limb can only constitute one 'electronic' element of the current produced. In case of the a-wave, current flow would probably not develop without specific reaction at the linkage between inner and outer limb, and similarly a b-wave current probably does not ensue unless structures proximal to the inner limbs [i.e. outer plexiform layer] participate in the excitation process.

It is, of course, necessary that the large currents recorded as electroretinograms in response to light be set up by simultaneous excitation of a number of closely packed elements of the same kind and orientation. Bartley (1941) suggested that the bipolars are this pathway, but Noell's evidence points to the inner limbs of the receptors and the bipolar cells. At the same time, his results serve to explain the difficulties raised by the integration of "area" into the electroretinogram, discussed above, as well as the work showing sensitivity of PII to several substances known to attack central nervous structures. Noell's results do so by emphasizing that for normal fast PII potentials the nearest plexiform layer is of greater importance than the outer limb of the receptors.

Noell's work suggests an interesting relation to some observations by Autrum (summaries, 1951, 1952) on insect eyes, which from a wholly new angle raise the question of the physiological significance of the neural layers behind the receptors. There are two extreme types of insect eyes, the electroretinograms of which are illustrated in Fig. 86, from Autrum's work. One type, represented in the figure by *Tachycines,* gives a very simple cornea-negative response to illumination, the other, *Calliphora,* a positive-negative deflection to a flash and in addition a complex off-response at cessation of illumination. To the latter type belong flies and bees, which Autrum finds follow high-intensity flicker up to 200–300 flashes per second, depending also upon

temperature. *Tachycines,* however, cannot follow faster rates than 20–30 flashes per second. If the ganglionic layers, including the one nearest to the receptors, are removed in *Calliphora* (Autrum and Gallwitz, 1951), its eye reacts with the monophasic response of *Tachycines.* This confirms an experiment of the same type in our laboratory by Bernhard (1942) with the similarly responding eye of *Dytiscus.* Autrum and Gallwitz, however, proceeded to remove the different ganglionic layers stepwise while determining the fusion frequency. The intact eye gave a flicker-fusion frequency of around 250/sec.; after removal of two of the ganglionic layers this value fell to 170/sec.,

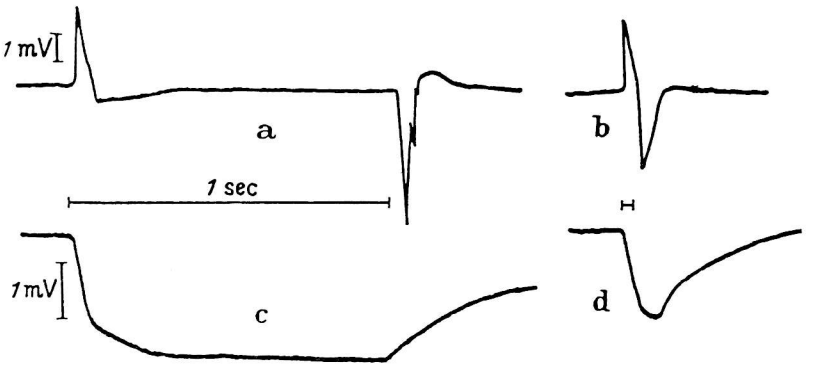

Fig. 86. Electroretinogram of *Calliphora* (*a, b*) and *Tachycines* (*c, d*). Stimulus duration in *a* and *c* 1 sec.; in *b* and *d* 1/20 sec. (Autrum, *Naturwissenschaften, 39,* 290. 1952.)

although the eye still gave complex responses to "on" and "off." When finally the pure monophasic receptor response had been isolated by removal of the nearest ganglion layer, the fusion frequency was only 10/sec.

These results suggest that the ganglionic components play an essential role in fast flicker. A remarkable confirmation of this conclusion was obtained with *Aeschna cyanea.* At the larval stage the first ganglionic layer is found at a distance from the receptor layer, the response to illumination is monophasic, and the fusion frequency is around 40. In the course of the insect's development to imago the first neural layer approaches the receptors, ultimately to become located just below them. The fusion frequency is then found to have risen to 175 and the response has become diphasic. Autrum concludes that the electrical processes in the ganglionic layers serve to restore the capacity of the receptors to respond to light, and he develops a tentative hypoth-

esis to explain how this occurs. For details I refer to his summaries. The important points in this connection are: his actual evidence for interdependence of potential changes in adjacent retinal layers, the demonstration of a definite functional role for this interdependence, and many suggestions for further work entailed in the results. The parallel to Noell's observations on a retina degenerated from "behind" is obvious and suggestive.

Are there any other results with vertebrate eyes that should be recalled in this connection? Long ago Creed and I (1933), while studying flicker in the cat's eye, removed the positive component PII with ether or asphyxia. We found the remaining negative PIII incapable of flickering. The result was surprising and inexplicable. It may be that the pathological condition had been carried too far by these methods of interference, so that only the slow cornea-negative component remained, but "the possibility that PII and PIII interact, when present together, is not excluded" (Creed and Granit, 1933, p. 430). In the frog's eye a PIII isolated with urea (Müller-Limmroth, et al., 1953b) seems capable of flickering, but there again one must raise the question of whether it actually was wholly free of PII and whether, if so, different methods of removing PII have a different effect on PIII, depending upon what they do to the nearest neural layer. Zetterström (1951) has made the interesting observation that the electroretinogram is absent in newborn children and slowly increases in size during the first 6–7 months, to become normal (initial phases studied) at an age of around 12 months. In prematurely born children it may last up to a fortnight before any response to light appears (Zetterström, 1952). The small electroretinograms of infants are also slow and wholly monophasic (b-waves). They cannot follow the fast flicker of the fully developed response (Zetterström, personal communication). Histological controls are not available, but at the outset it seems difficult to account for such results on the notion that the receptors—if they generate PII and PIII—would be deficient for half a year.

These observations are mentioned because they suggest that Autrum's idea of a kind of electrotonic feedback control of one layer by another deserves to be followed up experimentally in vertebrates. Such control would, indeed, provide a *raison d'être* for what now appears merely as a freak of nature, namely the addition to the retina of a nervous center that otherwise might just as well have been placed further "upstream" together with all other nervous centers. Electrical feedback mechanisms, all of which are run by nervous loops carrying impulses, are discussed in several places in these lectures (particularly

Chapters 3, 6, and 7). Similar effects may be carried equally well by electrotonic currents. I would not be surprised if work along these lines would soon be rewarded with success by the opening of a new chapter in electroretinography and lead to deeper understanding of the mode of function of our noblest sense organ.

For the sake of completeness it seems necessary to refer briefly to the attempts to study the vertebrate retina with penetrating microelectrodes under microscopic control, initiated by Tomita and his collaborators (Tomita, 1950; 1951–52). This line of work has since been taken up by Ottoson and Svaetichin (1952) and Noell (1953). At the moment there seems to be little agreement between the various workers, making it exceedingly difficult to review the results. Tomita and his collaborators, as well as Noell, critically discuss the volume conductor and the difficulties arising from the fact that all active cells are the seat of potential changes. They are also fully aware of the differences between the recording of a mass response and a more or less punctual lead, while Ottoson and Svaetichin identify the two and state that cones and rods produce monophasic potentials of opposite sign, which means identifying the positive PII with the rod response and the negative PIII with the cone response. Since it is well known that pure cone as well as pure rod retinae respond with both PII and PIII (see above), it is difficult to know just why they have lost the cornea-positive part of the cone response and the cornea-negative one of the rods.

In order to indicate briefly the nature of the difficulties encountered, some further comments might be made. Tomita, for instance, in pushing his microelectrode in from the side of the vitreous, finds that the a-wave goes through a minimum of potential, then disappears, and finally, on the other side of the bipolar layer, reverses its sign. On this basis he suggests that the microelectrode has approached, reached, and passed an electrical doublet in the bipolar layer, which is contradictory to Svaetichin's notion that the a-wave is part of a pure cone potential originating in the receptors. Svaetichin (1954a,b) and Ottoson and Svaetichin (1954) have also inserted fine microelectrodes from the receptor side of the eyes of fish (cones and rods) after scraping away the pigment layer. Their microelectrodes, finer than those of Tomita, cause less damage but may easily bend, and since the distance between the two limiting membranes is only 170μ, of which near the m. limitans externa 30μ is occupied by the bipolar cells, it is difficult in the absence of controls to be certain about this point. Ottoson and Svaetichin's (1954) diagram (their fig. 5) actually shows that when a microelectrode —recording against a second electrode on the surface of the receptor layer

—is pushed into the retina, the response begins to diminish rapidly from a point 100μ from the inner limiting membrane. At this point there would be no reason for a pure receptor potential to decrease, whereas this clearly would happen if the response were dependent upon both bipolars and receptors considered as "electronic elements" in Noell's sense. This result does not therefore seem to support their inference, which is that the electroretinogram originates in the receptors only. There can be no doubt whatever, of course, that receptors are electrically active, but it requires strict experimental comparisons between macro- and microleads before events in the two can be identified. Svaetichin (1954a) concludes that in pushing his microelectrode into a fish retina in which the pigment layer has been scraped away, he is recording the response of single cones. A very curious finding in this work is two kinds of "contact potentials," "expression of the characteristics of the material in the cell wall." There are both negative and positive surface materia, the negative materia on the outer segment of the receptor, the positive on the inner segment. The cone potential, which is a membrane positivity generating impulses (in contradistinction to results by others reviewed in Chapter 1), appears mainly at 40μ and 70μ. What makes it so difficult to interpret this work is the fact that it differs from, say, Katz's experiments (Chapter 1) in that the electrode tips are invisible. Yet Svaetichin claims to establish differentiation by 30μ. Concepts such as negative and positive surface materia, which are unique in the steadily increasing literature of work with outside and inside microelectrodes, suggest bending of the electrodes, bending of the receptors (left over after removal of the pigment), or simply variations of resistance (uncontrolled) in the small microelectrodes, with consequent variations of grid current. It would also seem more natural to study the cone action potential in a cone eye rather than in a damaged mixed eye. However, it seems certain that the opposite potentials, recorded from 1865 onward by so many experimenters (discussed in the last section of Chapter 1), also can be obtained by microrecording within the receptor layer. As such, the microelectrode is as sound an approach as any other, although it should be realized that it is elective and fails to provide answers to many of the problems raised by Autrum's and Noell's work reviewed above.

Chapter 6

Muscle Receptors and Their Reflexes

1. Introduction

THERE are several reasons why, in my desire to present one system of input-output relations with relative completeness, I should choose muscle receptors and their reflexes rather than e.g., skin or vestibular organs. First of all: with my discussion of this field I want to pay a tribute to the memory of my teacher, Sir Charles Sherrington, who has a greater right than any other physiologist to be called its pioneer and founder. The early fundamental results were presented in his Silliman Lectures delivered 50 years ago (published 1906), but many important observations were made later—indeed, as late as 1925 by Liddell and Sherrington. Again, problems of muscular receptivity and muscle reflexes have for something over a decade interested several laboratories in the United States as well as my own laboratory and for this reason, too, the theme seems fitting. Finally, we have a considerable number of new facts to weld into a preliminary integration, and it would seem of some interest to point out the deficiencies in our knowledge.

In 1945 the problem of centrifugal or motor control of muscle afferents was raised from a new angle in a thesis from our laboratory by Leksell. In this work he presented his discovery that the small efferent fibers in the ventral roots of mammals did not, when selectively stimulated, set up contractions but merely caused afferent firing from the muscle sense organs. This, of course, means that phasic and postural reflexes, spasticity, rigidity, etc. must be reconsidered from the point of view of the mechanism of efferent control. These questions will be discussed in Chapter 7.

2. The histological basis

More than 100 years ago the muscle spindles, according to Ruffini (1898), were discovered by Hassall (1851); in Ruffini's (1898)

opinion Weismann's paper of 1861 contains the first reliable histological description of them.* In his extensive histological studies on the innervation of muscle Kühne (1863a,b) described the structures in detail and named them muscle spindles. A review of the old literature is found in Ruffini's (1898) paper. Prior to the fundamental contributions by Sherrington (1894) and Ruffini (1897, 1898) there was actually an extensive literature on muscle spindles. Weismann's theory that they were muscular regeneration centers was supported by leading biologists like Kühne (1863a) and Kölliker (1863).

A great step forward was taken when Sherrington (1894), by degeneration experiments, traced their fibers into the dorsal roots and thus proved these structures to be sensory end-organs provided with afferents and over a period of about 40 years (1894–1930) finally developed the study of reflexes from muscles, the essential results of which for a long time have been part of general medical education. Ruffini's histological work was published in English in 1897 and 1898, and very little has since been added to his and Sherrington's descriptions of the structure of the muscle spindle. The detailed analysis of the function of this organ was left for the electronic era of research, but Ruffini made it perfectly clear that the spindles should be classified among the most highly developed sense organs in the body, being second only to the eye and the ear. He said: "Apart from the organs of special sense (eye, ear, etc.) the body possesses no terminal organ that can compare with these in richness of nerve-fibres and of nerve endings."

In addition to the muscle spindle there is another sensory structure, the Golgi tendon organ, of which something is known physiologically. It appears to work in close cooperation with the spindle and is located at the insertion of the tendons into the muscles but not so strictly that after cocainization or removal of the tendons one could be certain to have a preparation devoid of these receptors (see e.g. Barker, 1948). According to Sherrington (1894) and Barker, there are also tendon organs at the insertion of the muscle spindles themselves, even "frequently" in Barker's opinion. The tendon organs were discovered by Golgi and an excellent description of them is found in Vol. *1* of his Opera omnia (1870–83, later ed. 1903). The early work is well reviewed by Sherrington (1900b; cf. Cattaneo, 1888), who ascribes their discovery to Rollett (1876) and Golgi (1880). The latter differentiates between musculotendineous organs, apparently those which today are called Golgi tendon organs, and a second type consisting of varieties of Pacini bodies of different size.

* I have seen only A. H. Hassall's book of 1852 (The microscopic anatomy of the human body in health and disease, 2 vols. Taylor, Walton, and Maberley, London. 570 pp.). To an amateur histologist neither his nor Weismann's (1861) paper carries conviction, while Kühne's, and particularly Kölliker's, drawings leave no doubt about what they have seen.

Below we shall confine ourselves to muscle spindles and Golgi tendon organs, which are the only ones properly analyzed physiologically. There are also pain endings in muscles, which do not seem to differ from those described in other tissues.

The following description of the mammalian muscle spindle is based on the papers of Sherrington (1894), Ruffini (1897, 1898), Kühne (1863a,b), Kölliker (1863), Denny-Brown (in Creed *et al.,* 1932) and Barker (1948). Barker's paper is particularly complete. It provides a good reconstruction of a whole spindle from a rabbit, a number of interesting details, and a well-balanced discussion of the histological and physiological evidence available up to 1948. A great many new physiological results have since been added. Excellent reviews of muscle innervation as a whole have been written by Hinsey (1927) and Hines and Tower (1928). The most recent review is by Tiegs (1953).

The muscle spindle consists of a number of so-called *intrafusal* striated muscle fibers, in cats generally six, and differing from the ordinary motor or *extrafusal* fibers in several ways. The 4–6 intrafusal fibers form one organ in the sense that they come together, having often started proximally from different extrafusal fibers, and end together at a tendon in the distal part, sometimes there, also, attached to the extrafusal endomysium. The single intrafusal muscle fiber, illustrated in Fig. 87a, is seen to consist of two striated polar portions divided by a noncontractile *nuclear bag.* The transitional or *myotube* region on either side of the bag loses its striation as it approaches the middle of the bag. The main contractile portion receives a motor innervation of small fibers. The sensory afferents form two systems, one on the nuclear bag itself, called the primary ending—often, too, the annulospiral ending—the other the secondary or flower-spray ending located in the myotube region. All these terms are Ruffini's. In cats it appears legitimate (Barker) to regard the metaphorical terms as reasonably accurate, but in, e.g., rabbits and man it is not possible to distinguish the two types definitely on grounds other than that of location. Barker therefore prefers Ruffini's alternative terms "primary" and "secondary" endings. Fig. 87b shows simple and complex organizations in detail. In the simplest endings only one fiber is seen to have

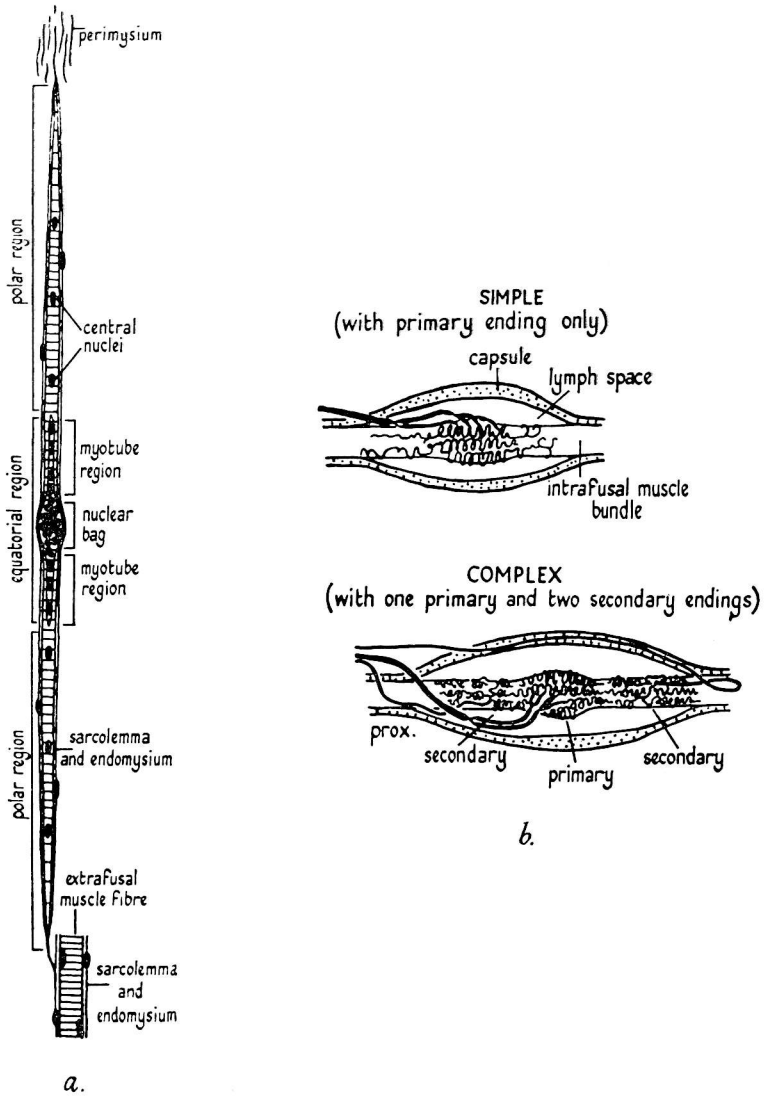

Fig. 87a. Diagram of a single intrafusal muscle fiber; each polar region has been shortened to about a third of its typical length.

Fig. 87b. Diagrams of the equatorial regions of two rabbit muscle spindles illustrating types of sensory innervation. Intrafusal muscle bundle shown in outline only, and area of nuclear bags indicated by exaggerated swelling. Spindle from m. vastus intermedius of quadriceps. Single and complex ending shown. (Barker, *Quart. J. Micr. Sci., 89,* 143. 1948.)

penetrated into the lymphatic space below the capsule of the bag to form a primary ending; greater complexity is introduced by single or double secondary endings, the latter, if double, on either side of the never missing primary ending. These complex organs are most common in cats. The primary or nuclear bag endings are "closely heaped together and occupy approximately 160μ of the equatorial region, the secondary ending is more scattered and covers a length of approximately 480μ" of the myotube region.

The afferent nerves of the primary endings are the largest ones known in the body of mammals, up to 20μ in diameter in the nerve (Sherrington, 1894), but those of the Golgi tendon organs fall into the same general category. The secondary endings have smaller fibers. In view of this it is somewhat unfortunate from the point of view of nomenclature that Matthews (1933) in making the first physiological identification called the primary endings A_2 and the secondary ones A_1. Perhaps new terms such as *nuclear bag endings* and *myotube endings* would help to counteract confusion and terminologically associate function with anatomy. Contraction of the spindle fiber would stretch the nuclear bag with its coil of terminals, while the myotube endings, being themselves in the "myo" or contractile part of the organ, might be less sensitive to this form of stimulation, the coil perhaps rather tending to crumple in the shortening process. However, as Fulton and Pi-Suñer (1927–28) first pointed out, since the intrafusal structure as a whole is placed parallel to extrafusal or ordinary muscle fibers, the contraction of the latter should unload the spindle organ and thus silence it. The Golgi tendon organs, again, being in series with the extrafusal fibers (unless some really are in series with the spindle) will record tension equally to stretch and contraction.

The final result of tendon and spindle messages relative to the state of the extrafusal fibers, on the other hand, might be altered if spindle and extrafusal fibers could contract independently. The relative tensions of intra- and extrafusal fibers would by such means be adjustable in a highly plastic fashion to a large variety of conditions. As we shall see, this is what actually happens, so that Ruffini's view that the spindle organ is second in complexity only to the eye and the ear has come true.

Fig. 88 illustrates the motor (*A*) and sensory (*B*) innervation of the muscle spindle (Barker's diagram). The salient point is that the intrafusal innervation by small fibers, mentioned above, is profuse in the sense that the individual fibers dichotomize to form several small motor end plates on both polar regions. It was shown by Hagbarth and Wohlfart (1952) that individual fibers also overlap on different

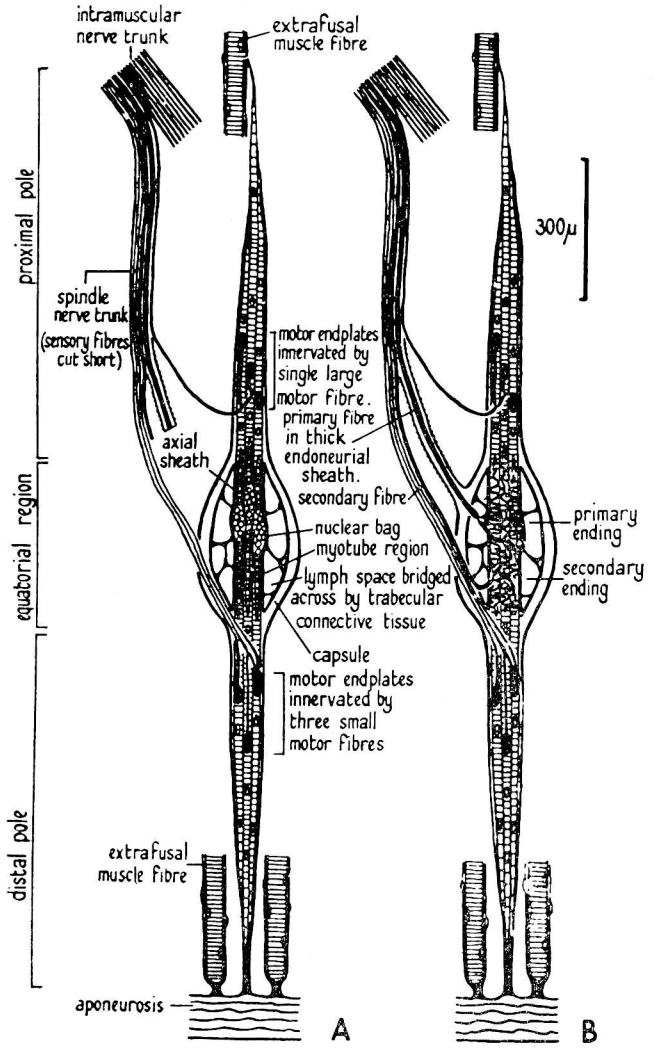

Fig. 88. Diagrams of an idealized rabbit muscle spindle; polar regions shortened to about half their typical length. In *A* the motor innervation is shown, but the sensory innervation has been omitted to demonstrate the morphology of the equatorial region. Motor end plates represented as black disks. *B* shows the same spindle with the addition of a sensory innervation comprising one primary and one secondary ending. (Barker, *Quart. J. Micr. Sci., 89,* 143. 1948.)

spindles. The intrafusal or spindle fibers therefore possess what is called multiple innervation. The small fibers of the spindles I shall call γ fibres in order to have a convenient term. The reason is that Leksell found (1945) that they conduct impulses at velocities of the order of 20–44 meters per second, which in the classification of Erlanger and Gasser (1937) would be γ rate of conduction. By contrast the large ordinary motor fibers conduct at α rates, 60–115 meters per second. These run to the extrafusal fibers, but in Fig. 88 Barker has also inserted a relatively large motor fiber for one polar region of the spindle (see Barker, for relevant literature). The physiological evidence on this point is controversial: Matthews (1933) and Leksell (1945) came to the conclusion that there may be some α innervation of the spindles also, but Hunt and Kuffler (1951a), after a careful search, maintain that this is not the case. Be this as it may, it nevertheless seems clear on their evidence that the main innervation of the spindles in ankle flexors and extensors is by γ fibers. There may well be differences between different muscles, and it is also clear from all fiber spectra so far published that some overlap in conduction rates between fibers with different tasks is to be expected. The terms α and γ are, however, good enough for practical purposes and stand for large-fiber and small-fiber innervation.

It was found by Tasaki and his collaborators (Tasaki and Mizutani, 1944; Tasaki and Tsukagoshi, 1944; Kobayashi, Oshima and Tasaki, 1952) that the effect of direct repetitive stimulation of toad motor nerves of small diameter was a slow graded muscular contraction accompanied by a non-propagated muscle potential of long duration. Further study of this system by Kuffler and Gerard (1947) and Kuffler, Laporte, and Ransmeier (1947) demonstrated that the muscle potential was confined to the region of the neuromuscular junction and that this system was widely distributed in the body and capable of developing considerable tension. Kuffler and Vaughan Williams (1953a,b) have since proved that the small fibers actually run to individual muscle fibers with specific slow or "tonic" properties as well as specific electrical properties, analyzed by them in considerable detail. Actually Krüger (1952) had found two types of muscle fiber in the frog and identified them with tonic and phasic muscles, and there is a considerable old literature on tonic and phasic types of contraction in frog muscle (for references see Tasaki and Mizutani, 1944; Kuffler and Vaughan Williams).

However, despite Krüger's statement that the two types of muscle occur also in mammals, Hunt and Kuffler (1951a,b) have failed to find

any evidence in favor of specific tonic muscle fibers in them. In agreement with Leksell (1954) they find that the small γ fibers innervate muscle spindles exclusively and do not set up any contractions. I need not therefore discuss the tonic system in frog muscles in this connection. It seems appropriate, however, to point out that the intrafusal or spindle fibers are likely to respond very much like the tonic system in the frog. We shall see below that all the evidence points to the intrafusal fibers being capable of slow graded contractions based on nonpropagated potentials and not on conducted action potentials (Kuffler, Hunt, and Quilliam, 1951). Kuffler and Vaughan Wiliams (1953b) have emphasized the close analogy between the mammalian small-nerve spindle system and the frog small-nerve tonus system.

There are several measurements of efferent and afferent fiber spectra of the nerves leading to the muscles on which the main part of the physiological work on mammalian spindles has been carried out (e.g. Eccles and Sherrington, 1930; Rexed and Therman, 1948; Lloyd and Chang, 1948; Fernand and Young, 1951; Hagbarth and Wohlfart, 1952). The muscle receptors have generally been studied in ankle flexors and extensors for the simple reason that fixation of the animal preparation is more reliable at knee and ankle than at hip and knee, and the spindles are extremely sensitive to movement or vibration. Fixation at three joints is necessary. There is also in the traditions from Sherrington's laboratory a stock of knowledge available about the reflex behavior of these muscles (see Creed *et al.*, 1932), which has been very useful. Another valuable preparation has been the tiny hip flexor *m. tenuissimus* which in the cat is a slender red band a couple of mm. in width and innervated by about 85 fibers (Adrian, 1925). This preparation has been used, e.g., in the important paper by Kuffler, Hunt, and Quilliam (1951).

In discussing afferent caliber spectra I am using Hagbarth and Wohlfart's data because these are the only ones that also contain spindle counts. The distributions of afferent fiber sizes and muscle spindles for gastrocnemius medialis, soleus, and tibialis anterior are shown in Fig. 89.

The big gastrocnemius medialis contained only 45 muscle spindles, as against 56 and 57 in the considerably smaller soleus and tibialis anterior. The nuclear bag endings of gastrocnemius medialis thus required only 45 of the 145 thick fibers available. The thin and medium-sized fibers were 25 per cent each. If the thick and medium-sized fibers are considered as supplying spindle organs, there will be 104 large fibers available for Golgi

tendon organs. The Pacinian corpuscles must be few in muscles (Wohlfart, personal communication). Gastrocnemius medialis probably therefore contains a large number of tendon organs. Again, in soleus 59 of the 144 afferents were thick and practically all would be used up by the 56 nuclear bag endings. There were 31 thin and 54 medium-sized fibers in the soleus.

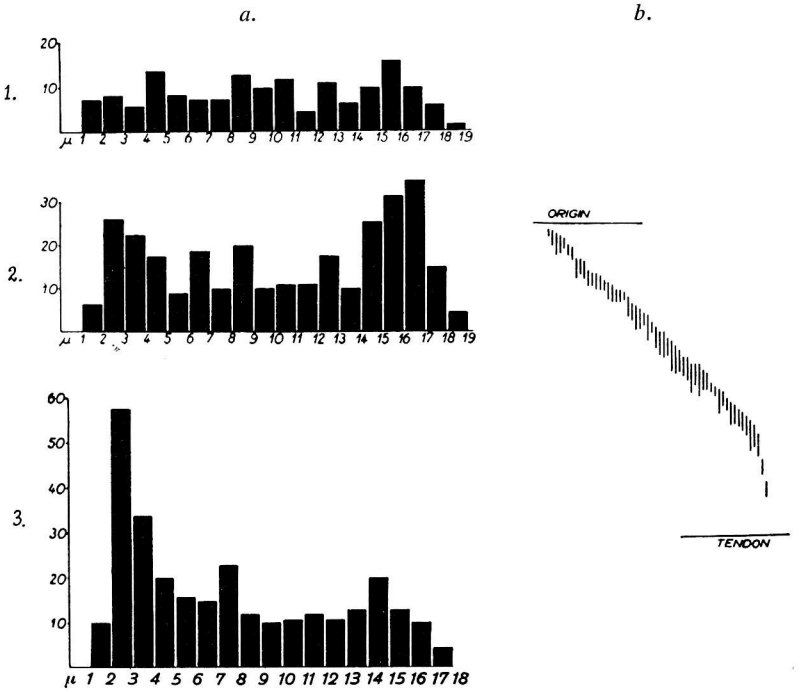

Fig. 89a. Number of muscle afferent fibers of different size plotted against fiber diameter in μ (caliber spectrum). 1: soleus, 2: gastrocnemius medialis, 3: tibialis anterior.

Fig. 89b. Distribution of muscle spindles in soleus. (Hagbarth and Wohlfart, *Acta anat., 15,* 85. 1952.)

In the tibialis anterior there were 276 afferent fibers, of which as many as 118 were thin, 81 medium, and 77 large. If the thick and medium-sized fibers are taken to supply the spindles, there will be 117 large fibers available for Golgi tendon organs and Pacinian corpuscles. Tibialis anterior is characterized by a particularly large number of the small and smallest afferents.

Golgi tendon organs conducting as rapidly as spindles are by no means difficult to find (Hunt and Kuffler, 1951b). For gastrocnemius and tibialis

anterior the anatomical evidence (Sherrington, Ruffini, Barker) cited above to the effect that the nuclear bag endings are innervated by the largest fibers and the myotube endings by somewhat smaller fibers is in agreement with Hagbarth and Wohlfart's data.

On the efferent side the situation seems simpler. Fig. 90, from the paper by Eccles and Sherrington (1930), shows that the fibers fall into two main groups, those which somewhat schematically have been called α and γ. For the comparisons with the three muscles discussed above I return to Hagbarth and Wohlfart's data. There were 430 efferent fibers in gastrocnemius medialis, 25–30 per cent of which

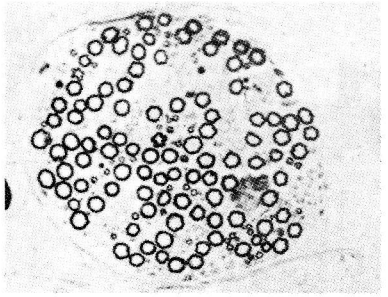

Fig. 90. Cross section of branch of deafferented motor nerve to the lateral gastrocnemius muscle. Note typical difference between large alpha fibers and small gamma fibers. (Eccles and Sherrington, *Proc. Roy. Soc. of Lond.*, B *106*, 326. 1930.)

were thin ones. The minimum number of γ fibers for the 45 muscle spindles, on the notion that there is at least one end plate to each polar region and 6 intrafusal fibers in the cat's spindle, is $2 \times 6 \times 45 = 450$, as against the 106–129 actually found by counting. The γ fibers must therefore branch and overlap profusely (cf. above, Barker). In soleus there would be about 200 α fibers (or motor units in the sense of Eccles and Sherrington, 1930) and 90 γ fibers, the number of γ being given by the latter authors as 31 per cent. In tibialis anterior Rexed and Therman (1948) found 38 per cent of γ fibers. This means, on Hagbarth and Wohlfart's data, that there are 206 such fibers and 337 α fibers or motor units. Since the number of muscle fibers in tibialis anterior was about 37,000, the motor unit comprises on an average 110 muscle fibers.

Eccles and Sherrington, in assigning maximum contraction values to the motor units, included the γ fibers, which at that time were not known

to supply spindles exclusively. Some recalculations may therefore be of interest. If for the parallel-fibered soleus we take approximately 265 efferent fibers, considering the data of both Eccles and Sherrington and Hagbarth and Wohlfart, 185 would belong to motor units capable of delivering a maximum tetanic contraction of 2230 grams, or approximately 12 g. per unit ($12 \times 185 = 2220$). The maximal twitch is taken to be 580 g. and thus for each motor unit (580:185) something around 3 g. Assuming these effects are given by some 100 extrafusal muscle fibers (see above for tib. ant.), it seems clear that the chance of obtaining a measurable amount of tension from an individual muscle spindle contracting maximally is nil. Even if all 56 spindles in soleus were stimulated together in a selective fashion, as with some luck may be done (see Chapter 7), it is unlikely that one would succeed in obtaining a measurable spindle contraction, considering how the spindles are distributed inside a muscle (see Fig. 89).

The calculations by Eccles and Sherrington, of which these are but a recalculation, have, however, been contested by Kobayashi, Oshima, and Tasaki (1952), who maintain that direct tetanic stimulation of *single* fibers running, e.g., to soleus, produces a tension of 1–2 g., the initial tension of the muscle being 50 g. They obtained values of the same order also by the technique of Eccles and Sherrington, that is, by stimulating the *whole* muscle nerve and dividing maximum tension by fiber number. It seems fairly obvious that their values cannot be correct. With tibialis anterior they themselves recorded on an average 2300 g. tension, a most probable value. This means about 7 g. for the motor unit, despite the low initial tension used, as against their own average value of 1.8 g. On their own tension values a similar calculation for soleus would give 2420/185 which is around 13 g. or almost exactly the figure given above (12 g.). There are apparently errors in their histological work, since in order to obtain their value (1.8 g.) they would have to have 1344 α fibers, which is 7–8 times more than anybody else has seen. The directly recorded values of the Japanese authors are likely to apply to minimal rather than maximal performance.

3. Physiological properties of muscle receptors

Following upon the early isolation of stretch receptors in muscles by Adrian and Zotterman (1926a), Matthews in a series of papers (1929, 1931a,b, 1933) studied them thoroughly by the single fiber technique and described the basic responses to stretch and contraction of muscle-nerve preparations. With the frog's muscle spindle (1931)

he first found evidence in support of Fulton and Pi-Suñer's (1927–28) prediction that the spindle organs would pause during a contraction of the extrafusal (motor) fibers because the intrafusal fibers were parallel to the contracting extrafusal ones and hence unloaded. Also, in isometric (constant length) contractions unloading would occur because the tendons are elastic, so that some shortening of the extrafusal muscle fibers actually could take place.

The diagram of Fig. 91 summarizes the behavior of a Golgi tendon organ and a muscle spindle sense organ in relation to muscle length. The following features, all taken from Matthews' (1933) work with mammalian muscle receptors, should be noted; the tendon organ has a slow spontaneous discharge at the slight initial tension

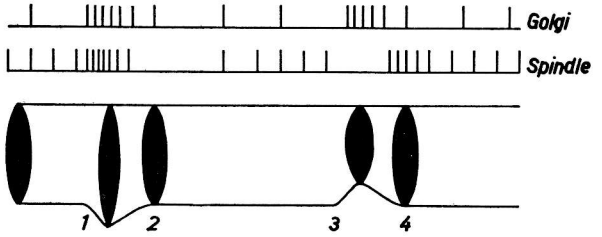

Fig. 91. Diagram illustrating the response of a Golgi tendon organ and a spindle ending during stretch and contraction of the muscle. The muscle is drawn below in black, between lines indicating its insertions. See text.

assumed to be given to the muscle, the spindle organ a faster one. The higher threshold of the tendon organ may, partly at least, account for this. At 1 the muscle is stretched and both organs fire, adaptation being more rapid in the spindle organ. At 2 the muscle resumes its original tension and length. There is a drop in frequency before the spontaneous activity returns in the spindle, partly (and probably largely) on account of the viscoelastic properties of the muscle fibers (Matthews), partly owing to postexcitatory inhibition with a positive swing of the potential recorded at the end-plate terminals (see Chapter 1, sec. 4). With the slow spontaneous discharge of the tendon organ the postexcitatory inhibition is less in evidence. At 3 the muscle is assumed to shorten, owing to tetanic stimulation of the α fibers of its nerve. The spindle organ is now unloaded and pauses at the time when the tendon organ, being in series with the contracting muscle, records the increased tension by a discharge. At 4 the muscle is pulled out by the myograph at cessation of stimulation. The slack spindles will now be pulled upon and consequently discharge, while

the tendon organs will be silenced by the drop of tension. Both nuclear bag and myotube endings in the spindle would in this test behave in a similar way. Thus, Matthews succeeded in differentiating clearly between spindle organs (his A-type) and tendon organs (his B-type). Their different behavior during contraction will hence be our main criterion for identification of single fiber discharges from a given muscle.

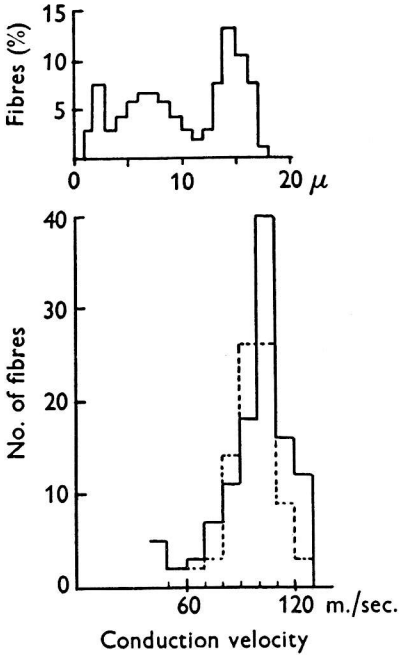

Fig. 92. Above: histological fiber diameter spectrum of nerve to soleus (cat) taken from Lloyd and Chang (1948). Below: conduction velocities of individual fibers from stretch receptors in soleus plotted against number of fibers. *Solid line:* A units spindles; *broken line:* B units Golgi. Scale of conduction velocity has been made comparable to scale of diameters in upper figure. Note lack of difference in velocities in A and B fibers. Both fall into the larger group (I) of the histological spectrum. (Hunt and Kuffler, *J. Physiol., 113,* 298. 1951b.)

Matthews' work also suggested a differentiation between nuclear bag and myotube endings in the spindle. The nuclear bag endings (A2) were found to give larger spikes than the other (A1), and slightly supramaximal stimuli (10–20 per cent) made them discharge during the pause showing—it was assumed—that the intrafusal fibers had been made to contract, and thus the endings were restimulated. He did

not succeed in making the myotube endings discharge during the pause. Thus, judging by spike height, Matthews concluded that the afferents of nuclear bag and tendon organs (*B*) had much the same range of conduction velocity, while those of the myotube endings conducted at a slower rate.

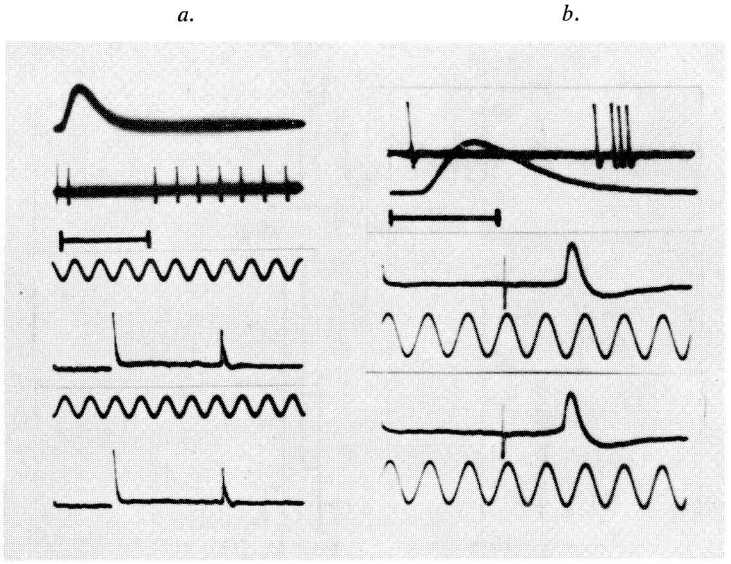

Fig. 93. Records from slow- and fast-conducting spindle afferents in tibialis anterior recorded in dorsal root filaments. The top records show the characteristic pause in discharge during active contraction of the muscle to a single maximal shock. Time calibration scales for top records 1/10 sec. In the lower records the nerve to tibialis was stimulated by electrodes close to the muscle and the interval between shock artifact and spike potential is a measure of conduction velocity. Time: 1,000 cy/sec. Conduction distance approximately 14 cms. For the slow afferent fiber in *a* the velocity is 33 m/sec., for the fast afferent in *b*, 100 m/sec. In *a* there was no change in latency when the nerve was cut between stimulating electrode and muscle; so the impulse recorded is not a back response from the muscle. (By courtesy of P. A. Merton, Nobel Institute for Neurophysiology, Stockholm.)

Hunt and Kuffler (1951b), with the sweep circuits nowadays available for latency measurements, isolated a very large number of single muscle spindle afferents in the dorsal roots of the cat and measured conduction velocities. They found only one type of spindle afferent, the nuclear bag ending, as identified by Matthews (1933), and Fig. 92 shows the distribution of their conduction velocities compared with

the afferent fiber spectrum of Lloyd and Chang (1948), which has a more marked group of medium-sized fibers than in many other measurements. All the spindle endings were found to belong to the group of large and fast fibers. In agreement with Matthews they also placed the Golgi tendon organs within the same group. In view of Matthews' results and the measurements by, e.g., Hagbarth and Wohlfart (1952) presented above, Merton (1953) concluded that they had missed the myotube endings and took up this question for reinvestigation. Matthews isolated the fibers in the muscle nerves and not in the roots, as did Hunt and Kuffler. In the work of the latter it seems that the more delicate medium-sized fibers tend to become inactive very quickly (Merton, 1953). Yet every now and then one finds slowly conducted responses of the spindle or A-type also in the roots, and Fig. 93 shows a comparison between a slowly and a rapidly conducted spindle response from the cat's tibialis anterior muscle recorded by Merton. At about the same time Hunt (1953) must have arrived at a similar conclusion, because at the Montreal congress he also presented results referring to slowly conducted endings of the spindle type. The results of Matthews therefore stand unchallenged: there are slowly and rapidly conducting spindle afferents, the latter conducting at much the same rate as the Golgi tendon organs. Actually, Matthews found the myotube endings to be in the majority (50%), as, indeed, all histological work (see above) has suggested.

4. The efferent spindle control

As pointed out above, it has been known for a very long time that the spindles are provided with motor end plates. Matthews (1933) found (with nuclear bag endings) that supramaximal stimuli of 10–20 per cent were needed to make a spindle contract so as to fill out the pause during contraction with a discharge. Leksell (1945) was the first to succeed in recording the electroneurogram of the γ fibers. Fig. 94a is from his paper and shows the large-fiber response succeeded by the small-fiber response, both elicited by a single shock to a muscle nerve. Fig. 94b is a record by Hunt (1951) showing similarly the response in one large fiber followed by that of a small fiber in the cat's tenuissimus. Leksell's measurements of conduction velocities gave values which for the small fibers were 20–38 per cent of those obtained with the fastest α fibers. These he found to conduct at rates of 90–115 meters per second.

Kuffler, Hunt, and Quilliam proceeded to work out these relations

in terms of single fiber responses and found for the cat's soleus small-fiber γ conduction rates of 15–50 m/sec with a peak at 30 m/sec.

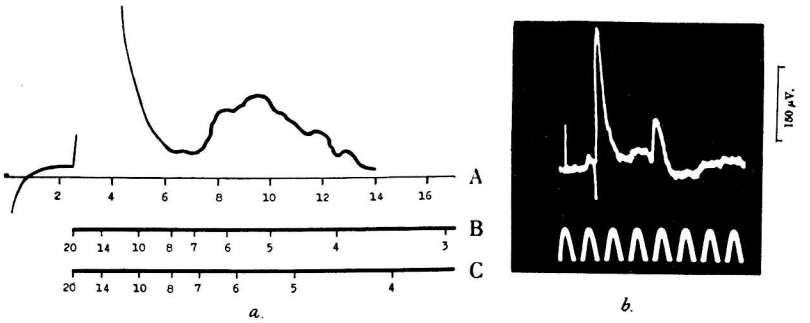

Fig. 94a. Correlation between the action potential and the size of the ventral root fibers. The action potential was recorded in the ventral root S_1 in response to stimulation of the tibial nerve. *A:* time scale in msec. *B* and *C:* caliber scales of the outside diameters of the nerve fibers in μ. Scale *B* corresponds to a direct relation between outside diameter and conduction velocity. Scale *C* corresponds to a direct relation between axon diameter and conduction velocity. (Leksell, *Acta physiol. scand., 10,* Suppl. 31. 1945.)

Fig. 94b. Recording from nerve to tenuissimus. Stimulation of single large and small fibers in ventral root filament. Note difference in potential size. Fiber giving larger potential conducted at 92 m/sec., the smaller at 30 m/sec. This corresponds to fiber diameters of 15 and 5μ. Time scale; 1000 cy/sec. Conduction distance 11 cm. (Hunt, *J. Physiol., 115,* 456. 1951.)

TABLE 4

Relative Threshold of Ventral Root Fibers *

Stimulated Nerve	*Recorded Ventral Root*	*Alpha Threshold*	*Alpha Maximum*	*Gamma Threshold*	*Gamma Maximum*
Sciatic	L 6	1	3.3	3.7	13
Peroneal	L 6	1	3.5	3.5	15
Peroneal	L 7	1	3.1	3.9	23
Gastroc. med.	S 1	1	3.3	4.0	12
Tibial	S 1	1	2.3	4.2	16

* Leksell, *Acta physiol. scand., 10,* Suppl. 31. 1945.

From Table 4 it appears that in order to bring in all the γ fibers by stimulation of the whole nerve trunk to a muscle, very strong shocks must be used. The whole α supply, as evidenced by both spike height and maximal contraction, is activated by stimuli which are but 2.3 to 3.5 times threshold strength (cf. O'Leary, Heinbecker, and Bishop,

1935). At 3.5 to 4.2 times the threshold the γ responses begin to occur, but full γ activation requires 12 to 23 times the α threshold. Since Matthews (1933) obtained effects upon the nuclear bag endings with shocks only 10–20 per cent suprathreshold, he must have used longer shocks than Leksell or else stimulated small α efferents capable of exciting mechanical effects upon suitably located spindles (Hunt and Kuffler, 1951a).

Leksell's next step was to show that it was possible by compression of the nerve to block the α fibers selectively (cf. Gasser and Erlanger, 1929). The remaining γ response was incapable of eliciting a muscle contraction. However, when the leading-off electrodes were shifted to the dorsal roots, selective γ stimulation was found to set up a heavy discharge from the muscle sense organs despite absence of contraction. For this, however, there had to be some tension in the muscle. He concluded that the γ fibers probably were motor for the intrafusal or spindle fibers.

Kuffler, Hunt, and Quilliam, by the technique of single-fiber isolation, confirmed Leksell's results and proved that the sense organs belonged to the spindle type, as Leksell had surmised. Golgi tendon organs did not respond. Fig. 95, from Kuffler, Hunt, and Quilliam's paper, illustrates the response of a spindle organ to stimulation of one γ fiber (soleus). This spindle seems to have been silent at zero tension. The favorable effects of tension and stimulus frequency on the discharge are beautifully recorded. Efferent fibers conducting below 55 m/sec. never succeeded in setting up contractions in the muscle and were always found to be destined for the spindles. Their detailed elaboration of the γ system thus corroborated Leksell's pioneer work. Several new facts were added. It is particularly interesting that peripheral postexcitatory facilitation of the spindle discharge was noted in addition to the expected postexcitatory inhibition (see above). Several spindles go on discharging after cessation of γ stimulation—in fact, Hunt and Kuffler (1951a) later reported that such effects could be noted up to 7 seconds after stimulation at 20/sec. for 1–2 seconds. Such relatively long-lasting after-effects of stimulation would be expected on the view (cf. above) that the intrafusal muscle fibers have the slow tonic properties of the specific tonic fibers in frogs and toads.

The γ mechanism of efferent control is capable of filling out the pause in the discharge of the spindle during isometric contraction. This is clear from Fig. 96, from Hunt and Kuffler's (1951a) work. *A* is the baseline discharge at three different tensions, *B* the effect of

stimulation of a single γ fiber which exclusively activates the spindle while the myograph record remains quiet. In *D* the muscle is made to contract by large fiber or α stimulation alone and the pause is clearly displayed. In *C* the small γ fiber has been stimulated as in *B* but this time together with the large α fibers as in *D*. The pause is now being filled out—the more efficiently, the greater the initial tension.

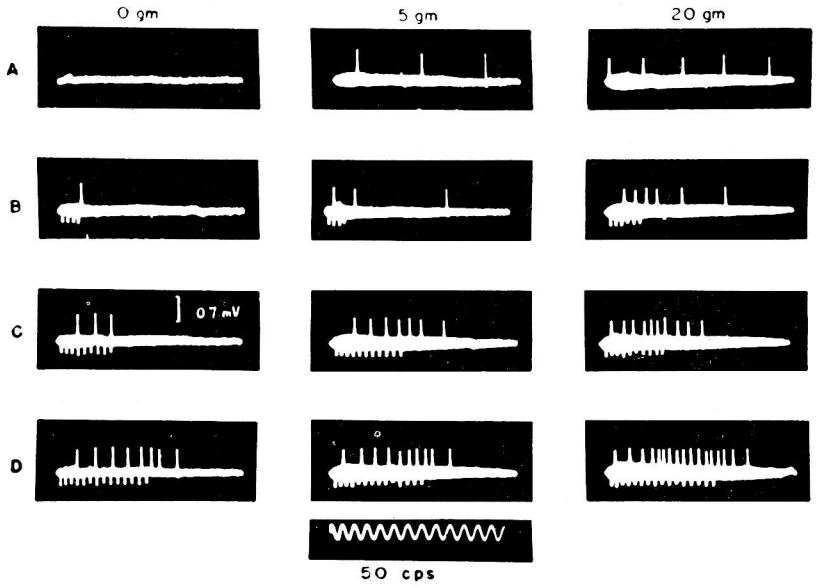

Fig. 95. Recording of single afferent discharges in dorsal root S_1 from soleus on sweep of 260 msec. duration. External stretch on muscle of 0, of 5 and 20 g. Stimulation of single small efferent fiber to soleus in S_2 at 100/sec. Artifacts indicated by small downward deflections. *A:* no stimulation, *B:* 4–6 stimuli, *C:* 9–11 stimuli, *D:* 14–16 stimuli. Note change in baseline discharge rate at different tensions. Effectiveness of small-nerve γ stimulation is greater at higher tensions and increases with number of stimuli. In this unit continued excitation at 100/sec. eventually established, after period of facilitation, response rate which was same as stimulus frequency ("driving"), even at zero tension. (Kuffler, Hunt, and Quilliam, *J. Neurophysiol., 14,* 29. 1951.)

In the anatomical section (above) it was also pointed out that the spindle efferents overlap profusely. By isolating single γ efferents Hunt and Kuffler (1951a) have confirmed this physiologically. All spindles examined from this point of view showed evidence of multiple innervation and three to five γ efferents to the same spindle could often be isolated. Some were more efficient, some less, and their effects were

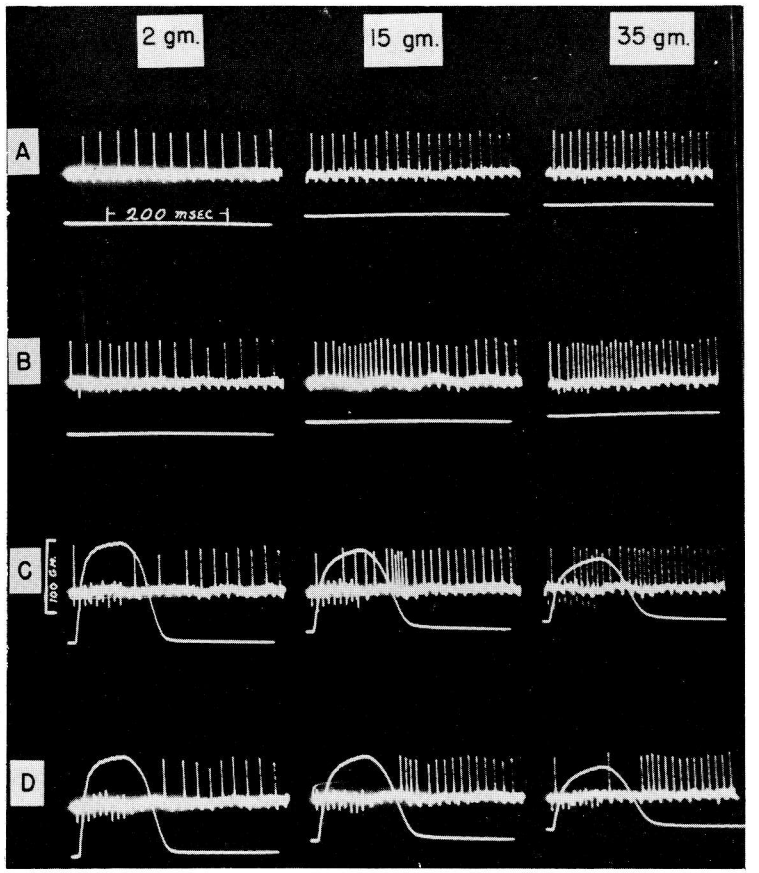

Fig. 96. Effect of contraction on response to small-nerve γ stimulation. Recording from single A or spindle receptor from flexor digitorum longus at initial tensions of 2, 15, and 35 g. Second beam indicates strain gauge response. *A:* baseline discharge. *B:* stimulation of isolated γ fiber (9 stimuli at 10 msec. intervals at beginning of sweep). Note that effect on afferent discharge increases as muscle tension is raised. No muscle contraction results. *D:* similar stimulation of a portion of the ventral root containing no γ fibers. Cessation of discharge during contraction. *C:* simultaneous stimulation of γ fiber as in *B* and large α fibers as in *D*. At 2 g. tension there is a pause in the discharge while at 15 and 35 g. γ stimulation becomes increasingly effective. Potentials 0.2 mV. Maximal tetanus tension 140 g. (Hunt and Kuffler, *J. Physiol., 113,* 283. 1951a.)

summed. A single shock to one single γ fiber rarely succeeded in activating the end organ, but one shock to two or several efferents elicited a discharge. We have already noted the favorable effect of stimulus iteration.

5. *The pause, the silent period, and the recurrent collaterals*

By the *pause* is meant the purely peripheral phenomenon, studied in so many of the records shown in the previous section—namely, that the muscle spindles do pause during a contraction unless they are specifically activated by efferents. They will not be activated during a twitch to α fibers alone, and so the question arises of what this pause in the afferent input may signify in the reflex output which the spindle afferents are likely to produce. Actually, Hoffmann (1919, 1922) found in man, using electromyography, that if by volitional contraction a steady background of action potentials was maintained in a muscle, these ceased for a while during a contraction. This is the *silent period* (Fig. 100, record 1). There were two early theories explaining the silent period: one, sponsored by Denny-Brown (1928), assumed that a refractory phase after a relatively synchronous motor volley was maintained afterward by inhibitory impulses from nuclear bag afferents, the other, by Fulton and Pi-Suñer (1927–28), ascribed it to cessation of spindle impulses (the pause) postulated to occur because of the anatomical arrangement of the intrafusal fibers parallel to the extrafusal ones. Hoffmann himself at the time thought of the silent period in terms of central refractoriness of some kind. Denny-Brown also demonstrated a period of silence in the motoneurones after an antidromic shock. This was limited to the muscle-nerve stimulated. The actual demonstration of the pause by Matthews in 1933 placed Fulton and Pi-Suñer's explanation of the silent period in the foreground, and made it unlikely that the spindles (which paused) could be responsible for the inhibition, even if inhibition did occur.

Today we know that the silent period is a complex integration of two peripheral factors, the pause and autogenetic inhibitory impulses from the muscle, and at least one, and possibly two, central factors. This will gradually become clear when I have described the reflex effects of the spindles and the tendon organs, as known from a large number of recent experiments. However, from other points of view the question of the silent period is an excellent introduction to all these problems and therefore deserves to be presented at this stage.

Thus, for instance, it is clear that either of the pausing end-organs—nuclear bag or myotube endings—must be excitatory if either or both play a role in the silent period. Inasmuch as inhibition is engaged in this phenomenon, the Golgi tendon organs, which fire during the contraction in proportion to the amount of tension developed, would have to be inhibitory, provided that the contraction is set up by α fibers alone.

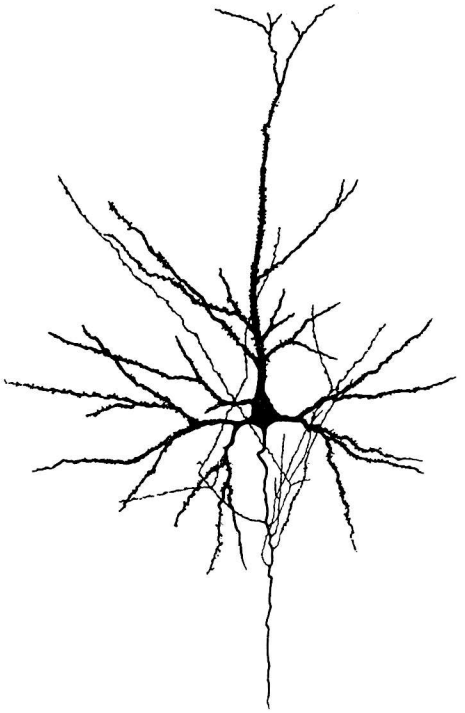

Fig. 97. Pyramidal cell from upper part of cat visual cortex. Golgi rapid preparation, 150 μ thick. Tracing from three plates at different focal planes. Note recurrent collaterals from axon. (By courtesy of D. A. Sholl, University College, London.)

As for the central factors, an important feature of the organization of the ventral horn cells is the presence of the recurrent axon collateral which, according to Cajal (1899, 1904), first was seen by Golgi. However, Cajal made a special study of this feature of neural organization and stated that recurrent axon collaterals are found in all nervous centers. In the ventral horn cell the axon divides about 1 mm. from the cell body, and one branch returns to the spinal cord. The beautiful

tracing by Sholl (Fig. 97) is actually of a pyramidal cell from the visual cortex but, as stated, these recurrent collaterals occur everywhere and have been extensively pictured by Cajal. Now, is this feedback excitatory or inhibitory on the ventral horn cell?

This problem was raised as early as 1914 by Graham Brown (cf. Denny-Brown, 1928; Forbes *et al.,* 1933), but Renshaw (1941) was the first to produce evidence to the effect that the synergists also of a given muscle were inhibited by a shock backfired (antidromically) into its ventral horn cells. This inhibition lasted for some 40–50 msec. In a second paper (1946) he made the remarkable observation that the inhibition coincided with a peculiar high-frequency discharge of up to 1500 impulses per second in cells located among the motor neurones. These impulses were picked up by microelectrodes inserted into the spinal cord. At the time alternative explanations of antidromic inhibition, such as purely electrical interaction or afterpositivity coupled with subnormal excitability (Eccles, 1931, 1953; Gasser, 1937) in the motoneurones had to be considered, but Eccles, Fatt, and Koketsu (1954), returning to this problem with the aid of an internal microelectrode inserted into a single ventral horn cell (Brock *et al.,* 1952), have since shown that this cell becomes hyperpolarized by an antidromic shock to synergist motoneurones just as it does when inhibited by other means (cf. Chapter 1, sec. 6, and below). This is illustrated in Fig. 98A, while 98B confirms the observation by Renshaw (1946) that the phase of hyperpolarization coincides with a high frequency discharge which they ascribe to cells located amongst the motoneurones and assume to inhibit the latter. The initial ripples on the hyperpolarization in record A are ascribed to these impulses.

The latent period of the effect agreed with the idea that the recurrent collaterals had traversed one synaptic junction. Renshaw (1941, 1946) also found the excitability of some motoneurones raised by the antidromic shock.

As soon as this notion of an inhibitory feedback through the reflex collaterals is accepted (and, indeed, if it merely were highly probable) it becomes very difficult, not to say impossible, to separate the inhibition from the state of subnormal excitability that follows in the wake of an impulse and which is preceded by a brief moment of genuine refractoriness. Every outgoing impulse in an efferent α fiber, just as every antidromic ingoing one, inhibits, if not its own, at any rate adjacent, ventral horn cells as soon as it has been returned through the small-cell internuncial neurones which serve as a kind of "commutator," switching the effect from excitation to inhibition. Another

matter is, then, to what extent this inhibition actually is effectual when pitted against excitation. This will depend on the state of excitability of the ventral horn cell. The role of the feedback is probably to stabilize

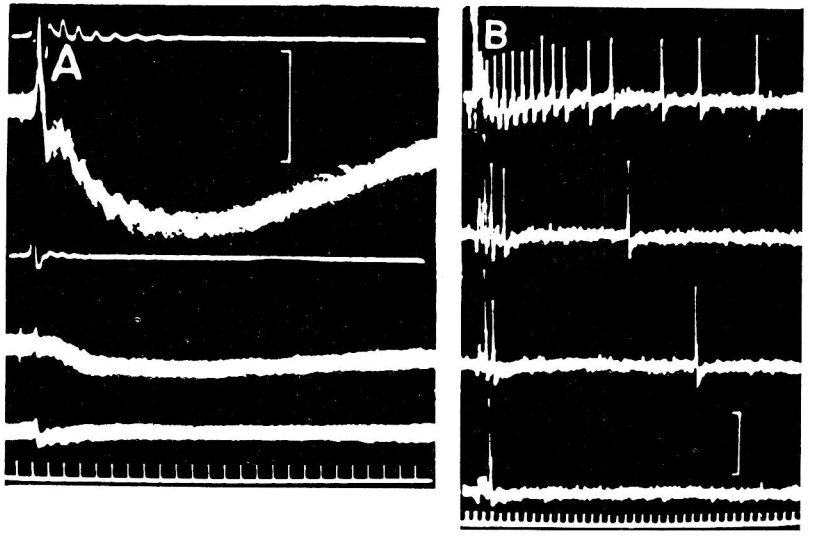

Fig. 98A. Intracellular recording from a biceps-semitendinosus motoneurone showing, from above downward, hyperpolarizations produced by antidromic volleys in the biceps-semitendinosus and in the semimembranosus motor axons, while lowest record shows zero effect of a plantaris antidromic volley. The motoneurone was not invaded antidromically by the impulse in its own motor axon; so in the uppermost record there is no complication by the positive after-potential. Potential simultaneously recorded by a surface lead on dorso-lateral aspect of spinal cord is shown above the first two intracellular records. All records made by superimposition of about 40 faint traces so as to eliminate random noise. Time: msec. Potential scale: 5 mV.

Fig. 98B. Upper record shows the rhythmic response set up in an interneurone by an antidromic volley in the biceps-semitendinosus motor axons. Other records, from above downward: responses of same interneurone elicited by antidromic volleys in the motor axons to gastrocnemius, flexor longus digitorum, and the deep peroneal group of muscles respectively. Time: msec. Potential scale: 0.5 mV.

(By courtesy of J. C. Eccles, Australian National University, Canberra.)

the output frequency to the low values adapted for driving muscular tissue.

Much work on reflex effects in recent years has been carried out with anesthetized preparations or acute spinal animals in which internuncial effects and slow changes of excitability are small or absent

at the same time that responses to single synchronous shocks are easily obtained. Synchronous tetanization of afferent muscle nerves elicits slow facilitatory effects, which are abolished by doses as small as 0.3 ml. of dial per kg. (Hagbarth and Naess, 1950b). The Renshaw feedback, if assumed to be maintained in operation by a persistent discharge, is likely to belong to this particular category of reflexes which require reasonably active preparations to exercise their normal function. In the experiment of Fig. 99a Holmgren and Merton (1953) therefore used an active decerebrate animal in which the electromyogram of the deafferented soleus was analyzed. Reflex activity in this muscle was obtained by rubbing the animal's contralateral flank (crossed extensor). Record 1 shows that an antidromic volley to the medial gastrocnemius nerve, which belongs to a close synergist, sets up a silent period. With less intense background discharge the silent period (in record 2) almost doubled its duration. Fig. 99b is a similar experiment, but in this case record 1 shows the block obtained by a maximal antidromic shock in the motor nerve to soleus and gastrocnemius lateralis. In record 2 a silent period of somewhat shorter duration is elicited by an orthodromic shock to the ipsilateral dorsal root L_7 setting up the synchronous monosynaptic reflex of Eccles and Pritchard (1937) and Renshaw (1940). Records 3 and 4 compare a maximal (3) with a partial antidromic volley. Even in the latter case the block is complete, though of shorter duration. Actually, Holmgren and Merton found that antidromic volleys as weak as 25% maximal sometimes succeeded in setting up a complete block. The interpretation is that the Renshaw feedback through the recurrent collaterals ramifies rather widely among the motor neurones of these synergist muscles.

In order to study the effect of the pause in the spindle discharge upon the silent period (see Denny-Brown, 1928; Lindsley, 1934; Hoff *et al.*, 1934; Moldaver, 1936) it is necessary, as pointed out by Merton (1950, 1951), to know the amount of extrafusal contraction. If this is kept the same, the silent period is extremely constant, and if the muscle contraction is slowed down by cooling, the silent period is lengthened accordingly. It thus expresses the pause in the spindle discharge shifted forward by the time of the conduction distance. Silent periods during contractions of soleus in man are illustrated in Fig. 100, myograms in the upper row, electromyograms below (Merton, 1954). Records 1 refer to a reflex soleus jerk elicited by tapping the tendon. The silent period follows close on the heels of the synchronous reflex volley before the muscle has started its reflex contraction. In

this early part central refractoriness, subnormal excitability due to positive after-potential, and the Renshaw feedback will be collaborat-

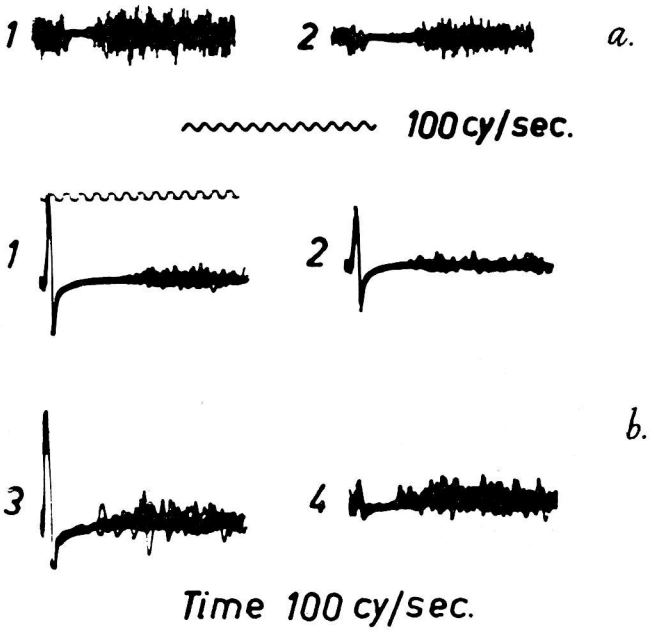

Fig. 99a. Decerebrate cat; electromyogram of deafferented soleus muscle. Ten sweeps superimposed in each record. Contraction elicited by rubbing skin of opposite flank. Blockage of soleus motoneurone discharge by an antidromic volley in the medial gastrocnemius nerve. Note also that the duration of block is briefer with a more intense background discharge (record 1).

Fig. 99b. Decerebrate cat; electromyogram of deafferented soleus muscle. Ten sweeps superimposed in each record. Contraction elicited by rubbing skin of opposite flank. 1: block produced by a maximal antidromic volley in the motor nerve to soleus and gastrocnemius lateralis. 2: block following intercurrent monosynaptic reflex set up by small shock to the cut ipsilateral L_7 dorsal root. Same gain as record 1. The character of the block is apparently the same with either anti- or orthodromic discharge of the motoneurone. 3 and 4: late in same experiment. Comparison of block due to 3, a maximal, and 4, a partial, antidromic volley. The small volley causes complete block of short duration.

(By courtesy of B. Holmgren and P. A. Merton, Nobel Institute for Neurophysiology, Stockholm.)

ing. Cessation of spindle activity follows and maintains silence in the electromyogram. In record 2 a weak shock to the nerve in the fossa poplitea has stimulated the large-diameter afferents but only a very small number of efferents, too small to give a myogram. Conse-

quently, there is only a small initial hump after about 10 msec. in the electromyogram, confirming Hoffmann (1924) and Magladery and his co-workers (e.g. Magladery *et al.,* 1950). Then follows the large electromyographic response of the reflex, succeeded by the silent period. In record 3 the myogram refers to the gastrocnemius muscle but the electromyogram is still recorded in soleus. The lateral gastrocnemius has contracted alone in response to stimulation of its motor point; yet a silent period is seen in the soleus. Its cause is likely to be the Renshaw feedback-inhibition spreading from the gastrocnemius to the soleus neurones, lengthened by autogenetic inhibitory impulses from the contracting gastrocnemius (Granit, 1950a; see also below). Since the silent period corresponds to the briefer duration of the gastrocnemius twitch rather than to the longer one of the slow soleus muscle, the pause in the gastrocnemius may be assumed to have withdrawn facilitatory support from its synergist soleus.

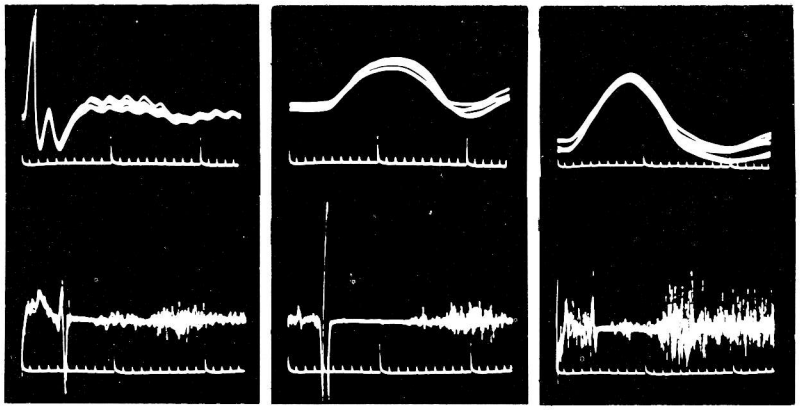

Fig. 100. Silent periods in the human soleus recorded with a needle electrode. A hinge fitted beneath the heel of the subject and tension in the ankle extensors (top trace) recorded as the downward pressure at the toe. Time: 10 and 100 msec. Five superimposed records in each picture. 1: silent period during a tendon jerk elicited by a tap in the Achilles tendon. Contact of the hammer with skin triggers sweep. 2: during a reflex contraction set up by a shock to afferent fibers in the popliteal fossa. 3. during a twitch in the lateral part of gastrocnemius set up by a stimulus over that muscle. Note that soleus itself is not excited by the stimulus. (By courtesy of P. A. Merton, National Hospital, Queen Square, London.)

6. *Comments on methodical limitations*

When attempting to understand the reflex effects of stretch and contraction in terms of the spindle and Golgi tendon organs, it is imperative to realize that one method alone used on one type of preparation cannot be expected to give all the information desired. Sherrington's early discoveries (Sherrington, 1900b, 1906, 1909, 1913, 1924) followed by the later ones of Liddell and Sherrington (1924, 1925) were made on the decerebrate preparation with the aid of myography, in the later work isometric recording checked by simultaneous electromyography. Today it should be realized that reflexes on α and γ efferents must be separately studied and that the γ-loop through the muscle spindles must be considered in connection with both the mechanical events in the muscle and its effect upon the ventral horn cells through nuclear bag and myotube afferents. As will be shown in Chapter 7, it is necessary to study stretch and contraction with and without the γ-loop. In the latter case one will often be forced to de-efferent, i.e. sever, the ventral roots. One then loses the two indicators of reflex activity, myogram and electromyogram, and so is restricted to the method of monosynaptic testing (see below) or some other method by means of which the effect can be recorded electrically from the cut ventral roots. A further advantage of these methods is that muscle nerves can be stimulated electrically to give pure afferent effects, lacking the antidromic depolarization followed by activation of recurrent collaterals, which complicate reflex work based on myography alone. The contribution to the total effect of these (antidromic) factors may be insignificant in anesthetized or acutely spinalized animals but cannot without proof to the contrary be assumed to be so in the normal animal or in the decerebrated one. Again in the latter, as we shall see, inhibitory effects are often suppressed in the hyperexcited extensor muscles and therefore identification of some receptor effects is better carried out under anesthesia or after spinalization.

Hoffmann and his collaborators (Hoffmann, 1922; Hoffmann and Keller, 1928) in work on man had come to the conclusion that the earliest reflexes from muscle afferents, seen when tendons are tapped, are monosynaptic ones carried directly by large afferents to the ventral horn cells, even though Hoffmann and Keller were careful to enunciate this view as a theory. On account of the brief latency of these reflexes (see Fig. 100), it seemed highly plausible even at that time. Magladery and his group (Magladery *et al.,* 1950, 1951), also working on man, have called them H-reflexes; Hoffmann spoke of

"Eigenreflexe." By a histological degeneration method Szentágothai (1948) has verified the existence of a monosynaptic arc from muscle afferents. Eccles and Pritchard (1937) and Renshaw (1940), by direct recording from the ventral roots, demonstrated a monosynaptic reflex to stimulation of the dorsal roots,* and Lloyd (1943b) proved it to be elicitable by brief phasic stretch and to be capable of being run at maximal afferent conduction velocities of 116m/sec. This, in terms of the anatomical and physiological knowledge then available and since confirmed (see above), could only mean that either type of large afferent, from nuclear bag endings or Golgi tendon organs, was responsible for the monosynaptic reflex effect which, in agreement with Sherrington's old results (1906, 1909, 1913) and Hoffmann's work, was found to be facilitatory on the ventral horn cells of the stretched muscles. This reflex undoubtedly is part of the classical stretch reflex of Liddell and Sherrington.

Renshaw (1940) and Lloyd (1941, 1943a) on this basis developed a method of monosynaptic testing of reflex excitability which has proved very useful. The principle of this method is simple: an electrical shock, say, to the medial gastrocnemius nerve is kept weak enough to stimulate large afferents only. Let us assume that it succeeds in activating 25 per cent of the ventral horn cells, which will respond with a synchronous reflex volley 25 per cent maximal. If, then, the same or a synergist motoneurone "pool" is activated in advance by a subthreshold conditioning shock to the medial or lateral gastrocnemius nerve, the monosynaptic reflex will be found to have increased to, say, 75 per cent maximal. This signifies that additional ventral horn cells, remaining in a state of subliminal excitability (the "subliminal fringe" of Denny-Brown and Sherrington, 1928) after the first or conditioning shock, were raised to firing level by the monosynaptic test shock. The advantage of this method of measuring reflex excitability by the size of the subliminal fringe is that it avoids the complications of antidromic stimulation and of the γ-loop because the ventral roots may be cut.

From what has been stated above it is clear that this advantage is to be had in full measure only if the first or conditioning shock actually has been subliminal, so that no neurones have fired and consequently were not able to backfire into the spinal cord by the Renshaw feedback. In trying to develop monosynaptic testing for use with stretch or contraction of the muscle as a conditioning stimulus, I found it (1950a) to work reasonably well with anesthetized animals, and also if the

* Actually, Eccles and Sherrington (1931) saw a reflex latency as short as 0.4 msec.

monosynaptic test volley was elicited from the cut nerve of a synergist to the stretched or contracting muscle. For this situation Brock, Eccles, and Rall (1951) introduced the term *heterosynaptic testing* (i.e. synergist testing). By *homosynaptic* testing they meant conditioning and test volleys traveling in the same afferent nerve, a situation likely to introduce some complications from firing, unless the excitability of the spinal cord be lowered by anesthesia.

Actually, Brooks, Downman, and Eccles (1950a,b) held that the ventral horn cells became depressed in excitability even by afferent shocks at strengths below firing level for the efferents, their so-called "subsynaptic depression." It is difficult today to accept this notion without further evidence. The reason for this is twofold: partly, as will be shown below, that there are both excitatory and inhibitory afferents represented among the rapidly conducting fibers, partly that the Renshaw feedback does not require many firing cells to come into operation (see above), and in recording from undivided roots it is very difficult to be certain whether or not a few fibers have fired.

As pointed out by Granit and Job (1952) and by Hunt (1952a) the results obtained in studying reflex effects of stretch and contraction differ according to whether motoneurone excitability is defined by monosynaptic testing or by myography and electromyography in the classical way (cf. Job, 1953a,b). This we understand still better today, now that the role of the recurrent collaterals has been clarified by the work referred to. Thus, for instance, the higher the initial tension, the greater, within limits, the reflex contractile response to stretch (Liddell and Sherrington's stretch reflex); yet, by contrast, monosynaptic testing will in general indicate the greatest amount of facilitation to stretch in very light initial tension. There are other situations, such as anesthesia, spinalization, etc. (Granit and Job, 1952), in which electromyography and monosynaptic testing are at variance, partly, at least, because the latter test measures the number of neurones in the subliminal fringe, many of which may not fire, or if they do may exert a stronger feedback inhibition upon the subliminally activated neurones in the fringe than upon those which are kept active by a particularly large number of facilitatory channels. There may also be physiologically significant differences, at the moment unknown, in the strategic organization of mono- and polysynaptic projections on the ventral horn cells. Stretch is a far more complicated stimulus than a test shock.

The new methods of testing have not abrogated the old standards of control based upon proper fixation, denervations of the limb, and isolation of the muscles the reflexes of which are to be studied. These methods

were developed in Sherrington's laboratory and should be well known. Yet in much work of recent years, not to be taken up in this chapter, attention has not been paid to such precautions, and for this reason the results are often difficult to interpret.

7. *The stretch reflexes on α-efferents*

The classical work of the Sherrington school established the well-known facilitatory stretch reflex, phasic and postural (tonic), which was mainly studied on the decerebrate preparation in which, as we shall see, the reflexes of the γ fibers also are particularly lively. These were not known at the time. They will be discussed in Chapter 7. Myography and electromyography being the only indicators available at that time, the output had to be considered in terms of α fibers alone. When in the decerebrate animal a limb was excessively bent, the extensors were found to put up reflex resistance, which increased up to a point and then suddenly gave way. This was the "clasp-knife" or "lengthening" reaction (Sherrington, 1909, 1913) assumed to be caused by stimulation of high-threshold inhibitory receptors by excessive tension, so-called autogenetic inhibition. The term "autogenetic" implies reflexes which arise in the muscle studied and return to it. As we shall see, no reflexes are strictly autogenetic. The facilitatory stretch reflex Sherrington found to be inhibitory on the antagonist muscles, and thus it fitted into his scheme of reciprocal innervation (see also Creed *et al.,* 1932). Lloyd (1941, 1946a,b) later propounded the view that the inhibition on the antagonists also was monosynaptic, but the recent work by Eccles, Fatt, and Landgren (1954) does not support it. They find that antagonist inhibition to stretch is disynaptic, thus involving—as one might put it—an inhibitory "commutator." For the present purpose this difference of opinion can be neglected.

The previous sections have made it clear that our first aim should be to describe the reflex effects of two rapidly conducted types of afferents arriving from nuclear bag endings and Golgi tendon organs respectively, as well as of one from the slower myotube endings. From Lloyd's measurements, mentioned above, it was clear that either nuclear bag endings or Golgi tendon organs must be responsible for autogenetic excitation. Approaching this problem from the other end, that of autogenetic inhibition, I made use (1950a) of the arrangement for monosynaptic testing illustrated in Fig. 101a. The ventral root is cut (together with all adjacent ventral roots) and recording electrodes for the monosynaptic test response applied to the central stump. Through

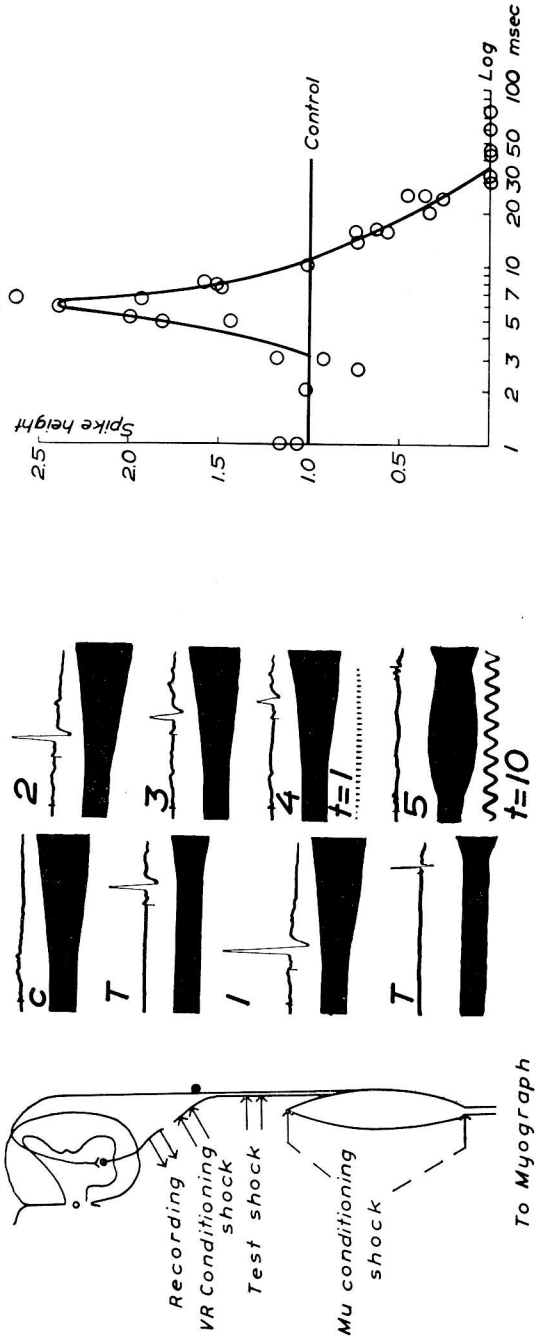

Fig. 101a. Cat. Dial. Excitability of gastrocnemius during contraction of gastrocnemius. *Left:* diagram illustrating experimental arrangement. *Right: c,* conditioning shock alone, its discharge above, its myogram below; *T* (*upper*), test shock with its myogram; 1–4, both together at different time intervals (t = 1 msec.); *T* (*lower*), test shock alone at $t = 10$ msec.; 5, together with conditioning shock at $t = 10$ msec.

Fig. 101b. Cat. Dial. Variation of spike height relative to monosynaptic control = 1.0 plotted against interval between conditioning and test shock. Conditioning shock on ventral root L_7, test shock on med. and lat. gastroc. nerves. Initial tension 250 gm. Conditioning shock elicits contraction of 550 gm. (Granit, *J. Neurophysiol., 13,* 351. 1950a.)

the peripheral stump a contraction could be elicited, and also by direct stimulation of the muscle. The test shock for the monosynaptic volley was applied to the muscle nerve, alternatively to a cut branch of a synergist for heterosynaptic testing. Both methods were used.

The control monosynaptic response is shown in *T* (Fig. 101a), and in *C* the very small reflex response from the contracting muscle, small owing to barbiturate anesthesia. Samples illustrating the initial facilitation and the later depression of the monosynaptic response are shown in 1–5, for different sweep speeds of the cathode ray. On the right is the curve obtained. Thus, reflex contraction works with self-regulation. It is first speeded up by facilitation, then brakes are applied to stop further self-excitation (cf. Granit and Suursoet, 1949, and for work on man, Magladery *et al.,* 1951).

Fig. 102 illustrates an experiment (Granit, 1950a) with heterosynaptic or synergist testing, the contraction (lower record) being in the ankle extensor gastrocnemius, the test (upper record) in the hip extensor quadriceps. The animal was in Dial anesthesia and in addition was spinalized. To the left, contraction is elicited with a single shock, to the right with a tetanus. There is profound inhibition, the monosynaptic test response (control in record 1) being completely obliterated during the whole period of just maximal tetanic stimulation, i.e. at stimulus strength below the value necessary for activating the muscle spindles by γ fibers. Clearly, then, inhibition cannot be due to a sense organ of spindle type that, unless specifically activated, pauses during a pure α contraction. This experiment has since been confirmed by Hunt (1952a), who has drawn the same conclusion.

These results on autogenetic inhibition naturally pointed to the Golgi tendon organs, the more so because at the same time McCouch and his collaborators (1950) were carrying out experiments with electrical stimulation of the quadriceps tendon and in some experiments succeeded in obtaining a relatively pure early inhibition which they also ascribed to tendon endings. It proved difficult to obtain inhibition selectively; they had, in fact, an early facilitation lasting about 2 msec., which suggested that the stimulus first activated another type of receptor.

In our experiments the early facilitation speeding up the muscle contraction was often of shorter duration than in Fig. 101. Again, in the livelier decerebrate preparation, inhibition is often concealed but can then easily be uncovered by superimposing stretch upon contraction (Hagbarth and Naess, 1950a). Inhibition was favored by an increase in initial tension (Granit, 1950a), in agreement with the fact

that the tendon organs have higher thresholds than the muscle spindles (Matthews, 1933, since repeatedly confirmed by Kuffler, Hunt, and

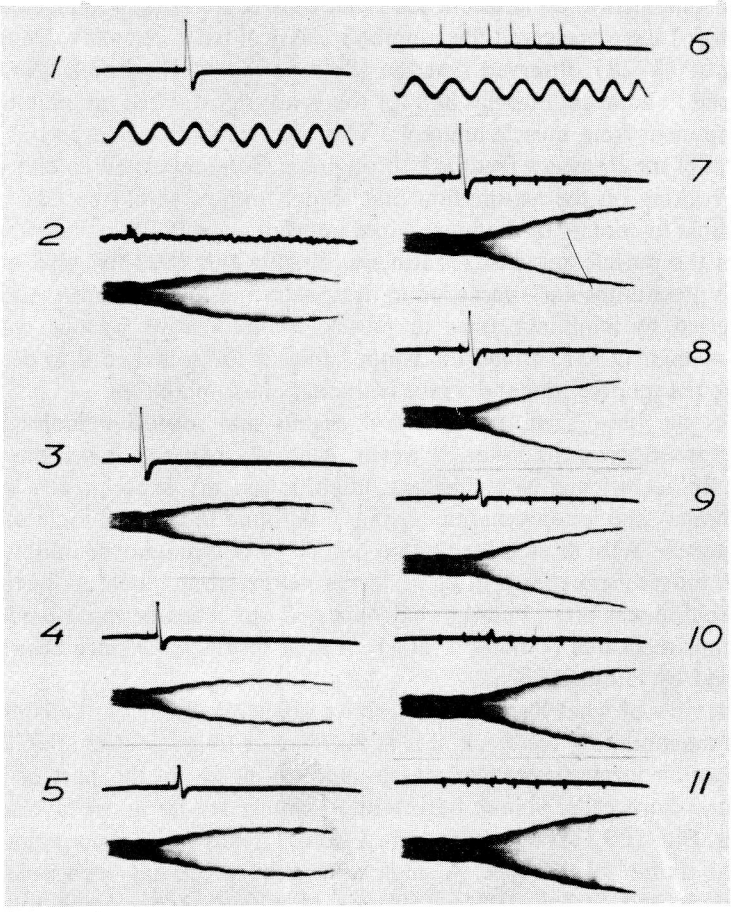

Fig. 102. Experimental arrangement as in Fig. 101. Stimulation of severed ventral root to elicit gastrocnemius contraction, during which the spinal center of the quadriceps muscle is studied by monosynaptic testing. 1: quadriceps monosynaptic control, 2: effect of conditioning shock alone at high amplification, 3–5: combined responses, 6: form of tetanic stimulus, 7–11: combined responses showing complete inhibition that lasted within the visible range of the tetanic gastrocnemius contraction, while with the single shock (left) inhibition nowhere in the contraction went below minimum illustrated in record 5. Time: 100 cy/sec. (Granit, *J. Neurophysiol., 13,* 351. 1950a.)

our group). Job (1953b) made a special comparison of decerebrate and spinal animals and in the latter found autogenetic inhibition domi-

nating autogenetic excitation. He also confirmed the fact illustrated by Fig. 102 that autogenetic inhibition actually is distributed to distant synergists at an adjacent joint and thus is not strictly autogenetic, though I have preserved Sherrington's classical term. Actually, Denny-Brown (1928) observed that the silent period (orthodromic shock) spread to adjacent muscles and for this reason postulated an inhibitory component from muscle afferents. This one would now interpret as an effect of the Renshaw feedback through the Golgi recurrent collaterals.

Working on the assumption that tendon organs would be less susceptible to cooling of the muscle and interference with its blood supply than the muscle spindles (Matthews, 1933), Job (1953b) also tried such procedures and succeeded in demonstrating that excitatory effects reverted to inhibitory ones in muscle maltreated in various ways. Henneman (1951) found the temperature of the spinal cord to determine the relative preponderance of excitation or inhibition.

As we have seen, both tendon organs and muscle spindles are stretch-sensitive, the latter, however, generally being of lower threshold. In accordance with this fact, inhibition in my experiments, both by homo- and heterosynaptic testing, was found to succeed facilitation to stretch. With stretch facilitation tended to dominate over inhibition and, indeed, sometimes in light stretch increased as much as fivefold. Inhibition was often found to be concealed but could be uncovered by various measures (Granit, 1950a). Similar results have since been reported by Hunt (1952a).

In view of what has been said above about the recurrent collaterals and the inhibitory feedback, it is of importance to investigate inhibition to stretch in circumstances which suppress firing on the part of the ventral horn cells. Spinal, barbiturate animals are the most favorable ones. Fig. 103 (arrangement as in Fig. 101) illustrates an experiment on an animal of this type. A single ventral horn cell has been isolated (Granit and Ström, 1951a). It was identified as belonging to the gastrocnemius muscle. In the uppermost record it has been activated by a shock to the gastrocnemius nerve. In the next record the test shock (see artifact) has been tried again but in this case after the experimenter has very slowly weighed down the thread joining muscle and myograph so as to increase initial tension and yet avoid reflex activation. During pressure maintained thus the ventral horn cell became inhibited to the extent of refusing to discharge to the test shock. This happened without reflex firing of the cell. The experiment has since been repeated and confirmed by Hunt (1952a). With the mass

response from the root it has also been carried out by Henneman (1951).

From this experiment alone it could not be concluded that the inhibition arose only in Golgi tendon organs. I had found (Granit, 1950a) that when the nerve to a limb extensor was compressed, excitation to stretch disappeared shortly before inhibition, suggesting that

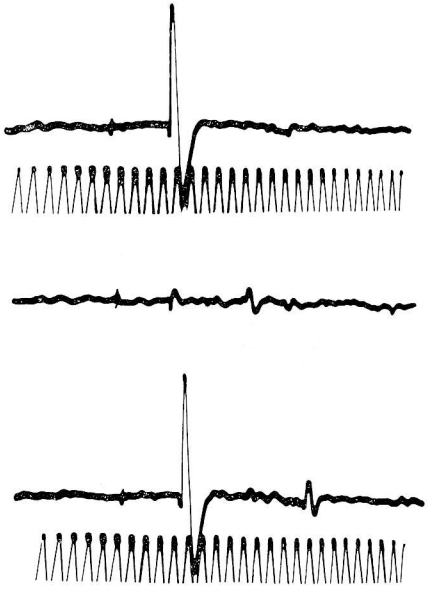

Fig. 103. Single ventral root fiber reflexly activated by test shock to gastrocnemius nerves (note shock artifact). *Uppermost* record taken with muscle at light tension. *Middle,* effect of test shock completely inhibited during permanent pressure on string joining muscle and myograph. *Bottom,* after release of pressure. No phasic stretch. Time in msec. (Granit and Ström, *J. Neurophysiol., 14,* 113. 1951a.)

among the slowly conducting extensor afferents there would be a relatively greater number of inhibitory ones. In the same paper it was reported that when an extensor muscle was stimulated (in the arrangement of Fig. 101) through the cut ventral root at strengths sufficient to activate γ efferents the effect was an increase of inhibition, although, of course, the myogram remained uninfluenced. We (Granit and Ström, 1951a) therefore tried to find out how early single ventral horn cells could be inhibited at high initial tensions in the absence of firing.

The experiment of Fig. 104 (arrangement as in Fig. 101) was car-

ried out on a single ventral horn cell stimulated by stretch. The monosynaptic test shock in the upper half of the figure (low initial tension) was just subliminal, so that in ten control trials without stretch it failed to fire the ventral horn cell. The test shock was elicited from the medial gastrocnemius nerve. The lateral branch could neither

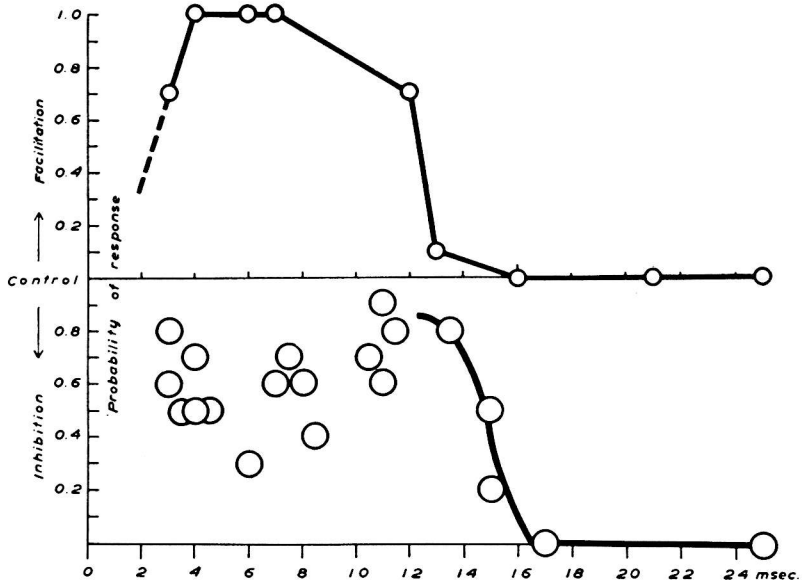

Fig. 104. Early facilitation at light tension and early inhibition at high tension during slow stretch starting at zero abscissa. Single fiber preparation analyzed in terms of probability (Pr) of response.

A neurone tested during stretch by shock from med. gastroc. nerve. *Upper curve:* light tension and stretch. Test shock (Pr = 0/10 at rest) subliminal so as to reveal level of excitability during facilitation by stretch. *Lower curve:* med. gastroc. nerve now tied below electrodes, and muscle at high initial tension. Pr put at 10/10. Afferent discharge (through lat. gastroc. nerve), as shown by large number of observations taken (200), now gave inhibition from beginning. (Granit and Ström, *J. Neurophysiol., 14,* 113. 1951a.)

by itself nor supported by afferent stretch impulses from both nerves elicit an effect to a supramaximal test shock. The upper curve illustrates that with light tension and 2 mm. stretch (proceeding at constant rate along the abscissa) there was facilitation as long as the medial gastrocnemius nerve was intact. The ordinates show probability of response (*Pr*) in ten trials for each moment of stretch tested. Each experimental point is therefore based on 10 observations. The single

ventral horn cell did not fire in response to the test shock alone ($Pr = 0$), but facilitated by stretch it fired with a probability (*Pr*) of 10/10, i.e. ten times in ten trials. Then, in order to curtail the afferent inflow, the medial gastrocnemius nerve was severed and at the same time the muscle was put under high initial tension to increase autogenetic inhibition. With the curtailed inflow this proved possible without eliciting a natural reflex impulse to stretch. The test was adjusted to give a control probability of response of 10/10($Pr = 1.0$) and this basic value was repeatedly checked. Now there was inhibition (lower curve) from the very beginning. The experiment demonstrates that the inhibitory organs require high tension in order to overcome the effect of the excitatory ones and that under such circumstances they may succeed in blocking the discharge as quickly as the excitatory ones can facilitate it.

It seemed fairly clear from all these experiments that there are inhibitory fibers just as fast as those responsible for excitation and, also, that they are capable of exercising their effect during contraction when the spindles are silent. It was hence concluded that the spindle endings represented in fast afferents were destined to become the excitatory monosynaptic ones of Lloyd (1943b), while autogenetic inhibition was carried by the similarly fast Golgi tendon organs.

Szentágothai (1948) had reported that the afferent fibers from the jaw closing muscles enter the brain stem by way of the *motor* root, while those of the tendon organs pass through the *sensory* root. This interesting anomaly was utilized by McIntyre (1951) to demonstrate that responses of endings having the characteristics of spindle receptors actually were obtained from the severed motor root of the fifth cranial nerve. Since these were large-fiber afferents, McIntyre concluded that they were of the nuclear bag type.

Denny-Brown (1928) saw activation of the antagonist flexor during contraction in the ankle extensor and associated it with genuine inhibition during the silent period. Fig. 105 shows an analysis of the reciprocal component of gastrocnemius excitation as measured by the behavior of the monosynaptic response elicited in the nerve stem to the ankle flexors. It is seen that during the rising phase of the gastrocnemius contraction, which is the time of the pause in the spindle discharge, the flexor monosynaptic response is facilitated. The autogenetic extensor inhibition thus provides reciprocal excitation to the antagonist flexor. This reciprocal effect could occasionally be demonstrated with stretch, but it hardly ever failed to appear even in submaximal contraction in agreement with the fact mentioned that contraction stimulates the

tendon organs far more powerfully than stretch and also sets up more autogenetic inhibition (Granit, 1950a, 1952a). The same experiment has been performed by Hunt (1952a), with the same outcome. These results should also be interpreted in the light of the statement made in sec. 5 to the effect that autogenetic inhibition is integrated into the silent period as one of the brakes in reflex self-regulation of the muscle contraction. Cessation of spindle firing leaves the discharge from the Golgi tendon organs in possession of the field.

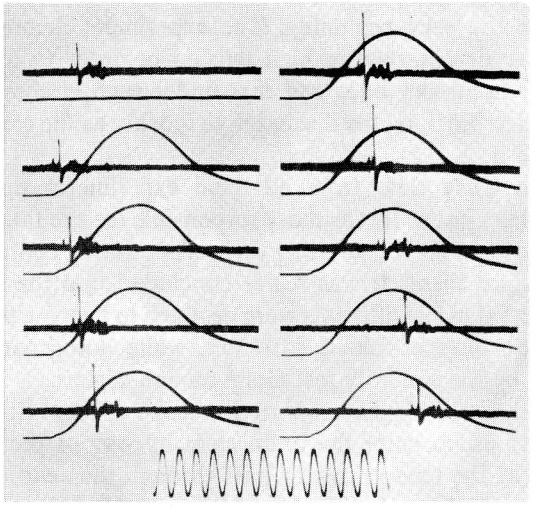

Fig. 105. Cat, decerebrated, spinal. Four supramaximal stimuli to S_1 cut ventral root, setting up contraction of gastrocnemius (extensor). Monosynaptic test response from deep peroneal nerve (to flexors) recorded from L_7 ventral root. Monosynaptic control uppermost record, left. Time: 100 cy/sec. (Granit, *J. Neurophysiol., 15,* 269. 1952a.)

The decerebrate preparation used in classical reflexology made it easy to study the effects of stretch and contraction of flexors upon extensors which, on account of the postural contraction, provided a good background for both excitation and inhibition. The old work had made it clear (see e.g. Sherrington, 1909, 1913; Cooper and Creed, 1927a,b; Liddell and Sherrington, 1925) that stretch or contraction of the flexors regularly inhibited the extensors. Similarly, from Lloyd's work (1946a,b) it appeared that his monosynaptic facilitatory stretch reflex behaved in the same manner. Thus, autogenetic facilitation, like autogenetic inhibition, is organized in a reciprocal fashion. Ankle flexors and extensors act according to the principle of Sherrington's

(1913) "double reciprocal innervation." In terms of receptors: the spindles facilitate their own muscle and inhibit the antagonist, the Golgi tendon organs do the reverse. The net result of this may sometimes be simultaneous contraction or slackening of both flexors and extensors. Observing such "exceptions," some have concluded that true reciprocal innervation does not exist. Sherrington, however, real-

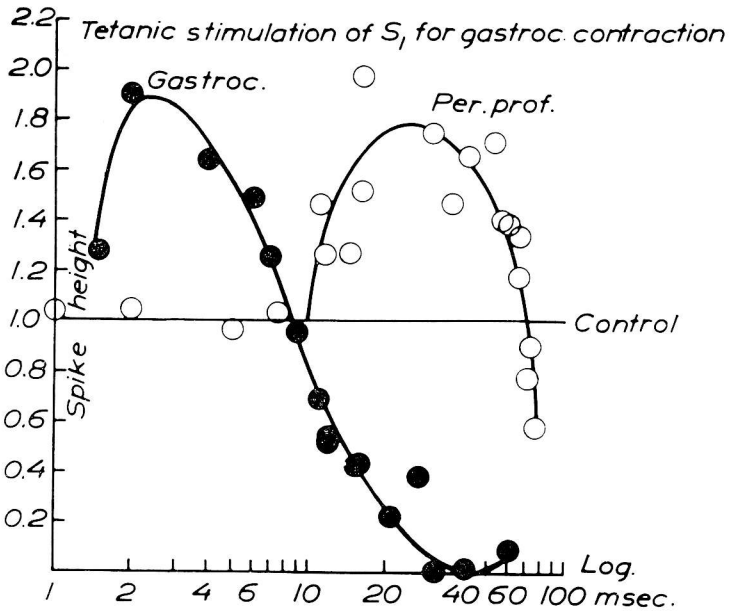

Fig. 106. Effect of a tetanic gastrocnemius contraction from the severed ventral root S_1 on its own spinal center (Gastroc.) and that of the antagonist flexor (Per. prof.). Spinal cat. Dial. Tetanic stimulation at 15 × threshold, proceeding at a rate of 240/sec. Analysis of variations in monosynaptic responses recorded from L_7 ventral root, as described in text. Gastrocnemius contraction at good initial tension. (Granit, *J. Neurophysiol., 15,* 269. 1952a.)

ized from the beginning that reciprocal action on antagonists meant something only in terms of one type of receptor.

While double reciprocal innervation is the principle of reflex organization, this does not necessarily mean that the effects are symmetrical in flexors and extensors. In fact, I have never found it to be so. In the anatomical section it was pointed out that the afferent caliber spectra of the ankle extensors also differed considerably from that of the ankle flexor (tib. ant.). The typical physiological result, if both systems are tested in the same preparation, is illustrated in Fig. 106. The flexor

response (per. prof.) was tested during gastrocnemius contraction. There was no early reciprocal inhibition in the flexor corresponding to the early facilitation in the gastrocnemius system (tested afterward heterosynaptically). The autogenetic inhibition in the gastrocnemius—as in Fig. 105 and practically always—activated the flexor center reciprocally. Again, with the ankle flexor contraction one generally obtains pure inhibition of the extensor system, not the reciprocal facilitation from tendon organs. The two systems moving the limb around the ankle are therefore highly asymmetrical: the reciprocal effect of the flexor upon the extensor is chiefly run by the spindles and consists of reciprocal inhibition, while the corresponding effect of the extensor upon the flexor is run by the Golgi tendon organs—and probably by myotube endings—and consists of excitation. According to the recent results by Hunt (1953) the myotube endings are inhibitory on extensors and excitatory on flexors. The double reciprocal effects can be found, but special measures must be taken to uncover them (cf. Hunt, 1952a, 1953). Normally they are concealed (Granit, 1952a) below the dominant factor in the sum total of events.

The asymmetry may seem surprising, but with Sherrington (1913) we have to inquire into the "biological meaning" of it, and then it seems reasonable. The powerful extensor muscles support the weight of the body, while the step is started by the less well-developed flexors, the leg being lifted from the ground. The flexor contraction immediately inhibits the extensors reciprocally, and this process, as we have seen, is started by the spindles in the flexor. This initial inhibition upon the extensors, however, is soon overcome by the powerful stretch reflex started in their spindles (nuclear bag endings) when the knee is bent in being lifted from the ground, with consequent stretch of the extensors. The extensors contract and the leg is swung forward. Overswing is prevented by the tension exerted by the contraction upon the Golgi tendon organs, which inhibit the extensor contraction and at the same time help to fix the leg by eliciting a reciprocal contraction in the flexors. It should be clearly understood that the step is regulated by other spinal mechanisms (Sherrington, 1913, Graham Brown, 1914), including the efferent spindle innervation, but the general principles of peripheral self-regulation are laid down in this asymmetrical system of double reciprocal innervation that I have described. Into this the events in the myotube endings should be fitted. The systems are beautifully organized and we shall see later how the efferent spindle innervation adds to the perfection.

The general conclusions concerning the reflex effects of nuclear bag

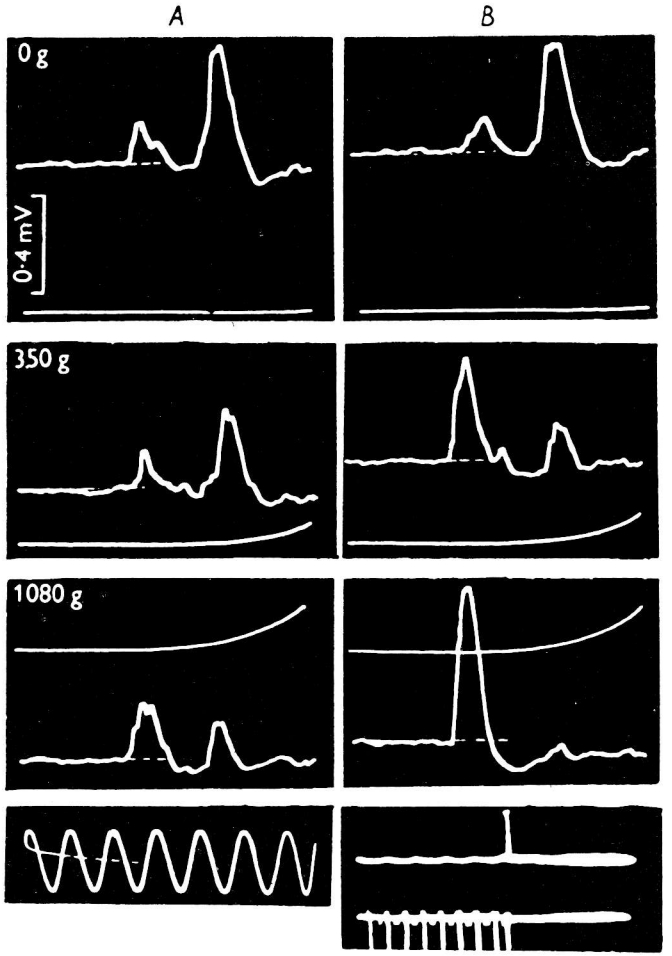

Fig. 107. Decerebrate cat. Record of group monosynaptic response to single shock stimulation of intact nerve of gastrocnemius medialis at 0, 350, and 1080 g. initial tension. *Second trace:* strain gauge record. Muscle nerve stimulus at beginning of sweep. *A:* control responses. *B:* same with preceding stimulation of 28 small-nerve fibers to this muscle—muscle nerve shock (MN) at onset of sweep coincides with last of a train of 9 stimuli at 100/sec. to small-nerve fibers (SN), as shown on reduced time-base speed in bottom record. Time signal: 1,000 cy/sec. Note that in *A* monosynaptic response with latency of 2–5 msec. is followed by a second potential (less at higher tensions). At zero tension, small-nerve stimulation has no demonstrable effect, while at 350 g. the monosynaptic response is facilitated (*B*) and the second potential reduced. At 1080 g. the facilitation is greater. (Hunt, *J. Physiol., 117,* 359. 1952a.)

endings and Golgi tendon organs have been tested and confirmed by Hunt (1952a), who also approached the problems with the technique of setting up a contraction in the intrafusal fibers by selective stimulation of γ fibers. Some of his results on the spindles are shown in Fig. 107. As expected, the spindles were found to be responsible for autogenetic facilitation, i.e. the autogenetic stretch reflex. As for the Golgi tendon organs in the knee extensors, he concluded that they were responsible for autogenetic inhibition and reciprocal facilitation of the flexors. It should be realized, however, that at the time of publication of this work Hunt had not yet considered it necessary or possible to separate the effects of nuclear bag and myotube endings. Just how, or if at all, γ stimulation differentiates between nuclear bag and myotube endings is unknown.

In another manner these problems have been approached by Hagbarth and Naess (1950b), Laporte and Lloyd (1952), and Eccles and his collaborators (see below), all working with shocks to severed muscular afferents. Hagbarth and Naess first established a strength of conditioning shock that gave Lloyd's well-known curve of monosynaptic facilitation, illustrated in Fig. 108. It was then expected that tetanic conditioning at this strength would maintain the facilitation, but contrary to expectation tetanic conditioning often disclosed an inhibition which they therefore concluded had been carried by afferents of the same size (same threshold) as those eliciting facilitation. The result was held to confirm the conclusion (Granit, 1950a; Granit and Ström, 1951a) that both excitatory and inhibitory effects were represented among the large-fiber afferents. It might be pointed out that in all such experiments it is only the upper range of conduction velocities that are being established. There may be any number of inhibitory and excitatory afferents of lower conduction velocity (smaller fiber diameter). It should be made perfectly clear that there are methodical limitations in work of this kind ultimately ascribable to the fact that reflexes are averages based upon effects in a large number of afferents. We have tried, but failed, to elicit reflex action from a very small number of fibers split within the muscular tissue.

Starting similarly with the summation curve for monosynaptic autogenetic facilitation of Fig. 108, Laporte and Lloyd (1952) noted deviations from it in the direction of inhibition at shock strength which sufficed to activate only large afferents. The inhibition appeared after a central delay of roughly one half additional msec., suggesting one additional synapse. This then, on their evidence, is a disynaptic inhibition carried by large afferents, which like the one studied above with

stretch and contraction was widely distributed to synergists and facilitated antagonists. Their method of using "canonical" curves for excitation and inhibition obtained by shocks to mixed muscle nerves, and drawing conclusions from their deviations, has been criticized by Bradley, Easton, and Eccles (1953). Yet, with the support of Lloyd's

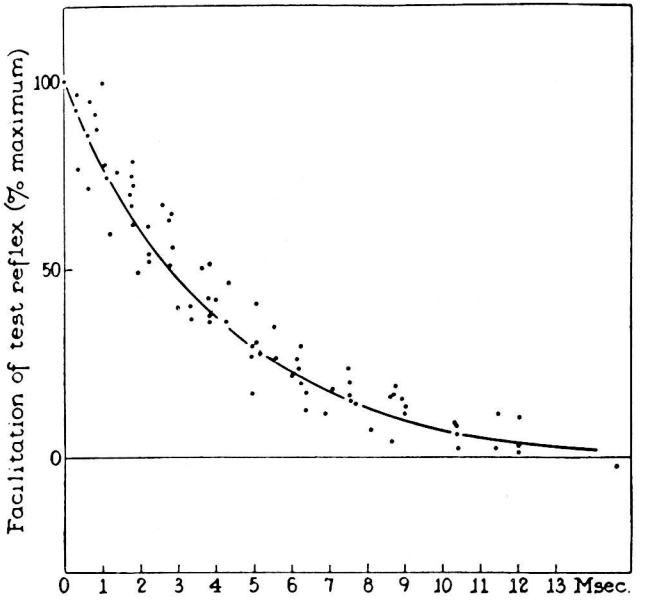

Fig. 108. Facilitation of motoneurones by impulses in primary afferent fibers. Points from seven experiments, scaled on the ordinates to coincide at the time of maximum facilitation. Relative facilitation, expressed in per cent maximum, is plotted as a function of time. The plotted curve is an exponential regression having successive half-values at 2.8, 5.6, 8.4, 11.2, and 14 msec. In four experiments facilitation in flexor nuclei was examined; the remaining three were concerned with extensor nuclei. (Lloyd, *J. Neurophysiol., 9,* 421. 1946a.)

considerable experience, it apparently has worked well enough to deliver results in substantial agreement with our results and those of Hunt on autogenetic inhibition from the Golgi tendon organs.

Eccles and his collaborators (Brock, Eccles, and Rall, 1951; Eccles and Rall, 1951; Bradley and Eccles, 1953; Bradley, Easton, and Eccles, 1953) find that the large excitatory and inhibitory afferents (autogenetic) in the quadriceps muscle actually are grouped around two maxima, just separable. The monosynaptic excitatory afferents are

faster and conduction velocities range from 95 to 114 m/sec. For the inhibitory ones values from 80 to 95 m/sec were obtained (Bradley and Eccles, 1953). They hold that the latter are derived from Golgi tendon organs. In the ankle muscles there is no such differentiation.

The experiments so far described have been carried out with animals in which the external loop through the muscle has been eliminated by de-efferentation or else (Hunt, 1952a) controlled. The effects of the γ efferents have thus also been eliminated. We have concluded that the nuclear bag endings are facilitatory for autogenetic reflexes, and this can hardly be doubted. However, there are some complications not yet understood. The first experiment undertaken to study the reflex effect of γ efferents (Granit, 1950a) showed, on the contrary, that increased autogenetic inhibition was obtained by stimulating the γ system. This is illustrated in Fig. 109. The experimental arrangement is that of Fig. 101. The efferent root is divided, the peripheral stump being used for stimulation of the gastrocnemius muscle (twitch), while the central stump records the monosynaptic test response. Two moments, one 15 msec., the other 32, after the conditioning shock eliciting the twitch have been picked out to demonstrate the size of the monosynaptic reflex volley (ordinate) as a function of stimulus strength (abscissa), which was carried far beyond the range that is supramaximal for the extrafusal fibers (cf. Table 4, p. 206). Thus, with increasing strength more intrafusal fibers are brought in by the activation of γ efferents. It is clear from Fig. 109 that γ stimulation of increasing strength also may augment inhibition. This experiment was repeated and confirmed by Hagbarth and Naess (1950a). Then Hunt (1952a) repeated it with tetanic conditioning, which still more effectively stimulates the γ fibers, and again confirmed it. I had already pointed out myself that the effect was not always demonstrable but, when present, it was definite. This, at the time, was a puzzling result. I drew attention to the fact that both Sherrington (1894) and Barker (1948) had also seen Golgi tendon organs in the spindles at their insertion points. But clearly, inhibitory spindle organs (myotube endings) will now have to be considered (Hunt, 1953).

Hunt (1953) has since studied separately the reflex effects of the slowly conducted impulses from myotube endings in the spindles and found them to be in the flexor pattern, i.e. inhibitory on the extensors and excitatory on the flexors. The results have not at the present time been published in full. Clearly, the lack of knowledge about the role of the myotube endings in the spindles, which, according to Matthews (1933), are the most common ones, has been a deficiency in the picture so far established. It is satisfactory to know that these are being studied.

A great deal has been said above about the monosynaptic stretch reflex in the nuclear bag afferents, so useful in testing reflex excitability. Can we assume that the nuclear bag endings act exclusively by

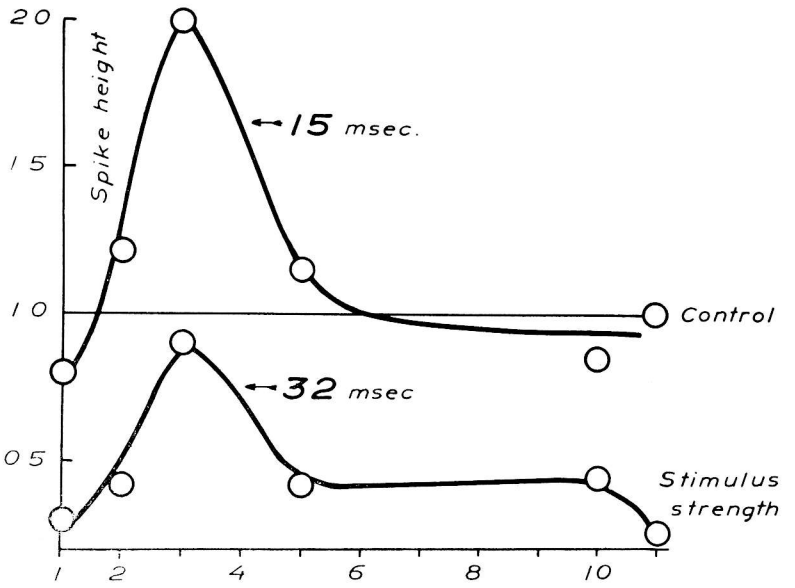

Fig. 109. Cat. Experimental arrangement as in Fig. 101. Gastrocnemius muscle stimulated by shock to cut ventral root, and the afferent effect on the spinal center analyzed by monosynaptic testing. Analysis of effect of stimulus strength.

Effect of strength of conditioning shock for gastrocnemius muscle from ventral root S_1 on size of monosynaptic response at intervals 15 (upper) and 32 (lower) msec. between conditioning and test shock. Abscissae: stimulus strength in multiples of threshold strength. Modest initial tension. (Granit, *J. Neurophysiol., 13,* 351. 1950a.)

monosynaptic paths to the ventral horn cells? This conclusion would undoubtedly be premature. On purely histological grounds it seems exceedingly unlikely that the fibers of the nuclear bag afferents would fail to branch into polysynaptic paths when coursing from dorsal to ventral roots. Again, if we make this unlikely assumption, it is to be remembered that, e.g., in the muscle gastrocnemius medialis some 45 afferent fibers would be responsible for the stretch reflex in about 300 motoneurones. In view of the large subliminal fringe, the overlap would

have to be considerable and consequently the reflex very easy to elicit. This, however, is by no means the case. The monosynaptic response is often far more difficult to elicit than the stretch reflex. The two may even behave as if there were some competition. The stretch reflex tends, for instance, to disappear in light anesthesia when the monosynaptic response may be better than before (cf. similar observations by Brooks and Fuortes, 1952; Alvord and Fuortes, 1953). Park, Teasdall, and Magladery (1951) and Dodt and Gohl (1952) point out that for man the monosynaptic response (their H-reflex or Hoffmann-reflex) may often be absent in patients who to all appearances have excellent muscular control.

Liddell and Sherrington (1924, 1925) and Lloyd (1943b) held the stretch reflex to be highly autogenetic. Granit and Ström (1951a) found that despite light anesthesia some individual ventral horn cells were fired by both the medial and lateral gastrocnemius nerve provided that some facilitation by stretch was added. Job (1953a), in our laboratory, made a special study of this question by recording from both severed ventral roots and severed peripheral nerves and proved that synergists could fire each other's motoneurones under a variety of conditions, all defined by sufficient facilitatory support from themselves or other systems. This has been confirmed independently by Roberts (1952), Cohen (1953), and Alvord and Fuortes (1953).

Many of the questions dealt with in this chapter closely concern the physiology of the spinal cord. It has been necessary, however, to delimit the subject and make a halt somewhere as an alternative to writing a chapter on the spinal cord. The latter subject will be found extensively treated by Lloyd in Howell's textbook of physiology, edited by Fulton (1946), as well as by Eccles (1953) in a recent monograph (cf. Creed *et al.*, 1932).

Chapter 7

Spinal and Supraspinal Control of Posture and Movement by the Loop to the Muscle Spindles. Rigidity. Spasticity

1. Introduction

It appears that Rossi (see below) in 1927 was the first to envisage a role for the spindle innervation corresponding to the ideas prevalent today. Leksell (1945) realized that his work required completion with a study of reflex effects of the γ fibers but did not himself attempt experimentation along these lines. Granit (1950a) and Hagbarth and Naess (1950a) next published the experiments already mentioned and were surprised to find inhibition with supramaximal stimulation of the ventral root of sufficient strength to bring in γ efferents. On Hunt's (1953) recent evidence this inhibition may well have arisen in the myotube endings of the muscle spindles.

Granit and Ström (1951b, 1952), studying the stretch reflex at light initial tension in decerebrate animals, found earlier facilitation if the external loop was left intact than after de-efferentation and concluded that the spindles were tonically innervated by the γ fibers. Sommer (1940) and Hoffmann (1951) suggested that activation of the tendon jerk in man by Jendrassik's well-known method was due to spindle activation because it was found to take place without an increase of tension in the muscle concerned.

However, most of the new information on reflexes and supraspinal control in terms of spindle afferents and γ efferents has come from the direct approach of Hunt (1951, 1952a, 1953), Kobayashi *et al.* (1952), Granit and Kaada (1952), Granit, Job, and Kaada (1952), Eldred, Granit, and Merton (1953), Eldred and Hagbarth (1954), and Granit, Holmgren, and Merton (1954). In presenting the results I shall try to build up a synthetic view based on the results of Hunt, the Japanese authors, and our group, all of which deal with the functional interpretation of records from γ fibers and spindle afferents.

Fig. 110 presents a schematic diagram of the experimental arrangement used in this kind of work unless the records are taken directly from γ efferents. The nuclear bag afferent in a root filament serves as indicator of spindle activation. The advantage of studying the spindle afferent rather than the γ efferent is that the mechanical muscular events are integrated into the picture.

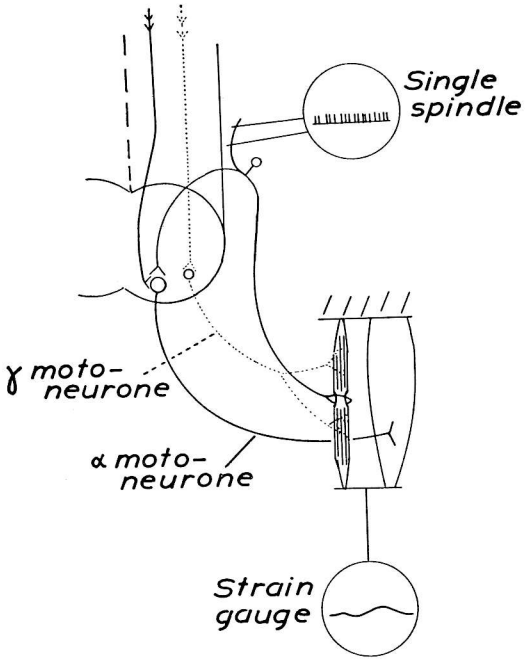

Fig. 110. Diagram illustrating arrangement of experiment for reflex work with simultaneous spindle control. Muscle with parallel intrafusal fiber containing spindle connected to strain gauge. Afferent fiber discharge from spindle isolated in dorsal root and projected on oscilloscope. Destination of α and γ fiber from ventral root of spinal cord shown. (Granit, Holmgren, and Merton, 1954.)

2. *The tonic discharge and its effect on extensor spindles*

Tasaki and his collaborators appear to have been the first to study the activity of individual γ fibers, and their work from 1944 onward has recently been summarized in English (Kobayashi, Oshima, and Tasaki, 1952). Having been ignorant of Leksell's (1945) simultaneous work, they did not realize that the small efferents in mammals

were the motor fibers of intrafusal muscle (cf. preceding chapter), but they did record their discharge. It is perfectly clear from Fig. 111 that they noted the tonic firing in the fibers, found by Kuffler, Hunt, and Quilliam (1951), Hunt (1951), and Granit and Kaada (1952), which firing, indeed, is such a very striking feature of this system. The tonic resting frequencies are high. Even in his spinal animals Hunt (1951) recorded values from 20 to 60 per sec.

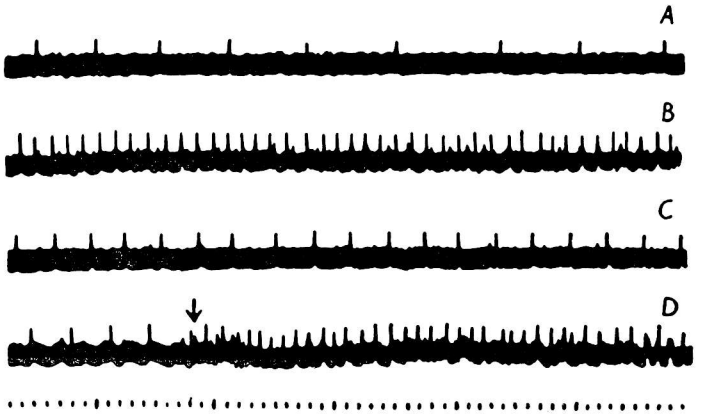

Fig. 111. Cat under urethane. Action currents recorded from three myelinated fibers of below 5 μ in diameter innervating the medial head of gastrocnemius. *A:* spontaneous efferent discharge from the spinal cord, *B:* increase in the frequency of discharge by decerebration, *C:* record taken about 10 min. after decerebration, *D:* increase of the frequency by repetitive induction shocks applied to the contralateral sciatic nerve (started at the arrow). Time: 10 msec. (Kobayashi, Oshima, and Tasaki, *J. Physiol., 117,* 152. 1952.)

As shown by Fig. 111, Kobayashi *et al.* found the discharge to increase after decerebration and to accompany reflex action. Their results with the well-known spinal reflexes agree with those of Hunt insofar as γ activity is concerned, but their interpretation is that these fibers are tonic motor fibers capable of supporting decerebrate rigidity by themselves. This conclusion is based on the observation that the large α fibers were found to be silent in decerebrate rigidity. However, long ago Dusser de Barenne (1911) and Buytendijk (1912) showed that string galvanometer records of the electromyogram in decerebrate rigidity indicated persistent activity, for some time afterward spoken of as the Dusser de Barenne-Buytendijk vibrations, and so it is rather improbable that their view can be correct even if, as pointed out above, functions to some extent will overlap in caliber spectra. Long ago

Denny-Brown (1929) and Adrian and Bronk (1929) studied this tonic activity in single motor units. Granit and Kaada (1952) isolated a large number of small and large fibers in ventral roots. In general it seems true that most small fibers discharge tonically while most large fibers are silent, but even in barbiturate anesthesia there will be active α fibers. Recently Gernandt (1952) has studied vestibular reflexes (cf. Adrian and Bronk, 1929) in decerebrate animals and has had no difficulties in finding persistent α activity.

In order to make clear what the tonic γ discharge signifies in terms of spindle activity Fig. 112,*B*, compares, for a decerebrate animal, the spontaneous activity of the spindle with intact innervation with *C*, the

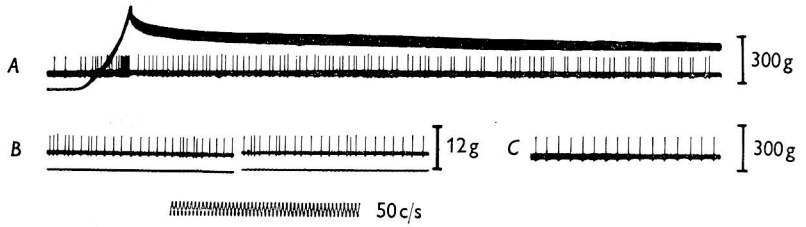

Fig. 112. Effect of activity in γ motor fibers on spindle discharge. *A:* irregular discharge before and during a 10 mm. stretch. Note rhythmic bursts. *B:* samples at high myograph sensitivity to show irregularity in the absence of any corresponding muscle contraction. *C:* same spindle after de-efferentation, responding with characteristic regularity. Anemic decerebration and chloralose (20 mg/kg.). Spindle in gastrocnemius. Myograph on second trace. (Eldred, Granit, and Merton, *J. Physiol., 122,* 498. 1953.)

same baseline discharge after de-efferentation. When here, as elsewhere, I speak of spindle activity I refer to a nuclear bag afferent as indicator because the single fibers have been isolated in the roots (Fig. 110) in which myotube afferents are but rarely obtained. The excited spindle exhibits a persistent irregular discharge, often grouped, while the nonexcited spindle (which is identical with the purely peripheral muscle-nerve preparation hitherto discussed) has a very much lower rate of spontaneous firing. This also is characteristically regular unless too low. A spindle discharging at a rate below some five impulses per second does not seem to be able to fire regularly (cf. Matthews, 1933). Also in barbiturate anesthesia there is irregular firing in excited spindles. In Fig. 112,*A*, stretch has been applied and the grouping of the spindle discharges may well indicate synchronous rhythmic γ outbursts to the intrafusal fibers. For convenience I shall speak below of excited and nonexcited spindles when comparing discharges before and after

de-efferentation. In our work de-efferentation has been used as a standard of comparison for describing effects of γ efferents against a reference point of zero γ control.

The two upper records of Fig. 113 illustrate a 10 mm. stretch of the muscle for an excited spindle with a spontaneous rate as high as 40/sec. at the zero initial tension used, the lower ones the same experiment after de-efferentation. The strain gauge myograph had

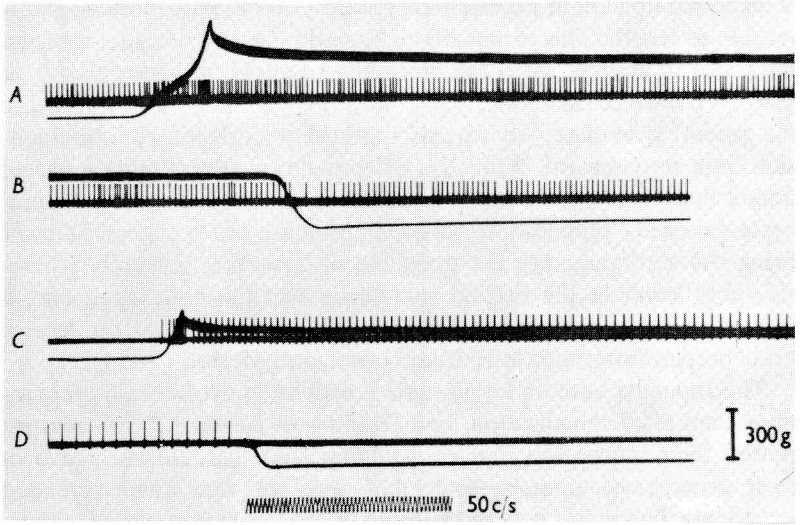

Fig. 113. Effect of γ activity during phasic stretch. Records from a gastrocnemius spindle. *A:* muscle slack and then extended 10 mm. *B:* continuation of *A* after a break of 10 sec. *C:* a similar stretch after cutting the ventral roots; smaller myograph excursion due to absence of stretch reflex. *D:* continuation of *C* after a break of 32 sec. Same spindle as in Fig. 112. (Eldred, Granit, and Merton, *J. Physiol., 122,* 498. 1953.)

been mounted on rollers and movement started with the muscle just slack. There is clearly a considerable stretch reflex in the intact preparation *A–B* (decerebrate cat) as can be seen by comparing the myograms of, respectively, the upper and lower sets of records. The nonexcited spindle *C–D* was silent at zero tension when stretch started. While stretch is maintained, some adaptation takes place, as has been shown by Adrian and Zotterman (1926a) and Matthews (1933) for the nonexcited spindles they always used, even though these organs belong to the category of receptors which have little adaptation compared with rapidly adapting ones. Part of this adaptation will be due to the viscoelastic properties of the stretched tissues but—as in other

receptors—there must be a genuine adaptive mechanism superimposed upon the effects of the mechanical factors. Adaptation in stretch receptors has been studied by Bronk (1929) and Matthews (1931). Now, when comparing the adaptive process in excited and nonexcited spindles, we found that the impulse frequencies, though throughout very much higher for the excited spindle, tend to drop along roughly parallel curves in both instances, but for the excited spindles this curve is displaced upward in a coordinate system of frequency plotted against tension or length. This means that γ bias still must be considerable at a time, late in stretch, when the nonexcited spindle fires very slowly or may even have ceased altogether to respond. The same shift upward in the general level of activity was also noticed at all degrees of initial tension from zero upward. While it is quite common at zero tension to find nonexcited or de-efferented spindles silent, those of the intact decerebrate (excited) preparations in good condition are practically always firing. As a consequence the threshold of excitation generally is considerably lower in the excited spindle than in the nonexcited one, a fact of great physiological importance. These observations on decerebrate preparations refer to Eldred, Granit, and Merton (1953).

The Japanese authors found more γ activity in decerebrate preparations than after spinalization, and Granit and Kaada (1952) also reported their impression that the spindles were particularly active in their decerebrate animals. Since that time our very much extended experience has made it possible to state that in cats decerebrated by pre- or intercollicular sections the spindles uniformly fire at exceptionally high rates and do so even in the absence of rigidity (α activity). Hunt noted that when, in decerebrate animals, a spontaneous increase of tension took place, this too was accompanied by efferent γ firing, and Granit and Kaada confirmed this, using the spindle as afferent indicator.

In order further to elucidate this question an experiment was devised, based on the principle of the anemic decerebration of Pollock and Davis (1930). The basilar artery of the cat (chloralose) was tied under ether at the operating table and slings placed around the common carotids. When the strings were pulled, anemic decerebration took place. As soon as the rise in tension began, or at the latest when it was maximal, the slings were released and the animal allowed gradually to return to the *status quo ante*. This kind of decerebration has the advantage that it can be repeated several times.

Fig. 114 is an evaluation of spindle frequencies and myograph values during this procedure. It is seen to have taken 20 seconds of carotid

occlusion to release the formidable rise of tension which is the initial phase of anemic decerebration. The soleus muscle was used, and it has apparently contracted to the maximum obtainable (cf. the maximal tetanic contraction values for this muscle given by Eccles and Sherrington, 1930 and in Chapter 6). The interesting point, however, is that this activity not only is initiated in the spindles (cf. Hunt, 1951) but that in addition the spindle discharge is maintained high throughout the slow tonic contraction. This would hardly be possible against

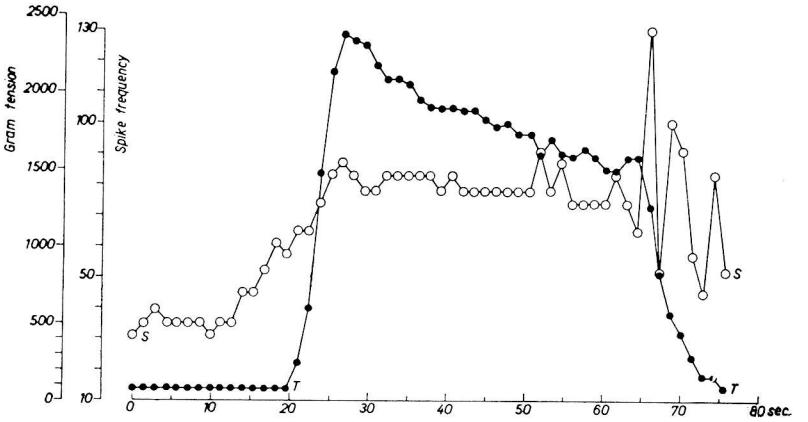

Fig. 114. Cat. Chloralose 20 mg/kg. Permanent clamp on basilar artery. Slings around carotids. The two ordinates refer to myogram (*T* and *filled circles*) and spindle frequency (*S* and *open circles*). At zero abscissa, carotids occluded and released when tension reached maximum. Compare curves *S* and *T*.

the strong extrafusal contraction without intrafusal contraction of much the same order. When the muscle tension drops, the spindle continues to fire for some time. Hence the contracted intrafusal fibers are pulled upon and consequently stimulated. There are, thus, a number of violent intrafusal stretches superimposed upon the fall of the tonic extrafusal contraction toward the baseline. By themselves the spindles do not succeed in causing a renewed rise of tension (fatigue of the muscle?), but they may have retarded the fall. This experiment, as stated, is easily repeatable 3 to 4 times in the same cat and has given the same result in a number of animals. Hence it supports the conclusion that γ hyperactivity leading to intrafusal cramp is an important feature of rigidity.

If the carotids are left occluded, there is a fall in tension after the

strong initial effect described above. When later on smaller postural contractions spontaneously return and disappear, the same sequence of events is observed. It will be shown below that after permanent anemic decerebration of animals left to recover from the ether narcosis without additional anesthetics, a curious disintegration of α from γ activity takes place. In fact, decerebration by the anemic and trephine methods respectively produces two different types of rigidity. The latter method alone can be relied upon to elicit with great regularity a high level of spindle activity.

Sherrington (1898) pointed out that the anomalous state which he called decerebrate rigidity may not be the only kind of rigidity and it is clear from very satisfactory evidence that states of the same general type may occur in animals deprived by de-afferentation of both γ loop and postural limb reflexes (see for references the recent review by Moruzzi, 1953). I shall return to this question below. Sherrington used to speak of the state of decerebrate rigidity as exaggerated posture. Apparently the spindles through their facilitatory effects on the ventral horn cells contribute their full share of this exaggeration.

3. *Inhibition of γ fibers in stretch. Integration of α and γ in the "lengthening reaction"*

One of the most important observations made by Hunt (1951) on γ fibers is recorded in Fig. 115. Records 1 and 2 from a spinal cat show a few efferent α and γ fibers in isolation. In record 1 the baseline or tonic discharge, as usual, consists of pure γ activity. When the muscle is stretched (2), reflex α activity appears but the γ outflow is inhibited. This, at the moment, is the only known *proprioceptive* reflex on the γ motoneurones. Biologically the purpose of the γ inhibition must be to suppress excessive spindle stimulation at a time when the spindle already is being stimulated by stretch, one more example of a reflex self-regulation which is similar to the autogenetic inhibition from the Golgi tendon organs. It is not yet known whether the inhibition of γ activity also is initiated by the tendon organs and thus is strictly parallel to the autogenetic α inhibition described in the previous chapter. Possibly the effect derives from the myotube endings. Nevertheless it seems clear that both inhibitions are likely to be coordinated in reflex self-regulation of muscle activity and for this reason it is of interest to examine the "lengthening reaction" with, if possible, simultaneous records from spindle and Golgi afferents.

The lengthening reaction, as originally described by Sherrington

(1909), cannot be wholly autogenetic. To be sure, the true autogenetic inhibition from the Golgi tendon organs must on the evidence of Chapter 6 be one of its essential components but actually Sherrington's experiments were performed with otherwise intact decerebrate animals and it does not succeed very well with muscles in isolation after proper denervations of other limb muscles. The sudden clasp-knife cessation of muscular resistance is well developed only if the extensive synergist inhibition set up by the tendon organs in response to muscular tension (Granit, 1950a and Chapter 6, sec. 6) is allowed free play.

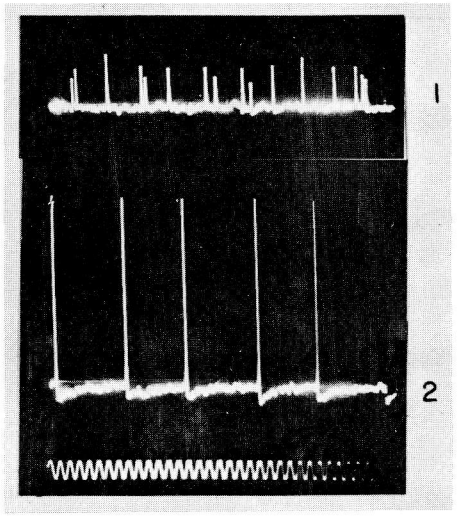

Fig. 115. Spinal cat. Ventral root filaments containing one large fiber and small fibers. 1: small fibers show continuous activity while large fiber is silent. 2: during stretch reflex excitation of large fiber and reflex inhibition of small fibers. (Hunt, *J. Physiol., 115,* 456. 1951.)

In Fig. 116 is shown an experiment (Eldred *et al.,* 1953) in which the limb innervation of a decerebrate animal is intact except for a tiny filament in the dorsal root in which one spindle and one Golgi tendon organ have been identified as belonging to the ankle extensor. The limb was intact, so also the Achilles tendon, but a small opening had been made for placing electrodes on the nerves of the ankle extensors so as to obtain a twitch to a test shock. The first record on the left (*A*) is a response to this shock. The myograph could not be used with the intact animal, but it can easily be seen that the large spike responds and the small spike is silent early in the record *A* where the twitch occurred. The small spike thus gave the pause of the spindles, the large

spike the tendon organ increase of spike frequency to the increase in tension during the twitch. This identification of the small spike as a spindle was confirmed (records on the extreme right) by its behavior in the pinna reflex. Granit, Job, and Kaada (1952) showed that there are very active pinna reflexes (see Fig. 120) on the γ fibers, often without any ef-

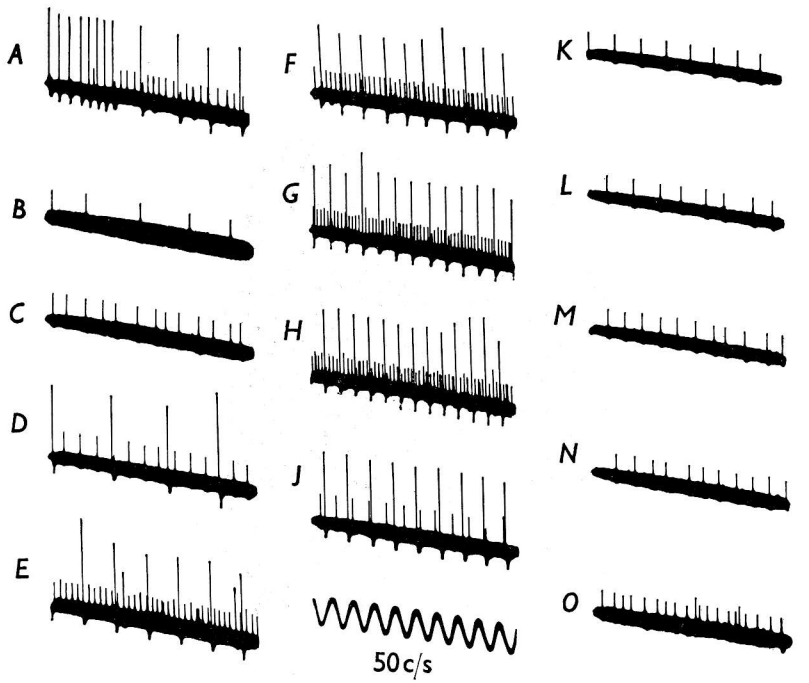

Fig. 116. Inhibition of γ discharge by stretch. Records from a spindle (small spike) and a Golgi tendon organ (large spike) in the ankle extensors. *A:* responses during twitch (no myograph). *B:* base-line discharge with ankle fully extended. *C–J:* responses during slow continued flexion of the ankle. *K:* second base-line. *L–O:* response during twist of pinna. Decerebrate cat. (Eldred, Granit, and Merton, *J. Physiol., 122,* 498. 1953.)

fect on the motor contraction, and this method of identification we generally use in our laboratory, in addition to testing with a twitch. There was a good response in this case (see records *N* and *O*). The Golgi tendon organ, which was silent as long as the limb was held straight, did not fire to twisting of the cat's pinna.

The experimenter, then, to elicit the lengthening reaction, grasped the animal's leg with one hand, steadying its knee with the other. After

a while he started to bend the leg slowly, thus stretching the ankle extensors, and the records from *B* onward are taken during this act of bending the leg up to its minimal angle. The spindle firing as directly recorded, and the stretch reflex, as felt, increase steadily from record to record and ultimately the discharge frequency reaches the exceedingly high maintained value of 300 impulses per second in *G*. The greatest tension is in *H*, where the Golgi tendon organ has its peak frequency. The latter picked up tension relatively late (in *D*) owing to its characteristically high threshold. Then, quite suddenly in *I*, the spindle discharge is inhibited and this inhibition must have been very strong to suppress its activity to such a low level despite the increased pull due to continued bending of the leg. At the same time the muscle relaxes, as is clearly demonstrated objectively by the slowing of the Golgi tendon organ. This sudden drop of tension is Sherrington's lengthening reaction. There is thus perfect cooperation between spindle inhibition and tendon autogenetic inhibition in preventing excessive states of tension in stretch, a self-regulation run with a double safety mechanism comparable to the triple safety arrangements in the silent period. This double safety mechanism is supported by the extensive inhibitory overlap to synergists described above (see Chapter 6), by means of which it can overcome the tremendous facilitatory background of stretch combined with spindle cramp (decerebrate animal). Sherrington's lengthening reaction has thus been satisfactorily explained and has also served to lay bare the details of an important integrative mechanism in reflex self-regulation of muscle activity.

Attention should also be called to the steady and very high rate of firing of the excited spindle in the intact limb (Fig. 116), hardly to be expected in view of Hunt's inhibition of the γ efferents by stretch. (Fig. 115. Probably Hunt carried out this type of experiment only on spinal animals.) A frequency of 300 per second can be obtained with nonexcited spindles only in the very beginning of sudden, heavy stretch. Inhibition of the γ discharge by stretch in a decerebrate animal apparently requires a considerable amount of tension. It behaves in this respect like the autogenetic inhibition from the Golgi tendon organs (cf. Job, 1953b). Both inhibitions are probably suppressed in the decerebrated state by hyperexcitation from higher sources, direct as well as indirect through the γ loop.

These high frequencies are interesting from many other points of view. Thus one may well ask what is achieved in the centers by such high rates in view of the low firing frequency of the motoneurones (Adrian and Bronk, 1929; Denny-Brown, 1929). Do they mobilize other systems more

effectively than the monosynaptic one? The discharge frequency of the motoneurones is apparently regulated within narrow limits by the Renshaw feedback, but the high frequency effect may well be piled up elsewhere—for instance in the reticular structures, which to high frequencies set up lasting states of excitation (see below). High frequencies are by no means restricted to muscle spindles. In the retina it is common to find maintained rates of discharge up to 400/sec. (Granit, 1944) and for short times values between 800 and 900 per second have been recorded by Enroth (1952) and Kuffler (1953). They also present an interesting problem from the point of view of impulse generation. How can the generator potential maintain such high frequencies in the face of accommodation and cathodal depression?

With stretch mobilizing excitatory and inhibitory afferents for the α motoneurones as well as inhibitory ones for the γ motoneurones, one may well ask what the sum total will turn out to be in terms of reflex contraction. There is no general answer to this question. It will vary with type of preparation, state of excitability in motor and premotor neurones, as always is the case with reflex effects. The simplest way of attacking this question is by means of monosynaptic (heterosynaptic) testing, because it is possible to cut a number of sample filaments in the ventral root for permanent recording of the effect of the monosynaptic test volley while the rest are (a) left intact and (b) afterward severed. The principle of this mode of approach may be studied in Fig. 117, and it has been tried by Granit and Ström (1951b, 1952) on decerebrate animals. Their intention was to study the excitability of the ventral horn cells of the ankle extensors with excited and non-excited spindles. At low initial tension it was actually possible to demonstrate that in stretch monosynaptic facilitation started earlier *before* de-efferentation than *after,* but the difference was small and later on in stretch not at all definite. However, when high initial tension was used, there was no such difference early in stretch but, later on, actually more inhibition with the γ loop through the intact muscle. Thus, as soon as initial tension is sufficiently high, the sum total in the balance of excitatory and inhibitory reflexes, even in the decerebrate preparation, is in favor of inhibition. This does not seem difficult to understand. In the de-efferented state there is no reflex motor contraction. However, with the loop intact there is a stretch reflex which augments the sum total of tension enough to mobilize autogenetic inhibition for both α and γ motoneurones.

These experiments on stretch reflexes show what a complex machinery is put into operation when, as was done exclusively in classical reflexology, the contracting muscle itself with its highly differentiated receptors was used to measure any single reflex. Even the simple stretch response of Liddell and Sherrington consists of a minimum of

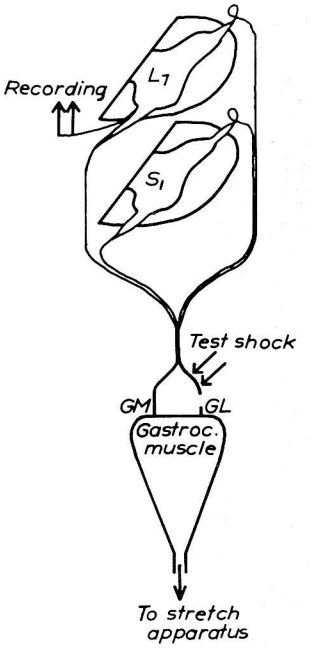

Fig. 117. Diagram illustrating semisections of spinal cord at the segmental levels of L_7 and S_1, and arrangement of experiment. Test shock to severed lateral gastroc. nerve (*GL*), recording of monosynaptic reflex response from filament of ventral root L_7 as well as the whole of S_1 ventral root connected with gastroc. muscle through medial gastroc. nerve (*GM*). (Granit and Ström, *Acta physiol. scand., 27,* 255. 1952.)

four reflexes: (1) facilitation from nuclear bag endings upon the ventral horn cells, (2) inhibition from Golgi tendon organs upon the ventral horn cells (α inhibition), and (3) inhibition from unknown endings upon the γ cells (γ inhibition), with consequent indirect removal of excitation upon the α motoneurones from nuclear bag endings. Also (4), the myotube endings, as stated, will add inhibition to the extensors and excitation to the flexors (Hunt, 1953).

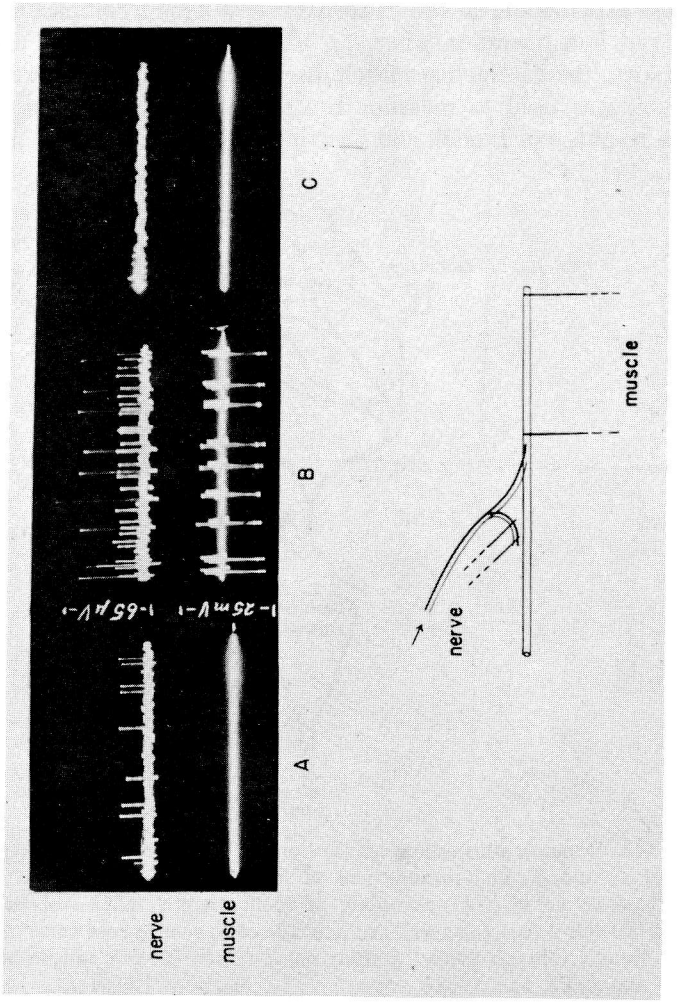

Fig. 118. Spinal cat. Simultaneous recording from central end of cut upper nerve branch to tenuissimus and from lower end of muscle with intact innervation. Note difference in amplification. *A:* baseline in "resting" state. Note discharge in nerve giving impulses of small potential, while no potentials are recorded from the muscle surface. *B:* ipsilateral foot touched. Small-nerve discharge increased and activity set up in fiber giving large potentials. Each large-nerve impulse is accompanied by propagated potentials recorded from the muscle surface. *C:* contralateral foot touched. Background small-nerve discharge completely inhibited. Diagram illustrates leading conditions. (Hunt, *J. Physiol., 115,* 456. 1951.)

4. Some skin reflexes on the γ system

Hunt (1951) as well as the Japanese authors (Kobayashi *et al.,* 1952) described the spinal γ reflexes in very similar terms. By carefully grading stimulation in the flexion reflex it was shown that the γ system responded more readily to touch of the skin than the α system. With increasing stimulus strength both systems went off. Fig. 118 is an illustration from Hunt's paper, reproducing α and γ reflexes together with the electromyogram. Fig. 119, by the Japanese authors, demon-

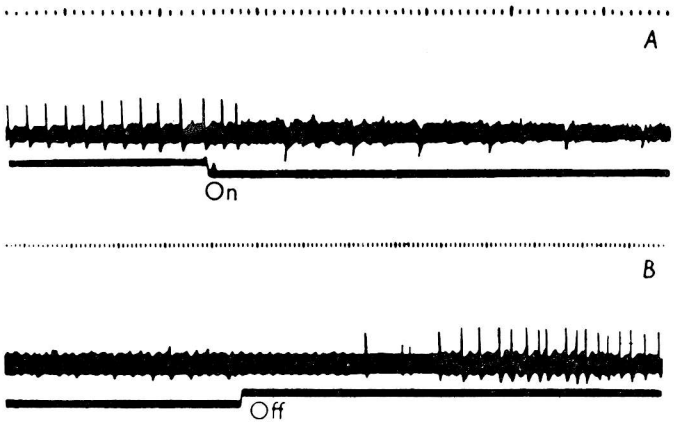

Fig. 119. Inhibition of contralateral extension reflex by induction shocks applied to the ipsilateral peroneal nerve. Action currents were led from five fibers, between 20 and 5 μ, innervating the lateral head of gastrocnemius of a decerebrated cat. The crossed reflex was maintained by continued stimulation of the contralateral peroneal nerve. Only one fiber of 5 μ is active in the crossed reflex. Time: 10 msec. (Kobayashi, Oshima and Tasaki, *J. Physiol., 117,* 152. 1952.)

strates with a γ efferent fiber the inhibition of a contralateral extension reflex by ipsilateral electrical stimulation. In the well-known spinal reflexes it appears that there is strict correlation between α and γ activation. The typical response will therefore be intra- and extrafusal co-contraction. Hunt, in particular, emphasized that the γ fibers have receptive fields from a large variety of end organs.

Granit, Job, and Kaada (1952) studied Sherrington's pinna reflex with both γ efferents and muscle spindle afferents. This reflex has a very strong γ component. Upon touching the ear sometimes pure excitation is obtained, sometimes inhibition which is later followed by a vigorous excitatory rebound when the pinna is released. An example

of the first type is shown in Fig. 120. Very often the γ reflex is obtained in isolation; sometimes it leads up to a contraction (isolated limb muscle) during which the intrafusal fibers are co-activated to such an extent

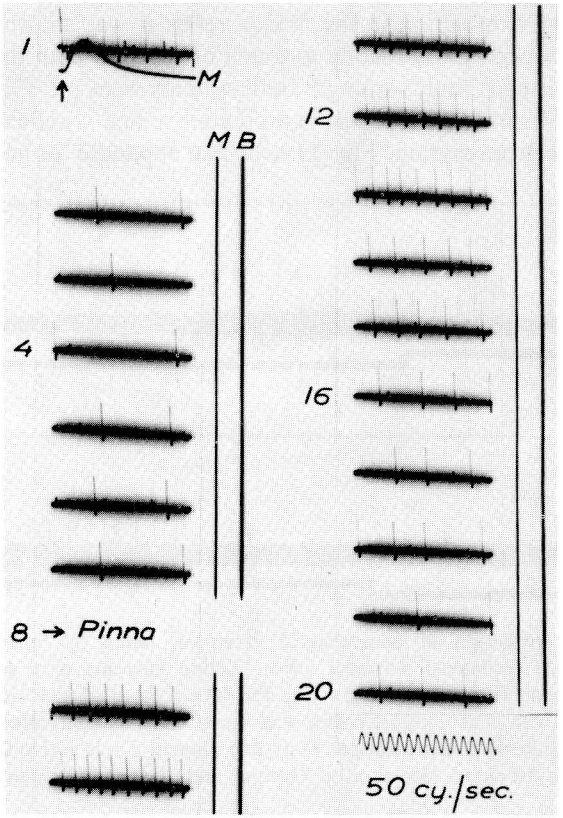

Fig. 120. Effect of twisting ear on muscle spindle afferent from gastrocnemius. Dial-chloralose. Initial tension 35 g. Myogram (*M*) in record 1, horizontally; in the successive sweeps, 2–20, vertically. Distance between *M* and baseline (*B*) corresponds to 15 g. Contraction of 118 g. in record 1 to demonstrate spindle-character of ending. 2–7: control, 8: twist of ear, (marked "Pinna"), 9–20: acceleration of spindle discharge in pinna reflex from a baseline discharge of about 7/sec. to about 36/sec. Interval between sweeps 2 sec. (Granit, Job, and Kaada, *Acta physiol. scand., 27,* 161. 1952.)

that the effect of extrafusal unloading is more than neutralized. As with onset of rigidity (Hunt, 1951; Kobayashi *et al.,* 1952, and Fig. 114 above) both γ and spindle discharges generally precede the α discharge. In the pinna reflex on the hind limb the γ action apparently serves to

prepare the ground for the postural and phasic changes leading up to a scratch reflex (cf. Sherrington, 1917).

The muscle-skin organization of reflexes, discovered by Hagbarth (1952), is particularly well suited for analysis of γ reflexes because

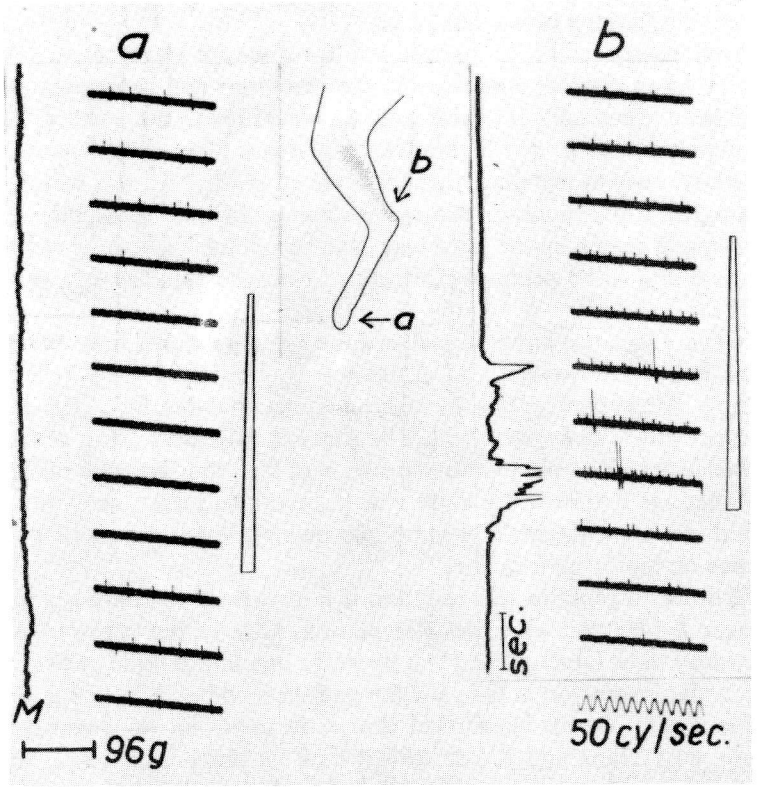

Fig. 121. Spinal cat. Records from central end of cut branch of medial gastrocnemius nerve. Vertical lines to the right indicate the approximate duration and strength of pinches applied to the skin at the sites indicated by arrows. γ fiber activity, represented by the short spikes, is inhibited from the toe-pads (*a*) but facilitated from the skin on the dorsal aspect of the leg (*b*). With stronger stimulus at the latter site, tall spikes of an α fiber appear together with a deflection of myograph (*M*). Initial tensions in this and succeeding illustrations about 40 grams. (Eldred and Hagbarth, *J. Neurophysiol., 17,* 59. 1954.)

of its strict reciprocal organization. Hagbarth (cf. Chapter 2, sec. 4) found that independently of whether limb flexors or limb extensors were studied, the receptors in the skin above any particular muscle facilitated the motoneurones of this muscle and inhibited those of

antagonists. Eldred and Hagbarth (1954) then investigated Hagbarth's system with a view of correlating α and γ activity. Their results uniformly fell out as illustrated by Fig. 121. Co-excitation and co-inhibition was precise and strictly reciprocal in both types of efferents. The γ neurones had a lower reflex threshold than the α fibers and generally started discharging before the latter.

Even when needles are inserted into the brain for electrical stimulation or when cortical structures in the cerebrum and cerebellum are stimulated electrically (Granit and Kaada, 1952), the γ fibers are commonly found to go off in advance of the α fibers, and it is comparatively easy to stimulate them in a selective way. All this can only mean that connections to this system are profuse in the spinal and supraspinal centers in the same way as in the muscles where γ innervation is found to be profusely distributed over the spindles (cf. Hunt, 1951).

In every instance hitherto analyzed the α and γ reflexes have proved to be linked, co-excited, and co-inhibited, often with the γ reflexes leading. All experimenters have been struck by this fact. The significance of α-γ linkage may now be preliminarily assessed in general terms: excitation of the α motoneurones over the γ loop through nuclear bag afferents is sufficiently important to be organized for cooperation with direct α excitation. Is it important enough to have a decisive influence on motor performance?

In order to reply to this question it is necessary to study α and γ reflexes *before* and *after* de-afferentation. Clearly the reply to our question will be largely dependent upon the amount of tonic or permanent activity going on in the γ system and the spindles. Suspecting that this was controlled from cortical centers in the brain stem and elsewhere, we (Granit and Kaada, 1952) took up this problem first. The next step in our research involved de-afferentation. Below, in presenting the results, I shall follow the same order of procedure.

5. *Supraspinal control of the muscle spindles*

It proved particularly easy to obtain selective γ excitation from many places within the brain stem reticular system. In Fig. 122 are shown some records from a few fibers in the ventral root S_1. In *A* a 3 msec. shock to the motor cortex is seen to have activated only the small γ efferent at low strength, while a somewhat stronger shock also activated the large spike of the α fiber. These records are given merely to show that there was one α and one γ fiber in the filament

that had been picked up. Then the mesencephalic tegmentum was stimulated repetitively in *B* between "Stim on" and "Stim off." The α fiber remained silent but the γ fiber's firing frequency gradually rose from 8 to 40/sec. and very slowly fell back to the resting value. The

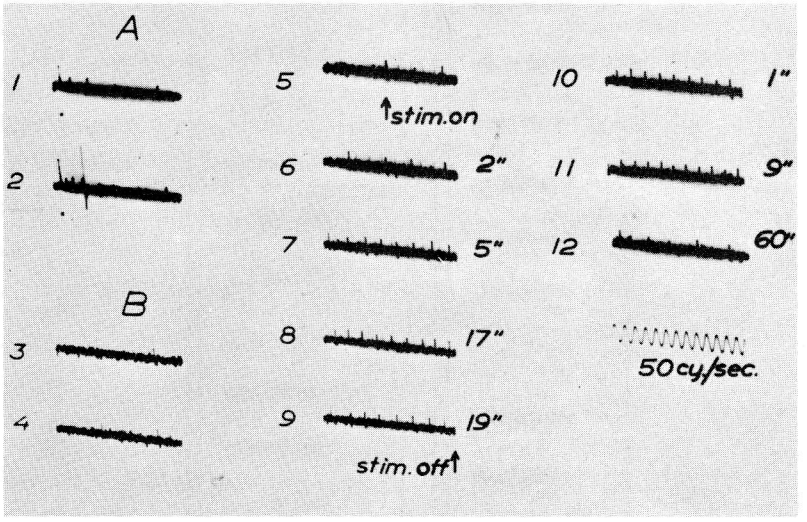

Fig. 122. Effect of stimulation of motor cortex (*A*) and mesencephalic tegmentum (*B*) on discharges in ventral root S_1. Dial-chloralose. *A:* single shock to motor cortex, as marked by large shock artifact (point)—1: relative strength 5, only small fiber responds, 2: relative strength 6, large fiber is also brought in. *B* same experiment directly continued with tegmental stimulation—3–4: spontaneous rate of firing of the small unit; 5–9: tegmentum stimulated at a rate of 32/sec. for 19 sec. Timing of sweeps marked on records. "Driving" of small-fiber discharge at the stimulus rate in 7 and 8. 10–12: after stimulation, at times marked on records.

Note: gradual recruitment of discharge rate of small spike during stimulation from originally around 8/sec. to maximally 40/sec. without a large spike activation. Note also after-discharge. (Granit and Kaada, *Acta physiol. scand., 27,* 130. 1952.)

spindle counterpart of this experiment is shown in Fig. 123 for a nuclear bag afferent from the gastrocnemius. Above is the test with a motor twitch to demonstrate the pause of the spindle. The myograph was then shifted to *M* alongside the record and 4 sweeps 2 seconds apart are given to illustrate the baseline discharge. Stimulation of the midbrain tegmentum (between arrows) gradually excited the spindle, which still fired at maximum frequency 20 seconds after cessation of

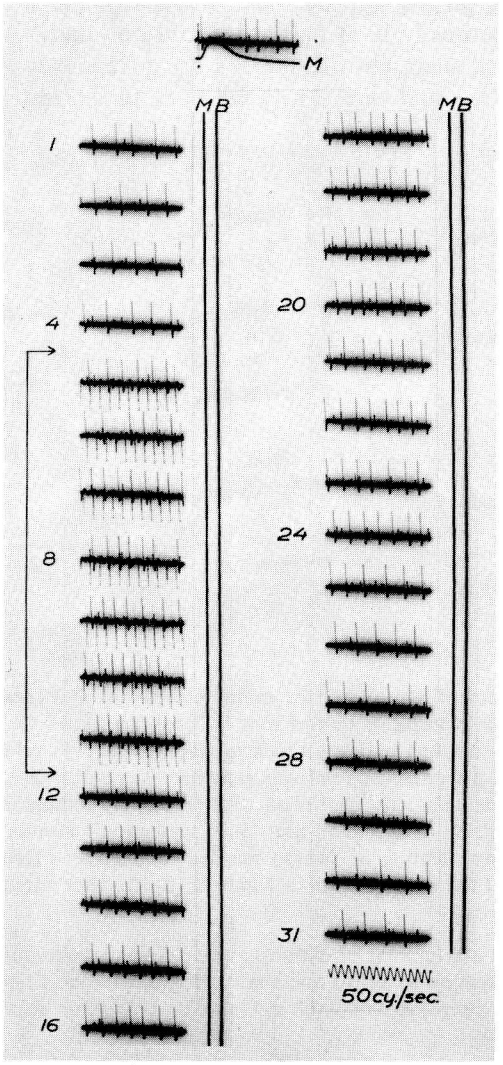

Fig. 123. Effect of brain stem reticular (midbrain tegmentum) stimulation (between sweeps 4 and 12) on a gastrocnemius muscle spindle afferent. Above: contraction of 134 g. at low myograph sensitivity to demonstrate pause of large unit. Initial tension throughout: 52 g. Dial-chloralose. 1–4: control before reticular stimulation; 5–11: during stimulation at a frequency of 37/sec.; 12–31: after stimulation. Consecutive sweeps at 2-sec. intervals. Myograph (*M*) alongside film. Distance *M–B* (baseline) corresponds to 10 g. (Granit and Kaada, *Acta physiol. scand., 27,* 130. 1952.)

stimulation. The muscle was silent; hence the stimulus was again highly selective. Such recruitment and long-lasting after effect are typical for the brain stem and diencephalic reticular system and are comparable to the recruitment and after effect seen by facilitation of reflex and cortically induced movements as a result of stimulation of the same structures. We generally tested for cortically induced movement when stimulating the reticular structures, and the outcome was practically always positive.

It seems likely that all along the motor path, from the cortex downward, fibers are directed to γ centers in this region. In one instance we also stimulated the pyramidal tract with a needle electrode. There was some selective activation of the spindle but it did not have the slowly recruiting character of the typical reticular response. Since Brodal and Walberg (1952) and Brodal and Kaada (1953) recently have demonstrated afferents in the pyramidal path by histological and electrophysiological methods, we thought it necessary to make a double-sided resection of the motor cortex in this experiment. The pyramidal effect proved to be uninfluenced. So far this is the only exception to the rule that γ effects rise and fall slowly.

Magoun and his collaborators (Magoun, 1944; Magoun and Rhines, 1945, 1946; Niemer and Magoun, 1947) have described a diffuse bulboreticular inhibitory system. Inhibition of stretch reflexes and tonus have been obtained from the anterior limbic gyrus (Smith, 1945; Kaada, 1951; Hodes, Peacock, and Heath, 1951). Cerebellar inhibition of rigidity is well known from early papers by Loewenthal and Horsley (1897) and Sherrington (1898). These three inhibitory sites were stimulated in the experiment of Fig. 124, in which some α and γ fibers were isolated in the ventral root L_7. Complete inhibition of both α and γ discharge was obtained in all three cases. Similar experiments were also carried out with isolated spindle afferents.

In view of the fact that onset of decerebrate rigidity is marked by γ excitation, it is of particular interest to perform the classical experiment on cerebellar inhibition of rigidity in order to see if it can be done with the γ system alone. It is actually possible to make inhibitory stimulation highly selective. The experiment of Fig. 125 was carried out on a decerebrate animal slightly clonic, as shown by the response (record 1) to the shock for the test twitch. There follows the baseline discharge (2–4) of the isolated spindle afferent. Stimulation of the anterior lobe of the cerebellum between records 5 and 10 gave complete inhibition of the spindle with some escape at the end. Nothing hap-

pened in the muscle. The effect was readily reproducible. It was, indeed, quite a striking experience to watch the screen of the cathode ray and the wholly quiet animal and listen to the sudden cessation of detonations in the loudspeaker when this long-range control of a sense organ was put into operation. It is of some interest to note that a

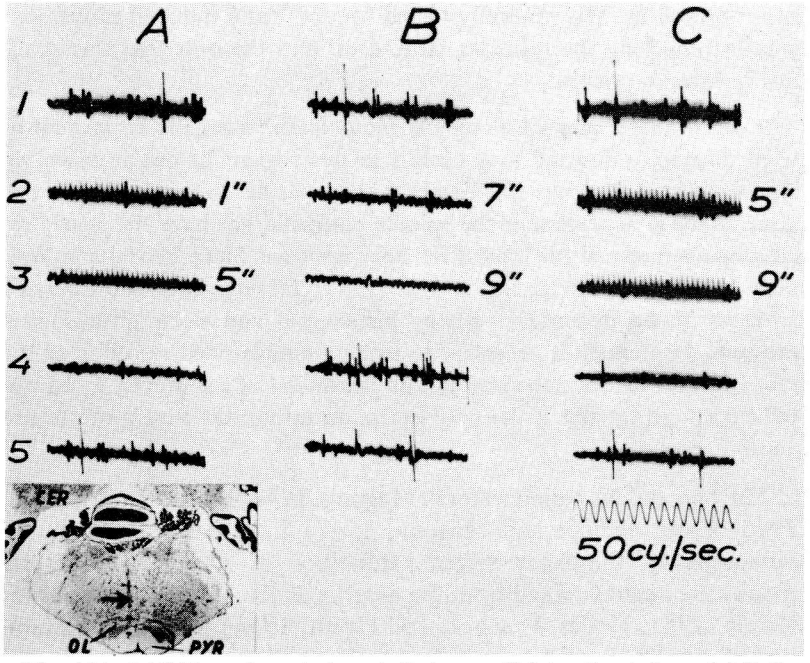

Fig. 124. Inhibition of ventral root discharges (L7) to stimulation of (*A*) the bulboreticular inhibitory system (at arrow on section), (*B*) the anterior lobe of cerebellum, and (*C*) the anterior limbic (cingular) area. Nembutal. 1 (in each column): control before stimulation (note small and large spikes); 2–3: during stimulation at 120/sec. for 10 sec. Time from onset of stimulation marked on records. 4–5: 1 and 10 sec. respectively after cessation of stimulation. Note the practically complete inhibition in records *A*3 and *B*3 and the rebound in *B*4 after cessation of cerebellar stimulation. (Granit and Kaada, *Acta physiol. scand., 27,* 130. 1952.)

cerebello-bulbo-reticular pathway for inhibition has been found by Snider, McCulloch, and Magoun (1949).

Cerebellar excitation may also be obtained by electrical stimulation (e.g. Moruzzi, 1950). In some cases we succeeded in stimulating the spindles from the cerebellum.

It is hardly necessary to adduce further examples to illustrate the main results of Granit and Kaada, which were that (1) there is close

correlation between α and γ activity in the various systems in the brain known to be engaged in motor activity; (2) it is often easy in Dial

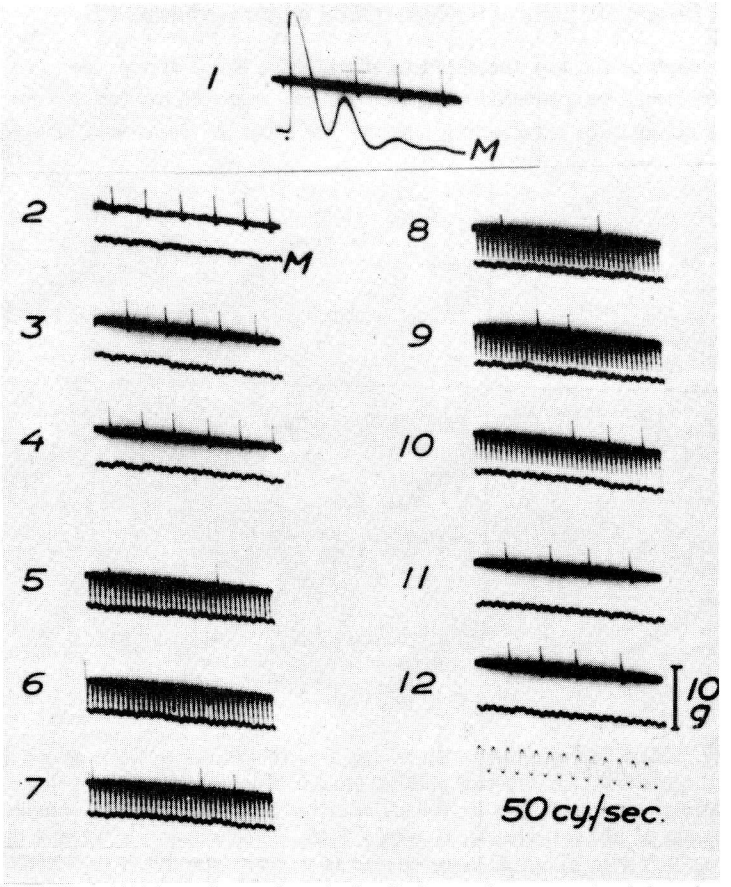

Fig. 125. Inhibition of muscle spindle discharge from anterior lobe of cerebellum (culmen). Decerebrate animal. Gastrocnemius. Initial tension 66 g. Myograph at maximum sensitivity (see record 12) except in 1, in which (clonic) contraction to single shock to the gastrocnemius nerves demonstrates silent period. 2–4: controls before stimulation, 5–10: during cerebellar stimulation at 140/sec. with 1-msec. shocks for 26 sec., 5–7: after 18–20 sec., 8–10: after 24–26 sec., 11–12: immediately after cessation of stimulation. Note: drop in spindle frequency from about 20/sec. to an irregular discharge frequency of about 5/sec. (Granit and Kaada, *Acta physiol. scand., 27,* 130. 1952.)

or chloralose animals to activate or inhibit the γ neurones selectively; (3) there is considerable supraspinal tonic activity going on all the time in a good preparation; and (4) powerful excitatory effects are

with great regularity obtained from the excitatory brain stem and diencephalic reticular formation as well as corresponding inhibitory ones from those parts of it which inhibit motor performance.

In view of the low threshold to stimulation, the γ system also in these regions must be provided with rich diffuse connections, but somewhere there ought to be a collecting network for them. It seems very likely that

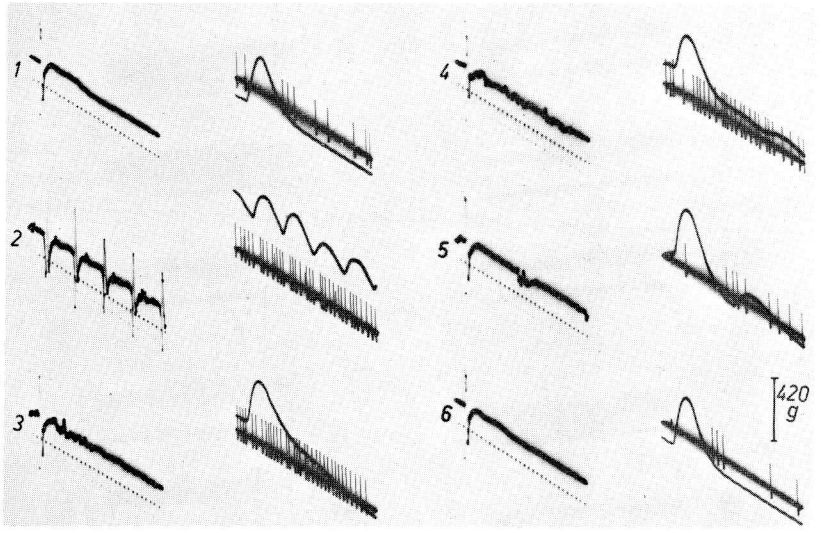

Fig. 126. Effect of stimulation of leg area in chloralose (20 mg/kg.). Each set of records taken with two parallel, double-beam oscilloscopes. On the left, electromyogram and time in 100 cy/sec.; on the right, tib. ant. spindle and myogram of tib. ant. muscle. 1: single shock, 2: stimulation at 15/sec. during 3 sec., 3–5: rate of stimulation reduced to 1/sec. Note effects on spindle discharge.

the reticular formation from diencephalon down to the spinal cord serves in this capacity. In the bulb and the brain stem this extensive system has lately attracted a great deal of attention (cf. Chapter 3). It includes parts of the bulbar reticular formation, the pontile tegmentum, the central grey matter and tegmentum of the mesencephalon (Magoun, 1944; Rhines and Magoun, 1946), the ventral diencephalon—sub- and hypothalamus—(Murphy and Gellhorn, 1945; Rhines and Magoun, 1946), parts of the midline and intralaminar group of thalamic nuclei, and certain of the specific thalamic nuclei as well (Murphy and Gellhorn, 1945; Jasper, 1949; Austin and Jasper, 1950; Peacock and Hodes, 1951). This facilitatory system of large dimensions has properties characteristic of γ activity, such as long duration, broad front of attack, and great range, and may therefore play a leading role in γ activation, even when the γ neurones are excited over the motor cortex.

With sufficiently long shocks it is possible, even in the modestly developed cat's motor cortex, to elicit differentiated single contractions in single leg muscles, particularly from the tib. ant., which then responds in the twitchlike fashion illustrated in Fig. 126, record 1. This is very much of a pure α contraction, as seen by the pause of the spindle discharge. Yet the stimulus activates the γ system too (Granit and Kaada, 1952), as can be seen by making it repetitive, as in record 2. Its destination may be by extrapyramidal paths to the similarly extrapyramidal activating centers in the reticular formation, because the effect does not look at all like the differential α outbursts setting up the rhythmic contraction in record 2. Characteristically, the γ activation lasts for a long time, as seen when the original firing rate of once per second was reinstalled. The pause is filled out in record 3, which is a definite sign of intrafusal contraction by γ activity, but gradually returns in records 4 to 6.

An interesting aspect of this result is its possible significance for Hughlings Jackson's well-known "march of movement," which signifies that the effect from a cortical point stimulated slowly at constant strength gradually spreads from muscle to muscle, just as does the focalized epileptogenic fit. Part of this spread may well also be indirect, facilitation by diffuse γ action of the ventral horn cells of muscle after muscle through the spindle loop. This question deserves to be investigated.

The notion that the general facilitatory and inhibitory systems of the brain stem are instrumental in determining the level of tonic facilitation through the spindle loop as well as in switching it on and off receives some support also from our attempts to determine the range of the effect, from maximum excitation to maximum inhibition. This question implies that two places must be found in the brain, one of which excites, another which inhibits the same sensitive spindle selectively. Fig. 127 illustrates an experiment with a low-threshold muscle spindle afferent in soleus which could be selectively excited from the contralateral inferior colliculus and similarly inhibited from a place in the contralateral internal capsule alongside the caudate nucleus. The sections showing the actual needle tracks are given in Fig. 128. The whole experiment was carried out with the same soleus spindle, which

was very sensitive and at the same time stable, so that it could ultimately be tested in the nonexcited state also, after de-efferentation. The central foci remained constant for hours and were highly selective. Fig. 127 illustrates this selectivity with myographic control during inhibition and excitation at stimulus rates and strengths which then were

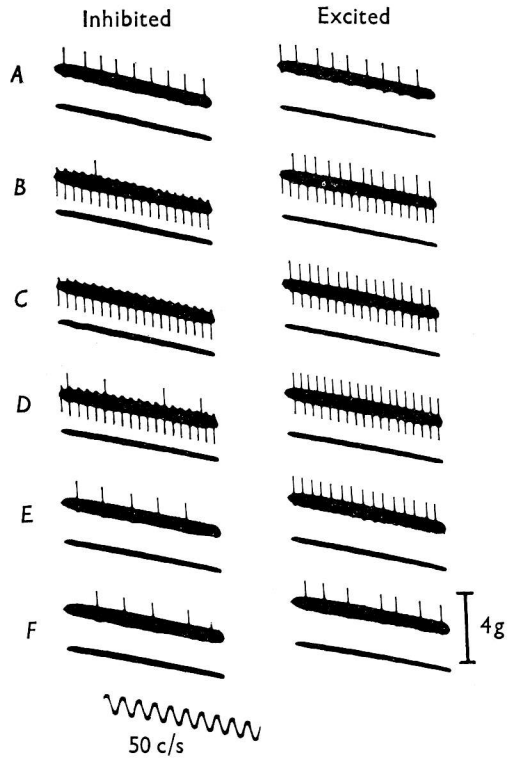

Fig. 127. Spindle in soleus. Effect of stimulation of the inhibitory and excitatory loci shown in Fig. 128. *A:* base-line, *B:* first record during stimulation (note shock artifacts), *C:* during stimulation, *D:* last record before cessation of stimulation, *E, F:* immediately afterward. Myograph record on lower trace; initial tension 55 g. Cat under chloralose and dial. (Eldred, Granit, and Merton, *J. Physiol., 122,* 498. 1953.)

preserved throughout the whole experiment. In this test it is necessary to be able to assert that the effects observed did not depend on mechanical events in the muscle set up by α activation. Very high myograph sensitivity was therefore used. There is, during inhibition, a slight fall of tension of 0.1–0.2 g. which may or may not have been accidental. If it had been due to concomitant inhibition the spindle would have

been pulled upon and hence accelerated. Actually it was inhibited down to zero. Therefore the fall in tension is inconsequential.

In Fig. 129 the same excitatory and inhibitory foci have been studied at different initial lengths increasing downward and shown to the left in the figure. The first vertical row illustrates the baseline discharge with loop intact, the second and third during supraspinal excitation and inhibition as in Fig. 127, the third the baseline of the de-efferented nonexcited spindle with which the first vertical row of the excited spindle should be compared. At 13 mm. extension a good initial ten-

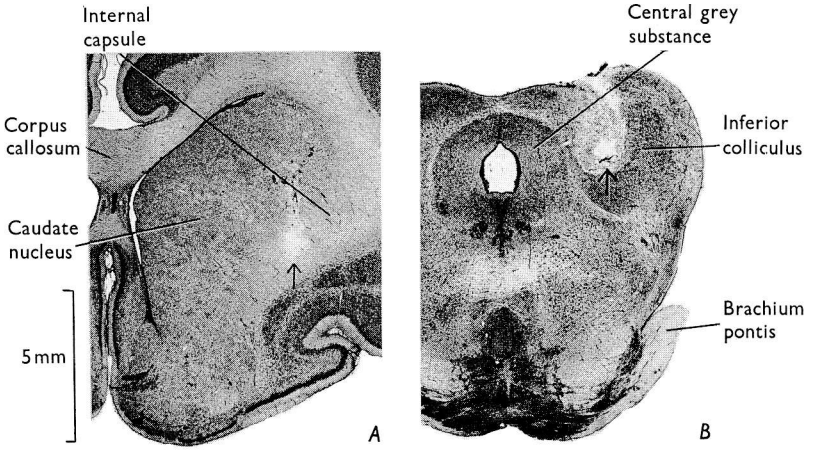

Fig. 128. Sections to show the position of the stimulating needles in the experiment illustrated in Figs. 127, 129, 130. *A:* the inhibitory point in the contralateral internal capsule, *B:* the excitatory point in the contralateral inferior colliculus. The scale applies to both sections. (Eldred, Granit, and Merton, *J. Physiol., 122,* 498. 1953.)

sion was developed—in fact 450 g. Again it can be seen that spindle excitation is sufficient to overcompensate for the γ inhibition to stretch, even though stimulation of the excitatory focus still is capable of causing further increase of the discharge. The initial effect of inhibition is actually to suppress the rate of firing below that of the nonexcited spindle, but this is certainly due to the sudden unloading which was shown by Matthews (1933) to cause a pause of several seconds, during which excitability was built up to the level characteristic for the new length (cf. Chapter 1, Katz's positive terminal potential, Figs. 6 and 7). This recovery can actually be seen in Fig. 127, which traces the inhibitory effect for several sweeps, while in Figs. 129 and 130 only the maxima of excitation and inhibition have been picked out.

The main results of the experiment are summarized in Fig. 130. The high rate of firing of the excited spindle should be noted. It reached a peak value of as much as 215/sec., averaged over a fifth of a second. The maximum range, which is the difference between spindle frequencies during central excitation and inhibition, is reached at an extension of about 8 mm. and is of the order of 160 impulses per second. It should further be noted that spindle excitation is considerable also at zero tension.

Eldred, Granit, and Merton (1953) have introduced the notion of excitatory spindle bias in terms of equivalent length. The bias is that shortening of the muscle which reduces the rate of discharge of the biased (excited) spindle to that of the unbiased (nonexcited) de-efferented spindle at the original length. I mention this concept not in order to elaborate its significance in detail, but merely to point out that at zero tension extrapolation of the curve for the excited spindle would give a bias as high as 5 mm. below the length of the slack muscle. The result suggests that a spindle under command from the supraspinal centers, and thus excited by natural means, would work also in isotonic contraction. The supraspinal commands clearly possess extreme range and potency. On the one hand it was possible to abolish normal γ bias completely; at the opposite end of the scale a state of spindle excitation was obtained which was so intense that it becomes doubtful whether further increase serves any practical purpose in the normal life of the animal.

The fact that the γ loop is at the disposal of powerful supraspinal mechanisms should also be considered in the light of the observations on the arousal reaction from the reticular activating system in the brain stem, discussed in Chapter 3, sec. 6, from other points of view. The spindle loop integrates motor and sensory performance in a curious and fascinating manner. The brain drives and sensitizes end organs, which in their turn are capable of driving the muscle which contains these end organs as well as its synergistic muscles. Now, muscle is the instrument of action, and so it seems natural that it should be made to feel the arousal reaction of an animal aroused. Again, considered from the sensory point of view, a pure extrafusal α arousal without concomitant γ arousal of the intrafusal fibers of the muscle spindle would make the sense organ pause and consequently be incapable of serving as an "internal measuring instrument" and hence useless for the animal at the very moment when it is needed.

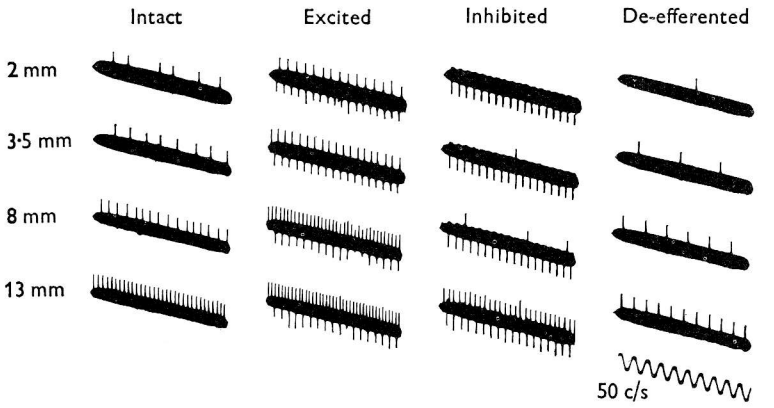

Fig. 129. Same spindle as Fig. 127. Records at various extensions of the resting, maximally excited, maximally inhibited, and de-efferented spindle. Stimulating loci as in Fig. 128. (Eldred, Granit, and Merton, *J. Physiol., 122,* 498. 1953.)

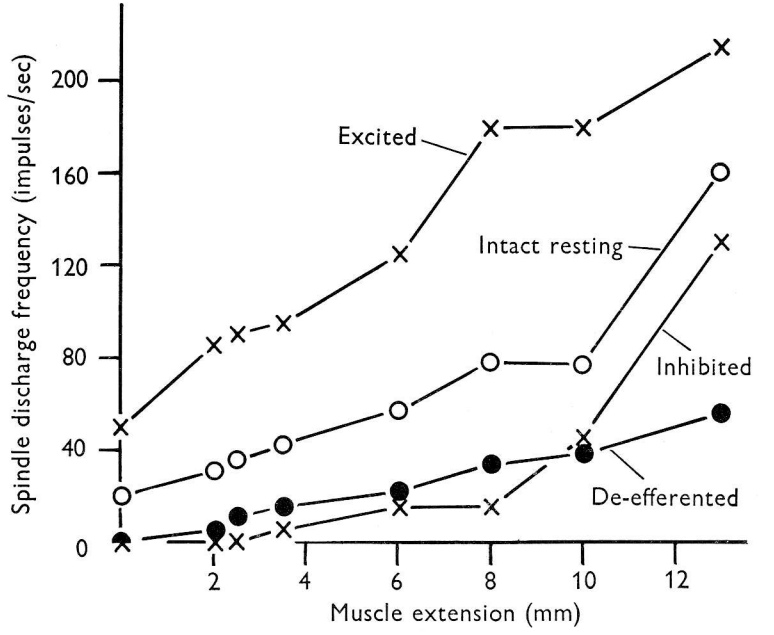

Fig. 130. Discharge frequency of a spindle in soleus at various extensions. The effect of stimulating an excitatory and inhibitory locus in the brain (shown in Fig. 128). The muscle afterward de-efferented. Same spindle as in Figs. 127 and 129. Spindle frequencies during stimulation averaged over 0.2 sec. instead of the usual 1.0 sec. (Eldred, Granit, and Merton, *J. Physiol., 122,* 498. 1953.)

6. *Reflexes before and after de-afferentation*

One of Sherrington's best known experiments proved that in the decerebrate animal rigidity of a limb could be abolished by acute severance of the dorsal roots. The remaining ventral roots could not maintain this state of activity unless the ventral horn cells received the facilitatory influx from the limb afferents. The level of excitation of the α

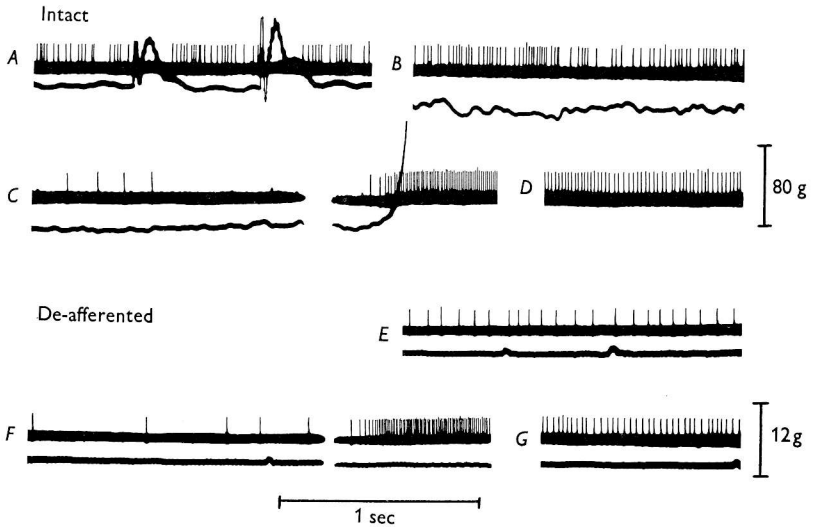

Fig. 131. Reflex activation of α and γ systems by head movement in the vertical plane. Rigid decerebrate cat with brisk ankle jerk and spontaneous α activity (record *A*). Myograph shows tendon tap succeeded by jerk. Records from soleus spindle with head level (record *B*), flexed backward (*C*), and suddenly (at the interruption of the traces) flexed downward and held there (*D*). After de-afferentation the same sequence (*E*–*G*) produces γ response but no α discharge. Initial tension approximately 85 g. (Eldred, Granit, and Merton, *J. Physiol., 122,* 498. 1953.)

system isolated from the proprioceptive inflow was too low. Do the γ cells share with the α cells this state of depression? Or are they relatively independent, despite α-γ linkage?

In the experiment of Fig. 131 (Eldred, Granit, and Merton, 1953) the tonic neck reflex of Magnus (1924) has been used to test this point. The receptors have been found to be in the ligaments of the joint (McCouch *et al.,* 1951). A spindle afferent has been isolated and in *A* some tendon jerks have been elicited to show that it pauses during the muscle contraction. The experimenter then grasped the animal's

head firmly and waited until the γ reflexes to touch and pressure had disappeared. In *B* is found the baseline discharge of the spindle together with the myograph record of tonic α activity, indicated by irregular small movements. The head was next turned upward to elicit the characteristic Magnus inhibition of hind limb tonus (cf. myograph), which also is reflected in the slowed rhythm of the spindle afferent (record *C*). During the interruption in the record the head was bent downward and held there (*D*). There followed in the muscle a violent contraction, carrying the cathode ray off the face of the tube, and a no less violent discharge of the spindle. In the lower half of Fig. 131

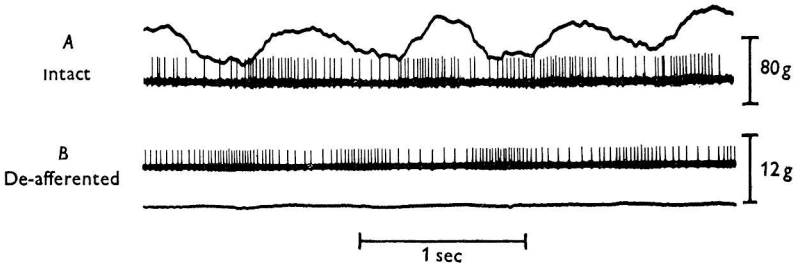

Fig. 132. Reflex activation of α and γ systems by rhythmic turning of the head in the horizontal plane. Records from soleus spindle. With intact reflex connections both α and γ systems responded synchronously. After de-afferentation α response vanished. Same experiment and spindle as Fig. 131. (Eldred, Granit, and Merton, *J. Physiol., 122,* 498. 1953.)

the same procedures were repeated at higher myograph sensitivity after de-afferentation. *E* is the baseline discharge. The muscle was silent throughout but the spindle (in *F*) repeated its previous performance (as in *C*). The motoneurones of the α system were thus greatly depressed by de-afferentation, but the γ motor cells, though slightly less active than before, were fully capable of responding to the stimulus in the normal way.

Similar experiments were successfully carried out with other reflexes as indicators. Fig. 132 illustrates the response to rhythmic movement of the head from right to left in the horizontal plane. Intrafusal spindle and extrafusal motor contraction go off together. After de-afferentation (lower record) the spindles alone respond as before, while the muscle is quiet.

The effects of central stimulation at different initial tensions of the muscle in the manner of Granit and Kaada were compared before and after de-afferentation. The γ effects studied in the spindles were in the main independent of whether the limb was intact or de-afferented.

At low tensions tonic spindle activity tended to be somewhat reduced. If a place was selected from which both γ and α activity could be obtained, the threshold for the latter effect was generally found to have risen a great deal after de-afferentation, while the γ system was practically as sensitive as before the operation.

The interpretation of all these experiments is that the γ system is there not only to improve the performance of the sense organ but also as an "ignition mechanism" to initiate movement as well as to maintain tonus. When the loop through the muscle to the ventral horn cell has been interrupted on its afferent side, the γ system still operates to carry out its task in the activation of the ventral horn cells, but the nuclear bag impulses are prevented from reaching the latter, and so the α reflexes do not come off. A consequence of this interpretation is that the muscles possessing spindles actually are provided with two motor systems. This being so, α-γ linkage, in which mostly γ activity is leading, means that a very large number of motor acts do not at all take place the way one imagined and held to be self-evident, namely that the α contraction simply was put on by whatever circuits happened to be activated. In many if not most natural contractions hitherto studied the γ loop was first started, the nuclear bag afferents then facilitated, and the appropriate α motor neurones and direct α activation came last or together with γ activity. With this arrangement the sense organs in the muscle are immediately ready to "measure" during the ensuing contraction.

For the first time this makes the existence of a monosynaptic reflex from muscle afferents intelligible. Half a millisecond one way or another can hardly as such be of any significance whatever for large limb muscles and bones of considerable inertia and momentum. But for the cerebral command to the loop it is essential that it be carried straight to the ventral horn cells by a fast path not subject to complex polysynaptic influences. Their role is a later modulation.

This should not be interpreted to mean that direct α action, such as seen by electrical stimulation of the brain by single shocks or in tendon jerks, is excluded. It does mean, however, that the relative significance of α and γ activation must be elucidated case by case. Merton (1951), investigating the servo-loop in the human subject, found, for instance, that sudden movements could always break through, presumably by direct α activation. Tendon jerks and single shocks to the motor cortex do the same.

The results on de-afferentation also mean that the α and γ systems are fundamentally independent. De-afferentation, as we have seen,

treated them very differently. Their respective motoneurones are converged upon by different influences. This being so, it is clear that the α-γ linkage is maintained by some property of organization. If it were possible to destroy the linkage experimentally, one could from such experiments derive some notion of where coordination takes place. Apparently such organizations exist at different levels in the neuraxis, to judge from the fact that α-γ linkage is found also in spinal animals. We have studied this question in the decerebrate preparation.

It is interesting to note that insofar as tonic firing is concerned, Rossi (1927) deduced an essentially correct picture of the role of spindle innervation. He thought of tonic firing of muscle spindles at various lengths of the muscle as a fixation of the intrafusal fibers at appropriate lengths by specific motor fibers to them. Thus, he said, it would become possible for the higher centers to be at rest while charging lower centers with the duty of keeping up a suitable amount of spindle or intrafusal contraction to maintain postural tonus. Now, twenty-five years later and unaware of his deductions, we have ultimately succeeded in proving him right, in the sense that tonic facilitation of the ventral horn cells is maintained by the spindle loop.

7. Experimental destruction of the α-γ linkage. The α animal

It is well known that the preparation obtained by anemic decerebration (Pollock and Davis, 1930), in which half the cerebellum and a considerable part of the pons is destroyed, is intensely rigid, despite de-afferentation (Pollock and Davis, 1931). Moruzzi (1953) and Kaada (1953) have recently reviewed the literature in this field and in Moruzzi's laboratory Terzuolo and Terzian (1953) have made a comprehensive study of this preparation after both acute and chronic de-afferentation. Rigidity was preserved in both cases, despite lack of support of the γ loop. Both inhibition and excitation of fore limb muscles could be obtained by appropriate electrical stimulation (cf. Moruzzi, 1950) of the cerebellum.

Here, then, is a state representing an exaggeration of standing which must be maintained by pure α activity. This, of course, does not exclude the possibility that the γ fibers might be as heavily biased as after intercollicular decerebration, or that they actively participate in both postural and phasic reflexes. The results mentioned show merely that α activity by itself is sufficient for rigidity in this particular case.

However, when we began to make anemic decerebrations, taking

care to tie both the internal and external carotids in addition to the basilar artery (adding intercollicular decerebration if the animals were restless), we were struck by the circumstance that though the spindles were excited, this bias generally was modest, particularly by comparison with the α activity as simultaneously recorded myographically by electrodes in the extensor muscles of the hind limb. Also, the α-γ linkage was broken. It is well known that the reflex behavior of this preparation is frequently erratic (Pollock and Davis, 1930, 1931), suggesting that something has gone wrong in the coordination of the events leading up to a reflex contraction. In the Sherrington decerebrate

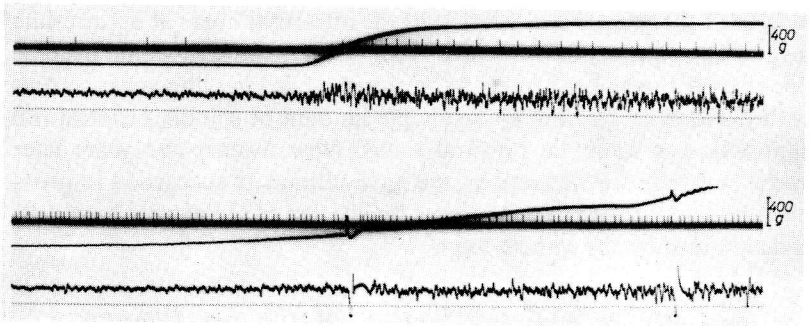

Fig. 133. Precollicular decerebration and section of cerebellar vermis removing culmen and lobulus med. Soleus muscle. Spindle discharge, myogram, electromyogram, and time in 100 cy/sec., recorded by four cathode ray beams.

Upper records: fast movement of head up. *Lower records:* same at slower rate with two taps on tendon of synergist gastrocnemius muscle. Note in both reflexes α activity, indicated by myogram and electromyogram, with little if any γ activity. Silent period in soleus, following taps on gastroc. tendon. (Observations by Granit, Holmgren, and Merton.)

animal one hardly ever fails to find both onset and cessation of rigidity as well as permanent high rigidity accompanied by the appropriate spindle adjustments as discussed above. This is not so in the Pollock-Davis animal. These behave like "α cats."

In the reflex responses, illustrated in Fig. 133, the spindle bias is obvious, to judge by the signs that by now should be familiar. Yet both the reflex contractions displayed—and they are big ones (cf. calibration)—begin with α activity. In the upper there is a very small increase of spindle discharge, in the lower practically pure α discharge, as shown also by the electromyogram. In Fig. 134 the experiment of Fig. 131 with the neck reflexes is repeated in an α animal, before and after de-afferentation. The spindles behave in a wholly passive manner, pausing

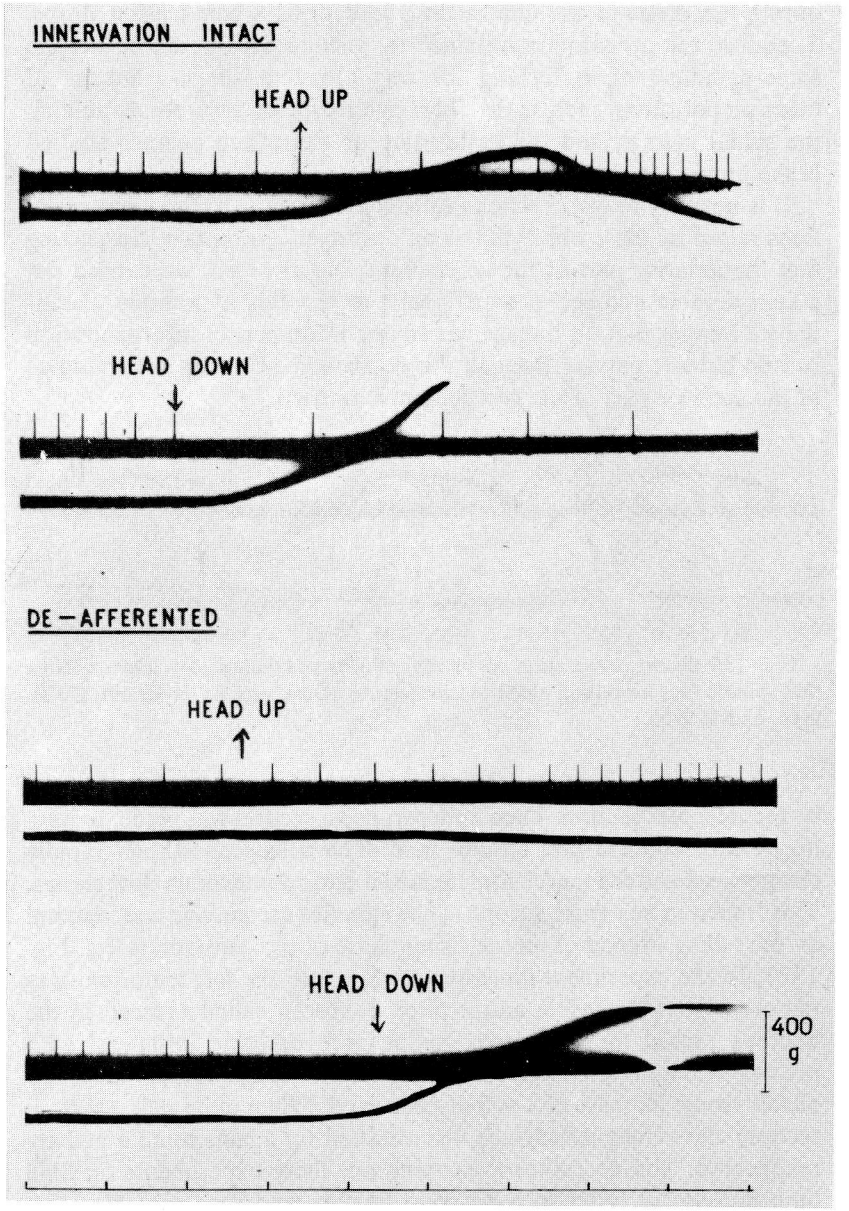

Fig. 134. Anemic decerebration. Soleus muscle before and after de-afferentation. Neck reflexes as indicated above records. Note that spindle fires on falling phase of reflex contraction. Time in 1/5 sec. (Observations by Granit, Holmgren, and Merton.)

during the onset of the contractions and firing when tension drops. Therefore the preparation obtained by anemic decerebration, despite some spindle bias, is lacking the very characteristic α-γ linkage of other preparations, such as the Sherrington type of decerebrate animal, the spinal animal, and the barbiturate or chloralose animals studied in the previous sections.

It is not easy to give a wholly satisfactory answer to the many questions raised by these observations on destroyed α-γ linkage. Suspecting that the anterior part of the cerebellum was involved, we carried out a considerable number of experiments to test this hypothesis. Essentially it implies that α-γ linkage has an important part of its organization run by circuits passing through the cerebellum. Cooling and removal of the anterior part of the cerebellum were tried.

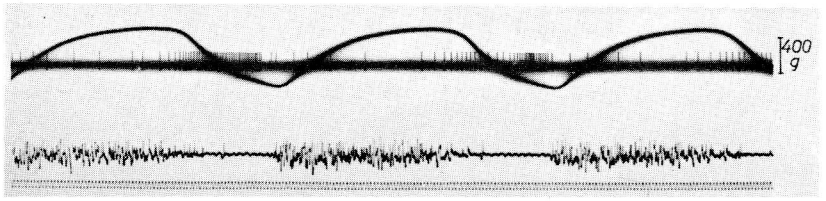

Fig. 135. Same preparation as in Fig. 133. Spontaneous slow clonus. Note that spindle fires on falling phase of contraction. (Observations by Granit, Holmgren, and Merton.)

In the experiment of Fig. 135 the animal was originally decerebrated by precollicular section. Then under trilene a section was made, removing vermis, culmen, and lobulus med. The trilene anesthesia rapidly disappeared and the muscle isolated went into spontaneous slow clonus. This is seen to be a pure α clonus. The spindles are passive and respond on the falling instead of on the rising phase of the contraction (cf. Fig. 132). In the experiment illustrated in Fig. 136 the left tentorium was removed from the inside and a piece of frozen saline (record in the middle) placed on the corresponding anterior lobe, ipsilateral with respect to the muscle isolated. The spindle activity disappeared completely, some increase of α activity occurred. When ultimately (bottom record) the cerebellar surface was warmed up again, spindle activity reappeared. The necessity of carrying out these experiments on hind limb muscles in order to have good fixation and long root filaments often makes the results less striking than they would be if fore limb muscles had been used, the latter responding more actively to destruction or cooling of the anterior lobe. However, when a definite effect

is observed, it is in the direction illustrated by the experiments of Figs. 135 and 136.

For this reason it seems likely that the cerebellum does play an important role in organizing α-γ linkage. Essentially the results presented signify that these types of preparation cannot use their "internal measuring instruments" in the spindles in the normal way because normal behavior is based on α-γ linkage. They are therefore to be regarded as objective evidence in favor of dysmetria, well known in connection with cerebellar disturbances.

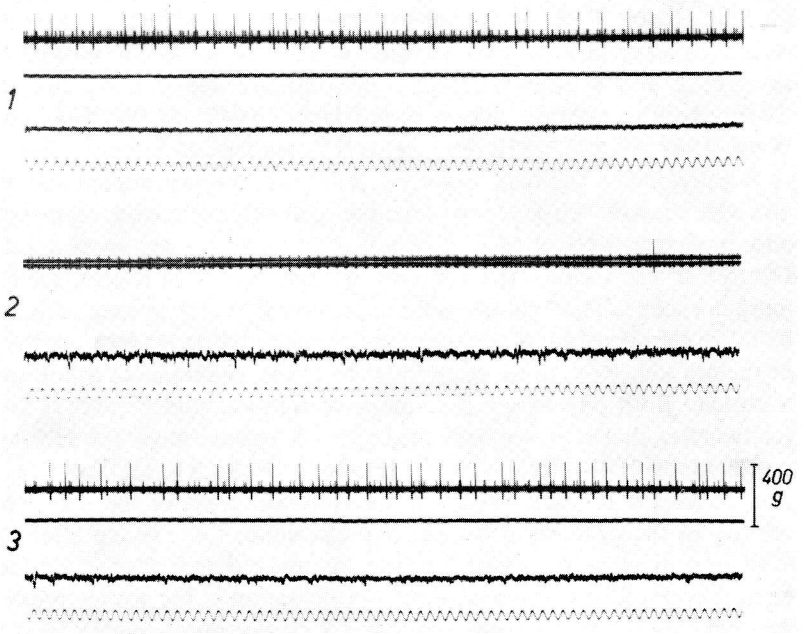

Fig. 136. Precollicular decerebration. Left side of tentorium removed. Left soleus. From above downward in each set of records: spindle, myogram, electromyogram, and time in 50 cy/sec. 1: basal activity before cooling, 2: cooling cerebellum with iced Ringer on culmen, 3: cerebellum warmed with Ringer at 38° C. Note, in record 2, rise of contraction shifting myograph record to coincide with spindle record. Spindle silenced. (Observations by Granit, Holmgren, and Merton.)

8. *Rigidity, spasticity*

The gist of this chapter has been to underline the realization that the ventral roots contain two motor systems, those that have been called

α and γ. This has compelled some revision of our concepts. Clearly much work still remains to be done before we are ready for a final assessment of the relative significance of α and γ components for movement in relation to muscular receptivity and central control. Thus, for instance, when the reflex effects of the myotube afferents have become fully worked out, a number of new facts will have to be incorporated into the picture. Even at the present stage, however, the clinician will be interested in what the new knowledge might mean for concepts such as rigidity and spasticity (for recent literature see Fulton, 1949b; Denny-Brown, 1950; Magoun and Rhines, 1947; Stella, 1944a,b; Ward, 1947; Cardin, 1952; Sprague and Chambers, 1953).

With regard to "rigidity" it is clear that the two types studied above, one with strongly active γ loop, the other with α hyperactivity, represent only limited aspects of rigidity regarded as a clinical proposition (cf. Denny-Brown, 1950). The new information, as far as it goes, raises more questions than it solves, but it does show that both systems should be taken into account. And it demonstrates in precise terms a number of factors that have to be considered in a test as simple as a pull on a muscle. Both physiological varieties of rigidity, studied above, are really better characterized in clinical terms as spastic states (cf. Hoefer and Putnam, 1940; Sprague and Chambers, 1953), i.e. by their exaggerated stretch reflexes. Whatever the ultimate cause of the γ hyperactivity in the ordinary decerebrate preparation, the ensuing afferent discharge must help toward keeping up some depolarization of the ventral horn cells and thus facilitate the elicitation of the stretch reflex. Yet this type of preparation may often lack persistent rigidity in the isolated hind limb muscles which have been used above for isolation of the factors concerned. The α cat, however, is always intensely rigid and spastic, even despite virtual absence of γ bias.

I have also tried to evaluate the tendon reflexes from these points of view, but at the moment it is perfectly clear that we do not understand why tendon reflexes are sometimes absent, sometimes enhanced. Even at the spinal level they cannot be explained in terms of a concept as simple as "excitability of the ventral horn cells." In a general way some increase of α excitability facilitates the appearance of tendon reflexes, and they are nearly always present in the α_4 cat. But it may happen that if this preparation is given sufficient pentobarbitone to stop persistent α activity and active stretch reflexes, the tendon jerk suddenly springs into existence in supernormal size. When stimulating various regions in the brain stem, one can easily demonstrate that under maintained iterative stimulation of long duration the tendon

jerk may come and go seemingly independent of the amount of spindle firing. It is true that it does tend to appear when a slow tonic contraction becomes visible in the muscle as a sign of increased excitability of the α cells. However, even this simple rule is not without exceptions, and after cessation of stimulation I have actually seen tendon jerks at their best when both α and γ activity to all appearance have been completely in abeyance. The tendon jerk is thus quite capable of surprising the experimenter just as much as is its nearest electrical equivalent, the monosynaptic reflex. In both cases it is best to admit that we do not yet understand all aspects of what constitutes "motoneurone excitability."

An exaggerated importance has in the past been attached to individual components in motor action and their topology. Yet Adrian and Moruzzi (1940) found impulses traveling in the pyramidal tract without corresponding motor contractions. In the light of the results by Brodal and Walberg (1952) and Brodal and Kaada (1953) one might suggest that some of them may have been sensory impulses, but we have also in the course of the present work seen several examples of intense spindle firing without motor action. Unless stimulation in any one system is highly synchronous, it is likely to be rather ineffective without support from some other system. And in all this there may well be unknown factors of strategic approach to the cell to be fired. Clearly motor, just as sensory, integration always involves the collaboration of several systems, general or unspecific as well as specific ones. I fail to see any fundamental necessity for excluding the possibility of specific action from what nowadays are often called systems for widespread diffuse action, such as those described by Magoun and discussed in Chapter 3 and above. The retina is a good example: there are some cells which integrate vast areas into a final common path of discharge, others which restrict themselves to picking up effects from highly circumscribed areas. In this vein I interpret the recent demonstrations by, e.g., Austin (1952), Gernandt (1952), and Sprague and Chambers (1954) that the brain stem reticular system, held to possess generalized action, also contains structures for differentiated action upon specific muscle groups.

9. *Sensory aspects*

Throughout my presentation of the muscle receptors the "muscle sense" has been deliberately kept in the background. This is because it would be premature at the present stage to venture much beyond

general statements. We are lacking detailed information about the central projections of the joint receptors which in this connection can hardly be neglected. On the muscle receptors the information is controversial. Thus, for instance, Mountcastle, Covian, and Harrison (1952), on the one hand, find only the smallest fibers of muscle nerves represented in the cerebrum, while McIntyre (1953), on the other, states that so-called Group II afferents containing what we have called myotube afferents definitely have such projections. Both agree that the nuclear bag afferents pass only to the cerebellum. These statements are subject to the limitations of the technique of evoked potentials and raise the question of whether a representation might not be found if one knew what systems it would be necessary to facilitate in order to make the technique more sensitive.

With regard to the muscle receptors being "private measuring instruments," it seems clear that the Golgi tendon organs would serve as tension recorders, while the impulses from the spindles probably would be appraised by a differential determined by the relative spike patterns in nuclear bag and myotube endings. Of the latter we know too little to say anything definite. They may well be in a state of rest when the contractile myotube portion is contracted and pulls on the passive nuclear bag. On the servo-theory it is possible to describe the nuclear bag endings as "length recorders" or misalinement detectors measuring the difference in length between intrafusal and extrafusal fibers. Sherrington (1900b, 1924) also thought of them as length recorders. In this capacity the nuclear bag endings have the property of discharging with a frequency roughly proportional to the length of the intrafusal fiber (Eldred, Granit, and Merton, 1953).

New information on stretch receptors in muscles other than those mentioned has been obtained by Cooper, Daniel, and Whitteridge (1951, 1953) from the intrinsic eye muscles of the goat. Cooper (1953) has recently described stretch receptors in the intrinsic muscles of the human tongue.

Chapter 8

Sensory Discrimination and Integration

1. General anatomical principles

By discrimination is meant the capacity to distinguish one sensory experience from another. Primarily this property is laid down as a differentiation in anatomical space and has culminated in the topographical map of projections on the cerebrum of the higher species, which have greatly developed special fields for special senses and motor performance. However, within the definition of topography also falls any single path or loop in a synaptic network by which the impulses from one point are carried along a route different from that of any other. A good example of the significance of the topographical factor is provided by the fovea of the primates, which is projected on the cortical striate area on a vastly enlarged scale. Another example is the map of somatic sensory projections of the body on the thalamus, worked out by Henneman and Mountcastle (1948) with the aid of the technique of evoked potentials. I shall return below to sensory projections. This brief introduction serves merely to emphasize the fundamental topographical principle. If we refuse to admit that discrimination is in some way based on different anatomical constituents differently located in the brain, we may as well give up altogether.

Whatever the nature of the central mechanisms, they must be capable of interpreting the frequency code. We first face the general problem of how uniqueness is established by these means, because if two adjacent touch spots on the skin can be discriminated, the frequency code must have transmitted "uniqueness" for each of them. Wherein are they unique? In the early chapters we had to give up the 1:1 relation of skin organ: nerve: brain cell which, if it had existed, might have been adduced in favor of uniqueness wholly anatomical. This would have been a solution of the problem similar to the one applied in photography and very generally in the technique of reproduction and based on what was called fineness of grain. The image is projected piecemeal for corresponding parts of prototype and reproduction, the

grain being made the finer, the greater the desired amount of detail. Skin and retina have been our examples (Chapter 2) for demonstrating that the frequency code has permitted application of principles, such as that of overlapping fields of different size, which would be deleterious in photographic reproduction. Fineness of grain has been shown above to be of some significance in the retina, and this is reasonable enough, but even for the fovea it has not been possible to demonstrate any single path from receptor to the optic nerve wholly disconnected from the synaptic network of specific internuncial cells. Man has some 3–6 million cones and 125 million rods and only around one million optic nerve fibers (Polyak, 1941). Thus, at any time internuncial effects might alter the nature of the message as a consequence of events in overlapping receptive fields and thus bring about changes similar to those in fibers from larger receptive fields. And so far we have omitted all possible interactions on the further passage upward.

Retina, ear, skin, and vestibular organs uniformly present the peripheral problem of discrimination as one of organization rather than of complete anatomical isolation. The receptive field, if large, is most sensitive in the middle. In the eye it can shrink or expand, depending *inter alia* upon the state of adaptation; this agrees with the fact that the dark-adapted eye with its strongly convergent highly sensitive rods integrates light at feeble illuminations (large fields), while the light-adapted eye (small fields) is an organ for differentiation (cf. Granit, 1947). However, both functions may be carried by the same nerve fiber since, depending upon the state of adaptation, its spectrum may be characteristic of the respective dominators of rods or cones (Chapter 1). In the two states of adaptation the fiber for the two dominators works, as it were, in different context and with other frequency patterns in itself and adjacent cells. In the one context it acts as scotopic, in the other as photopic dominator (Chapter 4). The modulators (Chapter 4), like some discrete and well localized modalities in the skin (Chapter 2), may well represent particularly small receptive fields.

In the vestibular organ (see Chapter 3), which deals with three space coordinates, there is an equivalent organization for transmitting the "local sign" of space as a pattern of permutations.

In the skin the receptive field (Chapter 2) is a complex structure of several intermingled modalities many of which actually are evoked together by the simplest kind of touch stimulus and many more by pressure. The fields again overlap and the larger ones are punctated by smaller fields, the smallest of all apparently referring to encapsulated or otherwise organized endings with highly developed specificity. Any one of the modalities may be pictured as a relief map over the skin, in which peaks represent high sensitivity and valleys low sensitivity. As low down as in the spinal cord segregation of paths from different senses takes place, as is well known from a host of clinical observations, e.g. on separation of pain and temperature sensations from those of pressure, as well as from discrimination of points and awareness of position. There is further separation by fiber size within each modality. Such anatomical segregation may aid differentiation within overlapping receptive fields.

Overlap in itself and alone should be a potent analyzer within any one modality, inasmuch as a number of adjacent touch spots may, for instance, activate one, two, or several fibers with different relative strength, depending upon their distance from the center of each field participating in the overlap. Several permutations are thus possible, not only because of the overlap but also because of the sensitivity variation from mid point to edge within each field.

In conclusion, then, it seems that the anatomical principle laid down as a peripheral basis for "uniqueness" might be described as a compromise between segregation and overlap. The sensory input is organized for a particular kind of receiver which can deal with the spike patterns from overlapping fields. I would not be surprised if the different central receivers were correspondingly organized, some to take care of large receptive fields and others of small ones. So far, however, the analysis of sensory projections has not been developed very much in terms of the properties of sense organs. It has dealt chiefly with gross anatomical differentiation of the sensory projections on different surfaces. We possess very little material for the second part of this theme: receptors and sensory perception regarded from the electrophysiological point of view.

A large amount of the thinking in the matter of sensory discrimination will at every phase of development assume the form of physical or technical analogies stimulated by the status of those subjects at the time of writing. Nowadays servo-mechanisms and electronics play this role. The adjustments in the sensori-motor loops through the muscle, the inhibitions to stretch that were studied in such detail in Chapters 6 and 7—these can be discussed in terms of negative and positive feedbacks of a servo-mechanism, but none of the many new discoveries were really actuated by this line of thinking; they arose from biological experimentation in the classical vein of this field. The concept of servo-control is practically as old as experimental physiology and if we want

to date it, Claude Bernard's idea of the constancy of the *milieu intérieur* enunciated in 1865 is based on a discussion of servo-mechanisms as penetrating as any of today's choosing. By these remarks I do not intend to dispute the fact that there may be workers who are induced to sound experimentation by taking off from a physical analogy.

My intention is merely to insist that our theories should be based on the actual biological evidence at hand, so as to prepare the ground for the next step in experimentation, and not primarily on physical analogies. The organized receptive field with its maximum sensitivity in the middle is one such definite datum, and so is the overlap. Timing and spike duration are similar examples, the frequency code another. Thus, for instance, time differences between sounds reaching the two ears are well-known aids to discrimination of auditory space. As for the centers, we know from Cajal's work (1900, 1904) that these are organized on the principle of overlap and expanding sectors; therefore the next step would be to approach the physiology of these "sectors" in peripheral terms. That this would be profitable has already been demonstrated by Marshall, Woolsey, and Bard (1941), who by the technique of evoked brain potentials studied the sensory representation to touching hairs on the skin of cats and monkeys. Each central region was found to consist of a spot of maximal primary response surrounded by a fringe of submaximal responses. There was considerable overlap of the submaximal margins for adjacent peripheral regions, and definite interaction was usually found within the overlap (see also Amassian, 1952; Chang, 1953).

2. *The frequency code*

The further upward we go from the receptor, the more the message is likely to be transformed. In the eye this happens even at the retinal stage, and we obtain the curious on/off response of variable on/off ratio that has been described in considerable detail. The very first question we can raise is how intensity (in man the basis of "brightness") is transmitted in an animal such as the cat in which the on/off ratio is so variable as to be likely to distort any primary relationship between stimulus intensity and impulse frequency. Fortunately we are in possession of a very satisfactory answer.

This will be easier to understand if muscle is considered first. The reflex effects from sense organs on muscle very definitely support the notion that the amount of reflex contraction is a function of input frequency unless this has been centrally inhibited. Adrian and Bronk

(1928, 1929) made a study of the motor side, first on the phrenic nerve innervating the diaphragm in respiration, then on the flexor reflex and the crossed extensor. It appeared that in these reflexes two mechanisms of gradation of the response operated. One was a gradation by *output frequency* to the muscle (diaphragm and flexor), the other was, in addition, by *number of firing motor units* (crossed extensor).

Going back to Fig. 123 (Chapter 7) we see that the muscle spindle has fired at a very high frequency when activated from the brain over the diffuse γ system without the slightest movement in the muscle. Clearly, then, high discharge frequency in one system alone may not be sufficient unless some additional factor, the one we call facilitation or level of excitability, is there to determine the *number* of neurones that will be available for the effect of frequency. In discussing monosynaptic testing it was also shown that around the active neurones, which fire into the muscle, there was a large fringe of subliminally excited fellow units which just failed to be excited by the natural stimulus. Number and frequency will therefore collaborate in determining the central effect in terms of "intensity." Cajal's principle of expanding sectors may well have as one of its biological purposes increase of number to guarantee an effect. Thus, in a spinal cord at a high level of excitability (many facilitated motoneurones) the slightest pull on the muscle suffices to elicit a stretch reflex (Chapter 6). The factor of "number" is in this center under constant control from other systems and will be also in the cerebral *sensory* centers, as shown by the arousal reactions from certain general facilitating systems, discussed in Chapter 3.

In view of these experiences from the motor field it is reasonable to suggest that unless a very small receptive area has a very large central projection, such as has the human fovea, its only chance of activating anything at all will be by being placed within a large overlapping field the way it actually is placed. This overlap will have to be transmitted to the center. Sholl (1954) has recently studied the visual cortex and on the basis of this work calculated that "some 5000 neurones may be directly activated by impulses from a single thalamic fibre" and "a neurone within the Gennari zone may embrace up to 4000 neurones within its own dendritic field." Most acts of discrimination in daily life are by overlapping fields already in the periphery. To this comes central expansion on an enormous scale, as Cajal pointed out.

The number of activated cells or fibers being, by all that is known about the mode of action of the central nervous system, an important factor in determining the effect in the organization interpreting the fre-

quency code, we would be ill-advised to try to explain sensory equivalents of "intensity" by frequency alone. However, as soon as the number of firing units becomes important, it becomes necessary to consider the behavior of a statistical assembly rather than a single sample unit.

The consequence of this is that a transformed frequency pattern, though it may lose some of its characteristics considered as a primary frequency representation of intensity, may nevertheless preserve this

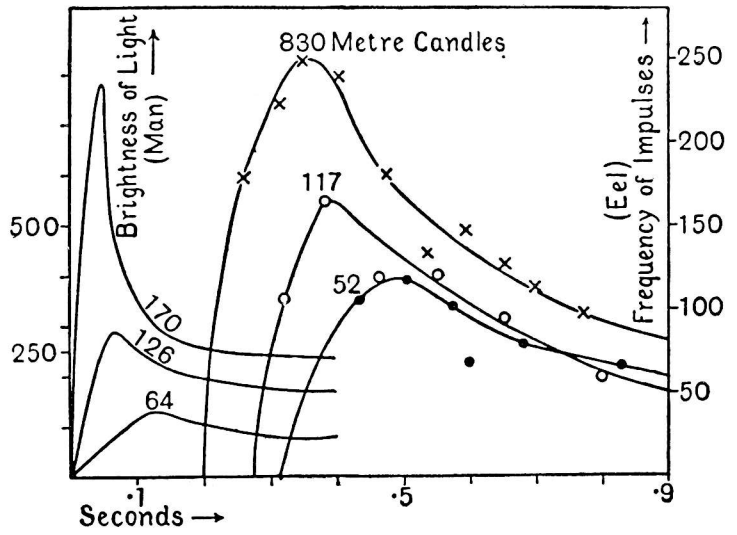

Fig. 137. Comparison of the rise in the sensation of brightness in man (Broca and Sulzer) with the rise in frequency of the discharge in the optic nerve of the eel. (Adrian, The basis of sensation, London, 1928.)

relationship in an over-all fashion. Another consequence is that the frequency code—as will be shown below—has a perfectly good chance of transmitting several types of information at the same time along a single line.

I can now return to specific cases, such as frequency and intensity in retina and vision. Fig. 137 is from Adrian's early summary (1928) and compares the brightness of light as perceived with the frequency variation in the eel's optic nerve. It should be recalled that in those days the frequency counts were rough counts obtained from the whole nerve and thus they illustrate the average function that has been discussed. The brightness variation is from measurements by Broca and Sulzer (1902), which have been repeatedly confirmed (see e.g. Granit

and Hammond, 1931). "Comparing," said Adrian, "the impulse discharge in an eel's optic nerve and the brightness of a visual image in man may be like the comparison of chalk with cheese, but it seems to be justified by the likeness of the two sets of curves. Those from the eel's nerve have much longer time relations, as we should naturally expect in a cold-blooded animal, but the general form with different intensities of light is surprisingly alike in the two cases" (p. 171).

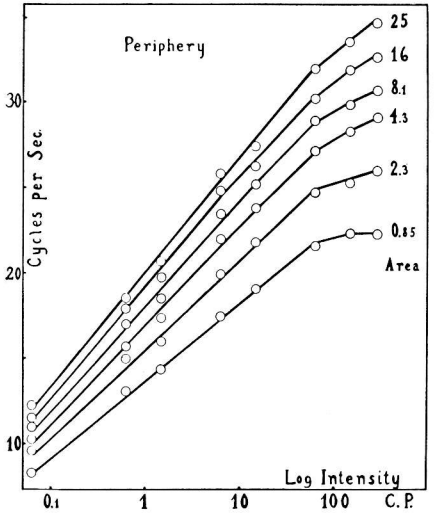

Fig. 138. Human periphery. Perceived fusion frequency plotted against log. intensity of the stimulus for different areas. Ordinates in cy/sec. should be multiplied by 2 to give flashes per second. Intensity in candle powers. (Granit and Harper, *Amer. J. Physiol., 95,* 211. 1930.)

Enroth (1952, 1953) has completed a piece of analysis which, to use Adrian's simile, is more like comparing two kinds of chalk. She has analyzed the fusion frequency of intermittent stimuli (flicker) for individual retinal elements and then studied its relation to impulse frequency in a large assortment of elements. To understand this it is necessary to know that brightness and fusion flicker frequency, as perceived, are related by a simple rule valid over a considerable range. This is the Ferry-Porter law (Ferry, 1892; Porter, 1898, 1902), which states that the frequency at which a flickering light appears fused is proportional to the logarithm of brightness (see Fig. 138). The principle of the flicker photometer for measuring brightness of differently colored lights is based on this law which makes it possible to circum-

vent the difficulty of comparing lights of different color. Clearly, then, if brightness is determined by impulse frequency as well as by fusion frequency, these two factors should be very simply related. Thus, in determining fusion frequency we have another way of approaching the relation between impulse frequency and brightness, assuming that cat and man cannot be very different in such very elementary properties of sight.

The fusion frequency of individual elements can be determined with considerable accuracy, both for the on- and the off-component of the discharge; it is that frequency at which each flash is no longer followed by a separate outburst of spikes. Fig. 75 (Chapter 5) illustrates a flickering response carried up to the point of fusion. Just before fusion occurs it is possible to measure the spike frequency within the individual outbursts of impulses caused by the flash, or by the cessation of the flash, if it is an off-discharge. Enroth generally counted the average spike frequency in the last four flashes before fusion occurred, and it did not make any difference if she went from flicker to fusion or from fusion to flicker. The details will be found in Enroth's thesis (1952).

From a very large number of data in which there was no difference between on-flicker and off-flicker with respect to fusion she (1953) then plotted the graph of Fig. 139, in which impulse frequency and fusion frequency are compared. The relation is one of direct proportionality. Thus, fusion frequency is a measure of impulse frequency. Since fusion frequency is also a measure of brightness, it is clear that brightness emerges as a simple function of the impulse frequency at the point of fusion. The same relation was later found to hold for the light-adapted eye stimulated with strong intensities (Dodt and Enroth, 1953).

One may with full justification say that the retinal events in flicker are exceedingly complex, both inhibition and excitation being at work, as is always true when more complex functions are studied. The high degree of temporal discrimination of light from darkness, which is also found in the large retinal units studied by Enroth and thus in units representing large receptive fields, would hardly have been possible on the basis of excitation alone. The results were interesting from this point of view also because they showed in detail how excitation and inhibition cooperate to make temporal differentiation possible. It is all the more surprising, therefore, that such a simple rule as hers emerges from the study of several units. All elements cannot go up to all values of fusion, but in a sufficiently large assembly of elements there

will always be a sufficient number capable of giving high impulse frequencies, and these will take care of the upper range of fusion frequencies.

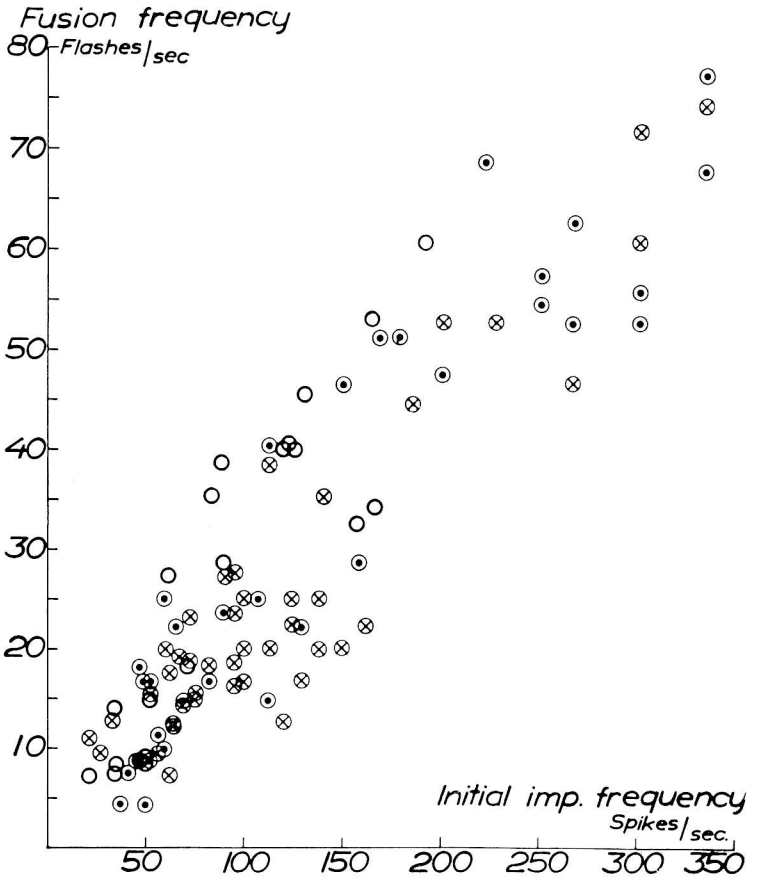

Fig. 139. Relation between fusion frequency and initial impulse frequency under varying conditions, as described in text. *Point in circle:* on-discharge; *crossed circle:* off-discharge; *open circle:* unidentified discharge. (Enroth, *Acta physiol. scand. 29,* 19. 1953.)

Enroth's results thus provide a physiological explanation of why flicker photometry is possible on the basis of the idea that impulse frequency should measure "intensity," which in vision has brightness for its equivalent. The individual elements behave in many different ways, but the relationship between intensity and impulse frequency is

preserved in an over-all fashion for the whole assembly. The necessity of considering a statistical approach to such problems has been adumbrated by McCulloch and Pitts (1948) in mathematical terms but, again, what is wanted is precise analysis in experimental terms, such as Enroth's correlating brightness, flicker fusion, and spike frequency.

A similar case is the perception of scotopic brightness, dependent upon the scotopic dominator (Chapter 4), which in its turn is dependent upon the spectral distribution of photosensitivity of visual purple. Donner and I (Chapter 4, Figs. 49–51) devoted a great deal of care to the study of the spectral distribution of sensitivity of individual dominators in the dark-adapted eye of the cat. The whole aim of the work was to multiply observations with the single spike until one could be certain of having obtained as many points as are compatible with the maintenance of a spike in a living eye under the microelectrode. We generally succeeded in observing each spike for several hours. It transpired (Chapter 4) that many of the elements isolated gave considerable and definite deviations from the spectral distribution of visual purple. By averaging the values for several spikes or, still better, by recording the same function electroretinographically with the new method of electrical resonance (Granit and Wirth, 1953), one obtained the average scotopic visibility curve for which the values fell on the points established on man by psychophysical measurements (Stiles and Smith, 1944) and by Gunter (1952), who measured perceived brightness in cats by behavioristic tests. This shows that the psychophysical process involves selection, averaging, or taking a weighted mean. Theoretically this case is of great interest, because there is such a perfect series of correlations at different levels: the spectral photosensitivity distribution of visual purple in the receptors; its precise reproduction by the average electroretinogram of a rod-dominated eye in the dark; then, at the optic nerve level, considerable variations within individual fibers—such as humps and skew distributions—owing to the complex nature of the receptive fields and interaction within them. Finally, there is a resynthesis of the original photochemical curve at the psychological level, either by some process of averaging or perhaps by selection, in case the visual purple curve should be represented by a greater number of individual elements than the curves showing deviations from it. Averaging on the basis of number seems most likely because of the nonhomogeneity of the receptive fields. The function concerned again is one of brightness or intensity and may just as well have been derived from the average spike frequency of an assembly.

I have emphasized above that large overlapping receptive fields are part of the peripheral organization. Since, as has been shown, it is necessary to conceive the interpretation of intensity ("brightness" in vision) on the basis of spike frequency as some kind of averaging process, it is clear that in this task large overlapping fields would be able to play the very useful role of supporting the process of averaging. The largest ganglion cells in the cat's retina collect information from thousands of receptors. These, the dominators, are aptly designed for the purpose of averaging the brightness distribution; their own deviations from the mean in terms of spike frequencies will be averaged a second time in the center on the basis of number.

The examples chosen have the clarity of all precise relations, as contrasted with general conjectures, and show how the frequency code on a statistical basis can transmit stimulus intensity in terms of its psychophysical equivalent, brightness, in spite of considerable retinal interaction with consequent transformation of the message. They also serve to illustrate what is meant by the statement that it is necessary to go ahead with the factual information available rather than to elaborate analogies.

Have we any evidence for the possibility that one fiber can transmit several messages at the same time? There is available another interesting example from the field of vision. The results were obtained with isolated spikes from the cat's retina and form the basis of a thesis by Donner (1950). It should again be recalled that the spike frequency of the retinal element, which is being studied in the dark-adapted state, reproduces in rough outline the broad dominator curve of spectral distribution that is characteristic of the photochemical absorption of visual purple. On the other hand, the element, as pointed out, is a convergence unit representing a very large number of receptors. The question raised was whether the presence of receptors other than those charged with visual purple, so easily demonstrable in individual dominator curves, can be signaled by the frequency code of a single element. If we assume first that this would not be the case, the curves illustrating—for different wave lengths—spike frequency as a function of time (as in Fig. 137) could be made identical if the energy values in all wave lengths were adjusted to correspond to unitary stimulation of visual purple, i.e. constant amount absorbed. This proved not to be possible, except with a limited number of elements. With the spectrum adjusted in this fashion it was clear that for many other elements the rate of rise of spike frequency against time, the so-called spike frequency/time differential, varied in a specific fashion with wave

length. An instance is given in Fig. 140 for a single spike. It was found that for the wave lengths 6,000 Å (red), 5200 Å (green), and 4600 Å (blue) the spike frequency/time differentials had their maxima at respectively 0.03, 0.17, and 0.24 seconds. This being so, it is clearly possible to measure the spike frequencies at those three moments and plot three functions through the spectrum, as has been done in Fig. 141. There emerges a color specificity expressed in terms of spike frequency at the three optima. A most interesting by-product is the secondary rise of the red maximum toward the violet, suggesting a physiological basis

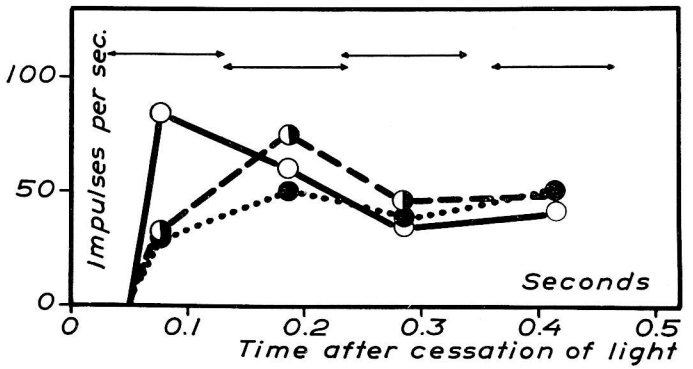

Fig. 140. Frequency-time curves for the off-effect of an on/off element. *Open circles:* 6,000 Å; *half-filled circles:* 5200 Å; *filled circles:* 4600 Å. 100 times the threshold. Spontaneous background activity was 27 impulses per second. Equal visual purple stimulation for all wave lengths. (Donner, *Acta physiol. scand., 21,* Suppl. 72. 1950.)

for the fact that violet appears as a mixture of red and blue. The retinal basis for this result may be a property of the receptors, of the neural structures, or of both, but it clearly does not lie in the ganglion cell, which merely serves to sum up and transmit the finished product in terms of the frequency code. Motokawa's (1949a–c, 1950) results based on the increased retinal sensitivity to a polarizing current after preillumination with various wave lengths show a similar relative order of time factors in color perception, and so does the rate of rise of different colors as perceived (for a summary of old work, see e.g. Bills, 1920; Kleitman and Piéron, 1925). According to Chang (1952a,b) the same relative order of events can be traced to the cortical station in cats.

Cats are generally held to be color-blind which may or may not be true. The point I have raised is not necessarily dependent upon the extent to which this animal uses a mechanism of color reception that

may well be rudimentary and damped by scotopic and photopic dominators, which with rare exceptions are the only ones that have been obtained in this animal with the aid of single spikes (without recourse to indirect methods such as the one just mentioned as well as electrical polarization or selective adaptation). For be that as it may, the essential point here is to establish experimentally the fact that a single spike is capable of transmitting different types of information by utilizing the frequency code.

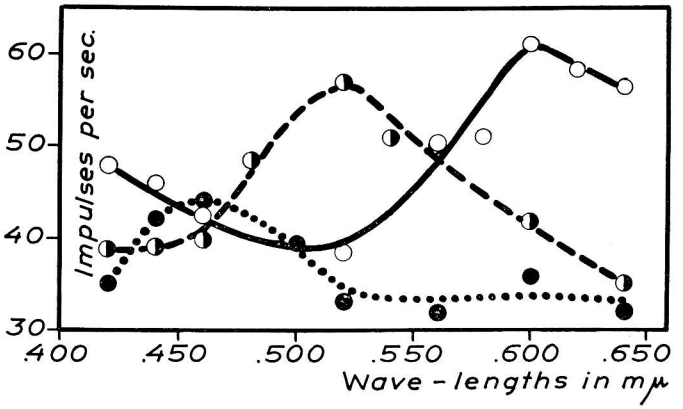

Fig. 141. Analysis of 9 elements. Average spike frequency for counting period of 0.1 sec. located on top of the three maxima for red, green, and blue as explained in text. *Open circles:* 5 curves, average delay of counting period 0.03 sec.; *half-filled circles:* 5 curves, average delay 0.17 sec.; *filled circles:* 4 curves, average delay 0.24 sec. Equal visual purple stimulation. (Donner, *Acta physiol. scand., 21,* Suppl. 72. 1950.)

In animals well supplied with modulators, such as snakes, pigeons, and to some extent frogs (see Chapter 4), color reception is likely to be based on both "topography" ("place" or "local sign") carried by modulators and on specific frequency patterns. These frequency-time differentials have not yet been analyzed for modulators. The color-theoretical generalizations known as trichromatic, four-component, or polychromatic theories need not concern us very much as long as it is unknown how the brain, in particular the striate area, evaluates the information it receives. A process of averaging may well be carried out on a trichromatic principle, and I fail to see how any of these theories ever could be adduced as an argument against the data that physiologists obtain from optic nerve fibers. With equal justification it is possible to argue that the data on dominators are meaningless because these

but rarely have the form of the canonical curves averaged from sensory measurements of brightness distributions in photopic and scotopic vision. The physiologists will have to proceed by their own methods and follow them to the end. Color discrimination is certainly easier to understand on the basis of the dominator-modulator theory (Granit, 1945b, 1947) than on any other theory where it emerges from calculations, even from computations with wholly imaginary curves such as those of Hecht (1931), or from curves which bear a greater resemblance to anything that is likely to be found in nature. Such calculations prove two things: (1) that nature's way of dealing with the visual information is sufficiently consistent to be synthesized in the form of logical structures from a moiety of reasonably good psychophysical data and (2) that the research worker has been ingenious enough to deduce one possible logical connection between the data available.

Discrimination of brightness and color are only two aspects of the visual message. The same fiber also carries on- and off-discharges. One would therefore expect to see a red flash twice, once at "on" and once at "off." Yet we do not see a red message from a brief illumination twice in succession but rather tend to see green (off) after red (on). How this well-known mechanism of successive contrast is organized is at the moment wholly unknown, but it may be profitable to inquire what else an off-discharge might be capable of doing that would not be better achieved by silence at "off," such as in the fibers giving postexcitatory inhibition. The most obvious answer is: "movement" and its direction. Movement of a line or point across the visual field will light up with sparks of on- and off-impulses, and the trail of off-impulses will fix its direction and do so better than "silence" (cf. Barlow, 1953a,b). Movement, and with it the on/off transition, is likely to play a role, too, in the fixation of contours. The eye is rarely wholly quiet; it moves from point to point and even in fixation (Lord, 1952; Barlow, 1952) makes small flicker or saccadic movements, and so on/off transitions may raise a dynamic pattern around spatial gradients of intensity or color.* Riggs *et al.* (1953) have compared "stopped images" with images in normal and exaggerated eye movements and find that in the first case they tend to disappear in accordance with the old work on "fixation blindness." By the small saccadic movements the eye may also

* Owing to the introduction of contact lenses for the reflected light beam, recording the eye movements, this fact has now been established with a very high degree of accuracy (L. A. Riggs, J. C. Armington, and F. Ratliff, *J. Opt. Soc. Amer., 44,* 315–21, 1954; R. W. Ditchburn and B. L. Ginsborg, *J. Physiol., 119,* 1–17, 1953).

receive some aid in counteracting its well-known deficiencies as an optical instrument. I do not think that these suggestions completely account for the existence of an off-discharge. Its role is not yet fully understood, especially in relation to the variations in the on/off ratio. Of these variations it is possible to say only that they probably serve creation of patterns to aid discrimination.

A single fiber can thus do a great deal with the frequency code, particularly when it operates as a "final common path" after one or several stages of neural transformation. And so far the organization of the central receivers has been left wholly out of account because of lack of information. The simplest pattern-sensitive receiver that I happen to be aware of is a peripheral one, the opener muscle of the hermit crab (*Eupagurus bernhardus*) studied by Wiersma and his collaborators (Wiersma and Adams, 1950; Wiersma, 1951; Ripley and Wiersma, 1953). Stimulation of a single axon running to the claw opener produces two types of contraction, fast or slow, depending upon how the stimuli are spaced. It is not yet known if this effect presupposes two types of end plates or if it is due to properties of different muscle fibers. However, it is present only in certain types of fast crab muscle.

3. *Comments on cortical sensory representation*

In classical psychophysics vision used to be described as a synthetic, and audition as an analytic sense. The reason for this was—to put it simply—that the trained ear can analyze vibrations into components while the eye in matching, for instance, the famous Rayleigh equation (Rayleigh, 1881), lithium red + thallium green = sodium yellow, cannot distinguish the components of the left half of the match from the homogeneous yellow of the right. Yet both the eye and the ear are designed as sentient surfaces with very precise central projections (as well reviewed by Fulton, 1949b). The eye, however, in spite of its being such a "good mixer" with regard to color, refuses to mix space coordinates except for definite purposes in the perception of depth. The early anatomical work proved that the visual projection on both cortex and superior colliculus (eye movements) was a singularly precise map of the retina, and this has been confirmed by the electrical technique of "evoked potentials" (see e.g. for cortex: Talbot, 1940; Talbot, Woolsey, and Thompson, 1946; Thompson, Woolsey, and Talbot, 1950; for colliculus: Apter, 1945). Color is not part of the spatial layout in the visual projections, while pitch of a tone, though in many

other respects the acoustic pendant of color, recurs centrally as a spatial pattern corresponding to the tonal properties of the sentient surface in the periphery. This topographical differentiation is probably the basis of the analytical properties of the ear. The visual projections, though carefully analyzed in terms of anatomy, have hitherto attracted very little interest from the point of view of the discrimination of brightness, color, and binocular vision. We know them chiefly in electrical terms (see e.g. Wang, 1934; Gerard, Marshall, and Saul, 1936; Marshall, 1949; Marshall, Talbot, and Ades, 1943; Bishop and Clare, 1953; Chang and Kaada, 1950; and for recent microelectrode work Jung, Von Baumgarten, and Baumgartner, 1952), which at the moment possess relatively little meaning for the interpretation of the visual act. I shall therefore discuss the auditory projections, which are better known from the point of view of sensation, and finish by considering some important psychological experiments on visual perceptions *in statu nascendi*.

It is necessary to start—as so often in these discussions—with a pioneer contribution by Adrian (1941), who found a double projection of the digits of the cat in two separate cortical regions and thereby originated the notion of double sensory representation. Talbot, Woolsey, and Thompson (1946) showed that the visual projections also had a double cortical representation; Woolsey and Walzl (1942) and Ades (1943) gave the first description of auditory areas I and II (for early work see Bremer and Dow, 1939). A considerable literature has since arisen, particularly on somatic areas I and II and the auditory and visual areas I and II (for a review see e.g. Fulton, 1949b). This cannot be dealt with here, but for a convenient elementary summary of the areas localized Fig. 142, from a review by Bremer (1952), should be studied. The figure is self-explanatory.

The auditory area, with which I shall deal in a moment, is of particular interest because of the tonal localization within the organ of Corti in the ear and its manner of representation on the sensory cortex. To this end I must return to the periphery for a while to consider the organization of the acoustic "xylophone" made up of the basilar membrane winding its way through the spiral of the cochlea as a floor for the organ of Corti. This membrane changes width from base to apex of the cochlea, being narrow at the base and broader at the top. On it ride the sensitive mechanoreceptors, hair cells, the hairs of which are in contact with a thin tectorial membrane serving as their roof. Mechanoreceptors of this general type (vestibular organ, lateral line) have already been considered in Chapter 3. For the present purposes the

winding of the basilar membrane may be disregarded. It can be thought of as a flattened-out sentient surface exhibiting tonal localization.

In the light of later work the essential feature of Von Helmholtz's famous resonance theory of hearing (the historical background of which has been well reviewed by Von Békésy and Rosenblith, 1948) has become its insistence on tonal localization to specific receptors rather than on a particular mechanism of resonance in terms of the physics of Von Helmholtz's day. This topographical element of the theory has since been investigated by every generation of research

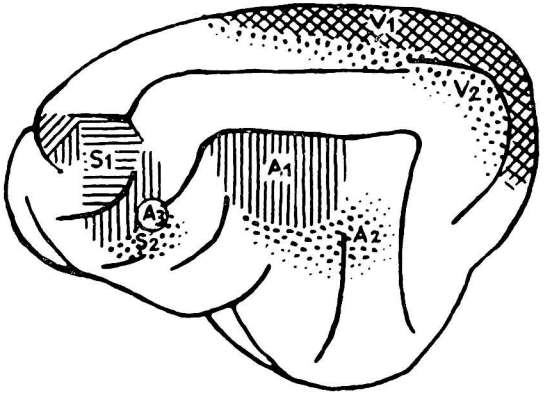

Fig. 142. Sensory projection areas on the cat's brain. S_1: somatic area I, with its somatotopic subdivisions; S_2: somatic area II, with subdivisions not indicated; A_1, A_2, A_3: auditory areas I, II, and III; V_1, V_2: visual areas I and II. (Bremer, Les Aires auditives de l'écorce cérébrale, Paris, 1952.)

workers with the techniques available at each period and generally also been confirmed. If I begin as late as 1942 with Von Békésy's (English trans. 1949) well-known experiments on his cochlear model, carried over into direct observations of the vibration of the cochlear partition in post-mortem material, it is because this was the first application of reliable micromethods to this organ. In addition to demonstrating the complex type of vibration pattern to sound waves it led to a frequency map for the distribution of tones over the cochlea in good agreement with maps, based on other less direct methods. The low tones of the frequency band arise in the upper turns of the cochlea, the high tones at the base, as was always assumed. Tasaki, Davis, and Legouix (1952) have recently brought forward another confirmation by localized recording of the cochlear microphonics with microelectrodes. Ultimately Tasaki (1953b) with the Gerard-Ling type of microelectrode (cf. above, p.

20) has succeeded in picking up the discharge from single cochlear nerve fibers, thus again confirming tonal localization with an extremely direct and delicate method.

In a sense, then, the sentient surface is a kind of xylophone, but Von Békésy also proved that there could be no question of lined-up resonators because direct observation of the wave form, as visualized in post-mortem material by a stroboscopic technique (the light being reflected from minute silver crystals strewn over the cochlear partition), showed the basilar membrane together with the organ of Corti and its tectorial membrane to respond to a vibration by a damped traveling wave having a relatively broad displacement area. The maximum amplitude shifted along the basilar membrane with frequency of stimulation in the manner mentioned above. The organ of Corti is thus a kind of frequency analyzer, though with a fairly low mechanical resolving power. Actually, it improves in the higher frequency ranges, at least as far as it has been possible to measure them (4,000 cps.). It does not compare favorably in selectivity with a high-class electronic vibration analyzer. In this it reminds one of the eye, the optics of which is by no means remarkable compared to high-class lenses. The image of a point source is surrounded by a considerable halo of diminishing brightness. For the eye it has already been shown how the image may be sharpened by neural mechanisms.

Whatever additional inside mechanisms the ear may contain, it must in the end fall back upon the frequency code, and here there is considerable similarity between eye and ear. Both have a spontaneous discharge which after the second neurone is often found to be inhibited by light or noise respectively. There is an off-discharge in the acoustic path too. This has been picked up with microelectrodes in the frog's brain by Ek and C. von Euler (1943) and in the geniculate body of cats by Galambos and his collaborators (Galambos, 1952; cf. Galambos, Rose, *et al.,* 1952) as well as earlier by Bremer (1943) in the cortical auditory area. Galambos mentions that some neurones, spontaneously active, are silenced by noise and discharge at "off." Just as in the eye, the frequency of discharge of individual neurones may behave very differently with respect to an increase of stimulus intensity. Some may increase their spike frequency and respond after shorter latencies in the higher intensity ranges, others may become inhibited, thus showing diametrically opposed behavior. The results on visual flicker in individual fibers demonstrated that despite these irregularities intensity is represented by frequency in an over-all manner.

There is no corresponding detailed analysis of auditory spike frequencies. We are better informed about the use of the frequency code in vision. However, the close analogy between vision and audition suggests that utilization of this code for the two senses follows similar principles, and this in itself seems significant. The advance made in either field will have repercussions upon the other. Again, with respect to modulation of the mechanical vibration analyzer within the ear, there are the well-known results by Galambos and Davis (1943, 1944) according to which single neurones exhibit very narrow tuning at the

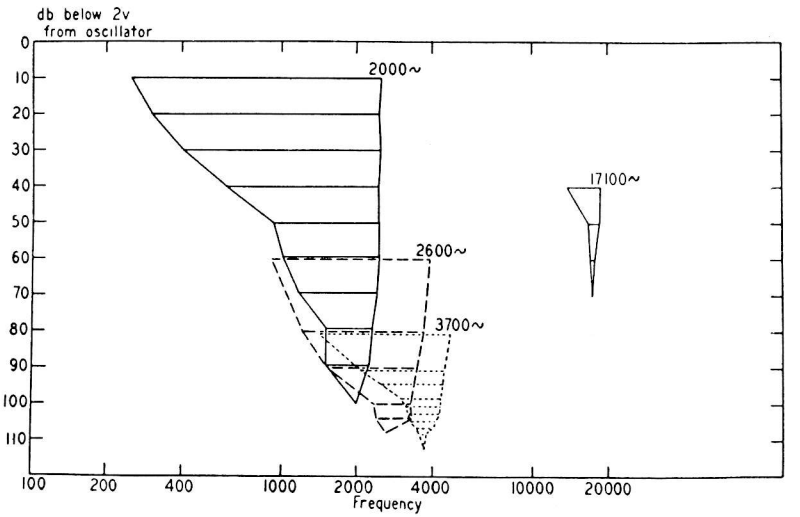

Fig. 143. Response areas for 4 different fibers. The three at the left of the figure are from the same animal. (Galambos and Davis, *J. Neurophysiol., 6,* 45. 1943.)

threshold, as shown in Fig. 143, reminiscent of the retinal modulators. The frequency bands broaden at higher stimulation intensities. It seems likely that neural inhibition between adjacent frequency bands within a region of overlap serves to sharpen the tuning of the mechanical vibration analyzer in the organ of Corti because, when ultimately the message reaches the cortical receiving station, it is found to be beautifully organized as a spatial lay-out in auditory areas I and II (Woolsey and Walzl, 1942; Tunturi, 1950a,b; Hind, 1953, and others).

Tunturi's work on dogs is of particular interest because he used a modification of Dusser de Barenne's (1934) well-known strychnine technique for local sensitization of spots within the cortical auditory areas to potentials evoked by tonal stimulation. The strychnine was

applied locally with 1 sq. mm. strips of filter paper dipped in a 3 per cent solution of strychnine sulphate colored with toluidine blue. The paper was quickly removed and the spot tested by calibrated tonal stimulation near threshold intensity. This enhances the size of the "evoked potential" (Curtis, 1940). Afterward the activity in the spot thus localized was suppressed by application of a similar filter paper dipped in 6 per cent pentobarbital sodium, and attention was turned to the next spot.

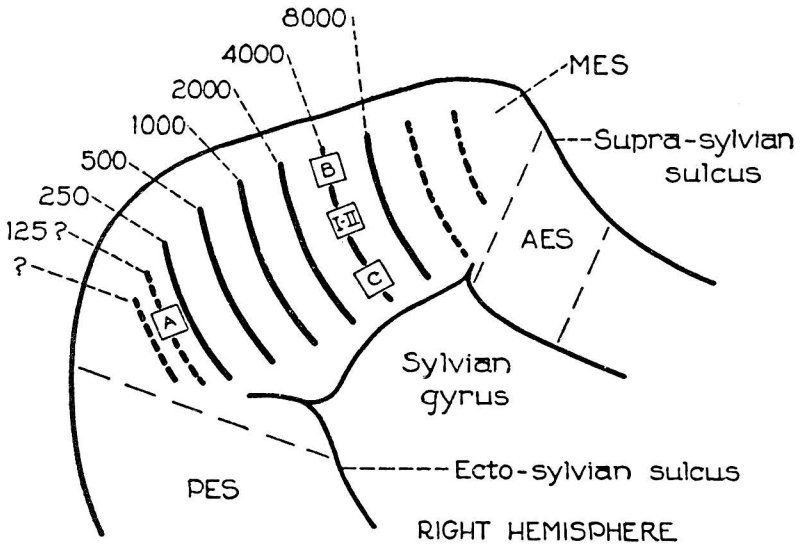

Fig. 144. Arrangement of afferent fiber endings in middle ectosylvian area. *AES:* anterior ectosylvian area, *MES:* middle ectosylvian area, *PES:* posterior ectosylvian area. 125–8,000 represent frequency in cps. which caused induced strychnine spikes with lowest intensity level in band indicated. Spacing between bands is 2 mm., and each band is drawn to a width of 0.2 mm., representing 0.1 octave. Squares indicate position of strychninized cortex for response curves found in the original paper, Figs. 4 and 5. Bands indicated by broken lines were not determined experimentally, but their location is suggested by the data. (Tunturi, *Amer. J. Physiol., 162,* 489. 1950.)

Fig. 144, from Tunturi's work (1950b), illustrates that the "xylophone" on the basilar membrane is actually reproduced as a cortical pendant of great perfection and regularity. This is all the more remarkable when one takes into account how difficult it has been to understand the message at intermediate levels in terms of spike frequency and when one considers the complexity of the auditory path. This runs through a very much longer chain of relays than does the visual path,

and its different fibers have their first, second, and *n*th relay in different nuclei (Held, 1893). If there had been any reason to doubt that the seemingly unintelligible frequency code of Galambos and his collaborators could deal with the matter in hand, Tunturi's map should serve to dispel them! The high audio frequencies are found in the anterior part of the middle ectosylvian gyrus of the dog's cortex, the low frequencies in the posterior portion. The intermediate tonal bands are spaced 2 mm. apart and each represents one octave.

There is no better demonstration in the whole literature on sensory representation in the cortex of the significance of differentiation by spatial factors, which in the beginning of this chapter was laid down as the basic principle of sensory discrimination. Quality (pitch) within the acoustic modality just happens to be an ideal case because the peripheral sentient surface is itself spatially organized in terms of this quality. In the retina the attributes of quality (color) are spatially integrated within each minute fraction of the sentient surface, in the skin, modalities and qualities are similarly represented within much the same units of surface. Hence these two organs differentiate space and direction by their general topographical layout on the cortex, and it is not likely that, for instance, red, green, and blue would be found in different regions of the occipital pole of the brain (except as projections of the general retinal color fields). When we obtain the ultimate topographical analysis of the vestibular organs, this is likely to be similar to the one found for the cochlea.

Since this was written I have seen the results of work by Andersson and Gernandt (1954), in which Tunturi's strychnine method has been applied in order to study the responses to electrical stimulation of the nerve fibers to the utricle and two of the semicircular canals. All these have separate projections (1, 2, and 3 in Fig. 145) and the enhancement by strychnine is marked and selective, as seen in the figure.

At the moment I think it premature to discuss the puzzling and interesting secondary and tertiary sensory areas in electrophysiological terms. In this field it is hardly possible to go much beyond the descriptive stage. For valuable comments I refer to Bremer's recent lectures (1953), Fulton's (1949b) "Physiology of the nervous system," and Ruch's (1951) review, "Sensory mechanisms."

4. *Comments on sensory integration*

In the previous sections the formidable problem of sensory integration has been encountered and presented as a physiological develop-

ment of classical psychophysics. The major problem of the latter has been aptly reformulated for physiologists by Klüver (1942) as the problem of stimulus equivalence. Originally the experimenters at-

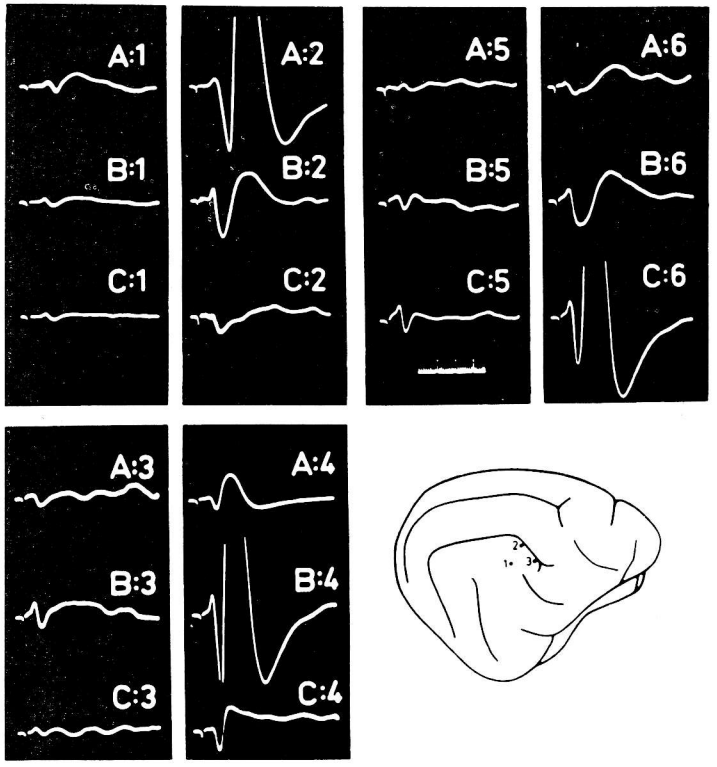

Fig. 145. Component vestibular responses of various cortical areas recorded from points 1, 2, and 3, indicated on the surface of diagrammatic cat's brain. Point 1 is a utricular projection, 2 belongs to the lateral, 3 to the superior semicircular canal. Strychnine in *a* on point 1, in *b* on point 2, in *c* on point 3. *A*:1, *A*:3, and *A*:5 (utricle); *B*:1, *B*:3, and *B*:5 (superior ampulla); *C*:1, *C*:3, and *C*:5 (lateral ampulla)—before local strychninization. *A*:2, *A*:4, and *A*:6 (utricle); *B*:2, *B*:4, and *B*:6 (superior ampulla); *C*:2, *C*:4, and *C*:6 (lateral ampulla)—after strychninization. Time in 1 and 10 msec. (By courtesy of B. Gernandt, Medical School, Gothenburg, Sweden.)

tempted to establish correlations between physics and psychology (phenomenology), e.g. in c.g.s. units of wave length or frequency for color of light and pitch of tone. The electronic era of research brought about a change of viewpoint. I have illustrated this change by presenting attempts to explain stimulus equivalence in terms of frequency

code, cell number, properties of receptors, their receptive fields, and sensory projection areas. In this sense physiology is a science of "cues" for sensory integration. The psychological datum itself, e.g. brightness, color, or pitch, is a primary datum of experience approached from another point of view and can be studied only by psychological analysis of the building up of experience, of which I shall give an example below. It is not and never can be a physiological datum. The physiological "cues" for sensory data do not derive their interest merely from their role as cues. A much greater number of cues is likely to enter into the sensory evaluation of any given stimulus situation than we can ever hope to unravel. They are interesting in themselves as contributions to the understanding of that organization of function in the nervous system on which ultimately our theoretical and practical medicine will have to be based. This is clearly shown by the parallels drawn between the motor (Chapters 6 and 7) and the sensory spheres.

I have not paid any attention to explanations devoid of an experimental basis. These often tend to assume the character of merely labeling events with names such as "Gestalt," "reverberating circuits," "feedbacks," etc. I have, indeed, mentioned newly discovered examples of sensory "feedback" but only in cases where it has been possible to demonstrate how the feedback actually works. As for reverberating circuits, I have no doubt whatever that they are of importance for sensory performance, but I have not been able to put my finger on any specific explanation of just how. And as for Gestalt (remembering gratefully that I was introduced to these problems in 1922 by E. Kaila and the late A. Gelb), I have never been able to persuade myself that this concept has been successfully disentangled from the averaging on the basis of experience which in this context has been exemplified by the sensory interpretation of visual brightness by means of the frequency code (cf. Morgan, 1951; Hilgard, 1951; Lawrence, 1949). However, the factor "experience" in perception deserves further comment.

Among the most remarkable experiments ever performed on the organization and building up of experience were those carried out in this country by Stratton (1896, 1897) more than half a century ago. Stratton studied vision without inversion of the retinal image. The experiments were done monocularly with an inversion lens, the other eye being covered. He wore this lens for eight consecutive days. Physiologically this amounted to a blatant clash between the information from the sensory fields representing the body (surface, muscle, joints, etc.) and those organized to deal with visual space, in which, now, right was

left or up was down. From Stratton's vivid description it is clear that two realities were encountered. One the second day of his experiment the room was upside down but the body was represented in pre-experimental terms and was felt as a standard. "I could voluntarily feel my feet strike on the ground seen in the upper part of my visual field." On the fourth day it was quite clear that the tactile areas would win the game and force the visual perceptions to obedience. "When I looked at my legs and arms, upright but if I looked away everything upside down." On the fifth day the new visual space had established itself so well that there was no anticipatory drawing in of chin and chest when a solid object passed through the visual field in the direction which in normal vision would have meant a blow. On the eighth day it was clear that as long as the new localization of the experimenter's body was vivid the general experience was harmonious. "But when . . . [an involuntary lapse into the older memory materials, or a willful recall of these older forms] the pre-experimental localization of my body was prominently in mind, then as I looked out on the scene before me the scene was involuntarily taken as the standard of right directions, and my body was felt to be in an inharmonious position with reference to the rest. I seemed to be viewing the scene from an inverted body."

These experiments have often been repeated and recently by Kohler (1951) with a number of observers, who varied them in several ways, with results of great interest. With binocular inversion spectacles he found, like Stratton with monocular ones, that the two "realities" were directed by the sensations from the body. On the tenth day, for instance, a weight was swung on a cord in front of the observer and appeared upside down but as soon as he was allowed to touch the upper end in order to swing it himself it reverted instantaneously to the normal type of pendulum movement in the same way as Schröder's well-known staircase illusion suddenly inverts in front of one's gaze. The same happened to an inverted landscape while he was driving uphill in a car, so that gravity was allowed to come in as a cue. No wonder that the observer by the tenth day was perfect on skis (Innsbruck, Austria, at the foot of mountains). It took him only five days to complete reflex reorientation.

In another set of experiments (with several observers) Kohler used prismatic spectacles (angles 15–20°) carried both mono- and binocularly, maximally for 124 days. After 10 days bends and distortions were straightened out, but if the spectacles (binocular) were then taken away, there were after effects of bends in the opposite direction lasting for four days. Abnormal positions of the head occurred in compensation for disturbance of direction. Prisms deflect the long and short wave lengths of the spectrum differently, and the observers began by seeing "rainbows" at contrasting surfaces, the dominating colors of which depended upon whether the brighter field was to the right or to the left. After months of use of prisms, they ultimately succeeded in compensating for these color disturbances. The long time suggests the development of a mechanism of considerable precision. When ultimately the prisms were taken away, there occurred as after effect chromatic deviations of opposite nature, visible even in monochromatic yellow light. The after effects in this case lasted for weeks. Some mechanism had been established whereby the correct or normal cue for color had obtained an abnormal significance. Similar observations were made with glasses half-blue, half-yellow. It is regrettable that these transformations of sensations of color and brightness have not been analyzed with any of the many accurate psychophysical methods available for such purposes.

In all these cases the apparent plasticity of the psychological interpretation is an adaptation to the organism's needs. In this the conscious component follows and agrees with reflex motor performance. The psychological datum which we try to trap in psychophysical experiments is an organized response to a large number of cues. If experience proves them unreliable a new and better system of interpretation is elaborated. The brain chooses and rejects, connects and disconnects. It is possible, even without elaborate experiments, to see something of these processes of purposeful integration in the many well-known visual and tactual illusions. Methodical disturbing of cues, as in Kohler's observations, is another means to the same end. I have described them here in order to exemplify the element of experience in perception and the nature of the psychological or phenomenological data for which we as sensory physiologists try to supply cues.

The experiments just mentioned also gave a good illustration of what used to be thought of as a philosophical problem of illusion as against reality. The observer with inversion spectacles had two illusions or two realities, as when looking at the swinging pendulum. By touching the cord he instantaneously changed over from one reality (illusion) to another. Ernst Mach in his classical Analyse der Empfindungen (1919) discussed this pseudoproblem among others and pointed out that it had only a practical but no scientific meaning when one speaks of a difference between appearance and reality. In the last instance reality is organized experience based on our sensations. Continuing on the line of Berkeley and Hume, Mach pointed the way to modern logical

positivism by emphasizing that it is meaningless to ask how material processes are translated into conscious psychological events when the distinction made between the two concerns merely the way in which we approach one and the same *Bewusstseinsinhalt,* as well as what system of relations and fundamentals we try to establish. Mach himself rightly states that his basic ideas had been expressed previously by Leibniz and Hume.

As is well known, our own time has seen the development of this attitude into a scrutiny of the foundations of logic and the definitions of language, in which Austrian and British thinkers have played a leading role—Carnap, Wittgenstein, Russell, and Whitehead, to mention only a few of the founders of logical positivism. I shall restrict my comments on epistemology to stating that the time is past when physiologists *ex cathedra* could issue naive views on the nature of knowledge, "brain and mind," reality and appearance, and similar concepts without penetrating the philosophical aspects of these problems in detail. They will merely be snared by their own lack of insight in the logical analysis of the conventions of language.

The physiologist's pragmatic business is with his own world of conventions, symbols, and relations—to determine whether they are any good and what they are good for. Faced with this situation, everyone makes his own selection from available knowledge, just as in these discussions I have made mine. It then remains to be seen if they stand the test of time and experimentation. However, one can be quite satisfied if they prove useful for the time being.

References

ADES, H. W. A secondary acoustic area in the cerebral cortex of the cat. *J. Neurophysiol., 6,* 59–63. 1943.

ADRIAN, E. D. The spread of activity in the tenuissimus muscle of the cat and in other complex muscles. *J. Physiol., 60,* 301–15. 1925.

——— The impulses produced by sensory nerve-endings. Part I. *J. Physiol., 61,* 49–72. 1926.

——— The impulses produced by sensory nerve-endings. Part 4. Impulses from pain receptors. *J. Physiol., 62,* 33–51. 1926–27.

——— The basis of sensation. The action of sense organs. Christophers, London, 1928. 122 pp.

——— Croonian Lecture. The messages in sensory nerve fibres and their interpretation. *Proc. Roy. Soc. of Lond.,* B*109,* 1–18. 1931a.

——— Potential changes in the isolated nervous system of *Dytiscus marginalis. J. Physiol., 72,* 132–51. 1931b.

——— The activity of the optic ganglion of *Dytiscus marginalis. J. Physiol., 75,* 26P. 1932a.

——— The mechanism of nervous action. Electrical studies of the neurone. Oxford University Press, London, 1932b. 103 pp.

——— Synchronous reactions in the optic ganglion of *Dytiscus. J. Physiol., 91,* 66–89. 1937.

——— Afferent discharges to the cerebral cortex from peripheral sense organs. *J. Physiol., 100,* 159–91. 1941.

——— Discharges from vestibular receptors in the cat. *J. Physiol., 101,* 389–407. 1943a.

——— Afferent areas in the cerebellum connected with the limbs. *Brain, 66,* 289–315. 1943b.

——— The electric response of the human eye. *J. Physiol., 104,* 84–104. 1945.

——— Rod and cone components in the electric response of the eye. *J. Physiol., 105,* 24–37. 1946.

——— The electrical activity of the mammalian olfactory bulb. *Electroenceph. Clin. Neurophysiol., 2,* 377–88. 1950.

——— Sensory messages and sensation. The response of the olfactory organ to different smells. *Acta physiol. scand., 29,* 5–14. 1953.

ADRIAN, E. D., and BRONK, D. W. The discharge of impulses in motor nerve fibres. Part I. Impulses in single fibres of the phrenic nerve. *J. Physiol., 66,* 81–101. 1928.

——— The discharge of impulses in motor nerve fibres. Part II. The fre-

quency of discharge in reflex and voluntary contractions. *J. Physiol., 67,* 119–51. 1929.

ADRIAN, E. D., CATTELL, MCK., and HOAGLAND, H. Sensory discharges in single cutaneous nerve fibres. *J. Physiol., 72,* 377–404. 1931.

ADRIAN, E. D., and MATTHEWS, R. The action of light on the eye. Part I. The discharge of impulses in the optic nerve and its relation to the electric change in the retina. *J. Physiol., 63,* 378–414. 1927a.

——— The action of light on the eye. Part II. The processes involved in retinal excitation. *J. Physiol., 64,* 279–301. 1927b.

——— The action of light on the eye. Part III. The interaction of retinal neurones. *J. Physiol., 65,* 273–98. 1928.

ADRIAN, E. D., and MORUZZI, G. Impulses in the pyramidal tract. *J. Physiol., 97,* 153–99. 1940.

ADRIAN, E. D., and UMRATH, K. The impulse discharge from the Pacinian corpuscle. *J. Physiol., 68,* 139–54. 1929.

ADRIAN, E. D., and ZOTTERMAN, Y. The impulses produced by sensory nerve-endings. Part 2. The response of a single end-organ. *J. Physiol., 61,* 151–71. 1926a.

——— The impulses produced by sensory nerve endings. Part 3. Impulses set up by touch and pressure. *J. Physiol., 61,* 465–83. 1926b.

AKERT, K., KOELLA, W. P., and HESS, R. Sleep produced by electrical stimulation of the thalamus. *Amer. J. Physiol., 168,* 260–7. 1952.

ALVAREZ-BUYLLA, R., and RAMIREZ DE ARELLANO, J. Local responses in Pacinian corpuscles. *Amer. J. Physiol., 172,* 237–44. 1953.

ALVORD, E. C., and FUORTES, M. G. F. Reflex activity of extensor motor units following afferent excitation. *J. Physiol., 122,* 302–21. 1953.

AMANN, A., and SCHAEFER, H. Ueber sensible Impulse im Herznerven. *Pflüg. Arch. ges. Physiol., 246,* 757–89. 1943.

AMASSIAN, V. E. Interaction in the somatovisceral projection system. *Res. Publ. Ass. Nerv. Ment. Dis., 30,* 371–402. 1952.

ANDERSSON, B. Polydipsia caused by intrahypothalamic injections of hypertonic NaCl-solutions. *Experientia, 8,* 157. 1952.

——— The effect of injections of hypertonic NaCl-solutions into different parts of the hypothalamus of goats. *Acta physiol. scand., 28,* 188–201. 1953.

ANDERSSON, S. and GERNANDT, B. E. Cortical projection of vestibular nerve in cat. *Acta Oto-Laryng.,* Suppl. 116, pp. 10–18. 1954.

APTER, J. T. Projection of the retina on superior colliculus of cats. *J. Neurophysiol., 8,* 123–34. 1945.

ARDEN, G. B. A narrow-band visual pigment obtained by a new technique. *J. Physiol., 122,* 13–4P. 1953.

——— Light-sensitive pigments in the visual cells of the frog. *J. Physiol., 123,* 377–85. 1954a.

——— The dark reactions in visual cell suspensions. *J. Physiol., 123,* 386–95. 1954b.

——— A narrow-band pigment present in visual cell suspensions. *J. Physiol., 123,* 396–408. 1954c.

——— Density of visual pigment in the frog retina. *Nature, 173,* 360–1. 1954d.

AREY, L. B. The function of the efferent fibres of the optic nerve of fishes. *J. Comp. Neurol., 26,* 213–45. 1916.

ARMINGTON, J. C. A component of the human electroretinogram associated with red color vision. *J. Opt. Soc. Amer., 42,* 393–401. 1952.

——— Electrical responses of the light-adapted eye. *J. Opt. Soc. Amer., 43,* 450–6. 1953.

ARMINGTON, J. C., JOHNSON, E. P., and RIGGS, L. A. The scotopic A-wave in the electrical response of the human retina. *J. Physiol., 118,* 289–98. 1952.

ARVANITAKI, A. Réactions déclenchées sur un axone au repos par l'activité d'un autre axone au niveau d'une zone de contact. Conditions de la transmission de l'excitation. *C. r. soc. biol.,* Paris, *133,* 39–42. 1940.

ASHER, H. The electroretinogram of the blind spot. *J. Physiol., 112,* 40P. 1951.

AUBERT, H. Physiologie der Netzhaut. Morgenstein, Breslau, 1865. 394 pp.

AUSTIN, G. M. Suprabulbar mechanisms of facilitation and inhibition of cord reflexes. *Res. Publ. Ass. Nerv. Ment. Dis., 30,* 196–222. 1952.

AUSTIN, G., and JASPER, H. Diencephalic and striatal mechanisms of facilitation and inhibition. *Proc. XVIII Int. Physiol. Congr.,* Copenhagen, p. 81. 1950.

AUTRUM, H. Erregungsvorgänge und Leistungen des Insektenauges. *Verh. dtsch. Zool. Gesellsch.,* Wilhelmshaven, pp. 133–43. 1951.

——— Ueber zeitliches Auflösungsvermögen und Primärvorgänge im Insektenauge. *Naturwissenschaften, 39,* 290–7. 1952.

AUTRUM, H., and GALLWITZ, U. Zur Analyse der Belichtungspotentiale des Insektenauges. *Z. vergl. Physiol., 33,* 407–35. 1951.

BACH, L. M. N., and MAGOUN, H. W. The vestibular nuclei as an excitatory mechanism for the cord. *J. Neurophysiol., 5,* 331–7. 1947.

BALL, S., COLLINS, F. D., MORTON, R. A., and STUBBS, A. L. Chemistry of visual processes. *Nature, 161,* 424–6. 1948.

BALL, S., GOODWIN, T. W., and MORTON, R. A. Retinene$_1$—vitamin A aldehyde. *Biochem. J., 40,* P. 59. 1946.

——— Studies on vitamin A. 5. The preparation of retinene$_1$—vitamin A aldehyde. *Biochem. J., 42,* 516–23. 1948.

BARKER, D. The innervation of the muscle spindles. *Quart. J. Micr. Sci., 89,* 143–86. 1948.

BARLOW, H. B. Eye movements during fixation. *J. Physiol., 116,* 290–306. 1952.

BARLOW, H. B. Action potentials from the frog's retina. *J. Physiol., 119,* 58–68. 1953a.

——— Summation and inhibition in the frog's retina. *J. Physiol., 119,* 69–88. 1953b.

BARRON, D. H. Central course of "recurrent" sensory discharges. *J. Neurophysiol., 3,* 403–6. 1940.

BARRON, D. H. and MATTHEWS, B. H. C. Intermittent conduction in the spinal cord. *J. Physiol., 85,* 73–103. 1935.

BARTLEY, H. S. Vision. A Study of its basis. Macmillan, London, 1941. 350 pp.

BARTLEY, H. S., and BISHOP, G. H. Optic nerve response to retinal stimulation in the rabbit. *Proc. Soc. Exp. Biol., 44,* 39–41. 1940.

——— Les théories photochimiques classiques et quantiques de la vision et l'inhibition nerveuse en vision liminaire. *Rev. d'optique théor. et instr., 28,* 661–90. 1950.

BAYLISS, L. E., LYTHGOE, R. J., and TANSLEY, K. Some new forms of visual purple found in sea fishes, with a note on the visual cells of origin. *Proc. Roy. Soc. of Lond., B120,* 95–113. 1936.

BAZETT, H. C., MCGLONE, B., WILLIAMS, R. G., and LUFKIN, H. M. Sensation I. Depth, distribution and probable identification in the prepuce of sensory end-organs concerned in sensations of temperature and touch; thermometric conductivity. *Arch. Neurol. Psychiat.,* Chicago, *27,* 489–517. 1932.

BEATON, L. E., MCKINLEY, W. A., BERRY, C. M., and RANSON, S. W. Localisation of cerebral center activating heat-loss mechanisms in monkeys. *J. Neurophysiol., 4,* 478–85. 1941.

BECK, A. Ueber die bei Belichtung der Netzhaut von Eledone moschata entstehenden Actionsströme. *Pflüg. Arch. ges. Physiol., 78,* 129–62. 1899.

BÉKÉSY, G. VON. The vibration of the cochlear partition in the anatomical preparation and models of the inner ear. *J. Acoust. Soc. Amer., 21,* 233–45. 1949. Trans. from *Akust. Z., 7,* 173–86. 1942.

——— DC resting potentials inside the cochlear partition. *J. Acoust. Soc. Amer., 24,* 72–6. 1952a.

——— Gross localization of the place of origin of the cochlear microphonics. *J. Acoust. Soc. Amer., 24,* 399–409. 1952b.

BÉKÉSY, G. VON, and ROSENBLITH, W. A. The early history of hearing-observations and theories. *J. Acoust. Soc. Amer., 20,* 727–48. 1948.

——— The mechanical properties of the ear. In Handbook of experimental psychology, ed. S. S. Stevens (1951). Pp. 1075–1115.

BELONOSCHKIN, B. Physiologisch-anatomische Untersuchungen über die Empfänger der Kaltempfindung. *Z. Zellforsch., 18,* 555–72. 1933.

BERGER, C. Area of retinal image and flicker fusion frequency. *Acta physiol. scand., 28,* 224–33. 1953.

BERGER, H. Ueber das Elektroenkephalogramm des Menschen. I. Mitteilung. *Arch. f. Psychiat., 87,* 527–70. 1929.

BERNARD, C. Introduction a l'étude de la médicine expérimentale. Baillière et fils, Paris, 1865. 400 pp.

BERNHARD, C. G. Isolation of retinal and optic ganglion response in the eye of *Dytiscus. J. Neurophysiol., 5,* 32–48. 1942.

BERNHARD, C. G., and GRANIT, R. Nerve as model temperature end organ. *J. gen. Physiol., 29,* 257–65. 1946.

BEST, W. Das menschliche Elektroretinogramm während der Dunkeladaptation. *Acta ophthal.,* Copenhagen, *31,* 95–116. 1953a.

——— Gleichzeitige Registrierung von Elektroretinogramm und spikes (Spitzenpotentialen) an der Netzhautoberfläche. *Z. Biol., 106,* 171–7. 1953b.

BIEDERMANN, W. Elektrophysiologie. Pt. 2, G. Fischer, Jena, 1895, 857 pp.

BILLS, M. A. The lag of visual sensation in its relation to wave lengths and intensity of light. *Psychol. Monogr., 28,* 1–101. 1920.

BING, A. I., and SKOUBY, A. P. Sensitization of cold receptors by substances with acethylcholine effect. *Acta physiol. scand., 21,* 286–302. 1950.

BISHOP, G. H., and CLARE, M. Sequence of events in optic cortex response to volleys of impulses in the radiation. *J. Neurophysiol., 16,* 490–8. 1953.

BISHOP, G. H., and O'LEARY, J. S. Electrical activity of the lateral geniculate of cats following optic nerve stimuli. *J. Neurophysiol., 3,* 308–22. 1940.

BISHOP, P. O., JEREMY, D., and LANCE, J. W. The optic nerve. Properties of a central tract. *J. Physiol., 121,* 415–32. 1953.

BJURSTEDT, A. G. H. Interaction of centrogenic and chemoreflex control of breathing during oxygen deficiency at rest. *Acta physiol. scand., 12,* Suppl. 38. 1946. 88 pp.

BLAKE, R. R., and RAMSEY, G. V., eds. Perception: An Approach to personality. Ronald Press, New York, 1951. 442 pp.

BLISS, A. F. The chemistry of daylight vision. *J. Gen. Physiol., 29,* 277–97. 1946.

——— The absorption spectra of visual purple of the squid and its bleaching products. *J. Biol. Chem., 176,* 563–9. 1948.

BLIX, M. Experimentela bidrag till lösning af frågan om hudnervernas specifika energi. *Upsala läkaref. förh., 18,* 87–102, 427–40. 1882–83.

——— Experimentelle Beiträge zur Lösung der Frage über die specifische Energie der Hautnerven. *Z. Biol., 20,* 141–56. 1884.

BOEHM, F., SIGG, B., and MONNIER, M. Elektroretinographische Untersuchungen am wachen Merschweinchen. *Helv. physiol. acta, 2,* 481–93. 1944.

BOENNINGHAUS, H.-G., HENATSCH, H.-D., and VILMAR, K.-F. Aktionsstromuntersuchungen am Nervus vestibularis des Warmblüters. *Arch. Ohr., Nas. u. Kehlk., 160,* 576–88. 1952.

BOHM, E., and GERNANDT, B. E. Comparison of off/on ratios in retina and geniculate body. *Acta physiol. scand., 21,* 187–94. 1950.

BOLL, F. Zur Anatomie und Physiologie der Retina. *Monatsber. Akad. Wiss.,* Berlin, *41,* 783–7. 1876.

——— Zur Anatomie und Physiologie der Retina. *Arch. Anat. Physiol.,* Leipzig, pp. 4–35. 1877.

BORNSCHEIN, H. Der Einfluss von Adaptationszustand und Reizintensität auf die Komponenten des menschlichen Elektroretinogramms. *Z. Biol., 105,* 454–63. 1953.

BOUMAN, M. A., and VAN DER VELDEN, H. A. The two-quanta explanation of the threshold values and visual acuity on the visual angle and the time of observation. *J. Opt. Soc. Amer., 37,* 908–19. 1947.

BOYNTON, R. M. Stray light and the human electroretinogram. *J. Opt. Soc. Amer., 43,* 442–9. 1953.

BOYNTON, R.M., and RIGGS, L. A. The effect of stimulus area and intensity upon the human retinal response. *J. Exp. Psychol., 42,* 217–26. 1951.

BRADLEY, K., EASTON, D. M., and ECCLES, J. C. An investigation of primary or direct inhibition. *J. Physiol., 122,* 474–88. 1953.

BRADLEY, K., and ECCLES, J. C. Analysis of fast afferent impulses from thigh muscles. *J. Physiol., 122,* 462–73. 1953.

BREMER, F. Cerveau "isolé" et physiologie du sommeil. *C. r. soc. biol.,* Paris, *118,* 1235–41. 1935.

——— Nouvelles recherches sur le mécanisme du sommeil. *C. r. soc. biol.,* Paris, *122,* 460–3. 1936a.

——— Activité électrique du cortex cérébral dans les états de sommeil et de veille chez le chat. *C. r. soc. biol.,* Paris, *122,* 464–7. 1936b.

——— Effets de la déafférentation complète d'une région de l'écorce cérébrale sur son activité électrique spontanée. *C. r. soc. biol.,* Paris, *127,* 355–8. 1938.

——— Étude oscillographique des réponses sensorielles de l'aire acoustique corticale chez le chat. *Arch. Int. Physiol., 53,* 53–103. 1943.

——— Les Aires auditives de l'écorce cérébrale. *Cours int. d'audiologie clin.,* Paris, 1952. 22 pp.

——— Some problems in neurophysiology. Athlone Press, London, 1953. 79 pp.

BREMER, F., and DOW, R. S. The acoustic area of the cerebral cortex in the cat. A combined oscillographic and cytoarchitectonic study. *J. Neurophysiol., 2,* 308–18. 1939.

BREUER, J. Neue Versuche an den Ohrbogengängen. *Pflüg. Arch. ges. Physiol., 44,* 135–52. 1889.

BRINK, F., and BRONK, D. W. Rhythmic activity of single nerve fibres introduced by low calcium. *Proc. Soc. Exp. Biol., 37,* 94–5. 1937.

BROCA, A., and SULZER, D. La Sensation lumineuse en fonction du temps. *J. Physiol. Path. Gen., 4,* 632–40. 1902.

BROCK, L. G., COOMBS, J. S., and ECCLES, J. C. Action potentials of motoneurones with intracellular electrodes. *Proc. Univ. Otago Med. Sch., 29,* 14–5. 1951.

——— The recording of potentials from motoneurones with an intracellular electrode. *J. Physiol., 117,* 431–60. 1952.

BROCK, L. G., ECCLES, J. C., and RALL, W. Experimental investigations on the afferent fibres in muscle nerves. *Proc. Roy. Soc. of Lond.,* B*138,* 453–75. 1951.

BRODA, E. E., and GOODEVE, C. F. The behaviour of visual purple at low temperature. *Proc. Roy. Soc. of Lond.,* A*179,* 151–9. 1941.

BRODAL, A. The cerebellar connections of the nucleus reticularis lateralis (nucleus funiculi lateralis) in rabbit and cat. Experimental investigations. *Acta psychiat.,* Copenhagen, *18,* 171–233. 1943.

——— Spinal afferents to the lateral reticular nucleus of the medulla oblongata in the cat. An experimental study. *J. Comp. Neurol., 91,* 259–96. 1949.

BRODAL, A., and KAADA, B. R. Cutaneous and proprioceptive impulses in the pyramidal tract in cats. *Acta physiol. scand., 29,* 131–2. 1953.

BRODAL, A., and WALBERG, F. Ascending fibres in pyramidal tract of cat. *Arch. Neurol. Psychiat.,* Chicago, *68,* 755–75. 1952.

BRONK, D. W., Fatigue of sense organs in muscle. *J. Physiol., 67,* 270–81. 1929.

BRONK, D. W., and STELLA, G. Afferent impulses in the carotid sinus nerve I. The relation of the discharge from single end organs to arterial blood pressure. *J. Cell. Comp. Physiol., 1,* 113–30. 1932.

——— The response to steady pressures of single end organs in the isolated carotid sinus. *Amer. J. Physiol., 110,* 708–14. 1935.

BROOKHART, J. M., MORUZZI, G., and SNIDER, R. S. Spike discharges of single units in the cerebellar cortex. *J. Neurophysiol., 13,* 465–86. 1950.

BROOKS, C. McC., DOWNMAN, C. B. B., and ECCLES, J. C. After-potentials and excitability of spinal motoneurones following antidromic activation. *J. Neurophysiol., 13,* 9–38. 1950a.

——— After-potentials and excitability of spinal motoneurones following orthodromic activation. *J. Neurophysiol., 13,* 159–76. 1950b.

BROOKS, C. McC., and FUORTES, M. G. F. The relation of dorsal and ventral root potentials to reflex activity in mammals. *J. Physiol., 116,* 380–94. 1952.

BROUWER, B. Centrifugal influence on centripetal systems in the brain. *J. Nerv. and Ment. Dis., 77,* 621–7. 1933.

BROWN, G. L., and GRAY, J. A. B. Some effects of nicotine-like substances and their relation to sensory nerve endings. *J. Physiol., 107,* 306–17. 1948.

BRUESCH, S. R., and AREY, L. B. The number of myelinated and unmyelinated fibers in the optic nerve of vertebrates. *J. Comp. Neurol., 77,* 631–65. 1942.

BUCHTHAL, F. Potentialänderungen bei der Kontraktion einzelner Muskelfasern. *Skand. Arch. physiol., 78,* 187–201. 1934.

——— The mechanical properties of the single striated muscle fibre at rest and during contraction and their structural interpretation. *K. danske vidensk. selsk. biol. medd., 17,* No. 2. 1942. 138 pp.

BULLER, A. J., NICHOLLS, J. G., and STRÖM, G. Spontaneous fluctuations of excitability in the muscle spindle of the frog. *J. Physiol. 122,* 409–18. 1953.

BULLOCK, T. H., and COWLES, R. B. Physiology of an infrared receptor: the facial pit of pit vipers. *Science, 115,* 541–3. 1952.

BULLOCK, T. H., and FAULSTICK, D. A. Some properties of unit warm receptors. *Fed. Proc., 12,* 22. 1953.

BUYTENDIJK, F. J. J. Ueber die electrischen Erscheinungen bei der reflektorischen Innervation der Skelettmuskulatur des Säugetieres. *Z. Biol., 59,* 35–52. 1912.

CAMIS, M. The physiology of the vestibular apparatus, trans. and annotated by R. S. Creed. Clarendon Press, Oxford, 1930. 310 pp.

CARDIN, A. Il tono muscolare non e'di natura riflessa. Il Attivita del midollo spinale deafferentato. *Boll. soc. ital. biol. sper., 28,* Fascicle 3. 1952.

CATTANEO, A. Organes nerveux terminaux musculo-tendineux, leurs conditions normales et leur manière de se comporter après la section des racines nerveuses et des nerfs spinaux. *Arch. ital. biol., 10,* 337–57. 1888.

CATTELL, MCK., and HOAGLAND, H. Response of tactile receptors to intermittent stimulation. *J. Physiol., 72,* 392–404. 1931.

CHAFFEE, E. L., and SUTCLIFFE, E. The differences in electrical response of the retina of the frog and horned toad according to the position of the electrodes. *Amer. J. Physiol., 95,* 250–61. 1930.

CHAMBERS, W. W., and SPRAGUE, J. M. Differential effects of cerebellar anterior lobe cortex and fastigial nuclei on postural tonus in the cat. *Science, 114,* 324–5. 1951.

——— Role of the cerebellum in regulation of decerebrate spasticity in cats. *Fed. Proc., 11,* 23. 1952.

CHANG, H.-T. Patterns of organization in the central nervous system. *Res. Publ. Ass. Nerv. Ment. Dis., 30,* 430–53. 1952a.

——— Cortical response to stimulation of lateral geniculate body and the potentiation thereof by continuous illumination of retina. *J. Neurophysiol., 15,* 5–26. 1952b.

——— Interaction of evoked cortical potentials. *J. Neurophysiol., 16,* 133–44. 1953.

CHANG, H.-T., and KAADA, B. R. An analysis of primary response of visual cortex to optic nerve stimulation in cats. *J. Neurophysiol., 13,* 305–18. 1950.

CHARPENTIER, G. Das Elektroretinogramm normaler und hemeraloper Ratten. *Acta ophthal.,* Copenhagen, Suppl. 9. 1936.

CHATIN, J. Sur la valeur comparée des impressions monochromatiques chez les invertébrés. *C. r. acad. sci.,* Paris, *90,* 41–3. 1880.

CLAES, E. Contribution a l'étude physiologique de la fonction visuelle I. Analyse oscillographique de l'activité spontanée et sensorielle de l'aire visuelle corticale chez le chat non anesthésié. *Arch. Int. Physiol., 48,* 181–237. 1939.

CLARK, D., HUGHES, J., and GASSER, H. S. Afferent function in the group of nerve fibers of slowest conduction velocity. *Amer. J. Physiol., 114,* 69–84. 1935.

CLARK, W. E. LE GROS. Anatomical pattern as the essential basis of sensory discrimination. Robert Boyle Lecture, No. 49. Blackwells, Oxford, 1947. 16 pp.

COBB, W., and MORTON, H. B. The human retinogram in response to high-intensity flashes. *Electroenceph. Clin. Neurophysiol., 4,* 547–56. 1952.

COHEN, L. A. Localization of stretch reflex. *J. Neurophysiol., 16,* 272–85. 1953.

COLLINS, F. D., and MORTON, R. A. Studies on rhodopsin. 1. Methods of extraction and the absorption spectrum. *Biochem. J., 47,* 3–10. 1950a.

——— Studies in rhodopsin. 3. Rhodopsin and transient orange. *Biochem. J., 47,* 18–24. 1950b.

COMROE, J. H. The effects of direct chemical and electrical stimulation of the respiratory center in the cat. *Amer. J. Physiol., 139,* 490–8. 1943.

COOPER, S. Muscle spindles in the intrinsic muscles of the human tongue. *J. Physiol., 122,* 193–202. 1953.

COOPER, S., and CREED, R. S. Reflex effects of active muscular contraction. *J. Physiol., 62,* 273–9. 1927a.

——— More reflex effects of active muscular contraction. *J. Physiol., 64,* 199–214. 1927b.

COOPER, S., DANIEL, P. M., and WHITTERIDGE, D. Afferent impulses in the oculo-motor nerve, from the extrinsic eye muscles. *J. Physiol., 113,* 463–74. 1951.

——— Nerve impulses in the brain stem of the goat. Short latency responses obtained by stretching the extrinsic eye muscles and the jaw muscles. *J. Physiol., 120,* 471–90. 1953a.

——— Nerve impulses in the brain stem of the goat. Responses with long

latencies obtained by stretching the extrinsic eye muscles. *J. Physiol., 120,* 491–513. 1953b.

CRAIK, K. J. W., and VERNON, M. D. The nature of dark adaptation. *Brit. J. Psychol., 32,* 62–81. 1941.

CRAWFORD, B. H. The scotopic visibility function. *Proc. Phys. Soc. of Lond., 62,* 321–34. 1949.

CREED, R. S., DENNY-BROWN, D., ECCLES, J. C., LIDDELL, E. G. T., and SHERRINGTON, C. S. Reflex activity of the spinal cord. The Clarendon Press, Oxford, 1932. 183 pp.

CREED, R. S., and GRANIT, R. Observations on the retinal action potential with especial reference to the response to intermittent stimulation. *J. Physiol., 78,* 419–41. 1933.

CRESCITELLI, F., and DARTNALL, H. J. A. Human visual purple. *Nature, 172,* 195–7. 1953a.

——— Some characteristics of the visual pigment system of the carp (Cyprinus carpio). *Proc. XIX Int. Physiol. Congr.,* Montreal, p. 289. 1953b.

CURTIS, H. J. Cortical potential mediated by the corpus callosum. *Amer. J. Physiol., 129,* 341P. 1940.

CURTIS, H. J., and COLE, K. S. Membrane action potentials from the squid giant axon. *J. Cell. Comp. Physiol., 15,* 147–57. 1940.

DALE, H. Transmission of effects from nerve-endings. A survey of the significance of present knowledge. Oxford University Press, 1952. 19 pp.

DARTNALL, H. J. A. Visual purple and the photopic luminosity curve. *Brit. J. Ophthal., 32,* 793–811. 1948a.

——— Indicator yellow and retinene. *Nature, 162,* 222. 1948b.

——— The mode of action of the scotopic pigments on the rod cell. *Proc. XVIII Int. Physiol. Congr.,* Copenhagen, p. 25. 1950.

——— Visual pigment 467, a photosensitive pigment present in tench retinae. *J. Physiol., 116,* 257–89. 1952a.

——— A new visual pigment absorbing maximally at 510 mμ. *J. Physiol., 117,* 57P. 1952b.

——— The interpretation of spectral sensitivity curves. *Brit. Med. Bull., 9,* 24–30. 1953a.

——— Evidence for a visual pigment having modulator-like properties. *J. Physiol., 122,* 12–3P. 1953b.

DARTNALL, H. J. A., GOODEVE, C. F., and LYTHGOE, R. J. The quantitative analysis of the photochemical bleaching of visual purple in monochromatic light. *Proc. Roy. Soc. of Lond.,* A*156,* 158–70. 1936.

——— The effect of temperature on the photochemical bleaching of visual purple solutions. *Proc. Roy. Soc. of Lond.,* A*164,* 216–30. 1938.

DAVIS, H. Psychophysiology of hearing and deafness. In Handbook of experimental psychology, ed. S. S. Stevens (1951). Pp. 1116–42.

DAVIS, H., TASAKI, I., and GOLDSTEIN, R. The peripheral origin of activity with reference to the ear. *Cold Spr. Harb. Symp. Quant. Biol., 17,* 143–57. 1952.

DELL, P. Corrélations entre le système végétatif et le système de la vie de relation. Mesencéphale, diencéphale et cortex cérébral. *J. Physiol., 44,* 471–557. 1952.

DEMPSEY, E. W., and MORISON, R. S. The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. *Amer. J. Physiol., 135,* 293–300. 1942.

——— The electrical activity of a thalamocortical relay system. *Amer. J. Physiol., 138,* 283–96. 1943.

DENNY-BROWN, D. On inhibition as a reflex accompaniment of the tendon jerk and of other forms of active muscular response. *Proc. Roy. Soc. of Lond.,* B*103,* 321–36. 1928.

——— On the nature of postural reflexes. *Proc. Roy. Soc. of Lond.,* B*104,* 252–301. 1929.

——— Disintegration of motor function resulting from cerebral lesions. *J. Nerv. Ment. Dis., 112,* 1–45. 1950.

DENNY-BROWN, D., and SHERRINGTON, C. S. Subliminal fringe in spinal flexion. *J. Physiol., 66,* 175–80. 1928.

DENTON, E. J., and PIRENNE, M. H. The visual sensitivity of the toad *Xenopus laevis. J. Physiol., 125,* 181–207. 1954.

DETHIER, V. G. Chemoreception. In Insect physiology, ed. K. D. Roeder (1953). Pp. 544–76.

DEWAR, J., and M'KENDRICK, J. G. On the physiological action of light. No. 1. *J. Anat. Physiol., 7,* 275–82. 1873a.

——— On the physiological action of light. *Trans. Roy. Soc. of Edinb., 27,* 141–66. 1873b.

DICKINSON, C. J. Afferent nerves from the heart region. *J. Physiol., 111,* 399–407. 1950.

DODT, E. Cone electroretinography by flicker. *Nature, 168,* 738–9. 1951a.

——— Beiträge zur Elektrophysiologie des Auges. I. Mitteilung. Ueber die sekundäre Erhebung im Aktionspotential des menschlichen Auges bei Belichtung. *Von Graefes Arch. Ophthal., 151,* 672–92. 1951b.

——— Beiträge zur Elektrophysiologie des Auges. II Mitteilung. Ueber Hemmungsvorgänge in der menschlichen Retina. *Von Graefes Arch. Ophthal., 153,* 152–62. 1952a.

——— The behaviour of thermoceptors at low and high temperatures with special reference to Ebbecke's temperature phenomena. *Acta physiol. scand., 27,* 295–314. 1952b.

——— Differential thermosensitivity of mammalian A-fibres. *Acta physiol. scand., 29,* 91–108. 1953.

DODT, E., and ENROTH, C. Retinal flicker response in cat. *Acta physiol. scand., 30,* 375–90. 1953.

DODT, E., and GOHL, D. Ein Fall fehlender Sehnenreflexe bei einem gesunden Menschen und seine neurophysiologische Untersuchung. *Dtsch. Z. Nervenheilk., 168,* 30–4. 1952.

DODT, E., and HECK, J. Einflüsse des Adaptationszustandes auf die Rezeption intermittierender Lichtreize. *Pflüg. Arch. ges. Physiol., 259,* 212–25. 1954a.

——— Retinapotentiale der zapfenfreien Netzhaut des Gecko (Sphaerodactycus muralis). *Pflüg. Arch. ges. Physiol., 259,* 226–30. 1954b.

DODT, E., SKOUBY, A. P., and ZOTTERMAN, Y. The effect of cholinergic substances on the discharges from thermal receptors. *Acta physiol. scand., 28,* 101–14. 1953.

DODT, E., and WADENSTEN, L. The use of flicker electroretinography in the human eye. Observations on some normal and pathological retinae. *Acta ophthal.,* Copenhagen. To be published in 1954.

DODT, E., and WIRTH, A. Differentiation between rods and cones by flicker electroretinography in pigeon and guinea pig. *Acta physiol. scand., 30,* 80–9. 1953.

DODT, E., and ZOTTERMAN, Y. Mode of action of warm receptors. *Acta physiol. scand., 26,* 345–57. 1952a.

——— The discharge of specific cold fibres at high temperatures. *Acta physiol. scand., 26,* 358–65. 1952b.

DOGIEL, A. S. Die Retina der Vögel. *Arch. mikr. Anat., 44,* 622–48. 1895.

DOHLMAN, G. Some practical and theoretical points in labyrinthology. *Proc. Roy. Soc. Med., 28,* 1371–84. 1935.

——— Die Rolle der Perilymphe bei den vestibulären Reaktionen. *Arch. Ohr., Nas. u. Kehlk., 150,* 25–30. 1941.

DONNER, K. O. The spike frequencies of mammalian retinal elements as a function of wave-length of light. *Acta physiol. scand., 21,* Suppl. 72. 1950. 59 pp.

——— The spectral sensitivity of the pigeon's retinal elements. *J. Physiol., 122,* 524–37. 1953.

DONNER, K. O., and GRANIT, R. Scotopic dominator and state of visual purple in the retina. *Acta physiol. scand., 17,* 161–9. 1949.

DONNER, K. O., and WILLMER, E. N. An analysis of the response from single visual-purple-dependent elements in the retina of the cat. *J. Physiol., 111,* 160–73. 1950.

DOUGLAS, W. W., and GRAY, J. A. B. The excitant action of acetylcholine and other substances on cutaneous sensory pathways and its prevention by hexamethonium and d-tubocurarine. *J Physiol., 119,* 118–28. 1953.

DOW, R. S. Cerebellar action potentials in response to stimulation of various afferent connections. *J. Neurophysiol., 2,* 543–55. 1939.

DU BOIS REYMOND, E. Untersuchungen über thierische Elektricität. G. Reimer, Berlin, *2,* Pt. I, 256–7. 1849.

DUN, F.-T., and FINLEY, C. B. The rate of adaptation of cutaneous nerve endings in the frog. *J. Physiol., 94,* 170–6. 1938.

DUSSER DE BARENNE, J. G. Die elektromotorischen Erscheinungen im Muskel bei der reziproken Innervation der quergestreiften Skelettmuskulatur. *Zbl. Physiol., 25,* 334–6. 1911.

——— Central levels of sensory integration. *Res. Publ. Ass. Nerv. Ment. Dis., 15,* 274–88. 1934.

DUSSER DE BARENNE, J. G., and MCCULLOCH, W. S. The direct functional interrelation of sensory cortex and optic thalamus. *J. Neurophysiol., 1,* 176–86. 1938.

ECCLES, J. C. Studies on the flexor reflex. III. The central effects produced by an antidromic volley. *Proc. Roy. Soc. of Lond.,* B*107,* 557–85. 1931.

——— The neurophysiological basis of mind. The principles of neurophysiology. Waynflete Lectures. Clarendon Press, Oxford, 1953. 314 pp.

ECCLES, J. C., FATT, P., and KOKETSU, K. Cholinergic and inhibitory synapses in a central nervous pathway. To be published. 1954.

ECCLES, J. C., FATT, P., and LANDGREN, S. The "direct" inhibitory pathway in the spinal cord. *Austr. J. Sci., 16,* 130–34. 1954.

ECCLES, J. C., KATZ, B., and KUFFLER, S. W. Nature of the "endplate potential" in curarized muscle. *J. Neurophysiol., 5,* 362–87. 1941.

ECCLES, J. C., and O'CONNOR, W. J. Responses which nerve impulses evoke in mammalian striated muscles. *J. Physiol., 97,* 44–102. 1939.

ECCLES, J. C., and PRITCHARD, J. J. The action potential of motoneurones. *J. Physiol., 89,* 43P. 1937.

ECCLES, J. C., and RALL, W. Repetitive monosynaptic activation of motoneurones. *Proc. Roy. Soc. of Lond.,* B*138,* 475–98. 1951.

ECCLES, J. C., and SHERRINGTON, C. S. Numbers and contraction-values of individual motor-units examined in some muscles of the limb. *Proc. Roy. Soc. of Lond.,* B*106,* 326–57. 1930.

——— Studies on the flexor reflex. I. Latent period. *Proc. Roy. Soc. of Lond.,* B*107,* 511–34. 1931.

ECHLIN, F., and PROPPER, N. "Sensitization" by injury of the cutaneous nerve endings in the frog. *J. Physiol., 88,* 388–400. 1937.

EINTHOVEN, W., and JOLLY, W. A. The form and magnitude of the electrical response of the eye to stimulation by light at various intensities. *Quart. J. Exp. Physiol., 1,* 373–416. 1908.

EK, J., and EULER, C. VON. Electrical responses from the primary acoustic centre of the frog. *Nature, 152,* 132. 1943.

ELDRED, E., GRANIT, R., and MERTON, P. A. Supraspinal control of the muscle spindles and its significance. *J. Physiol., 122,* 498–523. 1953.

ELDRED, E., and HAGBARTH, K.-E. Facilitation and inhibition of gamma afferents by stimulation of certain skin areas. *J. Neurophysiol., 17,* 59–65. 1954.

ENROTH, C. The mechanism of flicker and fusion studied on single retinal elements in the dark-adapted eye of the cat. *Acta physiol. scand., 27,* Suppl. 100. 1952.

——— Spike frequency and flicker fusion frequency in retinal ganglion cells. *Acta physiol. scand., 29,* 19–21. 1953.

ERLANGER, J. The interpretation of the action potentials in cutaneous and muscle nerve. *Amer. J. Physiol., 82,* 644–55. 1927.

ERLANGER, J., and GASSER, H. S. Electrical signs of nervous activity. Johnson Foundation Lectures. University of Pennsylvania Press, Philadelphia, 1937. 221 pp.

EULER, C. VON. Selective responses to thermal stimulation of mammalian nerves. *Acta physiol. scand., 14,* Suppl. 45. 1947. 75 pp.

——— Slow "temperature potentials" in the hypothalamus. *J. Cell. Comp. Physiol., 36,* 333–50. 1950.

——— A preliminary note on slow hypothalamic "osmo-potentials." *Acta physiol. scand., 29,* 133–6. 1953.

EULER, C. VON, and SÖDERBERG, U. Medullary chemosensitive receptors. *J. Physiol., 118,* 545–54. 1952a.

——— Slow potentials in the respiratory centres. *J. Physiol., 118,* 555–64. 1952b.

EULER, H. VON, and ADLER, E. Beobachtungen über den Sehpurpur. *Ark. kemi. min. geol., 11*B, No. 20. 1933. 6 pp.

EULER, U. S. VON, LILJESTRAND, G., and ZOTTERMAN, Y. The excitation mechanism of the chemoreceptors of the carotid body. *Skand. Arch. physiol., 83,* 132–52. 1939.

——— Baroceptive impulses in the carotid sinus and their relation to the pressure reflex. *Acta physiol. scand., 2,* 1–9. 1941.

EWALD, J. R. Zur Physiologie der Bogengänge. *Pflüg. Arch. ges. Physiol., 41,* 463–83. 1887.

FATT, P., and KATZ, B. An analysis of the end-plate potential recorded with an intra-cellular electrode. *J. Physiol., 115,* 320–70. 1951.

——— Spontaneous subthreshold activity at motor nerve endings. *J. Physiol., 117,* 109–28. 1952a.

——— The action of inhibitory nerve impulses on the surface membrane of crustacean muscle fibres. *J. Physiol., 118,* 47P. 1952b.

FECHNER, G. T. Elemente der Psychophysik. Breitkopf and Härtel, Leipzig, 1862. *2,* 571 pp.

FENG, T. P. Reversible inexcitability of tactile endings in skin injury. *J. Physiol., 79,* 103–8. 1933.

FERNAND, V. S. V., and YOUNG, J. Z. The sizes of the nerve fibres of muscle nerves. *Proc. Roy. Soc. of Lond.,* B*139,* 38–58. 1951.

FERNÁNDEZ, C. The innervation of the cochlea (guinea pig). *Laryngoscope, 61,* 1152–72. 1951.

FERRY, E. S. Persistence of vision. *Amer. J. Sci., 44* (3), 192–207. 1892.

FESSARD, A. Propriétés rythmiques de la matière vivante. *Actualités scientifiques et industrielles, 417, 418.* Hermann, Paris, 1936. 99 + 63 pp.

FESSARD, A., and SEGERS, M. Quelques caractères différentiels des récepteurs cutanés de la Grenouille, *C. r. soc. biol.,* Paris, *137,* 212–3. 1943.

FITZGERALD, O. Discharges from the sensory organs of the cat's vibrissae and the modification in their activity by ions. *J. Physiol., 98,* 163–78. 1940.

FLOURENS, M. Expériences sur les canaux semi-circulaires de l'oreille dans les oiseaux. *Mém. acad. roy. sci.,* Paris, *9,* 455–66. 1830a.

——— Expériences sur les canaux semi-circulaires de l'oreille dans les mammifères. *Mém acad. roy. sci.,* Paris, *9,* 466–77. 1830b.

FOLKOW, B., STRÖM, G., and UVNÄS, B. Cutaneous vasodilatation elicited by local heating of the anterior hypothalamus in cats and dogs. *Acta physiol. scand., 17,* 317–26. 1949a.

——— Efferent pathways involved in cutaneous vasodilatation induced by activation of hypothalamic heat loss mechanism. *Acta physiol. scand., 17,* 327–38. 1949b.

FORBES, A., and BURLEIGH, S. Retinal response to color shift. *Fed. Proc., 11,* 47. 1952.

FORBES, A., RENSHAW, B., and REMPEL, B. Units of electrical activity in the cerebral cortex. *Amer. J. Physiol., 119,* 309–10. 1937.

FORBES, A., SMITH, O. C., LAMBERT, E. F., CAVENESS, W. F., and DERBYSHIRE, A. J. The central inhibitory mechanism investigated by means of antidromic impulses. *Amer. J. Physiol., 103,* 131–42. 1933.

FORBES, A., and THACHER, C. Amplification of action currents with the electron tube in recording with the string galvanometer. *Amer. J. Physiol., 52,* 409–71. 1920.

FRANKENHAEUSER, B. Ischaemic paralysis of a uniform nerve. *Acta physiol. scand., 18,* 1–24. 1949.

——— The hypothesis of saltatory conduction. *Cold Spr. Harb. Symp. Quant. Biol., 17,* 27–32. 1952.

FRENCH, J. D., AMERONGEN, F. K. VAN, and MAGOUN, H. W. An activating system in brain stem of monkey. *Arch. Neurol. Psychiat.,* Chicago, *68,* 577–90. 1952.

FREY, M. VON. Beiträge zur Physiologie des Schmerzsinns. *Ber. kgl. sächs. Ges Wiss., 46,* 185–96. 1894a.

——— Beiträge zur Physiologie des Schmerzsinns II. *Ber. kgl. sächs. Ges. Wiss., 46,* 283–96. 1894b.

——— Beiträge zur Sinnesphysiologie der Haut. III. *Ber. kgl. sächs. Ges. Wiss., 47,* 166–84. 1895.

FREY, M. VON. Physiologie des Sinnesorgane des menschlichen Haut. *Ergebn, Physiol., 9,* 351–68. 1910.

FRISCH, K. VON. Die "Sprache" der Bienen und ihre Nutzanwendung in der Landwirtschaft. *Experientia, 2,* 397–404. 1946.

——— Die Polarisation des Himmelslichtes als orientierender Faktor bei den Tänzen der Bienen. *Experientia, 5,* 142–8. 1949.

——— Die Sonne als Kompass im Leben der Bienen. *Experientia, 6,* 210–21. 1950.

FRÖHLICH, F. W. Beiträge zur allgemeinen Physiologie der Sinnesorgane. *Z. Sinnesphysiol., 48,* 28–164. 1914.

——— Grundzüge einer Lehre vom Licht- und Farbensinnn. Ein Beitrag zur allgemeinen Physiologie der Sinne. Fischer, Jena, 1921. 86 pp.

FRY, G. A., and BARTLEY, S. H. The relation of strong light in the eye to the retinal action potential. *Amer. J. Physiol., 111,* 335–40. 1935.

FULTON, J. F. Howell's textbook of physiology. Saunders, Philadelphia, 1946. 1304 pp.

——— Functional localization in the frontal lobes and cerebellum. William Withering Memorial Lectures. Clarendon Press, Oxford, 1949a. 140 pp.

——— Physiology of the nervous system. Oxford Univ. Press, New York, 3d ed. 1949b. 667 pp.

——— Frontal lobotomy and affective behavior. A neurophysiological analysis. Chapman and Hall, London, 1951. 159 pp.

FULTON, J. F., LIDDELL, E. G. T., and RIOCH, D. MCK. The influence of unilateral destruction of the vestibular nuclei upon posture and the knee-jerk. *Brain, 53,* 327–43. 1930.

FULTON, J. F., and PI-SUÑER, J. A note concerning the probable function of various afferent end-organs in skeletal muscle. *Amer. J. Physiol., 83,* 554–62. 1927–28.

GAIRNS, F. W. Sensory nerve endings other than taste buds in the human tongue. *J. Physiol., 121,* 33–4P. 1953.

GALAMBOS, R. Cochlear potentials elicited from bats by supersonic sounds. *J. Acoust. Soc. Amer., 14,* 41–9. 1942.

——— Microelectrode studies on medial geniculate body of cat. III. Response to pure tones. *J. Neurophysiol., 15,* 381–400. 1952.

GALAMBOS, R., and DAVIS, H. The response of single auditory-nerve fibers to acoustic stimulation. *J. Neurophysiol., 6,* 39–58. 1943.

——— Inhibition of activity in single auditory nerve fibers by acoustic stimulation. *J. Neurophysiol., 7,* 283–303. 1944.

——— Action potentials from single auditory nerve fibers? *Science, 108,* 513. 1948.

GALAMBOS, R., and GRIFFIN, D. R. Obstacle avoidance by flying bats: the cries of bats. *J. Exp. Zool., 89,* 475–90. 1942.

GALAMBOS, R., ROSE, J. E., BROMILEY, R. B., and HUGHES, J. R. Microelectrode studies on medial geniculate body of cat. II. Responses to clicks. *J. Neurophysiol., 15,* 359–80. 1952.

GALLEGO, A. Procedimiento de impregnación de la retina entera. *Resum. Coll. Probl. Opt. de la Vision.* Madrid, 1953.

GAMMON, G. D., and BRONK, D. W. The discharge of impulses from Pacinian corpuscles in the mesentery and its relation to vascular changes. *Amer. J. Physiol., 114,* 77–84. 1935.

GAROL, H. W. The "motor" cortex of the cat. *J. Neuropath., 1,* 139–45. 1942.

GASSER, H. S. Conduction in nerves in relation to fiber types. *Res. Publ. Ass. Nerv. Ment. Dis., 15,* 35–59. 1934.

——— in Erlanger and Gasser (1937).

——— Pain-producing impulses in peripheral nerves. *Res. Publ. Ass. Nerv. Ment. Dis., 23,* 44–62. 1943.

——— Mammalian nerve fibers. In Les Prix Nobel. Norstedt and Söner, Stockholm, 1946. Pp. 128–41.

GASSER, H. S., and ERLANGER, J. The role of fiber size in the establishment of a nerve block by pressure or cocaine. *Amer. J. Physiol., 88,* 581–91. 1929.

GASSER, H. S., and GRUNDFEST, H. Axon diameters in relation to spike dimensions and the conduction velocity in mammalian A fibers. *Amer. J. Physiol., 127,* 393–414. 1939.

GASSER, H. S., and NEWCOMER, H. S. Physiological action currents in the phrenic nerve. An application of the thermionic vacuum tube to nerve physiology. *Amer. J. Physiol., 57,* 1–26. 1921.

GERARD, R. W., MARSHALL, W. H., and SAUL, L. J. Electrical activity of the cat's brain. *Arch. Neurol. Psychiat.,* Chicago, *36,* 675–735. 1936.

GERNANDT, B. E. The form variations of the spike recorded by a microelectrode applied on to the mammalian retina. *Acta physiol. scand., 15,* 88–92. 1948a.

——— Polarity of dark adapted retinal on/off-elements as a function of wave-length. *Acta physiol. scand., 15,* 286–9. 1948b.

——— Response of mammalian vestibular neurons to horizontal rotation and caloric stimulation. *J. Neurophysiol., 12,* 173–84. 1949.

——— The effect of vestibular stimulation upon the activity of the primary motor neurons of the spinal cord. *Acta physiol. scand., 27,* 169–82. 1952.

GERNANDT, B. E., and GRANIT, R. Single fibre analysis of inhibition and the polarity of the retinal elements. *J. Neurophysiol., 10,* 295–301. 1947.

GERNANDT, B. E., and ZOTTERMAN, Y. Intestinal pain; an electrophysiological investigation on mesenteric nerve. *Acta physiol. scand., 12,* 56–72. 1946.

GIBBS, F. A., and GIBBS, E. L. Atlas of electroencephalography. Addison-Wesley Press, Cambridge, Mass., 3d ed. 1948. 221 pp.

GOLGI, C. Sui nervi dei tendini dell'uomo e di altri vertebrati e di un

nuovo organo nervoso terminale musculo tendineo. Opera Omnia. Ulrico Hoepli, Milano, 1870–83. 2d ed. 1903. *1,* 171–98.

GÖPFERT, H., and SCHAEFER, T. Ueber den direkt und indirekt erregten Aktionsstrom und die Funktion der motorischen Endplatte. *Pflüg. Arch. ges. Physiol., 239,* 597–619. 1938.

GRAHAM, C. H. The relation of nerve response and retinal potential to number of sense cells illuminated in an eye lacking lateral connections. *J. Cell. Comp. Physiol., 2,* 295–310. 1932.

——— Visual perception. In Handbook of experimental psychology, ed. S. S. Stevens (1951). Pp. 868–920.

GRAHAM, C. H., and GRANIT, R. Comparative studies on the peripheral and central retina. VI. Inhibition, summation, and synchronization of impulses in the retina. *Amer. J. Physiol., 98,* 664–73. 1931.

GRAHAM, J., and GERARD, R. W. Membrance potentials and excitation of impaled single muscle fibres. *J. Cell. Comp. Physiol., 28,* 99–117. 1946.

GRAHAM BROWN, T. On the nature of the fundamental activity of the nervous centres; together with an analysis of the conditioning of rhythmic activity in progression, and a theory of the evolution of function in the nervous system. *J. Physiol., 48,* 18–46. 1914.

GRANIT, R. The components of the retinal action potential and their relation to the discharge in the optic nerve. *J. Physiol., 77,* 207–40. 1933.

——— Two types of retinae and their electrical responses to intermittent stimuli in light and dark adaptation. *J. Physiol., 85,* 421–38. 1935.

——— Processes of adaptation in the vertebrate retina in the light of recent photochemical and electrophysiological research. *Docum. Ophthal., 1,* 7–77. 1938.

——— Rotation of activity and spontaneous rhythms in the retina. *Acta physiol. scand., 1,* 370–9. 1941a.

——— The "red" receptor of Testudo. *Acta physiol. scand., 1,* 386–8. 1941b.

——— Isolation of colour-sensitive elements in a mammalian retina. *Acta physiol. scand., 2,* 93–109. 1941c.

——— A relation between rod and cone substances based on scotopic and photopic spectra of Cyprinus, Tinca, Anguilla and Testudo. *Acta physiol. scand., 2,* 334–46. 1941d.

——— Colour receptors of the frog's retina. *Acta physiol. scand., 3,* 137–51. 1942a.

——— Spectral properties of the visual receptor elements of the Guinea pig. *Acta physiol. scand., 3,* 318–28. 1942b.

——— The photopic spectrum of the pigeon. *Acta physiol. scand., 4,* 118–24. 1942c.

——— A physiological theory of colour perception. *Nature, 151,* 11–4. 1943a.

——— "Red" and "green" receptors in the retina of Tropidonotus. *Acta physiol. scand., 5,* 108–13. 1943b.

——— The spectral properties of the visual receptors of the cat. *Acta physiol. scand., 5,* 219–29. 1943c.

——— Stimulus intensity in relation to excitation and pre- and post-excitatory inhibition in isolated elements of mammalian retinae. *J. Physiol., 103,* 103–18. 1944.

——— Some properties of post-excitatory inhibition studied in the optic nerve with micro-electrodes. *Vet. akad. arkiv. f. zool.,* A*36,* No. 11. 1945a.

——— The electrophysiological analysis of the fundamental problem of colour reception. Thomas Young Oration, No. 14. *Proc. Phys. Soc. of Lond., 57,* 447–63. 1945b.

——— The colour receptors of the mammalian retina. *J. Neurophysiol., 8,* 195–210. 1945c.

——— Sensory mechanisms of the retina. Oxford University Press, London, 1947. 412 pp.

——— Neural organization of the retinal elements, as revealed by polarization. *J. Neurophysiol., 11,* 239–51. 1948.

——— The effect of two wave-lengths of light upon the same retinal element. *Acta physiol. scand., 18,* 281–94. 1949.

——— Reflex self-regulation of the muscle contraction and autogenetic inhibition. *J. Neurophysiol., 13,* 351–72. 1950a.

——— The organization of the vertebrate retinal elements. *Ergebn. Physiol., 46,* 31–70. 1950b.

——— The antagonism between the on- and off-systems in the cat's retina. *L'Anné psychol., 50,* 129–34. 1951.

——— Reflexes to stretch and contraction of antagonists around ankle joint. *J. Neurophysiol., 15,* 269–79. 1952a.

——— Aspects of excitation and inhibition in the retina. *Proc. Roy. Soc. of Lond.,* B*140,* 191–8. 1952b.

——— Effekter på retina vid stimulering i hjärnan. *Proc. Swed. Ophthal. Soc.,* Nov., 1953. Scheduled for publication in *Nord. Med.*

GRANIT, R., and HAMMOND, E. L. Comparative studies on the peripheral and central retina. V. The sensation-time curve and the time course of the fusion frequency of intermittent stimulation. *Amer. J. Physiol., 98,* 654–63. 1931.

GRANIT, R., and HARPER, P. Comparative studies on the peripheral and central retina. II. Synaptic reactions in the eye. *Amer. J. Physiol., 95,* 211–28. 1930.

GRANIT, R., and HELME, T. Changes in retinal excitability due to polarization and some observations on the relation between the processes in retina and nerve. *J. Neurophysiol., 2,* 556–65. 1939.

GRANIT, R., HOLMBERG, T., and ZEWI, M. On the mode of action of visual purple on the rod cell. *J. Physiol., 94,* 430–40. 1938.

GRANIT, R., HOLMGREN, B., and MERTON, P. A. To be published. 1954.
GRANIT, R., and JOB, C. Electromyographic and monosynaptic definition of reflex excitability during muscle stretch. *J. Neurophysiol., 15,* 409–20. 1952.
GRANIT, R., JOB, C., and KAADA, B. R. Activation of muscle spindles in pinna reflex. *Acta physiol. scand., 27,* 161–8. 1952.
GRANIT, R., and KAADA, B. R. Influence of stimulation of central nervous structures on muscle spindles in cat. *Acta physiol. scand., 27,* 130–60. 1952.
GRANIT, R., LEKSELL, L., and SKOGLUND, C. R. Fibre interaction in injured or compressed region of nerve. *Brain, 67,* 125–40. 1944.
GRANIT, R., and LUNDBERG, A. Heat- and cold-sensitive mammalian nerve fibres. Some somatic reflexes to thermostimulation. *Acta physiol. scand., 13,* 334–46. 1947.
GRANIT, R., and MUNSTERHJELM, A. The electrical response of dark-adapted frogs' eyes to monochromatic stimuli. *J. Physiol., 88,* 436–58. 1937.
GRANIT, R., MUNSTERHJELM, A., and ZEWI, M. The relation between concentration of visual purple and retinal sensitivity to light during dark-adaptation. *J. Physiol., 96,* 31–44. 1939.
GRANIT, R., and RIDDELL, H. A. The electrical responses of light- and dark-adapted frogs' eyes to rhythmic and continuous stimuli. *J. Physiol., 81,* 1–28. 1934.
GRANIT, R., RUBINSTEIN, B., and THERMAN, P. O. A new type of interaction experiment with the retinal action potential. *J. Physiol., 85,* 34P. 1935.
GRANIT, R., and SKOGLUND, C. R. Accommodation and autorhythmic mechanism in single sensory fibres. *J. Neurophysiol., 6,* 337–48. 1943.
GRANIT, R., SKOGLUND, S., and THESLEFF, S. Activation of muscle spindles by succinylcholine and decamethonium. The effects of curare. *Acta physiol. scand., 28,* 134–51. 1953.
GRANIT, R., and STRÖM, G. Autogenetic modulation of excitability of single ventral horn cells. *J. Neurophysiol., 14,* 113–32. 1951a.
——— Stretch reflexes before and after de-efferentation. *Acta physiol. scand., 25,* Suppl. 89. 1951b. P. 29.
——— Stretch-reflex before and after de-efferentation. *Acta physiol. scand., 27,* 255–64. 1952.
GRANIT, R., and SUURSOET, V. Self-regulation of the muscle contraction by facilitation and inhibition from its proprioceptors. *Nature, 164,* 270. 1949.
GRANIT, R., and SVAETICHIN, G. Principles and technique of the electrophysiological analysis of colour reception with the aid of microelectrodes. *Upsala läkaref. förh., 65,* 161–77. 1939.
GRANIT, R., and TANSLEY, K. Rods, cones and the localization of pre-

excitatory inhibition in the mammalian retina. *J. Physiol., 107,* 54–66. 1948.
GRANIT, R., and THERMAN, P. O. Inhibition of the off-effect in the optic nerve and its relation to the equivalent phase of the retinal response. *J. Physiol., 81,* 47P. 1934.
——— Excitation and inhibition in the retina and the optic nerve. *J. Physiol., 83,* 359–81. 1935.
——— Excitation and inhibition in the off-effect of the retina. *J. Physiol., 91,* 127–39. 1937.
——— The "slow potentials" associated with excitation and inhibition in the excised eye. *J. Physiol., 93,* 9P. 1938.
GRANIT, R., THERMAN, P. O., and WREDE, C. M. Selective effects of different adapting wave-lengths on the dark-adapted frog's retina. *Skand. arch. physiol., 80,* 142–55. 1938.
GRANIT, R., and WIRTH, A. A scotopic 'blue shift' obtained by electrical measurements of flicker resonance. *J. Physiol., 122,* 386–98. 1953.
GRANIT, R., and WREDE, C. M. The electrical responses of light-adapted frogs' eyes to monochromatic stimuli. *J. Physiol., 89,* 239–56. 1937.
GRANT, R. T. Physiological effects of heat and cold. *Ann. Rev. Physiol., 13,* 75–98. 1951.
GRAY, J. A. B., and MALCOLM, J. L. The initiation of nerve impulses by mesenteric Pacinian corpuscles. *Proc. Roy. Soc. of Lond.,* B*137,* 96–114. 1950.
GRAY, J. A. B., and MATTHEWS, P. B. C. A comparison of the adaptation of the Pacinian corpuscle with the accommodation of its own axon. *J. Physiol., 114,* 454–64. 1951.
GRAY, J. A. B., and SATO, M. Receptor potentials in Pacinian corpuscles. *J. Physiol., 122,* 27–8P. 1953a.
——— Properties of the receptor potential in Pacinian corpuscles. *J. Physiol., 122,* 610–36. 1953b.
GRIFFIN, D. R., and GALAMBOS, R. The sensory basis of obstacle avoidance by flying bats. *J. Exp. Zool., 86,* 481–506. 1941.
GRÖPPEL, F., HAASS, F., and KOHLRAUSCH, A. Aktionsströme und Gesichtsempfindungen des menschlichen Auges. *Z. Sinnesphysiol., 67,* 207–26. 1938.
GUNTER, R. The spectral sensitivity of dark-adapted cats. *J. Physiol., 118,* 395–404. 1952.
——— The spectral sensitivity of light-adapted cats. *J. Physiol., 123,* 409–15. 1954.

HABGOOD, J. S. Sensitization of sensory receptors in the frog's skin. *J. Physiol., 111,* 195–213. 1950.
HAGBARTH, K.-E. Excitatory and inhibitory skin areas for flexor and extensor motoneurones. *Acta physiol. scand., 26,* Suppl. 94. 1952.

HAGBARTH, K.-E., and KERR, D.I.B. MS communication to Int. Physiol. Congr., Montreal. 1953.

——— Central influences on spinal afferent conduction. *J. Neurophysiol., 17,* 295–307. 1954.

HAGBARTH, K.-E., and NAESS, K. The autogenetic inhibition during stretch and contraction of the muscle. *Acta physiol. scand.,* 21, 41–53. 1950a.

——— Reflex effects of tetanic stimulation of different afferent fibre-systems in the hind limb of the cat. *Acta physiol. scand., 21,* 336–61. 1950b.

HAGBARTH, K.-E., and WOHLFART, G. The number of muscle-spindles in certain muscles in cat in relation to the composition of the muscle nerves. *Acta anat., 15,* 85–104. 1952.

HAGEN, E., KNOCHE, H., SINCLAIR, D. C., and WEDDELL, G. The role of specialized nerve terminals in cutaneous sensibility. *Proc. Roy. Soc. of Lond.,* B*141,* 279–87. 1953.

HAGINS, W. A., and RUSHTON, W. A. H. The measurement of rhodopsin in the decerebrate albino rabbits. *J. Physiol., 120,* 61P. 1953.

HANBERY, J., and JASPER, H. Independence of diffuse thalamo-cortical projection system shown by specific nuclear destructions. *J. Neurophysiol., 16,* 252–71. 1953.

HARTLINE, H. K. A quantitative and descriptive study of the electrical response to illumination of the arthropod eye. *Amer. J. Physiol., 83,* 466–83. 1928.

——— Impulses in single optic nerve fibers of the vertebrate retina. *Amer. J. Physiol., 113,* 59P. 1935.

——— The response of single optic nerve fibers of the vertebrate eye to illumination of the retina. *Amer. J. Physiol., 121,* 400–15. 1938a.

——— The discharge of impulses in the optic nerve of Pecten in response to illumination of the eye. *J. Cell. Comp. Physiol., 11,* 465–78. 1938b.

——— The receptive field of the optic nerve fibers. *Amer. J. Physiol., 130,* 690–9. 1940a.

——— The effects of spatial summation in the retina on the excitation of the fibers of the optic nerve. *Amer. J. Physiol., 130,* 700–11. 1940b.

——— The nerve messages in the fibers of the visual pathway. *J. Opt. Soc. Amer., 30,* 239–47. 1940c.

——— Inhibition of visual receptors by illuminating nearby retinal areas in the Limulus eye. *Fed. Proc., 8,* 69. 1949.

HARTLINE, H. K., and GRAHAM, C. H. Nerve impulses from single receptors in the eye. *J. Cell. Comp. Physiol., 1,* 277–95. 1932.

HARTLINE, H. K., and MCDONALD, P. R. Light and dark adaptation of single photoreceptor elements in the eye of Limulus. *J. Cell. Comp. Physiol., 30,* 225–53. 1947.

HARTLINE, H. K., WAGNER, H. G., and MACNICHOL, E. F. The peripheral origin of nervous activity in the visual system. *Cold Spr. Harb. Symp. Quant. Biol., 17,* 125– 41. 1952.

HARTLINE, H. K., WAGNER, H. G., and TOMITA, T. Mutual inhibition among the receptors of the eye of Limulus. *Proc. XIX Int. Physiol. Congr.,* Montreal, pp. 441–2. 1953.

HARTRIDGE, H. The avoidance of objects by bats in their flight. *J. Physiol., 54,* 54–7. 1920.

——— Recent advances in the physiology of vision. Churchill, London, 1950. 401 pp.

HASSALL, A. H. (1851), quoted from Sherrington (1900b).

HEAD, H., and HOLMES, G. Sensory disturbances from cerebral lesions. *Brain, 34,* 102–254. 1911.

HEAD, H., RIVERS, W. H. R., and SHERREN, J. The afferent nervous system from a new aspect. *Brain, 28,* 99–115. 1905.

HECHT, S. The interrelation of various aspects of colour vision. *J. Opt. Soc. Amer., 21,* 615–39. 1931.

——— Rods, cones, and the chemical basis of vision. *Physiol. Rev., 17,* 239–90. 1937.

HECHT, S., SHLAER, S., and PIRENNE, M. H. Energy, quanta, and vision. *J. Gen. Physiol., 25,* 819–40. 1942.

HEINBECKER, P., BISHOP, G. H., and O'LEARY, J. Pain and touch fibers in peripheral nerves. *Arch. Neurol. Psychiat.,* Chicago, *29,* 771–89. 1933.

HEINBECKER, P., O'LEARY, J., and BISHOP, G. H. Analysis of sensation in terms of the nerve impulse. *Arch. Neurol. Psychiat.,* Chicago, *31,* 34–53. 1934.

HELD, H. Die centrale Gehörleitung. *Arch. Anat. Physiol.,* Leipzig, Anat. Abt., pp. 201–48. 1893.

HELMHOLTZ, H. Handbuch der physiologischen Optik. Leopold Voss, Leipzig, 1867. 874 pp.

HEMINGWAY, A., RASMUSSEN, T., WYCKOFF, H., and RASMUSSEN, A. T. Effects of heating hypothalamus of dogs by diathermy. *J. Neurophysiol., 3,* 329–38. 1940.

HENNEMAN, E. Excitability changes in monosynaptic reflex pathways of muscles subjected to stretch. *Trans. Amer. Neurol. Ass.,* 76th Meeting, pp. 194–6. 1951.

HENNEMANN, E., and MOUNTCASTLE, V. Tactile localization in the thalamus of cat and monkey. *Fed. Proc., 7,* 53. 1948.

HENSEL, H. Physiologie der Thermoreception. *Ergebn. Physiol., 47,* 165–368. 1952.

HENSEL, H., STRÖM, L., and ZOTTERMAN, Y. Electrophysiological measurements of depth of thermoreceptors. *J. Neurophysiol., 14,* 423–9. 1951.

HENSEL, H., and ZOTTERMAN, Y. Quantitative Beziehungen zwischen der Entladung einzelner Kältefasern und der Temperatur. *Acta physiol. scand., 23,* 291–319. 1951a.

——— The response of mechanoreceptors to thermal stimulation. *J. Physiol., 115,* 16–24. 1951b.

——— Action potentials of cold fibres and intracutaneous temperature gradient. *J. Neurophysiol., 14,* 377–85. 1951c.

HERING, E. Grundzüge der Lehre vom Lichtsinn. Handb. ges. Augenheilk. (Graefe-Saemisch), 2d ed., 1925, Vol. *3,* Pt. XII, 1–294.

HESS, W. R. Hypothalamische Adynamie. *Helv. physiol. acta, 2,* 137–47. 1944a.

——— Das Schlafsyndrom als Folge dienzephaler Reizung. *Helv. physiol. acta, 2,* 305–44. 1944b.

HEYMANS, C., and BOUCKAERT, J. J. Les Chémo-récepteurs du sinus carotidien. *Ergebn. Physiol., 41,* 28–55. 1939.

HEYMANS, J. F., and HEYMANS, C. Sur les modifications directes et sur la regulation réflexe de l'activité du centre respiratoire de la tête isolée du chien. *Arch. Int. Pharmacodyn, 33,* 273–372. 1927.

HILGARD, E. R. The role of learning in perception. In Blake and Ramsey (1951), pp. 95–120.

HILL, A. V. Excitation and accommodation in nerve. *Proc. Roy. Soc. of Lond.,* B*119,* 305–55. 1935–36.

——— The mechanics of active muscle. *Proc. Roy. Soc. of Lond.,* B*141,* 104–17. 1953.

HIND, J. E. An electrophysiological determination of tonotopic organization in auditory cortex of cat. *J. Neurophysiol., 16,* 475–89. 1953.

HINES, M., and TOWER, S. S. Studies on the innervation of skeletal muscles. II. Of muscle spindles in certain muscles of the kitten. *Bull. Johns Hopkins Hosp., 42,* 264–95. 1928.

HINSEY, J. C. Some observations on the innervation of skeletal muscle of the cat. *J. Comp. Neurol., 44,* 87–195. 1927–28.

HOAGLAND, H. Electrical responses from the lateral-line nerves of catfish. I. *J. Gen. Physiol., 16,* 695–714. 1933a.

——— Quantitative analysis of responses from lateral-line nerves of fishes. II. *J. Gen. Physiol., 16,* 715–32. 1933b.

——— Electrical responses from lateral-line nerves of fishes. III. *J. Gen. Physiol., 17,* 77–82. 1933–34a.

——— Electrical responses from the lateral-line nerves of fishes. IV. The repetitive discharge. *J. Gen. Physiol., 17,* 195–209. 1933–34b.

HODES, R., PEACOCK, S. M., and HEATH, R. G. Influence of the forebrain on somato-motor activity. I. Inhibition. *J. Comp. Neurol., 94,* 381–408. 1951.

HODGKIN, A. L., and HUXLEY, A. F. Action potentials recorded from inside a nerve fibre. *Nature, 144,* 710–1. 1939.

——— The dual effect of membrane potential on sodium conductance in the giant axon of *Loligo. J. Physiol., 116,* 497–506. 1952.

HOEFER, P. F. A., and PUTNAM, T. J. Action potentials of muscles in "spastic" conditions. *Arch. Neurol. Psychiat.,* Chicago, *43,* 1–22. 1940.

HOFF, H. E., HOFF, E. C., BUCY, P. C., and PI-SUÑER, J. The production of the silent period by the synchronization of discharge of motor neurones. *Amer. J. Physiol., 109,* 123–32. 1934.

HOFFMANN, P. Demonstration eines Hemmungsreflexes im menschlichen Rückenmark. *Z. Biol., 70,* 515–24. 1919–20.

——— Untersuchungen über die Eigenreflexe (Sehnenreflexe) menschlicher Muskeln. Springer, Berlin, 1922. 106 pp.

——— Untersuchungen über die refraktäre Periode des menschlichen Rückenmarkes. *Z. Biol., 81,* 37–48. 1924.

——— Die Aufklärung der Wirkung des Jendrassikschen Handgriffs durch die Arbeiten von Sommer und Kuffler. *Dtsch. Z. Nervenheilk., 166,* 60–4. 1951.

HOFFMANN, P., and KELLER, Ch. J. Ueber gleichzeitige willkürliche und künstliche Reizung von Nerven. *Z. Biol., 87,* 527–36. 1928.

HOGG, B. M. Slow impulses from cutaneous nerves of the frog. *J. Physiol., 84,* 250–8. 1935.

HOLMGREN, B., and MERTON, P. A. Local feedback control of motoneurones. *J. Physiol., 123,* 47P. 1953.

HOLMGREN, F. Method att objectivera effecten av ljusintryck på retina. *Upsala läkaref. förh., 1,* 177–91. 1865–66.

——— Om retinaströmmen. *Upsala läkaref. förh., 6,* 419–55. 1870–71.

HSIA, Y., and GRAHAM, C. H. Spectral sensitivity of the cones in the dark adapted human eye. *Proc. Nat. Acad. Sci.,* New York, *38,* 80–5. 1952.

HUBBARD, R., and WALD, G. Cis-trans isomers of vitamin A and retinene in the rhodopsin system. *J. Gen. Physiol., 36,* 269–315. 1952.

HUGHES, J., and GASSER, H. S. Some properties of the cord potentials evoked by a single afferent volley. *Amer. J. Physiol., 108,* 295–306. 1934.

HUNT, C. C. The reflex activity of mammalian small-nerve fibres. *J. Physiol., 115,* 456–69. 1951.

——— The effect of stretch receptors from muscle on the discharge of motoneurones. *J. Physiol., 117,* 359–79. 1952a.

——— Drug effects on mammalian small-nerve fibres. *Fed. Proc., 11,* 75. 1952b.

——— Diameter and function of afferent fibres from muscle. *Proc. XIX Int. Physiol. Congr.,* Montreal, pp. 485–6. 1953.

HUNT, C. C., and KUFFLER, S. W. Further study of efferent small-nerve fibres to mammalian muscle spindles. Multiple spindle innervation and activity during contraction. *J. Physiol., 113,* 283–97. 1951a.

HUNT, C. C., and KUFFLER, S. W. Stretch receptor discharges during muscle contraction. *J. Physiol., 113,* 298–315. 1951b.

HUNTER, J., and JASPER, H. H. Effects of thalamic stimulation in unanaesthetised animals. *Electroenceph. Clin. Neurophysiol., 1,* 305–24. 1949.

HURSH, J. B. Conduction velocity and diameter of nerve fibers. *Amer. J. Physiol., 127,* 131–9. 1939a.

——— The properties of growing nerve fibers. *Amer. J. Physiol., 127,* 140–53. 1939b.

——— Relayed impulses in ascending branches of dorsal root fibers. *J. Neurophysiol., 3,* 166–74. 1940.

INGVAR, D. H. Effects of reticular stimulation upon neuronally isolated cortex. A preliminary note. To be published. 1953.

——— Observations at this institute. Personal communication. 1954.

IVES, H. E. Studies in the photometry of lights of different colours. II. Spectral luminosity curves by the method of critical frequency. *Phil. Mag., 24,* 352–70. 1912.

JAHN, T. L. Colour vision and colour blindness in terms of modern evidence, *J. Opt. Soc. Amer., 36,* 595–603. 1946a.

——— The kinetics of visual dark adaptation. *J. Opt. Soc. Amer., 36,* 659–65. 1946b.

JALAVISTO, E., ORMA, E., and TAWAST, M. Ageing and relation between stimulus intensity and duration in corneal sensibility. *Acta physiol. scand., 23,* 224–33. 1951.

JANSEN, J., and BRODAL, A. Aspects of cerebellar anatomy. J. G. Tanum, Oslo, 1954. 423 pp.

JARISCH, A. Vom Herzen ausgehende Kreislaufreflexe. *Arch. Kreislaufforschg., 7,* 260–74. 1940.

——— Der Einfluss der Vagusausschaltung auf den Blutdruck. *Arch. Kreislaufforschg., 9,* 1–10. 1941.

JARISCH, A., and ZOTTERMAN, Y. Depressor reflexes from the heart. *Acta physiol. scand., 16,* 31–51. 1948.

JASPER, H. Diffuse projection systems: the integrative action of the thalamic reticular system. *Electroenceph. Clin. Neurophysiol., 1,* 405–20. 1949.

JASPER, H., AJMONE-MARSAN, C., and STOLL, J. Corticofugal projections to the brain stem. *Arch. Neurol Psychiat.,* Chicago, *67,* 155–71. 1952.

JENKINS, W. L. Somesthesis. In Handbook of experimental psychology, ed. S. S. Stevens (1951), pp. 1172–90.

JOB, C. Monosynaptische Impulsübertragung zwischen Synergisten. *Pflüg. Arch. ges. Physiol., 256,* 391–405. 1953a.

——— Ueber autogene Inhibition und Reflexumkehr bei spinalisierten und

decerebrierten Katzen. *Pflüg. Arch. ges. Physiol., 256,* 406–18. 1953b.

JOHNSON, E. P., and RIGGS, L. A. Electroretinal and psychophysical dark adaptation curves. *J. Exp. Psychol., 41,* 139–47. 1951.

JUNG, R., BAUMGARTEN, R. VON, and BAUMGARTNER, G. Mikroableitungen von einzelnen Nervenzellen im optischen Cortex der Katze: Die lichtaktivierten B-Neurone. *Arch. Psychiat. u. Z. Neurol., 189,* 521–39. 1952.

KAADA, B. R. Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of "rhinencephalic" and other structures in primates, cat and dog. *Acta physiol. scand., 24,* Suppl. 83. 1951. 283 pp.

——— Suprasegmental mechanisms. *Proc. XIX Int. Physiol. Congr.,* Montreal, pp. 81–6. 1953.

KAMPA, E. M. New forms of visual purple from the retinas of certain marine fishes: a re-examination. *J. Physiol., 119,* 400–9. 1953.

KARPE, G. The basis of clinical electroretinography. *Acta opthal.,* Copenhagen, Suppl. 24. 1945. 118 pp.

KARPE, G., and TANSLEY, K. The relationship between the change in the electroretinogram and the subjective dark-adaptation curve. *J. Physiol., 107,* 272–9. 1947.

KATSUKI, Y., MIZUHIRA, V., and YOSHINO, S. On the endorgan of the acoustico-lateralis system of fish. *Jap. J. Physiol., 2,* 93–102. 1951.

KATSUKI, Y., and YOSHINO, S. Response of the single lateral-line nerve fiber to the linearly rising current stimulating the endorgan. *Jap. J. Physiol., 2,* 219–31. 1952.

KATSUKI, Y., YOSHINO, S., and CHERR, J. Action currents of the single lateral-line nerve fiber of fish. 1. On the spontaneous discharge. *Jap. J. Physiol., 1,* 87–99. 1950.

KATZ, B. Electric excitation of nerve. A review. Oxford Univ. Press, London, 1939. 151 pp.

——— The electric response at a sensory nerve ending. *J. Physiol., 109,* 9P. 1949.

——— Action potentials from a sensory nerve ending. *J. Physiol., 111,* 248–60. 1950a.

——— Depolarization of sensory terminals and the initiation of impulses in the muscle spindle. *J. Physiol., 111,* 261–82. 1950b.

KLEITMAN, N., and PIÉRON, H. Sur la vitesse d'établissement de la sensation lumineuse et la grandeur de l'ondulation de prééquilibre pour des excitations monochromatiques d'intensité variable. *C. r. acad. sci.,* Paris, *180,* 393–6. 1925.

KLÜVER, H. Functional significance of the geniculo-striate system. *Biol. Symp., 7,* 253–99. 1942.

KOBAYASHI, Y., OSHIMA, K., and TASAKI, I. Analysis of afferent and efferent

systems in the muscle nerve of the toad and cat. *J. Physiol., 117,* 152–71. 1952.

KOHLER, J. Ueber Aufbau und Wandlungen der Wahrnehmungswelt. *Sitzber. Öster. Akad. Wiss., 227,* 118 pp. 1951.

KOHLRAUSCH, A. Die Netzhautströme der Wirbeltiere in Abhängigkeit von der Wellenlänge des Lichtes und dem Adaptationszustand des Auges. *Arch. Anat. Physiol.,* Leipzig, pp. 195–241. 1918.

——— Elektrische Erscheinungen am Auge. *Handb. Norm. Path. Physiol., 12,* No. 2, 1394–1496. 1931a.

——— Tagessehen, Dämmersehen, Adaptation. *Handb. Norm. Path. Physiol., 12,* No. 2, 1499–1594. 1931b.

KÖLLIKER, A. Untersuchungen über die letzten Endigungen der Nerven. *Z. wiss. Zool., 12,* 149–64. 1863.

KOLMER, W. Der Bau der Endapparate des Nervus octavus und deren physiologische Bedeutung. *Ergebn. Physiol., 11,* 372–416. 1911.

KÖNIG, A. Gesammelte Abhandlungen zur physiologischen Optik. Barth, Leipzig, 1903. 443 pp.

KÖNIG, F. H. Bluttemperatur und Wärmeregulation. *Pflüg. Arch. ges. Physiol., 246,* 693–708. 1943.

——— Bluttemperatur und Wärmeregulation. II. Mitteilung. *Pflüg. Arch. ges. Physiol., 247,* 497–513. 1944.

KÖTTGEN, E., and ABELSDORFF, G. Absorption und Zersetzung des Sehpurpurs bei den Wirbeltieren. *Z. Psychol. Physiol. Sinnesorg., 12,* 161–84. 1896.

KRAUSE, A. C., and SIDWELL, A. E. The absorption spectra of visual purple and its photodecomposition products. *Amer. J. Physiol., 121,* 215–23. 1938.

KRAUSE, W. Die terminalen Körperchen der einfach sensiblen Nerven. Hahn'sche Hofbuchhandlung, Hannover, 1860. 272 pp.

KRIES, J. VON. Ueber die Abhängigkeit der Erregungsvorgänge von dem zeitlichen Verlaufe der zur Reizung dienenden Elektricitäts-Bewegungen. *Arch. Anat. Physiol.,* Leipzig, pp. 337–72. 1884.

——— Ueber die Wahrnehmung des Flimmerns durch normale und durch total Farbenblinde Personen. *Z. Psychol. Physiol. Sinnesorg., 32,* 113–17. 1903.

——— Allgemeine Sinnesphysiologie. Vogel, Leipzig, 1923. 299 pp.

KRIES, J. VON, and EYSTER, J. A. E. Ueber die zur Erregung des Sehorgans erforderlichen Energiemengen. *Z. Sinnesphysiol., 41,* 373–94. 1907.

KRÜGER, P. Tetanus und Tonus der quergestreiften Skelettmuskeln der Wirbeltiere und des Menschen. Geest and Portig, Leipzig, 1952. 431 pp.

KUFFLER, S. W. Electric potential changes at an isolated nerve-muscle junction. *J. Neurophysiol., 5,* 18–26. 1942.

——— Transmitter mechanism at the nerve-muscle junction. *Arch. Sci. Physiol., 3,* 585–601. 1949.

——— Neurons in the retina: organization, inhibition and excitation problems. *Cold Spr. Harb. Symp. Quant. Biol., 17,* 281–92. 1952.

——— Discharge patterns and functional organization of mammalian retina. *J. Neurophysiol., 16,* 37–68. 1953.

KUFFLER, S. W., and GERARD, R. W. The small-nerve motor system to skeletal muscle. *J. Neurophysiol., 10,* 383–94. 1947.

KUFFLER, S. W., and HUNT, C. C. The mammalian small-nerve fibres: a system for efferent nervous regulation of muscle spindle discharge. *Res. Publ. Ass. Nerv. Ment. Dis., 30,* 24–47. 1952.

KUFFLER, S. W., HUNT, C. C., and QUILLIAM, J. P. Function of medullated small-nerve fibers in mammalian ventral roots: efferent muscle spindle innervation. *J. Neurophysiol., 14,* 29–54. 1951.

KUFFLER, S. W., and KATZ, B. Inhibition at the nerve muscle junction in crustacea. *J. Neurophysiol., 9,* 337–46. 1946.

KUFFLER, S. W., LAPORTE, Y., and RANSMEIER, R. E. The function of the frog's small-nerve motor system. *J. Neurophysiol., 10,* 395–408. 1947.

KUFFLER, S. W., and VAUGHAN WILLIAMS, E. M. Properties of the "slow" skeletal muscle fibres of the frog. *J. Physiol., 121,* 318–40. 1953a.

——— Small-nerve junctional potentials. The distribution of small motor nerve to frog skeletal muscle, and the membrane characteristics of the fibres they innervate. *J. Physiol., 121,* 289–317. 1953b.

KUGELBERG, E. Accommodation in human nerves. *Acta physiol. scand., 8,* Suppl. 24. 1944. 105 pp.

KÜHNE, W. Ueber die Endigung der Nerven in den Muskeln. *Virchows Arch., 27,* 508–33. 1863a.

——— Die Muskelspindeln. *Virchows Arch., 28,* 528–38. 1863b.

——— Ueber die Darstellung von Optogrammen im Froschauge. *Unters. Physiol. Inst.,* Heidelberg, *1,* 225–41. 1877–78.

——— Chemische Vorgänge in der Netzhaut. *Hermanns Handb. d. Physiol., 3,* 235–42. 1879.

KÜHNE, W., and SEWALL, A. Zur Physiologie des Sehepitels. *Unters. Physiol. Inst.,* Heidelberg, *3,* 221–77. 1879–80.

LAGET, P., and LUNDBERG, A. On the effect of K^+ and Ca^{++} on thermal stimulation and spontaneous activity of mammalian nerve fibres. *Acta physiol. scand., 18,* 128–38. 1949.

LANDGREN, S., LILJESTRAND, G., and ZOTTERMAN, Y. The effect of certain autonomic drugs on the action potentials of the sinus nerve. *Acta physiol. scand., 26,* 264–90. 1952.

LAPICQUE, L. Chronaxie, accommodation, climalyse: discussion théorique et expérimentale. *C. r. soc. biol.,* Paris, *127,* 875–8. 1938.

LAPICQUE, L., and LAPICQUE, M. Recherches expérimentales sur le seuil d'inefficacité des courants progressifs et ses rapports avec la chronaxie. *C. r. soc. biol.,* Paris, *125,* 260–4. 1937.

LAPORTE, Y., and LLOYD, D. P. C. Nature and significance of the reflex connections established by large afferent fibers of muscular origin. *Amer. J. Physiol., 169,* 609–21. 1952.

LARRABEE, M. G., and BRONK, D. W. Prolonged facilitation of synaptic excitation in sympathetic ganglion. *J. Neurophysiol., 10,* 139–54. 1947.

LAWRENCE, M. Studies in human behavior. Princeton University Press, Princeton, 1949. 181 pp.

LEEUWEN, S. VAN. Response of a frog's muscle spindle. *J. Physiol., 109,* 142–5. 1949.

LE GRAND, Y. Optique physiologique. Revue d'optique, Paris, 2 vols. 1952. 372 + 490 pp.

LEHMANN, A. Die Hauptgesetze des menschlichen Gefühlslebens. Reisland, Leipzig, 1892. 356 pp. (See p. 35.)

LEKSELL, L. The action potential and excitatory effects of the small ventral root fibres to skeletal muscle. *Acta physiol. scand., 10,* Suppl. 31. 1945. 84 pp.

LIDDELL, E. G. T., and SHERRINGTON, C. S. Reflexes in response to stretch (Myotatic reflexes). *Proc. Roy. Soc. of Lond.,* B*96,* 212–42. 1924.

——— Further observation on myotatic reflexes. *Proc. Roy. Soc. of Lond.,* B*97,* 267–83. 1925.

LINDSLEY, D. B. Inhibition as an accompaniment of the knee jerk. *Amer. J. Physiol., 109,* 181–91. 1934.

LINDSLEY, D. B., BOWDEN, J. W., and MAGOUN, H. W. Effect upon the EEG of acute injury to the brain stem activating system. *Electroenceph. Clin. Neurophysiol., 1,* 475–86. 1949.

LING, G., and GERARD, R. W. The normal membrane potential of frog sartorius fibers. *J. Cell. Comp. Physiol., 34,* 383–96. 1949.

LINKSZ, A. Physiology of the eye. Vol. *2,* Vision. Grune and Stratton, New York, 1952. 869 pp.

LLOYD, D. P. C. A direct central inhibitory action of dromically conducted impulses. *J. Neurophysiol., 4,* 184–90. 1941.

——— Neuron patterns controlling transmission of ipsilateral hind limb reflexes in cat. *J. Neurophysiol., 6,* 293–314. 1943a.

——— Conduction and synaptic transmission of reflex response to stretch in spinal cats. *J. Neurophysiol., 6,* 317–26. 1943b.

——— Facilitation and inhibition of spinal motoneurones. *J. Neurophysiol., 9,* 421–38. 1946a.

——— Integrative pattern of excitation and inhibition in two-neuron reflex arc. *J. Neurophysiol., 9,* 439–44. 1946b.

LLOYD, D. P. C., and CHANG, H.-T. Afferent fibers in muscle nerves. *J. Neurophysiol., 11,* 199–208. 1948.

LORD, M. P. Recherches récentes sur les mouvements des yeux a l'Imperial College de Londres. *Ann. d'opt. ocul., 1,* 13–23. 1952.

LORENTE de NÓ, R. and GRAHAM, H. T. Recovery cycle of motoneurons. *Amer. J. Physiol., 123,* 388–99. 1938.

LÖWENSTEIN, O. Effect of galvanic polarization on the impulse discharge from the horizontal ampulla of the isolated elasmobranch labyrinth. *Nature, 172,* 549–50. 1953.

LÖWENSTEIN, O., and SAND, A. The activity of the horizontal semicircular canal of the dogfish, *Scyllium canicula. J. Exp. Biol., 13,* 416–28. 1936.

——— The individual and integrated activity of the semicircular canals of the elasmobranch labyrinth. *J. Physiol., 99,* 89–101. 1940.

LÖWENTHAL, M., and HORSLEY, V. On the relations between the cerebellar and other centres (namely cerebral and spinal) with especial reference to antagonistic muscles. *Proc. Roy. Soc. of Lond.,* B*61.* 20–5. 1897.

LUCAS, K. On the rate of variation of the exciting current as a factor in electrical excitation. *J. Physiol., 36,* 253–74. 1907.

——— The conduction of the nervous impulse. Longmans Green, London, 1917. 102 pp.

LUDVIGH, E., and MCCARTHY, E. F. Absorption of visible light by the refractive media of the human eye. *Arch. Ophthal., 20,* 37–51. 1938.

LUNDBERG, A. Potassium and the differential thermosensitivity of membrane potential, spike and negative after-potential in mammalian A and C fibres. *Acta physiol. scand., 15,* Suppl. 50. 1948. 67 pp.

LYTHGOE, R. J. The absorption spectra of visual purple and of indicator yellow. *J. Physiol., 89,* 331–58. 1937.

——— The mechanism of dark adaptation. A critical resumé. *Brit. J. Ophthal., 24,* 21–43. 1940.

LYTHGOE, R. J., and QUILLIAM, J. P. The thermal decomposition of visual purple. *J. Physiol., 93,* 24–38. 1938.

LYTHGOE, R. J., and TANSLEY, K. The adaptation of the eye: its relation to the critical frequency of flicker. *Spec. Rep. Ser. Med. Res. Coun.,* London, No. 134. 1929.

MCCOUCH, G. P., DEERING, I. D., and LING, T. H. Location of receptors for tonic neck reflexes. *J. Neurophysiol., 14,* 191–5. 1951.

MCCOUCH, G. P., DEERING, I. D., and STEWART, W. B. Inhibition of knee jerk from tendon spindles of crureus. *J. Neurophysiol., 13,* 343–50. 1950.

MCCULLOCH, W. S., and PITTS, W. The statistical organization of nervous activity. *J. Amer. Statist. Ass., 4,* 91–9. 1948.

MCINTYRE, A. K. Afferent limb of the myotatic reflex arc. *Nature, 168,* 168–9. 1951.

——— Cortical projections of afferent impulses in muscle nerves. *Proc. Univ. Otago Med. Sch., 31,* 5–6. 1953.

MACH, E. Die Analyse der Empfindungen. Fischer, Jena, 8th ed. 1919. 323 pp.

MAGLADERY, J. W., and MCDOUGAL, D. B. Electrophysiological studies of nerve and reflex activity in normal man. I. Identification of certain reflexes in the electromyogram and the conduction velocity of peripheral nerve fibres. *Bull. Johns Hopkins Hosp., 86,* 205–90. 1950.

MAGLADERY, J. W., MCDOUGAL, D. B., and STOLL, J. Electrophysiological studies of nerve and reflex activity in normal man. II. The effects of peripheral ischemia. *Bull. Johns Hopkins Hosp., 86,* 291–312. 1950.

MAGLADERY, J. W., TEASDALL, R. D., PARK, A. M., and PORTER, W. E. Excitation and inhibition of two-neurone reflexes by afferent impulses in the same nerve trunk. *Bull. Johns Hopkins Hosp., 88,* 520–37. 1951.

MAGNUS, R. Körperstellung. Springer, Berlin, 1924. 740 pp.

MAGOUN, H. W. Bulbar inhibition and facilitation of motor activity. *Science, 100,* 549–50. 1944.

——— Caudal and cephalic influences of the brain stem reticular formation. *Physiol. Rev., 30,* 459–74. 1950.

——— An ascending reticular activating system in the brain stem. *Arch. Neurol. Psychiat.,* Chicago, *67,* 145–54. 1952.

MAGOUN, H. W., HARRISON, F., BROBECK, J. R., and RANSON, S. W. Activation of heat loss mechanisms by local heating of the brain. *J. Neurophysiol., 1,* 101–14. 1938.

MAGOUN, H. W., and RHINES, R. An inhibitory mechanism in the bulbar reticular formation. *Anat. Rec., 91,* 27. 1945.

——— An inhibitory mechanism in the bulbar reticular formation. *J. Neurophysiol., 9,* 165–71. 1946.

——— Spasticity. The stretch-reflex and extrapyramidal systems. Thomas, Springfield, Ill., 1947. 59 pp.

MARMONT, G., and WIERSMA, C. A. G. On the mechanism of inhibition and excitation of crayfish muscle. *J. Physiol., 93,* 173–93. 1938.

MARSHALL, W. H. Excitability cycle and interaction in geniculate-striate system of cat. *J. Neurophysiol., 12,* 277–88. 1949.

MARSHALL, W. H., TALBOT, S. A., and ADES, H. W. Cortical response of the anaesthetized cat to gross photic and electrical afferent stimulation. *J. Neurophysiol., 6,* 1–15. 1943.

MARSHALL, W. H., WOOLSEY, C. N., and BARD, P. Observations on cortical somatic sensory mechanisms of cat and monkey. *J. Neurophysiol., 4,* 1–24. 1941.

MARUHASHI, J., MIZUGUCHI, K., and TASAKI, I. Action currents in single afferent nerve fibres elicited by stimulation of the skin of the toad and the cat. *J. Physiol., 117,* 129–51. 1952.

MATTHEWS, B. H. C. Specific nerve impulses. *J. Physiol., 67,* 169–90. 1929.

——— The response of a single end organ. *J. Physiol., 71,* 64–110. 1931a.

——— The response of a muscle spindle during active contraction of a muscle. *J. Physiol., 72,* 153–74. 1931b.

——— Nerve endings in mammalian muscle. *J. Physiol., 78,* 1–33. 1933.

MERTON, P. A. Significance of the "silent period" of muscles. *Nature, 116,* 733. 1950.

——— The silent period in a muscle of the human hand. *J. Physiol., 114,* 183–98. 1951.

——— Slowly conducting muscle spindle afferents. *Acta physiol. scand., 29,* 87–8. 1953.

——— Work in course of preparation. 1954.

MESERVEY, A. B., and CHAFFEE, E. L. Electrical response of the retina in different types of cold-blooded animals. *J. Opt. Soc. Amer., 15,* 311–30. 1927.

MOLDAVER, J. Contribution à l'étude de la régulation réflexe des mouvements. *Arch. int. méd. expér., 11,* 405–76. 1936.

MONNIER, A. M. L'Excitation électrique des tissues. Essai d'interpretation physique. Hermann, Paris, 1934. 326 pp.

——— Properties of nerve axons (II). The damping factor as a functional criterion in nerve physiology. *Cold Spr. Harb. Symp. Quant. Biol., 17,* 69–95. 1952.

MONNIER, A. M., and COPPÉE, G. Nouvelles recherches sur la résonance des tissues excitables I. Relation entre la rhythmicité de la réponse nerveuse et la résonance. *Arch. Int. Physiol., 48,* 129–80. 1939.

MONNIER, M., and BOEHM, F. Beiträge zum Elektroretinogramm des Menschen I. Perimetrische Elektroretinographie. *Helv. physiol. acta., 5,* 205–24. 1947.

MORGAN, C. T. Some structural factors in perception. In Blake and Ramsey (1951), pp. 25–55.

MORISON, R. S., and DEMPSEY, E. W. A study of the thalamo-cortical relations. *Amer. J. Physiol., 135,* 281–92. 1942.

MORISON, R. S., FINLEY, K. H., and LOTHROP, G. N. Influence of basal forebrain areas on the electrocorticogram. *Amer. J. Physiol., 139,* 410–16. 1943.

MORTON, R. A., and GOODWIN, T. W. Preparation of retinene *in vitro*. *Nature, 153,* 405–6. 1944.

MORTON, R. A., SALAH, M. K., and STUBBS, A. L. Retinene$_2$ and vitamin A$_2$. *Nature, 159,* 744. 1947.

MORUZZI, G. Influence of brain stem reticular formation on cortical electrical activity. *Electroenceph. Clin. Neurophysiol., 1,* 519P. 1949.

——— Cerebellar physiology. Thomas, Springfield, Ill., 1950. 116 pp.

——— Cerebellar and cerebral mechanisms. *Proc. XIX Int. Physiol. Congr.,* Montreal, pp. 89–99. 1953.

MORUZZI, G., and MAGOUN, H. W. Brain stem reticular formation and activation of the EEG. *Electroenceph. Clin. Neurophysiol., 1,* 455–73. 1949.

MOTOKAWA, K. Retinal processes and their role in color vision. *J. Neurophysiol., 12,* 291–303. 1949a.

——— Physiological studies on mechanisms of color reception in normal and color-blind subjects. *J. Neurophysiol., 12,* 465–74. 1949b.

——— Physiological induction in human retina as basis of color and brightness contrast. *J. Neurophysiol., 12,* 475–88. 1949c.

——— Selective inhibitory action of colored light upon the retinal color processes and its usefulness for analysis of the mechanism of color reception. *Tohoku J. Exp. Med., 52,* 213–21. 1950.

MOTOKAWA, K., and EBE, M. Retinal receptors isolated with AC method and polychromatic theory. *J. Opt. Soc. Amer., 43,* 203–9. 1953.

MOTOKAWA, K., IWAMA, K., and TUKAHARA, S. Color processes in single retinal elements. *Tohoku J. Exp. Med., 53,* 399–416. 1951.

MOTOKAWA, K., and MITA, T. Ueber eine einfachere Untersuchungsmethode und Eigenschaften der Aktionsströme der Netzhaut des Menschen. *Tohoku J. Exp. Med., 42,* 114–33. 1942.

——— Das Elektroretinogramm des Menschen und die Gesichtswahrnehmung in Abhängigkeit von der Intensität und Farbe der Reizlichter. *Jap. J. Med. Sci. Biophys., 9,* 23–35. 1943.

——— Die Helligkeitsverteilung im Dispersionsspektrum und die Aktionsströme der menschlichen Netzhaut. *Tohoku J. Exp. Med., 48,* 267–84. 1945.

MOTOKAWA, K., and SUZUKI, K. Analysis of the retinal processes by selective inhibition. *Tohoku J. Exp. Med., 52,* 349–59. 1950.

MOUNTCASTLE, V. B., COVIAN, M. R., and HARRISON, C. R. The central representation of some forms of deep sensibility. *Res. Publ. Ass. Nerv. Ment. Dis., 30,* 339–70. 1952.

MÜLLER-LIMMROTH, H.-W., and ANDRÉE, G. Untersuchungen zur Differenzkonstruktion des Elektroretinogramms des Froschauges. *Z. Biol., 105,* 324–38. 1953a.

——— Das Elektroretinogramm bei Flimmerbelichtung. *Pflüg. Arch. ges. Physiol., 257,* 216–33. 1953b.

MÜLLER-LIMMROTH, H.-W., and LEMAITRE, M. Ueber das Bestandpotential des Auges und seine Beziehungen zum Elektroretinogramm. *Z. Biol., 105,* 348–62. 1953.

MURPHY, J. P., and GELLHORN, E. The Influence of hypothalamic stimulation on cortically induced movements and on action potentials of the cortex. *J. Neurophysiol., 8,* 341–63. 1945.

NAFE, J. P. Towards the quantification of psychology. *Psychol. Rev., 49,* 1–18. 1942.

NAFE, J. P., and WAGONER, K. S. The insensitivity of the cornea to heat and pain derived from high temperatures. *Amer. J. Psychol., 49,* 631–49. 1937.

NIEMER, W. T., and MAGOUN, H. W. Reticulospinal tracts influencing motor activity. *J. Comp. Neurol., 87,* 367–79. 1947.

NOELL, W. K. The effect of iodacetate on the vertebrate retina. *J. Cell. Comp. Physiol., 37,* 283–308. 1951.

——— The impairment of visual cell structure by iodoacetate. *J. Cell. Comp. Physiol., 40,* 25–55. 1952a.

——— Azide-sensitive potential difference across the eye-bulb. *Amer. J. Physiol., 170,* 217–38. 1952b.

——— Studies on the electrophysiology and the metabolism of the retina. USAF School of Aviation Medicine, Randolph Field, Texas, 1953. 122 pp.

O'DAY, K. Visual cells of the guinea pig. *Nature, 160,* 648. 1947.

O'LEARY, J., HEINBECKER, P., and BISHOP, G. H. Analysis of function of a nerve to muscle. *Amer. J. Physiol., 110,* 636–58. 1935.

OTTOSON, D., and SVAETICHIN, G. Electrophysiological investigations of the frog retina. *Cold Spr. Harb. Symp. Quant. Biol., 17,* 165–73. 1952.

——— Electrophysiological investigations of the origin of the ERG of the frog retina. *Acta physiol. scand., 29,* Suppl. 106. 1954. Pp. 538–64.

PAINTAL, A. S. The conduction velocities of respiratory and cardiovascular afferent fibres in the vagus nerve. *J. Physiol., 121,* 341–59. 1953a.

——— A study of right and left atrial receptors. *J. Physiol., 122,* 596–610. 1953b.

PARK, A. M., TEASDALL, R. D., and MAGLADERY, J. W. Certain effects of brief stretch. *Bull. Johns Hopkins Hosp., 88,* 549–61. 1951.

PARRY, D. A. The function of the insect ocellus. *J. Exp. Biol., 24,* 211–19. 1947.

PARRY, H. B., TANSLEY, K., and THOMSON, L. C. The electroretinogram of the dog. *J. Physiol., 120,* 28–40. 1953.

PEACOCK, S. M., and HODES, R. Influence of the forebrain on somatomotor activity II. Facilitation. *J. Comp. Neurol., 94,* 409–26. 1951.

PEELE, T. L. Cytoarchitecture of individual parietal areas in the monkey (Macaca mulatta) and the distribution of the efferent fibers. *J. Comp. Neurol., 77,* 693–737. 1942.

PIPER, H. Das elektromotorische Verhalten der Retina bei Eledone moschata. *Arch. Anat. Physiol.,* Leipzig, pp. 453–74. 1904.

——— Untersuchungen über das elektromotorische Verhalten der Netzhaut bei Warmblütern. *Arch. Anat. Physiol.,* Leipzig, Suppl. 1905. Pp. 133–92.

——— Die Aktionsströme der Vogel- und Säugernetzhaut bei Reizung

durch kurzdauernde Belichtung und Verdunkelung. *Arch. Anat. Physiol.*, Leipzig, Suppl. 1910. Pp. 461–6.

PIPER, H. Ueber die Netzhautströme. *Arch. Anat. Physiol.*, Leipzig, pp. 85–132. 1911.

PIRENNE, M. H. The absolute sensitivity of the eye and the variation of visual acuity with intensity. *Brit. Med. Bull., 9,* 61–7. 1953.

PIRENNE, M. H., and DENTON, E. J. Accuracy and sensitivity of the human eye. *Nature, 170,* 1039–41. 1952.

POLLOCK, L. J., and DAVIS, L. The reflex activities of a decerebrate animal. *J. Comp. Neurol., 50,* 377–411. 1930.

——— Studies in decerebration. VI. The effect of deafferentation upon decerebrate rigidity. *Amer. J. Physiol., 98,* 47–9. 1931.

POLYAK, S. L. The retina. Chicago Univ. Press, Chicago, 1941. 607 pp.

PORTER, T. C. Contributions to the study of "flicker." *Proc. Roy. Soc. of Lond., A63,* 347–56. 1898.

——— Contributions to the study of flicker II. *Proc. Roy. Soc. of Lond., A70,* 313–29. 1902.

PRITCHARD, B. The clinical significance of variations in tickle sensibility. *Proc. Roy. Soc. Med., 26,* 697–704. 1932.

RAMÓN Y CAJAL, S. Die Retina der Wirbeltiere. German trans. by R. Greeff in Verbindung mit dem Verf. zusammengestellt. Bergmann, Wiesbaden, 1894. 168 pp.

——— Textura del sistema nervioso del hombre y de los vertebrados. N. Moya, Madrid, 1899. 566 pp.

——— Studien über die Hirnrinde des Menschen. 1. Sehrinde. Barth, Leipzig, 1900. 77 pp.

——— Textura del sistema nervioso del hombre y de los vertebrados. N. Moya, Madrid, 1904. Vol. *2,* pt. II, 519–1209.

——— La rétine des vertébrés. *Trav. Lab. Rech. biol.,* Madrid, *28,* Suppl. 1933. 141 pp.

RANSON, S. W. Somnolence caused by hypothalamic lesions in the monkey. *Arch. Neurol. Psychiat.,* Chicago, *41,* 1–23. 1939.

——— Regulation of body temperature. *Res. Publ. Ass. Nerv. Ment. Dis., 20,* 342–99. 1940.

RANSON, S. W., and BILLINGSLEY, P. R. The conduction of painful afferent impulses in the spinal nerves. II. *Amer. J. Physiol., 40,* 571–84. 1916.

RANSON, S. W., and MAGOUN, H. W. The hypothalamus. *Ergebn. Physiol., 41,* 56–163. 1939.

RASMUSSEN, G. L. The olivary peduncle and other fiber projections of the superior olivary complex. *J. Comp. Neurol., 84,* 141–219. 1946.

——— Further observations on the termination of the so-called olivary peduncle. *Anat. Rec., 106,* 235. 1950.

RAUBER, A. Untersuchungen über das Vorkommen und die Bedeutung der Vater'schen Körper. Fritsch, Munich, 1867. 52 pp.

RAYLEIGH, Lord. Experiments on colour. *Nature, 25,* 64–6. 1881.

RENDAHL, I. Klinisk elektroretinografi med elektronblixten som retningsljus. (Preliminary report) *Nord. Med., 48,* 1594. 1952.

RENSHAW, B. Activity in the simplest spinal reflex pathways. *J. Neurophysiol., 3,* 373–87. 1940.

——— Influence of the discharge of motoneurons upon excitation of neighboring motoneurons. *J. Neurophysiol., 4,* 167–83. 1941.

——— Central effects of centripetal impulses in axons of spinal ventral roots. *J. Neurophysiol., 9,* 191–204. 1946.

RENSHAW, B., FORBES, A., and MORISON, B. R. Activity of isocortex and hippocampus: electrical studies with micro-electrodes. *J. Neurophysiol., 3,* 74–105. 1940.

RETZIUS, G. Biologische Untersuchungen. Vol. *4,* Samson and Wallin, Stockholm, 1892. 70 pp.

REXED, B., and REXED, U. Degeneration and regeneration of corneal nerves. *Brit. J. Ophthal., 35,* 38–49. 1951.

REXED, B., and THERMAN, P.-O. Calibre spectra of motor and sensory nerve fibres to flexor and extensor muscles. *J. Neurophysiol., 11,* 133–40. 1948.

RHINES, R., and MAGOUN, H. W. Brain stem facilitation of cortical motor response. *J. Neurophysiol., 9,* 219–29. 1946.

RIGGS, L. A. Dark adaptation in the frog eye as determined by the electrical response of the retina. *J. Cell. Comp. Physiol., 9,* 491–510. 1937.

RIGGS, L. A., BERRY, R. N., and WAYNER, M. A comparison of electrical and psychophysical determinations of the spectral sensitivity of the human eye. *J. Opt. Soc. Amer., 39,* 427–36. 1949.

RIGGS, L. A., RATLIFF, F., CORNSWEET, J. C., and CORNSWEET, T. N. The disappearance of steadily fixated visual test objects. *J. Opt. Soc. Amer., 43,* 495–501. 1953.

RIPLEY, S. H., and WIERSMA, C. A. G. The effect of spaced stimulation of excitatory and inhibitory axons of the crayfish. *Physiol. Comp., 3,* 1–17. 1953.

RIVERS, W. H. R., and HEAD, H. A human experiment in nerve division. *Brain, 31,* 323–450. 1908.

ROBERTS, T. D. M. Reflex interaction of synergic extensor muscles of the cat hind limb. *J. Physiol., 117,* 5P. 1952.

ROEDER, K. D., ed. Insect Physiology. Wiley and Sons, New York, 1953. 1100 pp.

ROGGENBAU, C., and WETTHAUER, A. Ueber die Durchlässigkeit der brechenden Augenmedien für langwelliges Licht nach Untersuchungen am Rindsauge. *Klin. Monatsbl. Augenheilk., 79,* 456–64. 1927.

ROLLETT, A. Ueber einen Nervenplexus und Nervenendigungen in einer Sehne. *Sitzb. Akad. Wiss.*, Vienna, Pt. III, *73,* 34–52. 1876.

ROSS, D. A. Electrical studies of the frog's labyrinth. *J. Physiol., 86,* 117–46. 1936.

ROSSI, G. Asimmetrie toniche posturale, ed asimmetrie motorie. *Arch. Fisiol., 25,* 146–57. 1927.

RUCH, T. C. Sensory mechanisms. In Handbook of experimental psychology, ed. S. S. Stevens (1951), pp. 121–53.

RUFFINI, A. Annuario d. R. Univ. di Bologna, anno scolast. 1891–92, pp. 185–6. Quoted in Ruffini (1905).

——— Sur un nouvel organe nerveux terminal et sur la présence des corpuscules Golgi-Mazzoni dans le conjonctif sous-cutané de la pulpe des doigts de l'homme. *Arch. ital. biol., 21,* 249–65. 1894.

——— Observations on sensory nerve-endings in voluntary muscles. *Brain, 20,* 368–74. 1897.

——— On the minute anatomy of the neuro-muscular spindles of the cat, and on their physiological significance. *J. Physiol., 23,* 190–208. 1898–99.

——— Les Dispositifs anatomiques de la sensibilité cutanée: sur les expansions nerveuses de la peau chez l'homme et quelques autres mammifères. *Rev. gén. histol., 1,* 421–540. 1905.

RUSHTON, W. A. H. The structure responsible for action potential spikes in the cat's retina. *Nature, 164,* 743–4. 1949.

——— A theory of the effects of fibre size in medullated nerve. *J. Physiol., 115,* 101–22. 1951.

——— Apparatus for analysing the light reflected from the eye of the cat. *J. Physiol., 117,* 47P. 1952.

——— Electric records from the vertebrate optic nerve. *Brit. Med. Bull., 9,* 68–74. 1953.

RUSHTON, W. A. H., and COHEN, R. D. Visual purple level and the course of dark adaptation. *Nature, 173,* 301–2. 1954.

SAITO, Z. Isolierung der Stäbchenaussenglieder und spektrale Untersuchung des daraus hergestellten Sehpurpurextraktes. *Tohoku J. Exp. Med., 32,* 432–46. 1938.

SAND, A. The mechanism of the lateral sense organs of fishes. *Proc. Roy. Soc. of Lond.,* B*123,* 472–95. 1937.

——— The function of the ampullae of Lorenzini, with some observations on the effect of temperature on sensory rhythms. *Proc. Roy. Soc. of Lond.,* B*125,* 524–53. 1938.

SATO, M. Repetitive responses of the nerve fiber, as determined by recovery process and accommodation. *Jap. J. Physiol., 2,* 277–89. 1952.

SCHAEFER, H. Elektrophysiologie der Herznerven. *Ergebn. Physiol., 46,* 71–125. 1950.

SCHMIDT, W. J. Polarisationsoptische Analyse eines Eiweiss-Lipoid-Systems, erläutert am Aussenglied der Sehzellen. *Kolloidzchr., 85,* 137–48. 1938.

SCHRIEVER, H. Aktionspotentiale des N. lateralis bei Reizung der Seitenorgane von Fischen. *Pflüg. Arch. ges. Physiol., 235,* 771–84. 1935.

SCHUBERT, G., and BORNSCHEIN, H. Beitrag zur Analyse des menschlichen Elektroretinogramms. *Ophthalmologica,* Basel, *123,* 396–413. 1952.

SCHUMACHER, S. VON. Beiträge zur Kenntnis des Baues und der Funktion der Lamellenkörperchen. *Arch. mikr. Anat., 77,* 157–93. 1911.

SHEEHAN, D. The clinical significance of nerve endings in the mesentery. *Lancet, 1,* 409–10. 1933.

SHERRINGTON, C. S. On the anatomical constitution of nerves of skeletal muscles; with remarks on recurrent fibres in the ventral spinal nerve-root. *J. Physiol., 17,* 211–58. 1894.

——— Decerebrate rigidity, and reflex coordination of movements. *J. Physiol., 22,* 319–32. 1898.

——— Cutaneous sensations. In Schäfer's Textbook of Physiology. Pentland, London and Edinburgh, 1900a. *2,* 920–1001.

——— The muscular sense. In Schäfer's Textbook of Physiology. Pentland, London and Edinburgh, 1900b. *2,* 1002–25.

——— The integrative action of the nervous system. Silliman Memorial Lectures. Yale Univ. Press, New Haven; Constable, London; 1906. 412 pp.

——— On plastic tonus and proprioceptive reflexes. *Quart. J. Exp. Physiol., 2,* 109–56. 1909.

——— Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *J. Physiol., 40,* 28–121. 1910.

——— Reflex inhibition as a factor in the co-ordination of movements and postures. *Quart. J. Exp. Physiol., 6,* 251–310. 1913.

——— Reflexes elicitable from the pinna, vibrissae, and jaws in the cat. *J. Physiol., 51,* 404–31. 1917.

——— Problems of muscular receptivity. *Nature, 113,* 892–4. 1924.

——— Man on his nature. The Gifford Lectures. Edinburgh, 1937–38. Macmillan, New York; Cambridge Univ. Press, Cambridge; 1941. 413 pp.

SHERRINGTON, C. S., and SOWTON, S. C. M. Reversal of reflex effect of an afferent nerve by altering the character of the electrical stimulus applied. *Proc. Roy. Soc. of Lond., 83,* 435–46. 1910–11.

SHOLL, D. A. The organization of the visual cortex. *J. Physiol., 124,* 23–4P. 1954.

SINCLAIR, D. C., WEDDELL, G., and ZANDER, E. The relationship of cutaneous sensibility to neurohistology in the human pinna. *J. Anat., 86,* 402–11. 1952.

SJÖQVIST, O. Studies on pain conduction in the trigeminal nerve. *Acta psychiat. neurol.,* Copenhagen, Suppl. 17. 1938. 139 pp.

SJÖSTRAND, F. S. An electron microscope study of the retinal rods of the guinea pig. *J. Cell. Comp. Physiol., 33,* 383–97. 1949.

——— The ultrastructure of the outer segments of rods and cones of the eye as revealed by the electron microscope. *J. Cell. Comp. Physiol., 42,* 15–44. 1953a.

——— The ultrastructure of the inner segments of the retinal rods of the guinea pig eye as revealed by electron microscopy *J. Cell. Comp. Physiol., 42,* 45–70. 1953b.

SKOGLUND, C. R. The response to linearly increasing currents in mammalian motor and sensory nerves. *Acta physiol. scand., 4,* Suppl. 12. 1942. 75 pp.

SKOUBY, A. P. Sensitization of pain receptors by cholinergic substances. *Acta physiol. scand., 24,* 174–91. 1952.

SLOAN, L. L. The effect of intensity of light, state of adaptation of the eye, and size of photometric field on the visibility curve. *Psych. Monogr., 38,* No. 1. 1928. 87 pp.

SMITH, W. K. The functional significance of the rostral cingular cortex as revealed by its responses to electrical excitation. *J. Neurophysiol., 8,* 241–55. 1945.

SNIDER, R. S. Recent contributions to the anatomy and physiology of the cerebellum. *Arch. Neurol. Psychiat.,* Chicago, *64,* 196–219. 1950.

SNIDER, R. S., MCCULLOCH, W. S., and MAGOUN, H. W. A cerebello-bulboreticular pathway for suppression. *J. Neurophysiol., 12,* 325–34. 1949.

SNIDER, R. S., and WOOLSEY, C. N. Extensor rigidity in cats produced by simultaneous ablation of the anterior lobe of the cerebellum and the pericruciate areas of the cerebral hemispheres. *Amer. J. Physiol., 133,* 454P. 1941.

SOLANDT, D. Y. The measurement of "accomodation" in nerve. *Proc. Roy. Soc. of Lond., B119,* 355–79. 1935–36.

SOMMER, J. Periphere Bahnung von Muskeleigenreflexen als Wesen des Jendrassikschen Phänomens. *Dtsch. Z. Nervenheilk., 150,* 249–62. 1940.

SPRAGUE, J. M., and CHAMBERS, W. W. Regulation of posture in intact and decerebrate cat. I. Cerebellum, reticular formation, vestibular nuclei. *J. Neurophysiol., 16,* 451–63. 1953.

——— Control of posture by reticular formation and cerebellum in the intact, anesthetized and unanesthetized and in the decerebrate dog. *Amer. J. Physiol., 176,* 52–64. 1954.

STARZL, T. E., TAYLOR, C. W., and MAGOUN, H. W. Ascending conduction in the reticular activating system with special reference to the diencephalon. *J. Neurophysiol., 14,* 461–77. 1951a.

——— Collateral afferent excitation of the reticular formation of the brain stem. *J. Neurophysiol., 14,* 479–96. 1951b.

STEINHAUSEN, W. Ueber den experimentellen Nachweis der Ablenkung der Cupula terminalis in der intakten Bogengangsampulle des Labyrinths bei der thermischen und adäquaten rotatorischen Reizung. *Z. Hals, Nas. u. Ohrenheilk., 29,* 211–4. 1931.

——— Über die Beobachtung der Cupula in den Bogengangsampullen des Labyrinths des lebenden Hechts. *Pflüg. Arch. ges. Physiol., 232,* 500–12. 1933.

STELLA, G. Sul mecanismo della rigidità da decerebrazione in arti deafferentati. *Atti soc. med. chir.,* Padua, *22,* 5–16. 1944a.

——— Influenza del cervelletto sulla rigidità da decerebrazione. *Atti soc. med. chir.,* Padua, *22,* 17–21. 1944b.

STEVENS, S. S., ed. *Handbook of experimental psychology.* Wiley and Sons, New York, 1951. 1436 pp.

ST. GEORGE, R. C. C., GOLDSTONE, J. M. and WALD, G. Squid rhodopsin. *Fed. Proc., 11,* 153. 1952.

STILES, W. S. The directional sensitivity of the retina and the spectral sensitivities of the rods and cones. *Proc Roy. Soc. of Lond., B127,* 64–105. 1939.

——— *Proc. Int. Conf. Physiol. Optics.,* Madrid. To be published. 1953.

STILES, W. S., and CRAWFORD, B. H. The luminous efficiency of rays entering the eye pupil at different points. *Proc. Roy. Soc. of Lond., B112,* 428–50. 1933.

STILES, W. S., and SMITH, T. A mean scotopic visibility curve. *Proc. Phys. Soc. of Lond., 56,* 251–5. 1944.

STÖHR, P. Das peripherische Nervensystem. *Handb. mikr. Anat. d. Menschen.,* Pt. I, *4,* 202–447. 1928.

STOLL, W. A. Beziehungen des Hypothalmus zur Temperaturregulierung. *Helv. physiol. acta, 1,* 329–57. 1943.

STRATTON, G. M. Some preliminary experiments on vision without inversion of the retinal image. *Psychol. Rev., 3,* 611–7. 1896.

——— Vision without inversion of the retinal image. *Psychol. Rev., 4,* 341–60; 463–81. 1897.

STRÖM, G. Influence of local thermal stimulation of the hypothalamus of the cat on cutaneous blood flow and the respiratory rate. *Acta physiol. scand., 20,* Suppl. 70. 1950a. Pp. 47–76.

——— Influence of skin temperature on vasodilator response to hypothalamic heating in cat. *Acta physiol. scand., 20,* Suppl. 70. 1950b. Pp. 77–81.

——— Vasomotor responses to thermal and electrical stimulation of frontal lobe and hypothalamus. *Acta physiol. scand., 20,* Suppl. 70. 1950c. Pp. 83–112.

STRÜMPELL, A. Ein Beitrag zur Theorie des Schlafs. *Pflüg. Arch. ges. Physiol., 15,* 573–4. 1877.

SVAETICHIN, G. The cone action potential. *Acta physiol. scand., 29,* Suppl. 106. 1954a. Pp. 565–600.

——— Studies on the vertebrate ERG. On the relationship between the

ERG and visual perception. *Acta physiol. scand., 29,* Suppl. 106. 1954b. Pp. 601–10.

SZENTÁGOTHAI, J. Anatomical considerations of monosynaptic reflex arcs. *J. Neurophysiol., 11,* 445–54. 1948.

TALAAT, M. The effect of ions on the cutaneous sensory endings of the frog. *J. Physiol., 79,* 500–7. 1933.

TALBOT, S. A. Arrangement of visual field on cat's cortex. *Amer. J. Physiol., 129,* 477P. 1940.

TALBOT, S. A., WOOLSEY, C. N., and THOMPSON, J. M. Visual areas I and II of cerebral cortex of rabbit. *Fed. Proc., 5,* 103. 1946.

TANSLEY, K. The regeneration of visual purple: its relation to dark adaptation and night blindness. *J. Physiol., 71,* 442–58. 1931.

TASAKI, I. Electrical excitation of the nerve fiber. Part I. Excitation by linearly increasing currents. *Jap. J. Physiol., 1,* 1–6. 1950.

——— Nervous transmission. Thomas, Springfield, Ill., 1953a. 164 pp.

——— Afferent impulses in individual cochlear nerve fibers of the guinea pig. *Fed. Proc., 12,* 142. 1953b.

TASAKI, I., DAVIS, H., and LEGOUIX, J.-P. The space-time pattern of the cochlear microphonics (guinea pig) as recorded by differential electrodes. *J. Acoust. Soc. Amer., 24,* 502–19. 1952.

TASAKI, I., and FERNÁNDEZ, C. Modification of cochlear microphonics and action potentials by KCl solution and by direct currents. *J. Neurophysiol., 15,* 497–512. 1952.

TASAKI, I., and MIZUTANI, K. Comparative studies of the activities of the muscle evoked by two kinds of motor nerve fibres. Part I. Myographic studies. *Jap. J. Med. Sci., 10,* 237–44. 1944.

TASAKI, I., and TSUKAGOSHI, M. Comparative studies on the activities of the muscle evoked by two kinds of motor nerve fibres. Part II. The electromyogram. *Jap. J. Med. Sci., 10,* 245–51. 1944.

TERZUOLO, C., and TERZIAN, H. Cerebellar increase of postural tonus after deafferentation and labyrinthectomy. *J. Neurophysiol., 16,* 551–61. 1953.

THAUER, R. Der Mechanismus der Wärmeregulation. *Ergebn. Physiol., 41,* 607–805. 1939.

THERMAN, P. O. The neurophysiology of the retina in the light of chemical methods of modifying its excitability. *Acta soc. sci. fenn.,* new ser. B, *2,* No. 1. 1938.

THOMPSON, J. M., WOOLSEY, C. N., and TALBOT, S. A. Visual areas I and II of cerebral cortex of rabbit. *J. Neurophysiol., 13,* 277–88. 1950.

THOMSON, L. C. Intensity discrimination of the central fovea measured with small fields. *J. Physiol., 108,* 78–91. 1949.

——— The localization of function in the rabbit retina. *J. Physiol., 119,* 191–209. 1953.

TIEGS, O. W. Innervation of voluntary muscle. *Physiol. Rev., 33,* 90–144. 1953.

TIGERSTEDT, R. Studien über mechanische Nervenreizung. Helsingfors, 1880. 92 pp.

TOENNIES, J. F. Reflex discharge from the spinal cord and the dorsal roots. *J. Neurophysiol., 1,* 378–90. 1938.

TOMITA, T. Studies on the intraretinal action potential. Part I. Relation between the localization of micro-pipette in the retina and the shape of the intraretinal action potential. *Jap. J. Physiol., 1,* 110–6. 1950.

TOMITA, T., and FUNAISHI, A. Studies on intraretinal action potential with low-resistance microelectrode. *J. Neurophysiol., 15,* 75–84. 1952.

TOMITA, T., FUNAISHI, A., and MIZUNO, H. Some properties of slow negative component in bullfrog's intraretinal action potential. *Proc. XIX. Int. Physiol. Congr.,* Montreal, pp. 829–30. 1953.

TOMITA, T., FUNAISHI, A., and SHINO, H. Studies on the intraretinal action potential. Part II. Effects of some chemical agents upon it. *Jap. J. Physiol., 2,* 147–53. 1951.

TOMITA, T., MIZUNO, H., and IDA, T. Studies on the intraretinal action potential. Part III. Intraretinal negative potential as compared with b-wave in the ERG. *Jap. J. Physiol., 2,* 171–7. 1952.

TOWER, S. S. Nerve impulses from receptors in the cornea. *Proc. Soc. Exp. Biol.,* N.Y., *32,* 590–2. 1934.

——— Unit for sensory reception in cornea. With notes on nerve impulses from sclera, iris and lens. *J. Neurophysiol., 3,* 486–500. 1940.

TUKAHARA, S. Modulators and dominators of the toad's retina. *Tohoku J. Exp. Med., 54,* 11–20. 1951.

TUNTURI, A. R. Physiological determination of the boundary of the acoustic area in the cerebral cortex of the dog. *Amer. J. Physiol., 160,* 395–401. 1950a.

——— Physiological determination of the arrangement of the afferent connections to the middle ectosylvian auditory area in the dog. *Amer. J. Physiol., 162,* 489–502. 1950b.

VERNEY, E. B. Croonian Lecture. The antidiuretic hormone and the factors which determine its release. *Proc. Roy. Soc. of Lond.,* B*135,* 25–106. 1947.

WALD, G. Photo-labile pigments of the chicken retina. *Nature, 140,* 545. 1937.

——— The chemistry of rod vision. *Science, 113,* 287–91. 1951.

——— The biochemistry of vision. *Ann. Rev. Biochem., 22,* 497–526. 1953.

WALD, G., and BROWN, P. K. The role of sulfhydryl groups in the bleaching and synthesis of rhodopsin. *J. Gen. Physiol., 35,* 797–821. 1952.

WALD, G., BROWN, P. K., and SMITH, P. H. Iodopsin. *Fed. Proc., 11,* 304. 1952.

——— Cyanopsin, a new pigment of cone vision. *Science, 118,* 505–8. 1953.

WALLS, G. L. The vertebrate eye and its adaptive radiation. Michigan, *Cranbrook Inst. Sci., Bulletin* No. 19. 1942. 785 pp.

WALSHE, F. M. R. Critical studies in neurology. E. and S. Livingstone, Edinburgh, 1948. 256 pp.

WANG, G.-H. Action potentials of the visual cortex and the superior colliculus induced by stimulation of the retina with light. *Chin. J. Physiol., 8,* 121–44. 1934.

WARD, A. A. Decerebrate rigidity. *J. Neurophysiol., 10,* 89–103. 1947.

WATERMAN, T. H. A light polarization analyzer in the compound eye of Limulus. *Science, 111,* 252–4. 1950.

WATERSTON, D. Observations on sensation. The sensory functions of the skin for touch and pain. *J. Physiol., 77,* 251–7. 1933.

WEALE, R. A. Spectral sensitivity and wave-length discrimination of the peripheral retina. *J. Physiol., 119,* 170–90. 1953a.

——— Photochemical reactions in the living cat's retina. *J. Physiol., 121,* 322–31. 1953b.

——— Personal communication. 1954.

WEBER, E. H. De pulsu resorptione, auditu et tactu annotationes. *Anat. et physiol.*, Leipzig. 1834. Pp. 135, 137. Quoted in Weber (1846).

——— Der Tastsinn und das Gemeingefühl. In Wagner's Handwörterbuch d. Physiologie (1846) *3,* No. 2, 481–588.

WEDDELL, G. The anatomy of cutaneous sensibility. *Brit. Med. Bull., 3,* 167–72. 1945.

WEISMANN, A. Ueber das Wachsen der quergestreiften Muskeln nach Beobachtungen am Frosch. *Z. rat. Med.,* 3d Ser., *10,* 263–84. 1861.

WEVER, E. G., and BRAY, C. W. Action currents in the auditory nerve in response to acoustical stimulation. *Proc. Nat. Acad. Sci.* Wash., *16,* 344–50. 1930.

WHITESIDE, J. A., and SNIDER, R. S. Relation of cerebellum to upper brain stem. *J. Neurophysiol., 16,* 397–413. 1953.

WHITTERIDGE, D. Afferent fibres from the heart and lungs in the cervical vagus. *J. Physiol., 107,* 496–512. 1948.

WIERSMA, C. A. G. A bifunctional single motor axon system of a crustacean muscle. *J. Exp. Biol., 28,* 13–21. 1951.

WIERSMA, C. A. G., and ADAMS, R. T. The influence of nerve impulse sequence on the contractions of different crustacean muscles. *Physiol. Comp., 2,* 20–33. 1950.

WILSKA, A., and HARTLINE, H. K. The origin of "off-responses" in the optic pathway. *Amer. J. Physiol., 133,* 491P. 1941.

WIRTH, A. Beiträge zu den Teilströmen des menschlichen Elektroretinogramms. *Von Graefes Arch. Opthal., 151,* 662–71. 1951.

——— Electroretinographic evaluation of the scotopic visibility function in cats and albino rabbits. *Acta physiol. scand., 29,* 22–30. 1953.

WIRTH, A., and ZETTERSTRÖM, B. The effect of area and intensity on size and shape of the ERG. The exclusion of stray light effect. *Brit. J. Ophthal., 38,* 257–65. 1954.

WOOLLARD, H. H. Observations on the terminations of cutaneous nerves. *Brain, 58,* 352–67. 1935.

——— Anatomy of peripheral sensation. *Brit. Med. J., 2,* 861–2. 1936.

——— Intra-epidermal nerve endings. *J. Anat., 71,* 54–60. 1936–37.

WOOLLARD, H. H., WEDDELL, G., and HARPMAN, J. J. Observations on the neurohistological basis of cutaneous pain. *J. Anat., 74,* 413–40. 1940.

WOOLSEY, C. N. Summary of the papers on the cerebellum. *Res. Publ. Ass. Nerv. Ment. Dis., 30,* 334–6. 1950.

WOOLSEY, C. N., and WALZL, E. M. Topical projection of nerve fibers from local regions of the cochlea to the cerebral cortex of the cat. *Bull. Johns Hopkins Hosp., 71,* 315–44. 1942.

WRIGHT, W. D. Researches on normal and defective colour vision. Kimpton, London, 1946. 383 pp.

WRIGHT, W. D., and GRANIT, R. On the correlation of some sensory and physiological phenomena of vision. *Brit. J. Ophthal.,* Suppl. 9. 1938.

WULFF, V. J. The electrical response of frog eyes to prolonged illumination. *J. Cell. Comp. Physiol., 32,* 31–43. 1948.

YOUNG, T. On the theory of light and colours. A Bakerian lecture (Read Nov. 12, 1801.) *Phil. Trans.,* 1802, p. 12. In Miscellaneous works of the late Thomas Young, ed. G. Peacock. John Murray, London, 1855. *1,* 140–69.

ZETTERSTRÖM, B. The clinical electroretinogram IV. The electroretinogram in children during the first year of life. *Acta ophthal.,* Copenhagen, *29,* 295–304. 1951.

——— The electroretinogram in prematurely children. *Acta ophthal.,* Copenhagen, *30,* 405–8. 1952.

ZEWI, M. On the regeneration of visual purple. *Acta soc. sci. fenn.,* new ser., B*2,* No. 4. 1939. 56 pp.

ZOTTERMAN, Y. Studies in the peripheral nervous mechanism of pain. *Acta med. scand., 80,* 185–242. 1933.

——— Action potentials in the glossopharyngeal nerve and in the chorda tympani. *Skand. Arch. physiol., 72,* 73–7. 1935.

——— Specific action potentials in the lingual nerve of cat. *Skand. Arch. physiol., 75,* 105–20. 1936.

——— Touch, pain and tickling: an electrophysiological investigation on cutaneous sensory nerves. *J. Physiol., 95,* 1–28. 1939.

——— The microphonic effect of teleost labyrinths and its biological significance. *J. Physiol., 102,* 313–8. 1943.

ZOTTERMAN, Y. Special senses: thermal receptors. *Ann. Rev. Physiol., 15,* 357–72. 1953.

ZÜRN, J. Vergleichend histologische Untersuchungen über die Retina und die Area centralis retinae der Haussäugethiere. *Arch. Anat. Physiol.,* Leipzig, Suppl., *1,* 1902. Pp. 99–146.

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