NERVE IMPULSE



Transactions of the Fourth Conference
March 4, 5 and 6, 1953

Editor
DAVID NACHMANSOHN, M.D.

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Transactions of the Fourth Conference
March 4, 5 and 6, 1953, Princeton, N. J.

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THE JOSIAH MACY, JR. FOUNDATION CONFERENCE PROGRAM

AS AN INTRODUCTION to these Transactions of the Fourth Conference on Nerve Impulse, I should like to outline what it is that the Foundation hopes to accomplish by its Conference Program. We are interested, first of all, in furthering knowledge about nerve impulse, and to this end the participants were brought together to exchange ideas, experiences, data, and methods. In addition to this particular goal, however, there is a further, and perhaps more fundamental, aim which is shared by all our conference groups. This is the promotion of meaningful communication between scientific disciplines.

The problem of communication between disciplines we feel to be a very real and urgent one, the most effective advancement of the whole of science being to a large extent dependent upon it. Because of the accelerating rate at which new knowledge is accumulating, and because discoveries in one field so often result from information gained in quite another, channels must be established for the most effective dissemination and exchange of this knowledge.

The increasing realization that nature itself recognizes no boundaries makes it evident that the continued isolation of the several branches of science is a serious obstacle to scientific progress. Particularly is it true in medicine that the limited view through the lens of one discipline is no longer enough. For example, today medicine must be well versed in nuclear physics because of the tracer techniques and the injury which can result from radiation. At the other extreme, medicine is certainly a social science and, through mental health, must be concerned with economic and social questions. The answer, then, is not further fragmentation into increasingly isolated specialities, disciplines, and departments, but the integration of science and scientific knowledge for the enrichment of all branches. This integration, we feel, can be encouraged by providing opportunities for a multiprofessional approach to given topics.

Although the fertility of the multidiscipline approach is recognized, adequate provision is not made for it by our universities, scientific societies, and journals. And perhaps the presence of other hindering factors must be admitted. Partly semantic in nature, they may also to some degree be psychological. Admittedly, it is oftentimes difficult to

accept data derived from methods with which one is unfamiliar. By making free and informal discussion the central core of our meetings, we hope to achieve an atmosphere which minimizes as much as possible these semantic and emotional barriers.

Thus, our conferences are in contrast to the usual scientific gatherings. Presentations are designed not to present neat solutions to tidy problems but rather to elicit provocative discussion of the difficulties which are being encountered in research and practice. We ask that the presentations be relatively brief, and emphasis is placed upon discussion as the heart of the meeting. Our hope is that the participants will come prepared not to defend a single point of view but, with open minds, to take full advantage of the meeting as an opportunity to speak with representatives of other disciplines in much the same way as they talk with their colleagues in their own laboratories.

During 1953 under the Conference Program conferences will be held on the following topics: administrative medicine, adrenal cortex, aging, connective tissues, consciousness, cybernetics, infancy and childhood, liver injury, metabolic interrelations, nerve impulse, renal function, and shock and circulatory homeostasis.

When a new conference group is organized, the Chairman, in consultation with the Foundation, selects fifteen scientists to be the nucleus of the group which will hold annual meetings for a period of five years. Every effort is made to include representatives from all pertinent disciplines. From time to time, however, new members are added by the group to fill gaps in viewpoint or techniques. A small number of guests is invited to attend each meeting, but, for the purposes of promoting full participation by all members and guests, attendance at any meeting is limited to twenty-five. During a conference's prescribed lifetime we cannot possibly include more than a small fraction of the key investigators in the field, and one of the difficulties in forming a group is that it is necessary to exclude so many investigators we should like to include.

The transactions of these meetings are recorded and published. This is done because the Foundation wishes to make current thinking in a field available to all those working in it, and to those in other fields who are concerned with science: for example, government officials, administrators, etc. Logic is a vital aspect of science, but equally essential is the intuitive or creative aspect. Research is as creative as the painting of a portrait or the composing of a symphony. Although logic is, of course, necessary in order to rearrange, to test, and to validate, research

thrives on creativity which has its source in unconscious, nonrational processes. Unfortunately, however, in the research reports which are presented to the world in scientific journals, this integral part of scientific endeavor is shriveled by the cold, white light of logic. By preserving the informality of our conferences in the published transactions, we hope to portray more accurately how the minds of scientists work and to give a truer picture of the role which creativity plays in scientific research.

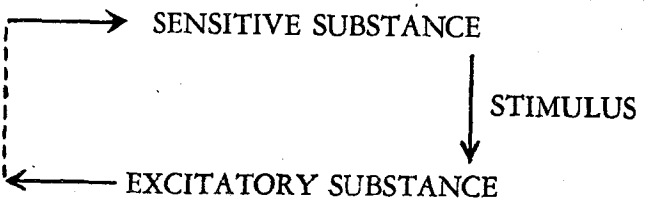
FRANK FREMONT-SMITH, M.D.
Medical Director

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MECHANISM OF VISION

GEORGE WALD
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I SHOULD LIKE to orient what I have to say toward a consideration of the mechanism of the excitation process. I take it for granted that at least the general arrangement of such processes is the same wherever one encounters them, whether in nerve, muscle, sense organs, or indeed in eggs. This general arrangement is plain even before one makes an experiment. It must take the form of some such diagram as follows:



Always there must be some sensitive substance or state which is changed by the stimulus to yield what may be called an excitatory substance or state. The sensitive substance or state must constantly be reconstituted or replenished; otherwise the organ could not continue to respond. The excitatory substance or state must also be rapidly removed; otherwise the organ would continue to respond long after the stimulus had ceased. If these last two processes were in fact one, so that the removal of the excitatory condition itself reconstituted the sensitive condition, then we should have a cycle, which would greatly help the economy of the system.

What I should like to do is to develop essentially four kinds of thought involving the excitatory process in vision. I will do this as rapidly as I can, and then hope that the discussion will bring out whatever more needs to be said.

The first of these is an anatomical consideration. I am sure that all of you are familiar with the arrangement of tissues that forms the fundus of the eye. Outermost is the cartilaginous sclera, a protective coat. Just inside this is the highly vascular choroid layer, the principal blood supply for the tissues at the back of the eyeball. Next comes a single layer of cells, the pigment epithelium. Then we are in the neural

retina: an outermost layer of cones and rods; next a layer of interconnections, containing the so-called "bipolar" cells and other connecting neurons; and finally the layer of ganglion cells from which spring the optic nerve fibers.

The excitation process in vision is completely enclosed within minute organelles, the outer segments of the cones and rods. These are not cells, but merely excrescences on cells. Virtually everything I shall talk about today is imprisoned within the small compass of these little structures. This is about as high a degree of isolation of a physiological function as one finds in the organism. It greatly simplifies our problem. It does something more, however, which I want to bring particularly to the attention of the axonologists. One of the most valuable characteristics of nerve fibers to the physiologist is their extraordinary specialization. One feels that here one can study almost in isolation the processes of excitation and conduction of excitation. What we have, however, in the outer segments of the rods and cones, is a further reach of isolation and specialization. Here we have dropped conduction, and are dealing simply with an excitatory organ.

It is particularly interesting, therefore, that one can remove these structures, and discard the remainder of the retina. In fact, one has to go to considerable pains to keep the outer segments of the rods and cones from breaking away from the remaining retinal tissues. In the frog retina the rods are particularly large. If one dissects out a frog retina, and then just treats it roughly, enormous numbers of rod outer segments stroke off and go into suspension in the medium. Such a suspension of rod outer segments is shown in Figure 1. One can make such suspensions as thick as one pleases, and then separate them cleanly from all the other retinal tissues by differential centrifugation. The outer segments of the rods are somewhat lighter in density than the other retinal tissues, and in concentrated sugar-solution remain in suspension while the other tissues sediment in the centrifuge.

Fremont-Smith: This is the excitatory end of those cells that you showed us?

Wald: Yes, each of these is the outer segment of a rod. These structures contain the whole photosensitive mechanism, the whole mechanism which turns light into a nervous excitation. You will be able to see this much more clearly in the figures which follow.

Brink: I have the impression, from Figure 1, that at one point you could see through a rod and observe another lying directly underneath it? Is that correct?

Wald: Yes, and sometimes, if a rod is lying across another, you can see that they bulge each other.

Brink: I had the impression that I could see right through one of those rods.

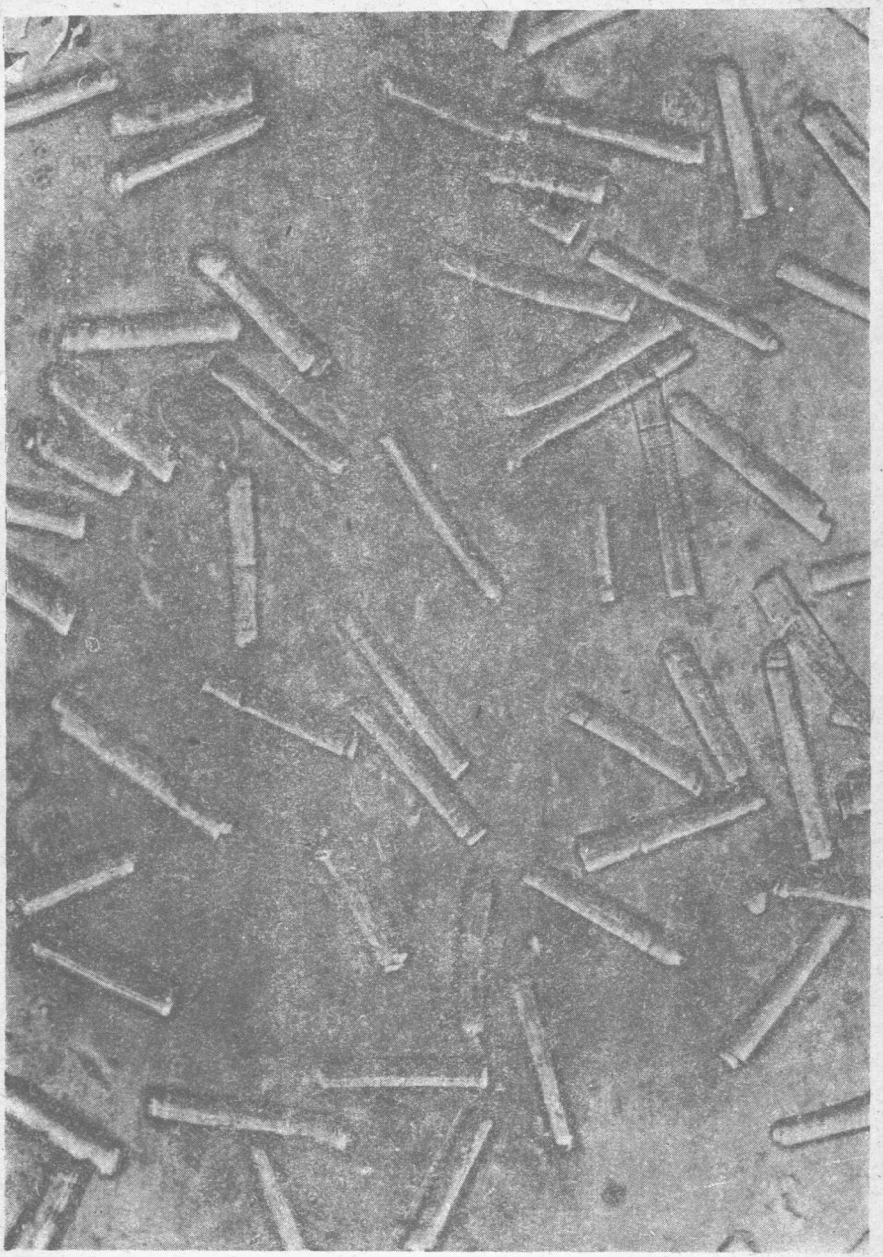


FIGURE 1. Suspension of outer segments of rods of the frog retina. These structures have merely been stroked off the retinal surface, and are lying in Ringer's solution. Various rods show evidences of both the longitudinal striation, which is characteristic of the fresh material, and the cross striations which become more prominent on standing. Reprinted, by permission, from Wald, G., and Hubbard, R.: The reduction of retinene$_1$ to vitamin A$_1$ *in vitro*. *J. Gen. Physiol.* **32**, *367 (1948)*.

Wald: Yes, they are transparent.

Figure 2* shows such an outer segment of a rod, and part of another one. In the frog and in amphibia generally, the rods are enormous compared to other vertebrates. These in the frog measure approximately from 6 to 9 x 60 micra. The figure shows what a fresh outer segment looks like just after it has been prepared. This is not fixed or stained; it is just lying in Ringer's solution. You will notice the longitudinal striations. One of the great nineteenth century microscopists, Max Schultze, saw these striations, but they have often been forgotten since. Sometimes they are mentioned with the thought that they may represent grooving or fluting on the column of the rod. One is indeed some-

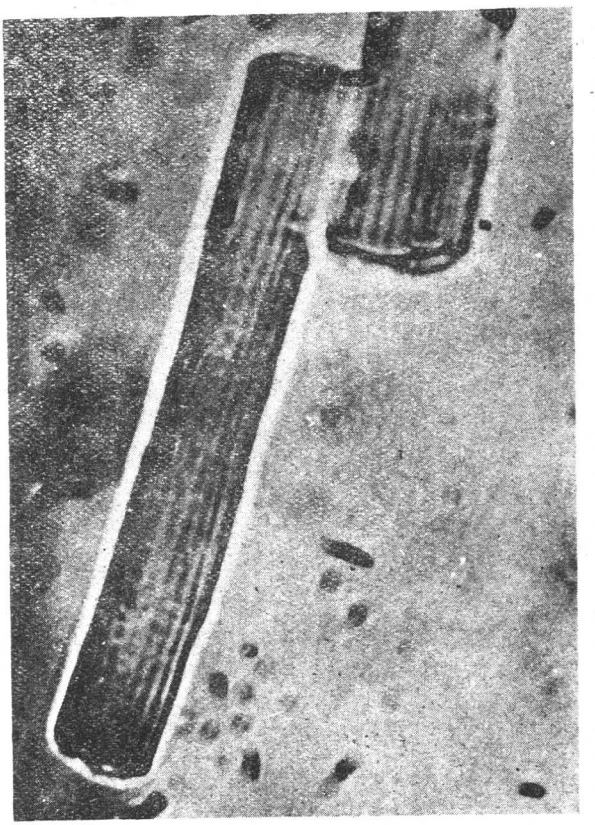


FIGURE 2. Two fresh outer segments of rods (frog), in Ringer's solution. The longitudinal striations show very prominently here. These rods measure about 6 to 9 × 60 micra.

*Some of the work described in the following figures was done in collaboration by Wald, G., and Hubbard, R.

times told that the protoplasmic processes from the pigment epithelium cells fit into these grooves on the outer sheath of the rod. We think on the contrary that these longitudinal striations probably represent fibrils inside the rod. Figure 3 shows a further indication of this. You can see here what looks like the broken end of a rod; and at the end a rather clear indication of the broken ends of what look to be fibrils, arranged around the circumference of this structure. The rod shown in Figure 3 is an outer segment which is already beginning to deteriorate. Superimposed on the longitudinal striations one sees the beginnings of cross striations. You will be able to see this much better shortly.

Fremont-Smith: Dr. Wald, is there one of these per cell, or several?

Wald: One per cell. If you look down at the top of a frog retina, you see the view shown in Figure 4. Each of the circular objects is the top of a rod. You can see that there is some kind of fine structure that yields a stippled effect through the whole cross section of the rod.

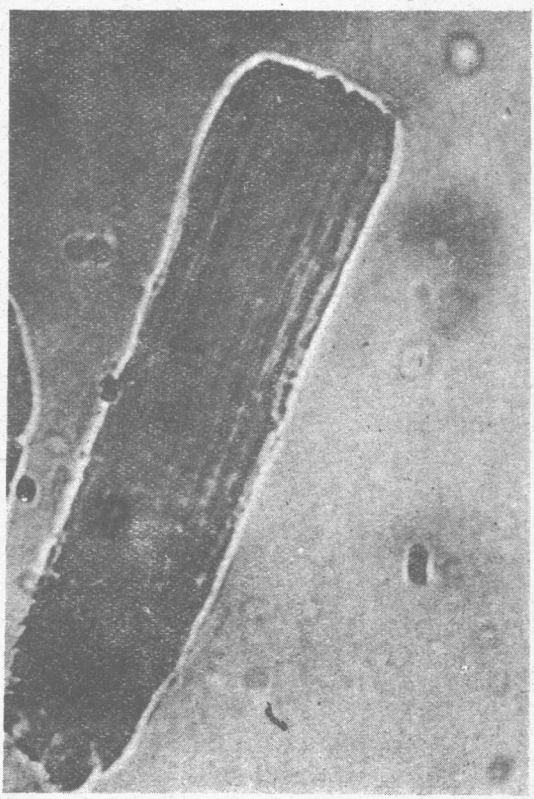


FIGURE 3. A frog rod, showing at the upper end what appear to be the ends of fibrils arranged around the circumference of the rod.

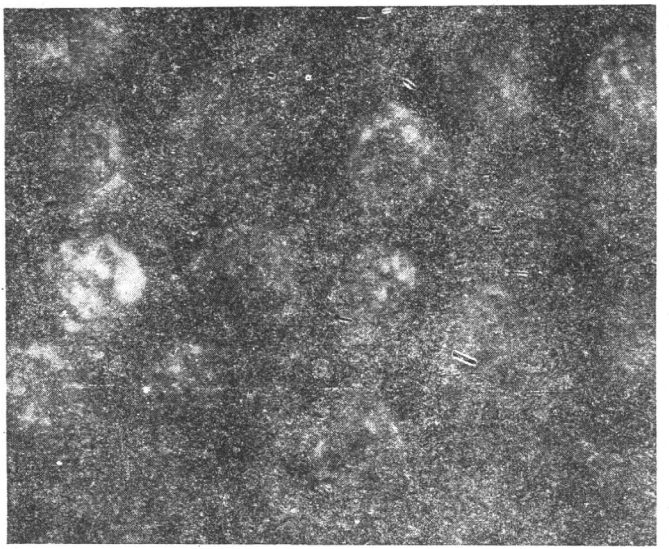


FIGURE 4. Top view of a fresh frog retina *(Rana pipiens)*. Each of the light circles is the top of a rod.

Indeed it looks as though these might be the ends of the fibrils, and that the rod contains a solid bundle of such fibrils. This view must be reconciled, however, with the indication in the preceding figure that the fibrils are in fact arranged around the periphery of the rod.

After a rod has lain in Ringer's awhile it develops a clearer and clearer pattern of cross striations, that may eventually almost obliterate the original appearance of longitudinal striations. Such rods are shown in Figure 5. These rods shown are about 50 micra long. As you see they display an amazingly regular pattern of cross striations. Throughout the entire length of the rod, there are about 120 cycles of dark and light bands. The average thickness of a dark or light band is therefore about 210 millimicra. This is just above the limit of resolution of the visible-light microscope.

Actually the microstructure of such a rod outer segment is a composite of the axial structures which appear as longitudinal striations, which we believe to be probably fibrils, and this cross striation. Figure 6 shows both types of structure. One sees here that the cross striations are in fact substructures of the fibrils. Just as in striated muscle, the cross striations remain in phase right across the rod, and one sees that where one fibril has a dark band, the others have dark bands at the same level. Perhaps for this reason, as one stage in the deterioration of a surviving rod outer segment, these transverse layers coalesce, eventually almost wiping out the longitudinal structure and leaving only the transverse layers visible.

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