# NERVE IMPULSE

**Transactions of the First Conference**
**March 2-3, 1950, New York, N. Y.**

Editor
DAVID NACHMANSOHN

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*First Conference on Problems of Nerve Impulse*

*March 2-3, 1950*

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*Josiah Macy, Jr. Foundation*

FRANK FREMONT-SMITH, MEDICAL DIRECTOR

JANET FREED, ASSISTANT FOR THE CONFERENCE PROGRAM

# TABLE OF CONTENTS

# JOSIAH MACY, JR. CONFERENCE PROGRAM

FRANK FREMONT-SMITH
*Medical Director*

I WANT TO tell you how happy we are to welcome you to this first meeting of the Conference on Nerve Impulse. The Foundation has brought you together to exchange ideas and experiences in an effort to further knowledge in this field.

May I explain the nature and goals of the Josiah Macy, Jr. Foundation's Conference Program which now includes thirteen groups. These cover a wide range of medical knowledge as follows: aging, adrenal cortex, biological antioxidants, blood clotting and allied problems, connective tissues, cybernetics, factors regulating blood pressure, infancy and childhood, liver injury, metabolic interrelations, nerve impulse, problems of consciousness, and renal function. Each group holds annual two-day meetings for a period of five years.

When a new conference is planned fifteen scientists are selected by the Chairman, in consultation with the Foundation, to be the original members. In this selection every effort is made to include representatives from all pertinent disciplines. For the purpose of promoting full participation of each member and guest, attendance at any meeting is limited to a total of twenty-five.

The Foundation is interested not only in furthering knowledge concerning the nerve impulse, but also in investigating the broad aspects of the problem of communication and of integration. The experience gained from the many research projects presented for consideration has led to the conviction that one of the greatest needs today is a reintegration of science, now artificially fragmented by the isolation of the several disciplines or specialties. We feel that the setting up of physiological and — what is more important — psychological barriers between the several branches of science is seriously interfering with scientific progress and that we need to make a constant effort to promote communication across these artificial barriers. Although the fertility of the multiprofessional approach is recognized, universities, scientific societies and journals have not yet made adequate provision for channels of interprofessional communication.

The Josiah Macy, Jr. Foundation's Conference Program hopes to encourage this reintegration. We are happy to say that as a result of our conferences, we have seen research plans and ideas modified, conclusions more clearly specified or placed in broader perspective, and we have watched spontaneous collaboration take place between investigators working in different departments in the same or different universities.

In contradistinction to the usual scientific meetings we place the emphasis upon discussion and not upon the presentation of formal papers. The introductory presentations at our conferences are merely the launching of the ship — the voyage is the important thing! The person opening a discussion is similar to the person who breaks the bottle of champagne over the bow of a new vessel. In other words we feel that the heart of these meetings is the discussions. We want you to speak freely and comfortably in the knowledge that even though everything said is being taken by the stenotypist you will have ample opportunity to edit, modify or delete any of your remarks which you do not want to appear in the published transactions.

From our experience with conferences we have learned that if one desires to successfully communicate with another person one cannot limit oneself merely to making statement *at* him, and increasing the power of one's transmitting set when he does not understand; some consideration of the receiving set is important. If the receiving set has filters which block out certain wave lengths, one must try another wave length. The reports of scientific work in recent years have been forced into a mold of logical sequence leading to inevitable conclusions. The processes of scientific inquiry take place in a much more flexible and unpredictable way. I do not for a moment mean to say that logic is not a most important component of scientific investigation; logic is often brought to bear upon the illogical or adventitious situations which arise. If you have read Walter B. Cannon's chapter on *Serendipity* in *The Way of an Investigator** you will know what I am talking about.

We are trying in our published transactions to maintain the informal nature of the conferences themselves, and to reproduce as nearly as possible the manner in which scientists think and work.

The Conference Program is an experiment and you are part of an experiment. The success of the undertaking is measured entirely upon what each participant gains from such an experience. We encourage your critique of this experiment and hope continuously to improve our techniques.

* New York: W. W. Norton and Co., Inc. 1945 (pp 68-78).

# INTRODUCTORY REMARKS

H. HOUSTON MERRITT,
*Chairman*

WHEN DR. Fremont-Smith brought up the subject matter of this conference group I thought it was a very excellent idea, but when he asked me to be Chairman I thought it was a little strange. I came to one of the meetings of another discussion group and I think I found out why he asked me. The Chairman of this other meeting knew so much about the subject and was so interested in it that he did not give the other members a chance to talk. I think Dr. Fremont-Smith had a great deal of method in his madness because he knows I will give you all the chance to talk.

Dr. David Nachmansohn has kindly consented to be the Editor for the transactions of this group. He will send you as soon as possible your discussions to edit and he will try to put them out in a form comparable to that of the books that have been demonstrated to you.

It seems to me that one of the most important functions of discussion groups such as this is to iron out differences of opinion; to see how your work differs from others, how you have perhaps made some mistakes, and how you can correct them.

I have given a great deal of thought as to whether the directors of the Macy Foundation are spending their money wisely in conducting conference groups like this, whether it would not be better for them to subsidize individual pieces of research. However, on thinking it over and talking with other people, I came to the conclusion that this is a very fruitful way for them to utilize funds because it gets men together who are working on a problem and gives them ideas of how they could better pursue their work.

Although we have scheduled official discussers, these men are not going to give papers. As Dr. Fremont-Smith has pointed out they are merely going to throw the subject open to you for discussion. They are going to give you some of their ideas so that you can take up the ball and carry it from there. The whole success of a conference group like this depends upon how much each one of you will participate. I don't know how many talkers we have here. I hope you won't feel like Dr. Fred Gibbs, who, when I sent him his discussion of various papers presented at a recent meeting of the American Neurological Association to edit wrote back and said, "Why can't I learn to keep my big mouth shut."

When one is interested in a subject it is hard to keep from talking. We want you all to actively participate in the discussion and in order to give the man who has the floor a chance, we shall appreciate it if you do not interrupt him; give me a signal that you want to talk next and I shall try to see that the meeting proceeds in an orderly manner.

If there are no further questions we will have Dr. Grundfest start right off on "Potentialities and Limitations of Electrophysiology." We are discussing the nerve impulse but I am sure we are going to go far afield in our discussions because there are a great many things that bear on this subject.

# POTENTIALITIES AND LIMITATIONS OF ELECTROPHYSIOLOGY

HARRY GRUNDFEST
*Department of Neurology,*
*College of Physicians and Surgeons, Columbia University*

I WOULD like to open the discussion by implementing the informality suggested by Dr. Frank Fremont-Smith. I hereby put down a bet of one dollar that the first idea relating the action current and the brain, particularly in reference to psychiatry, was presented in 1603. Are there any takers?

All of you should know the name of this great scientist because I am sure you have all seen Hamlet and remember when he asks the question "To be or not to be" with its discussions of revolution, suicide, psychiatry, and so on. He ends up with:

> "And thus the native hue of resolution
> Is sicklied o'er with the pale cast of thought,
> And enterprises of great pith and moment
> With this regard their currents turn awry,
> And lose the name of action."

The potentialities of electrophysiology — being an electrophysiologist, I will accentuate the positive first, or should I say the negative — are the ease and precision of measuring time or durations. The sequences of different potential components, for example, can be easily determined and I need not tell you that one can measure times within microseconds. The precision of measuring amplitudes, it can be computed, detects with a surface electrode one single nerve fiber in a population of 10,000. With microelectrodes in the spinal cord, one can also measure the potential of activity of a single nerve fiber or cell and that is one in millions. Then, of course, by various methods one can determine quite precisely various derivatives of these, like velocities, form. I want to start off with three figures which emphasize some electrophysiological studies in the central nervous system. Although they are somewhat far afield from the nerve impulse itself, I am using them to emphasize the relations between structure and function in electrophysiology.

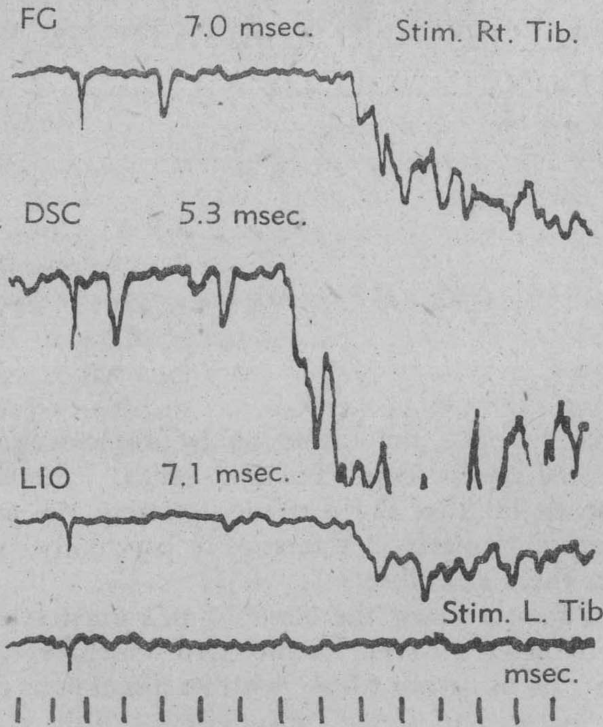


FIGURE 1. Records demonstrating an independent spino-olivary tract which ascends from the lower spinal cord levels. [H. GRUNDFEST, unpublished; preliminary note, *Federation Proc.* **5**, *38 (1946)*].

The first (Figure 1) are simply some records from three loci in the medulla when stimulating a peripheral nerve. In the right hand corner you will see that the stimulus is applied to the right tibial nerve and the uppermost tracing is a record from the dorsal columns. You see that the impulses arrive from the nerve up to the medulla in 7 milliseconds. The precision of this time measurement is within a tenth of a millisecond. The next record is of another tract, the dorsal spino-cerebellar, and the time of arrival is 5.3 - 5.5 milliseconds; then below is a record with an electrode deep in the medulla in a region which is coextensive with the inferior olive. It is found only on the opposite side and is the only other major potential which is found in the medulla, for the particular stimulus used. The reason I introduced this figure in the first place is that this represented a discovery of a tract which had not been suspected in the anatomical literature on spino-olivary tracts. As these records show it is a rapidly conducting crossed tract, and as other experiments show it crosses very high in the medulla. It is a relayed tract and one can tell from various combinations of electrophysiology

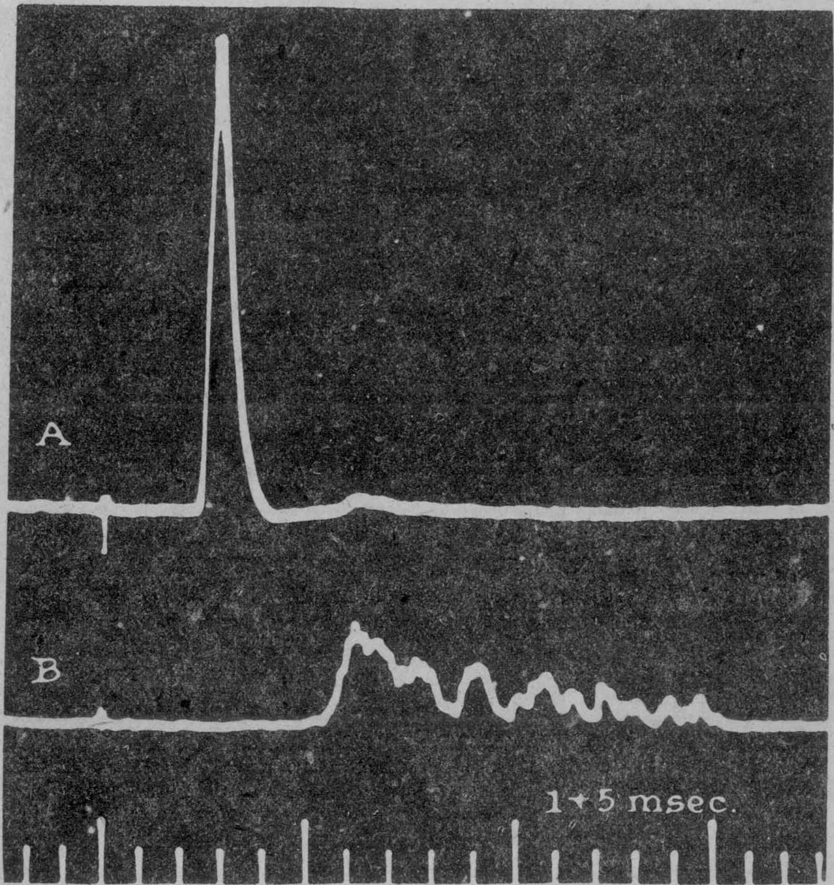


FIGURE 2.* Monosynaptic activation of motoneurons by large proprioceptive afferent is shown in the upper record. Skin afferents, on the other hand, activate the motoneurons only through multisynaptic arcs (lower record). [LLOYD, D. P. C.: *J. Neurophysiol.* **6,** *111 (1943)* Fig. 5].

with surgical procedures where it lies in the spinal cord and what some of its properties are. This sort of electrophysiology I think can be, but has not as yet been, of the greatest use in discovering anatomical structures and in studying the complex functioning of the organism.

The next figure (Figure 2) shows a record of reflex response. It is one of Lloyd's records of the motor reflex obtained by stimulating various afferent nerves. The upper tracing is of a motor nerve reflex discharge produced by stimulating the afferent nerve from muscle and the second shows the reflex response to stimulating a skin sensory nerve. One can see that the time relations are different

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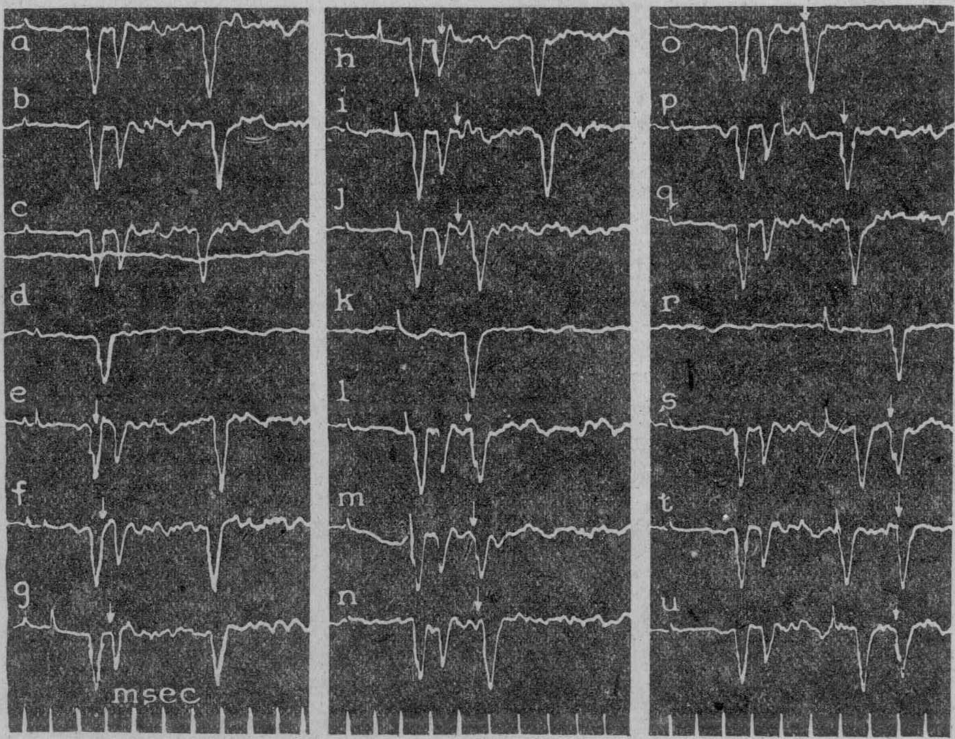


FIGURE 3.* Synaptic organization of cells responsible for activity in the dorso-lateral funiculus (Flechsig's tract). Description in text. [GRUNDFEST, H., AND CAMPBELL, B.: *J. Neurophysiol.* 5, 275 *(1942)* Fig. 7].

and that the form of the response is quite different. These differences were hinted at from anatomical considerations but were not well demonstrated until this type of electrophysiological data made it possible to do so.

The third figure (Figure 3) of this series is a record of single fiber spikes in the dorso-lateral column of the spinal cord with needle electrodes. One picks up spikes of individual tract fibers or sometimes of two fibers. These are post-synaptic discharges after relays from the afferent fibers sending off collaterals to Clark's column or to cells somewhere thereabouts.

From these responses one can work out what kind of synaptic configuration must exist in that particular system. Not only that, but you will notice that records a, b, and c, which are all alike, come from stimulating one nerve. Uniformly, there is a repetitive action sequence, with characteristic and different intervals. Records d, k,

*This figure reprinted through the courtesy and with the permission of the Journal of Neurophysiology.

and r show the lone response from stimulating another nerve. In the subsequent records the two stimuli are pitted one against the other and one can tell by their various interactions that we are dealing with the same synaptic system. For example, in e, the response to the stimulus that would ordinarily produce the response of d is missing because the synaptic system is already occupied and is, therefore, partly refractory. I would like to call your attention finally to record j. Inserting the extra stimulus into the first response, an extra response appeared like that in d, a little bit later than it should have developed. But when it appeared the last response of the repetitive sequence to the first stimulus disappeared. From records such as this, one can predict what relatively complex anatomical configurations can be expected and one can study what kind of synaptic properties are present in that system. I have used these three records simply to show a rather complex series of systems where relations of structure and function can be worked out by electrophysiology.

Among the general potentialities of electrophysiology is the fact that since electronic methods have been developed, the technical flexibility of electrophysiology has been increased a great deal. Measurements that were not impossible but rather difficult to make previously are now made routinely and actually as classroom demonstrations. You may remember that Johannes Muller predicted around 1840 that one could never measure the velocity of the nerve impulse and then about six years later Helmholtz, who was a student of Muller's, actually measured it.

Helmholtz was a great scientist in every way and he measured the event in nerve rather simply with an ordinary smoked drum, and with his ingenious gadgets, the Helmholtz coil and pendulum. Before the advent of the modern methods one could even measure form. It was again rather difficult, rather involved, but not impossibly so. The early measurements of form were done about 1886 by Bernstein with his differential rheotome.

As far as amplitude was concerned measurements were essentially hopeless until electronic methods came along. Accurate amplitude measurements were not possible really without electronic methods because these bio-electric potentials are produced by high impedance generators, whereas all that was available in the earlier days, with the exception of the intermediate range of the capillary electrometer, were current operated devices. The result was that the current that was drawn for the deflection distorted the potentials that one measured. Even at the present time electronic instrumentation has to be designed very carefully, especially in certain problems. For example, in measurements of the trans-membrane potentials, the instruments have to be designed so as not to distort the time course and the magnitudes we want to measure.

*Fremont-Smith:* Would you say the use of practically every instrument carries with it certain assumptions which are not always made explicit?

*Grundfest:* If the capabilities of the instrument are such that it is more high powered than you need, then the assumptions become negligible.

*Fremont-Smith:* With respect to power?

*Grundfest:* Yes.

*Fremont-Smith:* But there might be other assumptions with respect to form or otherwise that are not? I just throw that in. Perhaps we should not discuss it now in too great length. It seems to me that the use of an instrument is based on theoretical construct of some sort in which the basic underlying assumptions are often not explicit and sometimes looking for those is useful.

*Grundfest:* I would like to hear some discussion on this. I would say that in electrophysiology proper this is not essentially a problem. In some of the devices which use electrical methods, for example, I suppose in the oxygen electrode, in transducing oxygen concentration into electrical terms one has to be careful in avoiding such pitfalls, but by and large in straight electrophysiology I should not think that is a problem.

*Brink:* Is it not always true that test signals of a known kind are employed to determine what are the response characteristics of an apparatus? Theoretical considerations enter into the design, and practical compromises enter into the construction of an instrument but its final performance is always put to the test with a known signal. Thus, the effect of source impedance upon the shape and size of the action potential is ascertained by putting a known signal into the measuring circuit when its input is shunted by a similar impedance. As another example, the use of the oxygen electrode requires a calibration curve obtained by making measurements in solutions with known oxygen concentration. In addition, a control must be made to show that all of the measuring current is derived from the electrolysis of oxygen. In all instances that I can think of there is a primary physical or chemical standard with which the measured quantity is compared under similar conditions. This identification may be made by direct substitution, as in an impedance bridge. Or, the identification may be made by comparison with a previously established calibration curve. In every instance, the use of the instrument corresponds to comparing an unknown item