the field it covers, which is fairly well delimited. But it is mostly due to the thoroughness of the author and his clarity. No matter what difficulties the reader may find himself entangled in, he will be sure to find, somewhere in the book, a footnote which will untangle him.

PHILIP M. MORSE
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

SCIENTIFIC APPARATUS AND LABORATORY METHODS

A UNIVERSAL PRECISION STIMULATOR[1]

MODERN advances in the field of nerve physiology, involving high amplification of the action potential and its visual recording by means of the cathode ray oscillograph, have revealed that the customary methods of stimulation, especially at high rates, are unsatisfactory. Induction coils, condenser discharge systems, or in fact any system in which the essential circuit is interrupted by a mechanical key must of necessity prove unsatisfactory because keys do not close or open exactly the same each time, especially if they carry an appreciable voltage or current. Furthermore, the ordinary key will not operate accurately at frequencies greater than fifty per second. This contact difficulty is particularly serious when just-threshold responses are being observed at high amplification.

At the end of his very valuable review of all known methods of stimulation, Lullies[2] offers the opinion that the only satisfactory general methods of producing shocks of any desired characteristics are those involving photoelectric cells, such as that recently described by Nicolai.[3] In this method a rotating cylinder, patterned after the shape of the shock desired, interrupts a beam of light falling on a photocell, modulating an amplifying system, thus producing a shock. We evolved a similar apparatus independently, but abandoned this general method because of the extreme difficulty of obtaining quick shocks at low rates of stimulation, and because the large capacity between the stimulating circuit and ground makes the system unsatisfactory, especially for use with the cathode ray oscillograph. The gas discharge tube method is undesirable because of this capacity effect and because of the great difficulty of synchronizing the shock with externally applied excitation. We believe that the non-mechanical method described below[4] successfully overcomes all these difficulties.

Depending upon the position of switch S, the stimulator may be made to operate in either of two manners: (1) as a self-excited oscillator capable of stimulating at any desired rate, from once every few minutes up to 400 per second, or (2) by means of external excitation from any contact, such as that on the synchronizing rotator usually employed in connection with the oscillograph. We find this switch extremely handy. For example, in work on the effect of rapid stimulation on the after-potential of nerve, throwing it toward the short-circuiting position causes the nerve to be stimulated at any rapid rate desired; then, in order to examine the after-potential at any instant during the period of rapid stimulation, one has only to throw the switch in the other direction, in which case, with properly arranged amplification and synchronization, the after-potential may be examined or photographed. Switching back again to the short-circuiting position causes rapid unsynchronized stimulation to be resumed, the entire interruption lasting only a few seconds.

Considering the apparatus first as a self-excited oscillator, the essential mechanism is as follows: A condenser C charges through a resistance R until the critical ignition voltage of the Thyratron is reached, a value controlled by the grid bias, P. Having attained this potential, the mercury vapor becomes ionized, permitting condenser C to empty itself into the primary of T. This heavy current surge, having emptied the condenser, the Thyratron de-ionizes and the cycle is completed.

The current induced in the secondary of T then serves to stimulate the nerve or muscle, the intensity of the shock being determined by the relation of the variable resistance Ω to the fixed resistance, ω. If a L and N, four dial, 10,000 ohm resistance box is used for Ω, the strength of the shock may be graded in extremely small steps over a very wide range. This arrangement is particularly useful for work where the intensity of stimulation must be very accurately adjusted, as in studies on the single axon response. Actually, assuming a fairly high tissue resistance, the shock strength may be made almost directly proportional to Ω, by substituting a similar four dial resistance box for the fixed resistance, ω, and by adjusting the setting each time on Ω and ω so that the sum of the two resistances remains constant.

If the stimulator is to be actuated by an external contact, such as that on the rotator of the usual oscillograph synchronizer, the switch, S, must be thrown so as to include the secondary of the small step-up

[1] From the Department of Zoology, Washington University, St. Louis, Missouri.

[2] H. Lullies, *Handb. d. biol. Arbeitsmethoden*, Abt. V, Teil 5 A, Heft 6, 937, 1931.

[3] L. Nicolai, *Pflügers Archiv*, 225: 131, 572, 1930.

[4] The construction of this apparatus was made possible by a research grant to Washington University by the Rockefeller Foundation.

transformer, t, in the grid circuit, and the grid bias must be adjusted sufficiently negative to prevent automatic discharges. Upon closing contact, Ct, a surge is induced in the secondary of t, which is sufficient to ionize the Thyratron, thereby producing a shock. Since the Thyratron is activated only by a positive grid surge, either the make alone or the break alone will bring about ionization; this prevents stimulation by *both* the make and the break of the contact. It should be noted that the shock is absolutely independent of the character of the contact made through Ct. If contact is made at all, the Thyratron will ionize, and the shock produced will have characteristics determined only by the plate circuit.

In the manner just described, it is possible to apply this stimulator to the usual oscillographic equipment, simply by connecting the contacts of the rotating synchronizer, in the primary circuit of transformer t. Shocks are thus synchronized with the spreading mechanism and each nerve impulse is recorded on the oscillograph tube.

At high rates of stimulation it is obviously impossible to obtain synchronization by the usual mechanical means. We have therefore designed an entirely non-mechanical system by means of which each shock produced by this stimulator may be synchronized automatically with a spreading circuit.[5] By the use of a master oscillator, it is possible to vary the frequency of stimulation and of spreading, the speed of the line, and the position of the image on the tube, all independently. Such synchronization of each action potential at high rates of stimulation greatly facilitates photographic recording of fast waves.

[5] We expect to publish the details of this circuit shortly.

This stimulator may truly be called universal for the following reasons: (1) The rate of stimulation may be varied without changing the shape or the intensity of shock, simply by changing the resistance, R, or the "B" voltage; (2) the intensity of the shock may be changed without affecting any of the other characteristics, by adjustment of resistance Ω; (3) the shape and duration of shock may be varied by changing the condenser C, or by replacing the primary of T, by a readily interchangeable coil of different characteristics; (4) the duration of the shock may be reduced to a value less than 0.1σ because of the rapidity of the ionization of the mercury vapor; (5) owing to the fact that currents as high as 25 amperes may be passed momentarily by the Thyratron, high intensities of shock are realizable; this is a necessary feature if the shock is to be of short duration, and is a feature not possessed by other methods using gas discharge tubes, such as neon tubes; (6) the shock produced when the mechanical contact is closed is entirely independent of the nature of the contact; (7) owing to the fact that the secondary of T is not connected to ground, but is free floating, the shock

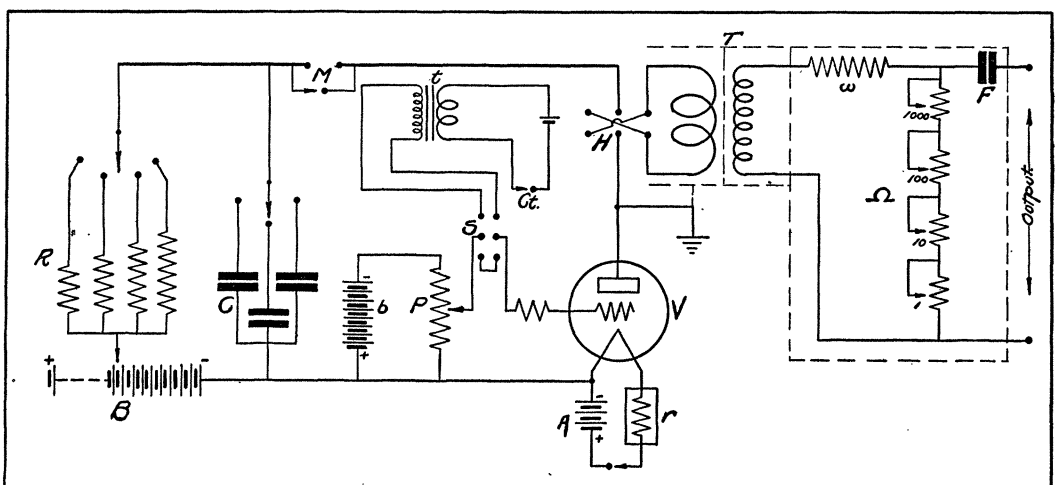

FIG. 1

A, 6 volt storage battery; (the use of alternating current and transformer to heat Thyratron filament is avoided because of the interference introduced into the oscillograph at high amplification); b, bias battery; B, 45–180 volt "B" battery; C, bank of 10 condensers from .001 to 2 m.f.d.; Ct, mechanical contact (synchronized with oscillograph spreader); F, condenser to block polarization currents; H, switch to reverse direction of shock; M, terminals to marking key for time recording; P, potentiometer to control ignition voltage of Thyratron; ω, fixed resistance (2,000 ohms); Ω, 4-dial L–N 10,000 ohm resistance box; r, 5 amp. ballast resistor; R, resistor bank (50,000 to 5 meg); S, double pole double throw switch; t, 16:1 step-up transformer; T, air core transformer; V, Thyratron tube, type F.G. 57.

artifact as seen on the oscillograph tube is reduced to an absolute minimum.

Finally, it might be pointed out that the circuit shown in Fig. 1 may find numerous other applications besides that of nerve or muscle stimulation. For example, by connecting an electro-magnetic marking key to the binding posts at (*M*), it is possible to record the moment of stimulation on a kymograph or similar apparatus. Furthermore, the unit may be calibrated and adjusted to mark any desired time intervals, from a frequency of once in fifteen minutes to the limiting frequency of the key. The entire apparatus, equipped for use as a stimulator and as a time recorder, may be enclosed in a small portable box suitable for research or for student use. If the device is to be used for nerve or muscle stimulation without oscillographic recording, the Thyratron filament may be heated by alternating current through a small transformer, rather than by a storage battery. The "B" batteries may likewise be replaced by an A.C. power pack, thus enclosing power supply and all in one box. Used as a master time recorder such a unit will turn out sufficient energy to operate a number of marking keys of the usual type.

OTTO H. A. SCHMITT
FRANCIS O. SCHMITT

SPECIAL ARTICLES

EXPERIMENTS UPON THE CAUSE OF WHOOPING COUGH[1]

IT is an accepted observation that it is frequently impossible to differentiate the symptoms and signs of the catarrhal stage of whooping cough from those of the common cold.[2]

Although the Bordet-Gengou bacillus is widely regarded as the specific etiological agent of whooping cough, it is fair to say that carefully controlled proof of this belief is scant. With the exception of the report of Sauer and Hambrecht,[3] in which it is stated that a characteristic paroxysmal cough had been produced in eight out of twenty-eight monkeys inoculated with *B. pertussis,* the reports of the experimental reproduction of this disease in animals are open to serious criticism.

On the other hand, the epidemiological, immunological and pathological aspects of whooping cough have led many to believe that a filterable virus might play a rôle as the causal agent. Recently this view has been stressed by McCordock,[4] who reports the finding of intranuclear inclusions in the lungs of twelve out of thirty-five patients with whooping cough, who had succumbed to pneumonia, which not infrequently occurs in pertussis. He suggests "that the possible rôle of a filterable virus must be considered in this disease."

It is evident that final judgment in regard to the etiological agent in whooping cough has not been reached, and it was with this in mind that we commenced our investigations upon the problem of pertussis.

Chimpanzees have been used in all the transmission experiments because of their well-known susceptibility to human diseases. During experimental periods the animals were in strict isolation, and rigorous precautions against cross infection were exercised by the attendants and observers.

Three apes, inoculated by spraying their throats with either Berkefeld V, W, or Seitz filtrates of sputum from early human cases of whooping cough and by subcutaneous inoculations of citrated blood from the same patients, developed febrile upper respiratory catarrhs after incubation periods of from five to seven days. A transfer of this catarrhal infection to a second ape was made by spraying its throat with a Berkefeld W. filtrate of the rhinopharyngeal washings from an ape infected with human filtrate. Two apes inoculated with unfiltered pertussis sputum developed similar catarrhal affections after two or three day incubation periods. These catarrhs differed only in minor points, such as length of incubation period, and absence of leukocytosis from the typical picture of experimental common colds in the apes. No cough occurred during or following these affections with one exception, which will be noted later. Cultures of all filtrates remained sterile on appropriate media and Bordet bacilli were cultivated in each instance from the unfiltered sputa.

One of the two apes inoculated with unfiltered sputum developed a second catarrhal affection thirty days after being inoculated. Within a few days a typical paroxysmal cough appeared and was accompanied by a leukocytosis and a marked absolute increase in the lymphocytes. Cough plates on Bordet medium on several occasions showed numerous Bordet bacilli. The cough lasted for seven weeks. Another

[1] From the Departments of Pathology and Bacteriology, Medicine and Pediatrics and the Biological Laboratory of the John J. Abel Fund for Research on the Common Cold, The Johns Hopkins University Medical School, Baltimore, Maryland.

[2] "Osler's Principles and Practice of Medicine," McCrae. Tenth edition. D. Appleton and Company, New York.

[3] L. W. Sauer and L. Hambrecht, *Am. J. Dis. Child.,* xxxvii: 732, 1929.

[4] H. A. McCordock, *Proc. Soc. Exp. Biol. and Med.,* xxix: 1288, June, 1932.