No attempt is or can be made at this time to translate the results of these experiments in terms appropriate for human application. They are reported, however, because we believe they represent the first definite evidence of significant protection with human convalescent serum under the experimental conditions.

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Electrical Rectification in Single Nerve Fibers.

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The electrical resistance of an ordinary conductor is independent of the magnitude or direction of a current sent through it, and a current may pass with equal ease in either direction. There have been suggestions, however, that in a nerve fiber membrane, current may pass more easily in one direction than in the other, or that the nerve fiber membrane behaves as a rectifier rather than a simple resistance.

Recently, Cole and Baker,[1] and Cole and Curtis[2] demonstrated rectification in the squid axon, using alternating current bridge methods and the needle electrode technic. Another paper, Cole,[3] shows that the previous failure of Cole and Hodgkin[4] to observe rectification in this axon was due to the fact that only small currents had been used and to the fact that the effect under the anode was approximately equal and opposite to the effect under the cathode, thus neutralizing it.

By killing one end of the nerve fiber, neutralization of rectification under one electrode by that under the other can be avoided, and it should be possible to observe rectification directly by means of a much simpler technic involving a direct current Wheatstone bridge.

The giant nerve fiber of the hindmost stellar nerve of the squid, *Loligo pealii,* was used throughout the experiments. It was care-

1 Cole, K. S., and Baker, R. F., *J. Gen. Physiol.*, 1941, **24**, 535.

2 Cole, K. S., and Curtis, H. J., *J. Gen. Physiol.*, 1941, **24**, 551.

3 Cole, K. S., *J. Gen. Physiol.*, 1941, **25**, 29.

4 Cole, K. S., and Hodgkin, A. L., *J. Gen. Physiol.*, 1939, **22**, 671.

fully dissected away from the smaller nerve fibers under sea water with the aid of a binocular microscope. Immediately after dissection the axon was threaded through a glass U tube filled with oil. Then the U tube was suspended by means of a glass rod cemented to it in such a way that one end of the fiber dipped into sea water, where it remained in good condition for many hours, and the other end into KCl isosmotic with sea water (0.52 M), which injured that end. The interelectrode region was about one cm and lay in oil. In some experiments a test solution, such as cocaine, was substituted for the sea water.

Two calomel electrodes lead to the measuring circuit, which consisted essentially of a direct current Wheatstone bridge (Fig. 1). The resting potential of the fiber was first balanced out by a potentiometer, P_2, using the bridge galvanometer, G. Then the variable resistance, R_3, was varied until balance was obtained in a galvanometer, G, used as a null point instrument, when a potential was applied to the bridge by means of a Leeds and Northrup student type potentiometer, P_1. The circuit included a switch, S, for reversing the direction of the current sent through the fiber.

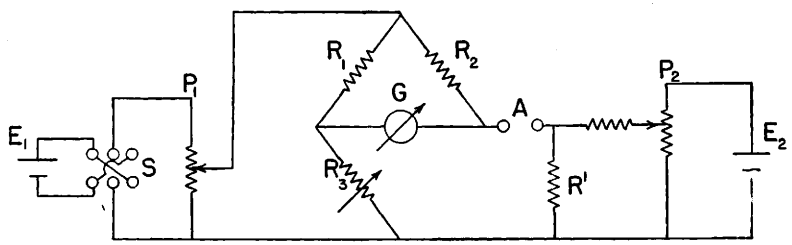

FIG. 1.

Measuring circuit, consisting of a D.C. Wheatstone bridge with ratio arms: R_1, 2000 ohms, and R_2, 5000 ohms; variable resistor, R_3, and galvanometer, G. E_1 and E_2 are 1.5 V. dry cells; S is a reversing switch; P_1, a student-type L. and N. potentiometer; P_2, a slide wire potentiometer; R^1, a 100 ohm resistor. A represents the axon.

A reading was made in the following way. After the potentiometer, P_1, had been set at the desired value, the reversing switch, S, was closed for an instant on one side. If a movement of the galvanometer needle occurred, showing that the bridge was off balance, the variable resistance, R_3, was reset, the amount of change necessary being estimated from the extent of the galvanometer needle swing. When balance was obtained the switch, S, was closed momentarily on the other side and a similar reading obtained for a current flowing in the opposite direction. Polarization of the fiber was minimized by this reversal of the current. During a run there were frequent returns to a reference E.M.F. value so that any shifting of

values with time during the run could be compensated for in the calculations. Every effort was made to send currents in for short times only and to allow relatively long and equal intervals between readings so that the condition of the fiber did not change materially even though the currents used were often considerably over rheobase. (Under these conditions the rheobase was in the range 1-10 μ amperes.) With such treatment a fiber usually lasted many hours, but each run required about 20 minutes.

Experiments were done on 31 single nerve fibers. The figures represent typical results. It was possible to balance the resting potential to within 0.1 mv. With the lowest currents sent through the fiber the bridge could be balanced to within 25 ohms, which was usually about 0.1%. With larger currents the precision was correspondingly higher.

The resistance of the fiber was determined as a function of impressed E.M.F.'s and the data are plotted as resistances vs. currents, Figs. 2 and 3.

When the fiber is completely dead, it follows Ohm's Law, and resistance is independent of current, Fig. 2D. When the fiber is alive, it does not follow Ohm's Law, and the resistance depends upon the current, Fig. 2A, 2B, and 2C. This means that the live nerve fiber is a rectifier and allows current to pass more easily outward than inward. As the nerve fiber dies, the fiber shows less and less rectification.

It was possible to correlate rectification with resting potential changes and excitability by means of simultaneous readings on the same fiber, Fig. 2. As time elapses, the resting potential of a fiber approaches zero. Excitability was measured by recording action potentials with a cathode ray oscillograph set-up. In Fig. 2A and 2B, the nerve fiber was excitable. In Fig. 2C there was evidence of local response, but no propagated impulse. In Fig. 2D, not even a local response was evident and there is no rectification.

Rectification also decreases when the axon is anesthetized, and this loss is partially reversible, Fig. 3. In Fig. 3A, the axon was in sea water with a good resting potential present. When 1.5% cocaine · HCl in sea water immersed the end which was formerly in pure sea water, the resting potential dropped and rectification decreased, Fig. 3B. When the experimental end was returned to sea water, the resting potential rose and rectification returned somewhat, Fig. 3C. When the experimental end was again treated with cocaine, Fig. 3D, rectification again decreased, but this was irreversible, Fig. 3E, since these runs were all made on the same axon

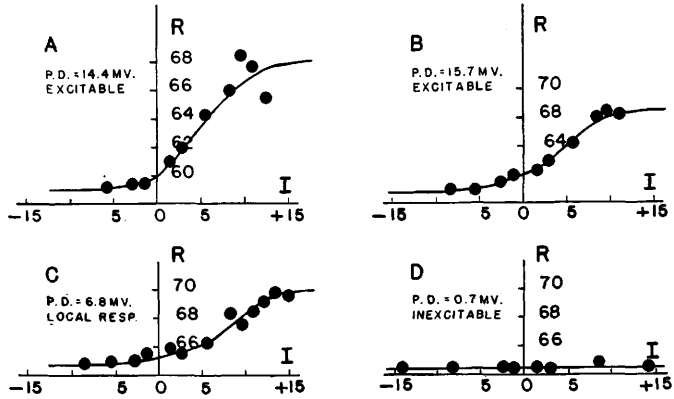

FIG. 2.

Loss of rectification with time in the squid giant nerve fiber. Time after completion of dissection: A, 6 min; B, ¾ hr; C, 2½ hr; D, 6½ hr. Current in microamperes, I, *vs.* resistance in thousands of ohms, R. Positive currents indicate that positive electrode is on uninjured portion of the nerve fiber. Resting potentials and excitability are noted for each run.

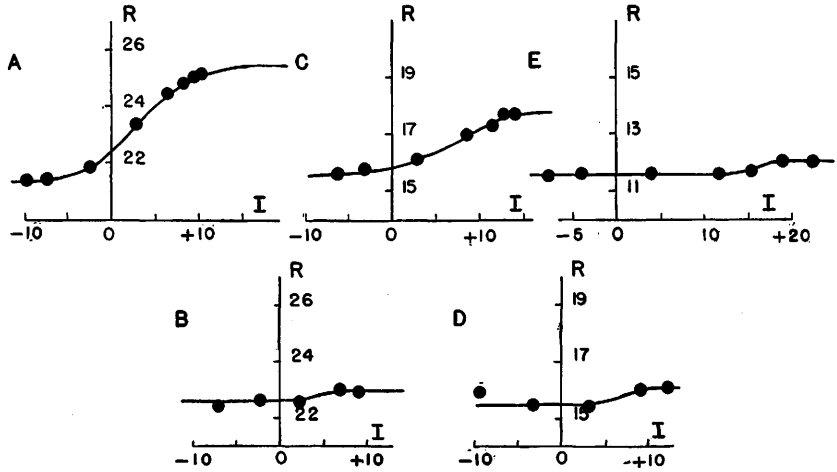

FIG. 3.

Partially reversible loss of rectification in the squid giant nerve fiber upon narcotization with cocaine • HCl in sea water. Time after completion of dissection: A, 1 hr; B, 1½ hr; C, 1¾ hr; D, 2¼ hr; E, 2½ hr. Current in microamperes, I, *vs.* resistance in thousands of ohms, R. Positive currents indicate that positive electrode is on uninjured portion of the nerve fiber. A, experimental end of fiber in sea water, P.D. = 30.0 mv.; B, experimental end in 1.5% cocaine, P.D. = 13.9 mv.; C, experimental end in sea water, P.D. = 27.4 mv.; D, experimental end in 1% cocaine, P.D. = 13.2 mv.; E, experimental end in sea water, P.D. = 12.8 mv.

and lasted a number of hours. After such prolonged treatment the fiber was no longer able to recover. Similar results were obtained with veratrine sulphate.[5]

[5] For the effect of narcotics upon the membrane resistance of muscle fibers, *cf.* Guttman, R., *J. Gen. Physiol.*, 1939, **22**, 567.

The measuring technic used in these experiments has certain advantages. It is simple and it permits one to use an axon immediately after dissection. The accuracy required is not difficult to obtain. On the other hand, runs take about 20 minutes, and the immediate problem is to speed up the measurements. Also, the procedure consisted in measuring the differences between parts of the fiber in each electrode chamber. No absolute values could thus be obtained since the condition of the part of the nerve fiber in the sea water chamber was always referred to that of the part of the fiber in the chamber containing isosmotic KCl.

The measurements show that rectification is lost when the nerve fiber becomes inexcitable, when it dies, or when it is anesthetized. Rectification thus seems to be associated with the normal functioning of nerve.

Membrane potential[1] and impedance[2] measurements indicate that the rectifier effect is situated in the membrane, and it seems reasonable to assume that membrane conductance is a measure of ion permeability. These measurements then indicate that there is an increased ion permeability under a cathode and a decreased ion permeability under an anode. Interpreting in a similar manner the results of Ebbecke[6] obtained on frog nerve, we find large permeability changes at both anode and cathode, superimposed upon which there was a small permeability difference between the anode and cathode regions. Blinks also studied rectification in the giant plant cell, *Valonia*.[7] Rectification is probably responsible for at least a part of the non-linear potentials obtained by Pumphrey, Schmitt and Young,[8] and termed a "physiological" response by them.

Rectification may assist in explaining various alternating current phenomena in nerve, such as the delay of excitation with alternating currents,[9] alternating current block,[10] and the time of rise of electrotonus being more rapid at the cathode than at the anode.[11] However, the explanation of rectification, itself, is not as yet available. It will probably also be an explanation of the mechanism of the ion permeability of the membrane.

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