WHEN certain tissues, such as nerve and muscle, are perturbed in specific ways they change their properties in a characteristic manner. They are "excitable tissues," and when stimulated they respond. A nerve trunk stimulated electrically may cause the innervated muscle to shorten: something has traveled from the point of stimulation to and then along the muscle, inducing contraction.

BEGINNINGS

By the mid-nineteenth century, Carlo Matteucci had shown that electric currents flowed between the muscle surface and its cut end; the associated voltage between the undamaged surface and a damaged region of nerve or muscle came to be called the "injury potential." Emil du Bois-Reymond had demonstrated not only that both nerve and muscle produced electricity but also that, after appropriate stimulation, they developed "action potentials," transient depolarizations from the injury potential measured at rest; Julius Bernstein found that the rapid decline and rise in voltage lasted only milliseconds. And Hermann von Helmholtz had determined that nerve impulses traveled at roughly 30 meters/second, which is much too slow for electricity passing along a conductor (such as wire), yet far too fast for substances flowing through tubes as thin as nerve.

A plausible explanation for this was provided by Bernstein's membrane theory, which was based on these observations and the new physical chemistry of Svante Arrhenius and Walther Nernst. In 1902 he proposed that plasma membranes served as insulating layers between cytoplasm and extracellular environment, and that
when these membranes were at rest they were selectively permeable to $K^+$ but impermeable to other cations and to all anions. The injury potential then represented a preexisting membrane potential, a diffusion potential for $K^+$ that can be described by the Nernst equation:

$$E_m = -(RT/F) \ln ([K^+]_{in}/[K^+]_{out})$$

where $E_m$ is the membrane potential, $R$ the gas constant, $T$ the absolute temperature, and $F$ Faraday's constant. The injury potential represented this resting membrane potential because the damaged region completed a circuit from the external electrode on the undamaged surface, through the membrane, through the cytoplasm, and out through the leaky damaged region to the second external electrode. That loop was, however, shortcircuited by current passing through the bathing medium from one electrode to the other, so that exact measurements of resting potentials were unobtainable.

To account for action potentials, Bernstein proposed transient and reversible breakdowns of the membrane in which the selectivity to ions was transiently and reversibly abolished. With the consequent general permeability to all ions, the $K^+$ diffusion potential disappeared and the membrane was depolarized toward 0 volts. This action potential was then propagated along the axon by "local circuits" that stimulated further regions of the membrane ahead. Among the consequences of Bernstein's formulation were resting membrane potentials depending precisely on extracellular $K^+$ concentrations and action potentials equaling at most the resting potential in magnitude.

Appearing in the same volume that had Bernstein's 1902 study were two even longer papers by Overton. These included analyses of ionic requirements for muscle activity, from which he concluded that $Na^+$ was required in the bathing medium for excitability. On this basis Overton suggested that the transient flow of current during action potentials might involve an exchange of extracellular $Na^+$ for intracellular $K^+$. But that mechanism entailed a significant cost: "the greatest difficulty in entertaining such a hypothesis lies in explaining how . . . sodium ions should be extruded from the interior of the fibers [for] if some sodium ions enter and some potassium ions leave . . . then the differences between internal and external cation concentration would gradually be leveled out unless there is some mechanism at work which opposes this equilibrium."  

Three further characteristics of propagated action potentials were established early this century. (1) For excitation, a minimal magnitude of current had to pass in a given time: there was a "threshold" for excitation. (2) Stimulation either resulted in an action potential of a distinct magnitude or it did not; action potential magnitude was not a function of stimulus magnitude except as it was above or below threshold—the "all-or-none" characteristic. (3) For a brief time after the action potential, a second stimulus could not excite another action potential. This was called the "refractory period."