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# Physicochemical Mechanisms in Convulsive Reactivity.*

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Since convulsions may be called forth by a great variety of causes, the question presents itself as to whether a common fundamental mechanism exists by which the epileptogenous agents act upon the nerve cells. According to Nernst, Bethe, and others, excitation is due to changes of ion concentration on semi-permeable cell surfaces. These changes in ion concentration are supposed to influence the nerve cells by increasing the cellular permeability (Hoeber, Lillie). One should, therefore, expect that agents which lower the density should also increase the excitability.

In order to study the effect of various epileptogenous agents upon the permeability in living animals (cats, rabbits), a method of measuring the permeability was employed similar to that used on artificial membranes.[1]

The conductivity of the part of the brain under study was determined by using alternating currents of various frequencies. Due to polarization on the cellular surfaces and interfaces the conductivity is the lower, the lower frequencies are used. It can be shown on artificial membranes that the difference in conductivity at a certain high and at a certain low frequency (polarization index $\Delta$†) is increased, if the membranes become more impermeable, and that it is diminished, if the permeability is increased. The measurement of $\Delta$ can, therefore, be used in order to study the permeability of the cellular surface films not only *in vitro,* but also *in vivo,* on animals, or on patients during operations. $\Delta$ is higher in the grey matter than in the white matter of the cerebral hemispheres, indicating the part played by the nerve cells in these polarization phenomena.

A study of the effects of the most important causes of convulsive disorders upon $\Delta$ gave the following results. Anoxemia

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[1] Spiegel-Adolf, M., and Spiegel, E., PROC. SOC. EXP. BIOL. AND MED., 1934, **32**, 139.

† This difference was always expressed in percentage of the conductivity at the lower frequency.

(asphyxia) increases the cellular permeability in the cerebral hemispheres as well as in the subcortical ganglia. Anemia, as produced by ligature of the cerebral arteries, diminishes the conductivity. In the majority of the experiments an initial drop of $\Delta$ was also observed; when the anemia is continued for several minutes, the curve of $\Delta$ may again rise, probably due to coagulation necrosis of a number of cells. Increase of intracranial pressure also lowers the conductivity; this is associated in the majority of the experiments with a drop of $\Delta$. Increase in the state of hydration (*e. g.,* by intravenous injection of distilled water or by artificial alcalosis) increases the permeability, independently of changes in conductivity. This effect is still observed if an increase in intracranial pressure is prevented by trephining the cranium. While alcalosis is accompanied by increase in permeability, acidosis has only a slight effect upon $\Delta$. Hyperventilation acts in a similar way, as does alcalosis. These effects are reversible. Anesthetics and hypnotics, such as ether, chloroform, dial, have the opposite effect; they increase $\Delta$, indicating an increase in density of the cellular films.

The inference is drawn from these experiments that epileptogenous agents may act upon the nervous system by either of the following mechanisms (or by both): 1st. Production of a change in ion concentration on the surfaces of the nerve cells (as for instance by injection of acids). If the change in concentration reaches the threshold, excitation (convulsion) results.

2nd. Diminution of the density of the cellular surface films (as observed in anoxemia, hydration, alcalosis). The increase in permeability of the cell surface that is an important part of the excitation process is facilitated, and the threshold of the cells for metabolic or other stimuli is lowered, the convulsive reactivity is increased. Thus the problem of convulsive reactivity is only part of the more general problem of relationship between excitability and permeability of cellular surface films.