meter allows Granit's tonic and phasic groups to be identified with the two groups defined here by duration of after-hyperpolarization. Hence we may conclude that the tonically discharging motoneurones have a much longer after-hyperpolarization than those phasically discharging. Correspondingly it has been found that the tonic motoneurones respond at a much lower frequency (10–20/sec.) than the phasic motoneurones (30–60/sec.)[5,6].

It has been postulated that the after-hyperpolarization of a motoneurone is responsible for determining the frequency at which it discharges when subjected to a continuous synaptic bonbardment[7]. This postulate is supported by the present evidence that the slowly discharging tonic motoneurones have a much longer after-hyperpolarization than the rapidly discharging phasic motoneurones.

J. C. Eccles
R. M. Eccles
A. Lundberg

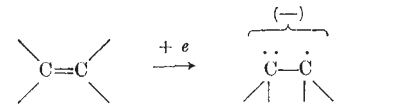
The John Curtin School
of Medical Research,
The Australian National University,
Canberra, A.C.T.
Jan. 4.

[1] Brock, L. G., Coombs, J. S., and Eccles, J. C. *J. Physiol.*, **117**, 103 (1952). Coombs, J. S., Eccles, J. C., and Fatt, P., *J. Physiol.*, **130**, 291 (1955).
[2] Eccles, J. C., Fatt, P., and Koketsu, K., *J. Physiol.*, **126**, 524 (1954).
[3] Eccles, J. C., and Sherrington, C. S., *Proc. Roy. Soc.*, B, **106**, 326 (1930). Hagbarth, K. E., and Wohlfart, G., *Acta Anat.*, **15**, 85 (1952).
[4] Hursh, J. B., *Amer. J. Physiol.*, **127**, 131 (1939). Rushton, W. A. H., *J. Physiol.*, **115**, 101 (1951).
[5] Granit, R., Henatsch, H.-D., and Steg, G., *Acta Physiol. Scand.*, **37**, 114 (1956). Granit, R., Phillips, C. G., Skoglund, S., and Steg, G., *J. Neurophysiol.* (in the press, 1957).
[6] Denny Brown, D., *Proc. Roy. Soc.*, B, **104**, 252 (1929).
[7] Eccles, J. C., "The Neurophysiological Basis of Mind: Principles of Neurophysiology" (Clarendon Press, Oxford, 1953).

Chemical Carcinogenesis

It has been shown that the free-radical content of tissue increases during metabolism[1] and the possible importance of free-radical states in carcinogenesis has been discussed by many authors. In particular, it has been suggested that the free-radical state of carcinogens is stabilized as an ion[2]. The simplest way of producing an ion from a neutral molecule is by the addition or removal of an electron, the former being more likely in tissue owing to the low oxidation-reduction potential[3].

Many compounds have a quinonoid character which predisposes them to take up an electron. Apart from the true quinones, they include many dyes and the 'crossed' systems mentioned by Waters[4] and discussed more fully by me[5]. The E_h of electron addition to such a compound will sometimes correspond to the E_h of tissue, so that a relatively high concentration of free-radical anion can persist under conditions of active metabolism. However, with most of these compounds, there is nothing particularly reactive about the free-radical anion produced by electron addition, beyond its tendency to give up the electron; the original planar mesomerism is retained. It is now suggested that carcinogenic properties arise when the added electron becomes localized in a portion of the molecule which thereby undergoes structural changes and becomes optically active. The example shown is an ethylenic double bond, which can be part of an aromatic system by bond fixation, and can also have polar substituents, as in the 1,2 bond of the known carcinogen 1-hydroxy 2-naphthylamine[6].



Planar inactive Pyramidal (optically active)

The pyramidal anion has a three-electron bond, which is only about half the strength of an ordinary C—C bond; it can therefore undergo further reactions, such as oxidative splitting and linkage to protein. Mesomeric stabilization of the free-radical anion is nevertheless possible because of the similar (pyramidal) configurations of the carbanion (isoelectronic with amino-nitrogen) and the carbon free radical[7]. In the true quinones and dyes a planar configuration can be retained after electron addition because of the possibility of transferring the free radical to carbonyl oxygen or imino-nitrogen. A planar configuration can also be retained with very large aromatic molecules where the added electron is strongly delocalized; these compounds therefore should no longer be carcinogenic. With decreasing molecular size, on the other hand, it seems that more and more polar substituents are required to satisfy the E_h condition, down to the aliphatic carcinogens dimethylnitrosamine and carbon tetrachloride.

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T. Nash

Air Hygiene Laboratory,
Central Public Health Laboratory,
Colindale Avenue,
London, N.W.9.
Dec. 31.

[1] Commoner, B., Townsend, J., and Pake, G. E., *Nature*, **174**, 689 (1954).
[2] Oppenheimer, B. S., Oppenheimer, Enid T., Stout, A. P., Danishefsky, I., and Eirich, F. R., *Science*, **118**, 783 (1953).
[3] Hewitt, L. F., "Oxidation-reduction Mechanisms in Bacteriology and Biochemistry", 6th edit. (Livingstone, Edinburgh, 1950).
[4] Waters, W. A., "Physical Aspects of Organic Chemistry", 4th edit. (Routledge, London, 1950).
[5] Nash, T., *J. App. Chem.*, **6**, 300 (1956).
[6] Boyland, E., and Watson, G., *Nature*, **177**, 836 (1956).
[7] Brand, J. C. D., *Chem. and Indust.*, 167 (1955).

Electron Microscopic Appearance of Fibrin in Thin Sections

The electron microscopic appearances of fibrin were first described by Hawn and Porter[1] and Hall[2], and these workers showed that *in vitro* fibrin had an axial periodicity of between 220 and 230 A. and a fibril width of approximately 150 A. Since that time, Levene[3] and Still and Boult[4] have investigated fibrin in pathological material and have shown that it possesses the same characters as artificially produced fibrin, and moreover seems to be bound in bundles which have a marked tendency to fold.

The appearance of fibrin in ultra-thin sections is, however, less well known. We have found when sectioning material which has taken all the specific fibrin stains that two electron-microscopic appearances are apparently distinguishable. The first (see