(60 min in 1·0 mmoles CTMB/L BFR) renders the surviving constituent fibers susceptible to reversible block by curare, neostigmine, and acetylcholine.[2-4] For example, after the CTMB pretreatment, 4×10^{-4} M neostigmine effects about a 73 per cent reduction of the A-potential in 30 min.[2] Though certainly not proving the original hypothesis, the uptake data reported here are in excellent agreement with the concept that ionic surfactants diminish permeability barriers and thus enhance the uptake of substances that are normally constrained to the extracellular spaces.

Department of Physiology,
University of Colorado School of Medicine,
Denver, Colo., U.S.A.

RAYMOND R. WALSH
JOHN E. BURTON

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Charge transfer, hydrogen bonding and drug action

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THE recent work of Lyons and Mackie on the electron-donating properties of reserpine and the phenothiazine tranquillizers[1] raises once again the question of a possible causative relation between charge transfer and drug action. As they pointed out, an immediate difficulty is that phenothiazine itself is not a tranquillizer, although it is just as strong an electron donor as its active derivatives. This note is intended to show how the original suggestion regarding charge transfer and drug action[2] can be preserved, by combining it with one of the classical postulates, i.e. hydrogen bonding.

We suggest that specific drug activity can result when a strong electron-donor or -acceptor molecule is provided with a side-chain capable of hydrogen bonding in the appropriate sense. Besides helping to anchor the drug to its substrate, the hydrogen bond is postulated to activate the substrate towards electron transfer in the complementary direction; in this way a simple irritant or fungicide can become a true drug (phenothiazine itself has anthelmintic properties). This suggestion is based on the fact that acridine becomes a strong electron acceptor in the presence of weak acids, the experimental conditions favouring hydrogen bonding rather than ionization.[3]

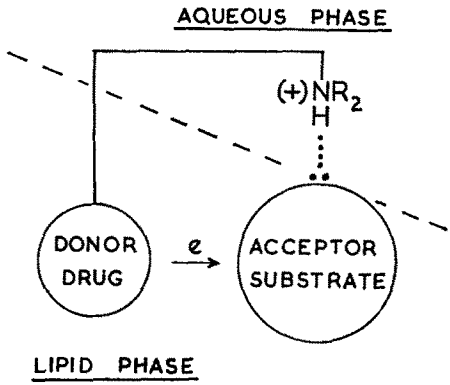

FIG. 1.

The presumed mode of action of chlorpromazine, for example, is illustrated in Fig. 1, the interface between lipid and aqueous phases being indicated by a dashed line. The substrate is assumed to have a lone pair conjugated with some aromatic centre, which can bond with the active hydrogen of the ionized drug side chain. Various other combinations of nucleus and side chain can be worked out, and analogues of known drugs can be proposed in which either the phase or the direction of electron transfer is reversed. For example, the lipid-phase analogue of chlorpromazine would have a side chain terminated, not by an amino group but by a lipid-soluble hydrogen donor such as resorcinol. It is hoped to present a more detailed study elsewhere.

T. NASH
A. C. ALLISON

Medical Research Council Air Pollution Research Unit,
*St. Bartholomew's Hospital Medical College, London, E.C.*1.
and
National Institute for Medical Research,
*Mill Hill, London, N.W.*7.

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