Tuesday. August 22

1 Drugs and Membranes. Introductory Remarks. C. A. M. HOGBEN (U.S.A.).

2 The Molecular Architecture of Cell Membrane and Cytoplasmic Membranes. F. S. SJÖSTRAND (U.S.A.).

Indirect methods revealing certain properties of the cell membrane combined with direct morphological analysis of the structure of various types of membranes by means of high resolution electron microscopy have allowed proposing models for the molecular architecture of these membranes. Electron microscopy, furthermore, can demonstrate structural changes in the membranes that can be correlated to variations in functional condition. The hypothesis will be discussed according to which the membranes represent enzymatically active structures involved in, for instance, oxidative phosphorylation in mitochondria and protein synthesis in certain other cytoplasmic membranes.

Membranes of various types represent the most common and spectacular structural components of the cytoplasm of cells and might be of great importance for co-ordination and regulation of the enzymatic activities of cells. The hypothesis regarding their functional importance can be tested. The role of the various membranes in connection with the action of drugs could be further explored by combined biochemical and morphological analysis. Possible approaches to this problem will be discussed.

3 Passage of Materials across Biological Membranes. H. H. USSING (Denmark).

A survey of current research on cell permeability indicates the lipoid-pore concept of the membrane as originally advanced by Collander and Bärlund is still tenable if it is supplemented by the concepts of active transport and facilitated diffusion.

The evidence for the existence of pores in the cell membranes or surfaces is of two kinds: (1) The dependence of diffusion rates on molecular diameter (Collander *et al.*, Pappenheimer *et al.*, Solomon *et al.*); and (2) The existence of "solvent drag" on molecules diffusing in an osmotic water stream through the membrane, a phenomenon which requires a continuous water phase (Ussing; Koefoed Johnsen and Ussing; Andersen and Ussing).

It is pointed out that "sandwich-membranes" consisting of two or more layers with different pore-sizes and different solubility properties may obtain a very high degree of specificity.

The concept of active transport as well as that of facilitated diffusion constitute transport phenomena which cannot be predicted on the basis of the lipoid-pore theory. They differ in that the active transport processes consume metabolic energy whereas the facilitated diffusion processes do not. Kinetically, both types of transport can often be described satisfactorily on the basis of specific membranes carriers, but it is better for the time being to consider the carriers only as abstractions. Despite our lack of detailed information concerning the molecular basis of these processes, the two concepts have proved themselves exceedingly useful in organizing a confusing array of observations into a framework from which predictions can be made.

Finally, it is pointed out that although the phenomenon of pinocytosis may be of importance in special cases, it is extremely unlikely to be among the main vehicles of membrane transport.

4 Biochemical Aspects of Transport. L. E. HOKIN and M. R. HOKIN (U.S.A.).

Evidence will be reviewed favouring the phosphatidic acid cycle as the mechanism of the Na^+ pump. In this cycle lipid soluble disodium phosphatidate is formed at the inner surface of the membrane from ATP, diglyceride, and 2 Na^+. Disodium phosphatidate crosses the membrane where it is hydrolyzed by phosphatidate phosphatase, releasing 2 Na^+ into the aqueous phase bounding the outer surface of the membrane. Diglyceride returns to the inner surface of the membrane where the cycle is repeated. There is no direct evidence on the mechanism of return of phosphate to the cytoplasm but it is postulated that in those cells which pump Na^+ in exchange for K^+ the phosphate returns with 2 K^+, and in those cells which pump NaCl the phosphate returns in exchange for two Cl^-. The following will be discussed in support of the cycle: (1) the increased renewal of phosphate in phosphatidate on stimulation of the avian salt gland with acetylcholine; (2) the time course of this increased renewal; (3) evidence that the phosphatidic acid effect is in secretory membranes: (4) evidence that the stimulated renewal of phosphate in phosphatidate is catalyzed by diglyceride kinase and phosphatidic acid phosphatase, both situated in the membrane; (5) the requirement of the cycle for Na^+; and (6) the presence of the phosphatidic acid cycle enzymes in the erythrocyte membrane and the evidence that the cycle enzymes may be components of the Na^+ and K^+ dependent membrane ATPase which appears to be closely related to the Na^+ and K^+ pumps.

5 Enzymatic Aspect of Active Transport of Na^+ and K^+ across the Cell Membrane. J. SKOU (DENMARK).

From peripheral crab nerves a submiscropic particle has been isolated which contains a system fulfilling a number of the requirements for a system involved in the active linked transport of Na^+ and K^+ across the cell membrane.

(1) It contains an enzyme which catalyses the transfer of energy from ATP to the system as an energy-rich phosphate bond.

(2) It has one site where there is an affinity for Na^+ which is higher than for any other monovalent ion and another site where the affinity for K^+ is highest.