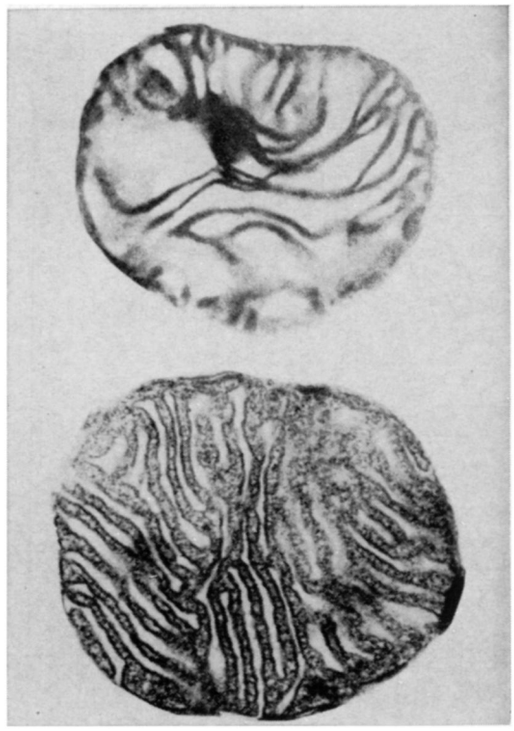
Moving molecules across membranes

Changes in structure may explain mechanism of active transport

by Barbara J. Culliton



Photos: Univ. of Wis.

De-energized (top) and energized membrane.

The transmission of nerve pulses is coupled to a process known as active transport—the movement of sodium and potassium ions across cell membranes. Disruption of the balance between calcium and magnesium ions in heart cell membranes can cause the heart to stop beating. Kidney function and the excretion of waste products from the body depend upon the active transport of sodium and potassium ions in kidney membranes.

Indeed, the active transport of various chemical ions in membranes is vital to maintaining the internal environment of virtually all cells, and maintaining that internal milieu is essential to normal biochemical activity. Active transport, however, is not among the most well known of biological phenomena; nor is it one that is particularly well understood.

"One of the central unsolved problems of biology," says Dr. David E. Green, codirector of the Institute for Enzyme Research of the University of Wisconsin, "is the mechanism by which ions are actively transported across cell membranes and concentrated in the interior spaces." With two colleagues, Drs. John H. Young and George A. Blondin, Dr. Green proposes a new theory to explain that mechanism. Discussed briefly at the recent meeting of the National Academy of Sciences (SN: 5/9, p. 459), details were presented at a June meeting on the chemistry of natural products in Riga, U.S.S.R.

One of the predominant theories of active transport is that cell membranes contain a protein that somehow acts as a pump, moving ions against a chemical gradient as if it were pushing water uphill from a low-level reservoir to a higher one. But that theory is supported more by speculation than by experimental evidence.

From experiments with mitochondria, the energy-producing storehouses of cells, Dr. Green has evidence that disputes the pump theory, replacing it with what he calls a conformational model of active transport. His theory suggests that ions, instead of being pumped uphill, flow smoothly through membranes because of conformational changes in the structure of the membranes themselves. In other words, cyclic variations in membrane structure, in effect, raise the lower reservoir to the level of the higher one, allowing ions to move freely down an electrochemical potential gradient rather than against it.

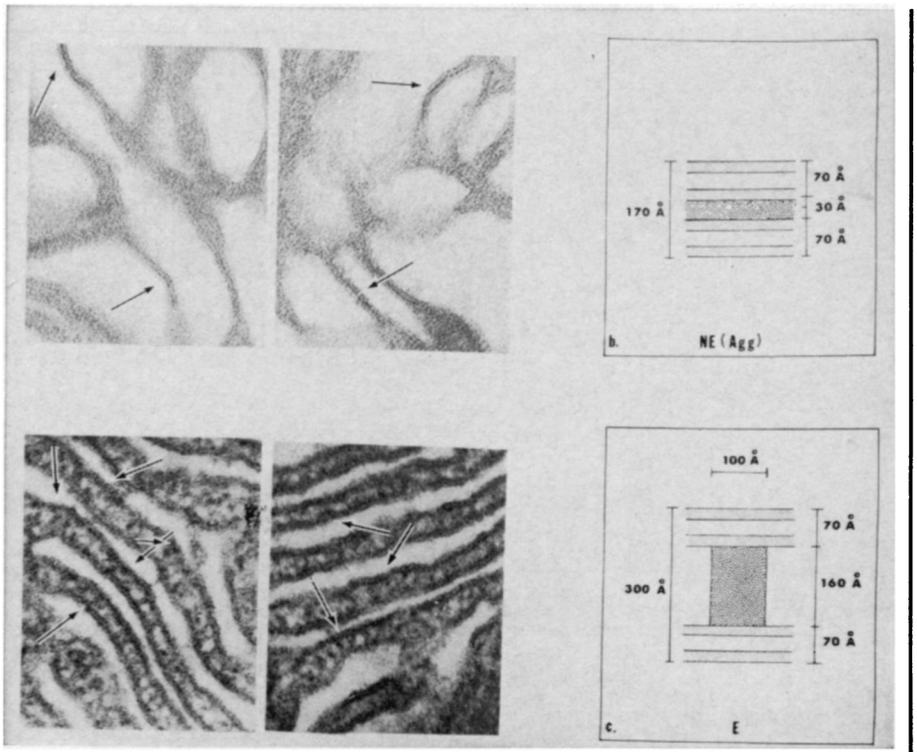
Mitochondrial membranes are built of dumbbell-shaped repeating units of lipids and proteins. According to the conformational model, units of the inner membrane synchronously undergo a cycle of being energized and de-energized. In this cyclic process, the membrane architecture changes. During the energized phase, the lipoprotein repeating units expose binding sites that, like a magnet, pull negatively charged ions such as inorganic phosphate or acetate to them. At the same time, positively charged counter ions move in to neutralize the energy state.

Development of the conformational model of active transport depended upon two prior discoveries. One was understanding of energy transduction in mitochondria. The other was isolation and characterization this year of molecules called ionophores within mitochondrial membranes.

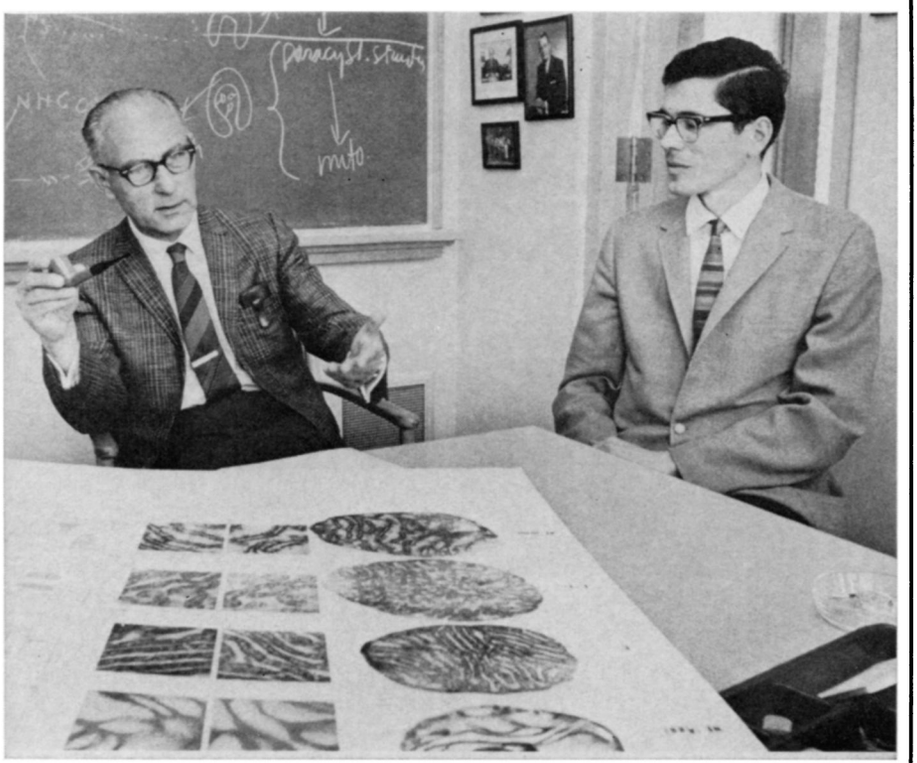
"Ordinarily," Dr. Green explains, "you cannot have a charged molecule through a lipid membrane." But Dr. Blondin, with Dr. Robert M. Hull, also of Wisconsin University, found that ionophores are vehicles that can get them through. They are doughnut-shaped carriers that enclose potassium or sodium ions within their centers and transport them through the membrane. Ionophores, in addition, are ion-specific. Thus, the concentration of potassium-receptive ionophores within a membrane, for example, plays a role in determining the quantities of potassium versus sodium ions that can get through. In individual mitochondrial membranes, these molecules are present in extremely small quantities. Those that were isolated by the Wisconsin scientists came from beef hearts, supplied in almost unlimited quantity by a Madison packinghouse.

Having determined the method by which ions are transported across membranes, Dr. Green and his colleagues went on to show that they are held inside the mitochondria by an electrochemical potential gradient established by the conformational change. In the de-energized phase, ions are released and the cycle begins again.

The key remaining question is whether the conformational model established from these experiments with mitochondria will hold for active trans-



Magnification and diagrams contrast energized and de-energized membranes.



Green and Young: A new answer to a central unsolved problem of biology.

port in all types of cell membranes. While active transport of ions is a central activity to many cells, including nerve, kidney and heart, it is not primary to mitochondrial function in the same way. The main business of mitochondria is making ATP (adenosinetriphosphate), the energy compound of cells. While ATP synthesis is one of the biochemical events associated with the introduction of the energized cycle of the membrane, present thinking holds that the subsequent transport of ions is merely a by-product of that activity in mitochondria. This point and other details of the active transport process in mitochondria have yet to be clarified. Says Dr. Young, "We think our model is essentially valid but we do not have all of the details sewed up." □