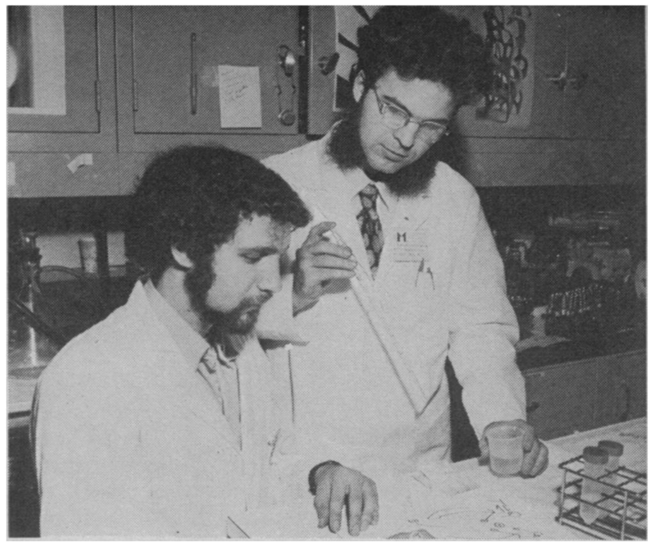
Opening the gate to the nerve cell

Protein channels in nerve-cell membranes may be the passageways for sodium entry



Lionel Demby

Rothschild and Stanley: Gate-in-the-membrane theory.

by Joan Arehart-Treichel

Sometimes life's most elegant activities turn out to be simple in concept. And sometimes the freshest insights into these activities come from young scientists. These facts were borne out at a national symposium on cell membranes, viruses and immune mechanisms held by the Bell Museum of Pathology at the University of Minnesota in June. Two biophysicists from the Massachusetts Institute of Technology—H. Eugene Stanley and Kenneth J. Rothschild—presented an attractive explanation for how the membrane of an excited nerve cell lets sodium into the cell. Sodium is the conductor of electric current inside a nerve cell.

The core of their theory is that strategic proteins on the nerve cell membrane selectively allow sodium ions to enter the cell. They did not attempt to explain how sodium entry into a nerve cell, or excitation of an individual cell, might tie in with the transmission of excitation *between* two nerve cells. Such transmission also appears to involve chemical reactions that take place on the cell membrane.

The MIT biophysicists' concept was well-received by biologists, pathologists and other medical scientists attending the symposium. A pioneeer in membrane work, S. J. Singer of the University of California at San Diego, admitted that the theory, while "conjectural," might have validity. Interestingly, their theory of membrane-sodium action meshes with Singer's fairly new theory of membrane structure that is rapidly becoming accepted.

Singer's attempt to explain cell membrane structure, and the effort of Rothschild and Stanley to explain nerve-cell excitation are extensions of the original membrane model proposed by Hugh Davson of the University College, London, and by James Danielli of the State University of New York at Buffalo some 35 years ago. The Davson and Danielli model holds that lipids are arranged in two layers, with the nonpolar tails of the lipids facing each other, and the polar heads of the lipids facing each side of the cell membrane. This lipid bilayer is then sandwiched between two sheets of proteins. The Davson-Danielli model is notable because it was suggested long before there was experimental evidence to support it. In fact, the clincher for the lipid bilayer came only last year through experiments conducted by Nobel Prize winner Maurice Wilkins of Cambridge University in England.

However, considerable other evidence has been mounting that tends to rule out the static, thin protein crusts on the bilipid layers in the Davson-Danielli model. The proteins in a cell membrane are now known to be globular, or tightly coiled, like little springs or balls. Different kinds of proteins, such as glycoproteins, have been identified in the cell membrane. Quite recently some proteins in the lymphocyte membrane were found to move and cluster in an immune reaction. Also, proteins tightly bound together in crusts could hardly allow ions to pass through a cell membrane into a cell, and such transport is the staff of life for cells. Most crucially, some proteins have been found to extend partially or all the way through the cell membrane. All this evidence, and more, conspires to mix the proteins of the cell membrane in with the lipids, rather than to have them form a sandwich around the lipids. Singer's lipid-globule protein membrane model includes this crucial alteration.

Rothschild's and Stanley's explanation of how sodium enters an excited nerve cell builds on Singer's model, which is an alteration of the Davson-Danielli model. But more than that, the two MIT biophysicists have rallied other experimental evidence to explain sodium passage during cell firing. For example, there is some evidence that nerve membranes have channels through them. Calcium is known to be present in the nerve cell and to keep sodium out when the cell is at rest. But when the nerve fires, sodium rushes into the cell. This calcium-sodium interplay appears specific to the nerve cells. It differs, say, from how sodium helps calcium out of intestinal cell (SN: 4/22/72, p. 263).

So Rothchild and Stanley conjecture that those proteins that extend all the way through the nerve cell membrane might form channels to allow strategic sodium molecules to pass during nerve firing. In other words, polar residues in the protein would ordinarily be bound to calcium ions. But when calcium binding to the protein ions is replaced by, say, potassium-ion binding there is a shift in molecular conformation or shape. Conceivably this molecular shift could cause a protein to open its channel, like a parting of the Red Sea, to allow sodium ions to slip through it, through the cell membrane and then into the cell.

Stanley and Rothschild have dubbed their channeled proteins "permions." They believe the permion theory can explain not just sodium entry into the excited nerve cell, but perhaps other kinds of ion transport through other kinds of cell membranes. If an energy molecule such as adenosinetriphosphate (ATP) is required to bring a certain ion into the cell against a concentration gradient, for example, ATP could conceivably cause the permion to open and close so that the right ions might ooze into the cell.

The Cambridge biophysicists are now faced with the challenge of experimentally confirming their theory. In the next several months they will try to obtain evidence that permions might indeed be regulating ion transport through the nerve cell membrane. They may use lasers to selectively examine proteins in the membrane, both when the nerve cell fires and is at rest, then to examine the proteins for their molecular configurations. They are also aware that the work of other scientists in the membrane field may eventually confirm or negate their theory. James Danielli was about their age when he proposed his membrane model, and he had to wait 35 years to have his vision confirmed. □