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PORES IN THE CELL MEMBRANE

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PORES IN THE CELL MEMBRANE

Molecules and ions pass in and out of the cell through tiny openings in the cell wall. Although the holes are too small to be seen with an electron microscope, their size has been measured experimentally

by Arthur K. Solomon

The living cell carries on a constant traffic with its surroundings. Like every other device, animate or inanimate, that does work, it must take in fuel and excrete waste products. Many cellular activities, such as the contraction of muscle and the transmission of nerve impulses, are accompanied by a shift of ions in one direction or the other. Tracing this pattern of flow is one of the major tasks of cellular biophysics, engaging investigators all over the world.

It is quite clear that the cell's outer membrane is not merely a passive barrier. Under the electron microscope it is revealed as a complex structure about 100 angstrom units thick. (An angstrom unit is a hundred millionth of a centimeter.) Some materials pass directly through the fabric of the membrane, either by dissolving in the membrane or by interacting chemically with its substance. But it seems equally certain that a large part of the traffic travels via holes in the wall. These are not necessarily fixed canals; as the living membrane responds to changing conditions inside or outside the cell, some pores may open and others may seal up. Nevertheless there is good reason to conceive of the membrane as containing, on the average, a uniform number of holes. Thus an understanding of the transport system turns on the question: How big are the holes? Our laboratory at the Harvard Medical School has devoted a good part of the past six years to this problem in molecular biology.

At the outset we had certain clues to the range in which the pore diameter must lie. These came primarily from observations of the behavior of sodium. Blood plasma and other extracellular fluids are chiefly solutions of sodium chloride—ordinary salt. On the other hand, the dominant salt within the cell is potassium chloride. Sodium, which leaks into the cell from the outside, is removed by a mechanism called the sodium pump. The principles of operation of this mechanism are still unkown. Clearly the work that the pump has to do is related to the size of the sodium leak. And if the work load is not to be very heavy, the pore diameter should not be much greater than the diameter of the sodium ion in water.

Both sodium and potassium ions in water solutions travel surrounded by a shell of water molecules. The diameter of the hydrated sodium ion is roughly five angstrom units. Thus the concept of a pore with a diameter of five to 10 angstrom units seemed an attractive working hypothesis.

There are three ways to measure the size of a hole: (1) directly, by placing a graduated scale across the entrance; (2) indirectly, by probing the hole with particles just large enough to be excluded by it; (3) inferentially, from the friction the hole exerts on particles small enough to pass through it. A hole 10 angstroms across cannot yet be resolved, even by the electron microscope. Therefore there was no hope of measuring the pores in the cell membrane directly.

The second method would have been quite simple if the probing particles (that is, individual molecules) were available in an infinitely fine gradation of sizes. But molecular size jumps discontinuously as more atoms are added, and so we could not be sure that the smallest excluded particles would be only minutely larger than the holes.

Accordingly we chose the third approach. It is also difficult; in retrospect it presents substantially greater problems than we had bargained for when we first embarked on the enterprise.

We first set out to measure the speed at which water diffuses across the cell membrane. In itself this measurement could not determine the average size of the individual pores, but it would tell us something about the total cross-sectional area of all of them. Specifically, the rate of diffusion is a measure of the total area of the pores divided by their average length: A/L.

For our experiments we chose human red blood cells. They are easy to isolate, since they float freely in their natural environment and are not attached to other structures in the body. Our plan was to immerse red cells in a solution containing water molecules labeled with atoms of radioactive hydrogen (tritium), and to determine the rate at which the labeled water entered the cells. This was not easy to do, because the reaction is very fast. The exchange of ordinary water inside the cell with radioactive water outside is essentially complete in only 20 milliseconds (thousandths of a second).

To follow the progress of the rapid diffusion, we adopted a method for studying fast reactions that was devised some 20 years ago by Hamilton Hartridge and F. J. W. Roughton of the University of Cambridge. The reacting substances are stored in separate containers and are discharged through fine jets into a chamber where they are mixed thoroughly and instantaneously. From the chamber the liquid passes into a long observation tube, through which it flows under pressure at a controlled and constant rate. The reaction begins as soon as the two streams make contact, and continues as the mixture moves down the tube. Thus at every point along the tube the reaction will have been proceeding for a definite, known length of

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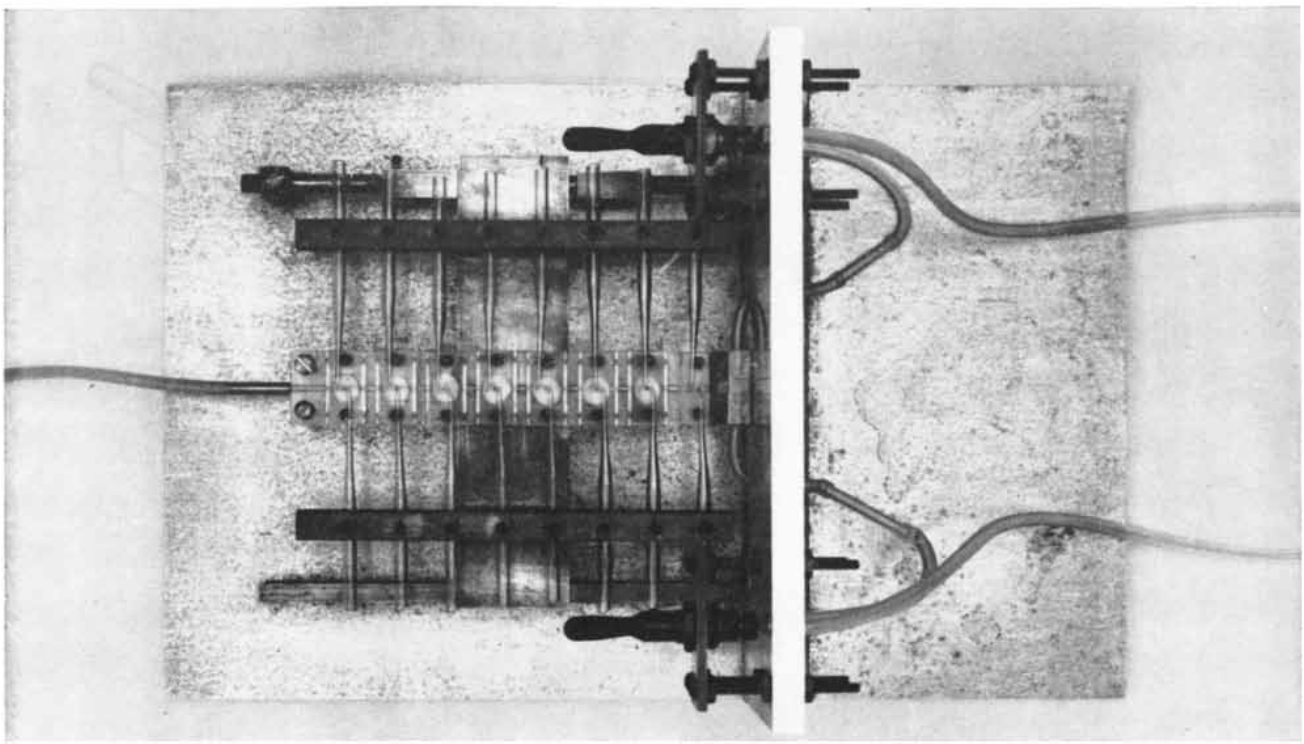
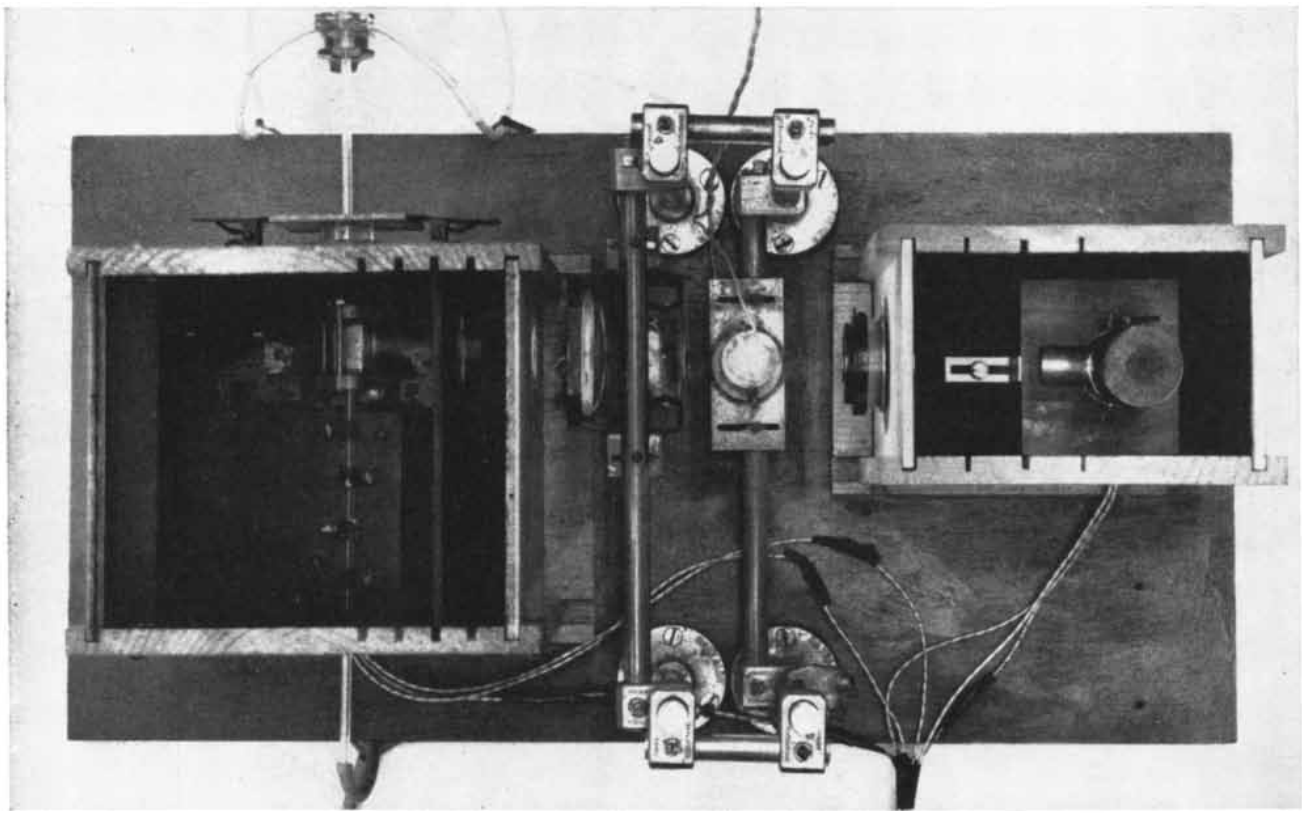


RAPID-FLOW APPARATUS was devised to study diffusion of water through membrane of human red blood cell. Tube extends through lucite block (*center*) from right to left. Suspension of red cells entered through one of the plastic tubes at right, and a solution of radioactive water entered through the other. Solutions mixed and traveled down observation tube. Samples were drawn off through the rows of glass tubes on both sides of observation tube. Diminished radioactivity of samples indicated diffusion rate.



LIGHT-SCATTERING APPARATUS is used to measure the volume of the red cells. Rate of change of volume of cells is a measure of rate at which substances move in or out through cell membrane. Volume of cells is determined by measuring the amount of light they scatter. Here a suspension of cells flows through the glass tube at left. Light from source at center strikes the suspension of cells and is scattered at right angles by a prism. Intensity of scattered light is measured by a photocell (*not visible*) and is compared to intensity of source (measured by photocell at right). Diagrams of the apparatus in these photographs appear on next page.

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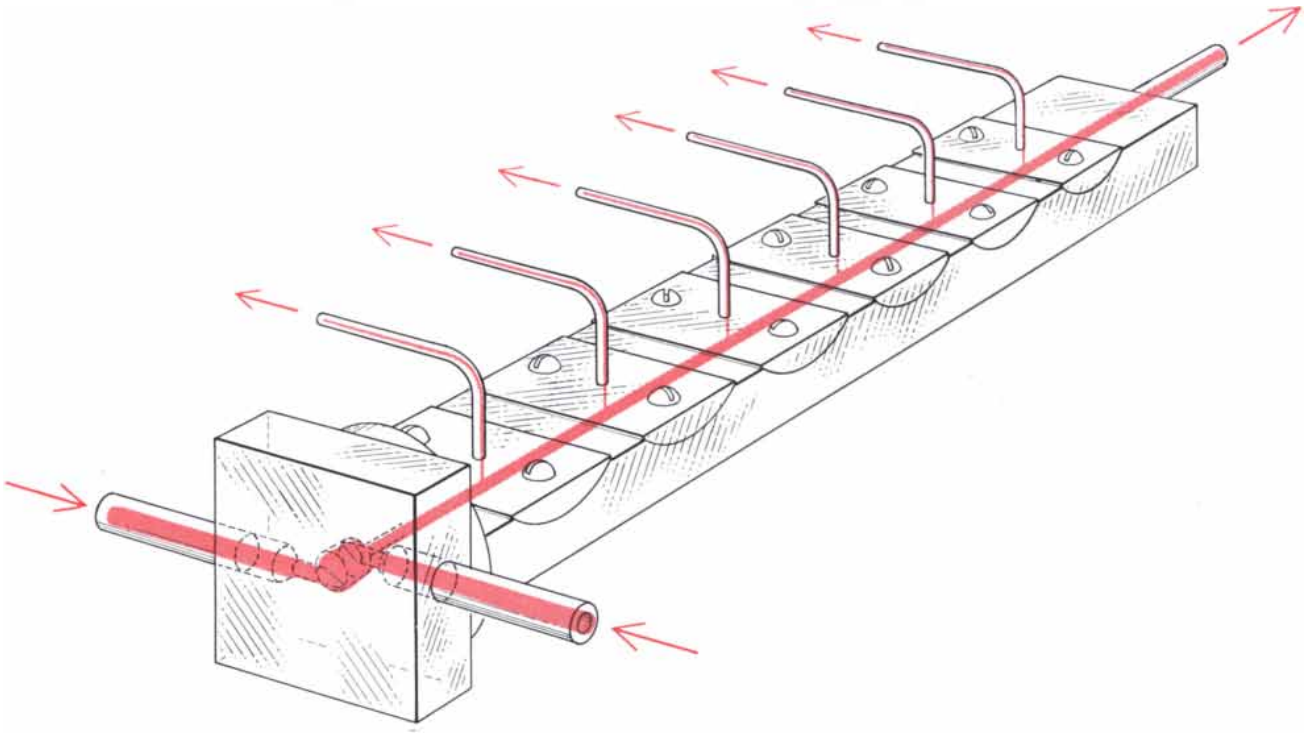

DIAGRAM OF DIFFUSION APPARATUS shown in photograph at top of preceding page indicates how suspension of red cells is mixed with radioactive water. Here the two liquids (*color*) enter at left and flow through observation tube and sampling tubes.

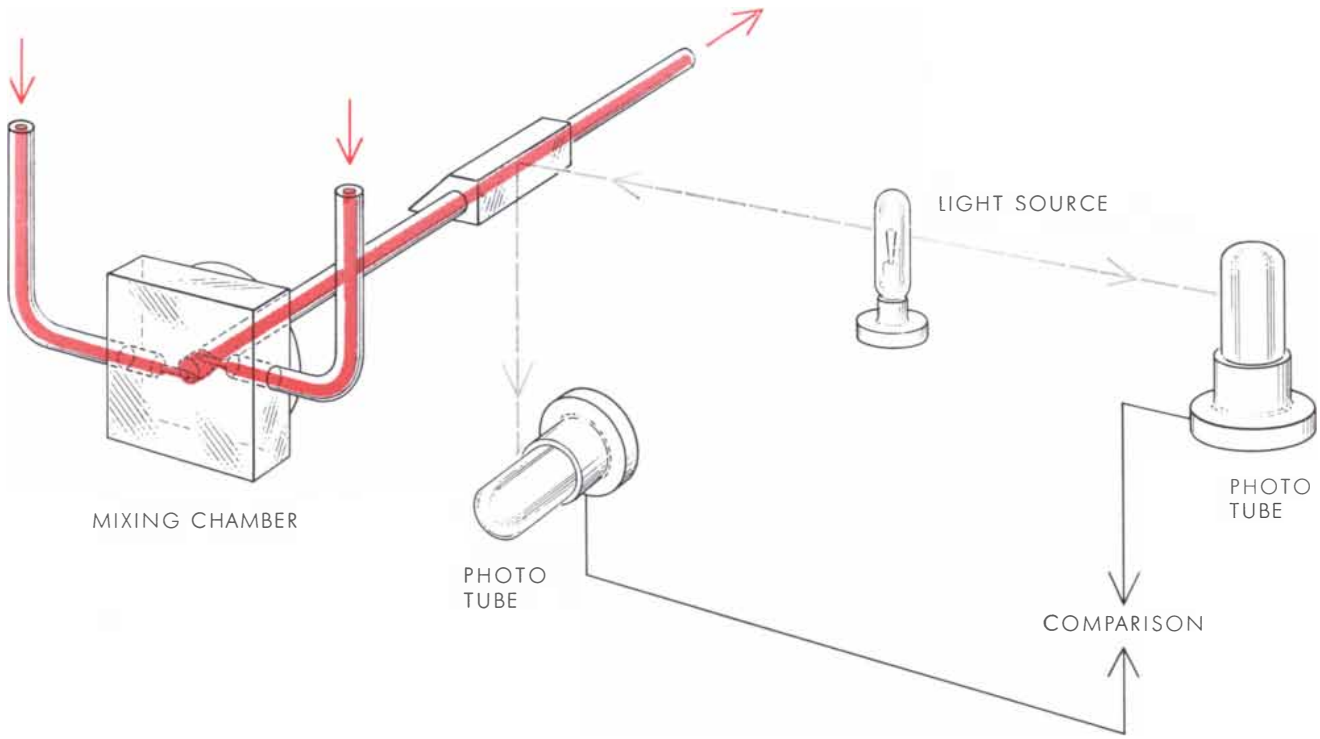

DIAGRAM OF LIGHT-SCATTERING APPARATUS shown in photograph at bottom of preceding page indicates how light scattered by suspension of red cells reaches the phototube (*bottom*). The output of this phototube is compared electronically to the brightness of the source, as measured by the phototube at far right. The observation time can be varied by moving the mixing chamber.

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time. Observing the solution at various distances from the mixing chamber provides, in effect, a time exposure of successive stages of the very fast reaction.

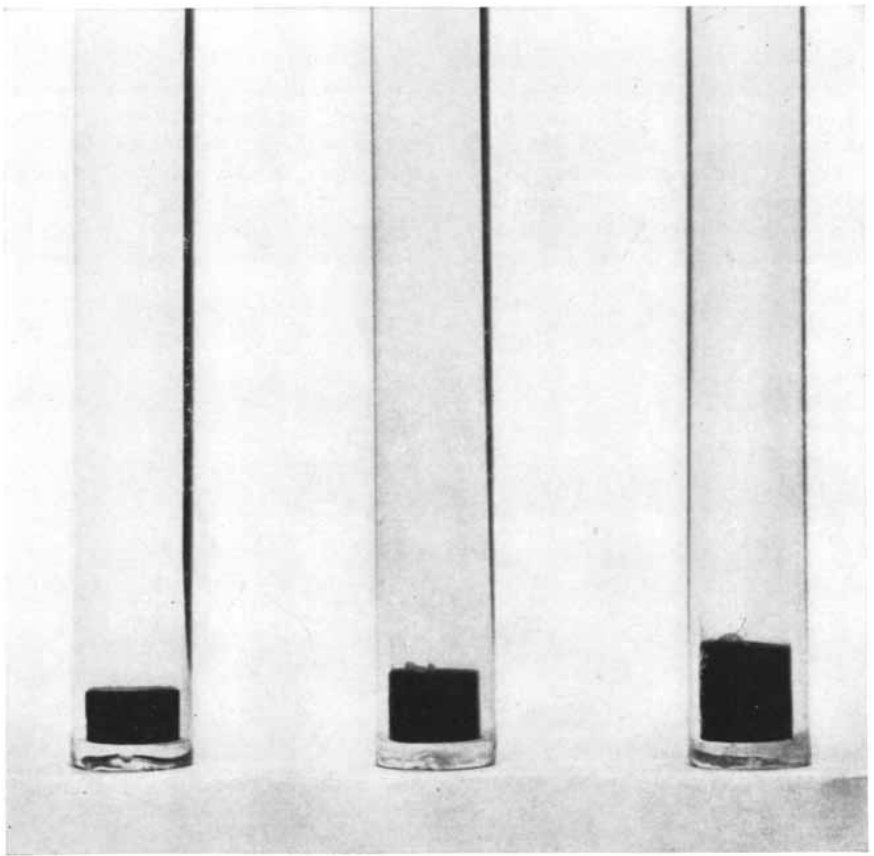
In the arrangement that Charles Paganelli and I devised [*see illustrations at left and at top of preceding page*] radioactive water and a solution of red cells were injected into a small, cylindrical chamber. After mixing, the fluid traveled down the observation tube at a rate of 10 meters per second (about the speed of a slow freight-train), so that a distance of one centimeter corresponded to a time interval of one millisecond. Of course red cells do not change appearance when they take up radioactive water, so we could not follow the reaction visually. Instead we collected samples of the tritium solution at intervals of about 1.5 centimeters. The pressure of two atmospheres that propelled the fluid through the system was enough to force water through ports sealed with Millipore filter paper (a special paper fine enough to hold back red blood cells). Small samples of fluid from each port were carefully diluted, and their radioactivity was determined by a very accurate procedure developed by Charles V. Robinson in our laboratory. From the activity of the liquid emerging from each port we could tell how much tritium had left the solution at that point and had therefore entered the cells. Observations covering the first nine milliseconds established that the half-time of the reaction—the time in which the cells take up half the equilibrium amount of radioactive water—was 3.6 milliseconds under our experimental conditions.

As has already been mentioned, this half-time enabled us to calculate the ratio of the total cross-sectional area of the pores to the average pore length (A/L). To derive the diameter of the individual pores from this ratio, we would have had to know the number of pores and their average length. We had no way of estimating the number of pores. As to the length, there was no guarantee that the path of the pores through the membrane was direct. In cellophane, for example, the pores have been found to be long and tortuous. Consequently we had to turn to another type of experiment for additional data.

The resistance offered by a pipe to the one-way flow of liquids under pressure is different from that opposing the two-way process of diffusion. It too is related to the diameter, but by another law, known as Poiseuille's law after the French physician who first placed the study of fluid flow on a quantitative basis. Applied to a membrane containing small pores, Poiseuille's law shows that the rate at which liquid crosses the membrane under pressure depends on the square of the pore diameter, as well as on total area and length ($d^2 \times A/L$). Thus by measuring the flow rate under pressure the value of $d^2 \times A/L$ can be determined. Substituting the value of A/L obtained in the diffusion experiment then leads to the diameter.

When we began our work, the possibility of finding pore diameters by combining two experiments had already been pointed out by John R. Pappenheimer of the Harvard Medical School and H. H. Ussing of Denmark. Pappenheimer had used the method to determine the size of the pores in the capillary bed in the leg of a cat. This membrane consists of many cells, held together by a connective material. We now proceeded to apply the same technique to determining the pore diameter in a single cellular membrane—that of the red cell. Since human red cells are small (some .0008 centimeter in diameter), it is not possible to apply hydrostatic pressure to one side of the membrane to force water to move across it in bulk. Instead we used the force of osmosis to push water through the membrane. The reader will recall that osmotic pressure results from the tendency of solutions separated by a porous membrane to equalize their concentrations. In classical demonstrations of the effect a solution of large molecules, such as polymer molecules, in one chamber is connected through a membrane to a chamber containing pure water. The membrane is semipermeable: its pores are small enough to admit water molecules but not polymer molecules. Water now passes into the polymer solution, raising the pressure in that chamber to a value that exactly balances the tendency of the water to move in. When the system reaches such an equilibrium, the flow stops.

Although the experiment is usually performed in the way just described, the liquid in the second chamber need not be pure water, but can also con-



RED BLOOD CELLS (*dark masses in tubes*) shrink or swell if immersed in a solution with an osmotic pressure different from their own. Each tube contains same number of cells. Cells in center are normal size. Cells in tube at left shrank after being placed in concentrated salt solution; cells in tube at right swelled after being placed in dilute salt solution.

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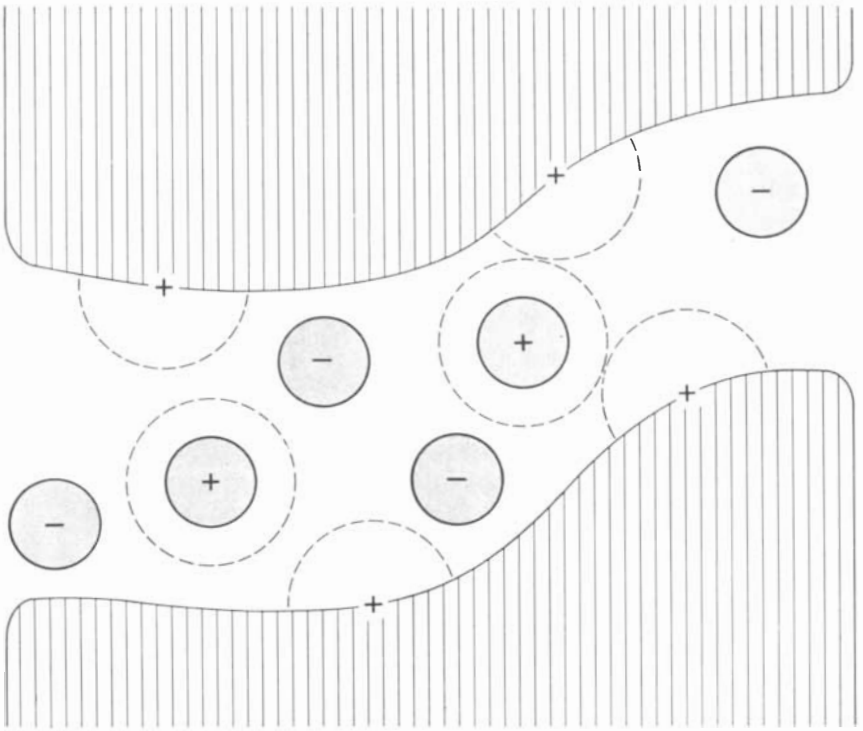
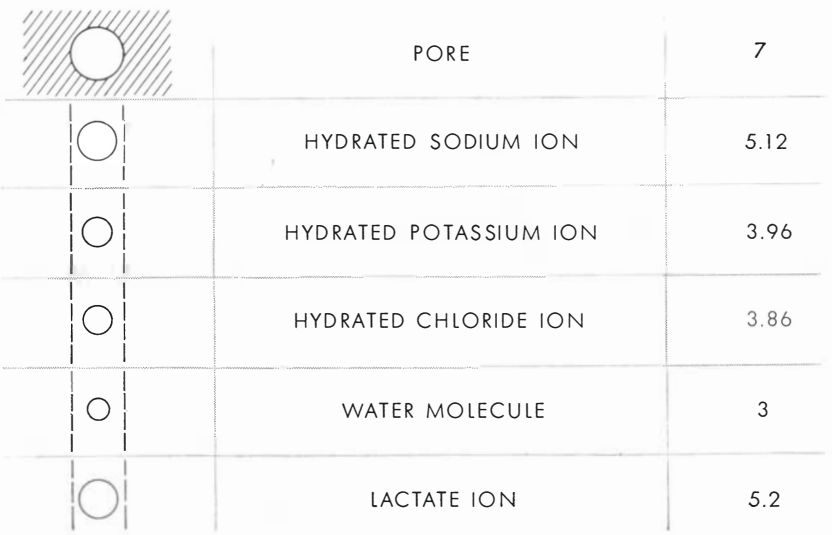


PORE in cell membrane is depicted in this schematic diagram. Pore is lined with molecules bearing a positive charge. "Sphere of influence" of these positive charges (*broken circles*) hinders the passage of positively charged ions, but does not retard negatively charged ones.

tain polymer. As long as there is a difference between the initial concentrations on the two sides of the membrane, osmotic pressure will develop, the amount of pressure depending on the relative concentrations. Thus a red cell in its normal plasma bath is in osmotic equilibrium. But if the cell is removed from the plasma and placed in distilled water, osmotic pressure forces enough water into the cell to burst it in less than a second. Since the potassium salts inside cross the cell membrane only at a negligible rate, they act as if the membrane were impermeable to them. By adding salt to the distilled water the osmotic pressure can be reduced or even reversed.



DIAMETER OF PORE is compared to the diameters of substances involved in cell metabolism (*left*). Sizes are given in angstrom units (10^{-8} centimeter) in column at right. Diameters of hydrated ions are derived from electrical conductivities measured in water solution.

That is what Victor W. Sidel and I did in our experiment. We placed red cells in sodium chloride solutions of almost the same concentration as that of the intracellular fluid, thus limiting the pressure to moderate values in one direction or the other. When the concentration was lower outside, a little water flowed into the cells, leaving them slightly swollen upon reaching equilibrium. When the conditions were reversed, water flowed out and the cells shrank. Thus we could set the pressure by adjusting the salt concentration, and determine the speed at which water crossed the membrane from the rate of swelling or shrinking.

Since the rate is very high, we turned again to the rapid-flow apparatus. This time we had a visible indication of the reaction rate in the changing volume of the cells. They move down the observation tube too fast to be observed under a microscope. Nevertheless we could use a simple optical measurement. When a beam of light is sent through the flow tube, some of it is reflected from the surface of the tumbling red cells. The amount of light reflected at an angle of 90 degrees from the incident beam turns out to be directly proportional to the volume of the cells. We measured the scattered light intensity at 50, 100, 150 and 200 milliseconds after mixing. The intensities were translated first into cell volume and then into the rate of water movement.

From these data we could establish a value for the resistance offered by the cellular membrane to the passage of water under pressure. As previously stated, the resistance depends on the quantity $d^2 \times A/L$. When the results of this computation were combined with the value of A/L determined in the diffusion experiment, we were able to calculate that the "equivalent diameter" of the red cell pores is seven angstrom units. The reason for the term "equivalent" will appear in a moment.

Now a pore seven angstroms wide would easily pass both sodium and potassium ions. Not only that, but it would fail completely to discriminate between the positively charged potassium ions and negatively charged chloride ions, which have almost identical hydrated diameters. Yet in fact chloride ions travel through the cell membrane almost a million times faster than potassium ions. We therefore supposed that the pores are lined with positive charges, which repel the positively charged ions and block their passage. The picture also fits well with other experimental facts. A seven-angstrom pore would exclude molecules

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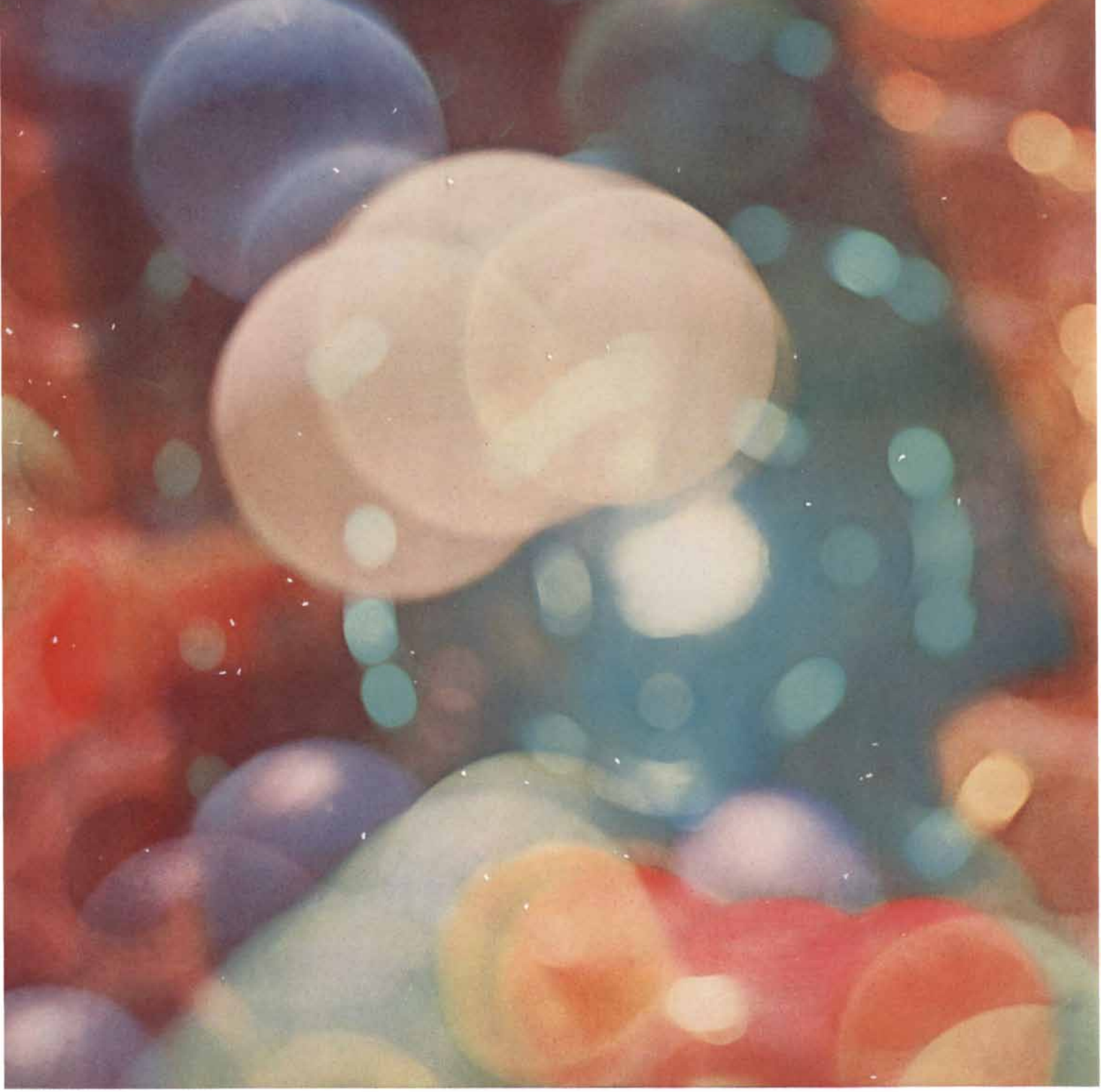

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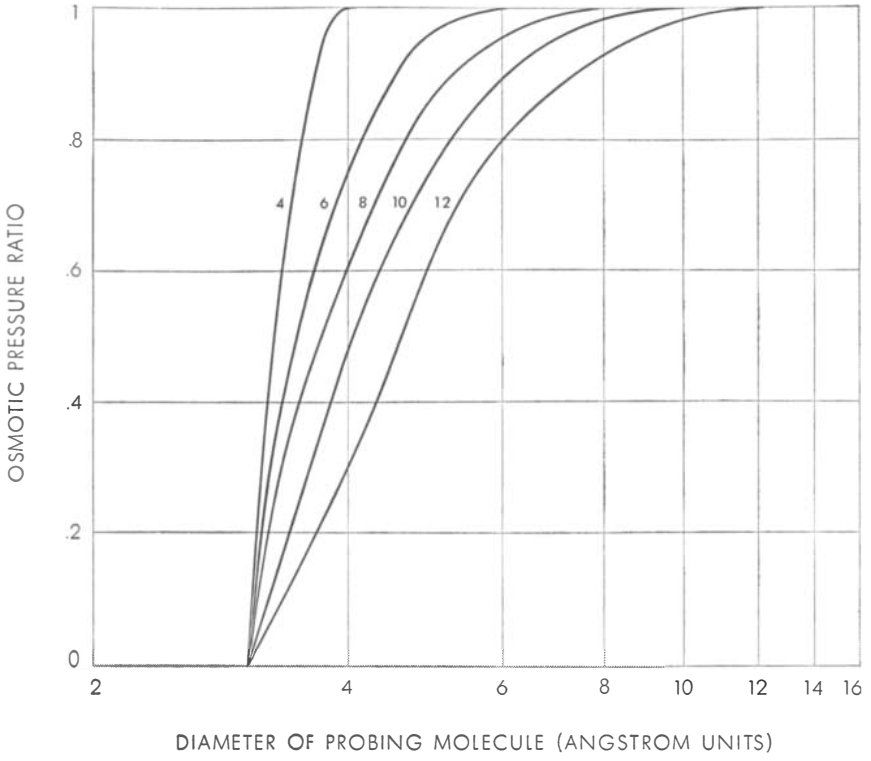
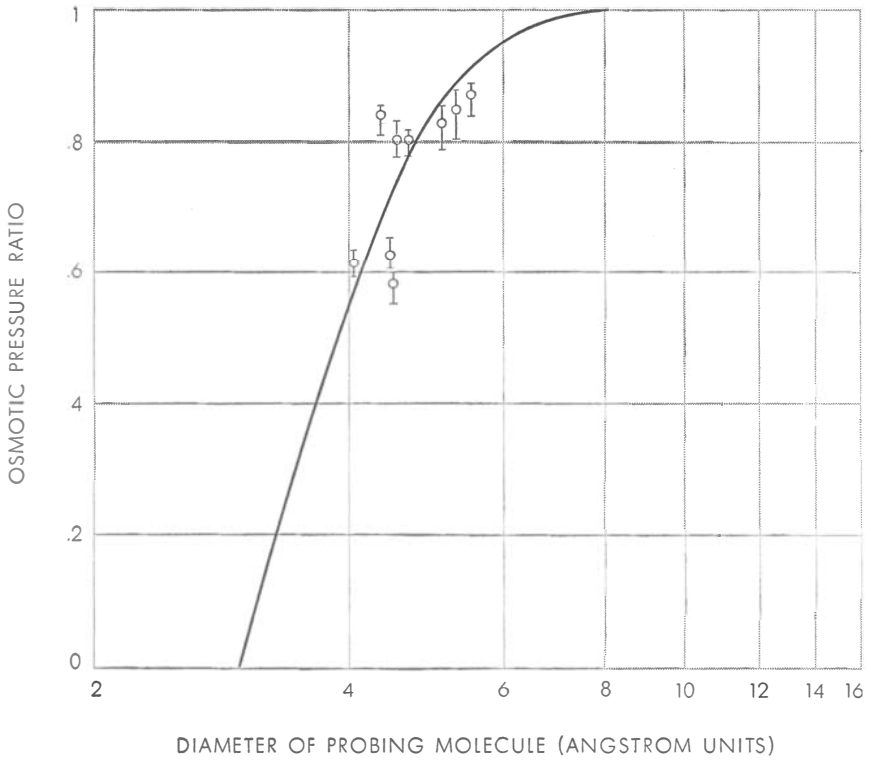
of glucose, the chief fuel of the cell. And in fact the red cell has developed a specific chemical transport system to take in glucose across the fabric of the membrane. The end product of glucose metabolism is the negatively charged lactate ion, which has only three carbon atoms as against six in glucose. This ion is small enough to escape through the pores. Thus no special excretory mechanism is required, and none has been found.

Having an idea of the size of the pores, we next tried to estimate how densely they are distributed over the surface of the membrane. If the length of the pores (L) were known, then their total area (A) could be found. On the assumption that the pores are 300 angstroms long, allowing a factor of three for their presumably tortuous path through the membrane, the total pore openings occupy only .06 per cent of the surface. If the holes were evenly spaced, each seven-angstrom pore would be surrounded by an unbroken square 200 angstroms on a side. Thus the red cell, whose membrane is the most permeable known, devotes only a minute fraction of its surface area to ionic communication with its environment.

The measurements so far described depend upon the validity of the laws governing flow by diffusion and under pressure. These laws were derived for macroscopic systems, where the diameter of a pipe is very much larger than that of the molecules flowing through it; the application of the laws to pores whose dimensions are measured in a small number of angstroms involves a considerable extrapolation. If one probes a seven-angstrom pore with a water molecule three angstroms in diameter, does Poiseuille's law apply? There is a good deal of experimental evidence that it is adequate to describe the flow of water through pores down to 40 angstroms in diameter, but almost none, save the self-consistency of our own results, showing that this law holds in a situation where the pore diameter is only two or three times as large as the water molecule. Similar objections can be made to the use of the ordinary laws of diffusion in this domain. In view of these theoretical difficulties we use the term "equivalent diameter" to show that the value we have calculated is the diameter an ideal pore would have if the macroscopic laws were adequate to describe the processes taking place in our experiments. The equivalent pore, like the ideal gas, is a concept applicable only in the limit. However, it does provide a physical



THEORETICAL CURVES show osmotic pressure ratio for molecules and pores of various sizes. Numbers on curves indicate diameter of pore in angstrom units. Ratio represents pressure across "leaky" membrane compared to that across an ideal semipermeable one.



EXPERIMENTAL CURVE of osmotic pressure ratio versus diameter of probing molecule can be compared to one of the curves at top of page to determine actual diameter of pore.

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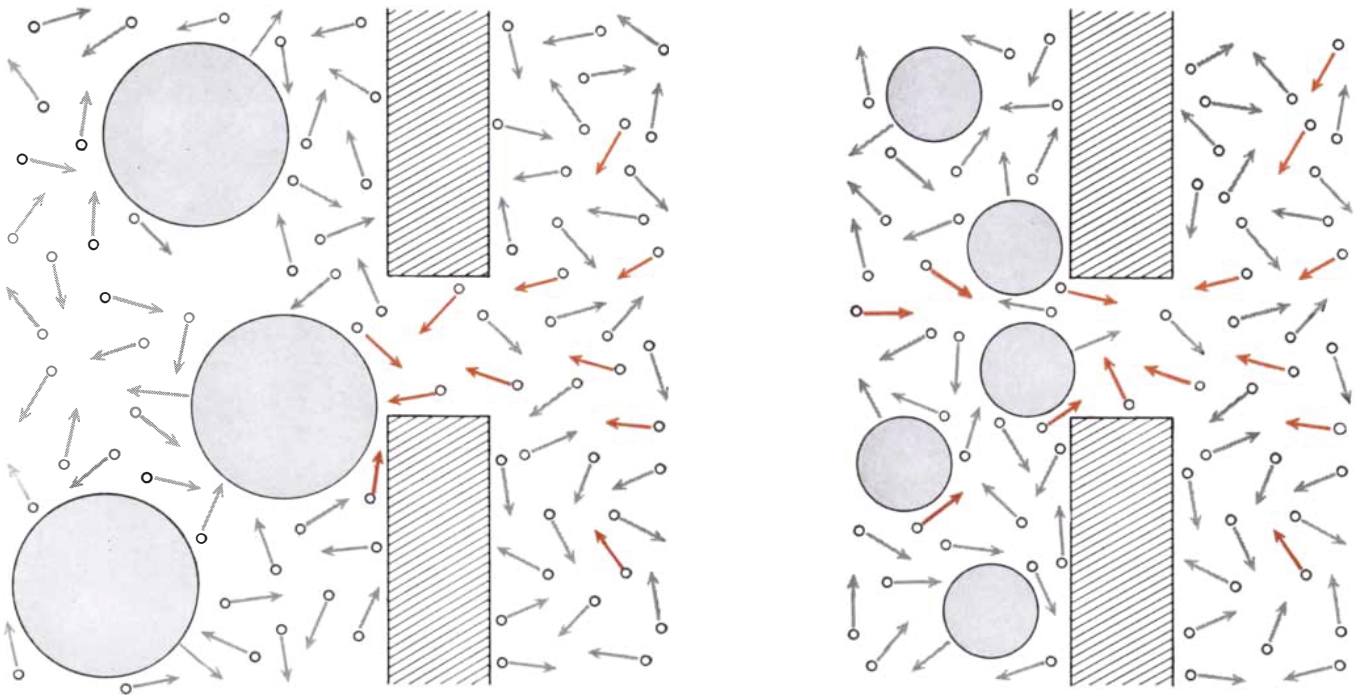
model by which we can visualize the membrane structure and predict the rates of passage of many molecules across it.

About a year ago we were delighted to find a way to check our estimates through an independent method of measuring pore diameter. It came from a careful examination of the very nature of osmotic pressure. The preceding discussion of osmosis dealt with water solutions in which the dissolved molecules are completely, or almost completely, unable to pass through the pores of the membrane separating them. But if these molecules are made smaller (or the pores larger), then they too can pass through the membrane, although not so easily as water molecules. The membrane is now leaky. If the chambers of our earlier example are separated by a membrane that is leaky to polymer molecules, osmosis will at first cause water to flow across the membrane into the polymer solution. As time goes on, however, the polymer molecules will gradually diffuse out of their chamber, and water will follow, so that the pressure will gradually diminish. Finally the polymer concentration will come to the same value on both sides of the membrane. At that point no osmotic pressure remains. Thus with leaky membranes the initial osmotic pressure is a transient phenomenon, dissipating at a rate that depends on the ease with which polymer molecules cross the membrane.

The Dutch chemist A. J. Staverman, who has studied osmosis in leaky membranes, pointed out that the osmotic pressure never reaches the value it would if the membrane were ideally semipermeable. Even at the first instant, before any polymer molecules diffuse across the membrane, the osmotic pressure is less than that across a perfect membrane. This is because the tendency of a polymer molecule to diffuse through the pore will partially counterbalance the force causing water to enter from the other side. Staverman's analysis demonstrated that the ratio of the initial osmotic pressure of a leaky membrane to the classical pressure developed by an ideal membrane would be a measure of the ability of the pores to discriminate between the polymer and water. This becomes clear if we imagine a polymer solution, containing molecules whose size can be altered at will, separated from a bath of pure water by a membrane. When the polymer molecules are larger than the membrane pores, the osmotic pressure has the maximum classical value. Now let the molecules begin to shrink. As soon as the polymer is small enough to just pass through the pores, the pressure will start to drop. As the polymer becomes smaller and smaller, and can pass more and more easily through the pore, it is obvious that the osmotic pressure will continue to diminish. Eventually, if the polymer molecule is the same size as the water molecule, there will be no osmotic pressure, because the membrane will be unable to discriminate between the two molecules. The argument shows that the initial osmotic pressure across a leaky membrane is a measure of the size of the polymer molecule if the diameter of the pores is known, or of the pore diameter if the molecular size is given.

How could these theoretical considerations be applied to the problem of the pore size of the human red cell, where osmotic pressure cannot be measured directly, but only the rate at which molecules of known size cross the membrane? Two further links in the theory were required. The first was supplied in 1955, when Richard P. Durbin, Heddy Frank and I put forward an equation relating the osmotic pressure across a leaky membrane to the relative rate of filtration of water and the molecule ("polymer") that caused the osmotic pressure. The relationship has since



CELL MEMBRANE (*cross-hatched area*) is not permeable to giant molecules like proteins (*largest circles*). Arrows indicate random motion of smaller molecules; colored arrows show paths that will carry molecules through pore in cell membrane. In diagram at left, proteins inhibit movement of small molecules from left to right, setting up large difference in osmotic pressure between inside and outside of cell. In diagram at center, molecules whose diameter is slightly smaller than diameter of pore "leak"

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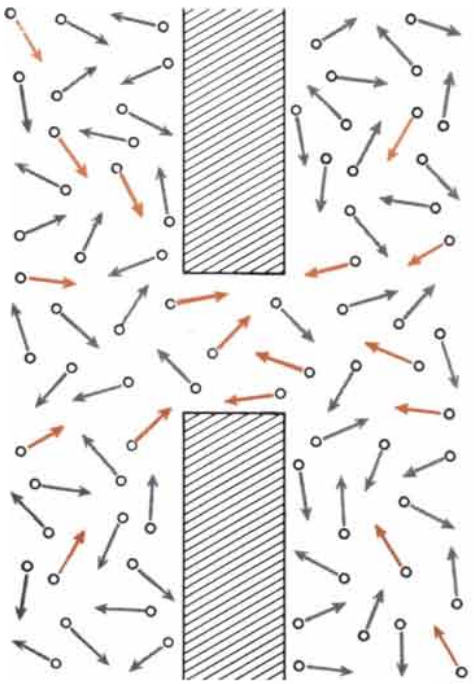
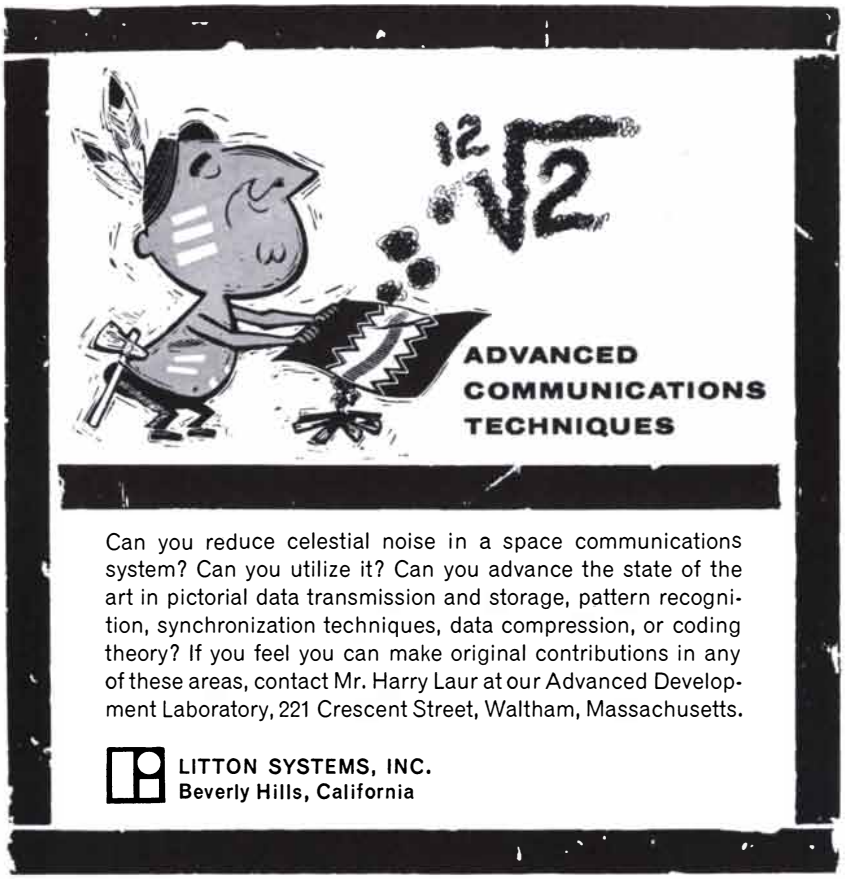
been studied extensively by Durbin, who has confirmed it down to pore diameters of about 40 angstroms.

We next needed to know how the rate of filtration depends upon the relative diameters of "polymer" and water. This problem had been tackled by Eugene M. Renkin, a student of Pappenheimer's. Renkin derived a set of theoretical curves that described the hindrance offered by the filter to molecules passing through it as the size of the molecule approached the size of the pore in the filter. Filtration turns out to be an extremely selective process: Very small differences in molecular size can be detected by quite gross filters. Durbin has shown, for example, that a filter with pores 160 angstroms in diameter will hold back heavy water more than ordinary water. The diameter of the heavy-water molecule is 3.4 angstroms, as compared with three angstroms for ordinary water! Thus it is clear that filtration experiments provide a method of extraordinary sensitivity for determining the equivalent pore diameter.

During the past four years David Goldstein and I have developed a new method for determining the equivalent pore diameter of the human red cell, based on the equations of Staverman, of



through membrane, resulting in small difference in osmotic pressure. Small molecules in diagram at right pass freely through pore, resulting in no difference in osmotic pressure.



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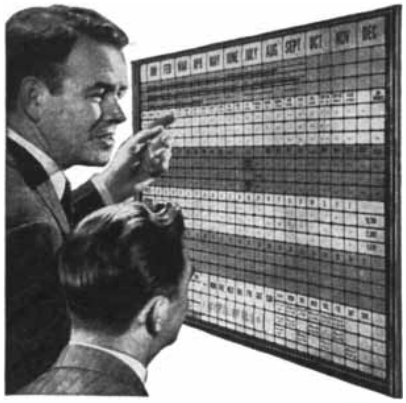

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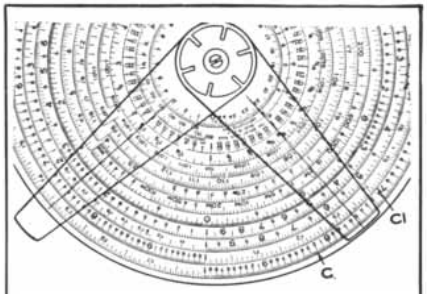

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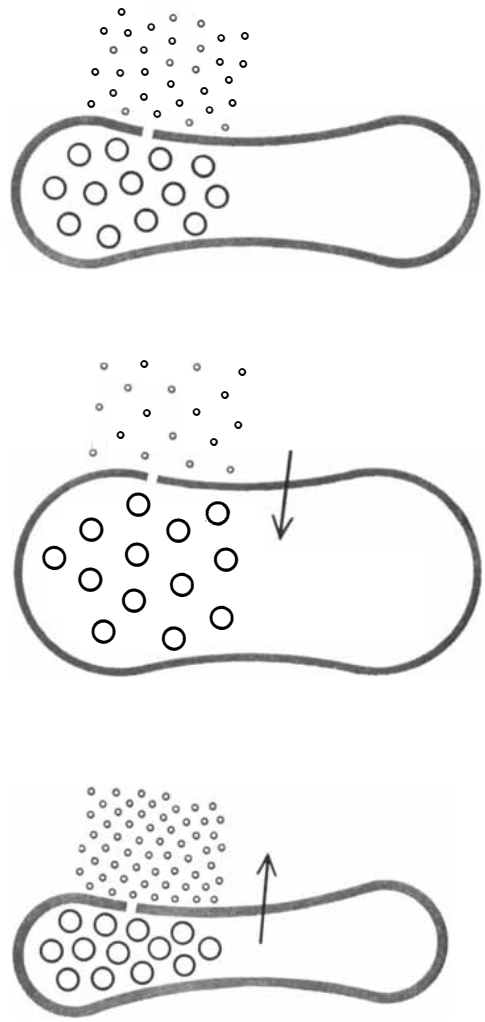
Renkin, and of Durbin, Frank and myself. (Although the relationships I have just outlined make it clear that a measurement of the osmotic pressure developed across a leaky membrane is equivalent to a measurement of pore diameter, this was not apparent to us when we embarked on the problem.) We immersed red cells in solutions of various molecules such as glycerol and urea, which are larger than water but small enough to pass through the pores. Before they diffuse into the cells, these molecules tend to offset the osmotic pressure due to the salts and proteins inside. Using the rapid-flow apparatus and the light-scattering technique that Sidel and I had developed, we measured the initial rate of swelling or shrinking in solutions of various concentrations. For each test molecule we adjusted the concentration to make the rate of flow across the membrane smaller and smaller. Extrapolating from these results, we were able to determine the concentration that initially would just balance the interior osmotic pressure. The smaller the probing molecule, the greater the concentration that was required, as compared with the concentration of a particle that could not cross the membrane at all. Thus the smallest molecule (urea) required a concentration 60 per cent higher than the classical value to produce transient equilibrium; the largest molecule (glycerol) needed only an excess of 14 per cent over the classical value.

Having determined these figures, we had in effect measured the osmotic pressure at zero time. At zero time none of the test molecules has entered the cell, so that the make-up of both the internal and external solutions is precisely known. Moreover, the technique has the advantage of not requiring absolute measurement of the true rate of swelling or shrinking. As a null method it depends only on the external concentration at which the initial rate of water flow across the membrane is zero.

Referring our results to the theoretical equations, we arrived at an equivalent pore diameter of 8.4 angstrom units—a result that agreed remarkably well with our earlier figure of seven angstrom units. The agreement is most heartening. It gives us increased confidence in the concept of the equivalent pore as a valid measure for single cellular membranes, and suggests that macroscopic laws do indeed continue to hold for very small dimensions. Recently the zero-time method has been applied to other tissues, leading to calculated equivalent pore diameters close to that of the red cell. It may very well be that pores of this approximate size are characteristic of membrane architecture. The broad applicability of our new zero-time method and the ease with which measurements can be made on a variety of cells lead us to believe that the way is now open for a general description of passive permeability in simple physical terms.



ZERO-TIME osmotic pressure was measured by immersing red blood cells (*shown here in schematic cross-sectional view*) in solution containing smaller molecules such as urea (*small circles*). Initial osmotic pressure caused by presence of molecules (*large circles*) that could not pass through membrane was balanced by greater concentration of smaller molecules outside (*top*). If concentration of smaller molecules was lowered, an excess of water (*arrow*) flowed into the cell, causing it to swell (*center*); if concentration was raised sharply, water flowed out, causing cell to shrink (*bottom*).

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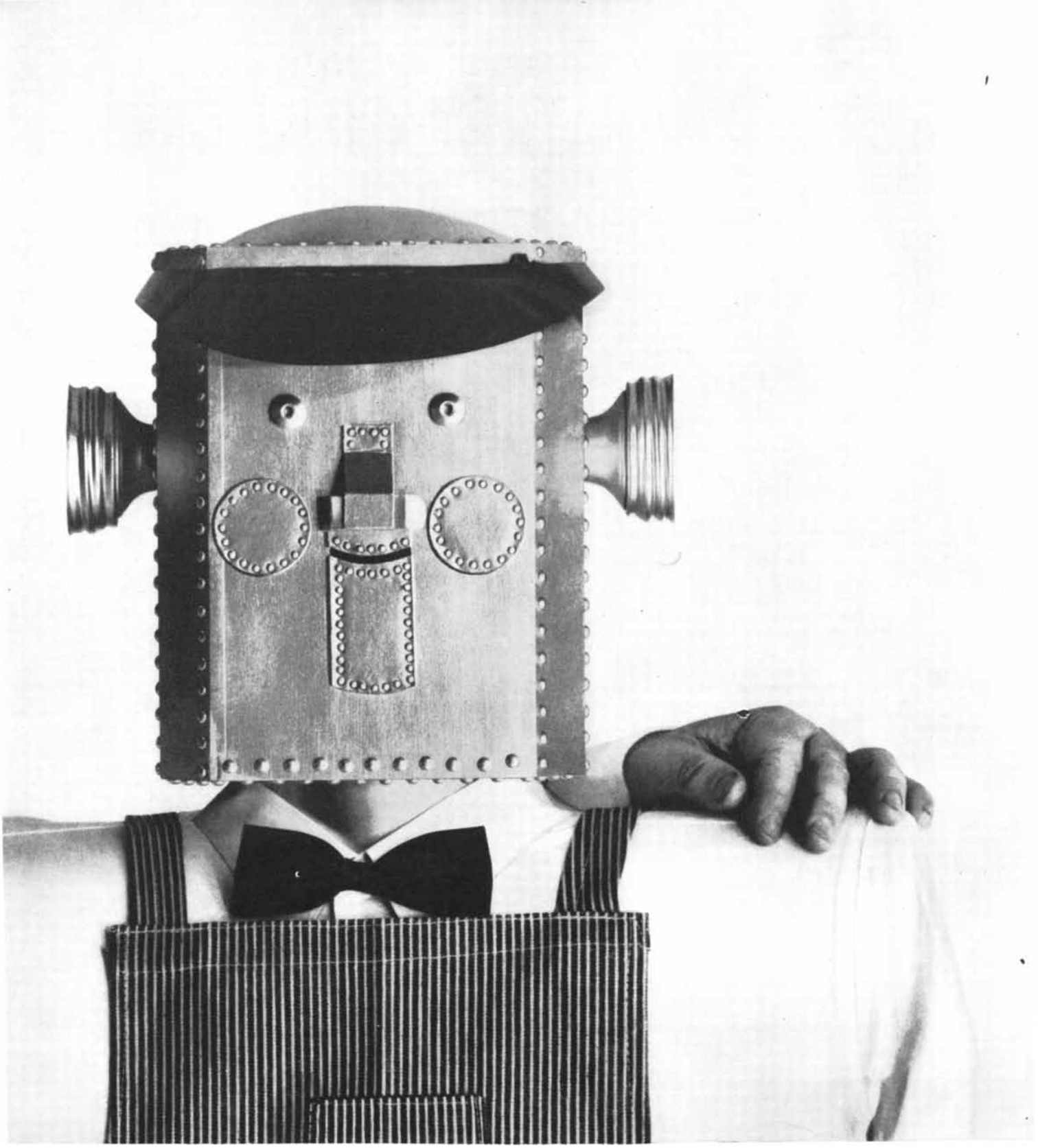

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