Membrane Transport Proteins

Proteins that appear to be parts of membrane transport systems are being isolated and characterized.

Arthur B. Pardee

Membranes that surround living cells are needed to hold cells together, to keep their metabolites from diffusing away, and to keep out toxic materials. The membrane constitutes a barrier to nutrients being brought in and waste products being excreted. However, transport systems are built into membranes in a way that provides for selective permeability. By this process, only the necessary materials are transported. In some cases transport systems do more; they actually "pump" substrates to create a higher concentration inside the cell than outside. This is an energy-requiring process, named active transport to distinguish it from the specific process called passive transport or facilitated diffusion which does not require energy (*1*). Substances are also pumped out (for example, sodium ions are pumped from animal cells).

The existence of these transport systems causes one to raise questions about their structure and how they work. What chemical machinery is required for the specific translocation of small molecules (substrates) from one side of a membrane to the other?

The usual biochemical approach to a problem of this nature is analysis followed by synthesis. First, one isolates the parts and studies their properties. Second, from this information plus observations on the intact system one devises a plausible model of how the complete system works. Eventually one hopes to put the parts together physically and obtain the entire operating system. The obvious difficulty with applying this approach to transport is that when one takes cells apart transport can no longer be measured. For many years there seemed to be no way of determining whether any isolated molecule was or was not part of a transport system.

Transport Kinetics—The Black-Box Approach

Until recently, therefore, transport has been studied with intact cells. Kinetics—the rates of inflow and outflow—were measured when conditions such as substrate concentration were varied (Fig. 1). This black-box approach has told us quite a lot about transport systems, and has been summarized in models that are consistent with the results (*1*). These models are important because they provide frameworks for our further ideas and limits to our speculations.

In a most general way we can indicate a set of steps in transport (Fig. 2). Models all assume that the first step is a specific binding of substrate to an active site on the outer membrane surface, very much like the binding of a substrate to an enzyme. This is followed by translocation of the substrate across the membrane, a process whose details are completely mysterious. The substrate is released inside the cell; then the system returns to its original state. Active transport systems supply energy at one of these steps, in a way which makes the inflow process more effective than the outflow process.

Some important observations are the following (*1*).

First, transport systems are quite specific, like enzymes. A single transport system can catalyze the translocation of a limited number of substrates with similar chemical structures. For example, one system transports glucose and the closely related sugars 3-*O*-methylglucose and 2-deoxyglucose into animal cells; most other sugars are excluded.

Second, a substrate's initial rate of entry depends on its concentration, as though there were a limited number of independent adsorption sites. An equation that describes the simpler cases is:

$$v = V\left(\frac{S_e}{K_e + S_e} - \frac{S_i}{K_i + S_i}\right)$$

The net rate of entry (v) increases as the external substrate concentration (S_e) increases; it approaches a maximum value (V). As the substrate concentration inside (S_i) increases, outflow reduces the net rate and finally equilibrium is reached, with $S_i/S_e = K_i/K_e$. The internal and external dissociation constants are K_i and K_e, respectively.

Third, flow of one substrate can stimulate flow of a second similar substrate in the opposite direction, as though the two processes shared a component of the system, such as a carrier molecule in the membrane that cycles between inward and outward states.

Fourth, active transport is inhibited when the cell's energy production is inhibited by compounds such as azide or iodoacetate, as would be expected for a process that does work by concentrating the substrate against a gradient.

Proteins should constitute the recognition sites because they are the only molecules which have the observed degree of specificity to discriminate between possible substrates. Other kinds of data obtained with whole cells also show that proteins are required. Thus, transport is inhibited by reagents, such as phenylisothiocyanate, which react with proteins (*1*). Also, inhibitors of protein synthesis, such as chloramphenicol, prevent transport systems from being synthesized by bacteria. The question then is whether these proteins can be isolated. The difficulty lies in finding an assay after transport is destroyed by breaking of the cells.

As to their positions, one expects transport proteins to be located on or near the cell membrane, according to the usual model. Electron-microscope photographs show that the membranes are three-layered structures about 70 angstroms thick. Isolated membranes consist of about 60 percent proteins and 40 percent phospholipids. For many years they were supposed to consist of a fatty center with a protein layer on either side. Now it appears more likely that there is a protein-lipid mosaic (*2*). Proteins might extend through the membrane in some places, providing specific

The author is Donner professor of science, Program in Biochemical Sciences, Moffett Laboratory, Princeton University, Princeton, N.J. 08540.

doors for transport processes. Physical chemical methods are now being used to study their structures (*3*), but the results are difficult to interpret because it is hard to predict actual interactions between membrane proteins and lipids from results obtained with the separate parts.

An additional barrier in bacteria is the cell wall. It lies outside of the membrane, and excludes larger molecules by a "molecular sieve" action (*4*).

Identification of Finding Transport Proteins Through Differential Labeling

Three general methods have been used to identify transport proteins. One is to label the protein specifically with a radioactive substance. A second is to measure the recognition (binding) of substrate. The third is to measure interaction of the protein with an energy source. These methods can be applied to either animal cells or bacteria, although most work has been done with bacteria.

Specific labeling of a transport protein usually depends on finding cells that make the protein and other cells that do not make it. For example, transport-negative mutants (that is, mutants that cannot transport the compound in question) can be produced which should not make the protein that normal cells should make. Or, the same strain might make it under one set of growth conditions but not under another, for example, under conditions of induction or repression (production of a specific protein, depending on the presence of a compound similar to the substrate or absence of a compound related to the product, respectively). Cells presumably containing the protein can be labeled with one isotope, and other cells which should lack the protein can be labeled in the same way with another isotope (for example, cells could be grown with ^{14}C-arginine and ^{3}H-arginine, respectively). The transport protein should then contain ^{14}C but not ^{3}H, whereas all other proteins should have both labels. When the cells are mixed, broken, and fractionated, the fraction with the highest ratio of ^{14}C to ^{3}H should contain the transport protein. Obviously, this technique does not depend on specific properties of the transport protein. Instead it depends on the specific synthesis of the protein. Kolber and Stein have applied this approach to isolation of a protein for specific transport of β-galactosides (*1*, *5*).

Using an ingenious modification of the double labeling technique which includes specific binding, Kennedy's laboratory has isolated a β-galactoside transport protein (*6*). *N*-Ethylmaleimide (NEM) was used as a label. It combines irreversibly with proteins' sulfhydryl groups and blocks transport of β-galactoside. The specificity of labeling was improved by first reacting all other proteins of both sets of bacteria (induced and not induced for the transport system) with unlabeled NEM in the presence of a substrate of the transport system, thiodigalactoside, which protected the transport protein's active site. Thiodigalactoside and NEM were removed; then the induced cells were reacted with ^{14}C-NEM, and the uninduced cells were reacted with ^{3}H-NEM. These bacteria were mixed and fractionated. The transport site should have been selectively labeled with ^{14}C-NEM. As hoped, the membrane fraction had a higher ratio of ^{14}C to ^{3}H (8 percent) than the cytoplasm. Fractionation was continued, and eventually a radiochemically pure protein was isolated. It was named the M protein because of its association with the membrane. There are at least 10^4 molecules of M protein per induced bacterium; its molecular weight is 31,000. Later experiments showed that it is absent in uninduced cells and in transport-negative mutants. This protein would have to be inactive in binding substrate because of the treatment with NEM. It does, however, represent a cleanly isolated transport protein.

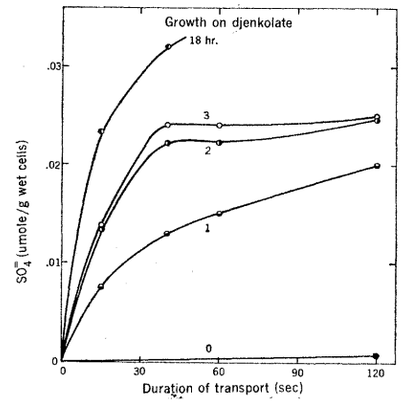

Fig. 1. Kinetics of sulfate transport by intact *S. typhimurium*. The bacteria were grown for various times on a poor sulfur source (djenkolate). These cells were assayed for their ability to take up $^{35}SO_4^{2-}$ as a function of time.

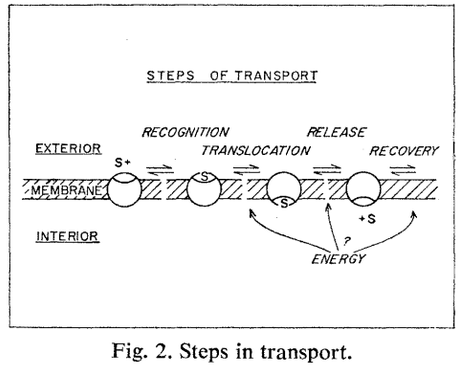

Fig. 2. Steps in transport.

Substrate Recognition by Transport Proteins

Another way of testing for transport proteins is to look for specific substrate binding by cell fractions. Binding is classically determined by equilibrium dialysis. The protein is inside a dialysis bag through which it cannot diffuse; the substrate dissolved in the inside and outside solutions is in equilibrium. If binding occurs, the substrate's total concentration is higher inside the bag than outside (*7*). Other techniques can be used. For example, a charged substrate can be absorbed onto an ion-exchange resin in equilibrium with the solution. When a binding protein is added to the solution, it shifts the equilibrium and releases more substrate from the resin into the solution (*8–10*). Another method is to pass the binding substance with substrate through a column (Sephadex) which separates substances according to size. Then the bound substrate will come off the column with the large molecules of binding protein (*11*).

Several proteins have now been isolated; binding assays were used to follow their purification. We have isolated and crystallized a sulfate-binding protein from *Salmonella typhimurium* (Fig. 3) (*9*). There are about 10^4 molecules of this protein per bacterium, when surplus is produced by growing the bacteria on a limiting sulfur source (derepression). Proteins that bind calcium ion have been isolated from several tissues of chicks and rats (*10*); a protein from *Escherichia coli* that binds neutral amino acids has been isolated and crystallized by Oxender (*7*). Anraku has also performed these experiments, and has isolated a protein that binds galactose (not to be confused with the galactoside-binding M protein discussed

Table 1. Properties of membrane transport proteins; f/f_0 is the ratio of the frictional coefficient of the molcule to the frictional coefficient of a sphere of the same mass; K, dissociation constant.

Organism	Substrate	Protein characteristic				
		Molecular weight ($\times 10^{-4}$)	f/f_0	Sites (No.)	K (mmole/liter)	Crystals
Salmonella typhimurium (*9*)	$SO_4^=$	3.2	1.3	1	0.03	Yes
Escherichia coli (*6*)	β-Galactosides	3.1				No
Escherichia coli (*7*)	Leucine	3.6		1	0.001	Yes
Escherichia coli (*11*)	Leucine	3.6	1.28	1	0.002	Yes
Escherichia coli (*11*)	Galactose	3.5	1.25	1	0.001	No
Escherichia coli (*15*)	PEP	0.9		1	Covalent	No
Chick duodenum (*10*)	Ca^{2+}	2.8		1	0.004	No
Beef brain (*23*)	Na^+,K^+	67				No

above) (*11*). Binding proteins for glucose (*12*), glucose-6-phosphate (*13*), and L-arabinose (*14*) are being investigated.

These proteins are similar but not identical (Tables 1 and 2). They are all of about the same size (30,000 molecular weight) and have one specific binding site with a dissociation constant of 10^{-5} to 10^{-6} mole/liter. No components other than amino acids have yet been reported.

Energy-Coupling Proteins

Two ways have been discovered by which energy is provided for active transport. In one the energy donor changes the substrate. In the other it changes the transport protein. Transport proteins have been isolated by methods in which each of these reactions for identification has been used.

An energy-supplying protein, HPr, has been related to the bacterial transport of nine sugars, in a remarkable series of investigations mainly from Roseman's laboratory (*15*). This energy donor itself is phosphorylated on a histidine residue by phosphoenolpyruvate (PEP), a reaction catalyzed by an enzyme named Enzyme I.

$$\text{PEP} + \text{HPr} \xrightarrow{\text{Enzyme I, } Mg^{2+}} \text{pyruvate} + \text{P-HPr}$$

$$\text{P-HPr} + \text{sugar} \xrightarrow{\text{Enzyme II}} \text{sugar-6-P} + \text{HPr}$$

Each of these sugars is released inside the cell as a phosphate derivative formed in a reaction catalyzed by Enzyme II. Active transport is thereby achieved, since the sugar phosphate cannot escape back through the membrane (*15, 16*). Active transport is effective only when P-HPr is available, being very weak in mutants which lack the ability to make either HPr or Enzyme I (*15–18*). There is little if any passive transport, which suggests that the energy donor is required for the translocation step. The protein HPr has been highly purified. It is relatively small (molecular weight, 9400) (Table 1), and has no affinity for the sugar substrates.

The part of each of these transport systems responsible for recognition of the specific sugar is called Enzyme II. There appears to be a specific Enzyme II for each sugar. These enzymes are bound to the cell membrane, but as yet none has been solubilized or purified. In one mutant that could not transport mannitol, the corresponding Enzyme II activity for catalyzing the reaction between mannitol and P-HPr was lacking (*18*).

The HPr system might not provide energy for transport of β-galactosides into *E. coli,* although it is used for this process by *Staphylococcus aureus* (*17*). Mutants of *E. coli* that lack Enzyme I can transport lactose (*18*), and the sugar does not seem to be phosphorylated (*19*). Facilitated diffusion of galactosides is rapid when the energy supply is inhibited (*20*). The energy-supplying reaction only decreases affinity for substrate inside the cell. Also, adenosine triphosphate (ATP) functions in galactoside transport. When *E. coli* is treated with a Tris buffer at *p*H 7.7, part of the ATP pool is lost. Then ATP stimulates transport about sixfold; many substrate molecules are transported per ATP molecule hydrolyzed (*6*). Strangely, ATP acts from outside, although the results of Winkler and Wilson (*20*) suggest that the energy source reduces the internal affinity. Kennedy and co-workers propose that ATP converts the M protein into a form with higher affinity. The energy supply for galactoside transport thus remains uncertain. There is in fact some suggestion of a role of the HPr system: some mutants that lack the ability to transport many sugars also utilize lactose poorly (*21*).

The energy supply for sodium and potassium transport is ATP, as shown by experiments in which ATP added inside membrane preparations of red blood cells stimulated transport (*22*), and an adenosine triphosphatase has been implicated in this transport system. Adenosine triphosphate phosphorylates a glutamyl-γ-carboxyl group of membrane protein. This enzyme's activity is stimulated by sodium and potassium ions, and is inhibited by compounds such as ouabain, which inhibit the transport process. The protein can be labeled by analogs of the specific inhibitor (*23*). Instability of the enzyme upon its release from the membrane makes its isolation difficult, but it has recently been stabilized with ATP and sodium or potassium ions and partly purified (*23*). It is a large lipoprotein (molecular weight, 670,000). Affinity sites for the substrates sodium and potassium ions as well as for the energy donor ATP have been found.

Are the Isolated Proteins Involved in Transport?

Most of the evidence linking these proteins with transport is indirect. One correlation is that transport-negative mutants lack the corresponding protein. Such mutants have been reported for the sulfate (*9*), β-galactoside (*6*), galactose (*11*), and HPr (*15–18*) systems. But since several proteins are usually necessary for transport, a given transport-negative mutant need not lack one specific protein. For example, some of the mutants that cannot transport several sugars possess HPr and lack Enzyme I; similarly, some that have Enzyme I lack HPr. Some that cannot transport sulfate lack the binding protein, and others do not. They presumably are defective in other proteins of the transport system, as would be expected because three genetic units of function (cistrons) have been identified as being necessary for this transport system.

Transport activities can be modified by growing the cells under different nutritional conditions (Fig. 1). A parallel change in the quantity of binding protein and transport has been found for the sulfate (*9*) and leucine systems (*7*). Similarly, the M protein is only produced in bacteria which are grown

(induced) so as to make the β-galactoside transport system (*6*). The calcium ion binding protein of animal cells and also calcium ion transport depend on the presence of vitamin D_3 (*10*).

The affinity constants for binding and for transport are similar under physiological conditions for most of these transport systems. The half-saturation concentrations for both binding and transport of leucine are ten times lower for one strain of *E. coli* than for another, a strong piece of evidence (*24*).

Reversible inhibitors such as substrate analogs, and also protein reagents that block binding of sulfate to cells, uniformly block sulfate transport into the cells (*9*).

The ideal demonstration of the role of a protein in transport would be to reconstitute the system; that is, add the protein to cells incapable of transport and obtain transport. Several investigations of this sort have been performed with various degrees of success, but most are not conclusive. A thorough study on restoration of galactose transport has been done by Anraku (*11*). Osmotically shocked *E. coli* (see below) lose about 70 percent of this transport activity. Addition of concentrated crude fluid released by osmotic shock can restore transport. The main effect is obtained with a protein that does not bind galactose; this protein is obtained from the fractionated shock fluid. Further addition of the galactose-binding protein helps somewhat.

In my laboratory, success has been obtained only occasionally in restoring sulfate transport to shocked *S. typhimurium*. The results are extremely variable and can be mimicked by nonspecific proteins under some conditions. Shocked cells are damaged in ways other than by loss of transport proteins (*25*); recovery can be aided nonspecifically as well as possibly specifically.

The HPr system for sugar transport has been successfully reconstituted (*16*). Vesicles made from membranes of disrupted *E. coli* require high concentrations of PEP, added to the medium, to concentrate α-methylglucoside or several other sugars. The α-methylglucoside is found mostly as its phosphate. A mutant lacking Enzyme I does not accumulate α-methylglucoside phosphate. The vesicles normally possess some HPr and Enzyme I, but after appropriate treatment of the membranes these proteins stimulate uptake (*26*). These experiments show a clear involvement of the HPr system in sugar transport. Furthermore, they indicate that the vesicles would be useful in other studies of transport.

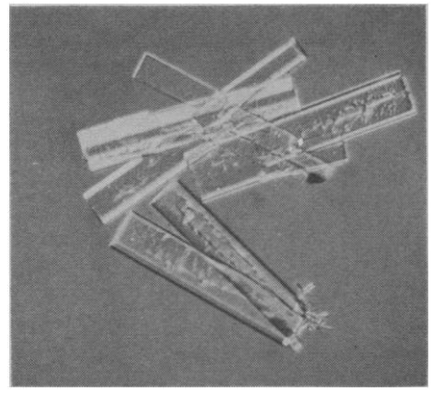

Fig. 3. Crystals of sulfate-binding protein. The crystals were up to about 0.1 mm long.

Restoration of thiomethyl-β-galactoside and α-methylglucoside transport to shocked *E. coli* was obtained with a partly purified preparation of HPr protein (*15*). The experiments were successful about half of the time. There is some difficulty in understanding these results, in spite of the role of HPr in transport of many sugars. In particular, HPr protein might not be involved in transport of β-galactosides by *E. coli*, and yet it restored transport of thiomethylgalactoside.

Transport might also be obtained by adding transport proteins to artificial phospholipid membranes. These membranes have been studied extensively; their specificity of ion transport can be modified by addition of various proteins including a bacterial fraction (*27*). Cyclic peptide antibiotics specifically increase transport across phospholipid membranes (*28*). Whether the peptides serve as diffusible transporters or as "portholes" of specific size is not clear. The sulfate-binding protein had no effect on sulfate transport through these membranes (*29*).

Location of Transport Proteins

The position of these proteins in the cell is important in deciding whether they might be involved in transport. Evidence is not yet very extensive. The bacterial proteins that recognize sulfate, galactosides, and leucine are released by osmotic shock—a relatively gentle treatment in which bacteria are rapidly transferred from a sucrose solution of high osmotic strength to a dilute salt solution (*25*). Shock releases a special group of proteins which are about 5 percent of the total. Heppel suggests that these proteins are located on or near the cell membrane.

Osmotic shock also releases most of the HPr protein (*15*), which is required as an energy source for sugar transport rather than for recognition. This protein must be close to the transport proteins (Enzyme II) which are bound to the membrane. Although the fact that these proteins can be released by osmotic shock suggests that they are located on the surface, it does not prove that the released proteins are involved in transport. Proteins that have no known role in transport are released by osmotic

Table 2. Amino acid composition of membrane transport proteins. Values are moles.

Amino acid *	Substrate				
	Salmonella typhimurium $SO_4^=$	*Escherichia coli*			Chick duodenum Ca^{2+}
		Leucine (*11*)	Galactose (*11*)	PEP (*15*)	
Alanine	23	42	42	10	15
Aspartate	30	38	49	4	28
Arginine	8	7	6	1	5
Cystine	0	1		0	3†
Glutamate	21	36	28	16	32
Glycine	17	33	22	7	15
Histidine	4	4	3	2	3
Isoleucine	12	18	15	4	9
Leucine	16	22	24	8	24
Lysine	19	28	30	8	20
Methionine	1	4	6	2	4
Phenylalanine	9	10	7	4	11
Proline	9	14	9	2	3
Serine	13	11	13	6	9
Threonine	11	16	12	10	8
Tryptophan	5	3	4	0	
Tyrosine	9	12	6	0	8
Valine	17	23	29	8	6

* Analysis by A. Tsugita; † Cystine (cysteine not done).

shock (*25*). Many are nucleases or phosphatases, of which alkaline phosphatase is the first example. Of particular interest is the R_2 protein of *E. coli* which appears to be involved in regulation of alkaline phosphatase synthesis (*30*). Mutants which cannot make this protein are constitutive; that is, they produce phosphatase in large amounts even when phosphate is present, a condition which prevents the nonmutant bacteria from forming the enzyme. The R_2 protein is like the binding proteins; it has a molecular weight of about 30,000 and binds phosphate firmly. But mutant and nonmutant bacteria transport phosphate with the same kinetics, and so the protein does not seem to function in phosphate transport (*31*).

The sulfate-binding protein is on or near the surface because it reacts with a protein reagent (diazotized aminonaphthylene-disulfonate) that cannot penetrate the cell membrane (*9*). Also, sulfate is bound by bacterial mutants into which it cannot penetrate. Experiments in Oxender's laboratory have used antibodies specific to the leucine-binding protein to label this protein in acetone-treated *E. coli*; then the antibodies are located at the cell surface with the electron microscope (*7*). In both cases, the antibody does not inhibit binding by intact bacteria, although it does with the purified proteins (*7*, *9*).

Not all recognition proteins are released by shock. The M protein and sodium-and-potassium-activated adenosine triphosphatase are bound to the membrane. They are released by detergents, and so are not held by covalent bonds. Red blood-cell ghosts similarly hold the adenosine triphosphatase of sodium and potassium transport (*22*, *23*). The Enzymes II of sugar transport are associated with membrane and have not yet been solubilized (*15*). They are on the bacterial membrane vesicles prepared by Kaback (*16*).

Speculations on Translocation

The unique step in transport is movement of substrate across the membrane. Two general mechanisms have been suggested for this translocation. The first might be called the permease hypothesis, since the name permease implies an enzyme. The basic assumption in this model is that the recognition protein is an enzyme that catalyzes bond formation between substrate and a low-molecular-weight transporter in the membrane. This compound is assumed to be soluble in membrane lipids and to diffuse across to the inner side where it dissociates and releases substrate (*32*). Phospholipids have been suggested as transporters; but the turnover of radioactivity in phospholipids which would be expected during transport is not found (*33*).

According to a second hypothesis made by many workers (*1*), the recognition protein itself carries the substrate across the membrane. A variety of detailed mechanisms have been suggested for this translocation process. Basically, they require the proteins to undergo either diffusion (possibly rotational) or a conformational change which physically moves part of the protein across the membrane or else opens a passage through it. The latter is a particularly attractive idea because a small movement of even a single peptide chain might unbar a hole through the membrane. A small conformational change of this sort could easily be effected by reaction of the energy source at some other part of the protein (an allosteric transition).

That part of a protein can be exposed to either the exterior or interior of the membrane is suggested by the ability of external ATP to stimulate β-galactoside transport (*6*). Also, addition of HPr, Enzyme I, and PEP to the medium can cause phosphorylated α-methylglucoside to accumulate outside membrane vesicles (*34*).

There is no evidence to enable one to decide between these plausible mechanisms. Since the word permease at least implies a reaction involving an enzyme, in spite of early intent to be more general, it has created considerable confusion. Permease should be abandoned, and some less suggestive name such as transfor (to mean carrier-across) might well be substituted to mean the central proteins of transport.

One approach to understanding translocation should come from the properties of transport proteins. Most of these have not yet been studied in detail. However, we have obtained some information about the sulfate-binding protein which could be pertinent (*9*). This protein is long enough to stretch across the membrane (70 to 120 Å depending on assumptions of shape). Although its length does not prove that it passes through the membrane, this is clearly a possibility. This protein has not shown any enzyme activities, particularly no reactions with ATP such as exchanges or hydrolysis, although covalent linking of sulfate to a transporter would require energy. Therefore these results argue against the binder protein being an enzyme that carries out such a reaction. Nor is the binder protein soluble in lipid solvents, either with or without sulfate, indicating that it probably does not function by diffusing across the membrane with its bound substrate. Nor have any striking conformational changes been observed when sulfate is added. Since three other cistrons (genetic units of function) are involved, we anticipate a more complex mechanism.

The sodium-and-potassium-dependent adenosine triphosphatase is a much more complex structure (*23*). Now that it has been isolated, we can expect progress in relating its phosphorylation by ATP with binding of the ions, and also with possible conformational changes. The protein is amply large to extend through the membrane, so it might act as the primary carrier.

Summary

I have tried to summarize briefly the main trends in current research on membrane transport proteins. This has not been a historical review because nearly all of the work was reported within the last 2 years, and much has not yet appeared in detail. The isolation of these proteins answers one question about transport systems, showing where the specificity of recognition resides. Rapid progress is being made in discovering the way in which energy is linked to transport. Nature seems to have devised several different mechanisms for active transport; in some cases the energy source reacts with the substrate, and in others it reacts with proteins of the system. The question of how translocation across the membrane is performed can be approached by studies of the properties of these proteins, and with reconstituted systems such as membrane vesicles.

Although the evidence for every one of these proteins is not yet complete, the results certainly make it virtually certain that they are involved in transport. Transport systems cannot have many specific parts because few genes are involved in any one of them. This fact gives promise of our soon understanding transport to the degree that we understand enzyme catalysis.

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Matter versus Materials: A Historical View

Cyril Stanley Smith

Not many years ago, I was a practical industrial metallurgist, and it is with some surprise that I find myself delivering a lecture in honor of a great historian. George Sarton pioneered in the application of the techniques of the historian to the then-neglected area of science. His immense energy, his proper regard to rigorously checked detail, his respect for the boundaries of his chosen period, and his insistence on comprehensiveness within these boundaries set standards for two generations of scholars in the United States and for the entire discipline on a world scale. I have done detailed research in both science itself and its history, but I want to use this opportunity to make some general remarks on man's attitude toward materials (in contrast to matter) throughout the whole of history. These derive from the fact that I happen to have lived at the time of some rather exciting developments in materials science—in fact even its formation as a recognizable area of knowledge—and have had a moderately intimate (if one-sided) look both at the recent history of science and at archaeologists' findings of the earliest uses of materials of many kinds. I see science reversing the trend toward atomistic explanation that has been so triumphant in the last 400 years, and I predict a more human future based on the symbiosis of exact knowledge (which is by its very nature limited) and experience. This I do hesitantly, certain only that this is an important area for discussion at this particular stage of history. Materials provide a good illustration of the difficulties of applying exact knowledge to a complicated world.

Much of the history of materials has been rather dull, for man has usually been satisfied to make do with what he had, but there are three periods at which sharp changes occurred. These correspond to the first discoveries of the principal alloys and ceramic materials, the beginning of scientific explanation, and the very recent realization that, by the control of their structure, materials that possess almost any property in high degree can be designed and produced for special applications.

The Discovery of Materials

What Peter Drucker (*1*) has called the first technological revolution began more than 7000 years ago in the Middle East, where there arose an appreciation of the possibilities of technology combined with a pattern of social organization that both allowed the necessary

The author is Institute Professor at the Massachusetts Institute of Technology, Cambridge.

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