Mass Transport Phenomena In

The Human Circulatory System*

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The value of biological research in a chemical engineering graduate program is discussed by taking examples from the mass transport phenomena occurring in the human circulatory system. The particular points stressed are the broad range of such problems from molecular diffusion to artificial organ design, the relevance of the problems to traditional areas of engineering concern, and the value of research in the area as a technique for training engineering students.

The programs for meetings held over the past few years by the American Institute of Chemical Engineers and the American Society for Engineering Education bear witness to the emergence and persistent growth of interest in the interaction of engineering and biology. Almost every meeting has had at least one session devoted to some aspect of this interaction.

There are many possible explanations for such a development, all of them probably true to some extent. In the last decade, advances in the biological sciences have been the most dramatic in the scientific world and have called particular attention to the field. Morover, the social and humanistic awareness which seems to characterize the 1960's suggests that many people may find greater satisfaction in problems whose solutions appear to them to contribute directly to human welfare. Finally, the recognition and development of new kinds of unifying principles in chemical engineering, such as the transport phenomena, have greatly increased the range of applicability of chemical engineering techniques and perhaps have stimulated many of us to attempt to prove their usefulness in the unfamiliar and challenging areas of biology.

However, speculating on the reasons for the growth of biological engineering, while interesting, is not my purpose in this discussion. In keeping with the subject of the meeting, it would seem more appropriate to consider what effect this new area can or should have on graduate chemical engineering research. It is necessary to recognize that there are two extremes of organi-

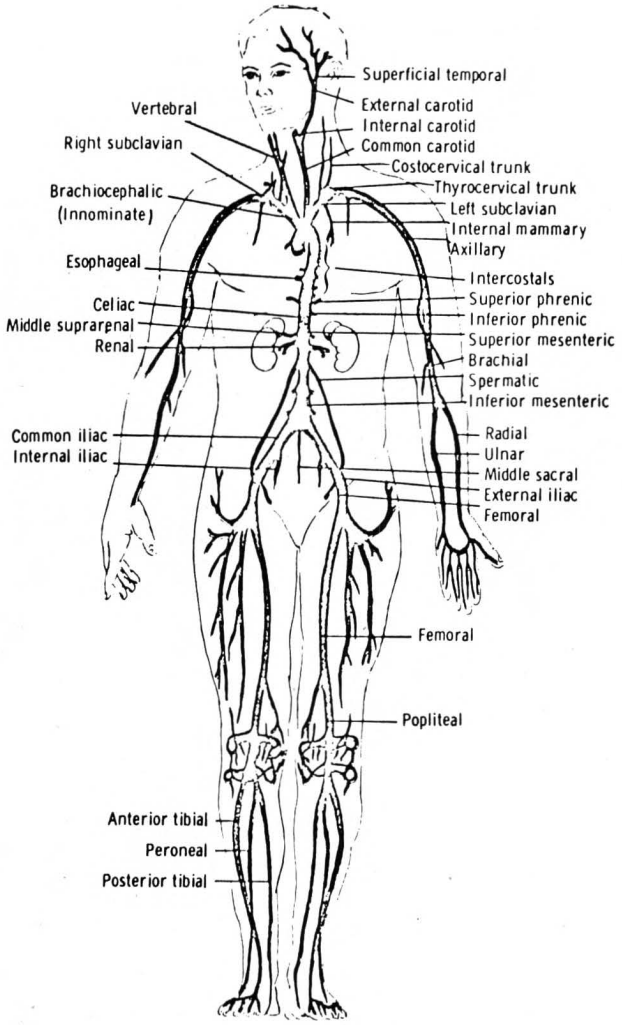

Fig. 1.—Human circulatory system.
From Chaffee and Greisheimer, *Basic Physiology and Anatomy*, with permission of J. B. Lippincott Co., Philadelphia.

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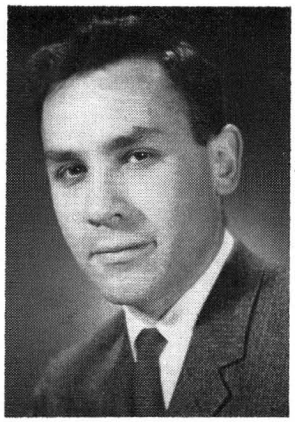

Dr. Keller did his undergraduate work at Columbia University and then spent four years in the Navy assigned to the Atomic Energy Commission. In 1959 and 1960, while in the Navy and attending the Johns Hopkins University part time, his interest in biologically-oriented problems developed. His full-time graduate research began in 1961 at Hopkins, centered on the phenomenon of augmented oxygen diffusion in hemoglobin solution. Since 1964 he has been an Assistant Professor of Chemical Engineering at the University of Minnesota and has continued and expanded his research interests in transport processes in biological systems. He is now directing research in diverse problems from protein diffusion studies to blood oxygenator design.

zation between which most bioengineering programs lie: the independent, formal bioengineering program, functioning through an interdisciplinary group joined together by a common interest in biology and the informal group whose research and teaching simply constitute one special area of a chemical engineering department. There is certainly no unanimity among people working in the field as to which, if either, of these extremes is the better for effective biological research, but obviously only the latter arrangement can benefit a chemical engineering department directly. Therefore my remarks will relate to this latter arrangement. In particular, I would like to illustrate:

a. The relevance of biological problems to the traditional areas of chemical engineering concern.

b. The wide range of problems in biology to which engineering analysis can be applied effectively.

c. The mutual benefit to biology and engineering which can result when engineers attack such problems.

d. The didactic value of having graduate students work in the biological area.

These points are best illustrated by example and the human circulatory system is a convenient one.* For many purposes the human body can be considered to be a highly complex chemical plant utilizing the energy of combustion to synthesize biological materials and to do work. The sites of reaction are distributed throughout the body and the circulatory system serves to deliver the reactants and remove the waste products; since the body functions isothermally, it must also remove excess heat. In addition the system serves a host of secondary functions: maintaining the proper water and salt content, distributing drugs and natural antitoxins, maintaining its own integrity by sealing "holes," adjusting pH to an optimal level, etc.

The magnitude of the job which the circulatory system must perform is evident from its design parameters. There are 5 to 6 liters of blood in the average human being (wholly contained within the circulatory system). The system's pump, the heart, has a capacity of about 6 liters/minute so that the circulation time through the body is slightly less than 1 minute. The average adult (70 kg) consumes about 14 liters (STP)/hr of 0_2 and releases about the same amount of CO_2, all of which is transported through the circulatory system.

The form of the system, as usually depicted in a medical text, is shown in Figure 1. Its most obvious characteristic is its high degree of branching, with main vessels branching in steps to large numbers of smaller vessels. However, from the point of view of mass transport, it is equally important to note that the system is bounded and that transfer into and out of the organs and tissues of the body must occur across the walls of the circulatory system. Such transfer takes place almost entirely in that region of the system made up of a network, or bed, of thin-walled, narrow bore tubes called capillaries. These capillaries are 10μ in diameter, have a wall thickness of about 1μ and a length of about 1 mm. Capillary beds are found in every organ and tissue of the body; since they are too small to be distinguished individually by the naked eye, it often appears that the blood is dispersed in a diffuse, continuous distribution through the tissue.

There are about 10^9 capillaries in the body so

*A useful and interesting introduction to the circulatory system is provided by Alan Burton's recent monograph.[1]

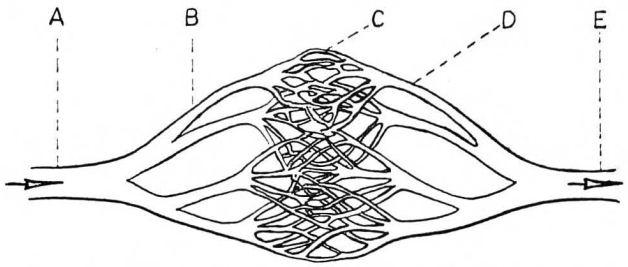

Fig. 2.—Schematic flow path to and from a single capillary bed. A. Artery; B, Arterioles; C, Capillaries; D, Venules; E, Vein.

that, despite the small size of each one, the total surface area available for transfer is about 340 ft^2. The extremely high surface to volume ratio in the system is evident from the fact that even with this large surface area, the capillaries contain less than a liter of blood at any instant. Transfer is so efficient that the residence time of blood in any capillary bed is only about 1 second.

The capillary beds are local structures and the rest of the circulatory system can be thought of as the piping to connect these structures and to carry materials and heat from one part of the body to another. The branching and progressive decrease in diameter of the system's piping is necessary to connect the central, large branches and the distributed, small branches. In Figure 2, one complete network is shown. Blood flows from the heart through the main artery (about 1" in diameter), branching to smaller terminal arteries, still smaller arterioles, and finally to capillaries. After exchange has taken place in the capillaries, the blood flows to larger venules, still larger veins, and finally to the principal veins of the body which lead back to the heart.

One of the key steps in defining engineering problems in a biological system is that of translating the description of the system into engineering terms. Consider, for example, how the schematic diagram of the circulatory system could be redrawn to the more familiar sort of schematic shown in Figure 3. The system is depicted as simply a set of single-pass shell (tissue) and tube (capillary) mass and heat exchangers connected in parallel. The arterioles and venules are the headers and the small arteries and veins are the connections to the main pipes. Pumping is provided by a double reciprocating pump and is, therefore, pulsatile. O_2 enters the system and CO_2 leaves the system in the exchanger called the lungs. Water, salt, and waste are removed through the exchanger called the kidney. On the shell side of the other exchangers, various chemical reactions take place which consume oxygen and produce carbon dioxide (muscles, brain, etc.). Heat is rejected from the body in the capillary beds, or exchangers, located in the vicinity of the outer surface of the body. Note that the heart and lungs are the only two organs through which *all* of the blood passes on each circuit.

The actual mass transport and transfer taking place in each of these units is not, of course, as simple as this picture would suggest. However, it does illustrate the transfer functions involved and thereby provides a basis for analyzing the behavior of each organ. It also establishes the functional requirements of any replacement or prosthetic unit, the design of which is one of the important areas of biological engineering.

If we proceed further and examine some of the transport and transfer processes in more detail, the efficiency and complexity of the circulatory system become evident as well as the range of challenging research problems to which chemical engineers have applied and should apply themselves.

Consider, for example, the process of oxygen transfer in the lungs. The blood, depleted of oxy-

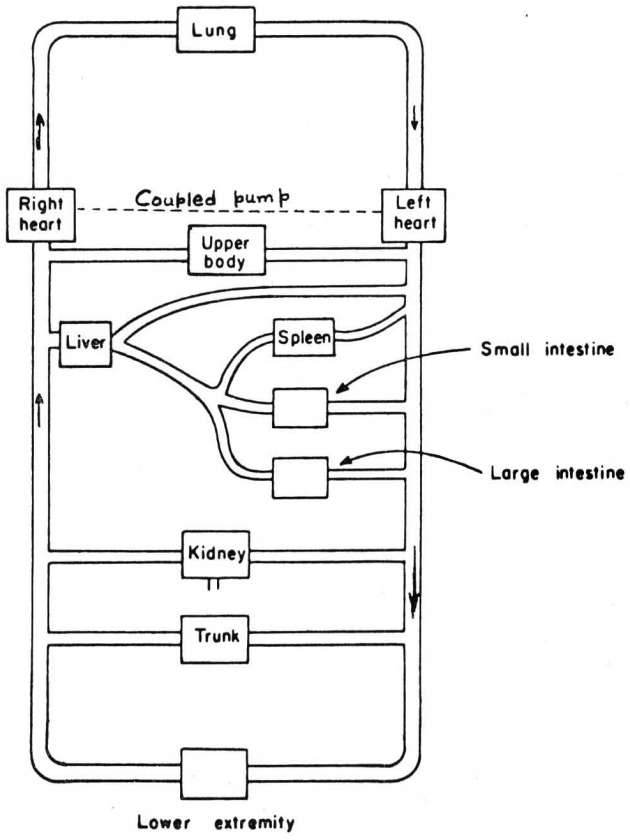

Fig. 3.—Schematic diagram of circulatory system.

gen by the tissues, enters the lung capillary bed at an oxygen tension* of about 60 mm Hg. It takes up oxygen and leaves the lungs at a tension of about 100 mm Hg. If oxygen uptake by the blood were limited to that which could be physically dissolved, a simple mass balance could be written to calculate the blood flow rate necessary to absorb the 14 liters (STP)/hr needed by the body for metabolism, i.e.

$$Q[(CO_2)_{out} - (CO_2)_{in}] = \frac{14}{60} \frac{\text{liters (STP)}}{\text{min}}$$

The concentrations can be calculated approximately from the physical solubility of oxygen in water (0.024 liters (STP)/liter H_2O atm). This equation can then be solved for Q, the volumetric flow rate, yielding a value of 185 liters/min, 31 times the actual flow rate available. Thus the circulatory system must have recourse to something other than the simple physical solubility of oxygen in order to absorb a sufficient amount of oxygen. This is provided for in blood by the large protein molecule, hemoglobin, which can combine reversibly with four oxygen molecules. Hemoglobin is present in blood to the extent of 15 gms/100 ml and, based on its molecular weight (68,000), if it is completely oxygenated, approximately 50 times as much oxygen can be carried in this combined form as is carried in the physically dissolved form. The combination must, of course, be reversible in order for the oxygen to be available to the tissues for metabolism. In

*Oxygen tension, in physiological parlance, is that concentration of oxygen in liquid which is in equilibrium with a gas phase having an oxygen partial pressure of the value stated.

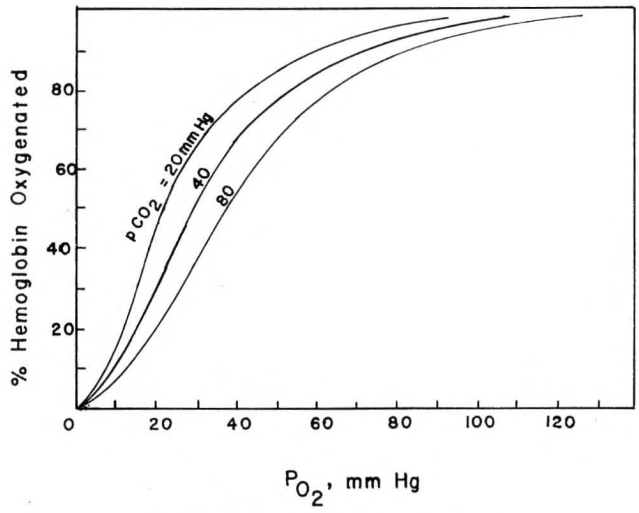

Fig. 4.—Typical equilibrium curves.

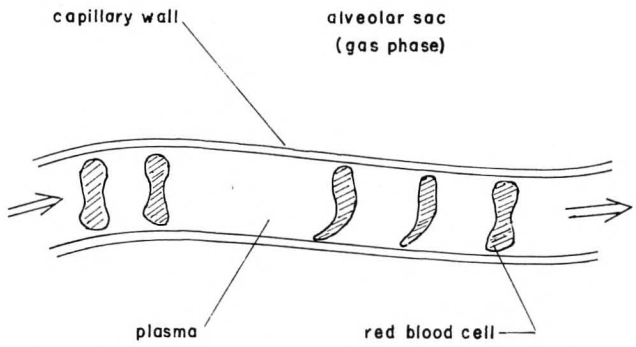

Fig. 5.—Red blood cells passing through a capillary.

fact, the equilibrium between hemoglobin and oxygen is not only reversible, but shifts conveniently to facilitate absorption and desorption. This is illustrated in Figure 4, which shows some typical oxygen-hemoglobin equilibrium curves. Note that at low CO_2 concentrations (which would exist in the lungs), the affinity of hemoglobin for oxygen is large and the hemoglobin is close to fully oxygenated at an oxygen tension of 100 mm Hg. However, at high CO_2 concentrations, such as those which are found in the body tissues, the affinity decreases and the degree of oxygenation for a given oxygen tension decreases markedly so that oxygen is readily available to the tissues.

Hemoglobin is not distributed homogeneously throughout the blood; it is contained in extremely high mass concentration (35 gms/100 ml) within the red blood cells which constitute 40-45 percent by volume of the blood. These red blood cells are biconcave discs approximately 8μ in diameter and varying from 1μ to 2.5μ in thickness. Thus, their diameter is almost equal to the inside diameter of the capillaries. In fact, in passing through the capillaries, the red blood cells line up in single file and slip through as shown in Figure 5. For the capillaries of the lung, note the complex diffusional process involved in getting oxygen from the gas sacs of the lung (alveoli) to the hemoglobin with which it must react. The oxygen must diffuse across the capillary wall, through a layer of plasma, across the red blood cell membrane, and then through the hemoglobin solution with which it simultaneously reacts. This gives rise to several interesting and not completely solved mass transfer problems. For example, which of these resistances is limiting on the total rate of uptake (or desorption) of oxygen? What path does the oxygen take in the plasma? Do the convective

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mixing patterns which must be set up in the plasma between cells increase the uptake rate? Is the red blood cell membrane equally permeable over its entire surface or do materials cross it in localized regions? What bearing, if any, does the shape of the cell have on mass transport?

The answers to such questions have an obvious bearing on the design of devices to replace inoperative transfer organs in the body. They may also be useful in the diagnosis of pathological (disease) conditions. But one of the important lessons in the development of engineering has been the recognition that it is possible to generalize results, to see the phenomenological similarities between processes in quite different systems and to relate the experimental and analytical results of one system to another. Thus, the results of studies of mass transfer across the membrane of a red blood cell should bear some relation to the problems of supplying nutrients to microbial cultures. They should also complement the work of cell physiologists studying general membrane properties. Similarly, information on diffusional behavior in hemoglobin is of interest to molecular biologists and biophysicists interested in characterizing macromolecules. Therefore I think it is necessary to avoid the narrow interpretation that biological engineering refers to clinically directed, biomedical problems. I have, in fact, avoided the use of the term "biomedical engineering" for precisely this reason.

A reasonable approach to understanding the uptake of oxygen in blood is to study separately each of the diffusion resistances involved. The easiest of these to study is the red blood cell (contents and membrane) since it can be easily removed and studied outside the body, or *in vitro*. Much of the early work in this area was done by F. J. W. Roughton who published a useful review article some years ago.[2]

In the cell itself, the transport process occurring is one of diffusion accompanied by reversible chemical reaction. In this context, it is analogous to such industrial processes as the absorption of chlorine by water which has been studied extensively by Vivien and Brian.[3] Therefore this is a typical problem in which the results of studies on the biologically important system have applicability to traditional engineering systems. Because the hemoglobin-oxygen reaction is accompanied by an easily detectable color change, it provides a simple experimental system and we are now using it to study unsteady gas absorption with reaction.

Studies on the hemoglobin-oxygen system have uncovered another mass transport phenomenon of engineering interest. In 1959 and 1960, Wittenberg[4] and Scholander[5] discovered that if a Millipore filter soaked in hemoglobin solution were placed between two gas chambers at different pressures, the steady-state diffusion of oxygen exceeded that of nitrogen by several-fold in certain concentration ranges although their driving forces were the same. This intriguing phenomenon has been studied in some detail by several workers, including Friedlander and myself[6,7] and the mechanism is fairly clear. Oxygen entering the liquid phase will combine reversibly with hemoglobin. Because of the equilibrium between combined and uncombined form, the concentration of oxygenated, or oxyhemoglobin, will depend upon the local concentration of oxygen. Since an oxygen gradient exists across the system, in certain ranges of concentration an oxyhemoglobin gradient will also exist and the total flux of oxygen will be the sum of the two resulting fluxes. The interesting engineering aspect of this is that such a system can be used effectively to separate gases if a reversibly reacting species can be found which reacts selectively with one of the gases. At General Electric, Ward has been examining such separation systems.[8]

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In the course of our investigations into this phenomenon, it was necessary to determine the diffusion coefficient of hemoglobin as a function of concentration. The subject of diffusion of large molecules in liquids at other than infinite dilution is one for which there are relatively few data and no useful theory. Yet, almost all

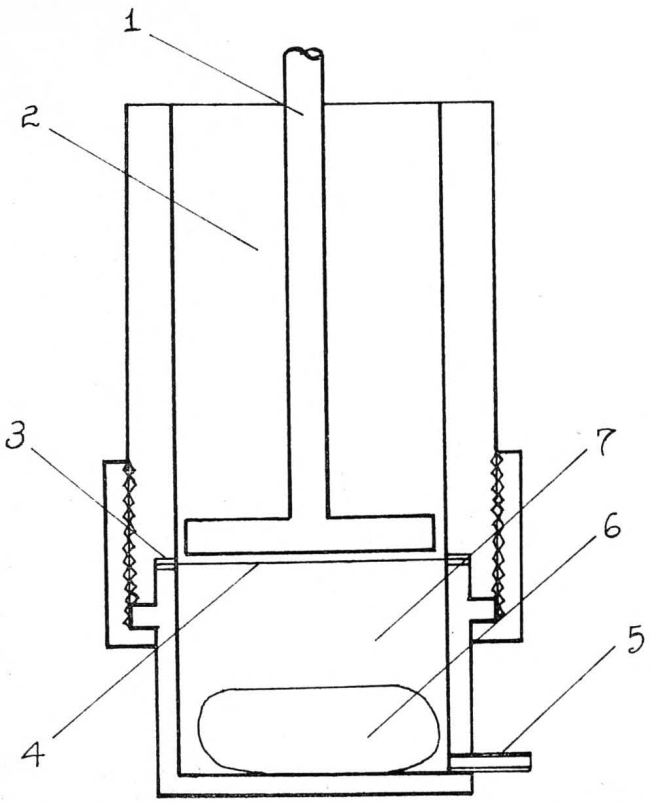

Fig. 6.—Diaphragm cell for methemoglobin diffusion coefficient measurements: 1,Stirrer; 2, Upper compartment; 3, Teflon gaskets; 4, Millipore filter; 5, Sample inlet; 6, Magnetic stirring bar; 7, Lower compartment.

living cells contain at least 20 percent by volume of large protein molecules, so that such data are necessary if intracellular diffusion problems are to be examined. We have developed a modified Stokes diaphragm diffusion cell which allows rapid measurement of protein diffusion coefficients[9]. In the cell, shown in Figure 6, diffusion takes place only in the thin, Millipore filter separating the two reservoirs. Because the filter is thin, steady state is achieved rapidly and diffusion fluxes are large enough to be measured despite the large size and correspondingly small diffusion coefficients of protein molecules. One feature of proteins which makes them desirable for such studies is the fact that radioactive tracers can be attached to them easily, thereby facilitating tracer diffusion measurements. This obviates the need for converting integral diffusion coefficients to differential diffusion coefficients, a process which has inherent inaccuracies.[10]

Some of our results with hemoglobin are plotted in Figure 7. It is interesting to note that at high concentrations, the diffusion coefficient decreases linearly with concentration. Other available data indicate similar behavior and have led us to a simple phenomenological theory for predicting diffusivities of proteins as a function of concentration. A question not yet investigated, but of great interest, is whether or not, as a result of the small size of the cell, proteins exist *in vivo* as liquid crystals with markedly different diffusional properties.

The membrane which forms the boundary of the red blood cell represents a separate area of investigation. Electron micrography has shown that the membrane is about 100 Å thick and composed of protein and lipid (fat-soluble) material. While there is still basis for argument, the so-called unit membrane shown in Figure 8 is often accepted as representative of the membrane structure. It is simply a bimolecular lipid film, oriented with polar ends outward toward the aqueous phases and non-polar ends inward, and sandwiched between protein layers. While the picture fits morphological evidence, it is of little help in understanding or choosing a model for explaining the transfer function. For example, should the membrane be modeled as a matrix of pores in an otherwise impermeable structure? This might explain a selective permeability based on the size of the diffusing molecule. On the other hand, if the membrane were modeled as a continuous, non-polar phase, selectivity would result from variations in phase partition coefficients among different molecules. Indeed, both kinds of selectivity occur and suggest that a more complex description is necessary to understand membrane function adequately.

Perhaps the most intriguing aspect of membrane transport is suggested by the observed distribution of cations inside and outside the red

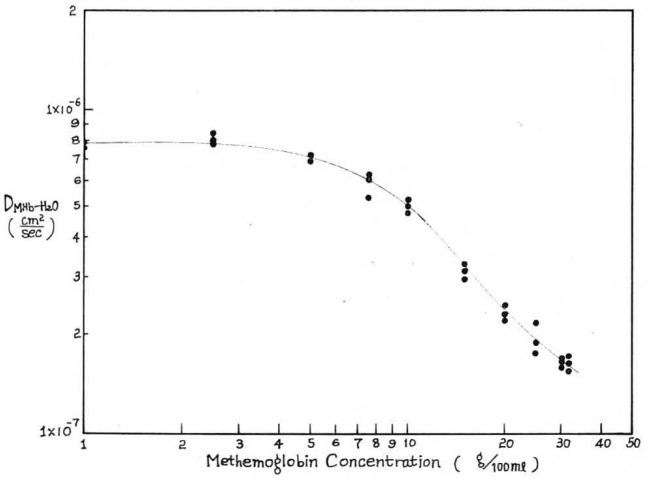

Fig. 7.—Diffusion coefficient of methemoglobin at 25°C.

blood cell. Inside the cell, the concentration of K^+ is 0.136 M while that of Na^+ is only 0.019 M. Outside the cell, the situation is reversed with the K^+ concentration only 0.005 M and the Na^+ concentration 0.112 M. Yet tracer studies show that both cations exchange across the membrane and, moreover, if an excess of K^+ is placed in the plasma, it is quickly taken in by the cell. The flux is thus in the opposite direction from that expected by simple diffusion theory. Close investigation shows that this flux is accompanied by chemical reaction in the membrane which provides the energy necessary to satisfy thermodynamic considerations. However, we are still far from understanding the mechanisms of this "active transport." A good deal of effort has been spent in describing the phenomenon in the formalism of irreversible thermo-dynamics,[11] but this simply begs the question. Since membranes are now thought to be responsible for most of the organizing and control functions of biological systems, research in this area is of great current importance.

Still another kind of mass transport exhibited by the circulatory system is that resulting from the flow patterns in the larger vessels. Throughout most of the circulatory system, the Reynolds' number is less than its critical value and flow is laminar. The laminar velocity profile is essentially parabolic, although somewhat flattened at the center because of the pulsatile and non-Newtonian character of blood flow. Normally in laminar tube flow, radial diffusion occurs only through Brownian motion. Blood, however, is particulate in nature and the red blood cells rotate as they flow under the influence of the velocity gradient. As they rotate they stir the plasma in their vicinity and thereby cause a mixing motion which can be interpreted as a particle-induced eddy diffusivity. This phenomenon should augment the radial transport of species dissolved in the plasma and, indeed, preliminary experiments indicate that it does.[12] We are now utilizing the effect to decrease the resistance of the plasma to diffusion in an artificial blood oxygenator. We hope that this will allow us to decrease the required surface-to-volume ratio of the oxygenator, an important design improvement. There is also evidence that the phenomenon may aid in understanding some of the transport mechanisms involved in arteriosclerosis. Finally, it seems possible that this phenomenon can be put to use in certain industrial processes. For example, if a diffusion limited wall-catalyzed reaction takes place in a continuous flow tubular reactor, it may be possible to increase its efficiency by introducing a suspension of inert particles to decrease diffusion resistance.

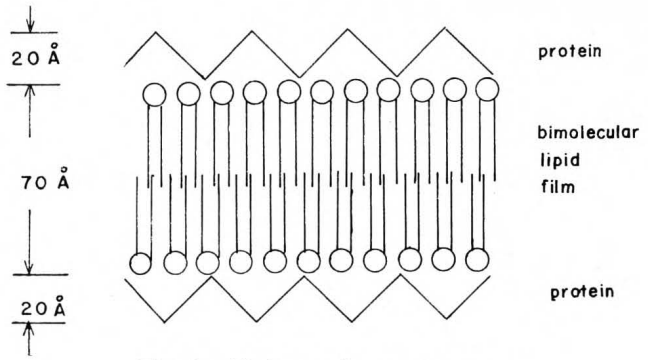

Fig. 8.—Unit membrane structure.

I have avoided a direct discussion of the design of artificial organs not because it is less important than these others, but because it is perhaps the most obvious area for engineering participation in biomedical research. It is, of course, profoundly important, and has given rise to many interesting problems in trying to duplicate the efficient transfer processes of the body and in trying to find materials compatible with blood. A review of the early design work in heart-lung assists is given by Galletti and Brecher[13] and a running account of the current state of things is available in the *Transactions of the American Society for Artificial Internal Organs.*

So much then for this cursory look at the range of mass transfer problems in the circulatory system. It is, I think, clear that these problems are the legitimate concern of chemical engineers. I am of the opinion that they are also challenging and interesting. Finally, I would like to stress my belief that they have a unique value in the training of chemical engineers. The language of biologists is not the language of engineers. Therefore the researcher must begin by distilling from the available biological descriptions the engineering essence of the problem. To accomplish this, he must first understand quite clearly the nature of engineering problems and the techniques of modeling. This adds an important facet to the training of researchers in an area which is often neglected. I think the result is not simply someone trained to examine biological problems, but in fact, someone better trained to examine any engineering problem.

(References listed on page 45).

ChE book reviews

Readers and others are invited to submit reviews of books of interest to the profession. Teachers are especially encouraged to write reviews of current textbooks they have tested in the classroom.

Non-Newtonian Flow and Heat Transfer
A.H.P. Skelland
John Wiley and Sons, New York (1967)
pp. vii + 469, 112 illustrations, $17.95

Many fluids involved in todays processing are non-Newtonian. For this area of study, Professor Skelland has provided the student engineer and the practicing engineer a text that is both detailed and lucid. To accomplish this he has excluded much of the mathematically complex and often obscure developments of rheology, and has included a wealth of practical examples. For the teaching of engineering methods and to the practicing engineer, who because of his age and the newness of the field managed to escape a depth of treatment, this book can be recommended. It was not written with the intent of being a text for advanced graduate research orientated courses, for these there are several books available; e.g. Frederickson, Lodge, or Brodkey.

A breakdown of the coverage is of interest. After introductory sections on classification of fluid behavior and experimental determination of flow properties, the author deals with the mechanics of steady flow in tubes; of this, about one third is on turbulent flow. Steady flow in annuli, parallel plates, and rectangular ducts are all briefly treated. The remaining half of the book covers optimization of non-Newtonian pipe systems, boundary layers, mixing and agitation, and heat transfer. The balance appears to be satisfactory considering the engineering nature of the text and the state of the literature in the field.

There are areas of interest to researchers that Skelland has avoided. Some may criticize him for this, but I feel he has done well to avoid them. With a cutoff time of early 1966 he could not include the very recent ideas on the second normal stress difference and drag reduction. Even today, such topics as these and the relations of viscoelasticity and thioxtropic behavior are still far from completely understood. I fail to see how one could write a universally satisfactory discussion of these factors, let alone how to account for the observed effects in engineering design. Much more work will have to appear in the literature before these topics can be adequately treated in an engineering text.

Finally, I should mention that this review and the feeling expressed herein are based on the use of the text for a quarter course at the advanced undergraduate level and introductory graduate level. The book was used for the undergraduates and master candidates who planned to terminate at these levels. With these, I considered the use of the book totally successful.

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