PERMEABILITY AND TRANSPORT STUDIES IN BATCH AND FLOW DIALYZERS WITH APPLICATIONS TO HEMODIALYSIS

by

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B.Ch.E., Cornell University (1964)

Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy at the Massachusetts Institute of Technology May 16, 1969

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JUN 24 1969
### ERRATA

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**4-33**

Minus sign (-) should be equal sign (=)

**5-4**

\[
RHS = D \frac{\partial^2 c}{\partial y^2}
\]

**5-7**

\[
LHS = -D \frac{\partial c}{\partial y}
\]

**5-16**

\[
RHS = \frac{r_D}{h^2}
\]

**5-25**

\[C^* = 1\]

**5-65**

\[
RHS = \sum_{m=0}^{\infty} B_m \exp[-2\beta_m x^*/3]
\]

**5-66**

\[LHS = B_m\]

**5-89**

Numerator should contain \[\frac{\partial Y_m}{\partial y^*}\] at \[y^* = 1/2\]

**5-93**

Minus sign (-) should be equal sign (=)

**5-103**

Insert equal sign (=) after \[Sh_{x,n}\]

**5-151**

\[
RHS = \frac{Y_Y}{Y_X}
\]
PERMEABILITY AND TRANSPORT STUDIES IN BATCH AND FLOW DIALYZERS WITH APPLICATIONS TO HEMODIALYSIS

by

Clark K. Colton

Submitted to the Department of Chemical Engineering on May 16, 1969, in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Massachusetts Institute of Technology

ABSTRACT

The overall objective of this thesis was to investigate solute transfer due to a concentration gradient in a hemodialyzer. This was accomplished through several independent but coordinated studies of mass transfer in membranes and in blood.

Membrane permeabilities of a variety of cellulosic membranes to a broad spectrum of solutes were measured with a batch dialyzer consisting of an unsupported membrane clamped between two stirred chambers. Theoretical and experimental studies were carried out to characterize the momentum and mass transport from the stirred fluid to the membrane surface, and a mass transfer correlation was obtained whereby the true membrane permeability could be estimated from a single experimental measurement. Permeation experiments demonstrated the profound decrease in solute effective diffusivity which accompanies membrane drying in the commercial cellophane manufacturing process.

Diffusion coefficients of various organic solutes were measured in stagnant water, plasma, and red cell suspensions using a micro-capillary technique. Comparison with a theoretical model showed that the red cells behave as a nearly impermeable suspended phase.

A flat plate dialyzer was constructed from which either solute diffusivity or membrane permeability could be determined by fitting experimental data to a theoretical model. Measured membrane permeabilities agreed excellently with results from the batch dialyzer. The effective diffusivity in flowing blood compared favorably with the stagnant diffusion model, indicating that no diffusion enhancement mechanisms were operative for the conditions studied.

A simulation of in vivo artificial kidney performance using experimental results from this study agreed well with literature data. Extension of this simulation to higher molecular weight solutes showed a cross-over from blood-limiting to membrane-limiting behavior.

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May 16, 1969

Professor E. Neal Hartley
Secretary of the Faculty
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Dear Professor Hartley:

In accordance with the regulations of the Faculty, I herewith submit a thesis, entitled "Permeability and Transport Studies in Batch and Flow Dialyzers With Applications to Hemodialysis," in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemical Engineering at the Massachusetts Institute of Technology.

Respectfully submitted.

Clark K. Colton
ACKNOWLEDGEMENTS

The author gratefully acknowledges the continued support and encouragement of Professor E. W. Merrill who first introduced the author to the interdisciplinary application of chemical engineering principles to biomedical problems. Professor K. A. Smith deserves special mention for his cooperation, patience, and enthusiasm for intellectually challenging problems. His influence pervades all aspects of this investigation.

Thanks are due to members of the department faculty and staff for their helpful technical discussions, including Professors L. B. Evans, E. R. Gilliland, T. K. Sherwood, and F. R. Cottrell, and Dr. P. S. L. Wong and Mrs. S. C. Liu. Conversations with former doctoral students R. G. Buckles, B. J. Lipps, D. J. Graves, J. Meyer and R. A. Britton are also appreciated.

The author was fortunate in having the collaboration of students working on B. S. and M. S. theses, including P. C. Farrell, L. B. Galpin, M. Laird, D. Phipps, J. M. Reese, and P. Stroeve, and the contributions of research assistants D. Voit and R. Martin. Design and construction of apparatus was aided by J. Moore and J. Balletti of Moore Mfg. Co.

The author would like to thank Professor E. F. Leonard of Columbia University and Professor A. L. Babb of the University of Washington for helpful discussions in the early phases of this investigation.

For their non-technical repartee which helped to break the tedium of the educational process, special thanks are due to J. T. Day, D. Cortez, and G. Margolis. The perseverance of my typists, Mrs. Elenore Kehoe, Miss Eleanor Baker, Miss Anita Hedberg, Miss Pat Costley and my wife Ellen, is also appreciated.

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Finally, the author wishes to express his unbounded debt of gratitude to his wife Ellen for her understanding and encouragement and for her contributions in all areas too numerous to mention; and to his parents whose sacrifices made his education possible.
To Ellen

and

My Parents
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A. Introduction

Hemodialysis has evolved from a curiosity to a life-saving clinical technique for the treatment of renal failure. The basic elements of hemodialysis are simple, as shown in Fig. 2-2. Blood flows on one side of a semipermeable membrane and dialyzate on the other side; excess electrolytes and waste products of metabolism permeate across the membrane.

The overall objective of this thesis was to investigate solute transfer due to a concentration gradient in a hemodialyzer. This was accomplished through several independent but coordinated studies of mass transfer in membranes and in blood. Membrane permeabilities of a variety of cellulosic membranes to a broad spectrum of solutes were measured in a transient diffusion experiment with a batch dialyzer consisting of an unsupported membrane clamped between two identical stirred chambers. Theoretical and experimental studies were carried out to characterize the momentum and mass transport from the stirred fluid to the membrane surface, and a mass transfer correlation was obtained whereby the true membrane permeability could be estimated from a single experimental measurement.

Diffusion coefficients of various solutes were measured in stagnant water, plasma, and red cell suspensions using a micro-capillary technique. A flat plate flow dialyzer was constructed from which either solute diffusivity or membrane permeability could be determined by fitting experimental data to a theoretical model. This permitted
independent verification of the membrane permeabilities measured with the batch dialyzer. Finally, a simulation of in vivo artificial kidney performance was made utilizing the experimental data obtained in this study.

B. Experimental Methods

1. Batch Dialyzer

The batch dialyzer, shown in Fig. 3-1, consisted of two identical, horizontal, water-jacketed lucite chambers between which the membrane was securely clamped. An axially-mounted four blade paddle impeller was positioned 1/8 in. from each side of the membrane, and a rotating mechanical seal was employed to prevent leakage around the shafts. Both impeller shafts were connected by timing belts to a single, variable speed motor. Chamber 1 was initially filled with solution containing the solute to be studied and chamber 2 with solvent alone. When an electrolyte was dialyzed, concentration in chamber 1 was monitored continuously by circulation through a conductivity flow cell located in a constant temperature bath. Discrete samples were taken from chamber 2 when dialyzing radioactively labelled organic solutes, and concentration was measured by liquid scintillation counting.

Solute employed included sodium chloride, urea, creatinine, uric acid, sucrose, vitamin B<sub>12</sub>, polyethylene glycol, inulin, heparin, and dextran. Additional measurements were made with five proteins in a simplified dialysis cell. Membranes studied included commercial cellophanes and wet gel regenerated cellulose. The membranes were
further characterized in terms of water content, solute distribution coefficients, strength, and by electron microscopy.

Measurements of liquid phase mass transfer coefficients were made in one chamber of the dialyzer with the membrane replaced by an aluminum endplate containing an insert of compressed benzoic acid. Both average and local coefficients were evaluated, the latter by measuring the depth of benzoic acid dissolved with a displacement transducer. Total power dissipation and torque expended on the membrane surface alone were studied in a full scale replica of one chamber of the dialyzer, as shown in Fig. 3-2. Membrane flutter was investigated by reflecting a laser beam off a membrane-nickel foil laminate placed in the agitated dialyzer. Fluid flow patterns within the boundary layer on the membrane were observed by using an optically thick suspension of tracer particles.

2. **Capillary Diffusion Measurements**

Diffusion coefficients were measured in a transient experiment with the microcapillary technique using radioactively labelled tracer solutes. Concentrations were measured with liquid scintillation counting techniques. Measurements were made with urea, creatinine, uric acid, sucrose, inulin, and dextran in saline, serum, and plasma, and with urea in red cell suspensions in saline and serum.

By using fine glass capillaries (radius ~500μ) and removing fibrinogen from the suspending medium, red cell sedimentation was minimized. All measurements were made
at 37°C. The serum, plasma, and blood were obtained fresh from a blood bank.

3. **Flat Plate Flow Dialyzer**

   The flat plate dialyzer consisted of four separate components as shown in Fig. 5-17. The main body of the dialyzer was composed of two virtually identical lucite blocks, in the center of which a channel was milled, with headers on either side, to contain a piece of highly porous nickel foam which served as a membrane support. The dialyzer was assembled horizontally and operated vertically. A sandwich arrangement was built up between the lucite blocks consisting essentially of two wet membranes separated by stainless steel spacers. The "blood" path was a thin channel with large aspect ratio defined by the membranes and spacers. Dialyzate flow in the nickel foam was perpendicular to the blood path. Particular attention was paid to the inlet and outlet header design to insure perfect fluid distribution.

   The blood side fluid was pumped through the dialyzer from a reservoir by a variable speed dual syringe pump. Dialyzate (water or saline) was pumped from a reservoir with a Moyno screw pump. Concentration measurements were made by the same techniques as described for the batch dialyzer. Sampling valves were located at the dialyzer inlet and outlet and all experiments were run at ambient temperature.

   Dye visualization studies were run to insure perfect fluid distribution obtained and to check for internal leaks. Transport in the dialyzate phase was characterized
by pressure drop measurements and by mass transfer coefficient measurements using a plate containing compressed benzoic acid.

C. Theoretical Analyses

1. Batch Dialyzer

A theoretical analysis was developed to model the torque on the membrane and mass transfer in the membrane boundary layer. The analysis was based upon existing solutions for the dynamics of a fluid rotating against a stationary surface and is summarized in Table 3-1. Two limiting cases were considered: 1) the fluid far from the boundary rotates with the same angular velocity as the impeller; and 2) the impeller was treated as though it were replaced by a disk, in which case two boundary layers form, one the disk and one the base, between which exists an inviscid core undergoing solid body rotation with an angular velocity equal to a fraction of the disk angular velocity.

For a laminar boundary layer, the known velocity field obtained from a solution to the Navier-Stokes equations was used to estimate the torque and to solve numerically the partial differential equations describing convective transport. Analytical solutions were developed for the "far field" conditions away from the surface and for the "entrance region" at the leading edge of the mass transfer surface. The latter was matched to the numerical solution. For a turbulent boundary layer, the solution of the momentum boundary layer integral equations, with Blasius semiempirical shear stress correlation, yielded an estimate of the torque.
Mass transfer raltionships were obtained from a modified form of the Chilton-Colburn transport analogy.

2. Diffusion in Stagnant Plasma and Blood

A theoretical model for predicting the effective diffusion coefficient in plasma was developed. Plasma was treated as a heterogeneous suspension of proteins in saline. The model incorporated an existing analysis for diffusion in a dilute suspension of prolate ellipsoids and included the effects of reversible solute binding by proteins and diffusion of the solute-protein complex.

Next, blood was modeled as a suspension of permeable ellipsoids in a homogeneous suspending medium. The predicted effective diffusivity in blood was a function of the shape and volume fraction of the red cells, the ratio of the solute diffusivity in the red cell to that in the suspending medium, and the equilibrium distribution of solute between red cells and suspending medium. An extensive evaluation of literature data was carried out to obtain quantitative estimates of the parameters required in the theoretical models.

Both models assumed equilibrium between the suspended phase and the suspending medium. The analysis was extended to the case of transient diffusion in heterogeneous media with non-equilibrium between phases. The transient model consisted of two simultaneous second-order partial differential equations coupled by an interphase transport term corresponding to capacitive effects between the red cells and the suspending medium. An analytical solution
was obtained for a linear solute distribution relationship. The model provided a definitive criterion for the validity of the equilibrium assumption.

3. **Flat Plate Flow Dialyzer**

A theoretical model was developed for dialysis of a solution in laminar flow between two semi-infinite parallel membranes. The problem differed from the classical Graetz problem in the boundary condition at the wall, which specified that the flux through the wall was proportional to the wall permeability. Use was made of existing analytical solutions for this case and for the analogous heat transfer problem. A modified method was employed which was more efficient on a digital computer. Limiting analytical solutions were obtained for the entrance region and for an asymptotic expression for the higher eigenvalues.

Techniques were developed to determine either the solute diffusivity or the membrane permeability by fitting experimental data to the theoretical model using a minimization algorithm. For this purpose, a "black box" computer program was written to permit very rapid calculation of the theoretical solution from the input parameters. The essential feature of this approach was a high order polynomial fit to the first seven eigenvalues.

D. **Results and Discussion**

1. **Batch Dialyzer**

Measured local mass transfer coefficients are compared with the theoretical solution in Figs. 3-17 and 3-18 for laminar and turbulent boundary layers, respectively. Except
in the vicinity of the chamber wall, the data fall between the two limiting cases. Torque data and average mass transfer coefficients are compared with theory in Figs. 3-16 and 3-19, respectively. The data and theory compare favorably, and together with the membrane flutter results, Fig. 3-22, the results show that a transition from a laminar to turbulent boundary layer occurs over a Reynolds number range of 20,000 to 30,000.

The "single point" determination of true membrane permeability is summarized in Table 3-2. The liquid phase mass transfer resistance is estimated from the correlation and subtracted from the overall measured resistance to yield the true membrane resistance.

Table 3-4 summarizes the permeability measurements with radioactive solutes. The results for Cuprophane PT-150 and Avisco wet gel are shown in Fig. 3-31, where the ratio of the membrane permeability to that of an equal thickness of water is plotted as a function of molecular size. The results show a) the very large decrease in the ratio as solute size increases, and b) the profound reduction in permeation properties which occurs when wet gel cellulose is dried, following glycerol plasticization, during the manufacture of cellulose. For solutes greater than about 10 Å in characteristic radius, the effective diffusivity in wet gel is more than an order of magnitude higher than in Cuprophane.

2. Capillary Diffusion Experiments

Measured diffusion coefficients in saline agreed well with literature data. Effective diffusivities in plasma
and serum were essentially identical. Diffusivities for all solutes decreased from the values for pure saline, the ratio between the two varying from about 0.62 for uric acid to 0.87 for inulin. Predicted diffusivities agreed well with measured values, indicating a strong influence of the degree of protein-solute interaction.

Diffusion measurements in red cell suspensions were made at seven different hematocrits, ranging from 38 to 72. Increasing hematocrit decreased the effective diffusivity. The data agreed well with the predicted values, corresponding to a permeability ratio between red cells and plasma of about 0.02.

The data and theoretical models showed that the red cells behave as a nearly impermeable suspended phase. However, the non-equilibrium model showed that, in the experiments performed, the red cell urea concentration could be assumed to be in equilibrium with the adjacent fluid. Quantitative criteria for the existence of equilibrium between phases were established for a variety of organic solutes.

3. Flat Plate Flow Dialyzer

Figure 5-23 shows the results of the mass transfer measurements in the dialyzate phase alone. The dialyzate mass transfer resistance calculated from the correlation was subtracted from the best-fit value of the "wall" resistance, yielding the membrane resistance. Dialyzer
performance with sodium chloride and Cuprophane PT-150 is shown in Fig. 5-24. The membrane permeability which best fit the data to the theoretical model agreed to within about one per cent with the value measured in the batch dialyzer.

Dialyzer performance with urea in whole human blood is shown in Fig. 5-31. The best-fit value of the effective diffusivity is compared with measurements in stagnant blood in Fig. 5-32. The results show that for the conditions studied the effective diffusivity in flowing blood is essentially the same as in stagnant blood, and any shear-induced augmentation effects are negligible.

4. Artificial Kidney Simulation

Using experimental data obtained in this study and the analytical model for transport in a flat plate dialyzer, predicted in vivo performance compared favorably with literature data. Extension of the simulation to higher molecular weight solutes showed a) a large drop-off in solute removal with increasing molecular size, b) a shift in the limiting resistance from blood to membrane-controlled behavior, and c) a significant potential gain in removal of larger solutes by replacement of currently used commercial cellophanes with wet gel cellulose.

E. Conclusions

The major conclusions from this study are as follows: 1. Momentum and mass transport to the flat bottom of a stirred cylindrical vessel agitated by an axially located
paddle impeller may be modelled in terms of a fluid rotating against a stationary surface.

2. Drying wet gel cellulose, following glycerol plasticizaton, and subsequent rewetting leads to a profound reduction in solute effective diffusivity within the membrane.

3. Diffusion of organic solutes in whole blood may be modelled as diffusion in a suspension of nearly impermeable solids.

4. Membrane permeabilities measured in both batch and flow dialyzers show excellent agreement.

5. With large channel heights and relatively low shear rates, no diffusion enhancement effects are operative with organic solutes in flowing blood.
CHAPTER 2

Introduction

A. Motivation and Purpose

Over the past two decades, hemodialysis has evolved from a curiosity to a life-saving clinical technique for the treatment of renal failure. However, the most recent estimates for the United States (45) show that only about three per cent of those individuals who require hemodialysis are receiving treatment (about 500-600 per year out of 15-20,000). Current hemodialysis therapy is plagued by high cost and inefficient and inconvenient operation.

The early development of hemodialyzers by medical practitioners was essentially empirical and often haphazard. However, as a mass transfer separation process, hemodialysis is a natural candidate for the application of chemical engineering principles and analysis to a biological system.

The overall purpose of this thesis was to obtain a fundamental understanding of the mass transport processes involved in hemodialysis. In addition to the engineering and scientific knowledge gained from this work, it is anticipated that the theoretical and experimental results will be of immediate practical value to medical science in two areas. First, it will provide the necessary theoretical framework and experimental data for the rational design of hemodialyzers. Secondly, it will show the capabilities and limitations of existing devices and point towards fruitful areas for further research.
B. The Natural Kidney

Before considering the operation of a hemodialyzer, it is necessary to have an understanding of the structure and function of the natural kidney. The discussion here will be brief. For further details, the reader is referred to a medical physiology text, such as Guyton (155) or the excellent quantitative analysis of kidney function by Albricht (1).

The kidney is one of the organs primarily responsible for homeostasis, or maintenance of the constancy of the internal environment. In doing this, the kidney performs several functions:

1) Water balance-removal of excess water
2) Electrolyte balance-regulation of plasma concentrations of ions
3) Acid-base balance-regulation of hydrogen ion concentration
4) Waste excretion-removal of nitrogenous end products of metabolism and solutes foreign to the body
5) Hormone and enzyme synthesis-renin and erythropoietin, the latter hormone being responsible for regulation of erythrocyte production by the bone marrow.

1. Anatomy of the Kidney

To perform the variety of functions described above, the kidney has a specialized structural organization. The kidney is an aggregation of about $10^6$ nephrons, each capable of producing urine by itself. A schematic diagram of a single nephron is shown in Fig. 2-1. Blood enters the glomerulus of the nephron and then flows through the peritubular capillary...
network surrounding the tubules of the nephrons and finally back to the veins. The glomerulus is a network of parallel capillaries encased in Bowman's capsule, in which fluid collects as it filters from the capillaries.

The fluid that filters through the glomerulus into Bowman's capsule flows through a sequential series of tubules and finally into the collecting tubule which collects fluid from the distal tubules of many nephrons. As this fluid flows through the tubules, most of its water and some of its solutes are reabsorbed into the peritubular capillaries; the water and solutes not reabsorbed become urine.

2. Renal Function

For every liter of urine produced about 180 liters of water are filtered, and nearly 2,000 liters of blood are recirculated through the kidney. Formation of urine involves the operation of three processes: filtration, reabsorption, and secretion. The first step is production of an ultra-filtrate of plasma by glomerular filtration, in which most of the largest molecules, such as plasma proteins, are retained but lower molecular weight solutes are passed. The glomerular filtrate is almost protein-free and contains all the smaller solutes present in plasma in the same concentration as in plasma except for small differences due to Donnan equilibrium.

During passage through the tubules, almost all the water and most of the solutes, except those to be excreted, are selectively reabsorbed from the filtrate. This process
Figure 2-1. Schematic Diagram of Kidney \[\text{denhron}].
From Guyton (155)
involves both passive and active transport, the latter occurring against a concentration gradient and requiring an expenditure of energy. In addition, certain solutes, in particular hydrogen and potassium ions, are secreted in the tubules.

From an engineering standpoint, the separation process carried out by the kidney is elegant. The essential element is the action of the tubules in being able to recognize solutes required by the body and being able to transfer them back into the blood stream while undesired solutes are not reabsorbed. Furthermore, this transport process acts in response to the solute concentration required in the blood by a self-regulating mechanism.

Diseases of the kidney can be classified into four different categories: 1) acute renal shut down, in which the kidneys stop working entirely; 2) renal insufficiency, in which nephrons are progressively destroyed until the kidneys cannot perform all the needed functions; 3) the nephrotic syndrome, in which the glomeruli have become more permeable than normal so that large amounts of protein are lost; and 4) specific tubular abnormalities, including lack of reabsorption of certain substances by the tubules.

In the case of acute renal failure, the pathologic state of the kidney may be repaired by the normal processes of the body if the individual can be kept alive for several weeks. For chronic renal failure, replacement of renal function is necessary for the remainder of his life, and
consequently the constraints placed upon an artificial device are more severe.

It is presently impossible to artificially duplicate the fifth major function of the kidney (hormone and enzyme synthesis). It is possible to replace the other four functions with a number of processing alternatives, none of which, however, operate in the same manner as the natural kidney. Some interesting comparison between natural and artificial kidneys have recently been made by Leonard (242).

C The Artificial Kidney

A number of processes have been considered for the replacement of renal function, including electrodialysis (31), gel filtration (433), and adsorption on ion exchange resins (447) and on activated charcoal (292). By far the most successful techniques have been dialysis and ultrafiltration, wherein solutes and water are transported across a semipermeable membrane by concentration and pressure driving forces, respectively.

The basic elements of hemodialysis are relatively simple, as illustrated in Fig. 2-2. In principle, blood flows in laminar flow on one side of a semipermeable membrane and dialyze, an osmotically balanced solution of electrolytes and glucose in water, flows on the other side. Blood is composed primarily of red cells and plasma, the latter containing organics, electrolytes, and proteins in water. During passage across the membrane, waste products and excess ions permeate across the membrane. In addition, water transport
occurs in either direction, depending upon the medical requirements, and is controlled by regulating the osmotic pressure of the dialyzate and the hydrostatic pressure difference between blood and dialyzate. With currently used membranes (cellophane-regenerated cellulose) and pressure gradients, the fluxes of solute and water are essentially independent, i.e., very little coupling occurs between the two. In this thesis, only solute transfer due to a concentration gradient will be considered.

In its simplest form, an artificial kidney is the mass transfer analogue of a double pipe heat exchanger. The overall mass transfer resistance is the sum of the resistances in series for the blood phase, membrane, and dialyzate phase.

A typical patient-artificial kidney circuit is shown schematically in Fig. 2-3. Blood flows from artery to vein through the extracorporeal circuit. A blood pump is used when needed, although the current trend is toward using hemo-dialyzers suitable for pumpless operation. The anticoagulant, heparin, is administered to prevent clotting as the blood contacts the foreign surfaces of the dialyzer. The heparin may be neutralized by infusion of protamine sulfate before the blood re-enters the body. This procedure is termed regional heparinization.

A thorough review and analysis of the artificial kidney literature covering the development and performance of hemo-dialyzers may be found in Appendix A. An earlier version of this review has been published by the National Institutes
A Double Pipe Mass Exchanger with Semipermeable Walls

Overall Mass Transfer Resistance = \sum \text{ Resistances} = \text{Blood Phase} + \text{Membrane} + \text{Dialyzate Phase}

Figure 2-2. Conceptual Illustration of Hemodialysis.
Figure 2-3. Typical Artificial Kidney Circuit
of Health (31). Appendix A contains a separate nomenclature and list of literature citations which is independent of the remainder of the thesis. It is pointed out in this analysis that with most currently used hemodialyzers, the blood side is a large, and in some cases limiting, mass transfer resistance for low molecular weight solutes. For higher molecular weight solutes, additional data is needed to draw definitive conclusions, but in general, the relative membrane resistance increases with increasing molecular weight.

D. Definition of the Separation Problem

From an engineering standpoint, the requirements of the separation process to replace kidney function are not well defined. The nature and amount of specific solutes to be removed and their degree of toxicity, as well as any pathological states which ensue from their lack of removal, are presently unclarified.

It is generally agreed that urea, creatinine, uric acid, and various excess electrolytes should be removed. Leonard and Dedrick (246) have tabulated estimates of daily excretion requirements for these compounds for a uremic patient on a restricted diet. Considerable research has been done, and is currently underway, to determine the toxicity of compounds whose blood concentrations have been found elevated in uremia. These comprise solutes primarily in the 200 to 600 molecular weight range (42). Included in this group are amino acids, both free and conjugated into small peptides (183, 258, 259, 296, 386, 442).
aromatic compounds (173, 224, 225, 289), hippurates (74), phenols (295, 346), guanidines (13), glucuronic acid and indican (295), and unidentified anions (353).

It has been speculated that significantly higher molecular weight toxins may be present in the uremic state (2). This may correlate with the clinically observed uremic neuropathy (18, 415) which tends to improve with intensified dialysis. However, no specific high molecular wt. compound (>1,000 M.W.) has yet been shown to be toxic upon isolation from uremic blood or the hemodialyzate fluid.

Concerning the possible toxicity of macromolecular solutes, it is only possible to speculate at the moment. In this respect, the monograph of King and Boyce (213) is particularly valuable. These authors presented a comprehensive review of available data on high molecular weight substances in human urine of normal individuals. Of the 433 mg/day of non-dialyzable solids found in human urine, only about 40% can be quantitatively accounted for. This fraction includes mucopolysaccharides, plasma proteins, blood group substances, uromucoid (excreted in the genitourinary tract), cellular debris, and oxalate crystals.

As for the remaining unidentified 60% of the non-dialyzable solids, these may represent normal components of the body, or 2) fragmented or altered components of tissue macromolecules which are not biologically normal, in the molecular weight range of 1,000 to 10,000. The authors believe compounds of the latter type can reasonably be expected to be found in normal urine. They represent a
leakage of atypical, improperly synthesized molecules, incompletely catabolized molecules, molecules derived from simple cell leakage or replacement, or other metabolic "end products." Thus, a substance that was a singular species in its original site could be present in urine as a family of molecules having various degrees of similarity to their "native" condition. Such substances might be in a denatured or atypical state when passing through the glomerulus and would not be reabsorbed.

King and Boyce further point out the difficulty in identifying such compounds in plasma. For example, if 180 liters/day (125 ml/min) of glomerular filtrate is derived from the 720 ml of plasma which perfuses renal excretory tissue each minute, then one mg of a completely cleared and non-reabsorbed component appearing in a 24 hr urine specimen by glomerular filtration alone may have been present in a concentration of one mg per 180 million mg of plasma water. Consequently, such compounds, even if elevated significantly, may go unnoticed in the analysis of uremic plasma or of dialyzate solution which has passed through a hemodialyzer.

Clearly, in terms of an engineering specification, it is not presently possible to delineate the separation requirements of a hemodialyzer beyond the lower molecular weight solutes mentioned at the beginning of this section. Nevertheless, it is essential to be cognizant of the fact that one is dealing with wide-ranging spectrum of solutes which undoubtedly vary in molecular weight, size, and shape, e.g.,
from hydrogen ions at one end to macromolecules of the order of 1,000 to 10,000 molecular weight at the other end.

E. Objectives of This Thesis

The overall objective of this thesis was to investigate solute transfer in a hemodialyzer. This was accomplished through separate studies of mass transfer in membranes and in blood. The specific objectives of these studies may best be summarized in the form of several questions:

1) How does one measure the true permeability of a highly permeable membrane?

2) What are the permeability characteristics of commercially available, modified commercial, and laboratory prepared cellulose membranes to sodium chloride and to organic solutes of varying molecular weight, size, and shape?

3) How does one characterize diffusion of organic solutes in stagnant plasma and whole blood?

4) Is the effective diffusion coefficient for a given solute in flowing blood the same as in stagnant blood?

5) How does one model the overall transport process in a hemodialyzer with a simple defined geometry?

6) Can in vitro data be used to predict in vivo performance of a hemodialyzer?

7) If the answer to (6) is yes, what can be learned about artificial kidney performance, limitations, and design by simulation of in vivo operation?
F. Overall Thesis Program

In order to accomplish the stated objectives, several independent but coordinated studies were carried out. Membrane permeabilities were measured in a transient diffusion experiment with a batch dialyzer consisting of an unsupported membrane clamped between two identical stirred chambers. Prior to the permeability measurements, theoretical and experimental studies were carried out to characterize the momentum and mass transport from the stirred fluid to the membrane surface from which a correlation was obtained for estimating the liquid phase mass transfer resistance.

Diffusion coefficients for various solutes were measured in water, plasma, and red cell suspensions using a micro-capillary technique. A flow dialyzer was constructed from which either solute diffusivity in the flowing fluid or membrane permeability could be determined by fitting experimental data to a theoretical model. Originally, a single capillary tube was contemplated. However, it was decided to use a flat plate device so that two independent permeability determinations of the same flat sheet membrane could be made. Measurements in the flow dialyzer were made with water, plasma, and whole blood.

A simulation of in vivo artificial kidney performance was made utilizing the laboratory experimental data and the model for solute transfer from fluid flowing between two flat, parallel, semi-infinite membranes. The results were compared with literature data and the analysis was extended
to higher molecular weight solutes for which *in vivo* data is unavailable.

The overall thesis program is summarized in the outline below:

A. Batch Dialyzer
   1. Momentum and mass transport from fluid to membrane surface.
      a. Theoretical Modeling
      b. Experimental Verification
   2. Membrane permeability measurements -- variety of membranes and solutes

B. Diffusion of organic solutes in water, plasma, and red cell suspensions using capillary technique, comparison with heterogeneous media theory.

C. Flow Dialyzer
   1. Theoretical modeling -- modified Graetz problem
   2. Experimental Studies
      a. Characterization of dialyzate phase
      b. Membrane permeability measurements
      c. Diffusion in flowing blood

D. Simulation of artificial kidney performance

G. Organization of Thesis Writeup

This thesis is organized into four major chapters, corresponding to the separate areas outlined above. In order to maintain continuity, each chapter is written as a self-sufficient entity, where possible. Consequently, intro-
ductory and background material, apparatus and procedure, and results and discussion are treated separately in each of the respective chapters.

H. Previous Work

No previous work concerning a comprehensive investigation of solute transport in hemodialysis has been reported in the literature. An analogous study to the work presented here for gas exchange in a membrane oxygenator was carried out by Buckles (57).

Although a rather complete study has not previously been carried out, various facets of the problem pertinent to this thesis have been investigated. These will be discussed in detail in each of the major chapters (see also Appendix A).
CHAPTER 3

Transport and Permeability Studies with the

Batch Dialyzer

A. Introduction

A series of coordinated experimental and theoretical studies were carried out with a batch dialyzer. The overall purposes of these investigations were to:

1) Develop a reliable and rapid technique for the measurement of the true permeability of a membrane; and

2) Evaluate the permeability of a variety of cellulosic membranes for a wide spectrum of solutes.

1. Measuring True Membrane Permeability

Evaluation of the transport properties of new synthetic polymers, as well as naturally-occurring materials, is the subject of much current research and development. Although the membrane evaluation literature is voluminous and historically quite old, much of it is of qualitative value only because insufficient attention has been paid to the difference between the overall measured transport properties and those of the membrane itself. This is particularly true of membranes for hemodialysis, where high permeability to most solutes is desirable. Consequently, the characterization of the mass transfer resistance in the liquid phase is a necessity for the measurement of the true membrane permeability.

It is only recently that many of the investigators studying membrane permeability have begun to realize that the permeability measured in an experiment is generally not an intrinsic quantity characteristic of the membrane. For example, Dainty (93)
has pointed out that the bulk of the published permeability data for natural biological membranes with rapidly permeating solutes may be considerably in error. He further suggests that the commonly accepted experimental proof of the existence of water filled pores in many natural membranes - the fact that osmotic permeability is higher than diffusive permeability - may be largely artifactual because of errors in measuring the diffusive permeability.

The ideal device for membrane permeability measurements would have a well-defined mass transfer resistance of constant magnitude over the entire membrane surface. Appropriate geometries meeting these conditions, the rotating cylinder and rotating disk, have recently been employed in reverse osmosis (381) and in liquid-membrane-gas (393) studies, where the membrane can be supported on one side. However, when two liquid phases are employed, as in dialysis, use of a membrane support is inconvenient and presents additional experimental problems in characterizing the resistance of the supported side.

A flow system employing a highly porous membrane support was originally suggested by Babb and Grimsrud (20). A flat plate flow dialyzer of this type was selected for measuring effective diffusivities in flowing blood (see Chapter 5) and it was desired to have an independent system for measuring membrane permeability.

Recently, Litt and Smith (250) presented a new technique in which the membrane was rotated between two stagnant liquid chambers. Using the theoretical equations for mass transfer to a rotating disc, they were able to evaluate the liquid phase
mass transfer coefficients and estimate the true permeability. However, the authors stated that the apparatus presented constructional and experimental difficulties and a need for continual replacement of component parts subject to wear.

Experimentally, the simplest and most popular configuration for flat sheet membranes, termed a batch dialyzer, consists of two stirred chambers separated by an unsupported membrane. Initially, chamber 1 is charged with a solution of the solute and chamber 2 with the pure solvent. The overall permeability or mass transfer coefficient is obtained by monitoring the change in concentration with time. Attempts to account for the liquid phase mass transfer resistance in such a system fall into three categories:

(1) Estimates of a hypothetical stagnant diffusion film thickness (141, 152, 166, 266).

(2) Operation above an empirically determined critical impeller speed where it is assumed that the liquid mass transfer resistances are eliminated (141, 229, 271, 405).

(3) Use of a modified Wilson plot (131, 197, 198, 214, 243, 441). Here the overall mass transfer resistance is broken down into its component membrane and fluid resistances in series:

\[ R_0 = R_m + R_{f1} + R_{f2} \] (3-1)

or in terms of mass transfer coefficients:

\[ \frac{1}{K_0} = \frac{1}{P_m} + \frac{1}{k_1} + \frac{1}{k_2} \] (3-2)

The two liquid phase resistances are assumed identical and
inversely proportional to the impeller speed, \( n \), raised to some exponent, \( c \). The overall measured resistance is plotted as a function of \((1/n)^c\) and the data extrapolated with the best straight line to infinite stirrer speed, yielding the estimated true membrane resistance. Values of the exponent, \( c \), have been chosen somewhat arbitrarily, ranging from 0.5 to 0.8. In a recent study, the exponent yielding the best statistical fit was found to be 0.68 (197).

All three methods suffer from certain drawbacks. Estimates of a stagnant film thickness present a misleading physical concept and have lacked generality because they fail to account for the influence of the relevant hydrodynamic, diffusional, and geometrical parameters. The same is true of a critical stirrer speed determined from a single calibration system. It is obvious that for a sufficiently permeable membrane the fluid resistance may be significant at any practical impeller speed. The use of a Wilson plot, while more rational than the other approaches, is extremely tedious experimentally, since it requires multiple evaluations of the overall resistance at a large number of speeds for extrapolation to the true membrane resistance. Operation at very high impeller speeds may cause the membrane to flex or flutter, possibly influencing the measured permeability. Furthermore, the Wilson plot implicitly assumes that a unique exponent yielding a straight line does exist over the entire range of speeds, or in effect that the flow regime of the boundary layer formed on the membrane, whether laminar or turbulent, is the same for all speeds. Finally, none
of the existing approaches recognize the influence of the membrane permeability upon the magnitude of the liquid phase mass transfer coefficients.

Clearly, knowledge of mass transfer in the liquid boundary layers adjacent to the membrane is necessary to provide a rapid and accurate assessment of true membrane permeability from a single experimental measurement. Existing literature on transport to fixed, flat surfaces in agitated vessels is limited. Calderbank and Moo-Young (62) presented a correlation based upon Kolmogoroff's theory of local isotropic turbulence (222). Johnson and Huang (192) studied mass transfer to the bottom of an unbaffled stirred tank, but their analysis was later questioned (269). Marangozis and Johnson (269) reviewed mass transfer to the bottom of a baffled agitated vessel and to suspended particles in an unbaffled vessel. Holmes et al. (182) investigated convective mass transfer in a diaphragm diffusion cell in which a magnetized stirring bar was rotated in a plane perpendicular to the diaphragm surface. Kaufmann and Leonard (797) recently presented a study of interfacial mass transfer based upon Wilson plot data obtained with a batch dialyzer.

2. Permeability of Membranes for Hemodialysis

Since the first application of hemodialysis to human beings (220) in 1944, all dialysis membranes employed have been regenerated cellulose, more commonly called cellophane. The primary reasons for its use have been availability, low cost, and reasonably high permeability. The materials in most common use today are Visking dialysis tubing number 36, manufactured by Union Carbide with the viscose process, and flat sheets of Cuprophane PT-150, manufactured by Bemberg and Co. (Germany)
using the cupro-ammonium process.

There are two concepts relating to the ideal hemodialyzer membrane. The first may be termed the "brute force" approach. By this concept, the membrane should be highly permeable to all solutes found in blood of a size smaller than serum albumin (Mol. wt. ~69,000, dimensions ~150Å by ~40Å). Important substances which should be retained (nutrients, vitamins, hormones, enzymes, amino acids) but which might pass through the membrane would be made up in the diet or added to the dialyzate bath.

The second concept is the selective removal of toxins. In this case, the membrane should be highly permeable to all solutes of a molecular weight below about 200 to 500 and selectively permeable to toxic substances of higher molecular weight. This would require no addition of vital components to the dialyzate bath.

While the second concept is clearly more desirable, current lack of knowledge of specific higher molecular weight toxins precludes the use of such membranes. As a viable alternative, size selective transport in the brute force approach must be employed. In this respect, regenerated cellulose is an ideal candidate for further research.

As discussed in Chapter 1, transport in a hemodialyzer may be caused by both concentration and pressure driving forces. This study is limited to membrane transport due to a concentration gradient only. A literature search was carried out to find published values of membrane permeability for cellophane. Apparently the first study was that of Britzinger and Osswald (54) in 1935. Since then, many investigations have been made, the most noteworthy being those of Craig and co-workers.
(84, 85, 86, 87, 88, 89) who studied the effects of the size and shape of permeating molecules. Unfortunately, the vast majority of available data is only of qualitative value. Table A-1 in Appendix A contains a compilation of published literature data on cellophane permeability which may be expressed in quantitative terms. In general, the results of various investigators show significant disagreement and only a few solutes have been studied. It was concluded that a reliable set of data for membranes currently used in hemodialysis did not exist.

Although much current research (261, 262, 263, 270) is oriented towards developing new polymeric materials for hemodialysis membranes, studies of the full potentialities of cellulosic membranes, either through modification of commercial materials or through totally new fabrication techniques, have been limited to those of Craig, cited above, and the recent work of Metzner, et al. (283). The results of these studies, however, have not been reported in usable quantitative terms. Consequently, it was decided to limit the scope of this study to evaluation of the permeability characteristics of a variety of cellulosic materials.

A detailed discussion of the many theories proposed to describe transport in artificial membranes is beyond the scope of this study. The reader is referred to the reviews of the subject by Kaufmann (196), Lakshminarayanaiah (228), and Heifferich (166). From a purely descriptive viewpoint, the application of irreversible thermodynamics to intramembrane transport has established a firm theoretical groundwork and provided an exact description of the physical process by defining the necessary number of phenomenological coefficients
required to characterize a particular membrane-solute system. Such an analysis was first described by Staverman (398, 399, 400) and was later extended by Kedem and Katchalsky (203, 204, 205) and Spiegler (397) to include a physical interpretation in terms of a frictional model. A comprehensive review of this area was recently made by Katchalsky and Curran (199).

For the permeation of a single non-electrolyte, the irreversible thermodynamic description of membrane transport is given as

\[ J_v = L_p \Delta P + L_{pD} RT \Delta C_s \]  \hspace{1cm} (3-3)

\[ J_D = L_{Dp} \Delta P + L_D RT \Delta C_s \]  \hspace{1cm} (3-4)

where \( J_v \) is the net volume flow, \( J_D \) is the velocity of solute relative to solvent, \( \Delta P \) is the hydrostatic pressure difference across the membrane, and \( \Delta C_s \) is the difference in the concentration in the liquid on either side of the membrane. From the Onsager reciprocal relation one finds

\[ L_{pD} = L_{Dp} \]  \hspace{1cm} (3-5)

Equations (3-3) and (3-4) are often expressed in an alternative form:

\[ J_v = L_p (\Delta P - \sigma \Delta \pi_s) \]  \hspace{1cm} (3-6)

\[ J_S = \bar{C}_s(1 - \sigma) J_v + \omega \Delta \pi_s \]  \hspace{1cm} (3-7)

where \( J_S \) is the solute flow, \( \sigma \) is the reflection coefficient, \( \bar{C}_s \) is the mean membrane concentration in the membrane, and \( \omega \) is the permeability coefficient.
For the case of zero volume flow, which is of primary interest in this study,

\[ \omega = \frac{J_s}{\Delta p_s} \bigg|_{J_v=0} = \frac{J_s}{RT \Delta C_s} \bigg|_{J_v=0} \quad (3-8) \]

This situation can be attained with equal hydrostatic pressures and balanced osmotic pressures on both sides of the membrane. To achieve the latter condition, the use of a low concentration of labelled tracer solute as the permeating molecule is particularly helpful.

Another expression for membrane permeability when only solute transport occurs is given by

\[ \dot{n} = P_m \Delta C \quad (3-9) \]

where \( C \) refers to the liquid concentration at the membrane-liquid interface. Since \( \dot{n} \) and \( J_s \) are the same quantities, comparison of eqns. (3-8) and (3-9) shows that

\[ P_m = \omega RT \quad (3-10) \]

Fick's first law for diffusion across the membrane, with a linear concentration gradient is

\[ \dot{n} = D_{eff} \frac{\Delta C}{t_m} \quad (3-11) \]

where \( D_{eff} \) is effective diffusion coefficient in the membrane, based on the external solution concentrations, and \( t_m \) is the membrane thickness. Consequently
\[ P_m = \frac{D_{\text{eff}}}{t_m} \]  \hspace{2cm} (3-12)

Both eqns. (3-9) and (3-11) are more properly written in terms of the concentrations inside the membrane. On this basis, \( P_m \) and \( D_{\text{eff}} \) both implicitly contain an equilibrium distribution coefficient, defined by

\[ K = \frac{C_{\text{membrane}}}{C_{\text{solution}}} \bigg|_{\text{eq.}} \]  \hspace{2cm} (3-13)

It should be noted that the definition of membrane permeability used in this study differs from that conventionally employed in gas permeation studies

\[ N = \frac{D_m}{t_m} \Delta C_m = \frac{D_m \alpha_m}{t_m} \Delta P = \frac{P}{t_m} \Delta P \]  \hspace{2cm} (3-14)

where \( \alpha_m \) is the Bunsen solubility coefficient and the permeability \( P \) is related to the partial pressure driving force and does not include the membrane thickness.

3. **Objectives of this Study**

Based upon the preliminary considerations discussed above, the specific objectives of this phase of the thesis fell into two categories. They were:

**Liquid Phase Transport in Batch Dialyzer**

1. Develop theoretical models to describe momentum and mass transport to the membrane surface for both laminar and turbulent flow in the adjacent fluid.
(2) Investigate the fluid dynamic conditions existing in the membrane boundary layer through measurements of total power dissipation in the dialyzer chamber and of torque delivered to the membrane surface, and through flow visualization studies.

(3) Characterize the liquid phase mass transfer from a rigid interface of soluble material.

(4) Explore the existence of membrane flutter and its influence on permeability evaluation.

(5) Develop suitable techniques, based on experimental and theoretical results, for the accurate determination of true membrane permeability from a single measurement.

**Permeability Measurements**

(6) Measure the permeability of commercially available cellophanes to a wide spectrum of solutes which are of potential interest for the artificial kidney.

(7) Perform similar measurements with various types of regenerated cellulose films.

An additional important objective of the permeability measurements was to serve as an independent check on the results obtained with the flow dialyzer (see Chapter 5).

B. **Experimental Methods**

Various types of apparatus and procedures were required for the different aspects of this thesis, as described below. Additional details of the experimental techniques, drawings, and photographs may be found in Appendix D.
1. Membrane Permeability Measurements with the Batch Dialyzer

The batch dialyzer for membrane permeability measurements was a modification of the design described by Kaufmann and Leonard (198), as shown in Figure 3-1. It consisted of two identical horizontal lucite chambers, 2.482 in. wide and 3.0 in. long, which were water-jacketed for temperature control (+ 0.1 °C), and between which the membrane was securely clamped. An axially-mounted, four blade paddle impeller, 2.235 in. in diameter, 1/4 in. wide, and 1/16 in. thick, was positioned 1/8 inch from each side of the membrane. A rotating mechanical seal was employed to prevent leakage at the points where the impeller shafts pierced the chamber end plates. Seal and bearing housings were also jacketed. Temperature was measured by thermistors inserted through the end plates. Each chamber contained about 240 ml and all metallic parts were stainless steel.

Both impeller shafts were connected by timing belts to the main drive shaft and rotated at the same speed. Speed was controlled (+ 1 rpm) by a tachometer-feedback, variable speed 0.1 hp motor coupled to a step function speed reducer; and it was measured by an AC tachometer and frequency counter accurate to ± 0.1 rpm.

One chamber (1) was initially filled with concentrated solution, the other (2) with distilled water or an osmotically balanced solution. Concentration in chamber 1 was monitored continuously. When dialyzing an electrolyte, the solution was circulated by a metering pump to a conductivity flow cell located in a constant temperature bath (+ 0.05°C.) and back to the chamber. Total external circuit volume was about 6.5 ml and
the residence time about 40 seconds. Zero time was taken as one minute after the impellers were started. Conductivity cell resistance was continuously determined by an impedance comparator and automatically recorded. The system was sensitive to a concentration change of 0.01% and accurate over long periods to 0.1%. With radioactively labelled organic solutes, a manifold containing two three-way valves was inserted into the external circuit and the conductivity cell was bypassed. At specified times, both valves were simultaneously switched for a fixed time period, and a calibrated volume of solution from the chamber was withdrawn into a plastic vial and stored for analysis, while an equal volume of replacement solution containing no solute was pumped into the chamber. With electrolytes, concentration measurements were obtained from the concentrated side, chamber (1). Sampling from both sides was tried with organic solutes, and higher accuracy was obtained by sampling from the dilute side, chamber (2). Material balances were checked by sampling from the other chamber at the end of a run. Details of the concentration measurement techniques may be found in Appendix D.

2. **Liquid Phase Mass Transfer**

Measurements of liquid phase mass transfer coefficients were carried out in one chamber of the dialyzer with the membrane replaced by an aluminum plate containing an insert of compressed benzoic acid covering the entire chamber diameter. The acid was compressed in an hydraulic press exerting 35,000 pounds force at about 120°C. to cause fusing of the particles
Figure 3-1. Schematic Diagram of Batch Dialyzer for Membrane Permeability Measurement
Figure 3-2. Schematic Diagram of Model of Single Dialyzer Chamber for Torque Measurements
into a smooth surface. After slow cooling for 30 minutes, the
disks were removed, sanded flat with fine sand paper, washed
with cold water, and dried. The solution initially charged to
the chamber was 0.02M. Average mass transfer coefficients were
determined by chamber concentration measurement, as described
above. Local coefficients at various radial positions were
determined by measuring the depth of benzoic acid dissolved,
using a displacement transducer sensitive to $3 \times 10^{-6}$ in. All
experiments were carried out at 25°C.

The influence of impeller size was studied by using a
second impeller with a 1.890 in. diameter. To determine the
effect of baffled operation, four lucite baffles supported by
stainless steel hoops were inserted into the chamber. The
baffles were 3.0 in. long with a 45° taper at the "membrane"
end, 0.20 in. wide, 1/16 in. thick, and cleared the vessel
wall by about 0.015 in.

3. Power Dissipation and Friction Factor

Torque measurements were made at room temperature in
a full scale replica of one chamber of the dialyzer, shown in
Figure 3-2, as a function of impeller speed, size, position,
and unbaffled or baffled operation. The impeller shaft was
driven by a variable speed motor with a step function speed
reducer. The vessel rested on a calibrated flexural pivot
which generated a voltage proportional to the applied torque,
and speed was measured by a DC tachometer. Both signals were
fed to an X-Y recorder through a sensitive electronics system
described elsewhere (378, 382). The chamber bottom was 0.020
in. smaller in diameter than the cylindrical wall. By careful
alignment, the bottom could rotate freely while the side wall was rigidly held, thereby yielding the torque applied to the flat interface alone. A mercury seal at the bottom prevented pumping of liquid out of the chamber. As impeller speed was increased during a run, the mercury level was increased to counter the centrifugal action of the impeller. Vortexing was prevented by maintaining the liquid level within the neck of the chamber. To measure the total power dissipation, the bottom was rigidly connected to the chamber wall with an O-ring and the entire vessel left free to rotate. The measurements were performed in collaboration with Phipps (321).

4. Membrane Flutter

A thin film of nickel foil, about $1 \times 10^{-4}$ in. thick, was bonded to a wet cellophane membrane (Du Pont PD-215) with laboratory viscose solution. The viscose was regenerated using conventional techniques (118) and the bond was sufficiently strong to prevent separation of the films during the experiment. The laminate was placed in the dialyzer as in normal operation. A one mm wide beam of light from a gas laser was aimed through the transparent lucite walls of the dialyzer and reflected off the membrane onto a screen on the opposite side. Movement of the membrane-foil laminate caused the reflected spot to move with amplified magnitude, and the amount of deflection from the original stationary position was measured with a cathetometer. A deflection of the reflected spot as small as about 0.003 in. could be observed.

5. Flow Visualization

Flow visualization studies were performed in a single
dialyzer chamber with the membrane replaced by a transparent lucite endplate. An optically thick aqueous suspension (<1% by volume) of Mearlmaid AQ natural pearl essence (Mearl Corp., N.Y.) containing a small amount of dye was placed in the chamber. The highly reflective, microscopic anisotropic particles aligned themselves in a shear field, permitting direct visualization of flow patterns within 1/64 in. of the endplate surface. Baffled and unbaffled chambers were observed and still photographs and motion pictures at 64 frames/sec were taken.

6. Solutes Employed

Sodium chloride was selected for initial studies with all membranes because of its ease of measurement, and because it has been most commonly employed in published investigations for the preliminary evaluation of candidates for hemodialysis membranes.

Nine organic solutes were studied. Urea, creatinine, and uric acid were selected for their relevance to the artificial kidney. Since the specific nature of other toxic solutes to be removed has not been elucidated, additional compounds were chosen to give a variety of molecular weight, size, and shape. By this means, membrane permeabilities could be evaluated for solutes of various characteristic types and the results generalized to broad classes of compounds for which removal by a hemodialyzer might be desirable. An additional constraint was that the compounds be available in radioactive form at reasonable cost. The additional compounds selected were: sucrose, vitamin B₁₂, polyethylene glycol (-4000 Mₘ), inulin, heparin, and dextran (-16,000 Mₘ).
Additional studies to investigate the cut-off point of the membranes were carried out with five proteins: myoglobin, \( \beta \)-lactoglobulin, \( \alpha \)-chymotripsinogen, ovalbumin and albumin. Since membrane permeabilities for these compounds were very low, it was not necessary to use the batch dialyzer. The membrane was clamped between two lucite chambers, each about 5 cm in diameter and 1 cm deep. Two glass beads were placed in each chamber and the assembly was rocked at about 30 cycles/sec to stir the fluid. An alternative means of stirring considered was to only partially fill each chamber. During shaking, the air bubbles would stir the fluid. This idea was rejected because of protein denaturation at the air-liquid interface. Protein concentrations were measured with acrylamide gel electrophoresis. The gels were dyed and the intensity of the electrophoresis patterns measured with a microdensitometer. This technique permitted differentiation between native and denatured proteins.

Sodium chloride was usually dialyzed against distilled water. Several runs were made with an equal concentration of urea in the other chamber to verify that osmotic effects were negligible. Organic solutes were studied with isotonic saline (0.15M) in both chambers. In some experiments additional unlabeled solute was employed in both chambers to study the effect of solute concentration. Because of adsorption of certain high molecular weight solutes on the lucite chamber walls, it was necessary to operate at high unlabeled concentration with these solutes. All solutions, during dialysis and storage, contained an anti-bacterial agent, generally formaldehyde at 200 ppm.

A discussion of the physical and chemical characteristics of the solutes employed may be found in Appendix B.
7. **Membranes Investigated**

Initial studies of sodium chloride permeation were made with the following commercially available cellophanes: Avisco 215 P-1, DuPont PD-215, Visking Dialysis Tubing No. 1 7/8 s.s., and Cuprophan PT-150. Additional membranes studied include:

1. **Avisco wet gel "ultra thin" - available in small lots from American Viscose Division, FMC Corp., Fredericksburg, Va. It is identical to the normal commercial material (extruded film) but it has never been dried.**

2. **DuPont wet gel - never dried cellulose membranes cast from viscose solution, obtained through the courtesy of Dr. V.C. Haskell of DuPont. These were in addition, modified by 1) aminoethylation and 2) subsequent heparinization by ionic bonding, following the procedures developed by Britton (53).**

3. **Avisco 215 P-1, soaked in 20% NaOH at room temperature for 10 minutes.**

4. **Neutral polyelectrolyte (Biolon BN-80) - swollen membrane obtained from Amicon Corp., Lexington, Mass.**

5. **Wet gel films cast by Farrell (11b). Farrell studied the permeation and strength characteristics of regenerated cellulose as a function of precipitation technique. The permeability measurements of Farrell were made in collaboration with the author. The reader is referred to the original work for a complete discussion of the results. Additional permeation studies were carried out by the author with Farrell’s most promising membrane, obtained by precipitation of viscose**
solution in a bath containing 20% sulfuric acid and 5% sodium sulfate.

The organic solute studies were made with the following membranes: Cuprophane PT-150, Avisco 215 P-1, Avisco wet gel, Bio' on neutral polyelectrolyte, aminoethylated cuprophane, heparinized aminoethylated cuprophane, and saponified cellulose acetate. The latter were prepared from a commercial film, DuPont CA148, by immersion in a 1% aqueous NaOH bath for four hours at 50°C, followed by rinsing in distilled water.

The aminoethylation and subsequent heparinization of DuPont wet gel cellulose and Cuprophane were carried out by Messrs. R. Gerson and R. Khanna under the direction of Professor E. W. Merrill.

Additional experiments were performed with blood-soaked cuprophane and heparinized cuprophane. The membranes were soaked in whole human blood overnight in a refrigerator at 4°C and then for one hour at room temperature. The purpose of these experiments was to determine if the potential deposition on the membranes of native or denatured proteins and/or formed elements affected permeability. Since the membranes were exposed to high fluid shearing forces in the batch dialyzer, only those materials strongly bound to the membrane would remain on the surface during a permeability measurement.

All commercial membranes were soaked for at least two hours in distilled water prior to a run to remove the glycerol and other additives in the film. Membranes were stored in the presence of 200 ppm in formaldehyde.
8. Membrane Characterization

Thickness measurements were made for all membranes with an Ames dial comparator, Model 412 (B. C. Ames Co., Waltham, Mass.). The smallest division on the dial was 0.1 mil and readings could be estimated to 0.01 mil. The comparator contained two springs. To reduce the compressive force on the wet membranes, the larger spring was removed. Two readings were made for each measurement, the thickness when the platen first touched the membrane and the value after about 10 seconds, during which time expression of surface water and possibly some compression occurred. The two readings which usually differed by about 0.05 to 0.1 mil, were averaged. At least three repeat measurements were made at six different points and the results averaged. The following additional means of characterization were employed with only some of the membranes.

Water content was measured by surface drying the wet membrane between damp filter papers and immediately weighing the film. The membranes were then dried in an oven at 100°C and reweighed. Because of the hygroscopic nature of cellulose, it was necessary to obtain this measurement immediately upon removal from the oven. The water content was calculated from the dry and wet weights and expressed as the volume fraction water after correction for the estimated density of cellulose.

Equilibrium distribution coefficients of organic solutes were measured by an equilibrium sorption experiment to relate the concentration in the membrane regarded as a homogeneous phase to that in the external solution. For each solute,
three or four pre-soaked membranes of known dimensions (∼50 cm² area) were placed in vials containing 10 ml isotonic saline and radioactively labelled tracer solute of known concentration. The membranes were equilibrated at 37°C for 72 hours, after which three one-ml samples of solution were removed for analysis. The membranes were then removed, surface dried between damp filter papers, and placed in similar vials containing only isotonic saline. After re-equilibration, three additional samples were removed for analysis. Duplicates were run for each membrane-solute combination and water content of membranes cut from the same sheet were also determined.

Stress-strain measurements were made with a table model Instron universal testing machine. Samples of wet membrane 4 in. long and 1/4 in. wide were cut with a steel die. One inch was placed in each jaw between filter paper to prevent fracture. Measurements were made with the membrane immersed in a constant temperature bath of distilled water at 25°C with a constant elongation rate of 0.2 in/min. A strip chart recorder, moving at 1 in/min, indicated the tensile force exerted on the sample. Sample stress was calculated by dividing the tensile force on the sample by the initial cross-sectional area. Sample strain was calculated by dividing the elongation by the initial sample length between the jaws. From the recorder trace, Young's modulus, ultimate tensile strength, and ultimate elongation could be obtained.

Electron photomicrographs of the membranes were obtained with a Philips electron microscope (Model EM 200). Initial attempts at replication of air-dried samples followed by chrome shadowing
were rejected as artifactual. The technique finally employed was to freeze-dry the wet membranes by immersion in liquid nitrogen followed by vacuum drying. The resulting films were embedded in methacrylate embedding material. These were then sliced in ultrathin cross sections using the Ultratome and were viewed in the electron microscope without shadowing.

9. **Data Reduction**

This study was concerned primarily with solute transfer under a concentration gradient in the absence of a hydrostatic pressure gradient. Any accompanying volume or osmotic flow was assumed negligible. Previous investigations (141, 197, 198) indicated that for conditions of constant chamber volumes and dilute solutions, the assumption was reasonable. However, this assumption does not limit the applicability of the results presented.

The membrane permeability to a concentration difference is defined by

\[
 \dot{M} = P_m A (C_{1s} - C_{2s}) \quad (3-15)
\]

where the subscript s refers to conditions at the membrane surface. The experimentally measured overall mass transfer or dialysis coefficient is defined by:

\[
 \dot{M}_1 = K_o A (C_1 - C_2) \quad (3-16)
\]

where the bulk phases in chambers 1 and 2 are assumed well mixed.

Combining equation (3-16) with a material balance for each chamber

\[
 \dot{M}_1 = \frac{d (V_1 C_1)}{dt} \quad (3-17)
\]
and integrating from \( t = 0 \) to \( t = t \) yields:

\[
\ln \left[ \frac{(C_1 - C_2) t}{(C_1 - C_2) t_0} \right] = -K_0 A t \left[ \frac{1}{V_1} + \frac{1}{V_2} \right] \tag{3-18}
\]

from which \( K_0 \) may be evaluated. With \( k_f \) estimated from the results to be presented and assumed equal on both sides of the membrane, \( P_m \) was calculated from equation (3-2).

Equation (3-18) applied to the sodium chloride runs, with \( V_1 \) including the volume of the external circuit. Concentration was monitored continuously and no samples were removed. With organic solutes, about 10cc of solution were removed from one chamber during the course of a run, each sample being replaced by isotonic saline with no solute. It was necessary to correct for this effect, and equation (3-18) was replaced by

\[
\sum_{m=0}^{m=n} \ln \left[ \frac{(C_1 - C_2) t_{m+1}}{(C_1' - C_2) t_m} \right] = -K_0 A t \left[ \frac{1}{V_1} + \frac{1}{V_2} \right] \tag{3-19}
\]

where

\[
C_{2m+1} = C_{2m} + \frac{V_1}{V_2} (C_{1m} - C_{1m+1}) \tag{3-20}
\]

\[
C_{1m}' = C_{1m} + \frac{V_r}{V_1} (C_r - C_{1m}) \tag{3-21}
\]

\( C_{1m} \) = concentration of \( m^{th} \) sample from Chamber 1

\( C_r \) = concentration of replacement solution

\( V_r \) = volume of sample removed and replaced.

All data analysis was performed on a digital computer. A more detailed discussion of the data analysis, program listings and sample output, and derivation of equation (3-19) may be found in Appendix I.

For the benzoic acid dissolution studies, equation (3-18)
Figure 3-3. Pertinent geometrical Variables for Batch Dialyzer
becomes:

\[ \ln \left( \frac{(C_w - C_1)_t}{(C_w - C_1)_0} \right) = - \frac{kAt}{V_1} \]  

(3-22)

The concentration at the wall, \( C_w \), was taken to be the saturation concentration. Seidell's (372) data on the solubility of benzoic acid in water at 25°C were used. Values of the molecular diffusion coefficient of benzoic acid in water as a function of concentration and temperature were taken from the results of Chang (409). Diffusivity was evaluated at the time-averaged film concentration.

Semilogarithmic plots of equations (3-18) and (3-19) yielded straight lines, and the standard deviation of the estimate of the slope was typically about one per cent of the absolute value of the slope for the sodium chloride runs and slightly higher with the organic solutes.

C. Theoretical Analysis of Momentum and Mass Transport in the Batch Dialyzer

1. The Physical Problem

Mass transfer in stirred vessels is a difficult problem to analyze because of the complexities of the fluid flow patterns. The particular problem of interest here is that of mass transfer to the flat bottom of a cylindrical vessel, above which an axially symmetrical turbine impeller is rotating. The geometry and pertinent geometrical variables are shown in Figure 3-3.

In formulating the theoretical model, end effects due to the presence of the chamber wall were neglected. It was assumed that these could be lumped with a single adjustable parameter, derived from the theory, for comparison with experimental data. The flow pattern considered was that of fluid rotating above a stationary base. The velocity components for this situation,
Figure 3-4. Three-Dimensional Velocity Profile for Fluid Rotating above a Stationary Base. From Schlichting (365)
taken from Schlicting (365), are illustrated in Figure 3-4. In the nomenclature of this study, components \( u \), \( v \), and \( w \) are denoted by \( V_r \), \( V_\phi \), \( V_z \), respectively.

At large distances from the boundary, the rotating fluid elements are in equilibrium under the influence of the centrifugal force which is balanced by a radial pressure gradient. The circumferential velocity near the boundary is decreased by friction, thus reducing the centrifugal force, whereas the radial pressure gradient remains the same as at large distances from the boundary. As a result, a radial flow occurs near the wall directed towards the \( z \) axis, and this gives rise to an axial flow upwards, as required by the equation of continuity. Such secondary flow may be observed after vigorously stirring the fluid in a teacup. The tea leaves flow radially inward and form a heap at the center.

An overall outline of the theoretical modeling for the batch dialyzer is given in Table 3-1. Two limiting cases were considered. First, it was assumed that the fluid far from the boundary rotates with the same angular velocity as the impeller. From the analytical solution of the Navier-Stokes equations, one obtains the velocity field for laminar flow conditions from which friction factors, i.e. the torque dissipated on the membrane surface, can be evaluated. With known velocity components, the partial differential equation describing convective diffusion could in principle be solved. Analytical solutions were developed for the "entrance region" at the leading edge of the mass transfer surface and for the "far-field" conditions away from the
TABLE 3-1

Theoretical Model of Momentum and Mass Transport in Batch Dialyzer

A. Unbounded fluid rotates at impeller angular velocity \( \omega \) above infinite stationary base, i.e. no velocity gradient between impeller and fluid. Region of interest is of radius \( b \)

1. Laminar boundary layer

   Analytical solution of Navier-Stokes equations yields
   
   Velocity field + Friction factors
   
   Numerical solution of convective diffusion equation
   (analytical solution for limited region) yields
   
   Concentration field + Mass transfer relationships

2. Turbulent boundary layer

   Analytical solution of von Karman momentum integral equations using Blasius' semi-empirical shear stress correlation yields
   
   Wall shear stress + Mass transfer relationships components from transport analogies

B. Impeller replaced by disc (radius \( a \)) rotating at angular velocity \( \omega \) above stationary base. Two boundary layers formed (on disc and on base), separated by inviscid core undergoing solid body rotation at angular velocity \( \gamma \omega, 0 < \gamma < 1.0 \).

For laminar and turbulent boundary layers

1. Equate torque on disc to torque on base

2. Evaluate \( \gamma \) as function of \( (b/a) \)

3. Correct friction factor, mass transfer relationships
surface. A solution for the concentration field over the entire surface was obtained by numerical techniques and was matched with the leading edge analytical solution. From the concentration field near the surface, various mass transfer relationships were deduced.

For a turbulent boundary layer, an analytical solution of the von Karman momentum integral equations, using Blasius' semi-empirical shear stress correlation, was employed to evaluate the wall shear stress components from which the mass transfer relationships could be obtained from the momentum-mass transport analogies for turbulent flow. The solution was valid only near the leading edge and actually applied to a finite base on which the momentum boundary layer development occurred on the leading edge, in contradistinction to the infinite base analysis used for a laminar boundary layer. The momentum integral approach could also be applied to the laminar regime.

In reality, the flow conditions in the vicinity of the rotating impeller are very complex, and one would not expect the fluid velocity far from the stationary surface to be the same as the impeller velocity. Rather, a velocity gradient would exist between the impeller and the fluid in its vicinity. As a second limiting case, the impeller was treated as though it were replaced by a disk of radius a. In this case, it was postulated that two separate boundary layers form, on the disk and on the base, between which exists an inviscid core undergoing solid body rotation with an angular velocity equal to a fraction of the disc angular velocity, i.e. \( \omega_{\text{core}} = \gamma \omega \), where \( 0 < \gamma < 1.0 \). The velocity patterns for this situation in a contained vessel
are illustrated in Figure 3-5 for a cross section through the axis of symmetry.

Figure 3-5. Velocity patterns between rotating disk and stationary base.

By equating the torque on the bottom face of the disk to the torque on the base, \( \gamma \) was evaluated as a function of \((b/a)\). The final friction factor and mass transfer relationships were obtained by substituting \( \gamma \omega \) for \( \omega \) in the results for the first limiting case. When comparing the theoretical relations with experimental data, it was expected that the same value of \( \gamma \) would fit both the mass transfer and friction factor results. This served as an internal check on the validity of the model.

2. Previous Work

Axially symmetrical boundary layers are essentially two dimensional and the mathematical difficulties encountered in the solution of the Navier-Stokes equations are considerably smaller than for three dimensional boundary layers. Consequently, the fluid dynamical aspects of the problem of interest here have
received considerable attention in the literature. Much of this work has been reviewed by Schlichting (365) and Dorfman (106).

A laminar boundary layer on a rotating disk was first considered by von Karman (195) by an approximate method and a more accurate solution was later obtained by Cochran (746) by matching a power series expansion valid at the disk surface with an asymptotic expansion for the region beyond the boundary layer. Bodewadt (46) used the same technique to solve the problem of an unbounded fluid rotating against a stationary base.

The momentum integral equations for a turbulent boundary layer on a dish were solved by von Karman (195) using the 1/7th-power velocity distribution derived from Blasius (41) semiempirical correlation for the wall shear stress in pipes. Goldstein (144) later solved the problem using a logarithmic velocity profile.

The limiting case of the impeller replaced by a disk is similar to that of a disk rotating in a casing. Dorfman (166) and Daily and Neice (92) have reviewed the theoretical and experimental studies in this area. The latter also studied the influence of the geometrical parameters b/a and s/a on the angular velocity in the inviscid core. Existing data indicates that if the width of the gap, s, is very small, the distribution of circumferential velocities has a character similar to the distribution in Couette flow. As s increases, separate boundary layers form on each surface.

Schultz-Grunow (369) first analyzed the two boundary layer problem for both laminar and turbulent boundary layers using
von Karman's momentum integrals and the 1/7-power power velocity distribution for the latter case. His results have direct applicability to this study. He assumed that the momentum boundary layer thickness was zero at the outer edge of the base and increased with decreasing radial distance from the axis of symmetry, in analogy to the leading edge of a flat plate. Okaya and Hasegawa (304) later modified this analysis and their results agreed better with experimental data. However, their assumption that the thickness of the turbulent boundary layer on the base increased with increasing radius appears to be incorrect.

The heat or mass transfer aspects of this problem have received little attention. Dorfman (166) briefly discusses some theoretical relations for heat transfer to a disc rotating in a casing. However, no previous treatment, either experimental or theoretical, could be found in the literature for heat or mass transfer to a stationary wall above which a fluid is rotating.

3. Fluid Dynamic Aspects

For steady-state, axially symmetric rotation of a fluid above a stationary surface, the Navier-Stokes equations in cylindrical coordinates may be written, assuming constant physical properties and negligible body forces, as:

\[ V_r \frac{\partial V_r}{\partial r} - \frac{V_\phi}{r} + V_z \frac{\partial V_r}{\partial z} = - \frac{1}{\rho} \frac{\partial P}{\partial r} + \nu \left( \frac{\partial^2 V_r}{\partial r^2} + \frac{1}{r} \frac{\partial V_r}{\partial r} - \frac{V_r}{r^2} + \frac{\partial^2 V_r}{\partial z^2} \right) \]  \hspace{1cm} (3-23)

\[ V_r \frac{\partial V_\phi}{\partial r} + \frac{V_r V_\phi}{r} + V_z \frac{\partial V_\phi}{\partial z} = \nu \left( \frac{\partial^2 V_\phi}{\partial r^2} + \frac{1}{r} \frac{\partial V_\phi}{\partial r} - \frac{V_\phi}{r^2} + \frac{\partial^2 V_\phi}{\partial z^2} \right) \]  \hspace{1cm} (3-24)

\[ V_r \frac{\partial V_z}{\partial r} + V_z \frac{\partial V_z}{\partial z} = - \frac{1}{\rho} \frac{\partial P}{\partial z} + \nu \left( \frac{\partial^2 V_z}{\partial r^2} + \frac{1}{r} \frac{\partial V_z}{\partial r} + \frac{\partial^2 V_z}{\partial z^2} \right) \]  \hspace{1cm} (3-25)
The boundary conditions are 1) no slip at the stationary surface, and 2) no radial velocity component far from the boundary. Thus,

B. C. 1 \( z = 0 \) \( V_r = 0 \) \( V_\phi = 0 \) \( V_z = 0 \)  

B. C. 2 \( z = \infty \) \( V_r = 0 \) \( V_\phi = r \omega \)  

The continuity equation in cylindrical coordinates is given by

\[
\frac{\partial V_r}{\partial r} + \frac{V_r}{r} + \frac{\partial V_z}{\partial z} = 0
\]

and the shear stress components in axially symmetric flow are given by

\[
\tau_{r\phi} = \mu r \frac{\partial}{\partial r} \left( \frac{V_\phi}{r} \right) = \mu \left( \frac{\partial V_\phi}{\partial r} \right)
\]

\[
\tau_{z\phi} = \mu \frac{\partial V_\phi}{\partial z}
\]

\[
\tau_{zr} = \mu \left( \frac{\partial V_z}{\partial z} + \frac{\partial V_z}{\partial r} \right)
\]

The equations may be put into dimensionless form by the following transformation of variables (195):

\[
\zeta = z \sqrt{\frac{\omega}{\nu}}
\]

\[
V_r = r \omega F(\zeta)
\]

\[
V_\phi = r \omega G(\zeta)
\]

\[
V_z = \sqrt{\nu \omega} H(\zeta)
\]
For the frictionless flow far from the wall, the radial pressure gradient can be obtained from eqn. (3-23) as

$$\frac{1}{\rho} \frac{\partial p}{\partial r} = \frac{V}{r^2} = r\omega^2$$  \hspace{1cm} (3-36)

Within the framework of boundary layer theory it is assumed that the same pressure gradient applies in the viscous region near the wall, i.e. $\partial p/\partial z=0$. Upon substitution of eqns. (3-32) through (3-36) into eqns. (3-23) through (3-28), and dropping eqn. (3-25) from order of magnitude considerations, one obtains a system of ordinary differential equations

$$F^2 - G^2 + HF' - F'' + 1 = 0$$  \hspace{1cm} (3-37)

$$2FG + HG' - G'' = 0$$  \hspace{1cm} (3-38)

$$2F + H' = 0$$  \hspace{1cm} (3-39)

with boundary conditions

$$\zeta = 0 \quad F = 0 \quad G = 0 \quad H = 0$$  \hspace{1cm} (3-40)

$$\zeta = \infty \quad F = 0 \quad G = 1$$

The system of equations and boundary conditions described above was first solved by Bodewadt [46] by representing $F$, $G$, and $H$ in the form of a power series around $\zeta=0$ and in the form of an asymptotic expansion of exponentials, $e^{-a\zeta}$, for $\zeta=\infty$. Each series satisfied its respective boundary condition, and the constants in the two expansions were calculated so that the functions $F$, $G$, and $H$ and the derivatives $F'$ and $G'$ remain continuous when the two series are matched at $\zeta=1$. 
The values of the functions, $F$, $G$, and $H$ determining the distribution of velocities in the boundary layer are plotted in Fig. 3-6 as a function of $\zeta$. It is noteworthy that the axial velocity is independent of $r$ and only a function of $\zeta$. At all points, flow is upwards with $V_z > 0$. As $\zeta$ increases, the flow components oscillate before reaching their asymptotic values. The radial component alternates between inwards and outwards flow, although radial flow inwards predominates. The cause of the oscillation in the flow components within the boundary layer is the presence of the Coriolis force, $V_r V_\phi / r$ in eqn. (3-24), which acts to accelerate the flow in the $\phi$ direction. As a result, the circumferential velocity component is greater in regions of the boundary layer than it is in the free stream. However, as $V_\phi$ increases, the centrifugal force, $V_\phi^2 / r$ in eqn. (3-23), becomes large enough to retard the radial velocity, caused by the radial pressure gradient, and causes it to reverse direction, lowering the circumferential and axial velocity components. The interaction of the Coriolis and centrifugal forces within the boundary layer results in an overshoot phenomenon which is damped out in the free stream as $V_r$ goes to zero. Without the Coriolis force, the interaction of the viscous, centrifugal, and inertial forces would result in a simple monotonic approach to the velocity of components to their free stream value.

If the boundary layer thickness, $\delta$, is defined as the height for which the deviation of the circumferential
Figure 3-6. Velocity Distribution of Fluid Rotating above Stationary Base. From Schlichting (305)
velocity becomes less than two per cent of the free stream value, one finds

$$\delta = 8 \sqrt{\frac{v}{\omega}}$$

(3-42)

This is about double the value one obtains for a rotating disk in a stationary fluid. This is reasonable because of the difference in direction of the axial velocity. For typical operating conditions in the batch dialyzer (water at 37°C, 200 rpm, $\omega = 22$ radians/sec) eqn. (3-42) yields

$\delta = 0.037$ in. = 1.5 mm.

The angle $\theta$ between the horizontal velocity component and the circumferential direction varies with $\zeta$. At the stationary base, $\theta$ is given by

$$\tan \theta = - \frac{\partial V_r / \partial z}{\partial V_\phi / \partial z} \bigg|_{z=0} = - \frac{F'(0)}{G'(0)}$$

(3-43)

From Bodewadt (46), $F'(0) = -0.94197$ and $G'(0) = 0.77324$, yielding $\theta_0 = 50.6^\circ$. This results in a spiral flow pattern, as shown in Fig. 3-4.

For an annular ring of width $dr$ and radius $r$, the turning moment or torque exerted by the fluid is the product of the force times the lever arm, i.e.

$$dM = 2\pi r \tau_{r \phi} r dr$$

(3-44)

where, from eqn. (3-34)

$$\tau_{r \phi} = \mu \frac{\partial V_\phi}{\partial z} \bigg|_{z=0} = \frac{\mu r^2}{\nu^{1/2}} G'(0)$$

(3-45)

Over a circular region of radius $b$, the entire torque
becomes

\[ M = 2\pi \int_0^b r^2 T_{z\phi} \, dr \]  
(3-46)

\[ = \frac{\pi G'(0)}{2} \rho \nu^{1/2} \omega 3/2 b^4 \]  
(3-47)

\[ = 1.215 \rho \nu^{1/2} \omega 3/2 b^4 \]  
(3-48)

The dimensionless moment coefficient \( C_M \) is defined as the torque divided by the product of the lever arm times the area times the free stream kinetic energy. Thus,

\[ C_M = \frac{M}{2\rho \omega^2 b^5} \]  
(3-49)

\[ = \pi G'(0) \left( \frac{\nu}{\omega b^2} \right)^{1/2} \]  
(3-50)

\[ = 2.429 \text{ Re}^{-1/2} \]  
(3-51)

where the Reynolds number, based upon the base radius \( b \), is defined by

\[ \text{Re} = \frac{\omega b^2}{\nu} \]  
(3-52)

For the second limiting case, that of the impeller replaced by a disc, the solution obtained by Schultz-Grunow (369) for a disk rotating in a casing was employed. His solution is summarized briefly below. For additional details, the reader is referred to the original work.

Let \( \delta \) and \( n \) refer to the boundary layer thickness on the base and the rotating disk, respectively, and let
\( \omega \) and \( \beta = \gamma \omega \) represent the angular velocity of the disk and the inviscid core respectively. Within the framework of boundary layer theory, eqn. (3-25) in terms of \( V_z \) may be ignored and the Navier-Stokes equations may be integrated over the boundary layer, subject to the appropriate boundary conditions, to yield the momentum integral equations for axially symmetric flow over a stationary base.

\[
\frac{\partial}{\partial r} \left[ r \int_0^\delta V_r^2 \, dz \right] - \int_0^\delta V_\phi^2 \, dz = \nu r \frac{\partial V_z}{\partial z} \bigg|_{z=0} - r \int_0^\delta \frac{\partial P_r}{\partial r} \, dz
\]

(3-53)

\[
\frac{\partial}{\partial r} \left[ r^2 \int_0^\delta V_r V_\phi \, dz \right] - r^2 \beta \frac{\partial}{\partial r} \left[ r \int_0^\delta V_r \, dz \right] = \nu r^2 \frac{\partial V_\phi}{\partial z} \bigg|_{z=0}
\]

(3-54)

The equations for a rotating disk are essentially identical, with the integration taken from 0 to \( \delta \) and a minus sign placed before the first term on the right hand side of eqn. (3-53).

For a laminar boundary layer, one assumes the following velocity profiles:

**Stationary base**

\[
V_r = V_0 \left[ 1 - \left( \frac{2z}{\delta} - 1 \right)^2 \right]
\]

(3-55)

\[
V_\phi = r \beta \left[ 1 - \left( 1 - \frac{z}{\delta} \right)^2 \right]
\]

(3-56)

**Rotating disc**

\[
V_r = V_0' \left[ 1 - \left( \frac{2z}{n} - 1 \right)^2 \right]
\]

(3-57)

\[
V_\phi = r \beta \left[ \frac{1}{\gamma} - \left( \frac{1}{\gamma} - 1 \right) \left( 1 - \left( \frac{z}{n} \right)^2 \right) \right]
\]

(3-58)
The boundary layer thickness on the disc is assumed independent of \( r \). On the base, Schultz-Grunow assumed it to be of the form

\[
\delta = \chi^p \sum_{n=0}^{\infty} a_n \chi^n \quad (3-59)
\]

where \( \chi = 1 - \frac{r}{b} \) \( (3-60) \)

Combining the assumed forms for the velocity components and boundary layer thicknesses with the integral equations, it is possible to solve for \( V_0 \) and \( \delta \) and for \( \nu' \) and \( \eta \).

Finally, with all velocity components known the torque on each surface is found to be

\[
M_{\text{base}} = 1.694 \rho \nu^{1/2} \beta^{3/2} b^4 \quad (3-61)
\]

\[
M_{\text{disk}} = 0.898 \rho \nu^{1/2} (\omega-\beta) \beta^{1/2} a^4 \left( \frac{3}{\gamma} + 2 \right)^{1/2} \left[ \frac{1.7}{\gamma} \right]^{1/4} \quad (3-62)
\]

By setting \( M_{\text{base}} = M_{\text{disk}} \), one may evaluate \( \gamma \) as a function of \( b/a \). For \( b/a = 1 \), \( \gamma = 0.538 \). For the batch dialyzer, \( b/a = 1.110 \). By trial and error evaluation, \( \gamma \) was found to be 0.44. It should be noted that for \( \gamma = 1 \) (\( \beta = \omega \)), equation (3-61) predicts a turning moment about one-third higher than that obtained from Bödewadt's solution, equation (3-48).

This is reasonable since the model of Schultz-Grunow assumes a developing boundary layer for which the circumferential wall shear stress component is higher at the leading edge. Because of end effects due to the chamber walls, it is not clear which equation should be applied to the batch dialyzer.
Bödewadt's solution was arbitrarily employed since it represents an exact solution of the boundary layer equations.

For a turbulent layer, the partial derivatives with respect to z evaluated at z = 0 on the right-hand side of equations (3-53) and (3-54) are evaluated in terms of the shear stress components at the boundary, \( \tau_{zr} \) and \( \tau_{z\phi} \). The assumed velocity profiles are:

**Stationary base**

\[
V_r = \alpha \beta r \left( \frac{Z_0}{Z} \right)^{1/7} \left( 1 - \frac{Z}{Z_0} \right) \quad (3-63)
\]

\[
V_\phi = r \beta \left( \frac{Z}{Z_0} \right)^{1/7} \quad (3-64)
\]

**Rotating disk**

\[
V_r = \alpha' r (\omega - \beta) (\frac{Z}{Z_0})^{1/7} \left( 1 - \frac{Z}{Z_0} \right) \quad (3-65)
\]

\[
V_\phi = r (\omega - \beta) \left[ 1 - (\frac{Z}{Z_0})^{1/7} \right] + r \beta \quad (3-66)
\]

Note that near the stationary base,

\[
\alpha = \frac{V_r}{V_\phi} = \frac{\tau_{zr}(0)}{\tau_{z\phi}(0)} \quad (3-77)
\]

Furthermore, the resultant relative velocity \( u \) of the fluid is given by

\[
u = (V_r^2 + V_\phi^2)^{1/2} \quad (3-78)
\]

\[
u = r \omega (\frac{Z}{Z_0})^{1/7} \sqrt{\alpha^2 (1 - \frac{Z}{Z_0})^2 + 1} \quad (3-79)
\]

Near the surface of the stationary base \( z = 0 \),

\[
u = r \beta \left( \frac{Z}{Z_0} \right)^{1/7} (\alpha^2 + 1)^{1/2} \quad (3-80)
\]

Defining the resultant hypoethical free stream velocity, \( U \),
beyond the boundary layer by

\[ \frac{u}{U} = \left( \frac{z}{\delta} \right)^{1/7} \]  \hspace{1cm} (3-81)

one obtains

\[ U = \rho B(\alpha^2 + 1)^{1/2} \]  \hspace{1cm} (3-82)

The \(1/7\)th-power velocity distribution low for pipes is given by (365)

\[ \frac{u}{V_*} = 8.74 \left( \frac{V_*^2}{V} \right)^{1/7} \]  \hspace{1cm} (3-83)

where

\[ V_* = \left( \frac{\tau_0}{\rho} \right)^{1/2} \]  \hspace{1cm} (3-84)

Solving eqns. (3-83) and (3-84) for \( \tau_0 \) and letting \( u = U \) at \( z = \delta \) gives

\[ \tau_0 = 0.0225 \rho U^2 \left( \frac{V}{U \delta} \right)^{1/4} \]  \hspace{1cm} (3-85)

Equation (3-85) is generally valid for channel and boundary layer flows. However, in its application here, \( U \) as defined by eqn. (3-82), not the true free stream velocity, must be employed in order that the local velocity near the boundary be properly scaled according to eqn. (3-81). Noting that

\[ \tau_0 = (\tau_0^2 + \tau_{zr})^{1/2} \]  \hspace{1cm} (3-86)

and using eqn. (3-77), one finds

\[ \tau_{z\phi} = 0.0225 \rho (1+\alpha^2)^{3/8} \beta^{7/4} \left( \frac{V}{\delta} \right)^{1/4} \]  \hspace{1cm} (3-87)

\[ \tau_{zr} = 0.0225 \rho (1+\alpha^2)^{3/8} \alpha \beta^{7/4} \left( \frac{V}{\delta} \right)^{1/4} \]  \hspace{1cm} (3-88)
Similar equations for $\tau_{z0}$ and $\tau_{zr}$ may be derived for the rotating disk.

Schultz-Grunow assumed that $n$ was proportional to $r^{3/5}$ and $\delta$ could be expressed in the form of equation (3-59). He solved the integral equations by assuming $(a^2 + 1)^{3/8} = 1$ and obtained

$$\alpha = \frac{\phi}{r^8 \delta}$$  \hspace{1cm} (3-89)

where

$$\delta^{1/4} = \chi^{1/10} \left( \frac{\nu}{\beta} \right)^{1/20} b^{3/20} D$$  \hspace{1cm} (3-90)

$$\phi = \chi^{9/10} \beta^{4/5} \nu^{1/5} b^{8/5} C$$  \hspace{1cm} (3-91)

$$C = 0.4254 - 1.894X + 4.47X^2 - 6.945X^3 + 6.78X^4$$  \hspace{1cm} (3-92)

$$D = 0.8554 - 1.063X + 0.814X^2 + 3.397X^3$$  \hspace{1cm} (3-93)

and $X$ is given by ecn. (3-60). $(a^2 + 1)^{3/8}$ was computed as a function of $X$ and found to be near unity only for the outer one-third of the base. Consequently, the solution is valid only in this region.

After appropriate substitutions and rearrangements of the solution, one obtains

$$M_{\text{base}} = 0.0537 \rho b^{23/5} \nu^{1/5} \beta^{9/5}$$  \hspace{1cm} (3-94)

$$M_{\text{disk}} = 0.0307 \rho \left( \frac{\nu}{\epsilon} \right)^{1/4} (\omega - \beta)^{7/4} a^{23}$$  \hspace{1cm} (3-95)

where

$$\epsilon^{1/4} = \left( \frac{\nu}{\beta} \right)^{1/20} \left( \frac{w - 1}{\beta - 1} \right)^{1/4} \left[ \frac{0.0225}{(0.313 \frac{\omega}{\beta} + 0.504)\alpha'} \right]^{1/5}$$  \hspace{1cm} (3-96)
\[(a')^2 = \frac{1}{\frac{\omega}{\beta} - 1} \cdot \frac{0.0278 \frac{\omega^2}{\beta^2} + 0.1944 \frac{\omega}{\beta} - 0.22}{1.058 \frac{\omega}{\beta} - 0.241} \]  

(3-97)

The constant 0.0537 in equation (3-94) was originally given as 0.0519. The corrected value was obtained by numerical integration of the appropriate integral in the original work.

Equating the torque on the disk to that on the base, one finds \( \gamma = 0.512 \) for \( b/a = 1 \) and \( \gamma = 0.48 \) for \( b/a = 1.11 \).

As a matter of record, the author checked the original derivation of Schultz-Grunow (369) carefully and found a number of typographical errors in intermediate calculations. The final results, however, were correct with the one exception cited above.

Okay and Hasegawa (304) studied the identical problem but modified the solution. For laminar conditions, they assumed the boundary layer thickness to be constant. However, their calculated \( \gamma \) for \( b/a = 1 \) was within one per cent of the value obtained by Schultz-Grunow. For a turbulent boundary layer, they assumed \( \delta \) proportional to \( r^{3/5} \) and found \( \gamma = 0.486 \) for \( b/a = 1 \), about 5% smaller than that obtained by Schultz-Grunow. Although their results agree better with experimental data (166), their assumption that \( \delta \) increases radially outwards, while the radial velocity component is directed radially inwards, is clearly untenable.

4. **Mass Transfer Aspects**

The steady state convection diffusion equation in
cylindrical coordinates for axially symmetrical flow and constant physical properties is

\[
V_r \frac{\partial C}{\partial r} + V_z \frac{\partial C}{\partial z} = D \left( \frac{\partial^2 C}{\partial z^2} + \frac{1}{r} \frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial r^2} \right) \tag{3-99}
\]

The physical problem studied was a fluid rotating against a stationary surface on which there is an area of radius b which is transferring mass to or from the fluid. The boundary conditions are constant concentration at the wall, symmetry about the z-axis, and constant ambient concentration at infinite distance from the surface. Thus,

\[
z = 0 \quad 0 \leq r \leq b \quad C = C_w \tag{3-100}
\]

\[
z = \infty \quad \text{all } r \quad C = C_\infty \tag{3-101}
\]

\[
\text{all } z \quad r = 0 \quad \frac{\partial C}{\partial r} = 0 \tag{3-102}
\]

\[
z > 0 \quad r = \infty \quad C = C_\infty \tag{3-103}
\]

The problem is put in dimensionless form by using eqns. (3-32) through (3-34) and

\[
X = \frac{r}{b} \tag{3-104}
\]

\[
\theta = \frac{C - C_\infty}{C_w - C_\infty} \tag{3-105}
\]

which results in

\[
X F \frac{\partial \theta}{\partial X} + H \frac{\partial \theta}{\partial \xi} = \frac{1}{Sc} \left[ \frac{\partial^2 \theta}{\partial \xi^2} \right. \left. + \frac{1}{Re} \frac{1}{\partial X} \left( \frac{\partial^2 \theta}{\partial X^2} + \frac{1}{X} \frac{\partial \theta}{\partial X} \right) \right] \tag{3-106}
\]

with boundary conditions

\[
\xi = 0 \quad 0 \leq X \leq 1 \quad \theta = 1 \tag{3-107}
\]

\[
\xi = \infty \quad \text{all } X \quad \theta = 0 \tag{3-108}
\]

\[
\text{all } \xi \quad X = 0 \quad \frac{\partial \theta}{\partial X} = 0 \tag{3-109}
\]

\[
\xi = 0 \quad X = \infty \quad \theta = 0 \tag{3-110}
\]
A modification of the problem is replacement of the wall by a permeable membrane. With respect to the batch dialyzer, the fluid dynamic conditions are identical on either side of the membrane. Assuming constant physical properties in all phases and identical liquid phase mass transfer coefficients on either side of the membrane, the system becomes symmetrical about the plane through the center of the membrane, and the concentration in this plane is constant.

For this case, the first boundary condition, eqn. (3-100), becomes

$$z = 0 \quad 0 \leq r \leq b \quad -D \frac{\partial C}{\partial z} = 2P_m (C_m - C_o) \quad (3-111)$$

where $C_m$ is the concentration in the center plane of the membrane multiplied by the external solution-membrane distribution coefficient and $C_o$ is the liquid phase concentration at the membrane surface. Let

$$\theta = \frac{C - C_\infty}{C_m - C_\infty} \quad (3-112)$$

$$\theta_o = \frac{C_o - C_\infty}{C_m - C_\infty} \quad (3-113)$$

$$Sh_w = \frac{2P_m}{D \sqrt{\frac{\rho}{\nu}}} \quad (3-114)$$

Then the first boundary condition becomes

$$\zeta = 0 \quad 0 \leq \eta \leq 1 \quad \frac{\partial \theta}{\partial \zeta} = -Sh_w (1 - \theta_o) \quad (3-115)$$

The wall Sherwood number, $Sh_w$, was obtained directly from the nondimensional form of the differential equations. A similar group was derived by Helfferich (166) on purely
physical grounds. From equation (3-42) for a laminar boundary layer,

\[ \delta_M \alpha \sqrt{\frac{v}{\omega}} \]  

(3-116)

and \( \delta_C \alpha \delta_M \),

(3-117)

where \( \delta_M \) and \( \delta_C \) are the momentum and concentration boundary layer thicknesses, respectively.

Thus,

\[ Sh_w \alpha \frac{P_m}{D/\delta_C} \alpha \frac{P_m}{k} \]  

(3-118)

and \( Sh_w \) is proportional to the ratio of the membrane permeability to the liquid phase mass transfer coefficient.

Equation (3-106) is of the same form as the equation for mass transfer from a disk rotating in a quiescent fluid. In the rotating disk problem, the concentration boundary layer is independent of \( r \) and the radial terms may be dropped leading to a straightforward solution (248, 394).

This cannot be done for the problem considered here because the directions of the velocity components \( V_r \) and \( V_z \) are opposite to those for the rotating disk. As a result, the concentration boundary layer thickness is a function of \( r \). This is clearly evident when one recognizes that the outer edge of the mass transfer surface is qualitatively equivalent to the leading edge of a flat plate where the boundary layer develops and increases in thickness with increasing distance.

Although equation (3-106) is variable-separable, the boundary conditions are not. An analytical solution to the
general problem could not readily be obtained and it was necessary to resort to a three-pronged approach. Analytical solutions were obtained for two limited regions: 1) The leading edge of the transfer surface for high Sc, where the concentration boundary layer is sufficiently small that the velocity components may be assumed to be given by the first term in their Taylor expansions (Solutions were obtained for both constant concentration and constant flux boundary conditions.); and 2) The concentration field far from the transfer surface where the radial velocity component is negligible and the surface appears as a point source of mass. The third approach was to obtain a numerical solution to the partial differential equation. In addition, a mass transfer correlation for a turbulent boundary layer was developed.

Figure 3-7 indicates the regions of applicability of the three solutions superimposed on a qualitative sketch of the concentration boundary layer (defined as ξ at which θ = 0.01) for Sc = 10^3, Re = 10^4. The regions in which the numerical and leading edge analytical solutions were expected to give accurate values overlap and hence serve as a check on each other. Of primary interest was the near-wall concentration field from which mass transfer coefficients could be calculated. The far field solution served primarily to show that, along r = 0, the concentration length scale was much greater in the axial direction than in the radial direction. This permitted some adjustment in the boundary conditions to aid in attaining a stable numerical solution.
Figure 3-7. Qualitative Sketch of Concentration Boundary Layer for Infinite Fluid Rotating Against Stationary Base.
Conditions: $Sc \approx 10^3$, $Re \approx 10^4$. Dotted Lines Indicate Region of Applicability of Each Solution.
The boundary layer profile shown in Fig. 3-7 is particularly interesting. Mass is convected radially inwards near the surface and upwards over the entire region. Axial diffusion acts in the same direction as axial convection, while radial diffusion acts in the opposite direction to radial convection. The net result for high Sc is to transfer mass inwards towards the axis of symmetry. Since axial convection is so much greater than radial diffusion away from the axis, an extremely long "plume" results. As Sc decreases, the plume recedes towards the surface since radial diffusion becomes more effective in depleting the region around the z axis, while simultaneously the boundary layer over the remainder of the transfer surface grows in thickness as axial diffusion becomes more important. At Sc=1, one would expect the concentration and velocity fields to be relatively similar (exact similarity doesn't hold because there is no analogue to the Coriolis force, centrifugal force, or the pressure gradient in the diffusion equation). For Sc<<1, it is not clear what the boundary layer would look like.

Equation (3-106) was solved numerically with a finite difference technique, using the alternating difference implicit procedure of Peaceman and Rachford (317) by iterating the transient to the steady state. Fig. 3-8 summarizes the problem to be solved numerically, including the dimensionless groups for correlation of the results. Since the equation could only be solved on a finite grid, the far field boundary condition was imposed at ζ = ζ∞ and the outer radial boundary condition at x=1. Numerical solutions
were obtained for sequentially increasing values of \( \xi \) until the concentrations near the wall (and in fact over most of the grid) became invariant with increases in \( \xi \). In addition, the axial coordinate \( \zeta \) was transformed in order to expand the region near the wall so that high accuracy could be obtained with large \( \xi \). Imposition of the radial boundary condition at \( x=1 \) led to inaccuracies in the first one or two grid slices in from the leading edge. Consequently, the numerical solution and analytical leading edge solution were matched at the point at which they crossed (generally about \( x=0.95 \)) and the leading edge solution employed from that point to \( x=1 \).

Using the boundary conditions described above, instabilities developed in the portion of the grid corresponding to low \( \Theta \) (large \( \zeta \) and large \( x \)). Numerical experiments were carried out using different boundary conditions, as shown in Fig. 3-8. The adjustment of the boundary conditions at \( x=1 \) and \( \zeta = \xi \) was justified by the results of the far field solution. Setting \( \Theta = 0 \) at \( x=1 \) had little beneficial effect. However, changing the far field boundary condition at \( \zeta = \xi \) to \( \partial \varphi / \partial y = 0 \) resulted in stable solutions for almost all conditions studied, except for the occasional appearance of small negative numbers in the region where \( \Theta < 10^{-3} \). Since the boundary condition at \( x=1 \) led to inaccuracies near the leading edge, attempts were made to modify it to a more physically reasonable condition. Using an insulated boundary condition at \( x=1 \) had little effect. Extending the grid beyond \( x=1 \) led to
Figure 3-8
Theoretical Modeling of Mass Transfer in Batch Dialyzer
(Laminar Boundary Layer)

Assumptions
1. Infinite base and fluid (neglect end effects due to wall)
2. Incompressible fluid
3. Axially symmetrical boundary layer
4. Constant physical properties

Differential Equation

\[ V_r \frac{\partial c}{\partial r} + V_z \frac{\partial c}{\partial z} = D \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial c}{\partial r} \right) + \frac{\partial^2 c}{\partial z^2} \right) \]

radial  axial  radial     axial
convection  diffusion

Boundary Conditions

\[ z = \infty \quad c = c_\infty \quad \text{or} \quad \frac{\partial c}{\partial z} = 0 \]
\[ r = a \quad \frac{\partial c}{\partial r} = 0 \]
\[ z = 0 \quad c = c_w \quad \text{Const. Concentration} \]

\[ \int_0^z -D \frac{\partial c}{\partial z} = 2P_m (c_m - c_w) \quad \text{Flux} \]

Dimensionless Groups for Correlation

\[ St = f(Sc, Re, b/a, s/a, Sh_w) \]

where

\[ St = \frac{k}{b}, \quad Sc = \frac{V}{D}, \quad Re = \frac{b}{\nu}, \quad Sh_w = \frac{2P_m \sqrt{\omega}}{D} \]
instabilities in the added region which propagated inward. Further experimentation along these lines was terminated, although the cause of the instabilities was never resolved.

In its final form, the computer program for the numerical solution could be run with 32 combinations of boundary conditions. The particular configuration employed to generate most of the results reported in this study were: \( \partial \theta/\partial x = 0 \) at \( x=0 \), \( \partial \theta/\partial \zeta = 0 \) at \( \zeta = \zeta_\infty \), and \( \theta = 0 \) at \( x = 0 \).

From the slope at the wall, local mass transfer coefficients were calculated from

\[
\dot{n} = k_x (C_w - C_\infty) = -D \left. \frac{\partial \theta}{\partial \zeta} \right|_{\zeta=0} \tag{3-119}
\]

or

\[
k_x = -D \frac{\sqrt{c_\infty}}{\zeta} \left. \frac{\partial \theta}{\partial \zeta} \right|_{\zeta=0} \tag{3-120}
\]

which in dimensionless form is

\[
St_x \frac{Sc \, Re^{1/2}}{} = - \left. \frac{\partial \theta}{\partial \zeta} \right|_{\zeta=0} \tag{3-121}
\]

The slope at the wall was evaluated from a separate set of finite difference expressions different from those used for the interior of the grid. Convergence of the solution was checked by varying grid spacing. The standard grid size adopted was 50 by 50.

5. **Theoretical Results**

This section will be restricted to representative results obtained from the theoretical solutions. Complete
derivations and details of the limiting analytic and numerical solutions may be found in Appendices G and H, respectively. In addition, Table H-2, Appendix H, contains a complete sample output from the computer program for $Sc=10^3$, $Re=10^4$.

The theoretically derived relationships for friction factor and mass transfer correlations are summarized below. They are expressed in terms of the angular velocity beyond the boundary layer on the stationary base, $\gamma \omega$, where $\omega$ is the impeller angular velocity. If the fluid in the vicinity of the impeller rotates with the same velocity as the impeller, $\gamma=1$. If the impeller is replaced by a disc, the values of $\gamma$ derived above are employed. The mass transfer results apply for high $Sc$.

Dimensionless Moment Coefficient

1. Laminar Boundary Layer - $C_M = 2.43 \gamma^{1/2} Re^{-1/2}$  \hspace{1cm} (3-122)
2. Turbulent Boundary Layer - $C_M = 0.107 \gamma^{1/2} Re^{-1/5}$  \hspace{1cm} (3-123)

Local Mass Transfer Coefficients

1. Laminar Boundary Layer

   Leading Edge (Const. Conc. B. C.):
   \[ S_{t_x} Sc^{2/3} = 0.528 \gamma^{1/2} Re^{-1/2} \left[ \ln \left( \frac{b}{r} \right) \right]^{1/3} \]  \hspace{1cm} (3-124)

   Leading Edge (Const. Flux B. C.):
   Multiply R.H. S. of eqn. (3-124) by 1.209.

   Numerical Soln - presented graphically below.
2. Turbulent Boundary Layer

\[ St_x Sc^{2/3} = 0.0225 \gamma^{1/5} Re^{-1/5} \left( \frac{1+a^2}{1-x} \right)^{3/8} x^{1/10} \frac{D}{D} \]  

(3-125)

where \( x, a, \) and \( D \) defined by eqns. (3-60) and (3-89) through (3-93).

Average Mass Transfer Coefficients (Const. Conc. B. C.)

1. Laminar Boundary Layer  
   \[ St_m Sc^{2/3} = 0.761 \gamma^{1/2} Re^{-1/2} \]  
   (From numerical solution)  
   (3-126)

2. Turbulent Boundary Layer  
   \[ St_m Sc^{2/3} = 0.0285 \gamma^{1/5} Re^{-1/5} \]  
   (3-127)

The concentration profiles obtained from the numerical solution are shown in Fig. 3-9 for \( Sc=10^3, Re=10^4 \), where \( \theta \) is plotted as a function of \( \zeta \) for various values \( x=r/b \). Concentration decays sharply near the leading edge but changes very slowly near the axis of symmetry. The increase in \( \theta \) for \( \zeta > 3 \) is caused by the reversal of direction of the radial flow component, as shown in Fig. 3-6.

The influence of the velocity distribution on the concentration profiles is shown more clearly in Fig. 3-10 where the same plot is given for \( Sc=1 \). The concentration profiles are quite similar to the axial velocity profile, except that there is an added radial dependence. The particular solution shown was obtained with \( \zeta_w = 15 \). The same problem was solved with \( \zeta_w = 1000 \). The results showed that \( \theta \) decayed very slowly beyond the momentum boundary layer. The numerical solution was automatically terminated after
Figure 3-9. Concentration Profiles for $Sc=10^3$, $Re=10^4$
$\theta$ as a Function of $\zeta$ for Various Values of $X$
Figure 3-10. Concentration Profiles for $Sc=1$, $Re=10^4$. $	heta$ as a Function of $\xi$ for Various Values of $x$. 
250 iterations (dimensionless time = 2000), although the concentration field was still propagating outwards slowly. Consequently, it could not be ascertained definitively that the far field solution had reached steady state.

The concentration boundary layer, defined as the value of \( \zeta \) at which \( \theta = 0.01 \), is shown in Fig. 3-11 where \( \zeta \text{ Sc}^{1/3} \) is plotted as a function of x for higher values of Sc. Also plotted are the values of \( \zeta \) corresponding to constant \( \theta \) equal to 0.2, 0.5, and 0.8, for Sc = 100. The concentration boundary layer builds up sharply at the leading edge and then increases in thickness less rapidly with decreasing radial distance. There is an inflection point as one proceeds radially inward from the edge, and then the boundary layer thickness grows more rapidly. For very high Sc, the results may be represented by a single curve of \( \zeta \text{Sc}^{1/3} \) as a function of x. This is consistent with both the leading edge and far field analytical solutions described in Appendix G. The results in Fig. 3-11 were obtained with \( \theta = 0 \) as the far field boundary condition.

The influence of Sc on the local mass transfer coefficient is shown in Fig. 3-12. \( \text{St}_x \text{ Sc}^{2/3} \text{Re}^{1/2} \) is plotted as a function of x for various values of Sc. The general shape of the curves is roughly the inverse of the boundary layer thickness. At \( x = 1 \) (r=b), the mass transfer coefficient is infinite, and it drops rapidly and continuously to a very small magnitude as x decreases to zero. The analytical leading edge solution is also plotted. For \( x > 0.90 \), it agrees well with the numerical solution for
high Sc. The analytical solution actually crosses the numerical solution at \( x = 0.95 \), the exact value depending slightly upon Sc. For calculation of average mass transfer coefficients, the analytical solution was employed beyond the point at which the solutions crossed.

Figure 3-13 is a similar plot which shows the influence of the wall Sherwood number on the liquid phase local mass transfer coefficient. As \( \text{Sh}_W \) increases to infinity, the solution tends towards that of the constant concentration boundary condition. Conversely, as \( \text{Sh}_W \) decreases to zero, the solution tends towards that corresponding to a constant flux boundary condition. In this respect, the solution behaves analogously to the flat plate dialyzer theoretical model discussed in Section 5.0.1. The analytical leading edge solution for a constant flux boundary condition compares favorably with the numerical solution for \( \text{Sh}_W = 0.1 \) beyond \( x = 0.9 \). Although the leading edge solutions predict a ratio of 1.209 between the two limiting boundary conditions, independent of radial position, the numerical solutions clearly show that as \( x \) decreases, the ratio between the mass transfer coefficient for any finite \( \text{Sh}_W \) and that for \( \text{Sh}_W = \infty \) becomes progressively larger as \( x \) decreases. The effect of \( \text{Sh}_W \) on the average mass transfer coefficient will be discussed later in conjunction with the estimation of true membrane permeability.

The relative magnitude of the local mass transfer coefficients are shown in Fig. 3-14 as a function of \( x \). The abscissa represents the local value divided by the average value. Except near the axis of symmetry, the curve is
Figure 3-11.
Concentration Boundary Layer as a Function of $x$ for Various Values of $Sc_{Re=10^4}$. Dashed lines are for $Sc=100$. 

$\theta=0.01$

$\theta=0.2$

$\theta=0.5$

$\theta=0.8$

$\varepsilon = \frac{3}{Sc}$

$0.4 \times \frac{x}{b}$

$0.5$

$0.6$

$0.7$

$0.8$

$0.9$

$1.0$
Figure 3-12. Influence of $Sc$ on Local Mass Transfer Coefficients $St_x Sc^{2/3} Re^{1/2}$ as a Function of $x$ for Various Values of $Sc$. $Re=10^4$

Leading Edge Solution (Const.Conc.B.C.)

$$St_x Sc^{2/3} Re^{1/2} = \left. \frac{-1}{Sc^{1/3} \frac{\partial \theta}{\partial r}} \right|_{r=0}$$

Sc = 10^5, 10^3, 10, 1.
Figure 3-13. Influence of $Sh_w$ on Local Mass Transfer Coefficients $St_x Sc^{2/3} Re^{1/2}$ as a Function of $x$ for Various Values of $Sh_w$. $Sc=10^3$, $Re=10^4$.
Figure 3-14. Relative Magnitude of Local Mass Transfer Coefficients as a Function of X for Various Values of Sc. Re=10^4
relatively independent of Sc. Because the local mass transfer coefficients are so much higher at the leading edge, the bulk of the mass transfer occurs in this region. From Table H-2, Appendix H, approximately 50% of the total mass transfer occurs in the outer 13% of the radial distance.

All the results reported above were obtained for Re=10^4. Numerical solutions were obtained for Sc=10^3 with Re ranging from 10^3 to 10^5. The calculated average mass transfer coefficients were almost identical indicating that, for the range of variables studied, the radial diffusion term contributed little to the solution near the leading edge.

D. Results and Discussion

Author's Note: Some of the material covered here has been previously published as part of an A.I.Ch. E. Symposium on the Artificial Kidney (390).

1. Momentum and Mass Transport in the Batch Dialyzer
   a. Flow Visualization

   Figures 3-15a and b are photographs taken during the flow visualization studies with the membrane replaced by an endplate of clear lucite. The depth of field observable is about 1/64 in. The flow patterns in the unbaffled vessel display a spiral-like behavior, qualitatively similar to the patterns near the boundary in Fig. 3-4. These studies were performed before the theoretical modeling of the system was attempted and served as the clue that the fluid dynamic conditions at the membrane face were essentially those of a fluid rotating against a stationary surface. The flow patterns in the baffled vessel are highly disordered,
as compared to the un baffled vessel, because of separation and eddy formation around the baffles. Although the motion pictures indicated an overall spiral-like flow pattern, the complex and somewhat disordered velocity patterns for the un baffled vessel obviate the kind of analysis performed for the un baffled vessel.

b. Power Dissipation and Torque

Total power dissipation was correlated (321) in terms of the conventional power number as a function of impeller Reynolds number. The results for both baffled and un baffled operation agreed very closely with values estimated from a published study on a similar system (26). The power number decreased with a decrease in b/a but was only weakly sensitive to large changes in s/a. A decrease in impeller diameter decreased power dissipation slightly, and use of baffles greatly increased it.

Torque on the bottom plate only was about an order of magnitude lower than that measured for the total vessel. The very low torque at low impeller speeds approached the limit of sensitivity of the experimental equipment; hence, the standard error is estimated to be ±20% for Re<10^4 and ±5% for Re>10^4. Measured torque values are presented in Fig. 3-16 in terms of the dimensionless moment coefficient as a function of Reynolds number for various values of s/a.

The theoretical lines are for γ=0.49 (laminar boundary layer) and γ=0.77 (turbulent boundary layer). These values of γ were obtained by visually finding the theoretical
a. Unbaffled, $Re = 27,000$

b. Baffled, $Re = 31,000$

Figure 3-15. Flow visualization in batch dialyzer
relationships which best fit both the moment coefficient and average mass transfer coefficient data. The laminar value compares favorably with the value predicted for the impeller replaced by a disk, \( \gamma = 0.44 \). The agreement for a turbulent boundary layer is poor but not surprising since the analysis is valid only for the outer portion of the surface. The data agree well with the theoretically calculated values for a laminar boundary layer up to a Reynolds number of about 20,000. Above \( Re = 30,000 \) the data show the characteristics of a turbulent boundary layer, although the magnitude of \( C_M \) is lower than predicted. For \( Re \) from 20,000 to 30,000, \( C_M \) is approximately constant, indicating the possible existence of a transition region. At \( s \) equal to 1/16 and 1/8 in., the data are virtually indistinguishable. Increasing \( s \) to 3/8 in. shows a definite decrease in \( C_M \). Overall, the effect of \( s/a \) appears quite small as long as the impeller remains in proximity to the bottom of the chamber. The effect of impeller diameter and baffles on the torque transmitted to the base is similar to that for the total power dissipation.

c. Liquid Phase Mass Transfer

The theoretical analysis and experimental data on the frictional resistance of enclosed rotating disks (92) indicate that the appropriate dimensionless groups which characterize mass transfer in the membrane boundary layer are as follows:
\[
Sh = \frac{kb}{D} \tag{3-128}
\]

\[
Re = \frac{\omega b^2}{v} \tag{3-129}
\]

\[
Sc = \frac{v}{D} \tag{3-130}
\]

\[
Sh_w = \frac{2pm\sqrt{\frac{v}{\omega}}}{D} \tag{3-131}
\]

and the geometrical groups

\[
\frac{b}{a} \text{ and } \frac{s}{a}.
\]

In place of the Sherwood number, \(Sh\), the Stanton number may be used,

\[
St = \frac{k}{\omega b} \tag{3-132}
\]

Previous studies of transport in agitated vessels have used dimensionless groups based upon various combinations of the impeller radius, \(a\), and tank radius, \(b\), but no evidence exists that any one group is preferable. For this reason, the vessel or membrane radius, \(b\), has been chosen arbitrarily for all characteristic length dimensions in this study, since the theoretical analysis does provide certain scaling rules on this basis.

The theoretical analysis showed that, to a good approximation, the benzoic acid mass transfer results could be correlated in the form

\[
St = A \text{Sc}^d \text{Re}^c \tag{3-133}
\]

or

\[
Sh = A \text{Sc}^{d+1} \text{Re}^{c+1} \tag{3-134}
\]
where

\[ A = f(b/a, s/a, Sh_W) \]  \hspace{1cm} (3-135) \]

The analysis indicated that for both laminar and turbulent boundary layers, \( d = -2/3 \) for sufficiently high Sc. This has been confirmed by experiment (197, 269) by others and was not tested experimentally in this study. In addition, the theoretical analysis predicts \( c \) equal to \(-0.5\) and \(-0.2\) for a laminar and turbulent boundary layer, respectively.

All mass transfer measurements were made with an axial gap distance, \( s \), of \( 1/8 \) in. Fig. 3-17 compares the experimentally measured local mass transfer coefficients for \( Re < 32,000 \) with the theoretically predicted curves for the two limiting cases with a laminar boundary layer. \( St_x Sc^{2/3} Re^{1/2} \) is plotted as a function of \( x \), and the theoretical curves are for \( Sc = 850 \) which applies for benzoic acid in water at \( 25^\circ C \). The bulk of the data falls between the two limiting theoretical solutions with the exception of the region near the wall, where boundary layer buildup on the chamber walls results in lower mass transfer coefficients than predicted.

Also plotted in Fig. 3-18 is a set of data for \( Re \approx 58,000 \) which displays a significantly different dependence on dimensionless radial distance. This difference is further illustrated in Fig. 3-18 which is a similar plot but with the abscissa replaced by \( St_x Sc^{2/3} Re^{1/5} \). The data are plotted for \( Re > 35,000 \). Again, the data falls between the two limiting solutions, in this case for a turbulent boundary layer. The theoretical curves are
FIGURE 3-16. MOMENT COEFFICIENT AS A FUNCTION OF REYNOLDS NUMBER FOR LARGE IMPELLER, \( a = 1.118 \text{ in.} \), AND VARIOUS VALUES OF AXIAL GAP, \( s \).

THEORETICAL LINES ARE FOR \( \gamma = 0.49 \) (LAMINAR) AND \( \gamma = 0.77 \) (TURBULENT)
Normalized Dimensionless Local Mass Transfer Coefficients as a Function of Dimensionless Radial Distance
(Benzoic Acid Dissolution From Dialyzer End plate)

Symbol  | Re
---|---
○  | 8,130
□  | 11,620
△  | 14,510
◆  | 20,420
●  | 23,244
●  | 31,980
▼  | 58,140

Laminar Boundary Layer

Turbulent Boundary Layer

St $\frac{Sc^{2/3} Re}{2} = \left(\frac{K_{D}}{D}\right)^{1/2}$

Figure 3-17. Results for Local Mass Transfer Coefficients, Low Re
Normalized Dimensionless Local Mass Transfer Coefficients as a Function of Dimensionless Radial Distance
(Benzoic Acid Dissolution From Dialyzer End plate)

\[ \text{St} \frac{Sc^{2/3}Re^{0.2}}{(\frac{K}{\omega b})^{1/3}} \text{ vs } \frac{r}{b} \]

- **Symbol**
  - ▼ Re 8,130
  - ▼ 35,700
  - ▼ 40,660
  - ▼ 46,570
  - ▼ 58,140
  - ▼ 65,090
  - ▼ 69,850
  - ▼ 81,250

- **Laminar Boundary Layer**
- **Turbulent Boundary Layer**

- **Theory, Turbulent Boundary Layer, } γ=1.0**

- **Theory, } γ=0.48 (Impeller replaced by disk)**

- **chamber wall**

Figure 3-18. Results for Local Mass Transfer Coefficients, High Re
Figure 3-19. Average Mass Transfer Correlation from Dissolution Rate
a = 1.118 in., s = 1/8 in. unhafted
limited to only about the outer one-third of the mass transfer surface. However, the data indicate that the local mass transfer coefficient becomes constant or decreases slightly towards the center of the mass transfer surface. This is in marked contrast to the behavior at lower Reynolds number, for which a set of data is also plotted, where the mass transfer coefficient decreases continuously to almost zero at the center.

At the leading edge, the mass transfer coefficients increase to a greater extent as \( x \) approaches unity than predicted by the turbulent boundary layer model. Drawing an analogy with flow over a flat plate, this behavior probably means that at the leading edge, the boundary layer is laminar for some distance until transition to a turbulent boundary layer occurs further downstream.

Average mass transfer coefficient data obtained with the large impeller in unbaffled operation are shown in Fig. 3-19 where \( S_{tm} \cdot Sc^{2/3} \) is plotted as a function of \( Re \). The theoretical lines correspond to the same values of \( \gamma \) as employed in Fig. 3-16. The experimental data are smooth and show excellent agreement with values predicted from the laminar boundary layer theory at low \( Re \) and appear to asymptote toward the turbulent boundary layer theory at high \( Re \). The best fit of the data to a straight line was determined using weighted least squares. The constants in eqns. (3-133) and (3-134) and the estimates of their standard deviations are as follows:
8000 < Re < 32,000

\[ A = 0.285 \pm 0.027; \quad c = -0.433 \pm 0.010 \tag{3-136} \]

32,000 < Re < 82,000

\[ A = 0.0443 \pm 0.012; \quad c = -0.254 \pm 0.023 \tag{3-137} \]

The correlation of average mass transfer coefficients indicates a transition from laminar to turbulent behavior around \( Re = 30,000 \), in agreement with the torque and local mass transfer coefficient data. The mass transfer data are sufficiently smooth to permit determination of the variation in the exponent, \( c \), with Reynolds number. This was accomplished by determining the slope at various Reynolds numbers using data points within a limited range. The results are presented in Fig. 3-20 and illustrate the transition from laminar to turbulent behavior.

The effect of impeller diameter and of baffled operation is illustrated in Fig. 3-21. The data are limited to the turbulent regime. Reducing the impeller diameter reduces the mass transfer coefficients. The best fit is found to be:

\[ St \ Sc^{2/3} = 0.0389 \ Re^{0.248} \tag{3-138} \]

Thus, an 18% decrease in impeller diameter produces a 12% decrease in mass transfer coefficient. The use of four baffles increases the mass transfer coefficient about 20%, yielding a best fit of:

\[ St \ Sc^{2/3} = 0.133 \ Re^{-0.346} \tag{3-139} \]
Figure 3-20. Apparent Exponent on Reynolds Number, $C$, as a Function of Reynolds Number.
Figure 3-21. Effect of Variation in Impeller Diameter and Baffled Operation on Mass Transfer Performance: \( s = 1/8 \) in.
These results are in agreement with the higher moment coefficient found for baffled operation. The correlation obtained by Marangozis and Johnson (269) for transport to the bottom of an agitated baffled vessel is:

\[
\frac{kL}{D} = 0.402 \left( \frac{v}{D} \right)^{1/3} \left( \frac{nd_1}{v} \right)^{0.65}
\]  

(3-140)

Introducing the characteristic lengths employed in this study transforms eqn. (3-140) into

\[
St \; Sc^{2/3} = 0.131 \; Re^{-0.35}
\]  

(3-141)

which is plotted in Fig. 3-21 and compares favorably with the results obtained. The higher coefficients found in this study are probably due to the closer proximity of the impeller to the transferring surface, since Marangozis and Johnson used an s/a ratio of 2. Despite the slightly higher coefficients obtained with baffled operation, the increased complexity probably does not warrant its application to membrane permeability measurement.

The correlation presented by Marangozis and Johnson (269) for transport in unbaffled vessels is also plotted in Fig. 3-21. It predicts significantly higher mass transfer coefficients than those measured and is thus completely inappropriate to the geometry studied in this investigation. It is interesting to note that Marangozis and Johnson have concluded that baffled operation results in reduced mass transfer, in contradistinction to the results reported here.
However, the data in their correlation was obtained exclusively from experiments on mass transfer to suspended particles.

With respect to the use of a Wilson plot, described in Section 3.A.1., the results depicted in Figs. 3-19 and 3-20 indicate that over a wide range of speeds a unique exponent for the impeller speed or Reynolds number does not exist. In reality, the "best" exponent which fits the data will depend upon the specific speed range employed, and the results of one investigator will not apply to another unless the same speed range is maintained. This may explain why various researchers have obtained their best results with different exponents for the Wilson Plot.

d. **Membrane Flutter**

The results of the membrane flutter investigation are shown in Fig. 3-22 where the observed deflection in the reflected spot is plotted as a function of Reynolds number. No flutter was observed for Re<29,500 at any radial position on the membrane. At higher Reynolds numbers, flutter increased roughly in proportion to impeller speed. The results plotted correspond to reflection off a point midway from the center to the edge of the membrane. Other positions gave similar results. The observed flutter may result from rippling and/or deflection perpendicular to the plane of the membrane. Differentiation between the two is impossible without more detailed investigation. The results apply specifically to those materials comparable to or weaker than cellophane.
Figure 3-22. Index of Membrane Flutter as a Function of Reynolds Number
These results are particularly striking in light of the conclusions obtained from the torque and mass transfer coefficient measurements. Together they clearly indicate the following: (1) Above Re=30,000, the membrane boundary layer is turbulent. (2) Below Re=20,000, the boundary layer is laminar. (3) A transition region may exist beginning at Re=20,000-25,000. (4) No membrane flutter exists until the boundary layer becomes turbulent, that is, until turbulent eddies penetrate close to the membrane surface. This occurs at Re=30,000, corresponding to an impeller speed of about 200 rpm at 37°C in the dialyzer studied.

The effects of membrane flutter on permeability measurement are difficult to gauge. Three possibilities are: (1) Enhanced diffusion arising within the membrane due to flexing of polymeric chains. (2) Enhanced fluid transport in the adjacent boundary layers, above that obtained with a rigid interface. (3) Bulging, stretching, or stress relaxation of the membrane, resulting in increased transport area and a thinner membrane.

Membranes were used in dialysis experiments with speeds ranging from 60 to 960 rpm. Above about 400 rpm (Re>60,000), upon removal from the dialyzer the membrane was often found to have sagged and to have increased in surface area. Occasionally circular score marks were found in the center, indicating that the membrane had bulged sufficiently (1/8 in.) to have come in contact with the impeller, although no membrane ever tore during operation. This tendency increased with higher speeds and with
repeated dialyses with the same membrane. Similar observations were noted if during filling the membrane was bulged by grossly unequal water levels in the two chambers. It is probable that such alterations would change the true membrane permeability in addition to possibly affecting the liquid phase resistance.

Based upon these preliminary experimental findings, a standard technique was established in which the dialysis was carried out at 200 rpm at 37°C, corresponding to a Reynolds number of about 29,700, a value for which membrane flutter was not significant.

e. Corrections for Modified Geometry, Schmidt No.

In order to extend the applicability of the results of this investigation to batch dialyzers with different geometries correction factors for b/a and s/a were derived from the theoretical analysis for the former quantity and from the experimental data of Daily and Neece (92) for the latter quantity. These factors were then normalized to yield 1.0 for the geometrical parameters of the dialyser described above. They may be applied to the correlation described above as multipliers of the coefficient A.

The correction factors \( \psi (b/a) \) and \( 0(s/a) \) are shown in Figs. 3-23 and 3-24, respectively. For \( 1.0 < b/a < 1.3 \), the graph for \( b/a \) is approximately linear and may be approximated by:
\[ \phi \left( \frac{b}{a} \right) = 2.449 - 1.305 \left( \frac{b}{a} \right) \]  

(3-142)

For \( 0.05 < s/a < 0.20 \) the correction for \( s/a \) may be approximated by:

\[ \phi \left( \frac{s}{a} \right) = 1.092 - 0.820 \left( \frac{s}{a} \right) \]  

(3-143)

The following limitations on the correction factors should be considered in their use:

(1) They were derived for a laminar boundary layer and apply to the correlation of equation (3-136).

(2) They are based on a semi-theoretical derivation and their range of applicability has not been tested experimentally.

An additional correction factor may be applied to the coefficient \( A \) to correct for the Schmidt number of the solute-solvent system employed. The benzoic acid results applied for \( Sc = 850 \). The effect of \( Sc \) on \( A \) was obtained from the numerical solution for \( Sc \) ranging from 200 to \( 10^5 \) and the resulting values normalized by the value for \( Sc = 850 \). The correction is:

\[ \eta(Sc) = 1.009 \left[ 1.0 - 0.00255(5.0 - \log_{10} Sc)^2 \right] \]  

(3-144)

valid for \( 200 < Sc < 10^5 \), and \( \eta(Sc) = 1.009 \) for \( Sc > 10^5 \). The correction factor is small, amounting to about 2% at \( Sc = 200 \), and is necessary only for high accuracy requirements.

f. Influence of \( Sh_w \)

The dissolution experiments with benzoic acid correspond to a boundary condition of constant concentration at the wall. In the membrane permeability evaluation, a
Figure 3.23: Correction Factor $\psi(h/a)$ as a Function of $h/a$
Figure 3-24. Correction Factor $\theta(s/a)$ as a Function of $s/a$
flux boundary condition is applicable, characterized by the wall Sherwood number, Sh_w. The two extremes, Sh_w = ∞ and Sh_w = 0, correspond to the constant concentration and constant flux boundary conditions. For any Sh_w < ∞, the actual mass transfer coefficients are higher than those obtained with benzoic acid and depend upon the magnitude of Sh_w, which in turn is a function of the membrane permeability.

To determine the dependence of the liquid mass transfer coefficients on Sh_w, the values of the coefficient A obtained from the numerical solution for various values of Sh_w were normalized to 1.0 for Sh_w = ∞, yielding an additional correction factor, φ(Sh_w), to be applied to the coefficient A. φ(Sh_w) is shown in Figure 3-25 as a function of Sh_w; it represents the ratio of the average mass transfer coefficient for any finite value of Sh_w to that obtained for Sh_w = ∞. Use of this correction factor implies that the effective value of γ for the batch dialyzer is invariant with Sh_w. The calculated values were fitted to a polynomial using a least squares procedure (see Appendix K) from which the curve in Figure 3-25 was generated. The polynomial agrees with the calculated values to better than 0.05% and is given by equation (3-145):

$$φ(Sh_w) = 0.1375 \left( B_0 + \sum_{n=1}^{3} B_n \left[ \tanh \left( 1.1086 - \log_{10} Sh_w \right) \right]^n \right) + 1.375 \quad (3-145)$$

where

$$B_0 = -0.00429$$
$$B_1 = 1.16569$$
$$B_2 = -0.01933$$
$$B_3 = -0.16800$$
In order to determine the true membrane permeability, the overall measured mass transfer coefficient \( K_0 \) is first assumed equal to the permeability \( P_m \), from which \( Sh_w \) is calculated. Then \( \phi (Sh_w) \) is estimated from Figure 3-25 and the liquid phase resistances are calculated from the corrected correlation and subtracted from the overall resistance to yield the true membrane resistance. The procedure may be repeated if desired, to obtain a new value of \( \phi (Sh_w) \), but this is seldom necessary. The procedure is summarized in Table 3-2. For the dialyzer used in this study, of course, \( \psi (b/a) = \psi (s/a) = 1.0. \)

It should be recognized that the \( \phi (Sh_w) \) correction applies to a laminar boundary layer. The \( Sh_w \) dependence of a turbulent boundary layer is unknown, but undoubtedly much smaller.

\( g. \) **Comparison with Results of Others**

The complete mass transfer correlation for the laminar regime is now:

\[
St \ Sc^{2/3} = \phi (Sh_w) \frac{b}{a} \Theta \left( \frac{s}{a} \right) \eta(Sc) A \ Re^c \quad (3-146)
\]

Where \( A \) and \( c \) are given in equation (3-136) and the correction factors are determined from Figures 3-23, 3-24, 3-25 and equation (3-144). To test the validity of the proposed correlation it was compared with the results of Kaufmann and Leonard (197) and Mackay and Meares (266).

Kaufman and Leonard (197) obtained a correlation for liquid phase mass transfer from permeability evaluations using a Wilson plot for speeds ranging from 46 to 500 rpm corresponding to Reynolds numbers of about 10,000 to 109,000.
Single Point Determination of True Membrane Permeability

1. Measure apparent permeability, $K_o$.

2. Let $P_m = K_o$ and evaluate wall Sherwood number

$$N_{Sh_w} = \frac{2P_m \sqrt{\frac{V}{\omega}}}{S}$$

3. Calculate fluid mass transfer coefficient from

$$N_{St} N_{Sc}^{2/3} = \phi(N_{Sh_w}) \psi\left(\frac{b}{a}\right) \Theta\left(\frac{s}{a}\right) \eta(N_{Sc}) A \eta(\frac{c}{N_{Re}})$$

Correction Factors

Benzoic Acid Results

4. Calculate true membrane permeability and effective diffusivity

$$\frac{1}{P_m} = \frac{1}{K_o} - \frac{2}{k_f}$$

$$D_{eff} = P_m \Delta X$$
Their correlation was:

\[ \frac{k d_i}{D} = 0.105 \left( \frac{v}{D} \right)^{0.32} \left( \frac{\omega d_i^2}{v} \right)^{0.68} \]  \hspace{1cm} (3-147)

Converting to the characteristic length employed in this work, using Kaufmann's own values, and rearranging to the form of equation (3-133) yields:

\[ \left( \frac{k}{\omega b} \right) \left( \frac{v}{D} \right)^{2/3} = 0.133 \left( \frac{v}{D} \right)^{0.0133} \left( \frac{\omega b^2}{v} \right)^{-0.32} \]  \hspace{1cm} (3-148)

With a Schmidt number of 850, corresponding to benzoic acid, equation (3-148) becomes:

\[ St \ Sc^{2/3} = 0.121 \ Re^{-0.32} \]  \hspace{1cm} (3-149)

This equation is plotted in Figure 3-26 as the "uncorrected" line. It predicts significantly higher coefficients than obtained with the benzoic acid. However, Kaufmann's data was obtained with membranes and with a slightly different geometry. Equation (3-149) must be corrected for these factors:

\[ (St \ Sc^{2/3})_{\text{corrected}} = \frac{0.121 \ Re^{-0.32}}{\phi(S_h_w) \left( \frac{b}{a} \right) \Theta \left( \frac{s}{a} \right)} \]  \hspace{1cm} (3-150)

From reported data, \( b/a = 1.043 \), \( s/a = 0.0553 \) and \( S_h_w = 0.1 \) to 2. From Figures 3-23, 3-24, and 3-25 \( \phi(b/a) = 1.061 \), \( \Theta(s/a) = 1.048 \), and \( \phi(S_h_w) = 1.24 \). Substituting these values into Equation 34 yields:

\[ St \ Sc^{2/3} = 0.0880 \ Re^{-0.32} \]  \hspace{1cm} (3-151)

Equation 35 is plotted in Figure 12 as the "corrected" correlation. It represents the estimate of the correlation. Kaufman would have obtained had he made the same dissolution measurements as reported here. The agreement is to
Figure 3-25. Correction Factor $\phi(Sh_w)$ as a Function of $Sh_w$
Figure 3-26. Comparison of Mass Transfer Correlation with Results of Others
within about 5 to 10%, even in the turbulent region where the correction factors are not strictly applicable. The exponent on the Reynolds number, -0.32, is approximately the same as that obtained if a single line is drawn through all the benzoic acid data (-0.36).

Mackay and Meares (266) reported stagnant film thicknesses which may be related to a mass transfer coefficient by

\[ K = \frac{D}{\delta_f} \]  

(3-152)

where \( \delta_f \) is the reported film thickness. Performing a similar analysis to the one described above, one obtains the "corrected" data points plotted in Figure 3-26. The agreement is again excellent.

2. Permeability Measurements and Membrane Characterization.
   a. Sodium Chloride

Several hundred runs were made with sodium chloride. A large number of these runs were made while the apparatus, procedure, and method of analysis were undergoing revision. An additional number were made to study the reproducibility of the measurements and the influence of various secondary variables. Rather than report in detail all the experiments performed, the relevant results will be summarized and discussed in this section.

Some typical results from a single run with the batch dialyzer are shown in Figure 3-27, where the natural logarithm of the dimensionless concentration is plotted as a
function of time. Although concentration was monitored continuously, discrete values were taken from the recorder trace at specified time intervals. Data points in Figure 3-27 are plotted for five minute time intervals. In the actual data analysis (see Appendix I), data points for one or two minute intervals were employed. Since the shortest runs were of about 25 minutes duration, at least 12 data points were used for each run. The excellent straight line relationship shown in Figure 3-27 is representative of all the sodium chloride runs (and virtually all the radioactive solute runs as well).

Since the diffusivity of sodium chloride in dilute aqueous solutions is dependent upon concentration (161, 406), calculation of the liquid phase mass transfer coefficients required a slight modification of the procedure described above. For the initial estimates, the diffusivity at infinite dilution was employed and the time-averaged concentrations in the solution at the surfaces of the membrane were calculated. The liquid resistances were then recalculated separately for each chamber of the dialyzer, using the diffusivity corresponding to the average film concentration (the average of the surface and bulk concentrations) and a new value of the membrane resistance was calculated. The entire procedure was repeated until the relative change in \( \phi (Sh_w) \) was less than 0.05\%, using the diffusivity evaluated at the average of the surface concentrations in \( Sh_w \). Generally, the initial calculation was sufficient to bring \( \phi (Sh_w) \) to within 0.2\% of its final value.
Figure 3-27. Typical Results from Single Run with Batch Dialyzer
The results for Cuprophane PT-150 (manufactured by J. P. Bemberg, Wuppertal, Germany) as a function of sodium chloride concentration are shown in Table 3-3. In successive columns, the following terms are tabulated: initial concentration charged to chamber 1, time-averaged concentration in chamber 1 at the membrane surface, time-averaged concentration at the center of the membrane (average of the two surfaces), sume of the liquid resistances, true membrane resistance and estimated standard deviation of the error, effective diffusivity, wall Sherwood number, and $\phi$ ($Sh_w$). The effective diffusivity was estimated from its defining equation:

$$P_m = \frac{D_{eff}}{\Delta x}$$

(3/153)

where $\Delta x$ is the wet thickness of the membrane.

The data were obtained from a single membrane at a fixed impeller speed, 200 rpm. All solutions contacting the membrane during dialysis or storage contained an antibacterial agent (formaldehyde, 200 ppm). The membrane was initially soaked in agitated distilled water at room temperature to remove glycerine. Chamber 2 was initially charged with distilled water.

The data cover a wide range of permeabilities: $Sh_w$ varies by a factor of about 7. As concentration increases, $Sh_w$ decreases and the liquid resistance increases. Membrane resistance decreases reapidly with increasing concentration at first and then appears to level out at about 14 min/cm at initial concentrations around 0.1M. The liquid phase resistances account for about 5% of the total resistance.
TABLE 3-3
Scdium Chloride Permeability of Cellophane at 37°C as a Function of Concentration
Membrane: Cuprophane PT-150
Dry thickness: 0.50 mil
Wet thickness: 1.14 mils

<table>
<thead>
<tr>
<th>C_{i0}</th>
<th>C_{is}</th>
<th>C_m</th>
<th>\frac{1}{k_1 k_2}</th>
<th>R_m</th>
<th>\pm Std Dev.</th>
<th>D_{eff}</th>
<th>Sh</th>
<th>\phi (Sh_{w})</th>
</tr>
</thead>
<tbody>
<tr>
<td>\text{mole/1} \times 10^2</td>
<td>\text{mole/1} \times 10^2</td>
<td>\text{mole/1} \times 10^2</td>
<td></td>
<td>\text{min/cm}</td>
<td>\text{min/cm}</td>
<td></td>
<td>\text{cm}^2/\text{sec} \times 10^5</td>
<td></td>
</tr>
<tr>
<td>0.10</td>
<td>0.095</td>
<td>0.050</td>
<td>5.84</td>
<td>88.5</td>
<td>1.9</td>
<td>0.0545</td>
<td>0.322</td>
<td>1.254</td>
</tr>
<tr>
<td>0.20</td>
<td>0.182</td>
<td>0.100</td>
<td>5.89</td>
<td>63.8</td>
<td>2.0</td>
<td>0.0757</td>
<td>0.449</td>
<td>1.249</td>
</tr>
<tr>
<td>0.50</td>
<td>0.415</td>
<td>0.251</td>
<td>6.00</td>
<td>32.3</td>
<td>1.0</td>
<td>0.150</td>
<td>0.894</td>
<td>1.233</td>
</tr>
<tr>
<td>1.00</td>
<td>0.784</td>
<td>0.502</td>
<td>6.10</td>
<td>20.7</td>
<td>1.0</td>
<td>0.233</td>
<td>1.40</td>
<td>1.218</td>
</tr>
<tr>
<td>1.98</td>
<td>1.56</td>
<td>0.993</td>
<td>6.17</td>
<td>17.1</td>
<td>1.0</td>
<td>0.282</td>
<td>1.72</td>
<td>1.210</td>
</tr>
<tr>
<td>4.94</td>
<td>3.86</td>
<td>2.48</td>
<td>6.28</td>
<td>14.2</td>
<td>1.0</td>
<td>0.339</td>
<td>2.08</td>
<td>1.201</td>
</tr>
<tr>
<td>9.79</td>
<td>7.64</td>
<td>4.92</td>
<td>6.36</td>
<td>14.1</td>
<td>1.0</td>
<td>0.343</td>
<td>2.14</td>
<td>1.200</td>
</tr>
<tr>
<td>19.2</td>
<td>14.4</td>
<td>9.67</td>
<td>6.57</td>
<td>13.8</td>
<td>1.0</td>
<td>0.350</td>
<td>2.22</td>
<td>1.198</td>
</tr>
</tbody>
</table>
for the lowest membrane permeability measured and about 32% for the highest. Failure to account for the liquid resistances at high solute concentration would thus cause about a 45% error in the estimate of the true membrane permeability. For all but the lowest concentrations, the estimated accuracy of a single measurement, obtained from a propagation of error analysis, is ±1 min/cm for the true membrane resistance. This estimate is dominated by the error associated with the liquid mass transfer coefficient calculation. The measured effective diffusivities range from about 0.055 to 0.35 x 10^{-5} cm²/sec, and are integral diffusivities, defined by:

$$D_{eff} = \frac{1}{C_{1s} - C_{2s}} \int_{C_{1s}}^{C_{2s}} D'_{m} dC$$

(3-154)

where the primes denote conditions within the membrane and the concentrations refer to time-average quantities. The true diffusivity as a function of concentration within the membrane, $D'_{m}$, is unknown. For comparison, the diffusivity of sodium chloride in water at 37° C and at the higher concentrations dialyzed is about 2.0 x 10^{-5} cm²/sec. Thus, the highest observed effective diffusivity is roughly one-sixth of that for diffusion through water.

Permeability measurements were made at the highest concentrations with the sodium chloride balanced by a urea solution of the same normality in chamber 2. The results were substantially identical, within experimental error. Since the diffusivity (see Appendix B) and membrane per-
meability of the two solutes differ by only about 10%, the osmotic pressure in each chamber was approximately constant and equal throughout the run. Consequently, osmotic effects with sodium chloride run alone were negligible.

The dependence of cellophane permeability to sodium chloride upon concentration may be explained qualitatively on the basis of Donnan membrane equilibrium (105). Cellophane (regenerated cellulose) is known to contain residual carboxylic acid groups (116, 117, 172), and measurements of their content range from about 0.02 to 0.05 milliequivalents per gram of dry cellophane, depending upon its source. The carboxyl groups dissociate in aqueous solution, giving a net negative charge to the membrane. Thus, cellophane behaves as a weak ion-exchange membrane, since it tends to exclude negative ions and take up positive ions. The counter-ion (Na⁺) concentration in the membrane becomes higher and the co-ion (Cl⁻) concentration lower than in the external solution. Since the fluxes of the cation and anion must be stoichiometrically equivalent to maintain electroneutrality the rate of electrolyte diffusion is controlled by diffusion of the co-ion.

Assuming ideal solutions (unit activity coefficients), the Donnan equilibrium may be represented as:

\[ K_{C1} = \frac{-(COO^-)_m + \sqrt{(COO^-)_m^2 + 4(Cl^-)_s}}{2(Cl^-)_s} \]  (3-155)

where \( K_{C1} \), the distribution coefficient for chloride ion, is defined as the concentration of chloride in the water
within the membrane divided by the concentration in the external solution.

The values of $K_{Cl}$ as a function of sodium chloride concentration predicted by equation (3-155) are plotted in Figure 3-28, using an estimate for (COO$^-$)$_m$ of 0.03 m equiv/gm dry cellophane. Since 1 gm of dry cellophane sorbs about 1 gm of water, this corresponds to about 0.03 equiv/liter of water in the membrane. Lonsdale, et al. (256) experimentally measured Na$^+$ and Cl$^-$ distribution coefficients in cellophane using radioactively tagged solutes. The experimental values of $K_{Cl}$ are also plotted in Figure 3-28 and agree with those predicted by equation (3-155) at higher sodium chloride concentrations. Below about 0.03 moles/l, they deviate systematically from the predicted values and decrease more slowly with decreasing concentration. The measured effective diffusivities for sodium chloride permeating through Cuprophan PT-150 are shown on Figure 3-28. They are plotted at concentrations corresponding to the time mean average of the two surface concentrations, $C_m$. The dependence of the effective diffusivity on sodium chloride concentration roughly parallels the dependence of the predicted $K_{Cl}$ values based upon Donnan equilibrium theory. A quantitative comparison of the concentration dependence of the measured effective diffusivity with a theoretical model requires detailed knowledge of the activity coefficients within the membrane (166). These quantities are unknown. However, the dependence of flux upon concentration in real
Figure 3-29. Effective Diffusivity for NaCl Permeation as a Function of Concentration at 37°C

Initial Concentration, moles/liter
Visking results. All diffusivities for wet gel membranes and the Avisco 215 P-1 membrane soaked in sodium hydroxide were significantly higher than those of the commercial materials, with Avisco wet gel the highest. Aminoethylating the surface of the DuPont wet gel decreased permeability about 10%. Subsequent heparinization increased permeability at high concentration but also increased the dependence on concentration. This is probably attributable to the increase in fixed negative charges on the membrane due to the presence of sulphate groups in the heparin molecule. The neutral polyelectrolyte shows a strong dependence on concentration over the entire range indicating a much larger residual charge concentration than on cellulose.

At high concentrations, the DuPont wet gel membrane and the membrane prepared by Farrell (118) were quite similar in permeation properties. Both membranes were cast from viscose solution and never dried. Farrell (118) hypothesized that extrusion of the commercial films, resulting in significant orientation of the cellulose chains and a higher volume fraction of impermeable crystalline regions, was responsible for the decreased effective diffusivities. However, the Avisco wet gel is an extruded but never dried film, and it gave the highest effective diffusivities. From these results, it is concluded that drying the membrane during the manufacturing process, after immersion in glycerol, is the primary reason for the lower effective diffusivities of the commercial films. This
is probably related to an irreversible collapse of the membrane structure to a more dense condition upon drying. Subsequent rewetting results in only a partial gain of the original, highly porous structure.

A Cuprophane membrane which had previously been tested was soaked in blood and then rinsed in saline. Permeability measurements with 0.1M sodium chloride showed about a five per cent decrease in permeability. Consequently, under the conditions employed in the batch dialyzer, the increase in membrane resistance for small molecules caused by adsorbed proteins is negligible.

The influence of temperature on the effective diffusivity of sodium chloride (0.1M) in Cuprophane PT-150 is shown on a semilogarithmic plot of D as a function of 1/T in Fig. 3-30. The data points fall approximately on a straight line, although some curvature is evident. Assuming that the effective diffusivity may be expressed in an Arrhenius-type relationship,

\[ D_{eff} = D_0 \exp(-E/RT) \]  \hspace{1cm} (3-156)

the activation energy and its estimated standard deviation were evaluated from a least squares straight line fit, yielding

\[ E = 3560 \pm 690 \text{ cal/mole, } ^\circ\text{K} \]  \hspace{1cm} (3-157)

This value is within the range normally associated with diffusion in ordinary liquids. From Table 3-3, \( D_{eff} \) for isotonic saline is about 0.345 \( \pm \) 0.025\times10^{-5} \text{ cm}^2/\text{sec}. Consequently,
\[ D_0 = 1.11 \pm 0.16 \times 10^{-3} \text{ cm}^2/\text{sec} \] (3-158)

These estimates were used to calculate Cuprophane permeability to sodium chloride for the flow dialyzer experiments described in Chapter 5.

In order to use a single measurement to characterize membrane permeability, it is essential to know the reproducibility which is characteristic of the experiment and the effect of variations in experimental technique. In pursuit of this, the following experimental observations are reported.

1) A single Cuprophane membrane was repeatedly dialyzed five times with 0.005 M sodium chloride, yielding a mean true mass transfer resistance of 38.8 min/cm and a standard deviation of \( \pm 1.3 \) min/cm, or 3.3%.

2) Membranes stored in the presence of different antibacterial agents (200 ppm formaldehyde and 1000 ppm Zephrian chloride) showed no permeability differences.

3) Two cellophane sheets from different manufacturers were cut into eight pieces. Half were boiled and half were soaked in agitated distilled water at room temperature for various periods of time. The results of dialysis with 0.005 M sodium chloride at 37°C are as follows:

Cuprophane PT-150

Soaked (1.2 hrs to 120 hrs) \( R_m = 40.5 \pm 1.1 \) min/cm

Boiled (10 min to 2 hrs) \( R_m = 55.5 \pm 2.3 \) min/cm
Figure 3-30. Influence of temperature on effective diffusivity of sodium chloride in Cuprophone PT-150 (0.1 M)
DuPont PD-215

Soaked (5 hrs to 120 hrs) \( R_m = 83.1 \pm 2.8 \) min/cm
Boiled (15 min to 2 hrs) \( R_m = 120 \pm 22 \) min/cm

Except for the boiled DuPont membranes, which showed a rapid decrease followed by an increase in permeability with boiling time, no systematic trends with duration of treatment were noted. Boiling appears to significantly reduce permeability.

4) Permeability variations for membranes cut from a single sheet were less than 5%. Sheet to sheet variations were usually about 10%, although individual variations as high as 20% were observed. Thickness variations (wet and dry) were slightly less than those observed for permeability.

5) A single Cuprophane membrane was stretched 20% in the longitudinal (machine extrusion) direction and 15% in the transverse direction, leaving 5% permanent deformation in both directions. Permeability increased 20% over the unstretched condition. Hemispherical bulging (1/4 in. at the center of a 3 in. diameter) with no permanent deformation gave only a 3% increase in permeability. These observations are in agreement with the qualitative findings of Craig (89).

6) Initial experiments with the dialyzer were made with anodized aluminum endplates. A single membrane repeatedly dialyzed 41 times over a two week period showed a sharp increase in permeability, followed by a gradual leveling off to about double its initial value. The permeability increase was traced to the formation of aluminum
chloride in solution, and the aluminum was replaced by stainless steel. This observation is consistent with the phenomena discussed by Ott and Spurlin (309) who state that any metallic ion which is hydrated in aqueous solution and solvated by alcohols will solvate cellulose. Consequently, the use of stainless steel or its equivalent is recommended for permeability studies of cellophane with electrolytes.

b. Organic Solutes

Ninety-five runs at 37°C were made with the nine radioactively labelled organic solutes. An additional set of runs with five proteins were carried out with the collaboration of M. Laird (227a). Appendix J contains a complete tabulation of all results obtained with the radioactive solutes.

Two experimental problems arose in the use of the radioactive solutes. First, despite all necessary precautions (see Appendix B), the solutes gave varying degrees of stability. As an economy measure, all concentrated tracer solutions were initially repeatedly reused. Repeat measurements with the same membrane sometimes resulted in progressively increasing permeability. As a result, it was often necessary to make up new stock solutions after one or two uses. Repeat measurements with new solutions were generally highly reproducible.

The second problem was solute adsorption on the Lucite walls of the batch dialyzer, causing large errors in measured permeability. Sorption and desorption studies
were carried out in a single chamber, with a Lucite endplate replacing the membrane, by monitoring the change in concentration with time. Sorption was rapid and appeared to be mass transfer controlled. Rough calculations of the number of molecules adsorbed indicated approximately a monomolecular layer of solute on the chamber walls. Desorption, however, was an exceedingly slow process. A single desorption run with dextran required 10 days of rinsing with water and soap solutions to remove almost all of the adsorbed solute. The compounds found to adsorb were inulin, heparin, and dextran. Experiments with various concentrations of unlabelled solute showed that 10 gm/l was sufficiently high to swamp out adsorptive effects. Hence, all measurements with these solutes were made at this concentration.

Adsorption studies with proteins indicated no measurable adsorption. However, since concentration measurements were made near the limit of resolution of the technique, some degree of adsorption cannot be ruled out.

Table 3-4 contains a summary of the permeability measurements with radioactive solutes. All runs were made in the presence of isotonic saline to eliminate effects of fixed charges on the membrane. Results are tabulated in terms of the membrane resistance, min/cm, and its estimated standard deviation. Additional data and results, including estimated liquid phase resistances and effective diffusivities in the membrane, are tabulated in Appendix J.
TABLE 3-4

Summary of Permeability Measurements with Radioactive Solute

Results Expressed as \( R_m \pm \sigma R_m \), min/cm

<table>
<thead>
<tr>
<th>Solute</th>
<th>No Unlabelled Solute</th>
<th>Unlabelled Solute (conc. in gm/l)</th>
<th>Blood Soaked</th>
<th>Amino-Ethylated</th>
<th>Heparinized</th>
<th>Aviso Wet Gel</th>
<th>Cast(118) Wet Gel</th>
<th>Saponified Cellulose Acetate (DuPont CA148)</th>
<th>Biolon (BE-80) Neutral Polyelectrolyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>1.10</td>
<td>1.10</td>
<td>1.08</td>
<td>1.15</td>
<td>1.13</td>
<td>2.59</td>
<td>1.58</td>
<td>1.32</td>
<td>2.52</td>
</tr>
<tr>
<td>(As high as 18.6)</td>
<td></td>
<td>(10.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>30.8±1.3</td>
<td>30.8±1.3</td>
<td>55.3±1.4</td>
<td>43.2±1.5</td>
<td>30.6±1.4</td>
<td>51.0±1.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10.0)</td>
<td></td>
<td>(10.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric Acid</td>
<td>32.0±2.1</td>
<td>46.2±1.5</td>
<td>46.9±1.5</td>
<td>54.7±1.5</td>
<td>33.6±1.4</td>
<td>46.3±1.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1.0)</td>
<td></td>
<td>(0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucrose</td>
<td>98.7±2.2</td>
<td>96.2±2.1</td>
<td>113 ± 2</td>
<td>118 ± 3</td>
<td>56.8±2.6</td>
<td>111 ± 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>242 ± 10</td>
<td>260 ± 9</td>
<td>242 ± 16</td>
<td>318 ± 15</td>
<td>108.9±3.8</td>
<td>110 ± 4</td>
<td>261 ± 15</td>
<td>198 ± 6</td>
<td></td>
</tr>
<tr>
<td>(0.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG</td>
<td>7310 ± 301</td>
<td>9570 ± 240</td>
<td></td>
<td></td>
<td></td>
<td>1020 ± 30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10.0)</td>
<td></td>
<td>(10.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inulin</td>
<td>522 ± 11</td>
<td>194 ± 8</td>
<td></td>
<td></td>
<td></td>
<td>1090 ± 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>24,500 b±1300</td>
<td>2390±44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16000±600</td>
</tr>
<tr>
<td>Dextran</td>
<td>843±30</td>
<td>1030±34</td>
<td>1130±50</td>
<td>288±13</td>
<td>1100±45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Membrane Wet Thickness, mils.

a. Precipitation conditions: 25°C with 20% sulfuric acid and 5% sodium sulfate.
b. Final measurement. Initial measurement gave 300 ± 50 min/cm.
The first two columns compare the effect of unlabelled solute concentration on membrane resistance. Concentrations of tracer solute were very small, generally of order $10^{-6}$ molar (see Appendix D). Except for uric acid, the results are concentration independent. Additional measurements at various concentrations were made with uric acid, and the results are summarized in Table 3-5. The specific reason for the concentration dependence is not clear.

**TABLE 3-5**

<table>
<thead>
<tr>
<th>Concentration gm/l</th>
<th>$R_m \pm \sigma_{R_m}$ min/cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>32.8 $\pm$ 2.1</td>
</tr>
<tr>
<td>0.05</td>
<td>35.0 $\pm$ 1.4</td>
</tr>
<tr>
<td>0.30</td>
<td>37.8 $\pm$ 1.4</td>
</tr>
<tr>
<td>1.0</td>
<td>46.2 $\pm$ 1.5</td>
</tr>
</tbody>
</table>

Uric acid is a weak acid, and, as discussed in Appendix B, varies significantly in percentage dissociation over the range examined. Furthermore, at the higher concentrations tested, uric acid existed in solution in a supersaturated state, presumably complexed with lithium carbonate (see Appendix B). The concentration level of physiological interest, 0.05 gm/l, was used for all subsequent measurements. All other solutes were run with tracer alone, except for the aforementioned high molecular weight compounds.
The first measurement of heparin permeability gave a resistance of 3000 min/cm. During repeat measurements with cuprophane, resistance increased significantly and then levelled off around the value tabulated in Table 3-4. This phenomenon was believed caused by the polydispersity of commercial heparin (see Appendix B). The lowest resistance was probably associated with the lowest molecular weight fraction (~4000) and the highest resistance with the major fraction, averaging around 12,000 molecular weight.

The relative decrease in permeability due to soaking the membrane in blood (column three) appears to increase with increasing solute size. However, the effect is not large, amounting to about 20% with dextran.

Columns four and five compare the effect of aminoethylation and subsequent heparinization on cuprophane permeability. Except for creatinine and uric acid, aminoethylation has only a small effect on permeability. Heparinization, however, results in a larger (20 to 30% maximum) decrease in permeability, except for the anomalous results with creatinine. Since the ionic bonding of heparin to the substrate is believed to occur throughout the membrane (53), it is possible that the heparin molecules block off a portion of the interstices within the membrane normally available for solute diffusion.

The last four columns contain the results for Avisco extruded wet gel, Farrell's (118) cast wet gel, saponified cellulose acetate, and a neutral, expanded polyelectrolyte. The saponified cellulose acetate, which had an acetyl
content of about zero, gave results comparable with Cuprophane on an equivalent thickness basis. By far the most permeable membrane tested was the Avisco wet gel. This is particularly noticeable with the higher molecular weight solutes. Both the cast wet gel and neutral polyelectrolyte were more permeable than Cuprophane but not quite as permeable as Avisco wet gel.

Table 3-6 summarizes the studies of protein permeation with three different membranes, Cuprophane, saponified cellulose acetate, and Avisco wet gel. All measurements were made at room temperature, 27 ± 1°C, with protein solutions of 10 gm/l initially. Where no permeation was observed, the number tabulated represents the highest permeability possible for which the downstream concentration was below the limits of resolution of measurement. The measured resistance of 27°C is tabulated, as well as the effective diffusivity, corrected to 37°C, for comparison with the results with radioactive solutes. The correction was made with the Stokes-Einstein equation. While this may not be strictly valid for membrane permeation, the correction is not large. The estimated accuracy of the measured values is ± 50%.

The complete set of permeabilities could be obtained only with the more permeable wet gel. The albumin measurement with Cuprophane required 96 hours. Two measurements of much shorter duration produced no measurable concentration on the downstream side. This result is noteworthy in that it shows that albumin does permeate through
<table>
<thead>
<tr>
<th>Solute</th>
<th>Cuprophan PT-150</th>
<th>Saponified Cellulose</th>
<th>Avisco Wet Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( R_m, 27^\circ C )</td>
<td>( D_{eff}, 37^\circ C )</td>
<td>( R_m, 27^\circ C )</td>
</tr>
<tr>
<td></td>
<td>min/cm</td>
<td>cm²/sec</td>
<td>min/cm</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>2.5×10⁵</td>
<td>2.5×10⁻¹⁰</td>
<td>2.1×10⁶</td>
</tr>
<tr>
<td>Chymotripsinogen</td>
<td>&gt;6.5×10⁵</td>
<td>&gt;2×10⁶</td>
<td>&gt;2×10⁶</td>
</tr>
<tr>
<td>( \beta )-Lactoglobulin</td>
<td>&gt;4.3×10⁵</td>
<td>&gt;2.2×10⁶</td>
<td></td>
</tr>
<tr>
<td>Ovalbumin</td>
<td>&gt;6×10⁶</td>
<td>&gt;2.3×10⁶</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>5.9×10⁵</td>
<td>1.1×10⁻¹⁰</td>
<td>&gt;5.6×10⁶</td>
</tr>
<tr>
<td>Albumin with whole plasma</td>
<td>4.2×10⁶</td>
<td>1.5×10⁻¹¹</td>
<td>&gt;5.9×10⁶</td>
</tr>
</tbody>
</table>
Cuprophan, although at an extremely small rate. An additional run of shorter duration also showed albumin on the downstream side. Of course, the possibility exists of microscopic pin hole flaws in the membranes tested. If this is the case, such flaws would probably be representative of commercially available Cuprophane.

An interesting aspect of the results is the measurement of albumin permeability with whole human plasma on the upstream side. The presence of a much higher total protein concentration results in a significant decrease in albumin permeability, by a factor of seven for Cuprophane and a factor of two for wet gel. This is presumably caused by a layer of adsorbed, and probably denatured proteins at the membrane surface. Since the wet gel has a much higher water content, perhaps a smaller fraction of the total membrane surface is covered by protein with this membrane.

Table A-1 in Appendix A contains a summary of published permeability data from the literature. Although data for Cuprophane PT-150 is sparse, comparison may be made with other commercial cellophanes in terms of the membrane resistance per mil wet thickness or the effective diffusivity. For the lower molecular weight compounds where a comparison may be made, the results of this study show reasonable agreement with those of several other investigators, in particular Friedman (131), Ginsburg and Katchalsky (141), Lane and Riggle (229), and the more recent data of Babh and coworkers. Consequently, most commercial cellophanes appear to have similar permeation properties, at least for lower molecular weight compounds.
C. Influence of Solute Size on Permeation Properties

Early investigators (54) studying the permeation properties of cellulosic dialysis membranes found that for lower molecular weight solutes, membrane permeability was roughly proportional to the square root of molecular weight. More recent studies have attempted to correlate permeation properties with calculated molecular radii and/or equivalent Stokes-Einstein radii (229, 342a). These investigators have viewed cellulosic membranes as a network of continuous, tortuous, cylindrical pores and have employed a theoretical relation based upon continuum mechanics to quantitatively account for the influence of molecular and pore radii on the reduction of permeation rate as molecular size increases.

The application of continuum mechanics on a molecular scale is dubious. Furthermore, the concept of cylindrical pores in cellulose, indeed the idea of a fixed, time invariant structure, is questionable. Cellulosic membranes are believed to consist of a distribution of crystalline and amorphous phases; i.e. regions of high and low structural order. Solute permeation most likely occurs only, or predominantly, through the amorphous areas. Within the amorphous regions, the cellulose polymer chains are presumably in continuous motion, constrained only by crosslinks and by the immobility of the adjacent crystalline areas. Consequently, a theoretical model treating the permeable portion of the membrane as a concentrated polymer solution would be more reasonable.

No attempt is made in this study to derive such a
theoretical model. However, it is instructive to consider the effect of molecular size and shape upon the permeation properties of the membranes investigated, if only from a semi-quantitative standpoint.

The molecular size and shape of the solutes used in the permeation studies were estimated from a variety of methods. A complete discussion and tabulation of these estimates may be found in Appendix B. Table 3-7 contains a summary of the estimated characteristic molecular dimension for each solute for use in correlating permeation data. The smaller solutes were approximated as compact spheres. The larger solutes, which were either random-coiling macromolecules or asymmetric, compact molecules, were more difficult to characterize. Indeed, the conformation of heparin and dextran in solution is not at all certain. In this analysis, heparin was assumed to be a random-coiling macromolecule with a stiff backbone, giving a worm-like conformation. Dextran was assumed to form a helical structure, resulting in a cylindrical rod-like conformation.

Selection of a characteristic length for the larger molecules required a number of assumptions. For polyethylene glycol, the equivalent hydrodynamic radius (smaller than the r.m.s. radius of gyration) was selected. Because heparin has a stiffer backbone, the r.m.s. radius of gyration was used. Asymmetric, two dimensional molecules were assumed to permeate primarily with the longest axis parallel to the longitudinal axis of the membrane interstices. Consequently, the shortest half-axis was used. The same assumption
### Table 3-7

**Estimated Characteristic Molecular Dimensions of Solutes Used in Permeation Studies**

<table>
<thead>
<tr>
<th>Solute</th>
<th>Characteristic Radius, Å</th>
<th>Dimension Employed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Chloride</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>3.1</td>
<td>Radius of equivalent sphere</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Sucrose</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>PEG</td>
<td>16.3</td>
<td>Equivalent hydrodynamic radius of random coiling macromolecule</td>
</tr>
<tr>
<td>Inulin</td>
<td>6.7</td>
<td>Minor half-axis of prolate ellipsoid</td>
</tr>
<tr>
<td>Heparin</td>
<td>15.0</td>
<td>Root-mean-square radius of gyration of stiff, wormlike chain</td>
</tr>
<tr>
<td>Dextran</td>
<td>10.1</td>
<td>Radius of cylindrical rod</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>17.5</td>
<td>Half axis, second smallest dimension (from x-ray diffraction data)</td>
</tr>
<tr>
<td>Ovalbumin</td>
<td>17.6</td>
<td>Minor half-axis of prolate ellipsoid</td>
</tr>
<tr>
<td>Albumin</td>
<td>22.5</td>
<td>Half axis, second smallest dimension (from x-ray diffraction data)</td>
</tr>
</tbody>
</table>

*was made for three dimensional molecules (proteins), but the largest half-axis in the plane perpendicular to the longest axis (the second smallest dimension) was selected.*
Because of the large absolute uncertainty in the dimensions of some of the proteins for which x-ray diffraction data is not available, these compounds were ignored. It should be noted that final selection of dimensions was not done a priori. Rather, the various estimated dimensions were compared with the permeability data and the values which roughly ordered the data qualitatively were selected. These then resulted in the necessary assumptions cited above.

The results of the analysis are shown in Figure 3-31 for both Cuprophane and Avisco wet gel. The ordinate is the ratio of the effective diffusivity in the membrane, defined by equation (3-153), to the diffusivity in water. Since $D_{\text{eff}}$ contains a membrane-solution distribution coefficient, the ordinate is equivalent to the permeability of the membrane divided by the permeability of a film of water of the same thickness as the membrane.

Within the context of the assumptions described, several conclusions may be drawn from Figure 3-31. For both membranes, a sharp cutoff point does not appear to exist. Instead, the diffusivity ratio for the larger solutes drops off approximately exponentially with increasing characteristic size (although the data are too scattered to prove that the exponential dependence is linear in radius). The diffusivity ratio drops with increasing size for Cuprophane, even for the smallest solutes. Avisco wet gel, on the other hand, shows an almost constant diffusivity ratio (around 0.3) up to a characteristic radius of about 10 Å. This difference in behavior implies that, on the average, the distance
Figure 3-31: Diffusivity Reduction as a Function of Molecular Size
between polymer chains (within the amorphous regions) is significantly greater in the wet gel than in Cuprophane, and that the magnitude of the mechanisms which serve to reduce the diffusivity ratio is much smaller in wet gel for solutes up to 10 Å in radius. A particularly striking result of this is that for the larger solutes, the effective diffusivity in wet gel is greater than in Cuprophane by more than an order of magnitude.

d. Membrane Characterization

1. Water Content

The weight fraction water content of the membranes was experimentally measured directly. From this data, the volume fraction water was calculated from

\[
\frac{V_W \rho_W}{V_W \rho_W + V_C \rho_C} = W
\]  

(3-159)

where \( V \) = volume fraction, \( \rho \) = density, \( W \) = weight fraction water, and the subscripts \( w \) and \( c \) refer to water and cellulose, respectively. The density of water and cellulose in the membrane was assumed to be 1.0 and 1.52 gm/cc (268a), respectively. Since \( V_C + V_W = 1.0 \), \( V_W \) could be calculated directly.

The results of the water content determinations are summarized in Table 3-8. The reproducibility of these measurements was about \( \pm 1.5\% \). However, although careful efforts were made to completely surface dry the membranes with damp filter paper, the possibility of a surface film of moisture remaining existed. Thus, the results may contain a systematic error of unknown (but probably small) magnitude. The three commercial cellophanes were quite similar,
Table 3-8

<table>
<thead>
<tr>
<th>Membrane</th>
<th>Per Cent Water by Weight</th>
<th>Per Cent Water by Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avisco 215 P-1</td>
<td>56.5</td>
<td>66.4</td>
</tr>
<tr>
<td>DuPont PD-215</td>
<td>57.3</td>
<td>67.1</td>
</tr>
<tr>
<td>Cuprophane PT-150</td>
<td>54.5</td>
<td>64.5</td>
</tr>
<tr>
<td>Saponified Cellulose Acetate (DuPont CA 148)</td>
<td>55.7</td>
<td>65.6</td>
</tr>
<tr>
<td>Cast Wet Gel (DuPont)</td>
<td>72.8</td>
<td>80.2</td>
</tr>
<tr>
<td>Cast Wet Gel (Farrell) (118)</td>
<td>67.5</td>
<td>75.9</td>
</tr>
<tr>
<td>Avisco Wet Gel</td>
<td>74.8</td>
<td>81.8</td>
</tr>
</tbody>
</table>

a. Calculated assuming cellulose density = 1.52 gm/cc

averaging about 56% water by weight and about 66% by volume.
All the wet gel membranes had significantly higher water
contents, with Avisco wet gel the highest at about 82% by
volume.

2. Equilibrium Distribution Coefficients

As described in Section 3.B.8, equilibrium distribution
coefficients were measured by two successive equilibrations.
For the first equilibration, a mass balance yields

\[ V_s C_{s_0} = V_s C_{s_1} + V_m C_{m_1} \]  \hspace{1cm} (3-160)

where the subscripts s and m refer to external solution and
membrane phases, respectively, and 0 and 1 denote the begin-
ing and end of the experiment. Thus

\[ C_{m_1} = \frac{V_s}{V_m} (C_{s_0} - C_{s_1}) \]  \hspace{1cm} (3-161)
and the membrane-solution distribution coefficient is given by

\[ K = \frac{C_{m1}}{C_{s1}} \left\| \begin{array}{c} \text{eq} \\ V_m \end{array} \right\| = \frac{V_s}{V_m} \left( \frac{C_{s0} - C_{s1}}{C_{s1}} \right) \]  

(3-162)

Similarly, from the second equilibration experiment,

\[ V_m C_{m1} = V_s C_{s2} + V_m C_{m2} \]  

(3-163)

\[ C_{m2} = C_{m1} - \frac{V_s}{V_m} C_{s2} \]  

(3-164)

and thus

\[ K = \frac{C_{m2}}{C_{s2}} \left\| \begin{array}{c} \text{eq} \\ \frac{C_{m1}}{C_{s2}} - \frac{V_s}{V_m} \end{array} \right\| \]  

(3-165)

If the distribution coefficient is independent of concentration, then \( K \) calculated from both experiments should be equal. However, since the solution to membrane volume ratio was large, small errors in the measured concentration difference, \( C_{s0} - C_{s1} \), were magnified, causing large errors and poor reproducibility in \( C_{m1} \) and \( K \). To circumvent this problem, \( K \) was assumed independent of concentration, in which case equation (3-164) may be written as

\[ K C_{s1} - K C_{s2} = \frac{V_s}{V_m} C_{s2} \]  

(3-166)

which yields

\[ K = \frac{V_s}{V_m} \left[ \frac{C_{s2}}{C_{s1} - C_{s2}} \right] \]  

(3-167)

Equation (3-167) was used for the results reported in this study. The distribution coefficient may also be expressed in terms of the solution within the membrane:
\[ K' = \frac{K}{\text{vol.frac.water}} \]  
(3-168)

The use of eqn. (3-168) assumes that all water in the membrane is available to the solute, i.e., the amount of water bound to cellulose is a negligible fraction of the total water content.

### Table 3-9

**Measured Equilibrium Distribution Coefficients**

<table>
<thead>
<tr>
<th>Solute</th>
<th>( K ) moles/cc total membrane</th>
<th>( K' ) moles/cc water in membrane(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>moles/cc external soln.</td>
<td>moles/cc external soln.</td>
</tr>
<tr>
<td>Urea</td>
<td>0.67</td>
<td>1.04</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.61</td>
<td>0.94</td>
</tr>
<tr>
<td>Uric Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>infinite</td>
<td>1.24</td>
<td>1.92</td>
</tr>
<tr>
<td>dilution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.76 gm/l unlabeled</td>
<td>0.80</td>
<td>1.24</td>
</tr>
<tr>
<td>Sucrose</td>
<td>0.63</td>
<td>0.98</td>
</tr>
<tr>
<td>Vitamin B(_{12})</td>
<td>0.97</td>
<td>1.50</td>
</tr>
<tr>
<td>PEG</td>
<td>0.15</td>
<td>0.24</td>
</tr>
<tr>
<td>Inulin</td>
<td>0.37</td>
<td>0.57</td>
</tr>
<tr>
<td>Heparin</td>
<td>0.14</td>
<td>0.22</td>
</tr>
<tr>
<td>Dextran</td>
<td>0.34</td>
<td>0.53</td>
</tr>
</tbody>
</table>

\(^a\) Volume fraction water = 0.645

Table 3-9 summarizes the measured equilibrium distribution coefficients for cuprophan at 37°C. The tabulated values are an average of three measurements, with an average standard deviation of about 10%. The values of \( K' \) for urea, creatinine, and sucrose are close to unity, indicating that cellulose is relatively inert towards these solutes. Uric acid and vitamin B\(_{12}\)
have $K'$ values significantly greater than unity, indicating positive interactions with the membrane. For the former solute, the increase in distribution coefficient with a decrease in concentration clearly parallels the concentration dependence of the measured membrane permeability.

The four largest solutes have $K'$ values significantly less than unity, with the random-coiling macromolecules, PEG and heparin, lower by a factor of about two than the compact, asymmetric molecules, inulin and dextran. While this behavior may be related to negative interactions with the membrane, a more likely cause stems from the effect of the membrane on the conformational entropy of the solutes (81a). For example, as a random-coiling molecule moves from the external solution to the interstices within the membrane, the available volume for the molecule is reduced by the presence of the cellulose chains, leading to a decrease in its conformational entropy and an increase in free energy. Since the chemical potential of the solute in the external solution and in the membrane must be equal at the membrane-solution interface, the increase in free energy requires that the concentration within the interstices of the membrane be lower than that in the free solution. Analogous effects occur for molecules of other shapes (414).

In order to quantitatively evaluate the reduction in diffusivity as a function of molecular size, Figure 3-31 should be replotted after dividing the diffusivity ratio by $K$. 
Since $K$ varies from solute to solute, the relative position of the data points would change somewhat. However, since the ordinate covers four decades, the changes would not substantially influence the conclusions drawn.

3. Strength Properties

Table 3-10 summarizes the measured membrane strength

<table>
<thead>
<tr>
<th>Membrane</th>
<th>Young's Modulus, $\text{psi} \times 10^{-3}$</th>
<th>Ultimate Tensile strength, $\text{psi} \times 10^{-3}$</th>
<th>Ultimate Break Elongation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avisco 215 P-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.D.</td>
<td>15.1±2.2(15%)</td>
<td>2.98±.31(10%)</td>
<td>34.3±4.3(13%)</td>
</tr>
<tr>
<td>T.D.</td>
<td>4.96±.42(9%)</td>
<td>1.00±.28(28%)</td>
<td>52.8±11.4(22%)</td>
</tr>
<tr>
<td>DuPont PD-215</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.D.</td>
<td>12.0±.82(7%)</td>
<td>2.52±.39(15%)</td>
<td>29.5±4.2(14%)</td>
</tr>
<tr>
<td>Cuprophane PD-215</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.D.</td>
<td>18.2±1.9(11%)</td>
<td>3.28±.47(14%)</td>
<td>17.3±3.2(18%)</td>
</tr>
<tr>
<td>T.D.</td>
<td>3.8±.6(15%)</td>
<td>.73±.23(31%)</td>
<td>48.2±14.3(30%)</td>
</tr>
<tr>
<td>Saponified Cellulose Acetate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.D.</td>
<td>2.0</td>
<td>0.485</td>
<td>28.2</td>
</tr>
<tr>
<td>T.D.</td>
<td>1.1</td>
<td>0.485</td>
<td>26.3</td>
</tr>
<tr>
<td>Cast Wet Gel (Du Pont)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.55</td>
<td>1.08</td>
<td>66</td>
</tr>
<tr>
<td>Cast Wet Gel (Farrell)(118)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.72</td>
<td>1.27</td>
<td>62</td>
</tr>
<tr>
<td>Avisco Wet Gel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.D.</td>
<td>3.29</td>
<td>1.18</td>
<td>22.7</td>
</tr>
<tr>
<td>T.D.</td>
<td>1.40</td>
<td>0.21</td>
<td>32.4</td>
</tr>
</tbody>
</table>

M.D. = Machine (Extrusion) Direction
T.D. = Transverse Direction (Perpendicular to M.D.)
properties. The three commercial cellophanes are relatively similar. For comparison between membranes for use in hemodialysis, properties of extruded films in the weaker, transverse direction should be employed. On this basis, the two cast wet gel membranes are comparable to Cuprophane, while the Avisco wet gel is significantly weaker. In addition, the Avisco wet gel exhibits a much lower tear strength than the other membranes handled.

For comparison, data supplied by the manufacturer for "ultra-thin" wet gel are tabulated below:

- Water content 80.9%
- Thickness 2.4-2.7 mils
- Ultimate Tensile Strength
  - M.D. 1015 psi
  - T.D. 735 psi
- Ultimate Break Elongation
  - M.D. 37%
  - T.D. 86%

Ultimate properties in the transverse direction are significantly higher than those measured in this study and compare more favorably with Cuprophane.

- Electron Microscopy

A preliminary investigation of membrane structure was made with the electron microscope. A single set of electron photomicrographs were obtained with Avisco wet gel and with Cuprophane PT-150. In view of the great potential for artifacts with any type of sample preparation, the preliminary results must be viewed as tentative until they are replicated with similar membranes. Furthermore, during sample preparation water-filled membranes were frozen by immersion in liquid nitrogen. The possibility of ice crystallization and its effect on the
structure subsequently observed is unknown. Exchange of the water for glycerol would help to resolve this question.

Figures 3-32 and 3-33 are electronphotomicrographs of Avisco wet gel. The membrane slices were about 500 Å thick and represent a view of the membrane from the edge. The membranes were not shadowed; thus electron absorption by dense solid material results in a darkened image while voids and less dense regions produce a lighter image. The limit of resolution is of the order of 25 Å.

Figure 3-32 shows the surface of the membrane. There appears to be a dense crust, cracked in spots, of roughly 0.25 to 0.5μ thickness. Below the crust lies a region of much lower density, approximately 1.5μ thick. This is followed by material which is more representative of the interior of the membrane, as shown in Figure 3-33. The interior shows a continuous gradation in properties on a small scale with variations from small dark patches to lighter spots. The brightest of these, which vary in size from the limit of resolution up to about 200 Å, may represent interstices or voids which go all the way through the 500 Å film.

Figure 3-34 shows the surface and interior of a Cuprophane membrane. The bright areas at the surface are believed to be void spaces between the membrane and the embedding material. As with Avisco wet gel, the surface region appears to have a structure different from the interior. In this case, it is more homogeneous and is about 2μ thick. The dominant feature of the interior appears to be a network of macropores ranging in diameter from about 200 Å to 5000 Å. Figure 3-35 is a magnification of the lower left-hand
portion of Figure 3-34. Careful observation reveals a structure resembling Swiss cheese or perhaps a disordered beehive.

A notable feature of Cuprophane is the total absence of any microporous structures analogous to the wet gel interior shown in Figure 3-33. It is possible that such a structure exists, but on a molecular scale too small to be seen with the magnification employed. This would be consistent with the diffusivity reduction behavior shown in Figure 3-31. On the basis of these preliminary findings, one might tentatively propose that drying wet gel regenerated cellulose results in almost complete collapse and densification of the membrane interior structure. Subsequent rewetting results in the creation of a macroporous network within a fairly uniform, dense cellulose matrix in which, presumably, there are both crystalline and amorphous regions.

Another point which needs further investigation is the influence of the observed "skin" on the permeation properties. Although the thickness of the skin is small compared to the total membrane thickness, it is possible that a significant portion of the total membrane resistance resides in the surface layer.

e. Implications for Hemodialysis

The results of this study show that drying a regenerated cellulose film causes a significant irreversible change in membrane structure which results in a large decrease in solute effective diffusivity through the membrane. The relative decrease becomes more pronounced as solute size increases. For solutes with a characteristic radius up to 10 Å, Avisco wet gel behaves as an ideal hemodialysis membrane, according to the "brute force"
Figure 3-35. Electronphotomicrograph of Gunophane interior.
Figure 3-34. Electronphotomicrograph of Cuprophane surface
approach described earlier, since the membrane permeability is directly proportional to solute diffusivity. If solutes larger than urea, creatinine, and uric acid should be removed by hemodialysis, then the use of a wet gel membrane would significantly increase the mass transfer rate of these compounds. This is considered quantitatively in Chapter 6.

On the negative side, the currently available Avisco wet gel is thicker than desirable and may be too weak for use in a hemodialyzer. Nevertheless, the results do show the potential of highly porous, hydrophilic wet gel membranes for hemodialysis.
CHAPTER 4

Diffusion of Organic Solutes in Stagnant Plasma and Blood

This chapter deals with the problem of diffusion of water soluble organic solutes in stagnant human plasma and whole blood, particularly those compounds of interest in hemodialysis. The purposes of this study were to: 1) Obtain experimental diffusion coefficients for various solutes in these solutions, and 2) Develop theoretical models to describe the phenomena.

The first section covers the relevant physical and chemical properties of plasma and blood. Next, two models are proposed for diffusion in these media. The third section describes the experimental methods used in this study, and the last section contains the results and discussion.

Because of the complexity of biological fluids, two necessary assumptions are implicit throughout this study: 1) The diffusion coefficient is independent of concentration, and 2) Binary diffusion coefficients can be used to describe diffusion in multicomponent systems.

A. The Nature of Blood

1. Physical and Chemical Properties

The primary function of blood is to transport oxygen and nourishment to the body tissues and to remove waste products
from tissue metabolism. Blood is a complex suspension composed of an amber-colored liquid medium, plasma, and several types of formed elements, the blood cells. The formed elements include the red cells, or erythrocytes, the white cells, or leukocytes, and the platelets, or thrombocytes. Some of the relevant physical properties of whole blood, plasma, and the formed elements are tabulated in Table 4-1.

The erythrocyte is by far the major particulate constituent, occupying about 45% of the total blood volume. The others represent only about 1-2% of the total volume. The white cells are important specifically for their function in combatting infection. The platelets play a major role in the mechanism of blood coagulation and clotting. However, insofar as diffusion in blood is concerned, they are of negligible importance and shall not be discussed further. In the discussion to follow, background material will be restricted to those areas germane to the present investigation. Additional information may be obtained from a number of reviews and monographs (37, 208, 265, 326, 333, 437) from which the following material was largely obtained.

a. Plasma

The plasma is a complex buffered salt solution containing electrolytes, organics, proteins, and other macromolecules numbering over a hundred significant compounds. A summary of the chemical composition of normal human plasma is given in Table 4-2. A more complete compilation may be found in the tabulation of Altman and Dittmer (6). When blood is allowed
TABLE 4-1

Physical Properties of Human Blood (6)
(Normal Adult-Mean Values)

<table>
<thead>
<tr>
<th>Whole Blood</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35-7.40</td>
</tr>
<tr>
<td>Relative Viscosity (37°C)</td>
<td>-3.0</td>
</tr>
<tr>
<td>Specific Gravity (25/4°C)</td>
<td>1.0564</td>
</tr>
<tr>
<td>Surface Tension</td>
<td>-75 dynes/cm²</td>
</tr>
<tr>
<td>Venous Hematocrit-Male</td>
<td>47</td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
</tr>
<tr>
<td>Whole Blood Volume</td>
<td>~8 ml/Kg body wt</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plasma or Serum</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Colloid Osmotic Pressure</td>
<td>-330 mm H₂O</td>
</tr>
<tr>
<td>pH</td>
<td>7.3-7.5</td>
</tr>
<tr>
<td>Relative Viscosity (37°C)</td>
<td>-1.32</td>
</tr>
<tr>
<td>Specific Gravity (25/4°C)</td>
<td>1.0239</td>
</tr>
<tr>
<td>Water Content</td>
<td>-93% by volume</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Formed Elements</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.396</td>
</tr>
<tr>
<td>Specific Gravity (25/4°C)</td>
<td>1.098</td>
</tr>
<tr>
<td>Count - Male</td>
<td>5.4×10⁹/ml whole blood</td>
</tr>
<tr>
<td>Female</td>
<td>4.8×10⁹/ml whole blood</td>
</tr>
<tr>
<td>Mean Corpuscular Volume</td>
<td>87μ³</td>
</tr>
<tr>
<td>Mass</td>
<td>95μµg</td>
</tr>
<tr>
<td>Diameter-Dry</td>
<td>7.5μ</td>
</tr>
<tr>
<td>Wet</td>
<td>8.4μ</td>
</tr>
<tr>
<td>Maximum Thickness-Dry</td>
<td>2.0μ</td>
</tr>
<tr>
<td>Wet</td>
<td>2.4μ</td>
</tr>
<tr>
<td>Minimum Thickness-Wet</td>
<td>1.0μ</td>
</tr>
<tr>
<td>Surface Area-Dry</td>
<td>135μ²</td>
</tr>
<tr>
<td>Wet</td>
<td>163μ²</td>
</tr>
<tr>
<td>Wet Specific Surface Area</td>
<td>1.87×10⁴cm²/cm³</td>
</tr>
<tr>
<td>Life Span</td>
<td>120 days</td>
</tr>
<tr>
<td>Production Rate</td>
<td>4.5×10⁹/ml whole blood/day</td>
</tr>
<tr>
<td>Hemoglobin Concentration</td>
<td>0.335 g/ml erythrocyte</td>
</tr>
<tr>
<td>Equivalent Shapes:</td>
<td></td>
</tr>
<tr>
<td>Radius of Sphere -</td>
<td></td>
</tr>
<tr>
<td>Constant Volume</td>
<td>2.75μ</td>
</tr>
<tr>
<td>Constant Area</td>
<td>3.60μ</td>
</tr>
<tr>
<td>Constant Specific Area</td>
<td>1.60μ</td>
</tr>
<tr>
<td>Height of Disc (8.4μ Diameter)</td>
<td></td>
</tr>
<tr>
<td>Constant volume</td>
<td>1.57μ</td>
</tr>
<tr>
<td>Constant Area</td>
<td>1.98μ</td>
</tr>
<tr>
<td>Constant Specific Area</td>
<td>1.44μ</td>
</tr>
</tbody>
</table>

| Leukocytes                                       |          |
| Count                                           | ~7.4×10⁶/ml whole blood |
| Diameter                                        | 7-20μ    |

| Platelets                                        |          |
| Count                                           | ~2.8×10⁸/ml whole blood |
| Diameter                                        | ~2-5μ    |
TABLE 4-2

Chemical Composition of Normal Human Plasma

<table>
<thead>
<tr>
<th>Osmotically Active Substances (155)</th>
<th>Concentration (m equiv/(\mu\text{H}_2\text{O}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solute</td>
<td></td>
</tr>
<tr>
<td>Na(^+)</td>
<td>144</td>
</tr>
<tr>
<td>K(^+)</td>
<td>5</td>
</tr>
<tr>
<td>Ca(^{++})</td>
<td>2.5</td>
</tr>
<tr>
<td>Mg(^{++})</td>
<td>1.5</td>
</tr>
<tr>
<td>Cl(^-)</td>
<td>107</td>
</tr>
<tr>
<td>HCO(_3)(^-)</td>
<td>27</td>
</tr>
<tr>
<td>HPO(_4)(^{--}) and H(_2)PO(_4)(^-)</td>
<td>2</td>
</tr>
<tr>
<td>SO(_4)(^{--})</td>
<td>0.5</td>
</tr>
<tr>
<td>Amino Acids</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.2</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.2</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.6</td>
</tr>
<tr>
<td>Protein</td>
<td>1.2</td>
</tr>
<tr>
<td>Urea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>303.7</td>
</tr>
</tbody>
</table>

Actual Osmolar Activity = 282.2 mosmols/\(\mu\)  
Total Osmotic Pressure at 30\(^\circ\)C = 5455 mm Hg

Overall Breakdown of Plasma Constituents (6)

<table>
<thead>
<tr>
<th>Type of Compound</th>
<th>Concentration (mg/100 ml plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteins</td>
<td>8218</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>745</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>577</td>
</tr>
<tr>
<td>Organic Acids</td>
<td>96</td>
</tr>
<tr>
<td>Nc.protein Nitrogenous Compounds</td>
<td>79.5</td>
</tr>
<tr>
<td>Free Lipids</td>
<td>-30</td>
</tr>
<tr>
<td>Vitamins</td>
<td>-28</td>
</tr>
<tr>
<td>Hormones</td>
<td>0.11</td>
</tr>
<tr>
<td>Enzymes</td>
<td>?(trace)</td>
</tr>
</tbody>
</table>

Total Dissolved Compounds 9770
to clot, one of the plasma proteins, fibrinogen, is removed in the clotting process. The remaining fluid, serum, is essentially identical in physical properties to plasma.

The osmotic pressure of plasma is often expressed in osmols, where one osmol equals one gram equivalent of a non-diffusible osmotically active solute. For many physicochemical purposes, plasma or serum may be treated simply as a 0.15 M univalent electrolyte solution buffered to a pH of approximately 7.4. "Isotonic saline" refers to a 0.15 M (0.9% by weight) sodium chloride solution which is in osmotic equilibrium with plasma and the erythrocytes.

The plasma proteins constitute about 85% by weight of the dissolved solutes in plasma. These may be broken down into three categories: albumin, fibrinogen, and the globulins. The former two proteins are obtainable as pure substances. The latter, however, are composed of a number of protein fractions, including simple proteins and those conjugated with lipids (lipoproteins) and mucopolysaccharides (mucoproteins and glycoproteins). The globulins are difficult to characterize; this is generally done by reactions with certain solvents, by electrophoretic and sedimentation data, and by specific functional behavior. All plasma proteins have a net negative charge at physiological pH.

A complete tabulation of plasma protein composition is given in Appendix E, Table E-1, in connection with a calculation of the influence of the proteins in diffusion through plasma. The determination of the conformation of plasma proteins has
received considerable attention. With the exception of the lipoproteins which are believed to be spherical (120), they have been modeled mathematically as prolate ellipsoids of revolution. Further discussion in this area may be found in Appendix B.

b. The Erythrocyte

The red cell is an easily deformable biconcave disc, as shown in Fig. 4-1. Its primary function is to transfer oxygen and carbon dioxide between the tissues and the lungs and to act as the main buffer of extracellular body fluids. The protein hemoglobin, which chemically combines with oxygen, comprises 90% of the solid matter of the human red cell and about 97% of its total protein. The cell dimensions tabulated in Table 4-1 are mean values. The normal variation in size is equivalent to a standard deviation of about 5% for each dimension. Small concentrations of a number of agents can cause spherling of the cells, and changes in the shape of the erythrocytes has been observed in various diseased states.
In normal blood flow, the cells are suspended individually, but at very low shear rates or at rest, they adhere to one another and aggregate to form irregularly shaped columns or rouleaux. The cells in rouleaux are probably held together by plasma protein molecules which form bridges between two surfaces, the length of the rouleaux being greater the higher the concentration of the proteins, fibrinogen and globulin (33).

The red cells themselves are not mobile, but rhythmical movements of the surface, causing rapid fluctuations in the thickness of the cell, have been observed under the phase-contrast microscope. It has been speculated (437) that such flickering is caused by brownian movement of solutes outside the cells which cause a greater bombardment of the outer surface of the cell than the more restricted movements of the hemoglobin inside the cell.

The red cell is generally thought to be enclosed by a membrane, with the interior composed of a concentrated hemoglobin solution. From the weight percent and density of hemoglobin, the interior solution is about 25% protein, by volume (45). X-ray analysis indicates some degree of structuring and order in the vicinity of any given molecule of hemoglobin. The molecules of hemoglobin are consequently thought to possess freedom to rotate but not to move about, and the physical state of the cell interior is believed to be that of a viscous fluid almost on the point of becoming paracrystalline (432).

Considerable work has been done to elucidate the red cell membrane structure and dimensions, and the available data has
been summarized by Parpart and Ballentine (313) and by Whittam (437). Whittam has suggested a schematic idealized model of the membrane, based upon chemical and physical data, as shown in Fig. 4-2. While obviously an oversimplification of reality, it is conceptually useful since it is consistent with the known physical properties of the membrane. From the point of view of transport in the red cell, the most salient feature is the simultaneous presence of bimolecular lipid layers and water filled channels. Assuming the latter to be straight cylindrical pores, estimates of pore radii in the range of 3.5 to 4.2 Å have been made from studies of osmotic and diffusive transport of water across the membrane (311,143). The physical models employed by these investigators were based on continuum mechanics and are clearly invalid in this size range. Nevertheless, the estimates probably represent a reasonable order of magnitude approximation to the effective pore size, assuming that water filled pores do exist.

Various estimates of the thickness of dry red cell membranes, tabulated by Whittam, range from 40 to 300 Å, with the majority falling between 50 and 150 Å. However, one study of birefringence using a polarizing microscope resulted in an estimate of an outer layer of 40 Å with strong birefringence and an inner layer of about 5,000 Å with weak birefringence. This inner layer would encompass all the cell interior, suggesting that almost the whole cell consists of membrane and implying a high degree of structure in the interior of the cell. This view is reinforced by the recent results obtained with ion etching of the red cell surface.
Figure 4-2. Conceptual Model of Erythrocyte Membrane. From Whittam (437)
and observation with the scanning electron microscope (48). This technique peels away the outer surface and photomicrographs reveal an ordered structure in the interior with filaments running perpendicular to the red cell surface.

The erythrocyte membrane is semipermeable and consequently the red cell behaves as an osmometer. Water flows rapidly across the cell membrane and it is this predominantly inward flow which causes hemolysis. (Hemolysis can also be caused by various chemical compounds and possibly by high shear rates). When placed in hypotonic solution, the red cell swells and changes to a spherical shape while keeping its surface area approximately constant (188). Rupture occurs at the point where the cell volume is about 160% of its original value (333), and this volume corresponds closely to that of a sphere having the same surface area as that of the original biconcave cell. Presumably, cell rupture occurs when the cell surface begins to be stretched. After rupture, hemoglobin leaves the cell and the red cell ghost returns to its original discoid shape.

The largest constituent of red cells is water. Vestergaard-Bogind and Hesselbo (424) found that the water phase accounted for 65% of the total volume. Savitz, et al. (357), using isotope dilution, reported a value of 0.717 ml water per ml cells. This agrees well with the value of 0.722 gm water per ml cells found by Ha:id, et al. (156). The amount of red cell swelling when placed in anisotonic solutions does not agree with the values calculated from the total water content of the cell. Two hypotheses have been advanced to explain this behavior. The first considers that
a portion of the intracellular water is protein bound and not available as solvent for all osmotically active solutes. The other explanations include rigidity of the cell wall and an anomalous osmotic coefficient of hemoglobin in such concentrated solutions as occur in the red cell (333). Savitz, et al. (357) examined both hypotheses and concluded their data was best explained if 20% of the total cell water, or about 14 gms/100 ml cells, was not available as solvent water. They compared this with a literature estimate of 0.34 gm water of hydration/gm anhydrous hemoglobin. On the basis of 35 gm hemoglobin/100 ml cells, which they measured, about 12 gm of water would be present as water of hydration. From this they concluded that the anomalous osmotic behavior of the red cell may be attributed to the non-solvent character of the water of hydration of intracellular hemoglobin.

The hematocrit is related to the volume percentage of red cells in the blood. It is usually measured by centrifugation of a tube filled with whole blood. The percentage height of the packed red cells at the tube bottom, compared to the total height, is taken to be the hematocrit. However, the packed cells include a portion of trapped plasma in the interstices. Savitz, et al. (357) found this to be less than 0.8%. Vestergaard-Bogind and Hesselbo (424) reported a trapped volume of 5.2%, while Guyton (155) estimates that about 3 to 8 percent plasma remains entrapped. He suggests an average value of 0.96 for the ratio of the true cell volume percent to the measured hematocrit.
Since the red cell has a higher density than the surrounding fluid, it will settle in a gravitational field. However, because of erythrocyte aggregation in stagnant blood, the erythrocyte sedimentation rate is much greater than predicted by Stokes' law from the size of the individual red cell. The sedimentation rate may vary from person to person and in pathological states. This has been correlated with variations in concentration of the plasma proteins (380, 412). Hardwich and Squire (160) found that the influence of the plasma proteins was to increase the in vitro sedimentation rate, the order of influence being fibrinogen > α₂-globulin > γ-globulin > albumin with the relative magnitude of influence being the ratio 10:5:2:1. Ditzel (102) observed a similar order of influence for in vivo aggregation except that γ-globulin had no effect and albumin had a negative effect. It is clear that the sedimentation of red cells represents a formidable problem in the experimental measurement of diffusion in stagnant whole blood. This problem might be partially alleviated by removal of those plasma proteins responsible for increasing the sedimentation rate.

As hematocrit increases, sedimentation rate decreases, and at a sufficiently high hematocrit, the blood will not settle at all. The literature concerning the influence of various factors on the sedimentation rate is immense. Of particular interest here are some observations of Meyer (254) who performed sedimentation experiments in a series of tubes of different diameter, ranging from 0.28 to 0.9 cm, using blood from the same source in each. While the sedimentation rate was consistent in repeated runs with the larger
tubes, large variations were observed with the smallest tube. The sedimentation rates were not reproducible and varied from normal rates to virtually a zero settling rate.

From many observations of this phenomena, Meyer proposed that the non-reproducibility was caused by a bridging effect. By this hypothesis, the red cells are assumed to continue aggregating to some extent while settling such that the network of rouleaux and aggregates builds up and eventually at certain points reaches the tube wall. The effect of this network will be to bridge the tube and prevent any further settling until sufficient aggregation occurs above the bridge for the aggregate weight to break up the network and allow settling to commence again.

If such bridging occurs evenly around the tube, the force required to break the network-wall interaction will be proportional to tube diameter, while the force available to break the network will be proportional to the mass of the aggregates and consequently to the square of the diameter. Thus, as tube diameter decreases, the ratio of aggregate mass to network strength decreases, and at sufficiently small diameter, such random network formation may be capable of significantly slowing the sedimentation rate or eliminating sedimentation completely.

In order to model the diffusion of organic solutes in whole blood, it is necessary to have a quantitative understanding of those factors which have an important influence, such as protein binding of solutes, plasma-erythrocyte solute distribution, and diffusive transport through the erythrocyte. These topics are discussed in the remainder of this section.
2. Protein Binding of Solutes

The plasma proteins constitute a specially designed and physiologically important carrier transport mechanism for the regulated distribution of naturally occurring and medicinal substances throughout the body (101, 142). This often has the effect of increasing the apparent solubility of some compounds in plasma. Such binding of solutes to proteins occurs usually through the action of Van der Waals forces and/or hydrogen bonding between the hydroxyl groups of the protein and the terminal O, N, or S atoms of the other molecule (101). Of all the plasma proteins, albumin shows the greatest diversity in its capacity for interaction, and all those compounds which interact with any of the proteins and have been adequately studied prove to combine also with albumin (142).

Varied associations of this type occur with a wide diversity of substances and the behavior of solutes in the blood may be profoundly influenced by these interactions. With reference to diffusion through plasma, solutes may be 1) irreversibly bound, in which case they are permanently removed from solution and non-diffusible, except for diffusion of the protein-solute complex, or 2) reversibly bound, in which case the complex may act as a source or sink for solute, although the bound solute is also not freely diffusible.

Perhaps the classical and most studied protein-solute interaction is that between hemoglobin and oxygen. Further discussion of this phenomena is beyond the scope of this study and the reader is referred to the recent comprehensive review by Roughton (350).

Goldstein (142) has reviewed the interaction between plasma proteins and a wide variety of solutes, poisons, dyes, and drugs.
He divides the methods of demonstrating interaction into three categories, based upon the behavior of solute and protein.

1. The free solute concentration and its thermodynamic activity are reduced. Methods based upon this reduction include biological action, dialysis, ultrafiltration, conductivity, measurement of colligative properties, and differential adsorption.

2. The solute may show changed properties. Methods include solubility, diffusion, compound stabilization, electrophoresis, and spectrometry.

3. The protein properties may be altered. Methods include precipitation, viscosity, electrophoretic mobility, sedimentation rate, and protein stabilization.

Wolsten also points out that many solute-protein interactions can be shown to follow an adsorption isotherm, in particular the Langmuir isotherm, for which the empirically derived constants can be related to the dissociation constant of the complex and the binding capacity of the protein. The Langmuir isotherm will accurately describe the situation only if the interaction is reversible and the data are obtained at equilibrium. Alvsaker (2) has pointed out that many common methods, such as dialysis, ultrafiltration, and paper electrophoresis, are inadequate for investigating reversible interactions, because such interactions will decrease as the concentration of the free solute decreases. In order to carry out quantitative studies on reversible interactions, it is necessary to keep the solute concentration constant during
the experiment. Consequently, many investigators who have reported no solute-protein binding for various systems may have overlooked reversible binding because of the limitations of their experimental technique.

a. Urea

The literature is in unanimous disagreement concerning interactions of urea with plasma proteins. Goldstein (142) classifies urea among substances which are generally regarded as unbound in plasma. He cites the electrophoresis studies of Bennhold which were carried out at concentrations over 100 mgm percent. Bickel and Bovet (35) studied the relationships between structure and albumin-binding of amines using crossing-paper electrophoresis at unspecified concentrations. They concluded that only tertiary amines with at least one substantial radical interact, whereas primary and secondary amines and quaternary ammonium salts do not. With mixed amines interaction occurs only if the tertiary nitrogen "dominates" the other amino groups. Urea, a primary amine, did not interact.

Contrary evidence was obtained by Rosenthal (252). The addition of small quantities of sodium oleate to whole blood increased the non-protein nitrogen in blood ultrafiltrates from 20 to 55 percent. He postulated that this quantity ordinarily remained attached to proteins. Malinow and Korzon (263) ultrafiltered blood through Visking cellophane tubing and found that the urea nitrogen concentration was two-thirds that of the plasma. Similar results were reported by Loiseleur and Collard (252). These results are partially contradicted by the data of Henderson et al. (168) who found a much smaller difference in concentration
between plasma and ultrafiltrate, some of which may have been associated with the buildup of a protein gel on the ultrafilter membrane.

Murdough and Doyle (293) studied the interaction of urea and free hemoglobin using equilibrium dialysis. They found the equilibrium ratio of urea concentration in a 20% hemoglobin suspension in isotonic saline to that in the saline alone was constant and equal to 1.13 over the concentration range 10 to 400 mgm percent. Using bovine hemoglobin and bovine albumin they found that urea binding was the same, per gm protein, for both. Gary-Babo and Lindenberg (137) on the other hand, were unable to find any binding by free hemoglobin.

The denaturing action of urea on albumin and other proteins at high concentration is well known (414). Pasynskii and Chernyak (214,315) used equilibrium dialysis to study sorption of urea, guanidine nitrate, and urethan on human serum albumin, γ-globulin, and hair and wool keratin, at high solute concentration. They found the results had the form of a Langmuir isotherm, including a linear relationship at low concentration and a maximum saturation of the proteins at high concentration. Their results for albumin and γ-globulin are shown in the first three columns of Table 4-3.

Columns four and five contain quantities calculated from the original data which will be of interest later. Column four contains a normalized equilibrium distribution or partition coefficient, defined as

\[ k' = \frac{\text{gm sorbed solute/gm protein}}{\text{gm free solute/ml protein free solution}} \]  

(4-1)
### TABLE 4-3

**Adsorption of Non-Electrolytes by Plasma Proteins**

From Pasynskii and Chernyak (314, 315)

<table>
<thead>
<tr>
<th>Solute</th>
<th>Equil. Conc. in prot. free soln gm/l</th>
<th>Sorbed Solute gm/gm protein</th>
<th>k' gm sorbed/gm protein</th>
<th>k = k'Cp a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human Serum Albumin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (M_r=60.1)</td>
<td>0.060</td>
<td>0.019</td>
<td>1.81</td>
<td>0.0724</td>
</tr>
<tr>
<td></td>
<td>0.548</td>
<td>0.055</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.12</td>
<td>0.113</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.65</td>
<td>0.192</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.46</td>
<td>0.267</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.28</td>
<td>0.369</td>
<td>1.88</td>
<td>0.0750</td>
</tr>
<tr>
<td></td>
<td>4.13</td>
<td>0.360</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guanidine Nitrate (M_r=104.1)</td>
<td>0.025</td>
<td>0.010</td>
<td>3.84</td>
<td>0.154</td>
</tr>
<tr>
<td></td>
<td>0.063</td>
<td>0.034</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.402</td>
<td>0.126</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.673</td>
<td>0.126</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethan (M_r=89.1)</td>
<td>0.684</td>
<td>0.010</td>
<td>1.51</td>
<td>0.0606</td>
</tr>
<tr>
<td></td>
<td>1.29</td>
<td>0.174</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.04</td>
<td>0.346</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Water</strong></td>
<td>0.75-0.80</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Human Serum γ-Globulin</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>0.82</td>
<td>0.055</td>
<td>1.12</td>
<td>0.0189</td>
</tr>
<tr>
<td></td>
<td>1.65</td>
<td>0.135</td>
<td>1.36</td>
<td>0.0230</td>
</tr>
<tr>
<td></td>
<td>2.46</td>
<td>0.258</td>
<td>1.75</td>
<td>0.0290</td>
</tr>
<tr>
<td></td>
<td>3.26</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.27</td>
<td>0.433</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.65</td>
<td>0.432</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guanidine Nitrate</td>
<td>0.16</td>
<td>0.034</td>
<td>2.04</td>
<td>0.0344</td>
</tr>
<tr>
<td></td>
<td>0.32</td>
<td>0.068</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.63</td>
<td>0.208</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.94</td>
<td>0.271</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethan</td>
<td>0.44</td>
<td>0.069</td>
<td>1.80</td>
<td>0.0297</td>
</tr>
<tr>
<td></td>
<td>1.34</td>
<td>0.135</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.78</td>
<td>0.201</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.22</td>
<td>0.278</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.78</td>
<td>0.280</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Water</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Calculated assuming 40 gm/l albumin and 16.9 gm/l γ-globulin in plasma (See Appendix E). Cp is the concentration of protein in normal plasma, gm/ml.*
Column five contains a distribution coefficient relating the concentration of solute bound to each protein at its normal plasma concentration to the concentration of solute in protein free plasma. Thus

\[ k = k'C_p \]

\[ = \frac{\text{gm solute sorbed to individual protein/ml plasma}}{\text{gm free solute/ml protein free plasma}} \]  \hspace{1cm} (4-2)

where \( C_p \) = normal protein concentration in plasma, gm/ml.

The distribution coefficient between the concentration of all the protein bound solute and the concentration in protein free plasma is simply

\[ k_p = \Sigma k_i \]  \hspace{1cm} (4-3)

where the summation is taken over all proteins present. Let the volume fraction of proteins in plasma be presented by \( \phi_p \). Then the distribution coefficient between bound and free solute, both concentrations being based upon the total plasma volume (including proteins) becomes

\[ \frac{k_p}{1 - \phi_p} = \frac{\text{gm sorbed solute/ml plasma}}{\text{gm free solute/ml plasma}} \]  \hspace{1cm} (4-4)

This ratio will be of interest in section 4.B.2. for the proposed model for diffusion in plasma.

The data in Table 4-3 indicates a very large maximum binding capacity for urea, which on a molar basis represents sorption of about 400 molecules of urea per albumin molecule, or roughly, one urea molecule per two amino acid residues. This maximum
capacity is not approached at the low physiological urea concentration (about 25 mg/100 ml blood); thus, the isotherm may be assumed linear at physiological concentrations. The reported value for albumin hydration differs considerably from other published estimates (431) of about 0.2 gm/gm per protein.

b. Creatinine

Binding data for creatinine was not found in the literature. The work of Bickel and Bovet (142) indicated positive interactions with albumin for some cyclical amines. Malinow and Korzon (252) found a reduction in ultrafiltrate concentration of creatinine, similar to that of urea. In view of the reported binding of urea, guanidine nitrate, and urethan, and of uric acid (discussed below), all nitrogenuous compounds, one may infer that a fraction of the plasma creatinine is protein-bound, although no quantitative estimate is presently possible.

c. Uric Acid

Until several years ago, there was no positive evidence for the existence in human blood of uric acid linked to macromolecules. Alvsaker (7) recently reviewed the earlier work and suggested that this conclusion applied only to irreversibly bound uric acid because of the techniques employed. He reinvestigated the interaction between the urate ion and human albumin using a gel filtration method and obtained the following results:

1) The occurrence of reversible interactions between urate ions and human albumin at pH 7.35 was established. The amount of urate interacting with albumin increased almost linearly with the
concentration of free urate ions at low concentration and levelled off to an approximately constant value above concentrations of 10 mg per 100 ml. The shape of the curve was qualitatively that of a Langmuir isotherm.

2) Some degree of specificity was shown by the fact that no interactions between urate ions and human γ-globulin or between albumin and xanthine or hypoxanthine were observed.

3) Similar experiments in whole plasma showed that the degree of interaction between uric acid and plasma was greater than that which was to be expected from the albumin content of plasma alone, indicating that other macromolecules besides albumin might have affinity for urate ions. Alvsaker's data are summarized in Table 4-4.

<table>
<thead>
<tr>
<th>Equil. Conc. of Free Uric Acid in protein free plasma</th>
<th>µg Uric Acid interacting with 50 mg Albumin</th>
<th>µg Uric Acid interacting with 1 ml plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>19.9</td>
<td>25.3</td>
</tr>
<tr>
<td>10.0</td>
<td>30.4</td>
<td>39.9</td>
</tr>
</tbody>
</table>

The maximum albumin binding capacity corresponds to about 0.6 mg uric acid/gm protein or roughly one urate ion for every four albumin molecules. The albumin-bound solute represents
about 60% of the total plasma bound material. In the range of normal physiological concentrations, 2-6 mg/100 ml plasma (\footnote{5}), the concentration of protein-bound uric acid is equal to about 50% of the freely diffusible uric acid concentration in protein free plasma (\(k_p \approx 0.50\)). Alvsaker points out that the protein binding is responsible for permitting a higher effective solubility for uric acid than that expected from its water solubility. In subsequent investigations (\footnote{8, 9}), he showed that, in addition to albumin, low density \(B_1\)-lipoprotein, \(B_2\)-macroglobulin, and an \(\alpha_1-\alpha_2\)-globulin interact reversibly with urate ions and that the variation in \(\alpha_1-\alpha_2\)-globulin plasma levels is the main cause for variation in the saturation limits of urate protein molecule interaction. He further hypothesized that the latter protein serves as a specific transport protein for uric acid in human blood, and he found that it is absent in plasma from patients with primary gout, wherein uric acid crystals precipitate from the blood and deposit in joints. It should be pointed out that Alvsaker used "urate ion" when referring to the protein-bound form of uric acid. However, he did not prove that the bound acid was in its dissociated form, and it is possible that he used the term interchangeably with "uric acid." As pointed out in Appendix B, uric acid is a weak acid and in pure water it is not completely dissociated.

d. Other Solutes

Goldstein (\footnote{142}) cites some evidence for the binding of about 30% of the total glucose in serum, but data for other sugars and carbohydrates was not given. Virtually all vitamins are protein-bound (\footnote{101}). Vitamin \(B_{12}\) binds specifically to some of
the globulin fractions.

Ponder and Ponder (327, 328) investigated the interaction of plasma proteins with dextran. For a 77,000 molecular weight dextran in a 0.5 to 2.0% solution, they found a complex formation with albumin and calculated it was composed of four dextran molecules per albumin molecule. However, their data could equally well be represented by other ratios, such as one dextran per eight albumin molecules. They found the complex formation was not instantaneous, requiring about four hours for completion; and they also noted decreased interaction after prolonged storage at 4°C and increased interaction with increasing molecular weight.

Loisleur and Collard (252) reported evidence for the adsorption of polypeptides by plasma proteins. Binding of amino acids has received some attention (276, 277). McMenamy, et al. (277) found all amino acids to be unbound, except for glutamic acid and tryptophan. For the latter compound, 70 percent of the amount added to plasma was not free to diffuse. However, since they dialyzed the plasma-solute fluid against distilled water, their technique would be sensitive primarily to irreversibly bound solute. No protein binding investigations were found in the literature for the other compounds of interest in this study.

3. **Solute Distribution Between Erythrocytes and Plasma**

The consideration of diffusion through a heterogeneous material requires knowledge of the distribution of solute between the various phases. Considerable work has been published concerning the distribution of organic solutes between the erythrocytes and plasma, much of it, particularly the early investigations, in
conjunction with studies of new analytical techniques for determining solute concentration in whole blood.

The erythrocyte solute distribution is commonly expressed in two ways:

1) The overall equilibrium distribution coefficient, $K_{eq}$, in which solute concentration is based on the entire volume of each phase.

2) The water phase equilibrium distribution coefficient, $R$, in which solute concentration is based on the volume of water in each phase.

If the system is in a state of thermodynamic equilibrium, and each phase is inert towards the solute, then for nonelectrolytes in media of equal ionic strength, one would expect the ratio $R$ to be unity. Using the values of 0.717 (357) and 0.93 (6) for the volume fraction water in red cells and plasma, respectively, the overall distribution coefficient would be 0.771. If, as has been postulated (357), 20% of the red cell water is bound to hemoglobin as water of hydration and unavailable for solvation, the water phase distribution coefficient would be 0.8 and the overall coefficient 0.618. Since there is disagreement among various investigators as to the state of the water in the red cell interior (333,437) it is impossible to specify which value represents the true inert case.

Literature data for some solutes of interest are summarized in Table 4-5. The data is presented in terms of $K_{eq}$. When the original data was presented in terms of $R$, $K_{eq}$ was calculated from the water volume fractions used above, or from the values
### TABLE 4-5

**Organic Solute Distribution Between Erythrocytes and Plasma**

Overall Equilibrium Distribution Coefficient, \( K_{eq} = \frac{\text{gm solute/ml erythrocytes}}{\text{gm solute/ml plasma}} \)

Water Phase Distribution Coefficient, \( R = \frac{\text{gm solute/ml erythrocyte Water}}{\text{gm solute/ml plasma water}} \)

<table>
<thead>
<tr>
<th></th>
<th>Creatinine</th>
<th>Uric Acid</th>
<th>Amino Acid Nitrogen</th>
<th>Glucose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.695</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.751</td>
<td>0.587</td>
<td>0.72(^a)</td>
<td></td>
<td>2.07</td>
<td></td>
</tr>
<tr>
<td>0.935</td>
<td>0.518</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.960</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.80</td>
<td>0.74</td>
<td>0.224(^a)</td>
<td>0.32(^a)</td>
<td>0.59(^a)</td>
<td></td>
</tr>
<tr>
<td><strong>(K_{eq})</strong></td>
<td>0.848</td>
<td>0.759</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(at 5 mMCl/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.773</td>
<td>0.542</td>
<td></td>
<td></td>
<td>0.932</td>
<td></td>
</tr>
<tr>
<td>0.824</td>
<td></td>
<td>0.55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.935 (lit)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.867 (data)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.885</td>
<td>2.0(^a)</td>
<td>0.492</td>
<td>1.71</td>
<td>0.969</td>
<td></td>
</tr>
<tr>
<td><strong>Avg</strong></td>
<td><strong>0.859(\pm)0.070</strong></td>
<td><strong>0.731(\pm)0.032</strong></td>
<td><strong>0.538(\pm)0.036</strong></td>
<td>1.54(\pm)0.63</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>(K_{eq})</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Avg R</strong></td>
<td><strong>1.11(\pm)0.091</strong></td>
<td><strong>0.949(\pm)0.042</strong></td>
<td><strong>0.698(\pm)0.046</strong></td>
<td>2.0(\pm)0.81</td>
<td>1.23</td>
</tr>
</tbody>
</table>

\(^a\)Not used in computing average.
used by the author if they were reported. The average values of R were calculated from the average values of $K_{eq}$. With the exception of a few radically different values, most of the data shows reasonable quantitative agreement.

The $K_{eq}$ values for urea varies from about 0.76 to 0.96. The lower values correspond to a relatively inert situation, while the higher values imply erythrocyte-urea interaction. The latter conclusion is indirectly supported by hemodialysis data obtained by Blackmore and Elder (39, 40). They hypothesized that the failure of dialysis to bring down the plasma urea to expected levels was caused by the existence of urea in red cell and plasma in diffusible and non-diffusible forms, and that the higher protein concentration in the red cell resulted in a greater ratio of non-diffusible to diffusible urea in the cell than in the plasma. They cited the data of Murdock and Doyle (283) in support of this theory. Rolls (336) also speculated that hemoglobin might form a non-diffusing urea complex. Assuming all urea in the red cell in excess of R equal to unity is hemoglobin-bound, his data, taken at about 12.5 mg urea/100 ml blood, indicated a binding of 0.04 mg urea per gm hemoglobin, or about one urea molecule for every 23 hemoglobin molecules. Rolls also found that after a meal, R dropped to below 1.0 for several hours, perhaps due to an influx of proteins into the plasma.

None of the investigators reported concentration effects, except for Gary-Bobo and Lindenberg (37). Their data is shown in Table 4-6.
Table 4-6

**Erythrocyte-Plasma Urea Distribution as a Function of Concentration (137)**

<table>
<thead>
<tr>
<th>Equil. Plasma Urea Concentration, Ce (mMol/liter)</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>1.03</td>
</tr>
<tr>
<td>5</td>
<td>1.10</td>
</tr>
<tr>
<td>0.5</td>
<td>1.17</td>
</tr>
<tr>
<td>0.05</td>
<td>2.26</td>
</tr>
</tbody>
</table>

They correlated their data in the form

\[
\frac{1}{R - 1} = K \log Ce + A \quad (4-5)
\]

obtaining \( K = -5 \) and \( A = -0.3 \). Phipps (322) replotted their data and found that the constants should be \( K = 4.9 \) and \( A = 6.98 \).

Gary-Bobo and Lindenberg were unable to find any adsorption of urea on the surface of isolated cell membranes or on free hemoglobin. Consequently, they hypothesized that the distribution was caused by a higher solubility of the polar urea in the erythrocyte water than in the plasma water, and they speculated that this occurred because the total ionic strengths of the two media differ. They showed experimentally that the water solubility of urea increased in the presence of neutral salts and that this "salting-in" effect becomes greater as the urea concentration decreases.
The data for creatinine and uric acid indicate progressively less deviation from an inert equilibrium, whereas glucose shows greater red cell solute interaction. The data for amino acids is highly scattered. Early work indicates significant solute-red cell interaction, while the data of Christensen, et al. (72) indicates an amino acid distribution similar to uric acid. McMenamy, et al. (76) reported data for a large number of amino acids, indicating that the distribution ratio varies widely from compound to compound.

The distribution of non-lipid soluble organic solutes between the various components of whole blood may be conceived in terms of the following relationship:

\[
\begin{align*}
\text{Plasma Proteins} & \leftrightarrow \text{Plasma Water} & \leftrightarrow & \text{Red Cell Water} & \leftrightarrow & \text{Hemoglobin} \\
\text{Membrane} & & & & & \\
\end{align*}
\]

where the question-marks indicate that protein binding may or may not occur at these locations. Lipid-soluble solutes would, in addition, be found dissolved in the erythrocyte membrane. It should be pointed out that there appears to be a conceptual error in most of the published literature concerning plasma-erythrocyte distribution of solute. Those workers investigating this phenomenon have focussed attention on the red cell primarily. To calculate the solute concentration in plasma water, they presumably divide the total mass of solute in a given volume of plasma by the volume of water in that volume of plasma, or equivalently, the total plasma concentration divided by the volume fraction water. However, if one is really interested in the plasma water -- erythrocyte water ratio, the fraction of bound solute (if any) in the
plasma should be subtracted from the total. This has not been
done by any of the investigators, most likely because reliable
data for plasma protein binding did not exist. The uric acid
binding data cited in the last section indicated that at physio-
logical concentrations, about one-third of the total uric acid
is bound. Dividing the results in Table 4-5 by 0.67 yields
about 0.81 for \( \kappa_{eq} \) and 1.05 for \( R \). These values are quite
reasonable for an inert distribution, if it is assumed that all
red cell water acts as solvent for uric acid. Despite this
conceptual limitation of \( R \), the value of \( \kappa_{eq} \) is nevertheless
useful as a phenomenological description of the distribution of
solute in all forms between the two phases.

Another effect which should be mentioned at this point is
adsorption or coating of solute on the surface of the red cell.
Such phenomena may result in a deceptively high apparent dis-
tribution and/or permeability of the erythrocyte. This occurs
with certain dyes (95) and macromolecules, such as dextran.
The interaction of the latter compound with the erythrocyte has
been discussed by Meiselman (279). The effect is probably of
minimal importance for solutes of interest in hemodialysis.

The distribution of electrolytes between plasma and erythro-
ocyte is a considerably more complex phenomena (437) and beyond
the scope of this discussion. It is noteworthy to point out,
however, that the value of \( R \) for potassium and sodium is about
27 and 0.16, respectively.
4. Diffusive Transport in the Erythrocyte

The erythrocyte is one of the commonest cells in the animal kingdom and was the first in which the permeability to a range of substances was systematically studied at the end of the nineteenth century. It still remains a favorite for the study of the diffusion and transport of substances across membranes, though much of the literature data is only of qualitative value.

Transport in the erythrocyte membrane is generally divided into two categories, passive and active (437). Passive connotes a downhill movement from a high to low chemical potential (or, in general, down a concentration gradient), and active implies an uphill movement. Passive transport is used generally to mean any movement not dependent on metabolism, whether it is simple diffusion or movement involving chemical reactions with components of the membrane. The latter phenomena is usually termed facilitated or mediated transfer, and involves reversible formation within the membrane of a complex between the diffusing solute and a carrier substrate. The next flux of solute across the membrane may consequently be augmented by diffusion of the carrier-complex. Under certain limited circumstances involving multicomponent transports, the existence of such a mobile carrier can actually lead to solute transport against a concentration gradient (437). Active transport implies movement against a concentration gradient with the expenditure of energy from metabolism. By such an energy input, the system may be kept in steady state and prevented from reaching thermodynamic equilibrium.
The classic case involving an explanation based upon active transport is the high selectivity shown by the cell membrane towards sodium and potassium. From the intracellular fluid, poor in sodium and rich in potassium, sodium ions are selectively transported outwards; and from plasma, poor in potassium and rich in sodium, potassium ions are selectively transported inwards. Such selective transport depends on the constant interaction of the membrane and adenosine triphosphate in the liberation of the energy of chemical bonds in food stuffs, and permits maintenance of a steady state in which leakage of ions due to passive diffusion is balanced by active transport in the opposite direction. The demonstration of true active transport in the red cell is confined to the sodium-potassium system (437), and for organic solutes of interest in hemodialysis, diffusive transport across the cell membrane may be considered to be limited to passive (including facilitated) diffusion.

a) Measurement of Permeability

A fairly simple quantitative treatment of erythrocyte permeability has been presented by Jacobs (135) and Whittam (437), and aspects of this analysis are discussed and amplified below. The diffusion of a nonelectrolyte across the cell membrane in the absence of volume flow and assuming constant physical properties may be described by Fick's first law:

\[
\frac{dN}{dt} = DAF \frac{Ce - C1}{\Delta X} \quad (4-6)
\]
where \( \frac{dN}{dt} \) is the rate of increase of solute within the cell, moles/sec, Ce and Ci its external and internal concentration adjacent to the membrane, moles/cc, \( \Delta X \) the membrane thickness, cm, \( A \) its area, cm\(^2\), D the diffusion coefficient of solute within the membrane, cm\(^2\)/sec, and F a partition factor or distribution coefficient which relates Ce and Ci to the immediately adjacent equilibrium concentrations within the membrane itself. This formulation assumes that at equilibrium, Ce and Ci are equal. In general, D and F are individually unknown, and estimates of the membrane thickness, \( \Delta X \) vary so widely that for practical purposes it is convenient to combine all unknown properties into a single empirical permeability constant defined by

\[
\frac{dN}{dt} = PA \Delta C
\]  

(4-7)

where \( P \) (in cm/sec) is the quantity of material that will cross unit area of the membrane in unit time with unit concentration difference. This definition of permeability is precisely the same as that used earlier for artificial membranes. In general, with \( V \) equal to the cell volume,

\[
\frac{dN}{dt} = \frac{d(VC)}{dt} = V \frac{dC}{dt} + C \frac{dV}{dt}
\]  

(4-8)
For the special case where the diffusion of solute is not accompanied by a change in the volume of the red cell by osmotic flow (such as in tracer diffusion from an iso-osmotic medium), and the external volume is sufficiently large compared to that of the cells so that Ce may be considered constant, Equations (4-7) and (4-8) may be combined and integrated to yield

\[ P = \frac{V}{At} \ln \frac{(Ce - Ci)_0}{(Ce - Ci)_t} \]  \hspace{1cm} (4-9)

where the subscript o refers to the initial conditions. In much of the literature, a specific rate constant is reported, defined by

\[ \frac{dN}{dt} = k_s \Delta C \]  \hspace{1cm} (4-10)

where \( k_s \) is expressed in units of time\(^{-1}\). This first order rate constant is also used to describe active transport, in the form

\[ \frac{dN}{dt} = k_s Ce \]  \hspace{1cm} (4-11)

Comparison of Equations (4-7) through (4-10) shows that

\[ k_s = P\left(\frac{A}{V}\right) = Ps \]  \hspace{1cm} (4-12)

where \( s \) is the specific area of the red cell. The dimensionless saturation of the red cell is defined by
\[ Z = \frac{C_{i_t} - C_{i_0}}{C_e - C_{i_0}} \]  

(4-13)

where \( Z = 0 \) at \( t = 0 \) and \( Z = 1 \) when \( C_i = C_e \). Combining Equations (4-9) and (4-13) yields

\[ P = -\frac{V}{A t_z} \ln (1 - Z) \]  

(4-14)

Equation (4-14) may be alternatively expressed as

\[ 1 - Z = e^{-P\left(\frac{A}{V}\right) t_z} = e^{-k_s t_z} \]  

(4-15)

from which it is evident that \( k_s \) is simply the reciprocal of the time constant for diffusion into the cell. The literature permeability data is often expressed as the saturation, \( Z \), achieved in a given time, \( t_z \), usually as the half time for saturation, \( t_{1/2} \).

The methods for studying the permeability of the erythrocyte have been summarized by Jacobs (186). These include methods based upon visibility changes within the cell, physiological changes, electrical changes, changes in chemical composition, and osmotic volume changes. The measurement of volume changes has been one of the most popular methods. For the special case in which the penetration rate of water is much faster than that of the solute, so that the cell is always at osmotic equilibrium, and the experiments are conducted in a solution iso-osmotic with the non-penetrating solutes in the red cell, Jacobs (186) has shown that the equations for calculating
diffusive permeability are particularly simple. A common variation of this technique is the hemolysis method. The red cells burst when they obtain a volume related to the original volume by a constant. This provides a sharp and easily measured endpoint for observations of osmotic volume changes. When the experimental conditions cited above do not hold, the analysis of transport is considerably more complex (167); it is also possible to obtain both the diffusive and osmotic permeabilities from a single measurement (158). It has been shown that the solute permeability is inversely proportional to the time required for hemolysis. Consequently, much early hemolysis data, such as that of Höber and Ørskov (177) can be used for qualitative comparison.

A major shortcoming, unknown to early investigators, in measuring solute diffusion when red cell volume changes are taking place, is that of the flow of water and solute are coupled and three phenomenological coefficients (rather than just two) are required to adequately describe the system. This is shown clearly by the application of irreversible thermodynamics to membrane phenomena (159). Consequently, reported diffusive permeability data may be somewhat in error if volume changes occurred during measurement. The use of the irreversible thermodynamic approach for erythrocyte transport has so far been limited to Solomon and co-workers (48, 143, 357, 359, 383).

Another limitation of reported data is that no attention has been paid to possible solute binding by plasma proteins and/or hemoglobin. Existence of this phenomena would require
alteration of the simple models used to describe the overall transport process and from which the permeability is calculated.

b) Qualitative Aspects

From both qualitative and quantitative permeability data, Jacobs (188) has concluded that observed results may be explained on the basis of several fundamental principles:

1) A change in an organic molecule that increases its relative affinity for organic solvents as compared with water tends to increase its ability to enter living cells, despite the increase in molecular weight and molecular volume which may accompany the change. In general, permeability is increased by addition of groups such as methyl, ethyl, and phenyl, occasionally producing spectacular increases. This suggests that non-polar solutes pass into the cell through the lipid region of the membrane which behaves as a non-specific solvent for molecules having a sufficiently non-polar hydrocarbon-type structure.

2) Other factors, such as lipid solubility being equal, the molecular size of the solute may have an important influence on its ability to enter the red cell. Höber and Ørskov (177) concluded that molecular size is the predominant factor in the penetration of water-soluble substances. For molecules of the same size, it is the specific chemical groups which determine penetration rate.

3) There appears to be a specific affinity for some solutes which is not explicable either in terms of non-specific lipid
solubility or a molecular sieve mechanism. The primary example of this is the relatively high permeability for urea. It can be accounted for neither by its molecular volume, which is nearly the same size as ethylene glycol, a more slowly penetrating solute, or by its lipid solubility, which is very low.

The permeability behavior of nonelectrolytes has led to the dual pathway concept of entry into the red cell, as shown in Fig. 4-3, wherein non-polar compounds pass through the lipid region of the membrane and polar compounds pass through water filled pores. This concept is compatible with the structure of the membrane as a mosaic of lipid and protein regions (see Fig. 4-2). The existence of pores would be expected to show a sharp demarcation with respect to molecular size within the same class of compounds, and this has in fact been found (437).

A number of compounds are believed to be transported in part by facilitated diffusion of a carrier complex. Whittam (437) has reviewed the overwhelming evidence for glucose. He points out, however, that critical evidence is lacking to distinguish between facilitated carrier transport and diffusion
through a limited number of selective pores. Within the last
decade, Lassen and co-workers (233, 234, 235, 236, 237, 310)
have demonstrated the characteristics of facilitated transport
for uric acid.

c) Quantitative Data

Meaningful data on the permeability of human erythrocytes
is limited. Some representative results are discussed here,
where the data was sufficiently quantitative that a permeability
could be calculated directly. It should be noted that by using
Equation (4-6), all investigators have implicitly assumed that
the equilibrium distribution coefficient of solute between the
fluids on each side of the red cell membrane is unity. From
the data presented in Section 4.A.3, this assumption appears
to be false and thus the reported permeabilities probably
contain some error. The same assumption will be made in this
study in analyzing literature data, since the additional error
will be no greater than that contained in the source data.

Table 4-7 shows the relative penetration rate of the
human erythrocyte to fatty acids at about 20°C. Permeability
values were calculated from saturation half times reported by
Green (151) using Equation (4-10). From C1 to C5, the acids
penetrate in the order of, but not in direct proportion to, their
relative solubility in olive oil. The maximum permeability is
reached at C5, valeric acid. The C6 to C8 acids do not follow
their relative solubilities, suggesting that in this range, in-
creasing molecular size may be a limiting factor in permeability.
The change in direction observed between butyric, valeric, and
caproic acids may represent a balance of two opposing forces,


**TABLE 4-7**

Permeability of Human Erythrocyte to Fatty Acids$^\text{a}$ (20°C)

*from Green (151)*

<table>
<thead>
<tr>
<th>Acid</th>
<th>No. Carbon Atoms, n</th>
<th>Saturation Half Time $t_{\frac{1}{2}}$, sec</th>
<th>Permeability $P$, cm/sec x 10$^6$</th>
<th>Olive Oil-Water Distribution Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formic</td>
<td>1</td>
<td>10.2</td>
<td>3.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Acetic</td>
<td>2</td>
<td>3.7</td>
<td>9.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Propionic</td>
<td>3</td>
<td>0.41</td>
<td>90</td>
<td>0.152</td>
</tr>
<tr>
<td>Butyric</td>
<td>4</td>
<td>0.38</td>
<td>98</td>
<td>0.443</td>
</tr>
<tr>
<td>Valeric</td>
<td>5</td>
<td>0.22</td>
<td>170</td>
<td>2.60</td>
</tr>
<tr>
<td>Caproic</td>
<td>6</td>
<td>0.36</td>
<td>100</td>
<td>9.47</td>
</tr>
<tr>
<td>Heptylic</td>
<td>7</td>
<td>1.04</td>
<td>36</td>
<td>49.3</td>
</tr>
<tr>
<td>Caprylic</td>
<td>8</td>
<td>0.88</td>
<td>42</td>
<td>31.9</td>
</tr>
</tbody>
</table>

$^\text{a}$ General Formula: $H(CH_2)_{n-1}COOH$
increasing molecular volume, on one hand, tending to retard penetration and increasing solubility in lipid regions, tending to increase the penetration rate.

Data for a wide variety of substances are tabulated in Table 4-8 in terms of $t_{1/2}$, $k_s$, and $P$. The raw data, obtained from various sources, was usually given as one of these three parameters. The others were calculated from Equations (4-12) and (4-14). The data of Savitz and Solomon (358) was given in terms of $\omega$, the coefficient of solute permeability at zero volume flow, mole/dyne sec. It is related to the diffusive permeability described above by the equation

$$P = \omega RT$$

(4-16)

where $R = \text{ideal gas constant, } 8.314 \times 10^7 \frac{\text{dyne-cm}}{\text{g mole } ^\circ\text{C}}$

$T = \text{temperature, } ^\circ\text{K}$

This represents a true diffusive permeability and may not be directly comparable with other literature values where red cell volume changes occurred. Much of the data cited in Table 4-8 was obtained by measuring radioactive tracer exchange rates where the constant volume assumption holds.

Perhaps the most distinctive feature of the permeability data is the enormous range of permeability constants, covering more than seven orders of magnitude. By far the most permeable compound is water, followed by methanol and urea. All other compounds tabulated are water soluble with extremely low lipid solubility. The exchange rate permeability of tracer ions is shown primarily for comparison. Chloride ion is by far the
<table>
<thead>
<tr>
<th>Solute</th>
<th>Temp. °C</th>
<th>Saturation Half Time</th>
<th>Specific Rate Constant, sec⁻¹</th>
<th>Permeability cm/sec</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl⁻</td>
<td>21-25</td>
<td>0.2 sec</td>
<td>3.5</td>
<td>1.9×10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>Br⁻</td>
<td></td>
<td>1.2 sec</td>
<td>0.6</td>
<td>3.2×10⁻⁵</td>
<td></td>
</tr>
<tr>
<td>F⁻</td>
<td></td>
<td>2.3 sec</td>
<td>0.3</td>
<td>1.6×10⁻⁵</td>
<td></td>
</tr>
<tr>
<td>I⁻</td>
<td></td>
<td>12 sec</td>
<td>0.06</td>
<td>3.2×10⁻⁶</td>
<td></td>
</tr>
<tr>
<td>Phosphate</td>
<td>37</td>
<td>-3 hrs</td>
<td>6.7×10⁻⁵</td>
<td>3.6×10⁻⁹</td>
<td></td>
</tr>
<tr>
<td>SO₄²⁻</td>
<td>?</td>
<td>-5 min</td>
<td>2.3×10⁻³</td>
<td>1.2×10⁻⁷</td>
<td>In Presence of Cl⁻, Eact = 19,800 cal/mole</td>
</tr>
<tr>
<td>K⁺</td>
<td>?</td>
<td>-35 hrs</td>
<td>5.5×10⁻⁶</td>
<td>4.0×10⁻⁸</td>
<td>In Presence of Citrate</td>
</tr>
<tr>
<td>Na⁺</td>
<td>?</td>
<td>-2.3 hrs</td>
<td>8.3×10⁻⁵</td>
<td>3.4×10⁻⁸</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>37</td>
<td>4.1 min</td>
<td>2.8×10⁻³</td>
<td>1.5×10⁻⁷</td>
<td></td>
</tr>
<tr>
<td>H₂O(311)</td>
<td>23</td>
<td>0.0042 sec</td>
<td>165.0</td>
<td>8.8×10⁻³</td>
<td>THO Diffusion</td>
</tr>
<tr>
<td>Urea (188)</td>
<td>20</td>
<td>0.19 sec</td>
<td>3.6</td>
<td>1.9×10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>Urea (358)</td>
<td>25?</td>
<td>0.088 sec</td>
<td>7.9</td>
<td>4.2×10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>Ethylene Glycol (358)</td>
<td>0.19 sec</td>
<td>3.7</td>
<td>2.0×10⁻⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melonamide (358)</td>
<td>37 sec</td>
<td>1.9×10⁻²</td>
<td>1.0×10⁻⁶</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 4-8 (Continued)

<table>
<thead>
<tr>
<th>Solute</th>
<th>Temp. °C</th>
<th>Saturation Half Time</th>
<th>Specific Rate Constant, sec⁻¹</th>
<th>Permeability cm/sec</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol (358)</td>
<td>25?</td>
<td>0.012 sec</td>
<td>56.1</td>
<td>3.0×10⁻³</td>
<td></td>
</tr>
<tr>
<td>Glycerol (188)</td>
<td>20</td>
<td>25 sec</td>
<td>0.028</td>
<td>1.5×10⁻⁶</td>
<td>$E_{act}=24,500$ Cal/mole (ox, 544)</td>
</tr>
<tr>
<td>Mannitol (188)</td>
<td>20</td>
<td>6.2 sec</td>
<td>0.11</td>
<td>6.0×10⁻⁶</td>
<td></td>
</tr>
<tr>
<td>Sucrose (188)</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Creatinine (138)</td>
<td>20</td>
<td>143 min</td>
<td>8.1×10⁻⁵</td>
<td>4.3×10⁻⁹</td>
<td>$E_{act}=28,800$ cal/mole</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>29.5 min</td>
<td>3.9×10⁻⁴</td>
<td>2.1×10⁻⁹</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>10 min</td>
<td>1.2×10⁻³</td>
<td>6.0×10⁻⁸</td>
<td></td>
</tr>
<tr>
<td>Uric Acid (138)</td>
<td>27</td>
<td>17 to 46 min</td>
<td>2.5 to 6.7×10⁻⁴</td>
<td>1.34 to 3.6×10⁻⁸</td>
<td>$E_{act}=15,800$ cal/mole</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conc'n dependent</td>
<td></td>
</tr>
<tr>
<td>Amino Acids (72)</td>
<td>37</td>
<td>30 to 200 min</td>
<td>5.8 to 39×10⁻⁵</td>
<td>3.0 to 21×10⁻⁹</td>
<td>Reported Range for various acids</td>
</tr>
</tbody>
</table>

a. Data obtained from Whittam (437) unless specified otherwise.

b. In the original work, Paganelli and Solomon gave $P=5.5×10⁻³$/cm/sec but did not give their basis of calculations from the reported half-time.
most permeable. It is noteworthy that the permeabilities for sodium and potassium are about four and six orders of magnitude lower, respectively, than chloride.

It is interesting to compare the tabulated permeabilities with data recently obtained by Reeves (341) with bilayer phospholipid membranes around 50 Å thick. For the permeability at 37°C he reported: urea - \( P = 6.9 \times 10^{-6} \) cm/sec, \( E_{ac} \approx 13,000 \) cal/mole; glycerol - \( P = 9.3 \times 10^{-6} \) cm/sec, \( E_{ac} \approx 17,000 \) cal/mole. The red cell urea permeability is about two orders of magnitude higher than that for the phospholipid bilayer, indicating that most of the urea must permeate across the non-lipid regions. For glycerol, the permeability values are of the same order of magnitude, but the activation energies differ considerably.

With increasing molecular weight, the permeability constant drops off sharply. For creatinine and uric acid, it is about four orders of magnitude lower than that for urea. The range for amino acids covers twelve different compounds. Christensen, et al. (72) noted that in the sequence

\[
\text{glycine} < \text{alanine} < \text{valine} < \text{leucine}
\]

the rate of uptake increased as the length of hydrocarbon chain increased. They hypothesized that the increasing lipophilic nature might permit passage across a lipid barrier, perhaps in the form of a complex in which the amino and carboxyl groups are masked or that a hydrophobic bond between the hydrocarbon side-chain helps to orient the amino acid molecule with reference to the two primary bonding points. The largest molecular weight
compound tabulated is sucrose, 342, for which Jacobs (185) reports no penetration into the erythrocyte. In the absence of any other data, this may be taken as the cut-off point for the penetration of water soluble and lipid insoluble solutes into the red cell. Another distinctive feature of the data is the uniformly high activation energy reported for three compounds. This might indicate significantly higher energy barriers than normally encountered in liquid diffusion (Eact ≈ 4,000 cal/mole).

It may be questioned as to whether the measured permeability includes a diffusional resistance from the fluid adjacent to the red cell. A rough estimate of the magnitude of this effect may be made by considering the red cell to be sphere suspended in a motionless fluid, for which the Sherwood number is given by (36).

\[
\frac{k_f d}{D_f} = 2 \tag{4-17}
\]

where \( k_f \) = fluid mass transfer coefficient, cm/sec
\( d \) = sphere diameter, cm
\( D_f \) = solute diffusivity in fluid, cm²/sec

The stiffest test corresponds to water diffusion in the red cell. The diffusivity of \( H_2O^{18} \) in a 10.6% by weight albumin solution (slightly more concentrated than plasma), extrapolated from the results of Wang, et al. (432) to 23°C using the Stokes-Einstein relation, is 2.02 x 10⁻⁵ cm²/sec. From Table 4-1, the largest
characteristic size (most conservative estimate) for an equivalent sphere is that for constant area, \(3.6 \times 10^{-4}\) cm. Substituting these values into eqn. (4-17) yields

\[
k_f = 1.11 \times 10^{-1} \text{ cm/sec}
\]

Assuming additivity of resistances, the measured overall permeability is expressed by

\[
\frac{1}{P} = \frac{1}{P_{\text{true}}} + \frac{1}{k_f}
\]

Substituting for \(P\) and \(k_f\), one obtains

\[
P_{\text{true}} = 9.5 \times 10^{-3} \text{ cm/sec}
\]

which is about 7.5% higher than the measured value. This represents the maximum error; for other solutes, permeability decreases much faster than diffusivity. Furthermore, some of the data was obtained using a rapid exchange mixing chamber (151, 311) similar to the technique originally devised by Hartridge and Roughton (162), which would be expected to yield higher fluid mass transfer coefficients due to turbulence and mixing. This is in fact indicated by recent experimental data on this system (377).

The reader should note that the symbol \(P\), rather than \(P_m\), where the subscript \(m\) denotes the membrane, has been used to denote the red cell permeability. It is clear that the lack of detailed structural knowledge of the erythrocyte interior precludes the assignment of this permeability to any specific portion of the cell, although most researchers refer to it as the red cell membrane permeability. The most reasonable picture
of the red cell is one of sharply decreasing structural order and increasing volume fraction water as one proceeds from the membrane to the interior, with a gradual change in the cell interior. The measured permeability represents a lumped parameter, the overall resistance being the effective sum of resistances in series of the entire red cell. It is possible that all the resistance resides in a thin "skin" at the surface or, on the other hand, that the resistance is equally distributed throughout the cell.

It is instructive to examine this question in a rough quantitative manner. Let us consider the extreme case that the measured permeability corresponds to a membrane of infinitesimal thickness surrounding the cell and includes no contribution from the interior. The question to be answered is: Would inclusion of the mass transfer resistance of the cell interior significantly alter the total measured permeability of the entire red cell? Assuming again, additivity of resistances, one obtains

$$\frac{1}{K_T} = \frac{1}{P_m} + \frac{1}{k_i}$$

(4-19)

where $K_T$ is the overall mass transfer coefficient or permeability, $k_i$ the mass transfer coefficient of the stagnant cell interior, and $P_m$ the measured "membrane" permeability. Let us further assume that $k_i$ may be expressed as

$$k_i = \frac{D_i}{L}$$

(4-20)
where $D_i$ is the solute diffusivity in the cell interior and $L$ is an effective length characteristic of the diffusion path in the cell. Combining eqns. (4-19) and (4-20) and rearranging gives, for the ratio of the internal mass transfer resistance to the total mass transfer resistance:

$$\frac{R_i}{R_T} = \frac{\frac{L}{D_i}}{\frac{1}{P_m} + \frac{L}{D_i}} = \frac{L P_m}{D_i + L P_m} \quad (4-21)$$

A similar relationship may be obtained by considering the boundary condition at the inside of the cell membrane in a direction normal to the membrane surface:

$$D_i \frac{\partial C_i}{\partial x} = P_m \Delta C_m \quad (4-22)$$

where $\Delta C_m$ is the concentration gradient across the membrane. To a first order approximation,

$$\frac{\partial C_i}{\partial x} \sim \frac{\Delta C_i}{L} \quad (4-23)$$

and consequently

$$\frac{\Delta C_i}{\Delta C_i + \Delta C_m} = \frac{L P_m}{D_i + L P_m} \quad (4-24)$$

As expected, the ratio of the internal to the total concentration difference is proportional to the relative resistances.

To evaluate these expressions, values for $D_i$ and $L$ are required. Assume that the interior is a uniform, unordered suspension of hemoglobin, 25% by volume. Wang,
et al. (432) found that a 24.5 percent by weight solution (19 percent by volume) of albumin reduced the self-diffusion coefficient of water to 58 percent of its value in pure water. A rough extrapolation to 25 volume percent yields about a 69 percent reduction. From Table 4-1, a disc of equivalent specific area would be 1.44μ by 8.4μ. Thus, as a rough approximation one may examine the two limiting dimensions for L, the half-thickness and radius, 0.72μ and 4.2μ, respectively.

Using these values, the fractional interior resistance was calculated for several solutes, and the results are shown in Table 4-9. D_i was calculated from water data shown in Table 4-10 and discussed further in Appendix B. The urea permeability at 37°C was calculated from the data at 25°C, assuming an activation energy of 20,000 cal/mole. This may be too high an estimate, since the solutes for which such information is available all show greater diffusional resistance.

With the possible exception of water, the addition of an interior cell resistance to the measured "membrane" resistance would add very little to the total if the cell interior is a simple hemoglobin solution. Consequently, the reported permeabilities may be assumed to reflect permeation through the entire cell. If the resistance is localized in a thin membrane, say of the order of 100 Å, then the cell interior may be assumed to be almost "well-mixed." On the other hand, it is possible that the entire
<table>
<thead>
<tr>
<th>Solute</th>
<th>T °C</th>
<th>$P_m$ cm/sec</th>
<th>$D_i$ cm²/sec×10⁵</th>
<th>$L = 0.72\mu$</th>
<th>$L = 4.2\mu$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>23</td>
<td>$8.8\times10^{-3}$</td>
<td>1.22</td>
<td>0.049</td>
<td>0.23</td>
</tr>
<tr>
<td>Urea</td>
<td>25</td>
<td>$4.2\times10^{-4}$</td>
<td>0.69</td>
<td>0.0044</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>$1.6\times10^{-3}$&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.90</td>
<td>0.0071</td>
<td>0.040</td>
</tr>
<tr>
<td>Creatinine</td>
<td>37</td>
<td>$6.0\times10^{-8}$</td>
<td>0.64</td>
<td>$6.8\times10^{-6}$</td>
<td>$3.9\times10^{-5}$</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>37</td>
<td>$3.6\times10^{-8}$</td>
<td>0.58</td>
<td>$4.5\times10^{-6}$</td>
<td>$2.6\times10^{-5}$</td>
</tr>
<tr>
<td>(1 mMole/Liter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Extrapolated to 37°C assuming $E_{act} = 20,000$ cal/mole
cell structure contributes to the diffusional resistance if the cell interior is highly structured.

In terms of modelling diffusion through whole blood, the erythrocytes may be considered in two ways: 1) as a homogeneous dispersed phase, characterized by a single effective permeability or diffusivity, or 2) as a heterogeneous dispersed phase, containing a highly permeable interior surrounded by a much less permeable surface "skin." Although the previous analysis indicates that for organics the second model is probably more reasonable, existing theoretical models in the literature for this case are not nearly as well developed as for the first model. This will be discussed further in Section 4.B.1. For use later, effective diffusivities characteristic of the entire red cell will be calculated at this point.

An indirect approach was used to obtain the effective diffusivity, as follows. From eqn.(4-15), the time required to reach 90 percent saturation was determined. Then, the time required for 90 percent saturation of a cell composed entirely of stagnant water was calculated, assuming various ideal shapes. From these two times, the effective diffusivity may be determined from

$$\frac{D_{\text{eff (red cell)}}}{D_{\text{water}}} = \frac{t_{0.9 \text{ (water)}}}{t_{0.9 \text{ (red cell)}}}$$ (4-25)

The red cell was modeled as a disc of equivalent specific area, as described above. Three cases were considered: 1) The faces are impermeable and the cell behaves like an
infinite cylinder, with diffusion through the rim; 2) The rim is impermeable and the cell behaves as if it were a thin sheet of infinite extent exposed on both faces to the diffusing material; 3) The entire disc surface is permeable. The infinite sheet model has previously been applied to the red cell by Roughton (349) and Jacobs (132). While the third model may at first seem most reasonable, the erythrocyte is not necessarily uniform over its entire surface in either its structural or diffusional properties. For example, Murphy (294) has shown that the exchange of cholesterol between red cell membranes and their suspending medium occurs preferentially in the edge region of the membrane, suggesting that it is different in its properties from the biconcave regions.

The mathematical solutions for transient diffusion in the infinite cylinder and infinite sheet, given graphically by Crank (90), were utilized. Ma and Evans (264) have recently considered various three-dimensional arbitrary shapes. Their results required interpolation for the disc shape employed here. At 90 percent saturation from an infinite bath, the following relations were obtained:

**Infinite Cylinder**

\[
\left( \frac{D t}{a^2} \right)^{1/2} = 0.58
\]

\[a = \text{cylinder radius} = 4.2 \times 10^{-4} \text{ cm}\]

**Infinite Sheet**

\[
\left( \frac{D t}{b^2} \right)^{1/2} = 0.92
\]

\[b = \text{half thickness} = 0.72 \times 10^{-4} \text{ cm}\]
Disc \((\text{height/diameter} \approx 6)\)

\[
\left(\frac{Dt}{\sigma^2}\right)^{1/2} \approx 1.1
\]  \hspace{1cm} (4-28)

\(\sigma = \text{volume/surface area} = 0.535 \times 10^{-4} \text{ cm}^3/\text{cm}^2\)

A more accurate calculation for the disc, using the Newman (297) method, gave essentially the same effective diffusivity ratios.

The times calculated from eqns. (4-26) through (4-28) are shown in Table (4-10), along with \(t_{0.9}\) for the erythrocyte and the ratio of the two quantities. The ratios for the infinite cylinder model are more than an order of magnitude higher than the other two, with the disc being lowest. For all the solutes shown the values are low, and only for water and perhaps urea at 37°C is it appreciably greater than zero. The exceedingly low ratios for creatinine and uric acid correspond to a diffusivity of order \(10^{-12}\). The scale of reduction may be appreciated by considering that this corresponds to the Brownian motion diffusivity in water of a molecule the size of a grain of sand (0.1 mm). If the effective diffusivity ratio had been calculated on the basis of a membrane of 100 Å thickness, the values would be about two orders of magnitude lower.

B. A Model for Diffusion in Plasma and Whole Blood

In this section, models will be proposed to describe the diffusion of solutes through plasma and through whole blood. From a diffusion standpoint, plasma may be viewed
<table>
<thead>
<tr>
<th>Solute</th>
<th>T °C</th>
<th>P (red cell) cm/sec</th>
<th>t₀.9 (red cell)(Water) sec×10⁶</th>
<th>D (Water) cm/sec×10⁵</th>
<th>t₀.9 (water)</th>
<th>t₀.9 (red cell)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>23</td>
<td>8.8×10⁻³</td>
<td>0.0140</td>
<td>2.4</td>
<td>0.18</td>
<td>0.14</td>
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<tr>
<td>Urea</td>
<td>25</td>
<td>4.2×10⁻⁴</td>
<td>0.291</td>
<td>1.38</td>
<td>4.3</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>1.6×10⁻³</td>
<td>0.0770</td>
<td>1.81</td>
<td>3.3</td>
<td>0.24</td>
</tr>
<tr>
<td>Creatinine</td>
<td>37</td>
<td>6.0×10⁻⁸</td>
<td>1920</td>
<td>1.29</td>
<td>4.6</td>
<td>0.34</td>
</tr>
<tr>
<td>Uric Acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1 mMole/37</td>
<td>37</td>
<td>3.6×10⁻⁸</td>
<td>3430</td>
<td>1.15</td>
<td>5.2</td>
<td>0.38</td>
</tr>
<tr>
<td>Liter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Extrapolated from data of Wang et al (432) assuming Dₜ/T constant.

- Extrapolated to 37°C assuming Eₜₐₜ = 20,000 cal/mole.
as a suspension of impermeable proteins in a complex aqueous media, and whole blood may be considered as a suspension of semipermeable red cells in plasma. In addition, the effects of binding of solute to plasma proteins and/or erythrocyte hemoglobin must be included. Before discussing these fluids specifically, the available literature on diffusion in heterogeneous media will be briefly reviewed.

1. **Diffusion in Heterogeneous Media**

   Consider the following problem. A solid or fluid possesses large-scale homogeneity and isotropy. On a smaller scale, it is composed of two materials or phases, A and B, each of known permeability. (In the general problem, both phases may be continuous, or one may be dispersed in the other). What is the effective permeability of the composite material? This is a classical problem and has been applied to many unrelated phenomena which are described by similar mathematical laws, including, for example, dielectric and magnetic polarization, electrical and thermal conduction, and mass diffusion. For the most part, existing analyses have been confined to the steady-state.

   a) **Steady-State Analysis**

   Many steady-state phenomena associated with multiphase materials are expected to obey analogous laws based on Laplace's equation:

   \[ \Delta^2 \phi = 0 \quad (4-29) \]

   where \( \phi \) is the potential. Maxwell (273) was the first to analyze this problem. He considered a continuum with immersed
spheres so far apart that the streamline pattern about each sphere was not influenced by those of its neighbors. His results are thus valid only for low volume fractions of dispersed phase. Rayleigh (239) further developed Maxwell's formula. Using potential theory, he calculated the influence on the flow pattern around any one sphere due to neighboring spheres forming a cubic array.

Subsequent treatments have been directed towards developing models valid for higher volume fractions and varied shapes of the dispersed phase. These include further extensions of Rayleigh's approach to account for higher orders of induced particle-particle interactions, treatments based on a statistical description of the heterogeneous media, empirically-based models and simplified models composed of parallel and/or series resistances, such as a regular lattice of rectangular parallelepipeds in a continuum. While similar mathematically, these treatments have appeared in the specialized literature of their respective fields, such as magnetic permeability (163), dielectric displacement (47, 56, 112, 174, 282, 323, 324, 343), electrical conductivity (60, 97, 132, 134, 136, 135, 136, 282), thermal conductivity (125, 146, 131, 227, 251, 351, 410, 411, 421, 426, 443, 445), and mass diffusion (25, 175, 329, 330, 431, 435). The existing literature is voluminous and the above list is by no means complete. For additional references the reader is referred to several original articles and reviews (25, 47, 56, 91, 125, 345, 427, 443). Particularly valuable in this respect is the review of Reynolds and Hough (343).
who have shown that most existing formulae are related to each other in being approximations to the same rigorous formulation of the problem.

A detailed analysis of individual treatments of the problem is beyond the scope of this work. However, examination of the existing literature yields the following conclusions:

1) With the exception of purely parallel or series arrangement or infinitely dilute suspensions of ellipsoids, it is presently impossible to obtain a rigorous model for the general problem. Most existing solutions differ from one another in the approximation(s) considered adequate.

2) All models indicate that the effective permeability is dependent upon the volume fractions, shape, and relative permeabilities of the various phases. Some treatments show that the spatial distribution of phases may be important. All agree that for a disperse phase, the "particle" size is not significant as long as it is very small compared to the total volume considered. However, no investigation was found in which this restriction was expressed in usable quantitative terms.

3) Experimental verification of the dozens of existing models is meager and often contradictory. The case of one permeable and one impermeable phase has been examined most often. For the general problem of a dispersed phase of arbitrary shape and permeability, the most developed area is that dealing with dielectric displacement, but even here a definitive comparison of existing models has
has not been made. The best agreement between theory and data has often been obtained with empirically-based models with an adjustable constant which usually cannot be applied to other media.

The available models for a dispersion of phase B in a continuum of phase A are most often described in terms of the dielectric constant of a mixture \((91, 343)\). In a pure phase,

\[ D_i = \varepsilon_i E_i \quad (4-30) \]

where

- \( D \) = dielectric displacement
- \( \varepsilon \) = dielectric constant
- \( E \) = electric field intensity

The mean or apparent dielectric permeability is given, for a multiphase mixture, as

\[ \varepsilon = \frac{\bar{D}}{\bar{E}} \quad (4-31) \]

where \( \bar{D} \) and \( \bar{E} \) are quantities averaged over the entire volume. The results can usually be expressed in the form

\[ \psi = \frac{\bar{D}}{D_A} = \frac{\varepsilon}{\varepsilon_A} = f(\phi, \text{shape of } B, \frac{\varepsilon_B}{\varepsilon_A}) \quad (4-32) \]

where \( \phi \) is the volume fraction of phase B \((\phi_A + \phi_B = 1)\) and \( D_A \) is the dielectric displacement in pure phase A. The quantity \( \psi \) is sometimes referred to as an "obstruction" factor. The expression \((4-32)\) is valid for equal forces acting across identical thicknesses of heterogeneous media.
(B dispersed in A) and of pure phase A.

As pointed out by Higuchi and Higuchi (175) and Crank and Park (91), the correct analogous expression for diffusion of mass is

\[
\psi = \frac{\bar{J}}{J_A} = \frac{\bar{p}}{P_A} - f(\phi, \text{shape of } B, \frac{K_{eq} D_B}{D_A}) \tag{4-33}
\]

where \( P \) represents the permeability. This expression holds for equal concentration driving forces for the two media. Higuchi and Higuchi have expressed \( P \) as the product of diffusivity and partition coefficient, the latter being the ratio of the activity coefficients in the phase or mixture under consideration to that in a third, external phase. If the reference phase is taken to be pure phase A, then the permeability ratio becomes

\[
\psi = \frac{D_{eff} K_{T/A}}{D_A} \tag{4-34}
\]

where \( K_{T/A} \) is the distribution coefficient between the composite mixture of A and B and pure A alone, i.e.,

\[
K_{T/A} = \frac{C_T}{C_A}_{eq.} \tag{4-35}
\]

where

\[
C_T = (1 - \phi) C_a + \phi C_b \tag{4-36}
\]

\[
= (1 - \phi + \phi K_{eq}) C_a \tag{4-37}
\]

and \( K_{eq} = \frac{C_b}{C_a} \) \( \tag{4-38} \)
C_a and C_b refer to the concentrations in phases A and B, and \( \phi \) is the volume fraction of the suspended phase. Similar reasoning is responsible for the formulation of the third group in parentheses in eqn. (4-33). This is discussed further in Appendix F.

b) Unsteady-State Analysis

Despite the proliferation of analyses for the stationary state, the literature is virtually devoid of considerations of the same problem for the unsteady-state. This situation is more complex because, for diffusion of mass, for example, one phase may lag behind the other because of a finite rate of mass transfer between the two phases. Similar capacitive effects may occur with other analogous processes. This deviation from equilibrium would be a function of time, and possibly of concentration, particularly if the equilibrium relationship is nonlinear. The questions which remain to be answered are: 1) Are the steady-state models valid in the unsteady-state if the phases are at equilibrium? 2) How does one predict if the phases are at equilibrium and, if they are not, how does one estimate the degree of deviation from equilibrium?

The problem has been considered qualitatively by Higuchi and Higuchi (175). They concluded, but did not prove, that, if the phases were at or very close to equilibrium, the steady-state model should hold. This would be true if the relaxation time in the microscopic heterogeneous region is small compared to the time scale of the change which is
occurring in the continuous phase. As a criterion for the existence of near-equilibrium conditions, they compared estimates of the relaxation time for entrance into the dispersed phase (assumed spherical) and for diffusion in the external phase with an estimate of the rate of change of concentration at any point, assuming the heterogeneous media to be a semi-infinite slab. Friedlander and Keller (129) have developed quantitative criteria for determining the conditions under which the equilibrium assumption is valid for chemically-reacting systems.

Appendix F contains a model developed by the author for transient diffusion in heterogeneous media with nonequilibrium between phases. The model permits precise definition of the equilibrium criterion for diffusion in a slab exposed to constant concentration at each face and yields a rough estimate of the departure from equilibrium when this is not large. The requirement for equilibrium at intermediate and long dimensionless times is

\[ K_1 + K_2 >> 1 \]

where

\[ K_2 = \frac{k_b s L^2}{D_A \Psi_A^*} \]

\[ K_1 = K_2 \left( \frac{\phi}{1 - \phi} \right) K_{eq} \]

\[ k_b = \text{interphase mass transfer coefficient} \]

\[ s = \text{specific area of phase B} \]

\[ L = \text{half-width of slab} \]

\[ D_A = \text{diffusion coefficient of solute in pure phase A} \]
\( \psi_A^* = \text{effective reduction of diffusion coefficient in phase A in heterogeneous media} \)

Furthermore, the fraction of the total dimensionless concentration in phase B which is in excess of the equilibrium values is approximately

\[
\Delta_B = \frac{\frac{\pi^2}{4}}{K_1 + K_2 + \frac{\pi^2}{4}}
\]

(4-40)

In order for this quantity to be 1% or less, it is required that

\[
K_1 + K_2 \geq 25\pi^2 \approx 250
\]

(4-41)

Additional details regarding the derivation and solution for the transient model may be found in Appendix F.

2. Diffusion in Plasma

In order to describe diffusion in plasma one must take into account 1) the obstruction effect caused by the protein molecules, and 2) the possible binding of solute by the plasma proteins. The solute binding may be visualized as a reaction of the form

\[
a \rightleftharpoons b
\]

(4-42)

where

\[
a = \text{concentration of freely diffusible solute per unit volume of plasma}
\]

\[
b = \text{concentration of protein-bound solute per unit volume of plasma}
\]
Consider the simultaneous steady-state diffusion of unbound solute and of the protein-solute complex

\[ J_a = -D_a \frac{\psi^o}{1-\phi_p} \frac{da}{dx} \]  \hspace{1cm} (4-43)  
\[ J_b = -D_b \frac{db}{dx} \]  \hspace{1cm} (4-44)

where \( \phi_p \) is the volume fraction proteins and \( \psi^o/(1-\phi_p) \) accounts for the decrease in the apparent diffusivity of free solute caused by the impermeable proteins, and

\[ \psi^o = f(\phi_p, \text{shape of proteins}) \]  \hspace{1cm} (4-45)

The total flux of bound and unbound solute in the \( x \) direction is

\[ J = J_a + J_b = -D_a \frac{\psi^o}{1-\phi_D} \frac{da}{dx} - D_b \frac{db}{dx} \]  \hspace{1cm} (4-46)  
\[ = -\left(D_a \frac{\psi^o}{1-\phi_D} + D_b \frac{\partial b}{\partial a}\right) \frac{da}{dx} \]  \hspace{1cm} (4-47)

As pointed out in Section 4.A.2, Protein Binding of Solutes, the binding isotherm may in general be nonlinear. However, assuming that one is operating on the linear portion of the curve, and that the bound and free solute are at equilibrium, then

\[ \frac{\partial b}{\partial a} = \frac{b}{a} = \frac{k_p}{1-\phi_D} \]  \hspace{1cm} (4-48)

Furthermore, the total concentration of solute, \( c \), is simply the sum of bound and unbound concentrations, i.e.,

\[ c = a + b = \left(1 + \frac{k_p}{1-\phi_D}\right)a \]  \hspace{1cm} (4-49)
Consequently,

\[ J = -\left( D_a \frac{\psi^o}{1 - \phi_p} + D_b \frac{k_p}{1 - \phi_p} \right) \frac{da}{dx} \quad (4-50) \]

\[ = -\left[ \frac{D_a}{1 + \frac{k_p}{1 - \phi_p}} \frac{\psi^o}{1 - \phi_p} + \frac{D_b}{1 + \frac{k_p}{1 - \phi_p}} \frac{k_p}{1 - \phi_p} \right] \frac{dc}{dx} \quad (4-51) \]

\[ = -\left[ D_a \frac{\psi^o}{1 - \phi_p} + \frac{D_b}{1 + \frac{k_p}{1 - \phi_p}} \frac{k_p}{1 - \phi_p} \right] \frac{dc}{dx} \quad (4-52) \]

\[ = - D_a \Theta_p \frac{dc}{dx} \quad (4-53) \]

\[ = - D_p \frac{\partial c}{\partial x} \quad (4-54) \]

The function \( \Theta_p \) is consequently the ratio of the apparent diffusion coefficient of solute in plasma to that in plasma with the proteins removed (essentially water). This set of equations is analogous to those derived by Olander \((305)\) for simultaneous mass transfer and equilibrium chemical reaction.

For the unsteady-state case,

\[ \frac{\partial a}{\partial t} = - D_A \frac{\psi^o}{1 - \phi_p} \frac{\partial^2 a}{\partial x^2} \quad (4-55) \]

\[ \frac{\partial b}{\partial t} = - D_B \frac{\partial^2 b}{\partial x^2} \quad (4-56) \]

Adding the equations for the two species and using eqn.\((4-48)\) yields

\[ \left( 1 + \frac{k_p}{1 - \phi_p} \right) \frac{\partial a}{\partial t} = - \left( D_A \frac{\psi^o}{1 - \phi_p} - D_B \frac{k_p}{1 - \phi_p} \right) \frac{\partial^2 a}{\partial x^2} \quad (4-57) \]
\[
\frac{3a}{at} = -D_p \frac{3a}{ax^2}
\]  

(4-58)

Substitution for \( a \) in terms of \( c \) does not change the expression for \( D_p \). For a steady-state experiment, however, comparison of eqns. (4-50) and (4-51) shows that the measured diffusivity in a steady-state experiment will depend upon the particular concentration driving force employed. Furthermore, if the concentration driving force in eqn. (4-52) were replaced by that of the freely-diffusible solute, based on protein-free plasma, then the denominator in brackets would vanish, since this quantity is simply the ratio of the total concentration in plasma to the free solute in protein-free plasma.

The selection of a theoretical model for \( \psi^o \) is somewhat arbitrary. In this work, the model of Wang (431) will be used. He developed a theory to treat quantitatively the self-diffusion of water in protein solutions. He expressed the obstruction factor as

\[
\psi^o = 1 - \bar{\alpha} \phi_p
\]  

(4-59)

and tabulated \( \bar{\alpha} \) for various values of the axial ratio for prolate and oblate ellipsoids of revolution. For spheres, \( \bar{\alpha} = 1.5 \) and for prolate ellipsoids with infinite axial ratio, \( \bar{\alpha} = 1.667 \). Consequently, \( \bar{\alpha} \) is relatively insensitive to the axial ratio used. Wang worked with solutions of a single protein, albumin. It is assumed here that for a mixture of various proteins, \( \psi^o \) may be calculated from

\[
\psi^o = 1 - \sum \bar{\alpha}_i \phi_{p_i}
\]  

(4-60)
where the summation is taken over all proteins present. An alternate expression would be

\[
\psi^o = \prod_{i=1}^{n} (1 - \alpha_i \phi_{pi})
\]  

(4-61)

There is no available analysis or data in the literature to choose between the two formulations. Fortunately, since \(\psi^o\) does not differ greatly from unity for plasma, eqns. (4-60) and (4-61) give close to the same numerical result.

Wang pointed out that the effective volume fraction which obstructs solute diffusion must include the water of hydration. Thus,

\[
\phi_{pi} = C_{pi} (\bar{V}_{pi} + H_i/d_0)
\]  

(4-62)

where

- \(C_p\) = gm anhydrous protein per cc of solution
- \(\bar{V}_p\) = apparent specific volume of anhydrous protein in aqueous solution
- \(H\) = hydration, gm bound water per gm anhydrous protein
- \(d_0\) = density of bound water (assumed that of pure water)

Wang's model was selected because of its simplicity of calculation and because it has been verified experimentally for protein solutions (432) and for dilute solutions of synthetic polymers (34). It has also been suggested as a model for diffusion in gels (238). The calculation of \(\psi^o\) is limited to dilute solutions. For this case, other equally valid and more accurate models could have been chosen. However, comparison of eqn. (4-59) with the model of Fricke, to be discussed in the next section, shows that for impermeable
spheres with a volume fraction of 0.08, the two models differ by only 0.6% in the estimate of \( \psi \).

Several investigators have used the Stokes-Einstein equation to estimate the diffusivity of oxygen in plasma from that in water by correcting for the viscosity difference (57, 132). Buckles (57) found that this estimate fit his data. However, both Wang, et al. (432) and Biancheria and Kages (34) found that the Stokes-Einstein equation overestimated the reduction in diffusivity and that the data were fitted better with Wang’s model (431).

3. **Diffusion in Whole Blood**

The proposed model for diffusion in blood treats both phases, plasma and erythrocytes, as being homogeneous. Diffusion in pure plasma is characterized by a single diffusion coefficient, \( D_p \), and diffusion in the red cell by \( D_{RC} \). Assuming that the concentrations in plasma and red cells, \( C_p \) and \( C_{RC} \), respectively, are in equilibrium, then

\[
K_{eq} = \frac{C_{RC}}{C_p} \tag{4-63}
\]

\[
C_{WB} = (1-\phi) C_p + \phi C_{RC} \tag{4-64}
\]

\[
= (1-\phi + \phi K_{eq}) C_p = K_{WB/p} C_p \tag{4-65}
\]

where \( K_{WB/p} \) = solute equilibrium distribution coefficient between blood and plasma

\( C_{WB} \) = concentration in whole blood

\( \phi \) = red cell volume fraction
Steady-state and transient diffusion is described by

\[ J = -D_{WB} \frac{dC_{WB}}{dx} \]  

(4-66)

\[ \frac{\partial C_{WB}}{\partial t} = D_{WB} \frac{\partial^2 C_{WB}}{\partial x^2} \]  

(4-67)

where

\[ \frac{P_{WB}}{P_p} = \frac{D_{WB}K_{WB/p}}{D_p} = \psi = f(\phi, \text{shape, } \frac{K_{eqD_{RC}}}{D_p}) \]  

(4-68)

This expression is valid when the effective diffusion coefficients are related to their respective fluxes by the total concentration in the media.

The complete model may thus be expressed as

\[ D_{WB} = D_{H_2O} \left( \frac{D_p}{D_{H_2O}} \right) \left( \frac{D_{WB}}{D_p} \right) \]  

(4-69)

\[ = D_{H_2O} \Theta_p \frac{\psi}{K_{WB/p}} \]  

(4-70)

The reductions in diffusion coefficient caused by the presence of the proteins and the red cells are treated as being independent. There are no previous treatments in the literature from which to verify this assumption. The problem is analogous to the question previously raised regarding the generalization of Wang's model for the presence of different kinds of proteins. However, if either \( \Theta_p \) or \( \psi \) is not greatly different from unity, the assumption is probably reasonable.
The mathematical treatment of the electric conductivity of a suspension of homogeneous spheroids derived by Fricke (132, 134a, 135) was used for the estimation of \( \psi \). Other models have been derived for a similar system (174, 175, 312). Fricke's model was selected because 1) it has been partially verified experimentally, for the case where the suspended phase is impermeable (132, 133, 134a); 2) it was originally applied to electrical conduction in blood; and 3) it has been utilized by others (55, 303) for the estimation of oxygen diffusivity in blood. It is clear, however, that the use of this model for comparison with the data is arbitrary; and, furthermore, the application of the model to systems where the permeability ratio of the two phases is not very small has never been tested.

Fricke's solution may be expressed in the following terms:

\[
\psi = \frac{1 + x \phi F(z,x)}{1 - \phi F(z,x)} \quad (4-71)
\]

where

\[
F(z,x) = \frac{z-1}{z+x} \quad (4-72)
\]

\[
x = -\left[\frac{z - 1 - \beta}{z - 1 - \beta}\right] \quad (4-73)
\]

\[
\beta = \frac{1}{3} \left[\frac{2}{1 + \frac{1}{z} M(z-1)} + \frac{1}{1 + (1-M)(z-1)}\right] (z-1) \quad (4-74)
\]

\[
z = \frac{P_{RC}}{P_p} = \frac{K_{eq}D_{RC}}{D_p} \quad (4-75)
\]
The quantity $M$ depends upon shape and axial ratio, $a/b$, of the disperse phase.

\[ M = \left( \frac{\gamma - \frac{1}{2} \sin 2\gamma}{\sin^3 \gamma} \right) \cos \gamma \]  

(4-76)

where

\[ \cos \gamma = \frac{a}{b} \]  

(4-77)

For oblate spheroids ($a < b$)

\[ M = \frac{1}{\sin^2 \gamma'} - \frac{1}{2} \left[ \frac{\cos^2 \gamma'}{\sin^3 \gamma'} \log \left( 1 + \sin \gamma' \right) \right] \]  

(4-78)

where

\[ \cos \gamma' = \frac{b}{a} \]  

(4-79)

For spheres, $x = 2$, and eqn.(4-71) reduces to Maxwell's original formula. Consequently, Fricke's analysis is subject to the same limitations and is strictly valid only at high dilution. In this respect, Higuchi's treatment (174,175) which attempts to account for particle-particle interactions, might be superior. For an impermeable disperse phase, $z = 0$, and eqn.(4-71) becomes

\[ \psi = \frac{1 - \phi}{1 - \phi - \beta \phi} \]  

(4-80)

This is analogous to Wang's expression, eqn.(4-59), with $\beta \equiv \bar{a}$. For low values of $\phi$, they are virtually identical.

Since the red cell is a biconcave disc, it can be best approximated, in terms of a spheroid, as an oblate ellipsoid. Values of $x$ and $l (z,x)$ for use in eqn.(4-71) are plotted
for an oblate ellipsoid in Figs. 4-4 and 4-5 as a function of $Z$ for various values of $b/a$. Fricke empirically found that conductivity data for canine blood was best fitted by an axial ratio of 4.25 for an oblate spheroid. In the absence of any experimental data on human blood, this was taken as an estimate for human erythrocytes.

An alternative formulation of the problem is to consider the dispersed phase to be composed of a permeable interior with a surface resistance. This situation has been discussed by Fricke and Curtis (133), Cole (90), and Higuchi and Higuchi (175). However, no advance has been made beyond the initial formulation of Maxwell (272) who derived an equation for the effective permeability for a coated sphere. This value is then used in one of the previously discussed models for a heterogeneous mixture of two homogeneous phases.

Maxwell's equation is given by Higuchi and Higuchi as

$$ P_B = \left[ \frac{(2P_0 + P_1)(r + t)^3 - 2(P_0 - P_1) r^3}{(2P_0 + P_1)(r + t)^3 - (P_0 - P_1) r^3} \right] P_0 $$

(4-81)

where $P_B$ = effective permeability of coated sphere

$P_0$ = permeability of outside coating

$P_1$ = permeability of interior sphere

$r$ = radius of interior sphere

$t$ = thickness of outside coating

The permeabilities are defined as a diffusivity times a distribution coefficient referred to an external reference phase.
Figure 4-4. X as a function of Z for various values of b/a (oblate ellipsoid)
Figure 4-5. $F(Z,X)$ as a function of $Z$ for various values of $b/a$ (oblate ellipsoid)
For red cells, $t \ll r$, and thus,

$$(r + t)^3 = r^3 + 3r^2 t$$  \hspace{1cm} (4-82)$$

In addition, $P_0 \ll P_1$. For this case, eqn.(4-81) reduces to

$$P_B = \frac{rP_0}{t}$$  \hspace{1cm} (4-83)$$

This expression is essentially identical to the formulation used above, and no improvement in the model is gained.

This can be shown as follows. $P_0/t$ is identical to the measured red cell permeability defined by eqn.(4-7), assuming all resistance to be localized in the membrane, with the reference phase taken to be the adjacent fluids (plasma). The characteristic length for the dispersed phase is $r$, and the product of the red cell permeability and its characteristic length is the effective diffusivity in the red cell.

The present treatment considers plasma as a homogeneous phase and does not differentiate between protein-bound and freely diffusible solutes, except insofar as this is included in $\theta_P$. This limitation would be important for solutes where the ratio $K_{eq} D_{RC}/D_P$ was not much less than unity. A second assumption is that all solute is freely and homogeneously distributed within the erythrocyte. While this is clearly an oversimplification, the amount of hemoglobin binding of most organic solutes is relatively small. A possible exception to this might be certain of the amino acids, as discussed in Section 4.A.3. The assumption is not true, however, for oxygen. Most of the oxygen carried in blood is reversibly chemically bound to hemoglobin. It is not clear whether the
total amount of erythrocyte oxygen, or just that fraction which is physically dissolved, should be used in calculating $K_{eq}$ for the determination of $\psi$. In addition, it has been shown that the diffusion of oxyhemoglobin significantly enhances oxygen transport in free hemoglobin solutions ($^{2620}$).

The operation of this mechanism within the erythrocyte is uncertain, particularly since the hemoglobin may be restrained from movement. If it does occur, then the model must be modified to account for this effect, e.g., an additional term would be added for the flux in phase B in the parallel model discussed in Appendix F.

The model also assumes equilibrium between erythrocytes and plasma. To test this, the equilibrium criterion developed in Appendix F was calculated for urea, creatinine, and uric acid, using parameters tabulated in Tables 4-5 and 4-10. The results are shown in Table 4-11. The nomenclature is that of Appendix F. Plasma diffusion coefficients used are those which were experimentally measured (see Section 4.D.2). The maximum value of $D_B/D_A$ was used for urea; for the other compounds, it is effectively zero. The quantity $k_b$ is equivalent to the red cell permeability defined earlier.

Of characteristic lengths (in this case, the half-width of a slab) down to the order of 0.01 cm, urea is in equilibrium between erythrocyte and plasma. Creatinine and uric acid, however, require lengths of the order of 0.5 cm before they can be considered to be in equilibrium between the two phases.
### TABLE 4-11

**Equilibrium Deviations for Diffusion in Blood**

<table>
<thead>
<tr>
<th>Solute</th>
<th>$K_{eq}$ cm$^2$/sec$\times 10^5$</th>
<th>$D_A$/$D_A$</th>
<th>$\psi$</th>
<th>$\psi_A^*$</th>
<th>$k_b^s_{DA}$/$\psi_A^*\times 10^5$</th>
<th>$(\pi^2/4)L^2_{K_1+K_2}$ cm$^2$$\times 10^5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td></td>
<td>1.46</td>
<td>0.054</td>
<td>0.485</td>
<td>0.465</td>
<td>12.1</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.73</td>
<td>0.87</td>
<td>-0</td>
<td>0.435</td>
<td>0.435</td>
<td>0.0032</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>0.54</td>
<td>0.75</td>
<td>-0</td>
<td>0.435</td>
<td>0.435</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

\[
\frac{\pi^2}{4} \frac{L}{K_1 + K_2}
\]

<table>
<thead>
<tr>
<th>Solute</th>
<th>$L$(cm)</th>
<th>1</th>
<th>0.5</th>
<th>0.2</th>
<th>0.1</th>
<th>0.05</th>
<th>0.02</th>
<th>0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td></td>
<td>1.3x10^{-6}</td>
<td>5.2x10^{-6}</td>
<td>3.3x10^{-5}</td>
<td>1.3x10^{-4}</td>
<td>5.2x10^{-4}</td>
<td>3.3x10^{-3}</td>
<td>1.3x10^{-2}</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td>0.0051</td>
<td>0.02</td>
<td>0.13</td>
<td>0.51</td>
<td>2.0</td>
<td>13</td>
<td>51</td>
</tr>
<tr>
<td>Uric Acid</td>
<td></td>
<td>0.0088</td>
<td>0.035</td>
<td>0.22</td>
<td>0.88</td>
<td>3.5</td>
<td>22</td>
<td>87.5</td>
</tr>
</tbody>
</table>

a. Calculated for $\phi = 0.40$, $T + 37^\circ C$
D. Experimental Methods

1. Selection of Experimental Method

The multitude of techniques which can be used to estimate the diffusion coefficient have been reviewed by Tuwiner (423) and Johnson and Babb (193). The most precise techniques in use today appear to be those utilizing optical methods, particularly interferometry, for continuously analyzing the changes of concentration with distance and time in a cell. The opacity of whole blood to transmitted light eliminates such techniques from consideration. Another popular method which combines reasonable experimental simplicity with accuracy is the diaphragm-cell technique, utilizing a device similar to the batch dialyzer with a calibrated porous diaphragm replacing the membrane. This technique requires stirring of the fluid adjacent to the diaphragm. Blood would thus be limited to placement within the diaphragm, since its presence in the adjacent fluid would lead to hemolysis and possible plugging of the pores by the liberated hemoglobin. Furthermore, the state of the blood inside the diaphragm could not be observed, and if the pores were not very much larger than red cell dimensions, the measured diffusion coefficient might depend upon pore size and geometry.

Among the remaining methods, the capillary cell technique was selected. It is one of the simplest and oldest procedures employed, and involves diffusion from a capillary tube into a much larger volume of solvent or solution of different concentration. Although this method was for a time in disfavor
compared to other methods, its use has been revived in the past twenty years for measurement of the self-diffusion coefficient, particularly with radioactive materials (12, 241, 289, 413, 429, 430).

For diffusion measurements in stagnant blood with radioactive tracer solutes, the capillary cell method has the following advantages:

1) It requires only small amounts of sample and radioactive solute, providing both economic and experimental incentives.

2) It permits a simultaneous run of many samples under identical conditions.

3) The mathematical analysis of data is simple and straightforward.

4) There exists the possibility of an "in situ" experiment, similar to the technique of Lipps (249) requiring no sampling.

In principle, capillaries of uniform diameter, sealed at the bottom, are filled with a solution of known concentration. Since the volume in the capillary is small compared to that in the vessel, the concentration in the latter may safely be assumed to remain constant throughout the experiment. At the end of an experiment, the diffusion coefficient can be determined by measuring either the concentration gradient in the capillary or the total amount of material passing into or out of the capillary.
The most difficult experimental problem in measuring diffusion coefficients in stagnant blood is the settling of the red cells. Based on the factors discussed in Section 4.A.1, Physical and Chemical Properties, attempts were made to overcome this difficulty with the following techniques:

1) Small diameter capillaries were employed, about one mm in diameter. This is sufficiently small so that network bridging effects might slow or totally eliminate sedimentation.

2) The effect of red cells alone was investigated with red cells in saline. In saline the erythrocytes do not agglomerate, and it was thought that the single cell settling rate in saline might be slow enough to be neglected.

3) Serum, instead of plasma, was used with the erythrocytes. It was expected that the removal of fibrinogen would greatly decrease sedimentation rate.

2. Apparatus and Procedure

Two methods were tried. The first utilized scintillation plastic in which capillaries were bored, similar to the technique used by Lipps (24S). When this technique proved unworkable, glass capillaries were employed.

a. Scintillation Plastic Diffusion Cells

Capillary diffusion cells were fabricated from a transparent plastic scintillator material (Pilot Scintillator B, Pilot Chem. Co., Waltham, Mass.). A schematic diagram is shown in Fig. 4-6a. Five vertical capillaries, each two cm long, were precision-drilled into the lower scintillator
b. Glass Capillaries

Lucite top view

a. Scintillation Plastic Cells

Figure 4-6. Schematic Diagram of Diffusion Cells
section. The capillaries were symmetrically located 3/8 in. from the cell axis. The top and bottom of the scintillator were coated with light reflecting paint, and a cylindrical lucite reservoir was epoxied to the upper surface of the scintillator plastic. The outside of cylindrical surface and overall length of the cell were machined to match the dimensions of a liquid scintillation counting vial, so that the diffusion cell fit snugly into the counting well of the Packard scintillation spectrometer.

At the start of a diffusion run, the capillaries were filled to the top with a radioactive tracer solution and the initial counting rate determined. The upper reservoir was then slowly filled with solution containing no tracer and the reservoir covered with a paraffin film. The original procedure planned for these experiments was that the cells would be placed in the scintillation counter for the entire run so that a continuous count rate measurement could be made. The counter refrigerator would be shut off and the cells maintained at room temperature. However, because of the number of other individuals using the spectrometer, and the long time required for the background counts to reach steady state after a change in temperature, this method proved impractical. Instead, the diffusion cell was placed in a constant temperature both during a run and then transferred to the counter at the end.

Lipps (242) appears to be the first to use this type of technique, although in situ counting using plastic scintilla-
tors has been described in the literature (286). The method offers the following advantages:

1) No sample transfer is required.

2) Each cell could be calibrated with solutes of known diffusivity to determine accurately an effective length.

3) Concentration analysis is simple. Furthermore, since the phosphors in the scintillator are only affected by radioactive material immediately adjacent to the surface (due to self-absorption of beta rays in the bulk of the fluid), the analysis would be unaffected by the nature of the fluid studied.

One run was made with urea in water at room temperature (≈26-27°C) yielding a diffusivity of $1.45 \times 10^{-5}$ cm²/sec, compared to a literature value of $1.38 \times 10^{-5}$ at 25°C (254). While the agreement is excellent, it may have been fortuitous since several problems arose with the cells.

First, the diffusion cell required a finite period of time to thermally equilibrate in the counter, during which time diffusion occurred at a decreasing rate, making the effective run time indefinite. Secondly, and more serious, significant adsorption of solute occurred on the capillary walls, causing excessively high background count rates after the capillary was emptied. Allowing the radioactive solution to evaporate before rinsing caused relatively irreversible adsorption. Abrasion of the walls with a fine wire and rinsing with a variety of organic solvents, acids, and a soap solution removed the solute slowly, but as much as a week was required for enough desorption to bring background rates down to normal. Using
plasma or blood in the capillaries decreased the magnitude of the effect, probably because of preferential protein adsorption on to the walls. As a result of the problem with aqueous solutions, the plastic scintillator cells were abandoned in favor of the glass capillaries described below. A technique which might have been tried with the aqueous solutions would have been to add a high concentration of unlabeled solute to the tracer solution to minimize the fraction of radioactive solute adsorbed. This method worked well with high molecular weight solutes in the batch dialyzer.

b. Glass Capillaries

Glass capillary diffusion cells were constructed from disposable glass micro-pipettes (Drummond "Microcaps"). The tubes were 11.54 cm long, about 1.05 mm in diameter, and were calibrated by the manufacturer to contain 0.1 ml (±1%). Two methods were used to fabricate capillaries of the desired length. Initially, the capillaries were broken into about 3 cm lengths. The broken end was dipped into melted paraffin wax, after which a straight piece of wire, from a bent paper clip of approximately the same diameter as the capillary inside diameter, was inserted about two cm into the capillary. The tube was inverted and heated above a hot plate; the wax was allowed to flow down the capillary until it contacted the cooler metal wire, whereupon it solidified. The closed end of the capillary was then inserted into a cork. The length of the open capillary was measured
with a rule calibrated in 64ths of an inch.

Most of the early runs were conducted with the wax-filled capillaries. However, after repeated usage at 37°C, some flow of the wax occurred, requiring remeasurement of the lengths before and after each run. To circumvent this problem, a second set of capillaries was fabricated. The entire tube was embedded in beeswax, one end of the capillary was epoxied to a piece of parafilm which in turn was epoxied to a cork. A schematic diagram of the glass capillaries is shown in Fig. 4-6b.

c. Transfer, Standardization, and Analysis of Samples

At the beginning of a run, the capillaries were filled with the solution to be studied containing the required amount of radioactively-labeled solute. Filling was accomplished with a 100 µl Hamilton gas-type syringe. Specially-designed flat-bottom 27-gauge hypodermic needles were used so that filling could be started at the bottom of the capillary, eliminating the problem of residual air bubbles within the capillary. Solution transfer was made very slowly to prevent degradation of macromolecular substances or red cells caused by high shear rates in the syringe needle.

Each capillary was immersed slowly into a glass vial containing about 20 ml isotonic saline. The vial was inverted, with the open end of the capillary up, and placed vertically in a holder at the bottom of a mildly agitated
constant temperature bath. At the end of a run, the capillarys were removed slowly from the vials and the contents removed with the microliter syringe. The syringe was initially filled with 50 µl of distilled water in order to flush all of the capillary solution out of the syringe needle. One or two more rinsings of the glass capillary were made with 50 µl water. The original and rinsing solutions were added directly to a liquid scintillation counting vial. Sample preparation and counting techniques are discussed in detail in Appendix D.

The primary experimental problems encountered were 1) obtaining an accurate estimate of the labeled solute present in the capillary at the start of a run, and 2) ensuring a quantitative transfer of remaining labeled solute from the capillary to the counting vial at the end of a run.

With reference to the first problem, standardizations of the initial solution were made by three methods:

1) Filling and immediately emptying the capillaries.

2) Using a microliter syringe for measuring out a known amount of the original solution.

3) Filling and emptying a 20 µl and 100 µl micropipette, followed by a rinse with water and then liquid scintillation solution. The third method with a 100 µl capillary proved to be the simplest and most accurate. The amount of solute initially present was calculated from the ratio of the capillary length to the micro-pipette length.
Repeated measurements of counting rate obtained by filling and emptying capillaries indicated a reproducibility of about 1%, implying a reasonably accurate quantitative transfer of solute. Of course, the possibility of a reproducible systematic error still existed, such as retention of adsorbed solute within the syringe or on the capillary walls. This could be checked further only by comparison of measured diffusivities with literature values.

An improved transfer technique was developed for the last few runs, and is discussed as a matter of record. The syringe was never filled with radioactive material. Instead, the syringe was filled entirely with distilled water and inserted into the capillary which was held horizontally with the open end over the mouth of the scintillation vial. The syringe contents were expelled, simultaneously flushing out the capillary tube. The procedure was repeated with water and/or scintillation solution. Besides increased speed and efficiency, this technique prevented the increased adsorption of solute onto the capillary walls, associated with evaporation of the solvent, because the capillary was always filled with liquid until after the final rinse.

d. **Preparation of Samples**

Diffusion experiments were performed with various radioactive solutes in isotonic saline, serum, plasma, and red blood cell suspensions in isotonic saline and serum. In each case, small aliquots of radioactive
stock solution (see Appendix D. Supplementary Details of Experimental Methods) were added to the solution of interest in order to yield an initial counting rate of about 10,000-20,000 cpm for the contents of each capillary.

The samples of serum, plasma, and blood used in this study were obtained from 0+ male donors in good health at the blood bank of the Massachusetts General Hospital, Boston. The blood was drawn by venipuncture and 450 ml of blood was collected into 67.5 ml of ACD solution by routine blood bank procedure. Standard vinyl bags (Fenwall, Code No. JA-5) were used. Blood was stored at 4°C and was used within two weeks of withdrawal. Serum and plasma, in 200 ml vinyl bags, were prepared from whole blood by blood bank personnel.

The following procedure was used in preparing the various red cell suspensions:

1) Whole blood was centrifuged for fifteen minutes at 6,000 rpm (4000 g) in a refrigerated centrifuge (Servall, model RC-2) held at 15°C.

2) Most of the plasma was removed by decantation. The remaining plasma layer and buffy coat was removed with a syringe having a large bore needle.

3) A volume of final suspending medium equal to the volume of the red cell pack was added to the centrifuge tube, the cells resuspended, and steps (1) and (2) repeated.

4) A suspension of the desired hematocrit was prepared by combining the required amount of final suspending
medium with a given volume of washed red cells.

Hematocrit was determined by filling heparinized
glass capillary tubes ("Red Tip," Biological Research,
St. Louis), 75 cm long and 1.2 mm in diameter, with blood
solution, sealing the bottom with a white vinyl clay com-
pound (Critoseal, Biological Research), and centrifuging
at 17,000 g for five minutes in a micro-capillary centri-
fuge (International Equipment Co., Boston, Model MB).
Hematocrit was calculated as the percentage ratio of the red
cell pack length to the total sample length. Usually,
three capillaries were used for each measurement, and the
range of measured values was always within 0.3 hematocrit
units.

3. Analysis of Data

Assuming that the diffusion coefficient is inde-
pendent of concentration and the capillary radius is suffi-
ciently small compared to the capillary length that only
one dimensional diffusion occurs, Fick's second law for this
system is

\[
\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}
\]  

(4-84)

Initially, the capillary is filled with a uniform concen-
tration of tracer solute. At the sealed end of the capil-
ulary, no flux occurs, i.e., an "insulated" boundary, while
at the open end of the capillary, the tracer concentration
is assumed to be zero throughout the run. Consequently,
the initial and boundary conditions are
\[ t = 0 \quad \text{all} \quad x \quad C = C_0 \quad (4-85) \]
\[ t > 0 \quad x = 0 \quad \frac{\partial C}{\partial x} = 0 \quad (4-86) \]
\[ x = L \quad C = 0 \quad (4-87) \]

The solution of eqn. (4-84) with initial and boundary conditions (4-85) to (4-86) for the average concentration within the capillary as a function of time is (90):

\[ \frac{C}{C_0} = \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp \left[ -\frac{(2n+1)^2 \pi^2 D t}{4L^2} \right] \quad (4-88) \]

The derivation of this solution is a simpler analogue to that given for a two-phase material in Appendix F.

This mathematical model of diffusion in a capillary represents an idealization which deviates from the real physical situation. In reality, at the open end of the capillary (x=L) at any time (t>0), the concentration differs from zero because the solute diffuses at a finite rate into the liquid surrounding the mouth of the capillary and is not removed therefrom at an infinite rate. As a result, the rate of diffusion is slower than if boundary condition (4-87) were actually met. This effect is equivalent to a correction to the length of the capillary, \( L' = L + \Delta L \), where \( L' \) is the effective capillary length.

Various workers (241, 288, 413, 429, 430) have investigated this effect experimentally with solutes of known diffusion coefficient. Estimates of \( \Delta L/L \) obtained have generally been about 1-2%. Some researchers have chosen
to stir the outside bath. This requires empirical evaluation of the correct stirring rate for which $\Delta L = 0$. There is the danger, when stirring, that convective currents may enter the mouth of the capillary, thus enhancing the diffusion rate.

Gergely, et al. (139) presented an approximate mathematical analysis of the problem. They assumed that the process of diffusion outside the capillary tube could be approximated by a model of diffusion from a point source into a hemisphere. The two simultaneous processes (diffusion inside the tube and diffusion from a point source outside the tube) were coupled by a flux boundary condition. A further approximation made was that the concentration was a linear function of radius in the fluid region above the capillary circumscribed by the capillary radius. The model was presented in terms of an integral equation, and numerical solutions were obtained for a length of four cm. The results showed that the deviation between the true diffusivity and the measured value increased with increasing tube radius and decreased with increasing values of $Dt/L^2$. For $L = 4$ cm and $Dt = 1.0$, the relative deviation for a tube of 0.5 mm radius was about 3.5%.

In view of the relatively small error caused by using boundary condition (4-87) as compared to accuracy limitations of the experimental procedure (see next section), no correction was employed in the use of eqn. (4-88). The solution presented by Gergely, et al. could be evaluated
for the length used in this study. However, it is unwarranted because of the small magnitude of the effect and the complexity of the calculation.

Values of $C/C_0$ were evaluated from eqn. (4-88) for increments in $Dt/L^2$ of 0.001, starting at 0.0. The ratio of the total disintegrations per minute in the capillary at the end of a run to that at the beginning was taken as $C/C_0$. From the known run time and capillary length, the diffusivity could then be evaluated from these values.

4. Error Analysis

The error in the measured diffusivity is attributable to two causes: 1) systematic errors in technique or analyses, and 2) random errors of precision in measuring the experimental variables. The presence of the former can be checked only by experiments with solutes of known diffusivity. The latter is amenable to analysis using a propagation of errors treatment (287).

For simplicity, let us consider the case where only the first term in eqn. (4-88) is significant. For example, for $C/C_0$ correct to 1%, using only one term it is required that $Dt/L^2 > 0.122$. Under these conditions

$$C^* = \frac{C}{C_0} = \frac{8}{\pi^2} e^{-\left(\frac{\pi^2 Dt}{4L^2}\right)}$$

or

$$D = \frac{4L^2}{t\pi^2} \frac{1}{\ln \frac{8}{\pi^2}}$$

(4-89)
where \( C^* \) denotes the dimensionless concentration which varies from one initially to zero at infinite time. From a propagation of error analysis, one finds

\[
\left( \frac{\sigma_D}{D} \right)^2 = \left( \frac{\sigma_t}{t} \right)^2 + \left( \frac{2\sigma_L}{L} \right)^2 + \left( \frac{1}{\ln C^*} \frac{\sigma_{C^*}}{C^*} \right)^2
\]  \tag{4-91}

where

\[
\left( \frac{\sigma_{C^*}}{C^*} \right)^2 = \left( \frac{\sigma_C}{C} \right)^2 + \left( \frac{\sigma_{C_0}}{C_0} \right)^2
\]  \tag{4-92}

The general quantity \( \sigma_A \) refers to the standard deviation or standard error of the measured variable, \( A \), and \( \sigma_A/A \) refers to the fractional error in the measurement of \( A \). The quantity \( \sigma_D/D \) is the estimated fractional standard deviation expected for many measurements of \( D \), or the fractional standard error for a single measurement of diffusivity (see Appendix K).

The following estimates of the fractional errors were made:

\[
\frac{\sigma_t}{t} \sim 0.02 \quad (\sim 15 \text{ min in 12 hr}) \tag{4-93}
\]

\[
\frac{\sigma_L}{L} \sim 0.02 \quad (\sim 1/64 \text{ in. in 2 cm}) \tag{4-94}
\]

These estimates are probably on the high side. Generally, three measurements were made of \( C_0 \), but only one estimate of \( C \) could be made from the contents of each capillary.
Consequently,

\[
\frac{\sigma_c}{C} \sim 2 \frac{\sigma_{C_0}}{C_0}
\]

(4-95)

and

\[
\left( \frac{\sigma^{*}}{C^{*}} \right)^2 \sim 5 \left( \frac{\sigma_{C_0}}{C_0} \right)^2
\]

(4-96)

Substituting these values into eqn. (4-91) yields

\[
\left( \frac{\sigma_{D}}{D} \right)^2 = 0.002 + 5 \left( \frac{1}{1.1 C^*} \right)^2 \left( \frac{\sigma_{C_0}}{C_0} \right)^2
\]

(4-97)

Numerical estimates of \( \sigma_{D}/D \) were made for various values of \( \sigma_{C_0}/C_0 \) as a function of \( C^* \). The results are shown in Fig. 4-7. On the upper abscissa, values of \( D_t/L^2 \) corresponding to the values of \( C/C_0 \) are plotted. At long times, where \( C/C_0 \to 0 \), the error approaches about 4.5%. At short times, where \( C/C_0 \to 1 \), the error associated with the concentration measurement dominates and the measured diffusivity becomes highly inaccurate because of the logarithmic dependence on concentration.

Most of the diffusion runs were carried out within the range \( 0.45 < C/C_0 < 0.7 \). The runs with high molecular weight compounds were usually around 0.6 to 0.7. Furthermore, the estimated values for \( \sigma_{C_0}/C_0 \) obtained from repeated measurements, are
Figure 4-7. Error Analysis for Capillary Diffusion Measurements. Estimated standard error in measured diffusivity as a function of dimensionless concentration and error in concentration measurement.
\[
\frac{\sigma_{C_0}}{C_0} \sim 0.01 \text{ to } 0.015 \text{ (water)}
\]

\[
\sim 0.015 \text{ to } 0.02 \text{ (plasma)}
\]

\[
\sim 0.02 \text{ to } 0.03 \text{ (blood)}
\]

Consequently, the estimated errors associated with a single diffusion coefficient measurement are as follows: water (5-10%), plasma (6-14%), blood (10-20%). The specific value for any particular run is dependent upon the dimensionless concentration attained.

E. Results and Discussion

All data presented in this section were obtained in conjunction with Reece (340) Reece's raw data were recalculated and a statistical analysis (discussed below) was used to eliminate data points which were suspect. Consequently, the diffusivities reported here may differ somewhat from those reported in Reece's thesis.

Diffusion measurements were made at 37 ±0.5°C, with the exception of the first few runs, where ±2°C variation occurred, although the temperature was held constant throughout any particular run. Where necessary, the measured diffusion coefficient was corrected to 37°C using the Stokes-Einstein relationship

\[
\frac{D_u}{T} = \text{constant} \quad (4-98)
\]

For any solute-solvent combination, eight to ten
capillaries were usually used for each run, thus providing a statistically meaningful sample. The diffusivities calculated for each run were often spread over a relatively wide range; a bunching of the majority of the diffusivities around one value with several significantly higher values was the most common occurrence. The procedure used in analyzing the data was as follows: The mean and standard deviation of all data was calculated. Any data more than 1.5 standard deviations away from the mean was eliminated and a new mean and standard deviation calculated. This usually meant dropping out the two or three highest values.

Several initial runs with urea in saline, for which the diffusion coefficient is known, showed that the highest measured values were incorrect and that the above procedure correctly eliminated spurious measurements. The appearance of such high values is consistent with the occasional occurrence of a systematic error in transferring solute from the capillary to the scintillation vial at the end of a run. If all the labeled solute were not transferred, the calculated dimensionless concentration would be lower than it should be, giving an incorrectly high diffusion coefficient.

1. Diffusion in Saline

Measurements of the diffusion coefficient in isotonic saline were made at 37°C with all solutes used in the membrane permeation studies: urea, creatinine,
uric acid, sucrose, vitamin B₁₂, polyethylene glycol (4,000 MW), insulin, heparin, and dextran (16,000 MW). The results are tabulated in Table 4-12, along with estimated diffusion coefficients and values taken from the literature. The reader is referred to Appendix B for a complete discussion of the estimated and literature diffusivities. All runs were made at infinite dilution (radioactive tracer alone) except for creatinine, vitamin B₁₂, and heparin, as indicated in the table. Initial runs with creatinine at infinite dilution gave very high diffusivities (≈5x10⁻⁵ cm²/sec) indicating possible adsorption on the capillary walls. The tabulated standard deviations were calculated from the experimental data.

The diffusivity of urea and sucrose have been studied most extensively of all compounds investigated in this study. The close agreement between the measured and literature values for these compounds indicates that the experimental technique was capable of generating relatively accurate results.

Most of the other solutes show reasonable agreement with estimated or literature values, with the exception of vitamin B₁₂ and dextran. The high value for vitamin B₁₂ may be due to degradation of solute. The radioactive stock solution contained 25 ppm benzyl alcohol as a bacteriocide. Two laboratory stock saline solutions were used, one containing
### TABLE 4-12

**Diffusion Coefficients in Isotonic Saline at 37°C**

<table>
<thead>
<tr>
<th>Solute</th>
<th>Run</th>
<th>No. of Data Pts</th>
<th>Measured Value</th>
<th>± σD</th>
<th>± %</th>
<th>Estimated Value</th>
<th>Literature Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>1</td>
<td>7</td>
<td>1.840</td>
<td>0.054</td>
<td>2.8</td>
<td>1.92</td>
<td>1.808 (254)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>155</td>
<td>8</td>
<td>1.215</td>
<td>0.142</td>
<td>11.7</td>
<td>1.29</td>
<td>1.08 (60)</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>104</td>
<td>3</td>
<td>1.210</td>
<td>0.121</td>
<td>10.0</td>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td>Sucrose</td>
<td>108</td>
<td>3</td>
<td>0.711</td>
<td>0.012</td>
<td>1.7</td>
<td>0.793</td>
<td>0.697b(253)</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>118</td>
<td>8</td>
<td>0.549</td>
<td>0.027</td>
<td>4.9</td>
<td>0.379</td>
<td></td>
</tr>
<tr>
<td>PEG (4000)</td>
<td>113</td>
<td>4</td>
<td>0.227</td>
<td>0.046</td>
<td>20.5</td>
<td>0.264</td>
<td>0.194b(348)</td>
</tr>
<tr>
<td>Inulin</td>
<td>112</td>
<td>4</td>
<td>0.240</td>
<td>0.030</td>
<td>12.5</td>
<td>0.242</td>
<td>0.205 (60)</td>
</tr>
<tr>
<td>Heparin</td>
<td>117</td>
<td>3</td>
<td>0.159</td>
<td>0.010</td>
<td>6.2</td>
<td>0.170</td>
<td>0.114b (239)</td>
</tr>
<tr>
<td>Dextran</td>
<td>145</td>
<td>2</td>
<td>0.293</td>
<td></td>
<td></td>
<td>0.163</td>
<td>0.12b (185)</td>
</tr>
</tbody>
</table>

a. Wilke-Chang (440) correlation for $M_w<1000$
   Polson (325) correlation for $M_w>1000$

b. Extrapolated to 37°C assuming $D_u/T = \text{const.}$

c. 10 gm/l unlabelled solute (heparin and creatinine), 1 gm/l (vitamin B₁₂)
25 ppm benzyl alcohol, the other 200 ppm formaldehyde. It is possible that the stock solution containing formaldehyde was inadvertently used. Vitamin B₁₂ is known to be unstable in the presence of aldehydes (401). No explanation is readily apparent for the high diffusivity of dextran. It is possible that a significant quantity of solute adsorbed on the glass capillary surface. This occurred in the lucite chamber of the batch dialyzer. However, inulin, which also sorbed on the lucite chamber, gave a measured diffusivity close to the literature value. Another possibility is degradation of the polymer in the syringe needle during filling.

Further discussion of the measured diffusion coefficients in saline can be found in Appendix B.

2. Diffusion in Plasma and Serum

The diffusion coefficient was measured in plasma and/or serum with urea, creatinine, uric acid, sucrose, inulin, and dextran. The results are tabulated in Table 4-13. When the amount of radioactive stock solution added to the serum or plasma diluted the fluid by more than 5 per cent, crystallized serum albumin was added to keep the total volume per cent protein constant. The same procedure was followed with the blood experiments.

A large number of runs were made with urea to perfect the experimental technique and to indicate, with a statis-
### TABLE 4-13

**Diffusion Coefficients in Plasma and Serum at 37°C**

<table>
<thead>
<tr>
<th>Solute</th>
<th>Solution</th>
<th>Run</th>
<th>Data Pts</th>
<th>(D_{\text{plasma}})</th>
<th>(\sigma_D)</th>
<th>(%)</th>
<th>(D_{\text{Sal.}})</th>
<th>(\theta_D^{plasma} = D_{\text{saline}})</th>
<th>(\sigma_{\theta_D})</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>Plasma</td>
<td>2</td>
<td>7</td>
<td>1.558</td>
<td>0.055</td>
<td>3.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>101</td>
<td>3</td>
<td>1.504</td>
<td>0.068</td>
<td>4.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>102</td>
<td>4</td>
<td>1.472</td>
<td>0.049</td>
<td>3.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>103</td>
<td>3</td>
<td>1.500</td>
<td>0.068</td>
<td>4.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>114</td>
<td>7</td>
<td>1.347</td>
<td>0.113</td>
<td>8.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>116</td>
<td>6</td>
<td>1.418</td>
<td>0.182</td>
<td>12.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combined Urea Data</strong></td>
<td></td>
<td>29</td>
<td></td>
<td>1.460</td>
<td>0.124</td>
<td>8.5</td>
<td>1.808</td>
<td>0.807</td>
<td>0.080</td>
<td>9.9</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Plasma</td>
<td>106</td>
<td>5</td>
<td>0.871</td>
<td>0.094</td>
<td>10.8</td>
<td>1.215</td>
<td>0.717</td>
<td>0.114</td>
<td>15.9</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>Plasma</td>
<td>107</td>
<td>4</td>
<td>0.745</td>
<td>0.034</td>
<td>4.5</td>
<td>1.210</td>
<td>0.616</td>
<td>0.067</td>
<td>11.0</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Serum</td>
<td>134</td>
<td>6</td>
<td>0.590</td>
<td>0.057</td>
<td>9.7</td>
<td>0.697</td>
<td>0.846</td>
<td>0.092</td>
<td>10.9</td>
</tr>
<tr>
<td>Inulin</td>
<td>Serum</td>
<td>148</td>
<td>3</td>
<td>0.217</td>
<td>0.010</td>
<td>4.9</td>
<td>0.240</td>
<td>0.883</td>
<td>0.120</td>
<td>13.4</td>
</tr>
<tr>
<td>Dextran</td>
<td>Serum</td>
<td>136</td>
<td>4</td>
<td>0.241</td>
<td>0.052</td>
<td>21.4</td>
<td>0.293</td>
<td>0.823</td>
<td>0.194</td>
<td>23.6</td>
</tr>
</tbody>
</table>
tically large sample, the degree of scatter present in consecutive runs with the same materials. The urea runs in plasma and serum are not distinguishable within the experimental error. This is not surprising, since serum is identical to plasma with the fibrinogen removed, and fibrinogen accounts for only about 3.4% of the total volume of plasma proteins. Consequently, diffusion coefficients measured in serum may be used interchangeably with data obtained in plasma (with the exception of solutes strongly bound to fibrinogen).

For urea and sucrose, the reference (saline) diffusion coefficient was taken to be the values reported in the literature, since the measured values were within 2%. For all other solutes, the value experimentally measured in this study were employed, so that any constant errors with a given solute might tend to cancel out.

The tabulated values of $\sigma_D$ were calculated directly from the experimental data. The standard error for $\Theta$, the ratio of the diffusion coefficient in plasma to that in saline, was calculated from

$$\left( \frac{\sigma_{\Theta_p}}{\Theta_n} \right)^2 = \left( \frac{\sigma_{D_S}}{D_S} \right)^2 + \left( \frac{\sigma_{D_P}}{D_P} \right)^2$$

(4-99)

where the subscripts $s$ and $p$ refer to saline and plasma, respectively. Estimates of $\sigma_D$ are given in Appendix B.

For all solutes, the diffusion coefficient in plasma is less than that in saline, and the ratio of the two
differs from solute to solute. It is instructive to compare the experimental data with the proposed model for diffusion in plasma.

In Section 4.B.2 it was proposed that

$$\theta_p = \frac{\psi^o + \frac{D_B}{D_A} k_p}{1 - \phi + k_p}$$

(4-100)

where $\psi^o/(1-\phi_p)$ is the obstruction factor of the plasma proteins, $D_a$ is the diffusivity of solute in water, $D_b$ is the diffusivity of solute-protein complex in water and $k_p$ is the equilibrium distribution coefficient between bound and unbound solute. If all parameters are known or can be estimated, then a prediction of $\theta_p$ can be made.

If values of $k_p$ are used which were determined from a binary system (protein plus one solute), it is implicitly assumed that the binding sites for all solutes present in plasma are independent, i.e., no competition exists between two or more solutes for the same binding site. This assumption is probably not true for all solutes (142, 215). Alternatively, eqn.(4-100) may be rearranged to determine what value of $k_p$ corresponds to the experimentally determined $\theta_p$. Thus,

$$k_p = \left[ \frac{\psi^o - \theta_p (1-\phi_p)}{D_b \left( \theta_p - \frac{D_b}{D_a} \right)} \right]$$

(4-101)
\( \psi^o \) was estimated from the model of Wang (31) using the plasma protein concentrations tabulated by Schultz and Heremans (33) and assuming an hydration of 0.2 gml/gm protein for all proteins. Details of the calculation may be found in Appendix E. The average \( \phi_p \) was calculated to be 0.0792 (range .0957-.0644). The total value of \( \Sigma \bar{\alpha} \phi \) summed over all proteins for the average plasma concentration was found to be 0.127, with a maximum range of 0.079 to 0.153 corresponding to the extremes of reported concentrations. From eqn.(4-55), this yields 0.873 for \( \psi^o \), with a maximum and minimum of 0.921 and 0.84%.

For any given solute, more than one protein may participate in binding. The true value of \( D_b \) is thus a weighted mean summed over all binding proteins. It is assumed here that \( D_b \) may be approximated by the diffusion coefficient of pure albumin in water which at 37°C is 0.0909 x 10^{-5} \text{cm}^2/\text{sec} (see Appendix B). This assumption implies that virtually all protein bound solute is bound to albumin and that the diffusion coefficient of the solute-protein complex is the same as the pure protein. The consequent error in calculating \( k_p \) is small when \( D_b/D_A << \theta_p \), which is the case for the solutes considered here.

Using \( D_b = 0.0909 \times 10^{-5} \) and \( \psi^o = 0.873 \), estimates of \( k_p \) were calculated from eqn.(4-101) using the experimental values of \( \theta_p \). The results are shown in Table 4-14.
Table 4-14

<table>
<thead>
<tr>
<th>Solute</th>
<th>$\theta_D$</th>
<th>$D_b/D_a$</th>
<th>$k_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>0.807</td>
<td>0.0503</td>
<td>0.172</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.717</td>
<td>0.0748</td>
<td>0.331</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>0.616</td>
<td>0.0751</td>
<td>0.557</td>
</tr>
<tr>
<td>Sucrose</td>
<td>0.846</td>
<td>0.1304</td>
<td>0.131</td>
</tr>
<tr>
<td>Inulin</td>
<td>0.883</td>
<td>0.379</td>
<td>0.107</td>
</tr>
<tr>
<td>Dextran</td>
<td>0.823</td>
<td>0.3102</td>
<td>0.127</td>
</tr>
</tbody>
</table>

Published quantitative data for $k_p$ exists only for urea and uric acid, among the compounds studied. From the urea data of Pasynskii and Chernyak (314, 315) given in Table 4-3, $k$ for albumin is about 0.073 and for $\gamma$-globulin about 0.023 ± 0.005. Assuming that these two proteins account for most or all of the adsorbed urea, one obtains, $k_p \approx 0.096$ for urea in plasma. From Alvarker's data (7) in Table 4-4, $k_p \approx 0.50$ for uric acid in plasma. The agreement between reported values of $k_p$ and those calculated from the diffusivity data is reasonable for these two compounds. Although the other compounds cannot be checked quantitatively, the calculated values of $k_p$ are not unreasonable.

Calculation of $k_p$ from plasma diffusion measurement is not a sensitive measure of $k_p$. From a propagation of error analysis of eqn.(4-101) (see Appendix K), one obtains
\[
\frac{(\sigma_{k_p})^2}{k_p} = \left\{ \frac{\psi^*}{\psi^* - \Theta_p(1-\phi_p)} \right\}^2 \left( \frac{\sigma_{\psi^*}}{\psi^*} \right)^2 \\
+ \left\{ \frac{[\psi^* - (1-\phi_p)R] \Theta_D}{(\Theta_p - R)[\psi^* - \Theta_p(1-\phi_p)]} \right\}^2 \left( \frac{\sigma_{\Theta_D}}{\Theta_D} \right)^2 \\
+ \left\{ \frac{\Theta_D \phi_D}{\psi^* - \Theta_p(1-\phi_p)} \right\}^2 \left( \frac{\sigma_{\phi_D}}{\phi_D} \right)^2 + \left( \frac{R}{\Theta_D - R} \right)^2 \left( \frac{\sigma_R}{R} \right)^2
\]

(4-102)

where \( R = D_b/D_a \). Using \( \sigma_{\psi^*}/\psi^* = 0.02, \sigma_{\phi_D}/\phi_D = 0.01, \sigma_{\Theta_D}/\Theta_D = 0.10, \) and the experimental value for \( \sigma_{\Theta_D}/\Theta_D \), one finds \( \sigma_{k_p}/k_p \) equals about 68% for urea and 33% for uric acid. The error estimated is dominated by the error in \( \Theta_D \).

Calculating \( \Theta_D \) from eqn. (4-100) using the literature values of \( k_p \) yields 0.863 for urea and 0.641 for uric acid. These estimates are in good agreement with the experimental measurements.

Lipps (212) found \( \Theta_D = 0.75 \) for urea diffusion in saline and plasma at 20°C. This agrees with the results of this study within the experimental error. No other comparable data for diffusion of organic solutes was found in the literature.

Cokelet (78) reported the viscosity of plasma to be 1.45 cp at 27°C. The viscosity of water at 27°C (218) is 0.8545 cp. Using the Stokes-Einstein relation to correct for the effect of viscosity gives
\[ \Theta_p = \frac{D_{\text{plasma}}}{D_{\text{water}}} = \frac{\nu_{\text{water}}}{\nu_{\text{plasma}}} = 0.589 \quad (4-103) \]

Comparison of this value with the experimental data in Table 4-13 shows the complete inapplicability of the Stokes-Einstein equation to this system. For a noninteracting solute, one would expect \( \Theta_p \sim 0.87 \), based on the proposed model. The Stokes-Einstein relation overcorrects for the influence the plasma proteins by a factor of about three.

In addition, Cokelet (145) reported approximately a 10% difference in viscosity between serum and plasma (an exact quantitative value for serum was not given; various values of the ratio were found in different parts of the thesis). However, no noticeable difference was found in this study for diffusion of urea through the two solutions.

Buckles, et al. (56) measured diffusion coefficients of oxygen in plasma and water flowing in an oxygen permeable tube and reported the diffusivity ratio to be 0.524. From this they concluded that the Stokes-Einstein correction was applicable. Spaeth (292) utilized this correction in calculating oxygen diffusivities in plasma. Hershey and Karhan (171) recently reported values of \( 2.25 \times 10^{-5} \) and \( 1.975 \times 10^{-5} \) cm\(^2\)/sec for the diffusivity of oxygen in water and plasma at 25°C, respectively. This yields a value for \( \Theta_p \) of 0.878, in close agreement with the proposed model (assuming oxygen does not bind to plasma proteins). Examination of the diffusion coefficient for oxygen in water used in these three
investigations reveals considerable discrepancy; this may account for the wide variation in reported diffusivity ratios for oxygen.

3. **Diffusion in Blood**

Diffusion experiments were performed with urea in red cell suspensions in saline and serum and with sucrose in serum suspensions over a wide range of hematocrits. Various other solutes in serum suspensions were studied with a hematocrit of 45. The major problem encountered was erythrocyte settling. The rate and amount of settling was not reproducible from run to run, or from capillary to capillary within the same run. In some capillaries, complete settling occurred rapidly, while in others it occurred very slowly. In several instances, virtually no settling occurred at all. Generally, rapid settling resulted in measured diffusion coefficients which were anomalously high, sometimes higher than that in pure water.

The following criterion was arbitrarily established to determine which data to include in the analysis. If, at the end of the run, the height of clear plasma was less than 1/8th of the total liquid height, the blood was assumed to have "not settled." If the plasma layer was greater than 1/8th, the blood was assumed to have "settled" and the measured diffusion coefficient ignored. In addition, the statistical test discussed above was also applied.
Application of this criterion left only the urea experiments for consideration as valid experimental data. In general, increasing the hematocrit decreased the tendency to settle. At the lowest hematocrit investigated, 20, the red cells in all the capillaries settled. Reece (340) has tabulated the measured diffusivities for all the runs. Only those for which settling did not occur, by the above criterion, are discussed here. This represents about 30% of the total number of data points obtained.

The results for urea diffusion in isotonic saline and serum red blood cell suspensions are shown in Table 4-15. Included in the table is the factor \( \Psi/K_{\text{suspension/solvent}} \), which corresponds to the ratio of the diffusion coefficient measured in the suspension to that measured in the suspending medium. Values of the standard deviation were calculated by an equation analogous to eqn.(4-88). In calculating the volume fraction of red cells, it was assumed that the red cell pack, from which hematocrit is calculated, contained 96 per cent red cells (155).

The last column contains calculated values of \( K \), obtained from the relation

\[
K_{\text{suspension/solvent}} = 1 - \phi + \phi K_{eq} \tag{4-104}
\]

where \( K_{eq} \) is simply \( K_{RC/p} \) for the red cell-serum experiments. For the red cell-saline experiments, the distribution coefficient must be modified by altering \( K_{eq} \), as follows:

\[
K_{RC/saline} = K_{RC/plasma} \cdot K_{plasma/saline} \tag{4-105}
\]
**TABLE 4-15**

**UREA DIFFUSION COEFFICIENTS IN RED BLOOD CELL SUSPENSIONS AT 37°C**

\[ \text{cm}^2/\text{sec} \times 10^5 \]

<table>
<thead>
<tr>
<th>Susp. Media</th>
<th>Run</th>
<th>Hematocrit</th>
<th>No.of Data Pts.</th>
<th>( D_{\text{susp.}} \pm \sigma_D )</th>
<th>( % )</th>
<th>( D_{\text{solv.}} )</th>
<th>Volume Fraction</th>
<th>( D_{\text{susp.}}/D_{\text{solv.}} \pm \sigma )</th>
<th>( % )</th>
<th>( K_{\text{susp./solv.}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotonic Saline</td>
<td>119</td>
<td>48</td>
<td>7</td>
<td>0.778 0.172</td>
<td>22.1</td>
<td>1.808 0.461</td>
<td>0.430 0.097</td>
<td>22.7 0.941</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>60</td>
<td>2</td>
<td>0.54 (0.08) (15.0)</td>
<td></td>
<td>0.576</td>
<td>0.299 0.052</td>
<td>17.2 0.927</td>
<td></td>
<td></td>
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<tr>
<td>Serum</td>
<td>124</td>
<td>38.5</td>
<td>4</td>
<td>0.635 0.061</td>
<td>9.5</td>
<td>1.460 0.370</td>
<td>0.435 0.055</td>
<td>12.7 0.948</td>
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<tr>
<td></td>
<td>125</td>
<td>45.7</td>
<td>4</td>
<td>0.563 0.085</td>
<td>15.1</td>
<td>0.439</td>
<td>0.386 0.067</td>
<td>17.3 0.938</td>
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<tr>
<td></td>
<td>126</td>
<td>53.0</td>
<td>6</td>
<td>0.533 ( \pm 0.050 )</td>
<td>9.4</td>
<td>0.509</td>
<td>0.365 0.046</td>
<td>12.7 0.928</td>
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<tr>
<td></td>
<td>127</td>
<td>65.0</td>
<td>5</td>
<td>0.463 ( \pm 0.034 )</td>
<td>7.3</td>
<td>0.624</td>
<td>0.317 0.036</td>
<td>11.2 0.912</td>
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<td></td>
<td>128</td>
<td>72.7</td>
<td>3</td>
<td>0.432 0.031</td>
<td>7.1</td>
<td>0.698</td>
<td>0.296 0.033</td>
<td>11.1 0.902</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Calculated assuming volume fraction = 0.96 \( \times \) \( \frac{\text{Hematocrit}}{100} \)

b. \( D_{\text{susp.}}/D_{\text{solv.}} = \psi/K_{\text{susp./solv.}} \).
where $K_{RC/plasma}$ equals $K_{eq}$ used above. It is assumed that the protein-free liquid in plasma is substantially identical with saline. Thus

$$K_{plasma/saline} = \frac{C_{free} + C_{bound}}{C_{saline}}$$  \hspace{1cm} (4-106)

$$= \frac{C_{free}(1 + \frac{C_{bound}}{C_{free}})}{C_{saline}}$$  \hspace{1cm} (4-107)

$$= \frac{(1 - \phi_p)(1 + \frac{k_p}{1 - \phi_p})}{C_{saline}}$$  \hspace{1cm} (4-108)

$$= \frac{1 - \phi_p + k_p}{C_{saline}}$$  \hspace{1cm} (4-109)

and

$$K_{RC-saline/saline} = 1 - \phi + \phi[K_{RC/plasma} \cdot (1 - \phi_p + k_p)]$$  \hspace{1cm} (4-110)

As expected, $\psi/K$ decreases as volume fraction increases.

In order to test the Fricke model discussed in Section 4.B.3, the experimental values of $\psi$ were plotted as a function of the volume fraction, $\phi$, and compared with the predicted curves from eqns. (4-71) to (4-76). The results are shown in Fig. 4-8. The theoretical curves correspond to an oblate ellipsoid with an axial ratio of 4.25. They are plotted for various values of $Z = K_{eq} \cdot D_B/D_A$, where $D_B$ is the effective diffusion coefficient in the suspended phase and $D_A$ is the
Figure 4-8. Diffusivity Reduction in Red Cell Suspensions. Comparison with Fricke Model (Oblate Ellipsoid, Axial Ratio = 4.25).
diffusion coefficient in the (homogeneous) suspending medium. The use of a steady-state model is valid for the experimental conditions employed. The calculations in Table 4-11 show that for a diffusion length of two cm, erythrocyte and plasma urea are in equilibrium.

The data points show a definite decrease in Ψ with increasing φ. The data for red cells in saline are not differentiable from the data for red cells in serum. The experimental dependence of Ψ upon φ does not correspond exactly to any of the theoretical curves and appears to be slightly more concave and less dependent upon φ, in the hematocrit range studied, than the theoretical curves. Most of the data falls within the region lying slightly below the theoretical curve corresponding to Z = 0 and the curve corresponding to Z = 0.1, with approximately equal scatter about the curve for Z = 0.02. Using the theoretical curve for 0.05 would lead to a maximum deviation between predicted and experimental values of 15 to 20 per cent.

From the data in Tables 4-5, 4-10, and 4-13, one finds for urea $K_{eq} = 0.86$, $D_{red\ cell}/D_{water} = 0.025$ to 0.043 and $\Theta_p = D_{plasma}/D_{water} = 0.807$. Consequently,

$$Z = \frac{D_B}{D_A}$$

(4-111)

$$= K_{eq} \left( \frac{D_{red\ cell}}{D_{water}} \right) \left( \frac{D_{water}}{D_{plasma}} \right)$$

(4-112)
\[
= \frac{K_{eq}}{\theta_p} \left( \frac{D_{\text{red cell}}}{D_{\text{water}}} \right)
\]  

(4-113)

and the predicted value of \( Z \) lies between 0.0027 and 0.046.

From this prediction, based on red cell permeability data, the red cell should behave as an impermeable, or almost impermeable phase. A comparison between the experimental data and the theoretical curves of the Fricke model indicates qualitative agreement with this conclusion. Of the two limits on the effective diffusivity of the erythrocyte, the lower estimate appears more reasonable, since it corresponds to permeation through the entire surface area of the red cell (modeled as a disc). Using this estimate, and assuming the Fricke model to be correct, one would expect the data to lie on the curve for \( Z = 0.0 \). In reality, the data shows a deviation away from the curve for \( Z \neq 0.0 \) and a slightly different dependence on \( \phi \). There are three possible reasons for this:

1) There is a systematic error in the data.

2) The Fricke model does not accurately portray the correct volume fraction dependence of \( \psi \), particularly for the complex shape of the red cell.

3) The true effective value of \( Z \) is about 0.02, and the deviation of the data from the predicted curve is the result of random experimental error. Without additional experimental verification of the Fricke equations with a simpler model system, one cannot choose between these possibilities. Nevertheless, from an engineering standpoint, the data and
theory agree sufficiently well that $\psi$ can be estimated from the Fricke model to within 10 to 15%.

The only previous work which is directly comparable to this investigation is that of Lipps (242). He measured diffusion coefficients of urea in whole blood over a hematocrit range of 50 to 78. His data differ grossly from the results found in this study. When plotted as in Fig. 4-7, the dependence of $\psi$ on $\phi$ is convex downwards towards the origin. For example, at a hematocrit of 50, his data corresponds to $\psi \sim 0.78$, as compared to $\psi \sim 0.37$ found in this study. A possible explanation for the discrepancy lies in Linns' use of scintillation plastic diffusion cells, which were found to significantly adsorb urea from solution.

Considerable research has been published dealing with oxygen diffusion through whole blood, the most recent of which is that of Hershey and Karhan (171) who also reviewed the bulk of the existing literature. These authors measured oxygen diffusivities in saturated whole blood. The decrease in diffusivity with increasing hematocrit was significantly smaller in magnitude than the data obtained in this study. Such a phenomenon is consistent with a much higher value of $K_{eq} D_B / D_A$. Oxygen diffusion in unsaturated blood is much more complex because of the nonlinearity of the oxygen saturation curve. An in-depth comparison of the results reported here with literature data for oxygen diffusion through blood is beyond the scope of this study.
4. **Estimation of Diffusivity in Whole Blood**

From the experimental results it can be concluded that a relatively accurate engineering estimate of the diffusion coefficient of an organic solute in whole blood may be obtained from the proposed model, which may be represented as

\[ D_{\text{blood}} = \Theta_p \frac{\psi}{K_{\text{WB/p}}} D_{\text{water}} \]  

(4-114)

An accurate estimate of \( \Theta_p \) requires knowledge of \( k_p \). In the absence of such information, a reasonable guess would be \( \Theta_p = 0.8 \) to 0.9 for non-nitrogenous solutes. Where \( k_p \) is known \( \Theta_p \) can be estimated from eqn. (4-100), letting \( \psi^0 = 0.873 \) and using the diffusivity of albumin for \( D_b \). Estimation of \( K_{\text{WB/p}} \) requires knowledge of hematocrit and the red cell-plasma distribution coefficient. In the absence of knowledge of the latter quantity, it may be assumed equal to unity.

As discussed in Section 4.A.4, urea permeates through the red cell much faster than almost all other organic solutes. The only exceptions to this are water and small lipid soluble solutes. Thus, \( Z = 0 \) for virtually all organic solutes larger than urea, and the appropriate curve from the Fricke model may be employed. Alternatively, assuming that for urea, as well, \( Z = 0 \), the empirically-derived curve may be employed. At normal hematocrits, 40-50, the difference is small. For volume fractions below 0.37, the model has not been tested.
However, it is clear that it must be at least qualitatively correct, since $\psi$ approaches unity as $\phi$ approaches zero.

The final limiting condition for applying the Fricke model is that the erythrocyte and plasma solute must be in equilibrium. If they are not, the effective diffusion coefficient is time and possibly concentration dependent, and a model such as that derived in Appendix F is required. For systems very far from equilibrium, the appropriate analytical models for predicting the effective diffusivity are presently not available.
Permeability and Transport Studies in the Flow Dialyzer

A. Introduction

Both theoretical and experimental studies were carried out with a flat plate flow dialyzer composed of flat, parallel membranes between which flowed the fluid to be dialyzed. The objectives of this phase of the thesis were to:

1) Develop the theoretical model for solute transfer in this system, including the necessary techniques from which the solute diffusivity or membrane permeability could be calculated from experimental data.

2) Design, fabricate, and test a flat plate flow dialyzer, including flow visualization studies and characterization of mass transfer in the dialyzate phase.

3) Verify the theoretical model with aqueous solutions and solutes of known diffusivity and a membrane of known permeability.

4) Use the system to make a preliminary study of diffusion of urea in flowing blood.

Initially, various flow geometrics were considered for the study of diffusion in flowing blood. Surfaces of "uniform accessibility" for which the mass transfer coefficient is well defined and constant, such as the rotating cylinder and rotating disc, were ruled out for the same reasons already discussed with respect to membrane permeability measurement in Chapter 3. This left flow in conduits for consideration.

A flat plate system was selected, as opposed to a single tube or collection of tubes, for two reasons:

1) The same membrane, or a membrane cut from the same sheet, could be tested in both the batch dialyzer and the flow
dialyzer. Since the true membrane permeability must be device independent, this serves as a rigorous check on both the experimental methods employed and the theoretically derived methods for calculating permeabilities.

2) Flat sheet cellulosic membranes are more readily available than membranes in tubular form. Cellulose triacetate hollow fibers were provided to the author through the generosity of Mrs. P. Oja of the Dow Chemical Co., Walnut Creek, Calif. These required saponification to be rendered permeable. Since the fabrication of tubular and sheet membranes utilizes substantially different manufacturing conditions, it was considered probable that the polymer morphology, and consequently the permeability, might differ between a sheet and tubular cellulose acetate film. Consequently, an independent check with the batch dialyzer would have been impossible.

In addition to these factors, most hemodialyzers that are in use today are of the flat plate type (See Appendix A. A Review of the Development and Performance of Hemodialyzers). Consequently, the theoretical framework developed here may be readily applied to the simulation of actual in vitro and in vivo operation of existing hemodialyzers. This topic is considered in Chapter 6.

Because of the possibility of hemolysis caused by turbulent flow all applications involving extracorporeal circulation of blood are limited to laminar flow. The experiments carried out in this study were also in the laminar regime, and consequently the theoretical treatment will be limited to this regime.

The system of interest is depicted in Fig. 5-1a. The solution to be dialyzed flows between two semi-infinite
parallel membranes. Thus the channel may be considered two dimensional. The initial concentration of solute is uniform and at a certain point (the origin of the coordinate system) the membrane becomes permeable to the solute, and the latter diffuses across the membrane to the dialyzate flowing on the other side. The solution to be dialyzed is in full-developed laminar flow before it contacts the semi-permeable membrane. It is assumed that the dialyzate flow rate is sufficiently greater than the solution flow rate that its concentration is essentially constant along the entire length of the membrane.

The terminology to be used here requires definition. In current industrial dialysis practice (67, 423, 425) the solution to be dialyzed is conventionally termed the "feed" or "liquor," and the dialyzed stream is called the "dialyzate." The inlet stream on the other side of the membrane is the solvent and the outlet is the diffusate. In this study, the nomenclature used in the hemodialysis literature will be employed. The solution to be dialyzed is the blood or "blood-side fluid," and the solution on the other side of the membrane is the dialyzate. This usage for "dialyzate" is the opposite of the industrial usage. The exact reason for this is not clear, and it is probable that the individual who first applied the term simply used it incorrectly.

The concentration profile perpendicular to the plane of the membrane, at a point far removed from the dialyzer inlet, is illustrated qualitatively in Fig. 5-1b. The concentration is a maximum at the centerline of the blood side fluid and decreases to a minimum beyond the concentration boundary layer in the dialyzate. There is a discontinuity in the
Figure 5-1. Diagram of Flat Plate Channel
concentration at one or both membrane faces, unless the distribution coefficient between the membrane and both fluids, based upon the total volume of the membrane, is unity. In Fig. 5-1b, the membrane concentration profile is plotted for a distribution coefficient less than unity. For the general case, the distribution coefficient between the two fluids may not be unity and one must be particularly careful to define the driving forces in each phase correctly. Fig. 5-1b has been drawn for a distribution coefficient between fluid phases of unity, and this will be assumed to be the case for the time being unless stated otherwise. This assumption is valid for simple aqueous solutions on both sides of the membrane. The more complex case is considered in Section 5.C.6.

Except at infinite dialyzate flow rate, there will always be a concentration gradient in the dialyzate phase. However, by assuming (a) that $C_0$, the concentration outside the dialyzate concentration boundary layer, is constant, and (b) the dialyzate-side mass transfer coefficient is constant, it is possible to lump the membrane and dialyzate mass transfer resistance together into a single constant transport resistance of the "wall," on the outside of which the concentration is constant. These assumptions are valid when a) $Q_D/Q_B$ is very large, and b) dialyzate flow is turbulent or well-mixed in the direction perpendicular to the membrane. Failure to make these assumptions significantly complicates the theoretical analysis. The conditions required for these assumptions will be met for the experimental conditions described later in Section 5.4, and they are usually satisfied in most operational hemodialyzers.
The problem, as defined, is analogous to laminar flow heat transfer between parallel plates of finite conductivity, outside of which the temperature is constant. Thus, the large body of literature available for the heat transfer case is of direct use in the analysis of this problem.

In this chapter, the previous relevant theoretical and experimental work will be discussed first. Then, the theoretical analysis for the system of interest here will be developed, including methods for obtaining the solute diffusivity and membrane permeability from experimental data. This will be followed by the experimental phase of the study.

B. Previous Work

The great amount of experimental data for laminar flow heat transfer in closed conduits is reviewed in a number of texts; such as those of McAdams (274) and Knudsen and Katz (216) and will not be considered here. Of primary interest are the theoretical treatments.

1. Theoretical

Laminar heat transfer in a tube with a constant temperature at the wall was first studied by Graetz (149, 150) in the 1880's, for both plug flow and a parabolic velocity distribution. Using separation of variables, he formulated the latter case as an eigenvalue problem and solved for the first two eigenvalues. This method of solution is highly accurate at distances far from the inlet, but in the thermal entrance region, the solution is slowly convergent and many eigenvalues may be required. Leveque (247) derived an approximate solution valid in the entrance region by assuming a linear velocity profile near the wall. These, and several
other early works have been summarized by Drew (108, 109) and Jakob (190).

Morris and Streid (299) summarized the entrance region, small dimensionless length, and asymptotic, large dimensionless length, solutions for both parallel plates and tubes. A Graetz-type solution for the parallel plate case was first considered by Purday (354) and was further developed by Prins, et al. (332). Dennis and Poots (100) derived a simpler approximate method for solving the parallel plate problem, and Butler and Plewes (61) considered the case of one wall insulated. Cess and Shaffer (65) studied unsymmetrical wall temperatures for parallel plates.

Sellars, Tribus, and Klein (374) developed an asymptotic solution valid for the higher eigenvalues for both the tube and parallel plates. They also applied superposition, using the Stieltjes integral, to extend the solution to cover arbitrary wall temperature or heat flux variations. Additional discussions of the mathematical aspects of the Graetz problem have been given by Singh (387) and Abromowitz (3). The most recent and complete analysis of the Graetz problem is the work of Brown (55). Using up to 50 significant figures for intermediate calculations, he tabulated the first 11 eigenvalues for the tube and the first 10 for parallel plates, with 12 significant digits, and compared his results with more than a dozen sets of estimates from the literature. Using Brown's tabulation for the lower eigenvalues and the asymptotic expression of Sellar's, et al., for the higher eigenvalues, one can consider the classical Graetz problem for both the tube and parallel plates to be completely solved.
For real physical systems, a constant temperature boundary condition at the wall represents one limiting case. The other limiting case is a constant flux boundary condition. This situation was studied by Siegel, et al. (384) who tabulated the first seven eigenvalues for a tube, and Cess and Shaffer (64) who reported the first three eigenvalues for parallel plates and derived an asymptotic expression for the higher eigenvalues. The latter authors also considered unsymmetrical heat fluxes at the two walls (66). A Leveque-type entrance region solution for constant flux in a tube has been discussed by Bird, Stewart, and Lightfoot (36); an extension of this treatment to non-Newtonian fluids has been presented by Bird (36a).

A large number of variations on the basic Graetz problem have been studied. Among those of at least passing interest here are simultaneously developing velocity and thermal boundary layers (200, 420), entrance region solutions, including the effect of axial convection (4, 280, 366, 388, 448) and transport in a rectangular channel (98, 356) and an annulus (260, 425). For small annular gaps, the latter geometry degenerates in the limit to a parallel plate configuration. Many of these theoretical treatments have been summarized by Kays and London (202).

Of particular interest here is the real situation intermediate between a constant temperature and constant flux boundary condition, that of a flux boundary condition characterized by the finite conductivity or permeability of the wall. This shall be termed the "modified" Graetz problem. Van der Does de Bye and Schenk (103) first considered this case for parallel plates, and Schenk and Dunmore (363)
studied a tube. Dennis and Poots (99) presented an approximate treatment for solving the parallel plate problem. Berry (32) discussed the effects of the wall Nusselt number on the inside local fluid Nusselt number, and Schenck (360) further extended this discussion, comparing both tubes and ducts. Schenck (361) also solved the parallel plate problem with one wall insulated, and Schenck and Beckers (362) considered unsymmetrical temperatures outside the plate walls and an arbitrary fluid temperature distribution at the inlet. A treatment for non-Newtonian flow in a tube has been given by Schenck and Van Laar (364).

Grimsrud and Babb (154) applied the theoretical model of Van der Does de Bye and Schenck (103) to mass transfer with laminar flow of a Newtonian fluid in a parallel plate dialyzer, using a modified mathematical method to obtain the eigenvalues. Both sets of authors evaluated only the first three eigenvalues. In addition, Grimsrud and Babb derived an approximate boundary layer solution for the inlet region. They also developed an approximate theoretical solution for the case of a rectangular channel. Their model predicted that the asymptotic overall Sherwood number was independent of the aspect ratio of the duct. This is in direct disagreement with all other analyses of heat transfer in a rectangular channel (73, 98, 356), and consequently their model is believed to be in error. In related publications (20, 21, 22), Babb and co-workers have presented a variety of methods for obtaining the solute diffusivity or the membrane permeability from experimental data. All these techniques, however, are based upon approximations to the theoretical solution and are valid only within certain limited ranges of the dimensionless
variables.

A related problem to that of interest here is heat transfer in a double pipe heat exchanger with both fluids in laminar flow and a tube with a finite conductivity. This problem has been treated by several investigators (300, 402, 403). In addition, Tien (419) has studied the analogous problem for a parallel plate dialyzer where the dialyzate fluid is in laminar flow. Another related problem, laminar convective diffusion in a rectangular duct with one catalytic wall, has been described by Salbrig and Gidaspow (391).

The theoretical analyses most pertinent to this study are those of Van der Does de Bye and Schenck, and Grimsrud and Babb and co-workers. In addition to reviewing the theoretical framework already available in the literature, the following new aspects of the modified Graetz problem were developed in this study:

1) Various mathematical solutions were investigated, and the most rapid and accurate method, not previously utilized, was employed to generate the eigenvalues.

2) The first seven eigenvalues, and their associated constants, were obtained for a variety of wall Sherwood numbers.

3) Various numerical relationships and physical aspects of the problem were investigated in considerable detail. In particular, the behavior of the log mean average Sherwood numbers were studied, whereas previous treatments have been limited essentially to the local Sherwood numbers.

4) A solution valid near the entrance of the dialyzer was developed using a perturbation analysis, and an
asymptotic expression for the higher eigenvalues was derived.

5) An approximate, but accurate technique for rapidly estimating the mass transfer behavior of the system was developed.

6) An exact and highly accurate method for obtaining solute diffusivities and membrane permeabilities from experimental data was developed.

7) To facilitate the method referred to in (5), and to permit accurate and economical simulation of dialyzer performance, a "block box" computer program was written which rapidly evaluated the theoretical solution for any input values of the dimensionless variables.

2. Experimental

The only previous experimental investigation of mass transfer in a parallel plate dialyzer relevant to this study has been the work of Grimsrud (153) and the related investigations of Babb and his associates (21, 22, 154). This, of course, is in addition to the considerable in vivo and in vitro data obtained with experimental and clinical hemodialyzers discussed in Appendix A. However, while the latter represents a sizeable body of empirical information, little or no previous attempts have been made to relate such data to a fundamental understanding of the mass transfer processes involved. This type of analysis will be considered further in Chapter 6.

Grimsrud (153) studied the transport of sodium and potassium chloride and urea in aqueous solution with a flat plate system, using Cuprophane PT-150 as the membrane. The membrane permeabilities he reported in his thesis differed significantly from the values obtained in this study with the
batch dialyzer, as discussed in Chapter 3. This difference is believed to be primarily related to his assumption that the dialyzate mass transfer resistance was negligible. This will be discussed further in Section 5.E.1. However, the subsequent publications, cited above, indicated closer agreement.

Grimsrud found that the experimental data agreed with the theoretical model for semi-infinite parallel plates only at smaller dimensionless lengths (higher blood-side fluid velocities). At larger dimensionless lengths (lower fluid velocities), the data diverged significantly from the semi-infinite plate model and asymptoted towards Grimsrud's theoretical solution for a rectangular channel. From this he concluded that the dialyzer was behaving as a rectangular channel with boundary layer buildup on the side walls, despite the fact the aspect ratios employed were of the order of 50:1 or higher. As pointed out above, his rectangular channel solution is considered to be invalid; and the deviation of the data from the semi-infinite model is most likely attributable to deviations of the experimental conditions from the assumptions made in the mathematical formulation of the problem. Two likely candidates for this are 1) shunting of the blood side fluid such that the velocity profile was not flat and uniform across the dialyzer; and 2) partial collapse of the membrane at low fluid velocities where the blood side pressure drop was very low, while the dialyzate (cross flow) pressure drop remained constant. The latter effect was found experimentally in this thesis.

Studies of diffusion in flowing blood have been limited to only a few investigations. Babb, et al. (22)
recently reported effective diffusivities for several organic solutes in blood during in vivo hemodialysis. They used the modified Babb-Grimsrud cell as a satellite hemodialyzer during a clinical hemodialysis treatment with the Kiil artificial kidney. However, they operated with a channel height such that the membrane was the limiting transport resistance. Thus, their reported data are of primarily qualitative significance. The only other study which has been reported with organic solutes was the preliminary investigation of Lipps (249) with stagnant blood.

Diffusion of oxygen in flowing blood has been studied by Buckles, et al. (57, 58) and Weissman and Mockros (434) in a tube, and by Spaeth and Friedlander (392, 393) with a rotating disc. Oxygen diffusion in stagnant blood was studied by Marx, et al. (272) and Hershey and Karhan (171). The latter authors have also reviewed most of the other work in this area. However, because of the added complexities associated with oxygen transport in blood, this work is only of tangential interest here.

As a result of the uncertainties associated with Grimsrud's study and the lack of agreement between experimental data and the simple parallel plate theory, a considerable part of the effort in this study was devoted towards verification of the theoretical model with aqueous solutions of sodium chloride and urea. After this objective was attained, the diffusion of urea in flowing plasma and whole blood was investigated.

C. Theory

1. Derivation

The following assumptions apply to the system shown in
Fig. 5-1:
1) Steady state conditions.
2) Constant physical properties.
3) Transport from a concentration gradient only (negligible hydrostatic and osmotic pressure differences between the fluids).
4) Homogeneous fluids with no sources or sinks.
5) Equal solute distribution coefficient for both fluids, i.e. at equilibrium, the concentrations on both sides of the membrane are equal.

With these assumptions, the partial differential equations describing convection and diffusion in the channel may be derived from a mass balance over a differential fluid element:

\[
V_x \frac{\partial c}{\partial x} = D \left[ \frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} \right] \quad (5-1)
\]

Schneider (366) has shown that for Peclet numbers based upon channel height greater than about 100, the axial conduction term in eqn. (5-1) is negligible compared to the other terms. In the dialyzer used in this study and in all operational hemodialyzers, the Peclet numbers are invariably in excess of this value, so that equation (5-1) becomes

\[
V_x \frac{\partial c}{\partial x} = D \frac{\partial^2 c}{\partial y^2} \quad (5-2)
\]

For fully-developed laminar flow of a Newtonian fluid between semi-infinite parallel plates, the velocity profile is given by

\[
V_x = \frac{3}{2} \bar{v} \left(1-4y^2/h^2\right) \quad (5-3)
\]

where \(\bar{v}\) is the average fluid velocity. Substitution of this into equation (5-2) yields

\[
\frac{3}{2} \bar{v} \left(1-4y^2/h^2\right) \frac{\partial c}{\partial x} = D \frac{\partial^2 c}{\partial y^2} \quad (5-4)
\]
The solution of equation (5-4) requires three boundary conditions. At the inlet to the mass transfer section of the dialyzer where the wall becomes permeable, the concentration is constant since no mass transfer has taken place.

1. \( x \leq 0, \text{ all } y \quad c = c_i \)  \hspace{1cm} (5-5)

The concentration profile at any axial distance is symmetric about the centerline so that the net flux across the centerline is zero.

2. \( \text{all } x, y = 0 \quad \frac{\partial c}{\partial y} = 0 \)  \hspace{1cm} (5-6)

The mass flux to the wall from the blood side fluid must equal the flux through the wall.

3. \( \text{all } x, y = \frac{h}{2} \quad \frac{\partial c}{\partial y} = k_w \left(c_w - c_o\right) \)  \hspace{1cm} (5-7)

In the third boundary condition, \( c_w \) is the blood-side fluid concentration at the wall and \( k_w \) is the wall mass transfer coefficient or permeability. The reciprocal of \( k_w \), the wall mass transfer resistance, is equal to the sum of the resistances of the membrane and the dialyzate solution:

\[
\frac{1}{k_w} = \frac{1}{R_m} + \frac{1}{R_d} \hspace{1cm} (5-8)
\]

Van der Does de Bye and Schenk (103) expressed the wall heat transfer coefficient in a form analogous to equation (5-8). Grimsrud and Babb (154) assumed that the entire wall resistance was localized in the membrane. This is in general not true, although the dialyzate resistance can often be made significantly smaller than the membrane resistance by using membrane supports which mix the dialyzate or by operating with
high dialyzate velocities in the turbulent regime.

Equation (5-4) and its associated boundary conditions may be expressed in dimensionless form by the appropriate change of variables. Let

\[ C^* = \frac{c - c_0}{c_i - c_0} \]  
\[ y^* = \frac{y}{h} \]  
\[ x^* = \frac{x}{\bar{v} h^2} \]  

The total channel spacing, h, has been taken as the characteristic length in the y direction, consistent with Van der Does de Bye and Schenk. Grimsrud and Babb used the half-channel dimension, a = h/2.

The dimensionless axial length, \( x^* \), which is similar to the original Graetz number (150) may be expressed in other forms, i.e.

\[ x^* = \frac{x/h}{Re \, Sc} \frac{x/h}{Pe} \]  

where

\[ Re = \frac{\bar{v} h}{\nu} \]  
\[ Sc = \frac{\nu}{\bar{v}} \]  
\[ Pe = \frac{\bar{v} h}{D} \]

If one defines the average residence time of the fluid in the dialyzer, \( t_r \), as the quotient of the length, divided by the average linear velocity, one obtains

\[ x^* = \frac{t_r}{h^2} \]  

which is analogous to the familiar Fourier number in transient heat conduction (110). Denoting the width of the channel by \( w \), the flow rate through the channel is given by
\[ Q = \text{wh} \bar{v} \quad (5-17) \]

and \( x^* \) may be expressed as
\[ x^* = \frac{x D \bar{w}}{Q h} \quad (5-18) \]

For a truly semi-infinite channel, \( Q/w \) is simply the flow rate per unit width.

In dimensionless form, equations (5-4) through (5-8) become

\[ \frac{3}{2} (1-4y^*^2) \frac{\partial C^*}{\partial x^*} = \frac{\partial^2 C^*}{\partial y^*^2} \quad (5-19) \]

B.C. 1 \( x^* \leq 0 \) all \( y^* \) \( c^* = 1 \) \quad (5-20)

B.C. 2 all \( x^* \) \( y^* = 0 \) \( \frac{\partial C^*}{\partial y^*} = 0 \) \quad (5-21)

B.C. 3 all \( x^* \) \( y^* = \frac{1}{2} \) \( -\frac{\partial C^*}{\partial y^*} = \frac{S}{h_w} C^* \) \quad (5-22)

where the "wall Sherwood number," \( Sh_w \), is defined by
\[ Sh_w = \frac{k_w h}{D} \quad (5-23) \]

It is analogous to the equivalent heat transfer modulus, the wall Nusselt number, originally defined by Van der Does de Bye and Schenk. Schneider (366) referred to the same quantity as the "ambient-side" Nusselt number. The wall Sherwood number is also quite similar to the Biot number in transient heat conduction (110).

The wall Sherwood number may be considered as the ratio of the fluid concentration gradient at the wall to the concentration gradient in the wall; this is proportional to the ratio of the mass transfer resistance in the fluid to that in the wall. When \( Sh_w \) is finite, there is a finite concen-
tration drop across the wall. If \( \text{Sh}_w = \infty \), the wall resistance is zero and \( c_w = c_0 \). In this case, a constant concentration exists at the wall and the third boundary condition becomes

**B.C. 3A** \[ \text{all } x \quad y = \frac{h}{2} \quad c = c_0 \]  
(5-24)

or in dimensionless form

\[ \text{all } x^* \quad y^* = \frac{1}{2} \quad C^* = 0 \]  
(5-25)

If \( \text{Sh}_w = 0 \), either the fluid resistance is zero, caused by \( h/D \) going to zero, or the wall resistance is infinite. In either case, the concentration profile on the blood side tends towards a straight line. With \( h/D \) going to zero, \( x^* \) goes to infinity. Consequently, a finite amount of transport takes place. In the limit of \( \text{Sh}_w = 0 \), the physical process corresponds in some respects to that of a constant flux at the wall. This will be seen more clearly from some of the mathematical results presented later. The third boundary condition for this case is

**B.C. 3B** \[ \text{all } x \quad y = \frac{h}{2} \quad -D \frac{\partial c}{\partial y} = n \]  
(5-26)

or in dimensionless form

\[ \text{all } x^* \quad y^* = \frac{1}{2} \quad \frac{\partial C^*}{\partial y^*} = 1 \]  
(5-27)

where \[ C^* = \frac{c - c_0}{\dot{n}h/D} \]  
(5-28)

The constant concentration and constant flux boundary conditions represent the two limiting cases for the system of interest here.

The analytical solution to equation (5-19) yields an expression for \( C^* \) (and therefore \( c \)) at any point in the tube
as a function of \(x^*, y^*, \) and \(Sh_w\). In addition it is necessary to obtain an expression for the average bulk or mixing cup concentration, \(c_b\), or its dimensionless equivalent, \(C_b^*\) which is defined by

\[
C_b^* = \int_{-1/2}^{1/2} C_v^* v_x^* \, dy^* \\
\int_{-1/2}^{1/2} v_x^* \, dy^*
\]

(5-29)

With this information, the solution is essentially complete. It should be noted that, as compared to the constant concentration and constant flux boundary conditions, the problem studied here requires specification of one additional parameter, the wall Sherwood number.

For purposes of design and analysis, it is useful to have analytical expressions for the mass transfer coefficients. The local, overall mass transfer coefficient is defined by

\[
\dot{n} = k_{x,0} (c_b - c_o) = -D \frac{\partial c}{\partial y} \bigg|_{y = \frac{h}{2}}
\]

(5-30)

Equation (5-30) may be placed in dimensionless form by multiplying both sides of the equation by \(h/[ D (c_1 - c_o)]\) and substituting for the expressions defined in equations (5-9) and (5-10) to obtain the local, overall Sherwood number:

\[
Sh_{x^*,0} = \frac{k_{x,0} h}{D} = -\frac{1}{C_b^*} \frac{\partial c^*}{\partial y^*} \bigg|_{y^* = \frac{1}{2}}
\]

(5-31)

An alternate and equally valid expression may be obtained from a material balance over a differential element of the channel of width \(w\), height \(h\), and length \(dx\):
\[ d\hat{A} = -Q \, dc_b = k_{x_*o} \, (c_b - c_o) \, dA \quad (5-32) \]

\[ = 2 \, k_{x_*o} \, (c_b - c_o) \, w dx \quad (5-33) \]

Multiplying each side by \( h/[ \int (c_1 - c_0)] \), substituting equation (5-17) for \( Q \), and rearranging yields

\[ Sh_{x_*o} = -\frac{1}{2c_b^*} \frac{dC_b^*}{dx^*} \quad (5-34) \]

Henceforth, the asterisk on the subscript of the local Sherwood number shall be deleted.

The overall mass transfer resistance is equal to the sum of the fluid and wall resistances:

\[ \frac{1}{k_{x_*o}} = \frac{1}{k_w} + \frac{1}{k_{x_*f}} \quad (5-35) \]

Hence,

\[ \frac{1}{Sh_{x_*o}} = \frac{1}{Sh_w} + \frac{1}{Sh_{x_*f}} \quad (5-36) \]

The local fluid side mass transfer coefficient and Sherwood number may be calculated from equations (5-35) and (5-36) or from their fundamental definitions:

\[ \hat{n} = k_{x_*f} \, (c_b - c_w) = \left. D \frac{\partial c}{\partial y} \right|_{y = \frac{h}{2}} \quad (5-37) \]

and

\[ Sh_{x_*f} = \frac{k_{x_*f} \, h}{D} = \left. \left( \frac{1}{C_b^* - C_w^*} \right) \frac{\partial C^*}{\partial y^*} \right|_{y^* = \frac{1}{2}} \quad (5-38) \]

Relationships analogous to equations (5-32) through (5-34) may also be derived.

Local mass transfer coefficients for fluids flowing in conduits are generally of limited utility because they require knowledge of conditions at a specific point. Of more practical
value are average mass transfer coefficients which relate to the inlet and outlet concentrations only. The choice of a particular type of average coefficient is arbitrary and valid so long as the appropriate average concentration driving force is employed. Norris and Streid (299) and Drew (108, 109) have discussed many of the alternative definitions which have been used in heat transfer, such as the inlet temperature difference, the arithmetic mean temperature difference, and the logarithmic mean temperature difference, and several others. The latter quantity was used throughout this study for three reasons:

1) It is most commonly used today.
2) At large \( x^* \), it asymptotes to the asymptotic local value.
3) It represents the true average of the local coefficient integrated over the entire length (201).

The logarithmic mean, overall mass transfer coefficient is defined by

\[
\dot{N} = k_{m,o} A \left[ \frac{(c_i - c_0) - (c_b - c_0)}{\ln \left( \frac{c_i - c_0}{c_b - c_0} \right)} \right] \tag{5-39}
\]

where the total mass transfer area, \( A \), equals \( 2wx \). The subscript "m" will be used throughout to denote the log-mean coefficient. The total mass transfer rate is also given by

\[
N = Q (c_i - c_b) = w \tilde{v} (c_i - c_b) \tag{5-40}
\]

Setting equations (5-39) and (5-40) equal and rearranging yields
\[ Sh_{m,o} = \frac{k_{m,o} h}{D} = \frac{1}{2x^*} \ln \left( \frac{1}{C_b^*} \right) \] (5-41)

Equation (5-34) may be rearranged as
\[ 2 \ Sh_{x,o} dx^* = - \frac{dC_b^*}{C_b^*} \] (5-42)

At \( x^*=0 \), \( C_b^*=1 \), and one may integrate to obtain
\[ 2 \int_0^{x^*} Sh_{x,o} dx^* = - \int_1^{C_b^*} \frac{dC_b^*}{C_b^*} = -\ln C_b^* \] (5-43)

Thus,
\[ \frac{1}{x^*} \int_0^{x^*} Sh_{x,o} dx^* = \frac{1}{2x^*} \ln \left( \frac{1}{C_b^*} \right) \] (5-44)

and comparison of equations (5-41) and (5-44) shows that
\[ \frac{1}{x^*} \int_0^{x^*} Sh_{x,o} dx^* = Sh_{m,o} \] (5-45)

In addition to demonstrating that the log mean average is the true length average of the local Sherwood number, equation (5-45) may be used to calculate \( Sh_{m,o} \) directly if the \( x^* \) dependence of \( Sh_{x,o} \) is readily integrable.

A definition analogous to equation (5-39) for the fluid-side log mean mass transfer coefficient cannot be formulated because, at the inlet, \( c_i = c_b = c_w \), and the log term becomes indeterminate. However, an equivalent fluid-side coefficient can be calculated from the additivity of resistances in series:
\[ \frac{1}{k_{m,o}} = \frac{1}{k_w} + \frac{1}{k_{m,f}} \] (5-46)
and thus

\[
\frac{1}{Sh_{m,o}} = \frac{1}{Sh_w} + \frac{1}{Sh_{m,f}} \tag{5-47}
\]

Alternatively, \(Sh_{m,f}\) may be obtained from the expression

\[
Sh_{m,f} = Sh_w \cdot \frac{1 + \frac{1}{x^*} \int_0^{x^*} \frac{Sh_{x,f}}{Sh_w + Sh_{x,f}} \, dx^*}{\frac{1}{x^*} \int_0^{x^*} \frac{Sh_{x,f}}{Sh_w + Sh_{x,f}} \, dx^*} \tag{5-48}
\]

This relation may be obtained by inverting equation (5-36) integrating the resulting expression for \(Sh_{x,o}\) as in equation (5-45), setting this equal to \(Sh_{m,o}\) from equation (5-47), and rearranging. Of course, the use of equation (5-47) directly is more tractable.

Although they were not extensively investigated, the equations for the arithmetic mean concentration difference are given here as a matter of record. For the overall coefficient,

\[
Q \frac{(c_i-c_0) - (c_b-c_0)}{2} = k_{a,o}(2wx) \frac{(c_i-c_0) + (c_b-c_0)}{2} \tag{5-49}
\]

and

\[
Sh_{a,o} = \frac{k_a h}{D} = \frac{2}{x^*} \left[ \frac{1-C_b^*}{1+C_b^*} \right] \tag{5-50}
\]

For the fluid-side coefficient,

\[
Q \frac{(c_i-c_0) - (c_b-c_0)}{2} = k_{a,f}(2wx) \frac{(c_i-c_{w1})+(c_b-c_{w})}{2} \tag{5-51}
\]

Note that \(c_i=c_{w1}\). Then

\[
Sh_{a,f} = \frac{2}{x^*} \frac{1-C_b^*}{C^*_b-C^*_c} \tag{5-52}
\]
2. Solution of Differential Equation

Equation (5-19), subject to the three boundary conditions (5-20) through (5-22) may be solved by the method of separation of variables. A solution is assumed of the form

\[ C^* (x^*, y^*) = X (x^*) Y (y^*) \]  \hspace{1cm} (5-53)

Substituting equation (5-53) into (5-19) yields

\[ \frac{3}{2} \left( \frac{1}{X} \right) \frac{dX}{dx^*} = \frac{1}{1 - 4y^*^2} \left( \frac{1}{Y} \right) \frac{d^2Y}{dy^*^2} \]  \hspace{1cm} (5-53)

Since the left hand side is a function of \( x^* \) only and the right hand side is a function of \( y^* \) only, both sides must be constant and may be set equal to a constant, \(-\beta^2\). From this, one obtains two independent ordinary differential equations and their associated boundary conditions for the axial and longitudinal components of the solution:

\[ \frac{dX}{dx^*} + \frac{2}{3} \beta^2 X = 0 \]  \hspace{1cm} (5-55)

B.C. \hspace{0.5cm} x^* = 0 \hspace{0.5cm} X = 1 \hspace{1cm} (5-56)

and

\[ \frac{d^2Y}{dy^*^2} + \beta^2 (1 - 4y^*^2) Y = 0 \]  \hspace{1cm} (5-57)

B.C. 1 \hspace{0.5cm} y^* = 0 \hspace{0.5cm} \frac{dY}{dy^*} = 0 \hspace{1cm} (5-58)

B.C. 2 \hspace{0.5cm} y^* = \frac{1}{2} \hspace{0.5cm} \frac{dY}{dy^*} = Sh_W Y \hspace{1cm} (5-59)

The solution to equation (5-55) and boundary condition (5-56) is

\[ X(x^*) = e^{-[2\beta^2 x^*/3]} \]  \hspace{1cm} (5-60)

Equation (5-57) and its boundary conditions are of the Sturm-Liouville type (176) which will give rise to an infinite set
of eigenvalues $\beta_m$, $m=0,1,2,\ldots$, and corresponding eigenfunctions $Y_m(y^*)$, $m=0,1,2,\ldots$. The functions $Y_m$ form an orthogonal set with respect to the weighting function $(1-4y^{*2})$, i.e.

$$\int_{-1/2}^{1/2} (1-4y^{*2}) Y_m(y^*) Y_n(y^*) \, dy^* = 0 \quad m \neq n \quad (5-61)$$

Consequently, the solution may be found by superposing all particular solutions to give

$$C^* = \sum_{m=0}^{\infty} A_m \exp \left[-2\beta_m^2 \frac{x^*}{3} \right] Y_m(y^*) \quad (5/62)$$

The eigenvalues $\beta_m$ and the constants $A_m$ are chosen to satisfy the appropriate boundary conditions. Using the first boundary condition ($C^* = 1$ at $x^* = 0$), multiplying both sides of equation (5-62) by $(1-4y^{*2}) Y_n$, integrating over $y^*$, and applying equation (5-61) yields for $A_m$:

$$A_m = \frac{\int_{-1/2}^{1/2} (1-4y^{*2}) Y_m \, dy^*}{\int_{-1/2}^{1/2} (1-4y^{*2}) Y_m^2 \, dy^*} \quad (5/63)$$

The bulk average concentration may be obtained by substituting equation (5-62) into equation (5-29) to yield

$$C_{b^*} = \frac{\sum_{m=0}^{\infty} A_m \exp\left[-2\beta_m^2 \frac{x^*}{3} \right] Y_m(1-4y^{*2}) \, dy^*}{\int_{-1/2}^{1/2} (1-4y^{*2}) \, dy^*} \quad (5-64)$$

$$= \sum_{m=0}^{\infty} \beta_m \exp \left[-2\beta_m^2 \frac{x^*}{3} \right] \quad (5-65)$$
where \( \beta_m = \frac{3}{2} A_m \int_{-1/2}^{1/2} (1-4y^*^2) Y_m \, dy^* \) \hspace{1cm} (5-66)

The dimensionless concentration at the wall, \( C_w^* \), may be obtained by substituting \( Y_m(1/2) \) for \( Y_m(y^*) \) in equation (5-62).

Equation (5-57) may be solved by assuming a form of the solution for \( Y(y^*) \). Previous solutions have been based upon two different forms for the solution

1) \( Y = \sum_n a_n y^*^n \) \hspace{1cm} (5-67)

2) \( Y = e^{-\beta y^*^2} \chi \) \hspace{1cm} (5-68)

Van der Does de Bye and Schenk (103) proposed both forms but used the latter, while Grimsrud and Babb (154) used the simple power series. Of course, many other forms for the solution are possible. Two different methods were also used for evaluating the definite integrals in equation (5-63):

3) Direct substitution of the solution for \( Y \), followed by integration (Grimsrud and Babb)

4) Rearrangement of the integrals into a modified form, similar to the original Graetz treatment (150) (Van der Does de Bye and Schenk).

Of the four possible combinations presented above, three were investigated in collaboration with Stroeve (409). These were 1-3, 1-4, and 2-4. All three methods were used to determine the first seven eigenvalues and their associated constants for \( \text{Sh}_w = 2.0 \). Calculations were performed on the IBM 360/65 digital computer with fourteen significant decimal digits. The methods were judged according to 1) the accuracy
attainable (some were more susceptible to round off errors than others) and 2) the computer time required for identical calculations.

Stroeve (409) has discussed the equations used and results obtained with each method. Combination 1-4, used by none of the previous investigators, was judged the most accurate and the fastest, while 2-4 was the slowest. For further details, the reader is referred to Stroeve's discussion. After the preliminary evaluation, combination 1-4 was used for all calculations, and the following discussion applies to this method only. A large portion of the numerical results presented in this study were taken from the extensive tabulations of Stroeve.

The definite integrals in equations (5-63) may be expressed as

\[ \int_{-1/2}^{1/2} (1-4 \, y^2) \, Y_m \, dy^* = \frac{2 \, Sh_w}{\beta_m^2} \, Y_m (1/2) \quad (5-69) \]

\[ \int_{-1/2}^{1/2} (1-4 \, y^2) \, Y_m^2 \, dy^* = \frac{Y_m^2 (1/2)}{\beta_m} \, \frac{dSh_w}{d\beta_m} \quad (5-70) \]

Van der Does de Bye and Schenk stated these equalities but presented no proof. A derivation of these relations, made by the author, may be found in Appendix L.

From equations (5-63), (5-69), and (5-70), \( A_m \) becomes

\[ A_m = \frac{2 \, Sh_w}{\beta_m \, Y_m (1/2) \, \frac{dSh_w}{d\beta_m}} \quad (5-71) \]

Combining equations (5-66) and (5-71) yields
\[ B_m = \frac{3 A_m Y_m(\frac{1}{2}) \text{Sh}_w}{\beta_m^2} \]  
(5-72)

and substitution for \( A_m \) gives

\[ B_m = \frac{6 \text{Sh}_w}{\beta_m^3 \frac{d\text{Sh}_w}{d\beta_m}} \]  
(5-73)

Upon substitution of equation (5-67) into equation (5-57) and setting the sum of the coefficients of like powers of \( y^* \) equal to zero one obtains the following recurrence formula for the coefficients \( a_n \):

\[ a_n = \frac{\beta^2}{n(n-1)} (4a_{n-4} - a_{n-2}) \]  
(5-74)

with

\[ a_0 = 1 \]
\[ a_1 = 0 \]  
(5-75)
\[ a_2 = -\beta^2/2 \]
\[ a_3 = 0 \]

The constant \( a_0 \) is arbitrarily set equal to unity; \( a_1 \) and all subsequent odd coefficients are equal to zero to meet the symmetry boundary condition (5-58).

The eigenvalues, \( \beta_m \), are chosen to satisfy the wall boundary condition (5-59). Thus

\[ Y_m(\frac{1}{2}) = \sum_{n=0}^{\infty} a_{m,n}(\frac{1}{2})^n \]  
(5-76)

\[ \left. \frac{dY_m}{dy^*} \right|_{y^*=\frac{1}{2}} = \sum_{n=0}^{\infty} na_{m,n}(\frac{1}{2})^{n-1} \]  
(5-77)

and

\[ \text{Sh}_w = -\frac{\sum_{n=0}^{\infty} na_{m,n}(\frac{1}{2})^{n-1}}{\sum_{n=0}^{\infty} a_{m,n}(\frac{1}{2})^n} \]  
(5-78)
It should be noted that had the half channel width been used as the characteristic length in the y direction \((y^* = y/a)\), equation (5-78) would be stated as

\[
Sh_w = - \sum_{n=0}^{\infty} \frac{n a_n}{\sum_{n=0}^{\infty} a_n} \tag{5-79}
\]

Babb and coworkers have consistently used the half-channel width. For comparative purposes, denoting quantities based on the half channel width with a subscript "a", one finds \(y^* = 1/2 \ y_a^*\), \(x^* = 1/4 \ x_a^*\), \(Sh_w = 2 \ Sh_{wa}\), \(\beta = 2 \beta_a\), while \(A_m = A_{ma}\) and \(B_m = B_{ma}\).

Because of the form of the solution, it is necessary to first pick a value of \(\beta_m\), evaluate the coefficients \(A_m, n\) from equations (5-74) and (5-75), and then calculate \(Sh_w\) from equation (5-78). By this procedure, a series of tables relating \(\beta_m\) to \(Sh_w\) may be generated. In general, one knows \(Sh_w\) and desires to calculate the \(\beta_m\). The eigenvalues for a particular wall Sherwood number may be picked off the appropriate curves graphically. However, this procedure is unworkable when highly accurate values of many eigenvalues are required, or when many repeated calculations are performed.

A technique was developed (409) to obtain the eigenvalues for a given wall Sherwood number on a digital computer. A new function was defined by

\[
F = \left| Sh_w + \sum_{n=0}^{\infty} \frac{n a_n (1/2)}{\sum_{n=0}^{\infty} a_n (1/2)^n} \right|^{n-1} \tag{5-80}
\]
When the correct value for \( \beta_m \) is inserted into eqn. (5-80), \( F \) is zero. Thus the problem of finding the correct eigenvalues for a particular \( \text{Sh}_w \) reduced to a one-dimensional optimization problem. In practice, an initial guess of \( \beta_m \) was made, and the value of \( \beta_m \) giving a minimum in the function \( F \) was found by a golden section search (429). The accuracy attainable was limited only by 1) the number of iterations used, and 2) the number of significant digits carried. Using double precision (14 significant digits), an accuracy of up to ten significant figures was attainable for the first three eigenvalues. For the higher eigenvalues, the infinite series converged more slowly and round-off error became noticeable. A modified technique was developed to yield relatively accurate values very rapidly; it is discussed in Section 5.C.5.b.

In order to calculate the coefficients \( A_m \) and \( B_m \), one needs an expression for \( d\text{Sh}_w/d\beta_m \). From the second boundary condition (5-59) one finds

\[
\frac{d\text{Sh}_w}{d\beta_m} = -\left\{ \frac{\partial}{\partial \beta_m} \left[ \left. \frac{\partial Y_m}{\partial y^*} \right|_{y^*=\frac{1}{2}} \right] \right\}
\]

\[
= - \left. \frac{\partial Y_m}{\partial y^*} \right|_{y^*=\frac{1}{2}} + \left. \frac{\partial Y_m}{\partial \beta_m} \right|_{y^*=\frac{1}{2}} \left( \frac{\partial Y_m}{\partial y^*} \right)_{y^*=\frac{1}{2}} (5-82)
\]

The quantities \( Y_m(\frac{1}{2}) \) and \( \left[ \frac{\partial Y_m}{\partial y^*} \right]_{y^*=\frac{1}{2}} \) have already been defined by equations (5-76) and (5-77). By differentiating these expressions with respect to \( \beta_m \), one obtains
\[
\frac{\alpha Y_m(\frac{1}{y})}{\alpha \beta_m} = \sum_{n=0}^{\infty} \frac{\alpha a_{m,n}}{\alpha \beta_m} (\frac{1}{y})^n
\]  
(5-83)

\[
\frac{\alpha}{\alpha \beta} \left[ \frac{\partial Y_m}{\partial y^*} \right]_{y^* = \frac{1}{y}} = \sum_{n=0}^{\infty} n \frac{\partial a_{m,n}}{\alpha \beta_m} (\frac{1}{y})^{n-1}
\]  
(5-84)

The derivatives of the coefficients, \( a_n \), with respect to the eigenvalue, \( \beta \), may be readily evaluated from eqns. (5-74) and (5-75). Thus

\[
\frac{\partial a_0}{\partial \beta} = 0
\]  
(5-85)

\[
\frac{\partial a_2}{\partial \beta} = -\beta
\]  
(5-86)

and

\[
\frac{\partial a_n}{\partial \beta} = \frac{2\beta (4a_{n-4} - a_{n-2})}{n(n-1)} + \beta^2 (4 \frac{\partial a_{n-4}}{\partial \beta} + \frac{\partial a_{n-2}}{\partial \beta})
\]  
(5-87)

All odd terms are zero.

The set of equations (5-67) and (5-71) through (5-87) represent the working formulas required to calculate all the quantities of interest. It may be noted that only single summations are employed in the method discussed. For both of the other methods described above, double summations were required at some point in the solution (409). It was found that these operations were particularly time-consuming since the outer summation had to be taken to several hundred terms for the higher eigenvalues.

From the solution described above, the local Sherwood numbers may be calculated as follows:
\[
\text{Sh}_{x,0} = -\frac{\sum_{m=0}^{\infty} A_m \exp[-2\beta_m^2 x^*/3] \frac{\partial Y_m}{\partial y^*} \bigg|_{y^*=y}}{\sum_{m=0}^{\infty} B_m \exp[-2\beta_m^2 x^*/3]}
\]

\[
\text{Sh}_{x,f} = -\frac{\sum_{m=0}^{\infty} A_m \exp[-2\beta_m^2 x^*/3] \frac{Y_m}{y^*} \bigg|_{y^*=y}}{\sum_{m=0}^{\infty} B_m \exp[-2\beta_m^2 x^*/3] - \sum_{m=0}^{\infty} A_m \exp[-2\beta_m^2 x^*/3] Y_m(y)}
\]

The log mean and arithmetic average Sherwood numbers may be obtained by direct substitution of \(C_b^*\) into their defining equations presented above.

For large values of \(x^*\), only the first terms in the summations in eqn. (5-88) are significant. Thus one finds for the asymptotic, local, overall Sherwood number

\[
\text{Sh}_{x,0,\infty} = \frac{A_1}{B_1} \frac{\partial Y_1}{\partial y^*} \bigg|_{y^*=y}
\]

Combination with eqns. (5-59), (5-72) and (5-73) yields

\[
\text{Sh}_{x,0,\infty} = \frac{1}{3} \beta_1^2
\]

Using eqn. (5-36), one finds for the asymptotic, local, fluid-side Sherwood number

\[
\text{Sh}_{x,f,\infty} = \frac{1}{\frac{3}{\beta_1^2} - \frac{1}{\text{Sh}_w}}
\]

As \(x^*\) increases to large values, the respective log-mean Sherwood numbers asymptote to the local Sherwood numbers.

3. Limiting Solutions

For the analogous case of fully-developed laminar heat transfer
between parallel plates, the best available solutions for the limiting boundary conditions of constant temperature and constant heat flux at the wall are due to Brown (55) and Cess and Shaffer (64), respectively. Both cases reduce to eigenvalue problems which may be solved in somewhat analogous fashion to the solution described above. The reader is referred to the original articles for details. In both cases, only a single Nusselt (or Sherwood) number is defined, characteristic of the internal fluid.

For a constant concentration boundary condition, analogous expressions for $C^*$ and $C_b^*$, equations (5-62) and (5-65), apply with constant $c_w$ replacing $c_0$. The local Sherwood number, $Sh_{x,c}$ (where the subscript "c" denotes constant concentration), is given by equation (5-88). In addition, equation (5-91) applies, and one finds for the asymptotic Sherwood number

$$Sh_{x,c,*} = \frac{k_{x,c,*}h}{D} = 3.77035 \quad (5-93)$$

For the constant flux boundary condition, the average bulk concentration is found directly from a simple overall mass balance:

$$\dot{N} = (2wx) \dot{n} = Q (c_b - c_i) \quad (5-94)$$

or

$$c_b - c_i = \frac{2xn}{\dot{h}V} \quad (5-95)$$

The solution for the local concentration profile and local Sherwood number is accomplished by defining a dimensionless concentration profile for the entrance region in excess of the asymptotic concentration profile. The solution for the
former quantity is an eigenvalue problem, and the total solution is obtained by adding the two concentration profiles. Of interest here is the local Sherwood number, defined by

\[
Sh_{x,n} = \frac{n \frac{h}{(c_w - c_b)}}{D} = \frac{k_{x,n} h}{D} \quad (5-96)
\]

where the subscript "n" refers to constant flux. Cess and Shaffer (64) used a characteristic length of 2h. With the nomenclature used in this study, their results are given by

\[
Sh_{x,n} = \frac{17}{35} + \frac{m}{\sum_{m=1}^{\infty}} c_m Y_m(\frac{1}{2}) \exp \left[-2\beta_m^2 x^*/3\right] \quad (5-97)
\]

Where \( Y_m(\frac{1}{2}) \) is equivalent to their \( \gamma_n(1) \), \( \beta_m \) equals twice their \( \beta_n \), and \( x^* \) is four times their \( (x/a)/Pe \). When \( x^* \) is very large, the summation term vanishes and one finds

\[
Sh_{x,n,\infty} = \frac{70}{17} = 4.11765 \quad (5-98)
\]

Comparison of equations (5-93) and (5-98) shows that the asymptotic local Sherwood number is higher for the constant flux case and the ratio is

\[
\frac{Sh_{x,n,\infty}}{Sh_{x,c,\infty}} = 1.0921 \quad (5-99)
\]

Kays (176) has pointed out that this difference can be explained simply by the slightly different shape of the dimensionless temperature (or concentration) profiles for the two cases.

For the constant flux case, a log-mean Sherwood number is not properly defined. With reference to equation (5-39), with \( c_w \) substituted for \( c_0 \), at the inlet \( c_i = c_w \) and the logarithmic term is minus infinity.
The Leveque entrance region solution for a constant temperature (concentration) boundary condition has been summarized by Knudsen and Katz. Brid (36a) apparently first solved the constant flux case, although Sellars, et al. (374) had earlier used superposition to solve for this boundary condition. All existing analyses have been applied to a tube, but the results may be easily generalized to the parallel plate case. The characteristic feature of these solutions is that the velocity is assumed to be a linear function of the distance from the wall.

For a Leveque-type solution, the local mass transfer coefficient is defined by

\[ k_x = -\frac{D}{c_i - c_w} \frac{\partial c}{\partial y} \bigg|_{y=\frac{h}{2}} \quad (5-100) \]

where, for constant flux,

\[ -D \frac{\partial c}{\partial y} \bigg|_{y=\frac{h}{2}} = n \quad (5-101) \]

Note that this differs from the definitions used above, in that \( c_b \) is replaced by \( c_i \). Thus the two types of coefficients are only comparable at very small \( x^* \) where little transport has occurred and \( c_i = c_b \).

For constant concentration, the solution may be expressed as

\[ Sh_{x,c} = \frac{3 \alpha^{1/3}}{\varphi^{1/3} \Gamma(1/3)} x^{*-1/3} \quad (5-102) \]

and for constant flux
\[ \text{Sh}_{x,n} = \frac{\Gamma (\frac{2}{3}) \alpha^{1/3}}{g^{1/3}} x^{1/3} \]  
(5-103)

(in Bird's original paper, \(g^{1/3}\) erroneously appears in the numerator) where \(\alpha\) is related to the shear rate at the wall:

\[ \frac{dV_x}{dy} \bigg|_{y=\frac{h}{2}} = \frac{\alpha}{h} \frac{v}{x} \]

For parallel plates, with \(V_x\) given by equation (5-3), \(\alpha = 6\) and one obtains

\[ \text{Sh}_{x,c} = 0.97828 \ x^{1/3} \]  
(5-104)

and

\[ \text{Sh}_{x,n} = 1.1829 \ x^{1/3} \]  
(5-105)

The ratio of the constant flux to constant concentration local Sherwood numbers in the entrance region is

\[ \frac{\text{Sh}_{x,n}}{\text{Sh}_{x,c}} = 1.2092 \]  
(5-106)

which is significantly different from the ratio of the asymptotic coefficients.

Using equation (5-45), one can evaluate the log-mean Sherwood number. Thus

\[ \frac{1}{x} \int_0^x A x^{-1/3} \, dx = 1.5 A x^{-1/3} \]  
(5-107)

and the log-mean Sherwood number from the Leveque-type analysis is 50 per cent higher than the local value.

Consequently,

\[ \text{Sh}_{m,c} = 1.4674 \ x^{1/3} \]  
(5-108)
For the wall flux boundary condition of interest in this study, a Leveque-type solution cannot be obtained because the similarity transformation one uses in such an analysis does not satisfy the wall boundary condition. A solution valid for $Sh_x x^{1/3} \ll 1$ was obtained by a perturbation analysis. It corresponds to "near constant flux" conditions.

A detailed derivation of the solution is given in Appendix M. Briefly, the velocity is assumed to be a linear function of the distance from the wall and the concentration is expressed as an infinite series of the form

$$c = c_i + (c_i - c_0) [\varepsilon f_1(\xi) + \varepsilon^2 f_2(\xi) + \ldots]$$

where

$$\varepsilon = 6^{-1/3} Sh_w x^{1/3}$$

$$\xi = 6^{1/3} y x^{-1/3}$$

With only the first term employed, $f_1$, the solution is the parallel plate analogue of Bird's constant flux solution for a tube (36a). Consequently, the functional dependence of $f_1(\xi)$ on $\xi$ is known. The solution for $f_2(\xi)$ was obtained numerically. Higher terms were not considered, and thus the solution constitutes a first order correction to the constant flux case for a non-zero $Sh_w$.

The Sherwood number relationships obtained were

$$Sh_{x,o} = Sh_w [1 - 0.8453 \ Sh_w x^{1/3}]$$

and

$$Sh_{x,f} = 1.1829 x^{-1/3} - 0.1320 \ Sh_w$$

From these results, several conclusions regarding the
entrance region behavior of the Sherwood numbers may be
drawn:

1) For $Sh_w = 0$, $Sh_{x,*0} = 0$ and $Sh_{x,*f}$ is given by the
   constant flux expression.

2) For $x^* = 0$, $Sh_{x,*0} = Sh_w$ and $Sh_{x,*f} = \infty$.

3) For $Sh_w x^{1/3} \ll 1$, $Sh_{x,*f}$ approaches the constant flux
   value for any $Sh_w$.

4) As $x^*$ increases from zero, $Sh_{x,*f}$ for successively
   lower values of $Sh_w$ will "peel off" the constant flux curve.

Grimsrud and Babb (154) developed a laminar boundary-
layer analysis for the entrance region of a flat plate dialyzer.
Their results are compared with the perturbation analysis in
Appendix M.

4. Calculated Theoretical Results

The first six eigenvalues are shown in Figure 5-2,
where $Sh_w$ is plotted as a function of $\beta$. Each eigenvalue
asymptotes towards a limiting value for $Sh_w = \infty$ and intersects
the $\beta$ axis for $Sh_w = 0$.

Eigenvalues for selected wall Sherwood numbers are
tabulated in Table 5-1. The ten eigenvalues for $Sh_w = \infty$ were
taken from the constant concentration (or temperature)
solution of Brown (55). They have been multiplied by two to
correct for the difference in characteristic length employed.
As $m$ becomes large, the asymptotic expression derived by
Sellars, et al. (374) applies. For the nomenclature used in
this study, it is

$$\beta_m = 8(m-1) + \frac{10}{3}$$ (5-114)
Figure 5-2. Dependence of First Six Eigenvalues on Wall Sherwood Number
The last column contains the first three eigenvalues for the constant flux case evaluated by Cess and Shaffer (64). The next to the last column contains the eigenvalues evaluated from equation (5-80) by setting \( Sh_w = 0 \). The first eigenvalue is zero. Thenceforth, one finds that

\[
\beta_m \bigg|_{Sh_w = 0} = \beta_{m-1} \quad \text{const. flux}
\] (5-115)

This clearly establishes certain mathematical similarities between the two cases. For large \( m \), Cess and Shaffer performed a similar analysis to that of Sellars, et al. and found

\[
\beta_m = 8 (m-1) + \frac{2}{3}
\] (5-116)

However, it should be noted that for \( Sh_w = 0 \), \( \beta_m \) converges to its asymptotic value for large \( m \) much more slowly than for \( Sh_w = \infty \).

For intermediate \( Sh_w \), the eigenvalues may be expressed in the form

\[
\beta_m = 8 (m-1) + f(m, Sh_w)
\] (5-117)

where the additional term is a function of both \( Sh_w \) and \( m \).

From Figure 5-2 it may be noted that although the relationship between the eigenvalues for \( Sh_w = 0 \) and \( Sh_w = \infty \) is invariant with \( m \), the shape of the curve for finite \( Sh_w \) changes as \( m \) increases. In the limit as \( m \to \infty \), the eigenvalue approaches a vertical line at the value of \( \beta_m \) corresponding to \( Sh_w = 0 \). A more detailed discussion of the asymptotic behavior of \( \beta_m \) for finite \( Sh_w \) is given in Appendix M, where an asymptotic
<table>
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<th>Sh_w=∞ (55)</th>
<th>Sh_w=100</th>
<th>Sh_w=10</th>
<th>Sh_w=4</th>
<th>Sh_w=1</th>
<th>Sh_w=0.1</th>
<th>Sh_w=0</th>
<th>$e_{m-1}$ (65)</th>
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<tbody>
<tr>
<td>1</td>
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<td>3.30672596</td>
<td>2.891947431</td>
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<td>1.55101554</td>
<td>0.54117720</td>
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<td></td>
</tr>
<tr>
<td>4</td>
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<td>27.11632948</td>
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<td>25.35457539</td>
<td>24.83852812</td>
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<td>32.81042639</td>
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<td>32.62904341</td>
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</tr>
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<td>48.638</td>
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</tr>
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</tr>
<tr>
<td>10</td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
expression valid for large \( m \) is derived for \( \beta_m, A_m, \) and \( B_m \).

It was found that the asymptotic expression gave a good approximation to the seventh eigenvalue. Consequently, the complete solution for the modified Graetz problem for parallel plates is now available. Using the Graetz-type solution, Stroev (409) found that more than 14 significant figures were required for generation of eigenvalues higher than the seventh. Additional numerical tabulations for the first seven eigenvalues may be found in Appendix N.

The change in \( C_b^* \) as a function of \( x^* \) is shown in Figure 5-3 for various values of \( Sh_w \). Over most of the plotted range, the curves are relatively straight on a semi-logarithmic plot because only the first eigenvalue is significant. The change in the \( C_b^* \) vs \( x^* \) relationship is small, going from \( Sh_w = - \) to \( Sh_w = 10 \), compared to the change from \( Sh_w = 10 \) to \( Sh_w = 1.0 \).

Three dotted curves are plotted to illustrate the dependence of \( C_b^* \) on individual variables. The common point for all three curves is at \( x^* = 0.5, Sh_w = 2.0 \). Changing \( k_w \) affects only \( Sh_w \); thus one moves along curve 1. \( Sh_w \) is inversely proportional to \( D \) while \( x^* \) is directly proportional to \( D \), so that one moves along curve 2 as \( D \) varies. The same curve applies to varying \( h \) while holding total flow rate constant. If instead \( \bar{v} \) is held constant and \( h \) is varied, curve 3 applies, since the \( x^* \) dependence on \( h \) is \( 1/h^2 \). Changes in \( x \) or \( \bar{v} \) do not affect \( Sh_w \).

Consequently one moves along a constant \( Sh_w \) curve. If one were on the \( Sh_w = - \) curve, then changes in any of the
Figure 5-3. Dimensionless Bulk Concentration as a Function of Dimensionless Length for Various Values of Wall Suction Number

(See text, Section 5.C.3, for explanation of dotted lines)
primary variables making up $x^*$ would cause movement solely along the constant $Sh_w$ curve.

Local and logarithmic-mean Sherwood numbers for $Sh_w = \cdots$ are shown in Figure 5-4 as a function of $x^*$. Various curves are plotted for one through ten eigenvalues, illustrating the number of eigenvalues required for a given $x^*$. The constant concentration Leveque solution is also plotted. Its region of applicability extends down to about $x^* = 10^{-3}$ to $2 \times 10^{-3}$. As $x^*$ decreases, the additional number of eigenvalues required per unit change in $x^*$ increases. For a given accuracy requirement in the calculated Sherwood number, the log-mean average requires more eigenvalues than the local value. Figure 5-4 also illustrates that the local Sherwood number reaches its asymptotic value at a much lower $x^*$ than that required for the log-mean Sherwood number to reach the asymptotic value. For finite $Sh_w$, the fluid-side Sherwood numbers behave qualitatively the same as those for $Sh_w = \cdots$. For fixed Sherwood number accuracy, the eigenvalue requirements are the same. The eigenvalue requirements for fixed accuracy in $C_b^*$ are discussed in Appendix N.

Figure 5-5 depicts the local and log-mean overall Sherwood numbers as a function of $x^*$ for various $Sh_w$. At the inlet, $x^* = 0$, the overall Sherwood numbers are equal to the wall Sherwood number. For $x^* > 0$, both Sherwood numbers decrease to their limiting value. As $Sh_w$ decreases, the difference between $Sh_{x,0}$ and $Sh_{m,0}$ at any $x^*$ decreases, and the difference between $Sh_w$ and the limiting Sherwood
Figure 5-4. Local and Log-Mean Sherwood Numbers for $Sh_W = \infty$

$m = \text{No of Eigenvalues}$
Figure 5-5. Local and Log-Mean Overall Sherwood Numbers for Finite $Sh_w$. 

$$x^* = \frac{xD_t}{\nu h}$$
number decreases. As $Sh_w$ tends to zero, both $Sh_{x,0}$ and $Sh_{m,0}$ tend to $Sh_w$ over the entire length.

Local fluid-side Sherwood numbers as a function of $x^*$ are shown for various $Sh_w$ in Figure 5-6. The smallest value of $x^*$ plotted, around $2 \times 10^{-3}$, represents approximately the limit for seven eigenvalues for four significant digit accuracy. At $x^* = 10^{-1}$, the Sherwood numbers have almost reached their asymptotic value.

Several important conclusions may be drawn from Figure 5-6. The constant concentration ($Sh_w = \infty$) and constant flux ($Sh_w = 0$) curves form an envelope between which the curves for all finite $Sh_w$ are located. However, the curves for finite $Sh_w$ are not parallel, neither to themselves, nor to either limiting case. As $x^*$ decreases, there is a small, but perceptible shift towards the constant flux case. This trend is considered in more detail with respect to the entrance region behavior of the solution in Appendix M.

Figure 5-7 illustrates the dependence of the limiting fluid side Sherwood number, $Sh_{x,f,\infty}$, on the wall Sherwood number. In addition the ratio

$$\phi(Sh_w) = \frac{Sh_{x,f,\infty}}{Sh_{x,c,\infty}}$$

which relates the limiting coefficient to that for $Sh_w = \infty$, is plotted as a function of $Sh_w$. The greatest change occurs between wall Sherwood numbers of 1 and 10. For $Sh_w > 10^2$ and $Sh_w < 10^{-1}$, the limiting values are very close to those for $Sh_w = \infty$ and $Sh_w = 0$, respectively.

For the fluid-side log-mean Sherwood number, a plot
Figure 5-6. Local fluid-side Sherwood Numbers.
Figure 5-7. Limiting Fluid-Side Sherwood Number as a Function of $Sh_w$.
qualitatively similar to Figure 5-6 can be constructed. The limiting value, of course, is the same as that plotted in Figure 5-7. The results of two such plots can be combined into a particularly informative graph, as shown in Figure 5-8. It is constructed as follows:

Let

\[ \phi_{m,f} (Sh_{w}, x*) = \frac{Sh_{m,f}}{Sh_{m,c}} \]  
(5-117)

\( \phi_{m,f} \) is simply the ratio of the fluid-side log-mean Sherwood number for a finite \( Sh_{w} \) to that for \( Sh_{w} = \infty \) at a particular value of \( x* \). The ratio of this quantity to \( \phi (Sh_{w}) \), from Figure 5-7, is plotted in Figure 5-8 as a function of \( x* \) for a wide range of \( Sh_{w} \). As expected, for large \( x* \), the ratio tends towards unity. As \( x* \) decreases, the ratio first decreases, and then increases, except for very low \( Sh_{w} \). The various curves for different \( Sh_{w} \) are not coincident and their dependence on \( x* \) changes. This is not unexpected, since the curves for the local fluid-side Sherwood numbers are not parallel, and the dependence of \( Sh_{m,f} \) on \( x* \), given by equation (5-48), is clearly complex.

The most noteworthy feature of Figure 5-8 is that for \( x* > 5 \times 10^{-3} \), the ratio generally does not deviate from unity by more than \( \pm 1 \% \). This means that \( \phi_{m,f} (Sh_{w}, x*) \) may be approximated by \( \phi (Sh_{w}) \) to within a fairly high degree of accuracy. The potential use of this relationship is as follows.

For many applications, it may be desirable to obtain relatively accurate estimates of \( C_{b*} \) as a function of \( x* \) and
Figure 5-8. Normalized Ratio for Fluid-Side Log-Mean Sherwood Number

\[ \frac{\phi_{m,f}(Sh_w, x^*)}{\phi(Sh_w)} \]

\[ x^* = \frac{xD}{vh^2} \]
Shw. The most accurate approach is to use the eigenvalue solution discussed in the previous section. This requires a computer or inordinately laborious hand calculations. However, if one knows or can estimate Shm,o, Cb* may be evaluated directly from equation (5-41).

Now, Shm,f was obtained from the calculated Shm,o by

\[
\frac{1}{Shm,f} = \frac{1}{Shm,o} - \frac{1}{Shw} \tag{5-118}
\]

Conversely, if Shm,f can be estimated, Shm,o may be calculated from equation (5-47). Finally, Shm,f can be estimated from

\[
Shm,f = \phi(Shw) Shm,c \tag{5-119}
\]

where Shm,c is plotted in Figure 5-4 or can be calculated directly from Brown's tabulated eigenvalues and constants (55). The value of this technique is that it bypasses the calculation of the eigenvalues for the particular Shw of interest. This method was tested by hand calculation with a wide range of values of Shw and x* and was found to yield an accuracy in Cb* of about 0.3%, or better.

To facilitate the use of this method for a quick calculation on a computer, \(\phi(Shw)\) was fitted to a least-squares polynomial after transformation to different coordinates, following the method outlined in Appendix K. The final result was

\[
\phi(Shw) = \frac{1}{a_\infty} \left\{ y (a_\infty - \tilde{a}) + \tilde{a} \right\} \tag{5-119}
\]

where

\[
a_\infty = Shc,= \tag{5-120}
\]

\[
a_o = Shn,= \tag{5-121}
\]

\[
\tilde{a} = a_\infty + a_o \tag{5-122}
\]
\[ Y = B_0 + \sum_{n=1}^{20} B_n \left[ \tanh x \right]^n \]  
\[ X = 10 \log_{10} (Sh_w) - 10 \log\left( 3.88 \right) \]

The coefficients \( B_n \) are tabulated in Table 5.2.

The polynomial fits the plotted value of \( \phi (Sh_w) \) to within a few per cent over the range \( 500 > Sh_w > 0.1 \). At the extremes of \( Sh_w \), the fit is poorer. In general, the fit attained for \( \phi (Sh_w) \) was not as good as that obtained for fitting other similarly shaped functions, as discussed in Appendix N. It is possible that a different transformation would yield better results.

5. Determining Wall Permeability and Solute Diffusivity from Experimental Data

The theoretical model presented in Sections 5.C.1. and 5.C.2 is a function of the wall permeability (or mass transfer coefficient), \( k_w \), solute diffusivity, \( D \), average linear velocity, \( \bar{V} \), length, \( x \), and channel height \( h \). If the flow rate and geometrical parameters are known, then it should be possible to evaluate \( k_w \) and \( D \) from two experiments or either \( k_w \) or \( D \) from a single experiment if the other variable is known. If the average dialyzate mass transfer coefficient is known or can be estimated from an independent experiment, then the membrane permeability, \( P_m \), can be evaluated from \( k_w \) by using equation (5-8).

a. Previous Methods

Six different methods for obtaining membrane permeability or solute diffusivity with a flat plate dialyzer have been
### TABLE 5-2

Coefficients for Curve-Fitting of $\phi(Sh_w)$

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<tr>
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<th>$B_n$</th>
<th>$n$</th>
<th>$B_n$</th>
</tr>
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<td>11</td>
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<tr>
<td>9</td>
<td>2102.238</td>
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<td>-14236.43</td>
</tr>
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</table>
proposed by Grimsrud, Babb, and co-workers. Implicit in all their work is the assumption that the wall Sherwood number may be represented by

\[ \text{Sh}_w = \frac{P_m h}{D} \]  \hspace{1cm} (5-124)

i.e. they have assumed that the dialyzate resistance is, or can be made, negligible. Since this is not always true, \( k_w \) will be substituted for \( P_m \) in discussing their work. The first two methods were originally suggested by Grimsrud (153). The others were proposed by Babb, et al. (21).

Method 1. It was shown earlier that the overall local Sherwood number can be calculated from

\[ \text{Sh}_{x,0} = -\frac{1}{2u_b} \frac{dC_b^*}{dx^*} \]  \hspace{1cm} (5-34)

Thus, \( \text{Sh}_{x,0} \) can be found directly from a plot of \( C_b^* \) as a function of \( x^* \) by evaluating the slope of the curve. At \( x^* = 0 \), \( \text{Sh}_{x,0} = \text{Sh}_w \), as shown in Figure 5-5. Thus, with \( h \) and \( D \) known, \( k_w \) can be evaluated from the slope at \( x^* = 0 \), where \( C_b^* = 1 \).

Method 2. The asymptotic local overall Sherwood number is given by

\[ \text{Sh}_{x,0,\infty} = \frac{1}{3} \beta_1^2 \]  \hspace{1cm} (5-91)

The log-mean overall Sherwood number may be evaluated from experimental data from equation (5-41). Grimsrud (153) states that "if the log mean mass transfer coefficient is calculated from experimental data between two \( x^* \) s outside the point where \( \text{Sh}_0 \) is a constant, the experimental mass transfer
coefficient would give a correct picture of what is happening between these two points in the channel." In other words,

\[
\begin{align*}
Sh_{m,o} \bigg|_{x_2^*} &= Sh_{x,o,\infty} \\
&= Sh_{x,o,\infty}
\end{align*}
\]  

(5-125)

and thus

\[
\beta_1 = (3 \, Sh_{m,o})^{1/2}
\]  

(5-126)

Knowing \( \beta_1 \), \( Sh_w \) can be calculated from equations (5-74) and (5-75) or obtained from a graph or table of \( Sh_w \) as a function of \( \beta_1 \). Then, either \( k_w \) or \( D \) can be evaluated if the other variable is known. However, Grimsrud proceeds to evaluate the experimental overall log-mean Sherwood number from the inlet and outlet solute bulk concentrations, which is different from the quantity referred to above. In order to use this method with the experimental Sherwood number calculated from inlet and outlet concentrations, measurements must be made under conditions where \( x^* \) is sufficiently large that \( Sh_{m,o} \) is equal to \( Sh_{x,o,\infty} \) to within some prescribed difference. Such an assumption is implicit in the use of this method, although it was apparently unrecognized by Grimsrud.

**Method 3.** The previous method was modified by Babb, et al. (21). From Figure 5-7, one finds that, to about ± 5%,

\[
Sh_{x,f,\infty} \approx 4
\]  

(5-127)

or

\[
k_{x,f,\infty} \approx \frac{4 \, D}{h}
\]  

(5-128)

Substituting this into equation (5-35) yields

\[
\frac{1}{k_{x,o,\infty}} = \frac{h}{4 \, D} + \frac{1}{k_w}
\]  

(5-129)
Finally, equating the measured overall log-mean coefficient, $k_{m,o}$, to $k_{x,o,\infty}$ allows one to solve for $D$ or $k_w$ from equation (5-129).

**Method 4.** This method involves two measurements made at different channel heights, $h'$ and $h''$. Denoting the reciprocal of the mass transfer coefficient by $R$, the mass transfer resistance, one finds

$$R'_{x,o,\infty} = \frac{h'}{4D} + R_w$$  \hspace{1cm} (5-130)

and

$$R''_{x,o,\infty} = \frac{h''}{4D} + R_w$$  \hspace{1cm} (5-131)

Upon subtraction, one obtains

$$\Delta R'_{x,o,\infty} = \frac{\Delta h}{4D}$$  \hspace{1cm} (5-132)

from which $D$ can be evaluated. Then substitution of $D$ into equation (5-130) or (5-131) yields a value for $R_w$.

**Method 5.** Measurements are first made with a single set of membranes, then repeated with a double set of membranes. The difference in the measured overall log-mean resistance equals the membrane resistance.

**Method 6.** Measurements are made with only one membrane and the membrane supports. Flow rates are high, minimizing liquid phase resistances. The stream containing solute is recirculated, and concentration change with time is monitored. From the measured resistance, the membrane resistance can be evaluated after correction for the liquid phase resistances. Termed the "dynamic" method, it is really the flat plate analogue of the batch dialyzer, except that much larger fluid
volumes are required and the transport rate is slower. The method is limited to membrane permeability measurements only, and thus is not of interest for the overall problem considered here.

The first method suffers from a practical drawback. Experimental data is invariably scattered to some extent about the "true" value. Obtaining the slope at any point of an experimentally derived curve which is nonlinear with respect to the independent variable is difficult and generally inaccurate. Curve fitting and numerical differentiation is particularly sensitive to scattered data points. Consequently, this method must be ruled out if feasible and accurate alternatives exist.

Methods 2 and 3 are limited in their utility. Grimsrud and Babb (154) stated that the method could be applied for \( x \, D / \sqrt{a^2} > 0.2 \), or \( x^* > 0.05 \), for which \( Sh_{x,f} \) is approximately constant. If this were true, it would still impose a limitation on the range of experimental variables which could be investigated. However, as pointed out above, the method is valid only when \( Sh_{m,o} \) is approximately equal to \( Sh_{x,f} \). Examination of Figures 5-4 and 5-5 shows that this condition is not usually reached until much higher values of \( x^* \). Only for very low \( Sh_w \), where the fluid-side resistance contributes little to the overall resistance, is the original assumption valid.

The consequences of using Method 2 is to yield too high a value of \( k_w \) or too low a value for \( D \). \( Sh_{m,o} \) will be higher
than the corresponding $Sh_{x, f, \infty}$, yielding too large a value of $\beta_1$ from equation (5-126) and consequently too large an estimate of $Sh_w$. Conversely, Method 3 may produce the opposite effect. Generally, $k_{m,f} > 4D/h$ and $k_{m,o} > k_{x,o,\infty}$; thus too low an estimate of $k_w$ is made.

Method 4 suffers from the same drawbacks. In addition, the necessity to dismantle the apparatus, change channel height, and reassemble the device without damaging the membrane results in a difficult and tedious experimental operation. This disadvantage also applies to Method 5. Furthermore, for the latter method, it is necessary that the second membrane be flush with the first with no entrapped fluid films between the membrane. It is difficult to ensure that this is the case and there is no way to determine if such an artifact occurs other than to check the measurement with another method.

It should also be pointed out that adding a second membrane changes $Sh_w$, which in turn alters the fluid-side Sherwood number, although the effect is not large. If the experimental difficulties could be overcome, and the analysis of Method 4 made more accurate, both methods 4 and 5 would have desirable aspects in that $D$ and/or $k_w$ could be evaluated without knowledge of the other parameter.

It is clear from the above discussion that all previously proposed methods for analysis of experimental data suffer from various drawbacks, and are limited in terms of the range of $x^*$ and $Sh_w$ for which they are valid. With several of the methods, it would be possible to put them on a more rigorous
theoretical framework. This would involve calculation of the theoretical log-mean Sherwood number, as opposed to use of the asymptotic value. Since both \( x^* \) and \( Sh_w \) are not known a priori, an iterative fitting of theory and data would be required.

An additional and important factor, apparently not previously considered by Babb and co-workers, is the question of sensitivity as related to the relative transport resistances. Since the overall resistance is the sum of the fluid and wall resistances, the fractional resistance in each phase is given by

\[
\frac{R_f}{R_o} = \frac{1/Sh_f}{1/Sh_f + 1/Sh_w}
\]

and

\[
\frac{R_w}{R_o} = \frac{1/Sh_w}{1/Sh_f + 1/Sh_w}
\]

When making wall permeability measurements, it is clearly desirable that the wall be the limiting resistance, while for solute diffusivity measurements, the fluid resistance should dominate. To a first approximation, \( Sh_f \gg 4 \). Thus, controllable experimental variables should be adjusted so that permeability measurements are made for \( Sh_w < 4 \) and solute diffusivity measurements are made with \( Sh_w > 4 \). This will be considered further in the next section.

b. Method Employed in This Study

After consideration of various alternatives, it was decided to bypass the calculation of experimental mass transfer
coefficients and fit the experimental data directly to the theoretical \( C_b^* - x^* \) relationship. The technique developed is valid for any value of \( x^* \) and \( Sh_w \). Basically the method is as follows.

One calculates the experimental values for \( C_b^* \). Then one makes an initial guess for \( D \) and/or \( k_w \). The true values of \( D \) and \( k_w \) are then defined as

\[
(k_w)_{\text{true}} = X_1 \ k_w
\]

\[
(D)_{\text{true}} = X_2 \ D
\]

whereupon the true value of \( Sh_w \) and \( x^* \) become

\[
Sh_w = \frac{X_1 \ k_w \ h}{X_2 \ D}
\]

\[
x^* = \frac{x(X2D)}{\bar{v} \ h^2}
\]

The initial guess for \( X_1 \) and \( X_2 \) is 1.0. If either \( k_w \) or \( D \) is known, then its correction factor \( X_1 \) or \( X_2 \) remains equal to unity during the entire procedure. Next, a suitable objective function is defined which is related to the difference between the experimentally measured bulk concentration, \( C_b^* \), and the theoretical value, \( C_{bt}^* \), calculated from the best guess of \( Sh_w \) and \( x^* \), i.e.

\[
F \propto C_b^* - C_{bt}^*
\]

The problem then becomes a minimization problem, that is, finding the values of \( X_1 \) and \( X_2 \) which minimize \( F \). Specific functional forms for \( F \) are discussed later in this section. Henceforth, the subscript "b" on the bulk concentration will be dropped and \( C^* \) will be taken to mean the bulk mixing-cup
concentration. From an experimental point of view, the dimensionless concentration at any point, \( C^* (x^*, y^*) \) is of no interest since it cannot be measured.

The proposed method requires the ability to calculate the theoretical value of \( C^* \) repetitively and accurately as a function of \( x^* \) and \( Sh_w \). This can only be accomplished through use of computer calculations. A computer program was written to calculate the theoretical solution in Fortran 4 for use on the IBM 360/65. Particular attention was paid to obtaining an accurate solution with the minimum amount of computer time, since \( C^* \) must be calculated many times in the minimization procedure.

The main problem was calculation of the required number of eigenvalues for a given \( Sh_w \). As pointed out in Section 5.C.2, this cannot be accomplished directly from equations (5-74) and (5-75). The problem was solved by transforming the \( Sh_w - \rho_m \) relationship and fitting the resulting data with least-squares polynomial. Details of the curve fitting procedure may be found in Appendix K. The program was capable of generating the first seven eigenvalues. The use of the asymptotic expression for higher eigenvalues was unnecessary for the \( x^* \) range studied experimentally.

The computer program, called THEORY, may be viewed as a self-contained "black box" subroutine. One inputs \( x^* \) and \( Sh_w \) and the program returns \( C_t^* \) accurate to 0.01% plus other information of interest. A description and listing of the program may be found in Appendix N.
Two problems remained to be answered: 1) the manner in which a set of experimental data is treated, i.e. consideration of all the data together, or each datum point individually; and 2) definition of the appropriate objective function. For the moment, consider the case of perfect data points with no experimental error. With a single datum point, it is possible to fit one unknown parameter with all others known. With two experimental data points, two parameters may be evaluated, and so on. Thus, the necessary and sufficient condition for fitting $n$ parameters is $n$ data points. In this study, at most only two parameters are unknown, $k_w$ and/or $D$, and $n-2$ or $n-1$ data points are redundant. With real, i.e. scattered data, the same principles apply, but the additional data points give greater statistical accuracy to the fitted parameters. The generation of such a set of $n$ data points might be made in various ways, for example by keeping all parameters fixed and varying flow rate.

For $n$ data points, three possible modes of treatment exist:

1) Fit two parameters simultaneously with all $n$ data points

2) Fit one parameter, using all $n$ points

3) Fit one parameter with each data point separately and average the results.

With real data, it may be necessary to eliminate spurious points before the fit is made with the first two modes. Elimination of statistically deviant results may be done after
fitting with the third mode.

Six different definitions for the objective function were considered. Let

$$\Delta = C^* - C_t^*$$  \hspace{1cm} (5-140)

where $\Delta$ is the residual between the experimental $C^*$ and the value calculated from the best current estimate of $X_1$ and $X_2$.

The objective functions were defined by

$$F_1 = \sum_n \Delta^2$$  \hspace{1cm} (5-141)

$$F_2 = \sum_n \Delta$$  \hspace{1cm} (5-142)

$$F_3 = \sum_n |\Delta|$$  \hspace{1cm} (5-143)

$$F_4 = \sum_n \left( \frac{\Delta}{C_t^*} \right)^2$$  \hspace{1cm} (5-144)

$$F_5 = \sum_n \frac{\Delta}{C_t^*}$$  \hspace{1cm} (5-145)

$$F_6 = \sum_n \left| \frac{\Delta}{C_t^*} \right|$$  \hspace{1cm} (5-146)

The first three functions correspond to the three types of residual expressions most commonly employed. The later three represent a weighting of each residual by the reciprocal of its respective $C_t^*$. The choice of a suitable objective function at first appeared to be arbitrary, although minimization of the sum of the squares of the residuals, the so-called least-squares criteria, corresponding to $F_1$ and $F_4$, was thought to be best.

To find the best type of operation for the analysis of experimental data, a series of computational experiments were
carried out. The first mode of operation was evaluated initially with a perfect set of 10 data points for \( \text{Sh}_W = 4 \), obtained from the tabulations of Stroeve (409). However, each value of \( x^* \) was multiplied by 1.25, so that the best fit would be obtained for \( X_1 = 0.8 \) and \( X_2 = 0.8 \). All six objective functions were then evaluated over a square grid of \( X_1, X_2 \), with each factor ranging from 0.6 to 1.0. \( C_t^* \) was calculated with subroutine THEORY referred to above.

A contour plot of the square root of \( F_w \) is given in Figure 5-9 as a function of \( X_1 \) and \( X_2 \). Response surfaces for the other objective functions were qualitatively similar. The locus of minima is qualitatively an hyperbola passing through (0.8, 0.8). The contours of constant \( F_w \) are roughly parallel to the locus of minima with a distorted elliptical overall shape. The global minimum appears to be at the expected point, although the contours there are too crowded to plot.

The same response surface of \( F_w \) is depicted in a modified fashion in Figure 5-10, where the square root of \( F_w \) is plotted as a function of \( X_2 \) for various values of \( X_1 \). Each curve represents a vertical slice from Figure 5-9 parallel to the \( X_2 \) axis. The global minimum at (0.8, 0.8) is clearly indicated, and the constant \( X_1 \) curves are not quite symmetrical about \( X_2 = 0.8 \). If the values of \( C_t^* \) and the calculated \( C_t^* \) were accurate to infinite significant figures, \( F_w \) (0.8, 0.8) would be zero. The actual value of \( F_w^{1/2} \) at the global minimum was about \( 10^{-5} \), or \( F_w \) about \( 10^{-10} \).
Figure 5-9. Contour Plot of $F_4^{1/2}$ as a Function of $X_1$ and $X_2$.
True Values: $X_1 = 0.8$, $X_2 = 0.8$. $Sh_w = 4.0$, Perfect Data
Figure 5-10. $F_4^{1/2}$ as a Function of $X_2$ for Constant Values of $X_1$. Same Conditions as in Figure 5-9
Since 10 values were used and \( C^* \) was of order unity, this gives \( \Delta^2 \sim 10^{-11} \) or \( \Delta \sim 3 \times 10^{-6} \) on the average for each data point. This error residual is related to the accuracy with which \( C^* \) was calculated.

Since the results indicated that in the region investigated only one minimum existed, a two-dimensional optimum seeking method could be employed to find \( X_1 \) and \( X_2 \). This was verified using Powell's method (328a) for finding the minimum of a function of several variables without calculating derivatives. A computer program written by Stroeve (27) was employed. Eight cases were tested for \( S_{W} = 4 \) using a variety of starting points and different values of \( X_1 \) and \( X_2 \). In seven cases, the program converged to the correct values. For one case, that described above, the optimization procedure stalled in the deep valley associated with the locus of minima. Such a "ridge" phenomena is not uncommon with optimization techniques. Another problem, which was overcome by forcing the program to continue, was that local "pseudo-minima" were encountered. These may be visualized as microscopic "pot-holes" on the response surface, caused by the fact that minute steps exist in the solution because the various infinite series were truncated when a specified accuracy criterion was met (see Appendix N). Before pursuing improvement in the two-dimensional optimization procedure, other problems became apparent which prevented use of this technique, as discussed below.

The behavior of the technique for "real" data was
considered by systematically introducing a prescribed amount of scatter into the perfect data discussed above. This included alternating deviations in $C^*$ of 1) fixed magnitude, and 2) fixed percentage of the true $C^*$. The results of such an analysis for $\pm 2\%$ scatter in $C^*$ is shown in Figure 5-11. The functions plotted are analogous to Figure 5-10. The most notable feature is that the global minimum does not occur at the "true" values (0.8, 0.8) but at about (0.855, 0.748). Thus, if one had a set of experimental data, each point of which was $\pm 2\%$ from the true value, the minimization of $F_4$ over all the data to obtain $X_1$ and $X_2$ would lead to estimates incorrect by $\pm 5\%$. The same effect occurs with the other objective function definitions. Random scatter in the data might lead to even worse estimates.

The data for $C^*$ were originally calculated such that $\Delta/C^*_t = 0.02$. Thus, one would expect

$$F_4 = \sum_{n=1}^{10} \left( \frac{\Delta}{C^*_t} \right)^2 \approx 4 \times 10^{-3} \tag{5-147}$$

and $F_4 \approx 0.063$. This, in fact, is approximately the value for (0.8, 0.8). However, Figure 5-11 shows that there is a combination of $X_1$ and $X_2$ which produces an even lower $F_4$. Hence, the scatter in $C^*$ is not correctly chosen for the defined objective functions, or conversely, the objective functions are not correctly defined to handle scattered data.

Similar numerical experiments were carried out with either $X_1$ or $X_2$ fixed and the other fitted. The results were essentially the same as for simultaneously fitting $X_1$ and
Figure 5-11. $F_4^{1/2}$ as a Function of $X_2$ for Constant Values of $X_1$. True Values: $X_1=0.8$, $X_2=0.8$.
$\text{Sh}_w=4.0$, Imperfect Data, $\pm 2\%$ Scatter in C*.

Locus of Minima
$X_2$. It is believed that the reason for the skewed results of this approach is that the response of the $C^* - x^*$ curve to a change in $X_1$ and/or $X_2$ is not quantitatively accounted for in the definition of the objective function. To simultaneously fit scattered data to a theoretical curve, each residual must be multiplied by the appropriate weighting function. For fitting a single parameter, for example $X_1$, the weight attached to each point might be the reciprocal of the square of the derivative of $C^*_t$ with respect to $X_1$ times the variance of $C^*$, i.e.

$$W(x^*, Sh_w) = \frac{1}{(\frac{\partial C^*_t}{\partial x})^2 \sigma C^*^2} \quad (5-148)$$

This quantity would have to be computed separately for each data point.

It was clear at this point in the study that in order to fit a complete set of data simultaneously for one or both parameters, considerable additional numerical investigation would be required to verify the technique. It was decided to operate with the third mode, to fit each point to the theoretical solution individually. This has three advantages: 1) The definition of the objective function used is not important since $\Delta$ must go to approximately zero; 2) Only a one dimensional minimization is required; 3) The results from the complete data set may be analyzed statistically to eliminate spurious data. The primary disadvantage is that only one parameter may be fitted at a time.
c. **Sensitivity Analysis**

An analysis was made to determine the sensitivity of the proposed method for the evaluation of \( X_1 \) or \( X_2 \), or in effect \( k_W \) or \( D \). The analysis indicated the error in \( X_1 \) or \( X_2 \) associated with either 1) perfect experimental data and an error in the calculation of \( C^*_L \) or 2) the correct estimate of \( C^*_L \) but an experimental error in \( C^* \). For both cases, it is assumed that all other parameters are known exactly.

The case considered was \( \text{Sh}_W \) equal to 4.0 with true values of \( X_1 \) and \( X_2 \) equal to 1.0. The objective function was calculated for a single data point for various values of \( x^* \) (or more properly \( C^* \)). First \( X_1 \) was held constant and \( X_2 \) was varied from 0.6 to 1.4, then the procedure was reversed.

The results of these calculations are shown in Figure 5-12 for \( \Delta/C^*_L \) and in Figure 5-13 for \( \Delta \) as a function of \( X_1 \) and \( X_2 \) for various values of \( x^* \). Each curve is the single point analogue of curve 6 in Figure 5-10 wherein the objective function is plotted for one of the unknown parameters held constant at its true value.

In Figure 5-12, the curves for large \( x^* \) are nearly symmetrical about 1.0 and the \( X_1 \) and \( X_2 \) curves are coincident. As \( x^* \) decreases, the curves fan out and diverge, and they are no longer symmetrical. The asymmetry is more clearly evident in Figure 5-13. For \( x^* > 0.20 \), the curves are almost coincident and fan out below the curve for \( x^* = 0.20 \). For clarity, they are not plotted.

For each \( X \), the deviation from unity is a measure of the error. Since the curves are not symmetrical, the average
Figure 5-12. $\Delta/C^*$ as a Function of $X_1$ and $X_2$ for Various Values of $X^*$. Conditions: $S_{m_w} = 4.0$, True Values - $X_1 = 1.0$, $X_2 = 1.0$. 
Figure 5-13. $\Delta$ as a Function of $X_1$ and $X_2$ for Various Values of $X^*$. Same conditions as Figure 5-12.
value of the absolute deviation from unity was calculated. This quantity represents the average fractional error in the calculation of each $X$.

These relationships are shown more clearly in Figures 5-14 and 5-15 where the percentage error in $X_1$ and $X_2$ is plotted as a function of $1-C^*$ and $X^*$ for various values of $\Delta/C^*$ in Figure 5-14 and $\Delta$ in Figure 5-15. Constant $\Delta/C^*$ represents a constant fractional error, whereas constant $\Delta$ means a constant deviation.

In general, for identical parameters, the error in $X_2$ is equal to or larger than the error in $X_1$. As both $X^*$ and $C^*$ decrease, the errors associated with both quantities increase sharply. However, for constant $\Delta$, in Figure 5-15, a minimum error occurs for $C^* = 0.45$.

The results indicate that at $Sh_w = 4$, measurements of $k_w$ may be significantly more accurate than measurements of $D$. This is reasonable, since a fixed relative change in $k_w$ at this $Sh_w$ has a greater effect on $C^*$ than the same relative change in $D$. This point is also illustrated in Figure 5-3. As $Sh_w$ increases, the $X_1$ error curve will move up and the $X_2$ curve down. A decrease in $Sh_w$ causes the opposite effect.

For extrapolation to other values of $Sh_w$, comparison at the same value of $C^*$ is probably better than the same $X^*$.

The error plotted is that due to the $C^*$ errors only. For real data, errors in $h$, $\bar{v}$, and the estimated $D$ or $k_w$ would contribute additional error. Even with this restriction the error can be quite high, showing that accurate concentra-
Figure 5-14. Per Cent Error in $X_1$ and $X_2$ as a Function of $C^*$ for Various Values of $\Delta/C^*$. Same Conditions as Figure 5-12.
Figure 5-15. Per Cent Error in $X_1$ and $X_2$ as a Function of $C^*$ for Various Values of $\Delta$.

Same Conditions as Figure 5-12.
tion measurement is extremely important. Clearly, lower errors are favored by measurements at lower C*. 


The theoretical model described in Section 5.C.1 must be modified when the fluids on each side of the membrane have different equilibrium distribution coefficients, i.e. when the fluid concentrations on each side of the membrane are unequal at equilibrium.

Figure 5-16. Activity and Concentration Profiles for Dissimilar Fluids on Each Side of Membrane

Consider the situation shown in Figure 5-16. The membrane phase, M, is surrounded by two different fluids, A and B. For purposes of discussion, B may be considered the dialyzate and A the blood-side fluid. Each phase is characterized by a local mass transfer coefficient associated with a driving force defined in terms of the concentration within that phase. Thus,
\[ \dot{n} = k_A (C_{1A} - C_{2A}) = k_M (C_{2M} - C_{3M}) = k_B (C_{3B} - C_{4B}) \]  
(5-149)

In general, the concentration profile is discontinuous, whereas the activity or chemical potential profile is always continuous, assuming that no interfacial resistance exists. The activity is defined by

\[ a = \gamma C \]  
(5-150)

where the activity coefficient will be assumed independent of concentration. In addition, the equilibrium distribution coefficient between two phases, \( x \) and \( y \), is defined as

\[ K_{x/y} = \frac{c_x}{c_y} \bigg|_{eq} = \frac{\gamma_x}{\gamma_y} \]  
(5-151)

Equation (5-147) may be rewritten as

\[ \dot{n} = k_A \left( \frac{a_1 - a_2}{\gamma_A} \right) = k_M \left( \frac{a_2 - a_3}{\gamma_M} \right) = k_B \left( \frac{a_3 - a_4}{\gamma_B} \right) \]  
(5-152)

The proper definition of a mass transport model for the system shown in Figure 5-16 will be first illustrated with a simple example. When diffusion through the membrane is investigated, identical fluids, say phase B, are on each side. Since the concentrations within the membrane at the membrane interface are usually not measurable, the flux is defined in terms of a permeability related to the measurable concentrations in the fluids. Thus

\[ \dot{n} = k_M (C_{2M} - C_{3M}) \]  
(5-153)

\[ = k_M \left( \frac{a_2 - a_3}{\gamma_M} \right) \]  
(5-154)

\[ = k_M \frac{\gamma_B}{\gamma_M} \left( \frac{a_2 - a_3}{\gamma_B} \right) \]  
(5-155)
\[ P_m (C_{2B} - C_{3B}) \]  

(5-156)

where

\[ P_m = k_m \frac{\gamma_B}{\gamma_M} = k_m K_{M/B} \]  

(5-157)

Consequently, the measured membrane permeability includes within its definition the solute distribution coefficient between phases, with phase B taken as the reference phase.

When three different phases are present, it is necessary to choose one of the three as the reference phase. For the problem of interest, phases M and B may be considered the "wall", and the differential equation describing convection and diffusion is written for phase A.

The wall mass transfer coefficient defined by equation (5-8) is based on phase B as the reference phase. Thus

\[ \dot{n} = k_m \left( \frac{a_2 - a_3}{\gamma_M} \right) = k_B \left( \frac{a_3 - a_4}{\gamma_B} \right) \]

\[ = \mu_m \left( \frac{a_2 - a_3}{\gamma_B} \right) = k_w \left( \frac{a_2 - a_4}{\gamma_B} \right) \]  

(5-158)

from which one obtains

\[ \frac{1}{k_w} = \frac{1}{k_m} \frac{\gamma_M}{\gamma_B} + \frac{1}{k_B} \]  

(5-159)

\[ = \frac{1}{P_m} + \frac{1}{k_B} \]  

(5-160)

Similarly, an overall mass transfer coefficient may be defined with reference to phase B as

\[ \dot{n} = k_o \left( \frac{a_1 - a_4}{\gamma_B} \right) = k_o \left( \frac{a_1}{\gamma_A} \frac{\gamma_A}{\gamma_B} - \frac{a_4}{\gamma_B} \right) = k_o (C_{1A} K_{B/A} - C_{4B}) \]  

(5-161)
Combination with equation (5-158) yields

\[ \frac{1}{k_o} = \frac{1}{k_A} \frac{\gamma_A}{\gamma_B} + \frac{1}{k_M} \frac{\gamma_M}{\gamma_B} + \frac{1}{k_B} \]  

(5-162)

\[ = \frac{K_{B/A}}{k_A} + \frac{1}{k_M} + \frac{1}{k_B} \]  

(5-163)

From this it is clear that the more common definition

\[ \dot{n} = k_o (C_{1A} - C_{4B}) \]  

(5-164)

has little meaning when phase A and B have different distribution coefficients.

The equations of interest for the flow dialyzer can now be written in terms of concentrations in phase A:

\[ V_x \frac{\partial c_A}{\partial x} = D_A \frac{\partial^2 c_A}{\partial y^2} \]  

(5-165)

with boundary conditions

B.C. 1 \( x < 0 \) all \( y \) \( c_A = c_{A1} \)  

(5-166)

B.C. 2 all \( x \) \( y = 0 \) \( \frac{\partial c_A}{\partial y} = 0 \)  

(5-167)

The third boundary condition, however, involves the other two phases. As expressed in Section 5.C.1, phase C is taken as the reference phase, since phase B is on both sides of the membrane. The third boundary condition from equation (5-7) corresponds to

\[ - D_A \frac{\partial c_A}{\partial y} \bigg|_{y=0} = k_w \left( \frac{a_2 - a_4}{\gamma_B} \right) \]  

(5-168)

For the system considered here, phase A is of primary interest. Furthermore, \( a_2/\gamma_B \), corresponding to the concentration at the wall in phase A referred to phase B, is not a measurable quantity. Equation (5-168) is therefore rewritten as
\[-DA \frac{\partial c_A}{\partial y} \frac{\partial y}{2} = k_w \frac{\gamma_A}{\gamma_B} \frac{a_2 - a_4}{\gamma_A} \]  
\[= k_w K_{B/A} (c_{A2} - c_{A1} K_{A/B}) \]  
(5-169)

Thus, one must redefine the dimensionless variables \(Sh_w\) and \(C^*\) as

\[Sh_w = \frac{k_w K_{B/A} h}{D_A} \]  
(5-171)

and

\[C^* = \frac{c_A - c_{Bo} K_{A/B}}{c_{A1} - c_{Bo} K_{A/B}} \]  
(5-172)

The variables \(x^*\) and \(y^*\) remain as defined before. If \(K_{B/A}\) is equal to unity, \(Sh_w\) and \(C^*\) are then identical with the earlier definitions. Also, if \(c_{Bo} = 0\), \(C^*\) is the same as before.

Of primary interest here are plasma or blood as phase A. Phase B, the dialyzate, may be considered to a good approximation as saline or water. Let the subscripts WB, P, and S refer to whole blood, plasma, and saline, respectively. Then for blood,

\[Sh_w = \frac{k_w K_{S/WB} h}{D_{WB}} \]  
(5-173)

\[C^* = \frac{c - c_{o} K_{WB/S}}{c_{i} - c_{o} K_{WB/S}} \]  
(5-174)

and for plasma,

\[Sh_w = \frac{k_w K_{S/P} h}{D_p} \]  
(5-175)

\[C^* = \frac{c - c_{o} K_{P/S}}{c_{i} - c_{o} K_{P/S}} \]  
(5-176)
For consistency, it is best to calculate \( Sh_w \) as defined by equations (5-173) and (5-175). However, it is interesting to examine the third boundary condition in terms of the model proposed in Chapter 4 for estimating the diffusion coefficient in blood. It was shown that

\[
D_{WB} = D_s \phi_p \frac{\psi}{k_{WB} / P}
\]  
(5-177)

where

\[
\phi_p = \frac{\psi^0 + D_b / \nu_a}{1 - \psi^0 + k_p}
\]  
(5-178)

It was also shown that

\[
K_{WP/S} = 1 - \phi_p + k_p
\]  
(5-179)

For the moment, consider \( D_b / D_a \sim 0 \). Then, assuming that

\[
K_{WB/S} = K_{WB} / P \ K_{WP/S}
\]  
(5-180)

equation (5-177) becomes

\[
D_{WB} = \frac{D_s \psi^0 \psi}{K_{WB/S}} = D_s \psi^0 \psi K_{S/WB}
\]  
(5-180)

Consequently, the third boundary condition, equation (5-170) may be written

\[
-D_{WB} \frac{\partial c_{WB}}{\partial y} \bigg|_{y=\frac{h}{2}} = k_w K_{S/WB} (c_{WB} - c_{So} K_{WB/S})
\]  
(5-181)

or

\[
-D_s \psi^0 \psi K_{S/WB} \frac{\partial c_{WB}}{\partial y} \bigg|_{y=\frac{h}{2}} = k_w K_{S/WB} (c_{WB} - c_{So} K_{WB/S})
\]  
(5-182)

from which the wall Sherwood number becomes

\[
Sh_w = \frac{k_w h}{D_s \psi^0 \psi}
\]  
(5-183)
Thus, $Sh_w$ can be formulated without calculating $K_{WB/S}$. However, the latter quantity is still needed for $D_{WB}$ used in calculating $x^*$, so that no real simplification in the model is obtained, unless there is a priori knowledge of $D_{WB}$.

D. **Apparatus and Procedure**

1. **Design Considerations**

In order to apply the theoretical development discussed in the preceding sections, it was necessary that the flat plate dialyzer meet the following requirements:

1) The membranes must be supported so that they are flat and parallel thought the mass transport section.

2) The transverse velocity profile on the blood side must be flat and uniform.

3) The blood side fluid must be in fully-developed laminar flow with a parabolic velocity profile before contacting the permeable wall.

The third requirement is most easily satisfied.

Several investigations on the fluid dynamic entrance length for incompressible laminar flow in tubes, parallel plates, and rectangular ducts have been reported. The results are usually presented as

$$\frac{x_e}{h} = \frac{\phi}{Re}$$  \hspace{1cm} (5-185)

Where $x_e$ = length required for attainment of 99% of the fully developed centerline velocity

$$Re = \frac{D_e \bar{v}}{\nu} = \text{Reynolds number}$$

$$D_e = \frac{4A}{\pi} = \text{hydraulic diameter}$$
\[ A_x = \text{flow cross sectional area} \]
\[ P = \text{wetted perimeter} \]

For a rectangular duct,
\[ D_e = \frac{4 \text{ wh}}{2(w+h)} \]
\[ = 2h \text{ (parallel plates with } w \gg h) \] (5-186)

For semi-infinite parallel plates, Schlichting (365) theoretically found \( \phi = 0.04 \). Sparrow, et al. (395) did not obtain a specific value for \( \phi \), but inspection of their graphical theoretical results indicates \( \phi \approx 0.05 \). Han (157) theoretically considered rectangular channels. For an aspect ratio greater than or equal to 50:1, his estimate is essentially identical with Schlichting's. Sparrow, et al. (394a) experimentally found \( \phi \approx 0.08 \) for an aspect ratio of 5:1, significantly higher than Han's estimate for the same aspect ratio. It is noteworthy that all estimates for semi-infinite parallel plates indicate more rapid velocity profile development than for tubes (230).

Since, for parallel plates,
\[ Q = \text{wh} \bar{v} \] (5-17

equation (5-185) may be rearranged as
\[ \frac{x_e}{h} = 2 \phi \frac{Q}{w \bar{v}} \] (5-187)

For the flat plate dialyzer used in this study, \( w \) was set at about 5 cm so that for maximum \( h = 1 \text{ mm} \), the aspect ratio would be 50:1. For the "worst" case, water at 37°C, \( \nu = 0.007 \text{ cm/sec} \). Using \( \phi = 0.05 \), one obtains
\[ \frac{x_e}{h} = 3 Q \] (5-188)
For the maximum flow rates utilized ($Q < 2$ cc/sec), it is required that $X_e/h \geq 6$, and for $h \approx 1$ mm, $X_e \approx 1$ cm.

The second requirement may be met by proper header design. The problem reduces itself to taking fluid which is being pumped through a tube and distributing it evenly between two parallel plates. Furthermore, it is desirable to do this before the velocity profile development section is encountered. From both theoretical (365) and experimental (114, 217, 264) studies of two-dimensional slot jets, it is clear that an orifice significantly smaller in size than the width of the plates is impractical, since very large lengths are required to evenly distribute the fluid. Consequently, it is necessary to discharge the inlet blood-side fluid along the entire length of a long slot.

Ideally, the slot is supplied from a large plenum chamber in which the pressure is uniform and the fluid velocity negligible. In this situation, the discharge angles are all 90 degrees and the transverse velocity profile is flat.

Consider a cylindrical channel with a long slot cut parallel to the direction of flow. If the duct flow cross sectional area is very much larger than the slot cross sectional area, the above-mentioned situation is achieved. Thus, however, would require an excessive volume of blood side fluid. The design of manifolds and distribution equipment of this type has received considerable study (165, 218, 219, 375, 404). Although a sufficiently large plenum chamber is usually not attainable, several methods to effectively
achieve this condition have been suggested:

1) Use turning vanes to straighten the flow.
2) Insert screens in front of the slot.
3) Feed from both ends of the duct.
4) Increase the pressure drop across the slot by lengthening the lips of the slot.

The first two methods are unusable here because of potential hemolysis of the blood. The fourth method is related to two basic principles for the attainment of equal flow distribution in a slot manifold (218, 219, 375): The pressure drop across the outlet slot must be much larger than 1) the pressure drop due to friction in the pipe, and 2) the kinetic energy of the inlet stream. As a rule of thumb, a ratio of 100:1 for both relationships is adequate. To obtain the high outlet pressure drop, a narrow parallel plate channel may be used for the slot, as illustrated in Figure 5-16a.

![Figure 5-16a. Schematic Illustration of Slot Header](image)

A rigorous analysis of the flow in this configuration is complex (375). The system is symmetrical about the centerline, and as a rough approximation for flow in the pipe, one can examine the worst case, i.e. no depletion of flow in the axial direction in the pipe until the centerline is reached.
Thus,

\[ \Delta P_{\text{plate}} = \frac{12 \mu Q L_2}{L_1 h^3} \]  \hspace{1cm} (5-189)

\[ \Delta P_{\text{pipe}} = \frac{8 \mu Q L_1}{\pi R^4} \]  \hspace{1cm} (5-190)

From the first condition,

\[ \frac{\Delta P_{\text{pipe}}}{\Delta P_{\text{plate}}} \leq \theta \]  \hspace{1cm} (5-191)

or \[ \frac{L_1}{L_2/R^4} \leq 4.71 \theta \]  \hspace{1cm} (5-192)

As specified previously, \( L_1 = 2.5 \text{ cm} \). To keep the total header volume below 10 cc, let \( R = 0.25 \text{ in} = 0.64 \text{ cm} \). Then

\[ \frac{h^3}{L_2} \leq 0.12 \theta \]  \hspace{1cm} (5-193)

The second condition requires that the inlet kinetic energy be negligible compared to the plate pressure drop:

\[ \frac{v^2}{2} = \left( \frac{Q}{\pi R^2} \right)^2 \leq \theta \left[ \frac{12 \mu Q L_2}{L_1 h^3} \right] \cdot \frac{1}{\rho} \]  \hspace{1cm} (5-194)

or \[ \frac{Q L_1 h^3}{R^4 L_2} \leq \left( 2 \pi^2 \cdot \frac{12 \mu}{\rho} \right) \theta \]  \hspace{1cm} (5-195)

where \( \rho = 1 \text{ gm/cc} \), and for the worst case (water at 37°C), \( \mu = 0.007 \) poise. Furthermore, \( R = 0.64 \text{ cm} \), \( L_1 = 2.5 \text{ cm} \), and for each header inlet, \( Q_{\text{max}} = 1 \text{ cc/sec} \). Substituting these values in equation (5-195) one obtains

\[ \frac{h^3}{L_2} \leq 0.04 \theta \]  \hspace{1cm} (5-196)

Comparison of equations (5-193) and (5-196) shows that the second condition is slightly more stringent. Taking \( \theta \) to be 0.01 and setting \( L_2 \) equal to 2.5 cm, one obtains

\[ h^3 \leq 0.001 \]
\[ h \leq 0.1 \text{ cm} = 0.04 \text{ in.} \quad (5-198) \]

or about 1/25 in.

The first major requirement discussed above relates to the selection of a membrane support. In addition to keeping the membrane flat, it should have high porosity, so as not to obstruct a significant portion of the membrane transport area, and it should minimize the dialyzate mass transfer resistance by promoting mixing of the dialyzate solution. Three types of supports were considered: 1) the grooved boards of the original Kiil hemodialyzer (211), 2) the multiple cone supports suggested by Bluemle, (224) and 3) the porous nickel foametal used by Babb and Grimsrud (20). From the available literature, on the subject, the foametal support was selected. Because of its filamentous nature, it provides random support points which tend to keep the membrane flatter than the other, more regular, supports.

Four additional criteria were applied in designing the flat plate dialyzer:

1) The overall contained volume should be minimized.
2) The mass transfer section should be long enough to obtain experimentally measurable transport under all conditions.
3) The blood-side channel height should be variable.
4) The volume of the blood-side outlet header should be kept as small as possible to minimize the volumetric throughput required to attain steady state.

2. Flat Plate Flow Dialyzer

The parallel plate dialyzer was a modification of the
design described by Grimsrud and Babb (154) as shown in a phantom view in Figure 5-17. It consisted of four separate components, the body of the dialyzer and inlet and outlet end plates. The main body of the dialyzer was composed of two virtually identical lucite blocks, 8 in. x 6 in. x 2 in., in the center of which was milled a 5 in. x 2 in. x 1/8 in. channel with headers on each side, producing a total of two inlet and two outlet dialyzate headers. A precut piece of low density nickel foametal (General Electric Co, Metallurgical Products Division) was bonded to the lucite base with shellac and the entire assembly machined flat. A piece of higher density foametal was also bonded to each inlet header to insure uniform dialyzate distribution.

The inlet endplate contained a 1/2 in. diameter by 2 1/2 in. long cylindrical header fed at both ends by inlet ports. The header was connected by a tapered entrance to a 2 in. x 1/32 in. slot channel which insured a flat transverse velocity profile. This in turn opened into a larger 2 in. x 1/8 in. header which fed into the dialyzer body. The outlet endplate consisted of a 1/8 in. deep header, connecting to two outlet ports by 1/16 in. converging channels. Both inlet and outlet endplates were fabricated in two half-pieces and then glued together.

The dialyzer was assembled in a horizontal position on a specially designed support and was operated vertically so that air was not trapped in the headers. The assembly procedure was as follows: All mating surfaces were coated
Figure 5-17 Phantom View of Flat Plate Flow Dialyzer
a thin film of high vacuum silicone grease to eliminate leaks. A sandwich arrangement was built up on one block in the following order: saran wrap, wet membrane, stainless steel spacer, wet membrane, saran wrap. The second lucite block was placed on top of this. The saran wrap was used under the area covered by the spacers to prevent puncturing of the membrane by the support. When necessary, the membranes were sprayed with water during assembly to keep them wet. All films were smoothed flat by hand, and all items in the sandwich arrangement were prepunched with holes to fit over positioning dowels in the bottom plate for proper alignment. The top dialyzer plate also had positioning holes. The assembled top and bottom plates were bolted together and the positions of the wet membranes sticking out from the sandwich were folded at right angles to adhere to the sides of the lucite blocks. The inlet and outlet end plates were then positioned in grooves milled on the sides of the dialyzer body and were bolted in place.

The flow path of blood-side fluid within the dialyzer, defined by the membranes and spacers, was normally 8 in. long and 2 in. wide, although the width could be varied by changing the spacerwidth. The channel thickness was calculated as the sum of the spacer and saran wrap thicknesses. The latter was 0.47 mil. thick for each film. Dialyzate flow in the foametal was cross-flow to the blood-side channel. The area available for solute transfer was a 2 in. square region defined by the cross-over of the blood channel and
the foametal. The entrance length for velocity profile development was 2 in. and an additional 2 in. were allotted beyond the mass transfer section to eliminate any disturbances caused by the outlet section.

Pressure taps were located 1) in the inlet and outlet headers of the endplates to monitor the blood-side pressure drop, and 2) in the inlet and outlet dialyzate headers to measure the pressure drop across the foametal. With this setup, it was also possible to monitor the transmembrane pressure difference.

Spacers of various thicknesses were cut from stainless steel shim stock (Roblinger Company, Boston, Mass.). Thicknesses were measured at eight different points with a micrometer and an average calculated. The local thickness generally varied less than 0.1 mil from the average.

All inlet and outlet headers were fed from two ports. All connectors were Swagelok stainless-steel fittings. On the blood side, a specially designed adapter was used to couple with chrome-plated Luer-1ok fittings.

The length of the mass transfer section was originally designed on the basis of published estimates of sodium chloride permeability for Cuprophan PT-150 (245). These turned out to be too high (see Chapter 3), and consequently the mass transfer capabilities were lower than expected. If the dialyzer were to be rebuilt, it is suggested that the length be increased.

A major experimental problem was fluid leakage. Each
assembly was tested for leaks and about 50% had to be dismantled and rebuilt. With experience, the optimum amount and distribution of silicone grease was ascertained and the percentage of leak-proof assemblies increased.

The initial runs were made without the saran wrap film. Dye injections and flow rate measurements during some of the runs revealed shunting of fluid from the blood-side to the dialyzate side through a microscopic puncture in the membrane under the spacer. At this point, saran wrap was employed to protect the membrane and the problem was alleviated.

Supplementary details, drawings, and photographs of the dialyzer may be found in Appendix D.

Some experimentation was also done with a test dialyzer supplied through the courtesy of Professor A. L. Babb of the University of Washington. It consisted of just two pieces with built in headers and nickel foametal supports of 1/16 in. thickness. Details of its construction have been described previously (21).

3. Flow System

The flow system is shown schematically in Figure 5-18. The blood-side fluid was contained in a reservoir and was pumped through the dialyzer with a continuous, reciprocating Harvard syringe pump. Three-way valves were positioned at the inlet and outlet for sampling. Dialyzate was pumped from a reservoir to the dialyzer with a Moyno screw pump. The circuit was set up so that the dialyzer could be bypassed and the dialyzate could be recirculated or sent to waste.
from several points. During mass transfer measurements, the system was operated with single pass.

Concentration measurements were made only on the blood-side, and dialyzate concentrations calculated by a mass balance. When an electrolyte was dialyzed, the outlet stream was sent through a conductivity flow cell located in a constant temperature bath (± 0.05°C). Conductivity cell resistance was determined by an impedance comparator and automatically recorded. For the initial experiments, the system was sensitive to a concentration change of 0.01% and accurate over long periods to 0.1%. Later, a less sensitive full scale deflection was used, multiplying these numbers by a factor of three.

Organic compounds were studied with radioactively labelled tracers and concentration was measured with liquid scintillation counting. Generally, three outlet samples were taken for each data point and stored in plastic vials until analyzed.

The Harvard syringe pump was controlled by a continuously variable DC motor and a multi-step gear box. The pump was calibrated, but the motor was sensitive to changes in line voltage. Flow rates were periodically measured to check pump performance and to monitor possible transmembrane leakage and ultrafiltration. Aqueous solutions were sent through a rotameter following the conductivity cell. Flow rates of nonaqueous solutions were measured by collection from the sampling valve into a graduated cylinder.
for a fixed time period.

The Moyno pump was controlled by a tachometer-feedback variable speed 3/4 hp DC motor. The flow rate calibration curve was nearly linear in the motor-control potentiometer setting and reproducible to better than 0.5%.

Two 50 cc syringes were employed with the syringe pump. When the plunger directions were reversed, the transition was not smooth and a fixed volumetric throughput was required before flow rate increased to its steady state value. The transient response of the dialyzer to the reversal in pump direction was investigated by continuously monitoring the outlet concentration during sodium chloride dialysis. The total volumetric throughput required to reach steady state in the outlet concentration was about 25 to 30 cc, and this value was nearly independent of flow rate. For a step change in flow rate without pump reversal, about 20 cc were required for steady state. Since only about 48 cc of the syringe contents could be pumped between reversals, it was not possible to study more than one flow rate per pump reversal. Thus, about 50 cc of blood-side fluid were required for each data point. With organic solutes, samples were usually collected during the last 10 cc of throughput before pump reversal.

Attempts were made to maintain constant temperature control at 37°C by jacketing the syringes, insulating all lines and the dialyzer, and heating the fluid reservoirs. This approach was unsuccessful. Immersion of the dialyzer
in a constant temperature bath was rejected on the basis of expediency, since considerable modification of the as-built system would have been required. Instead, experiments were run at ambient conditions. Temperature was measured with a thermometer at the dialyzate outlet and the entire dialyzer assumed to be in thermal equilibrium with this value. During the course of a single run, temperature usually remained constant to within better than ± 1° C.

All fittings on the dialyzate side were either plastic, generally nylon or polypropylene, or stainless steel. On the blood-side, chrome-plated Luer-lok fittings and polypropylene connectors were used throughout. The Luer-lok valves had brass bodies. All tubing was plastic (PVC, polyethylene, or teflon) throughout, except for a two foot section of stainless steel capillary tubing used as a heat exchanger in the conductivity cell constant temperature bath.

Pressure measurements were made with a mercury manometer. All connecting lines between pressure taps and manometer were filled with isotonic saline. The manometer was limited in its utility because of its slow response to pressure changes and its large volumetric displacement.

Equipment calibrations and additional details may be found in Appendix D.

4. Fluids Employed

Aqueous solutions containing sodium chloride (isotonic saline) and labelled urea-C\(^{14}\) were first employed as the blood-side fluid, with distilled water as the dialyzate. Then
whole human plasma and whole human blood were studied on the 
blood-side with isotonic saline as the dialyzate.

Fresh plasma and whole blood were obtained from the 
Massachusetts General Hospital Blood bank and were used 
within two weeks of collection. The blood was first 
filtered to remove small micro-clots. A small quantity of 
concentrated tracer stock solution (see Appendix D) was 
added to each fluid to yield about 20,000 cpn before dialysis. 
The condition of the blood, as received, and the measurement 
of hematocrit was identical to that described in Section 
4.C.2.d in relation to the stagnant blood diffusion measure-
ments.

In all experiments, the dialyzate solution contained at 
least 200 ppm formaldehyde to prevent bacterial growth.

5. Flow Visualization

In order to substantiate that the blood-side inlet 
header was properly designed, flow visualization experiments 
were conducted to investigate the transverse velocity profile. 
The two dialyzer body plates were replaced by clear lucite 
plates containing no foametal so that the blood-side flow 
path could be observed. The ends of the dummy body plates 
were designed to mate with the inlet and outlet endplates.

Water was pumped through the blank dialyzer, with no 
membrane in place, and a concentrated solution of Erichrome 
Black T dye was injected through the three-way valve at the 
dialyzer inlet. Movement of the colored solution was readily 
observed.
6. **Transport in Dialyzate Phase**

Measurements of dialyzate mass transfer coefficients were carried out with one of the dialyzer body plates, with the membrane "sandwich" and the other lucite plate replaced by an aluminum plate containing an insert of compressed benzoic acid. The benzoic acid covered a 2 in. by 2 in. square, duplicating the area and position of the mass transfer section of the dialyzer as normally assembled. Fabrication of the benzoic acid insert was identical with the procedure described in Chapter 3 with respect to liquid phase mass transfer coefficients in the batch dialyzer. The solution pumped through the system initially contained 0.002M benzoic acid. The outlet concentration was monitored with the conductivity cell. All experiments were performed at 25°C.

Mass transfer coefficients were calculated from the log-mean concentration driving force based on inlet and outlet conditions. From an overall material balance

\[
N = Q_d (C-C_i) = k wL \frac{(C_w-C_i) - (C_w-C)}{\ln \left( \frac{C_w-C_i}{C_w-C} \right)} \tag{5-198}
\]

which yields

\[
k = \frac{Q_d}{wL} \ln \left( \frac{C_w-C_i}{C_w-C} \right) \tag{5-199}
\]

As with the batch dialyzer experiments, the concentration at the wall, \(C_w\), was taken to be the saturation concentration. Seidell's (372) data on the solubility of benzoic acid in
water at 25°C were used. Values of the molecular diffusion coefficient of benzoic acid in water as a function of concentration and temperature were taken from the results of Chang (68). Diffusivity was evaluated at the average of the wall and outlet concentrations.

Measurements were made with and without the foametal supports in place. Similar experiments were also carried out with one-half of the Babb-Grimsrud test dialyzer, for which an aluminum plate of the proper dimensions was constructed. Pressure drop measurements during flow through the foametal were also made with a blank plate bolted to the dialyzer plate.

7. Data Reduction

All data reduction was performed on a digital computer. Separate programs were written for sodium chloride and radioactive solutes. Each program contained an error analysis.

Briefly, all raw experimental data and their standard deviation was fed into the program. The output consisted of a variety of calculated quantities and their estimated accuracy. The program contained built-in initial guesses for the diffusion coefficient and wall permeability, based upon the results described in Chapters 3 and 4. The output included the experimental values of C* and the estimated X* and Sh_w (with X_1 = X_2 = 1.0). These results were then used as input data for an optimization program which determined the best value of X_1 or X_2 for each data point. From
this, the value of \( D \) or \( k_w \) which fit the data best was estimated. With knowledge of \( k_d \), the dialyzate phase mass transfer coefficient, \( P_m \) could be estimated from \( k_w \). The raw data was then re-analyzed with the first program to produce the calculated quantities corresponding to the best fit of \( D \) or \( k_w \). Additional details of the data reduction, program listings, and sample output may be found in Appendix O.

E. Results and Discussion

1. Flow Visualization

The dialyzer was assembled as in normal operation, but with blank body plates and no membrane. Ten mil spacers were used with an aspect ratio of 200. Water was pumped on the blood-side and an aqueous dye solution was injected into the inlet line. When the dye had advanced into the mass transfer channel, the pump was stopped and a photograph immediately taken, as shown in Figure 5-19.

Because of the very thin channel thickness, the intensity of the dye is greatly diminished. However, it is possible to discern the dye solution-water interface. It is flat across the entire width of the channel, indicating a flat transverse velocity profile.

The experiment was repeated over a 200:1 flow rate range with identical results. From this it was concluded that the header was functioning properly and no shunting or boundary-layer buildup on the side of the channel occurred. During a mass transfer experiment, the flat faces of the channel were comprised of flexible membranes. In order that the flow
a. Overall Setup

b. Close-up of dye solution-water interface

Figure 5-19. Dye Visualization Studies in Flat Plate Dialyzer
remain ideal, it was necessary that the pressure on the bloodside be higher than that on the dialyzate side in order to
keep the membranes pressed against the foametal support.

2. Dialyzate Phase Characterization

a. Pressure Drop

Pressure drop measurements on the dialyzate side
are tabulated in Table 5-3. The data was obtained for flow
through a single slab of low density material, 2 in. wide,

<table>
<thead>
<tr>
<th>Qd (cc/sec)</th>
<th>ΔP (mm. Hq)</th>
<th>ΔP/Qd</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.932</td>
<td>1.6</td>
<td>0.184</td>
</tr>
<tr>
<td>2.79</td>
<td>2.5</td>
<td>0.032</td>
</tr>
<tr>
<td>4.70</td>
<td>3.6</td>
<td>0.0163</td>
</tr>
<tr>
<td>6.55</td>
<td>6.5</td>
<td>0.0151</td>
</tr>
<tr>
<td>8.43</td>
<td>10.4</td>
<td>0.0146</td>
</tr>
<tr>
<td>10.4</td>
<td>15.4</td>
<td>0.0143</td>
</tr>
<tr>
<td>12.1</td>
<td>21.7</td>
<td>0.0147</td>
</tr>
<tr>
<td>13.9</td>
<td>26.9</td>
<td>0.0138</td>
</tr>
<tr>
<td>15.8</td>
<td>32.0</td>
<td>0.0128</td>
</tr>
<tr>
<td>17.6</td>
<td>38.6</td>
<td>0.0124</td>
</tr>
<tr>
<td>19.4</td>
<td>46.3</td>
<td>0.0123</td>
</tr>
<tr>
<td>21.2</td>
<td>56.4</td>
<td>0.0126</td>
</tr>
<tr>
<td>23.0</td>
<td>66.6</td>
<td>0.0126</td>
</tr>
</tbody>
</table>
1/8 in. thick, and 6 in. long. The first two data points are not very accurate because of the low pressures measured, and accuracy increases with increasing pressure drop.

As flow rate increases, the quantity \( \Delta P/Q^2 \) tends to level off toward a constant value. The second order dependence of pressure drop on flow rate indicates that the flow through the foametal is not truly laminar, since this would yield a first order dependence.

The measured pressure drop was compared with that predicted for flow through packed beds. Ergun (115) showed that a wide variety of data could be correlated by

\[
f = 1.75 + \frac{150 (1-\epsilon)}{Re} \tag{5-200}
\]

where

\[
f = \frac{\Delta P \, D_p \, \epsilon^3}{\rho V_o^2 \, L \,(1-\epsilon)} = \text{friction factor} \tag{5-201}
\]

\[
Re = \frac{D_p \, V_o \, \rho}{\mu} \tag{5-202}
\]

and \( \epsilon = \text{porosity} \)

\( V_o = \text{superficial velocity, cm/sec} \)

\( \Delta P = \text{pressure drop, dynes/cm}^2 \)

\( L = \text{length, cm} \)

\( D_p = \frac{6}{a_v} = \text{mean particle diameter, cm} \)

\( a_v = \text{specific surface area, total particle surface/total particle volume} \)

The first term in equation (5-200) represents kinetic energy losses (form drag) while the second term represents viscous dissipation (skin drag).

The porosity of the foametal was measured by weighing a block
of known dimensions in air. Assuming the metal to have the
density of pure nickel, the solidity was found to be 0.0641,
giving a porosity of 0.936. To use equation (5-200), an
estimate of $D_p$ was needed. The foametal was examined under
an optical microscope. A micro-photograph of the foametal
may be found in Appendix D. Repeated measurements were made
of the width of the nickel filaments. The average strand
dimension (effectively the diameter of a cylinder) was about
0.03 cm, and the average maximum dimension of filament
intersections was about 0.075 cm.

Clearly, an a priori estimate of $D_p$ to better than a
factor of two was impossible. Instead, $D_p$ was treated as
an adjustable parameter and the data fitted to Ergun's
equation to find the effective value of $D_p$. The results are
shown in Figure 5-20 for $D_p = 0.05$ cm. Since for a cylinder,

$$a_v = \frac{4}{d_{cyl}}$$  \hspace{1cm} (5-203)

this value of $D_p$ corresponds to $d_{cyl} = 0.033$ cm, which is in
excellent agreement with the measured average filament
diameter.

Figure 5-20 shows that most of the data lies in the
region where kinetic energy losses predominate. During normal
operation, dialyze flowrate through each foametal channel
was about 300 cc/min, corresponding to $Re/(1 - \epsilon)$ of about
350. Grimsrud and Babb (154) stated that they operated with
a Reynolds number of 500, for which flow in the foametal was
turbulent. The author hesitates to call the flow regime
under these conditions turbulent, in the sense that at any
Figure 5-20. Pressure drop through foametal. Friction factor as a function of modified Reynolds number. Data plotted for $D_p = 0.05$ cm.

\[ f = 1.75 + \frac{150(1-\varepsilon)}{Re} \]

from Ergun (115)

\[ f = \frac{\Delta p}{\frac{D_p}{\rho v^2} \frac{\varepsilon^3}{\nu (1-\varepsilon)}} \]

\[ \frac{Re}{1-\varepsilon} = \frac{D_p}{\mu} \frac{v_o}{\rho} \cdot \frac{1}{1-\varepsilon} \]
point in the fluid the instantaneous velocities are purely random. On the other hand, the dominance of kinetic energy losses is likely due to 1) boundary layer separation during flow over the nickel filaments, and 2) sudden changes in flow direction, accompanied by secondary flows, as the fluid flows through the tortuous paths of the porous media. With reference to the former effect, the cylinder Reynolds number, defined by

\[ \text{Re}_{\text{cyl}} = \frac{V_0 d_{\text{cyl}} \rho}{\mu} \]  

(5-204)

was about 15 for \( Q_d = 300 \text{ cc/min} \). At this value of \( \text{Re}_{\text{cyl}} \), one would find standing eddies behind the nickel filaments. The result of these two phenomena would be to mix the fluid somewhat and consequently increase mass transfer in the dialyzate phase above that expected if the foametal were not present.

b. Mass Transfer

Mass transfer coefficients measured in the dialyzate phase with the membrane replaced by a plate of benzoic acid are shown in Figure 5-21. The results are plotted in terms of \( \text{Sh} \) as a function \( x^* \), where the channel (foametal) thickness is used as the characteristic length.

Without foametal present, the data are somewhat higher than that predicted by the Leveque solution for flow over a flat plate, equation (5-104), with the deviation increasing as \( x^* \) increases. The probable reason for this lack of agreement is that the flow was not fully developed. From
Figure 5-21. Dialyzate Mass Transfer, with and without foametal. $Sh$ as a function of $X^*$
equation (5-187), one finds that about 10 cm are required for velocity profile development for the highest flow rates used ( - 1000 cc/min), which is four times greater than the actual length available for flow development before contacting the benzoic acid.

With foametal in place, the mass transfer coefficients were almost three times higher, indicating significant mixing by the foametal support. The data was not corrected for the 6.4% solidity of the support, nor was any correction made in analyzing the dialysis runs. Also plotted are the data obtained with the Babb-Grimsrud dialyzer. The foametal they employed was substantially identical with the material used in this study, except that the support was one-half as thick (1/16 in.). The two sets of foametal data do not coincide, indicating the dimensionless variables used in the correlation are not correct. For a given flow rate, the mass transfer coefficients obtained with the Babb-Grimsrud cell were about 75% to 100% higher than those obtained with the cell used in this study.

A correlation was sought of the form

\[ Sh = a \ Re^b \ Sc^{1/3} \]  \hspace{1cm} (5-205)

The 1/3 dependence on Schmidt number is purely arbitrary and was not tested. However, since both laminar and turbulent mass transfer over a flat plate have a 1/3 Schmidt number dependence (216) when correlated in the form of equation (5-200), it was thought to be a reasonable guess.

Use of equation (5-205) required selection of a
characteristic dimension. Two possibilities were considered, the channel thickness, \( h_d \), and the length of the plate, \( L \), yielding
\[
\frac{k}{D} h_d = a \left( \frac{h_d \bar{v} \rho}{\mu} \right)^b \left( \frac{v}{D} \right)^{1/3}
\quad (5-206)
\]
and
\[
\frac{k L}{D} = a \left( \frac{L \bar{v} \rho}{\mu} \right)^b \left( \frac{v}{D} \right)^{1/3}
\quad (5-207)
\]

The correlation from equations (5-206) and (5-207) are shown in Figures 5-22 and 5-23, respectively. The best fit of the data to a straight line was determined by least-squares. The constants and their standard deviations are as follows:

Equation (5-206)
\[
a = 0.460 \pm 0.052 \quad (5-208)
b = 0.601 \pm 0.026
\]

Equation (5-207)
\[
a = 0.785 \pm 0.177 \quad (5-209)
b = 0.694 \pm 0.028
\]

Both correlations fit the data reasonably well. The correlation shown in Figure 5-22, corresponding to equation (5-206) was selected for further use, since a statistical analysis indicated a slightly better fit of the data. Thus, the equation for estimating the dialyzate mass transfer coefficient is
\[
\frac{k_d h_d}{D} = 0.460 \left( \frac{h_d \bar{v} \rho}{\mu} \right)^{0.601} \left( \frac{v}{D} \right)^{1/3}
\quad (5-210)
\]
Figure 5-22. Dialyzate mass transfer with foametal. $Sh/Sc^{1/3}$ as a function of $Re$. Channel thickness as characteristic dimension.
Figure 5-23. Dialyzate mass transfer with foametal
$Sh/Sc^{1/3}$ as a function of $Re$.
Channel length as characteristic dimension.
Two implicit assumptions should be noted in the use of equation (5-210). First, \( k_d \) is assumed constant over the entire length. Secondly, the value of \( k_d \) is assumed independent of the wall boundary condition i.e. the presence of a membrane with a finite resistance to transport does not alter \( k_d \). If the dialyzate flow were laminar, neither assumption would be valid. However, flow through the foametal bears significant similarities to turbulent flow, and in this regime the changes of the local mass transfer coefficient in the entrance region and the effects of \( \text{Sh}_W \) are greatly reduced. Consequently, the error introduced by the use of equation (5-210) should be quite small.

No previous investigation in the literature could be found dealing with mass transfer to a flat surface with fluid flowing through a porous media similar to foametal. Hanratty (158) studied the heat transfer coefficient from a tube wall to fluid flowing in packed beds of spheres and cylinders. Applying Danckwerts' surface renewal theory he derived the following relation, converted to the mass transfer nomenclature used in this study:

\[
\frac{k_d}{D} = 1.1 \left( \frac{d_p \bar{v}_p}{\varepsilon \mu} \right)^{1/2} \left( \frac{v}{D} \right)^{1/2}
\]

(5-211)

where \( d_p \) is the particle diameter. For comparison, this may be rearranged to

\[
\left( \frac{k_h}{D} \right) \left( \frac{v}{D} \right)^{1/3} = \frac{1.1}{\left( \frac{d_p}{h_d} \right)^{1/2} \left( \frac{1}{2} \right) \varepsilon} \text{Sc}^{1/6} \left( \frac{h_d \bar{v}_p}{\mu} \right)^{1/2}
\]

(5-212)
Using $d_p = 0.033 \text{ cm}$, $h_d = 0.3175 \text{ cm}$, $\epsilon = 0.936$, and $Sc = 825$ for the conditions applicable to this study, equation (5-212) becomes

$$\frac{Sh}{Sc^{1/3}} = 3.60 \text{ Re}^{1/2} \quad (5-213)$$

Yagi and Wakao (146) also studied heat transfer from air flowing in packed beds of spheres and broken solids to a tube wall. Their results were correlated by

$$\frac{k d_p}{D} = 0.2 \left(\frac{d_p \bar{v}}{\mu} \right)^{0.8} \left(\frac{\nu}{D} \right)^{1/3} \quad (5-214)$$

Upon rearrangement as above, their correlation is

$$\frac{Sh}{Sc^{1/3}} = 0.313 \text{ Re}^{0.8} \quad (5-215)$$

Equations (5-213) and (5-215) are plotted in Figure 22. Neither equation represents the data of this study well, although the correlation of Yagi and Wakao converges towards the data at low Reynolds number. The lack of agreement with either correlation is not surprising in view of the difference in the nature of the porous material employed.

3. Sodium Chloride Transport

A series of preliminary runs were made with isotonic saline on the blood side and distilled water as the dialyzate. The primary purpose of these studies was to verify the theoretical model and to determine the membrane permeability for comparison with the results obtained with the batch dialyzer. Since it was desired to study diffusion in blood with the same assembly as that used for the aqueous sodium chloride experiments, it was necessary to choose a spacer thickness which would yield $Sh_w < 4$ for the latter case and
Sh_w > 4 for the former case for maximum sensitivity. From calculations based on the results described in Chapters 3 and 4, a spacer was selected having a thickness of 20.16 mils (.0512 cm). All runs were made with Cuprophane PT-150 as the membrane. During any given run, all variables were held constant, except the blood side flow rate which was varied in order to vary x*. Since the entering dialyzate concentration was zero and the buildup in concentration negligible, C* was calculated as c/c_q. Also, the inlet blood-side concentration was sufficiently high so that the change in membrane permeability with concentration could be neglected.

<table>
<thead>
<tr>
<th>Table 5-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conditions of Operation, Sodium Chloride Runs</strong></td>
</tr>
<tr>
<td><strong>RUN</strong></td>
</tr>
<tr>
<td>Membrane thickness, mils</td>
</tr>
<tr>
<td>Temperature, °C</td>
</tr>
<tr>
<td>Solute Diffusivity, cm²/sec x 10⁵</td>
</tr>
<tr>
<td>Membrane Resistance, R_m, min/cm</td>
</tr>
<tr>
<td>Total Dialyzate Flow Rate</td>
</tr>
<tr>
<td>QD, CC/min</td>
</tr>
<tr>
<td>Dialyzate Resistance, R_m, min/cm</td>
</tr>
<tr>
<td>Wall Resistance, R_w, min/cm</td>
</tr>
<tr>
<td>Wall Sherwood number, Sh_w</td>
</tr>
</tbody>
</table>
The conditions of operation for the first three sodium chloride runs are listed in Table 5-4. Dialyzate flow rate of 617 cc/min corresponded to a pump setting of 30% of maximum flow rate. With the exception of membrane thickness, temperature, and dialyzate flow rate, all quantities tabulated are estimates (see Appendix O). During each run, temperature and concentration varied, and individual estimates were calculated for each data point. The values tabulated represent an average for each run. It is noteworthy that for sodium chloride, the wall Sherwood number is relatively insensitive to temperature changes.

The results for the first three runs are shown in Figure 5-24. Except for the data at low $x^*$ in run 2001, the data agree quite well with the theoretically predicted curve over the entire range investigated. During all runs, the difference between the inlet blood-side and inlet dialyzate pressures were monitored. The blood-side pressure was always significantly higher because of the large pressure drop in the capillary tubing heat exchanger in the conductivity cell bath.

A fourth run was made with sodium chloride. However, dye-injection into the blood-side inlet indicated bypassing of fluid into the dialyzate stream. Upon disassembly, a small puncture in the membrane was found, caused by pressure against the foametal. At this point, the saran wrap film was added for protection.

A final series of runs were made with sodium chloride
with the same assembly intact. The results are tabulated in Table 5-5, and additional details for run 2005.0 are shown in the sample computer output in Appendix 0. The differences in $Sh_w$ were due to small concentration and temperature differences for the data points in each run. $X_1$ was evaluated by the optimization routine relative to the $Sh_w$ pertinent to each run, then corrected relative to the average $Sh_w$ for all runs. The data shows excellent agreement with the predicted value of $Sh_w$. When the data which deviates from the mean by more than 1.5 standard deviations (points 19, 22, 29, 32) are dropped out, the average $X_1$ equals 1.0084. This applies to the estimate of $kw$. To find the correction to $P_m$ (or $R_m$), it is assumed that $R_d$ is correctly estimated. Thus

$$\frac{R_w}{X_1} = \frac{R_m}{\alpha} + R_d$$

(5-216)

where $\alpha$ is the correction factor for $P_m$. Then,

$$\alpha = \frac{R_m}{\frac{R_w}{X_1} - R_d}$$

(5-217)

The estimates for run 2005.0 were $R_m = 17.41$, $R_d = 5.11$, and $R_d = 22.52$. Substitution into equation (5-217) yields $\alpha = 1.011$. Thus, the membrane permeability which best fits the data is about 1.1% greater than that obtained from the batch dialyzer measurements, a difference which is well within the experimental error of both measuring systems.

Of course, such excellent agreement is probably fortuitous and may be the result of compensating errors. It should be noted that most of the individual data points do
Figure 5-24. $C^*$ as a Function of $X^*$ for Sodium Chloride (Preliminary Runs)
## TABLE 5-5

### Sodium Chloride Transport, Run 2005

<table>
<thead>
<tr>
<th>No.</th>
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<th>$Sh_w$</th>
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<th>$C^*$</th>
<th>$X_1$</th>
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<td></td>
<td></td>
<td>.104</td>
<td>.700</td>
<td>1.042</td>
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</tbody>
</table>

**Note:**

$X_1$ calculated relative to average $Sh_w$

Average for all data: $X_1 = 0.9925 + 0.0846 (8.5\%)$

*Without points 19, 22, 29, 32: $X_1 = T.0084 + 0.0483 (4.8\%)$

Best fit $Sh_w = (1.0084)(2.655) = 2.68$
scatter about the best fit, and one would expect that very high accuracy is only attainable when a statistically large number of data points are used.

The results of run 2005 are shown graphically in Figure 5-25, where $C^*$ is plotted as a function of $x^*$. The solid curve corresponds to $Sh_w = 2.68$. The dotted curves correspond to the wall Sherwood numbers calculated from the best fit Sherwood number plus or minus the estimated standard error in the Sherwood number. The calculation of this quantity is described in Appendix D.

Over the entire plotted range, the agreement between the experimental data and theoretical curve is excellent. It is noteworthy that all the data points lie within the region bounded by the dotted curves corresponding to the upper and lower estimates of $Sh_w$.

A large and systematic deviation between the theoretical curve and experimental data, as observed by Grimsrud and Babb (154), was not found in this study. A single data point (number 19 in Table 5-5), which was beyond the $X^*$ range of Figure 5-25 was significantly higher in $C^*$ than the predicted value. In addition, the last three plotted points (highest $x^*$ value) show a slight increasing deviation from the best fit curve. There are two possible reasons for this:

1) The blood-side sodium chloride concentration at the wall becomes low enough so that the reduction in membrane permeability with decreasing concentration becomes significant.

2) At high $x^*$, the blood-side velocity is very low and
Figure 5-25. $C^*$ as a function of $x^*$, Run 2005, Sodium Chloride. 

Best fit $Sh_w = 2.68 \pm 0.30$.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Run</th>
</tr>
</thead>
<tbody>
<tr>
<td>△</td>
<td>2005.0, 1.2</td>
</tr>
<tr>
<td>○</td>
<td>2005.3</td>
</tr>
<tr>
<td>□</td>
<td>2005.4</td>
</tr>
</tbody>
</table>

Estimated Standard Error

$x^* = \frac{xD}{\nu h^2}$
the pressure difference between the blood-side inlet and the dialyzate inlet decreases towards zero. Since dialyzate flow is crosswise to the blood-side flow, the corner of the membrane near the blood-side outlet and dialyzate inlet may be exposed to a higher pressure on the dialyzate side, causing the membrane to distend and collapse upon itself. This would reduce the area available for transport and cause shunting of the blood-side fluid.

The experimentally measured overall log-mean mass transfer coefficients are shown in Figure 5-26, where the overall log-mean Sherwood number is plotted as a function of \( x^* \). Virtually all the data is bounded by the two limiting curves. The scatter about the best fit curve and the estimated standard error are greater than in Figure 5-25 because calculation of \( Sh_{m,o} \) requires taking the logarithm of \( C^* \) and the errors in \( C^* \) are thus magnified.

The increased scatter is further illustrated in Figure 5-27, where the fluid-side log mean Sherwood number is plotted as a function of \( x^* \). \( Sh_{m,f} \) is obtained by subtracting the reciprocal of \( Sh_w \) from the reciprocal of \( Sh_{m,o} \), equation (5-47). Since nearly 2/3 of the total resistance is in the wall for run 2005, the measurements are not very sensitive for evaluating \( Sh_{m,f} \).

Since the data for run 2005 showed excellent agreement with the theoretical curve, Figure 5-25, a simultaneous fit of all the data points to evaluate \( X_1 \) was attempted. The results are shown in Figure 5-28, where the six different
Figure 5-26. Experimental overall log-mean Sherwood numbers. Run 2005.

- Theoretical Curve
- Estimated Standard Error

\[ x^* = \frac{x \cdot D}{v \cdot h^2} \]
Figure 5-27. Experimental fluid-side log-mean Sherwood numbers. Run 2005.

\[ \text{Sh}_{m,f} = \frac{k_m f \bar{h}}{D} \]

--- Theoretical Curve

Estimated Standard Error

\[ X^* = \frac{xD}{\nu h^2} \]
Table 5-6

Summary of Simultaneous Fit of $X_1$ and $X_2$, Run 2005

<table>
<thead>
<tr>
<th>Location of Minima</th>
<th>Objective Function</th>
<th>$X_1$ ($X_2 = 1.0$)</th>
<th>$X_2$ ($X_1 = 1.0$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_1$</td>
<td>1.021</td>
<td>1.036</td>
<td></td>
</tr>
<tr>
<td>$</td>
<td>F_2</td>
<td>$</td>
<td>1.019</td>
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<td>$F_3$</td>
<td>1.020</td>
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<td>$F_4$</td>
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<tr>
<td>$</td>
<td>F_5</td>
<td>$</td>
<td>1.014</td>
</tr>
<tr>
<td>$F_6$</td>
<td>1.005</td>
<td>1.008</td>
<td></td>
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</tbody>
</table>

Objective functions, equations (5-141) to (5-145), are plotted as a function of $X_1$ for $X_2 = 1.0$. The $Sh_w$ estimate was 2.655.

The location of the minima are listed in Table 5-6, including the values for fitting $X_1$ with $X_2$ held constant and vice versa. Each objective function reaches a minimum at a different point. For $X_1$, the range is 1.005 to 1.021, and for $X_2$ it is 1.008 to 1.043. The $X_1$ values compare well with the point by point average of all data, .9925, from Table 5-5, the maximum difference being about 3%. As expected from the sensitivity analysis of Section 5.C.5.b, the range of the best values of $X_2$ is larger than for $X_1$. In either case, the agreement is satisfactory with the point-by-point analysis. However, if the data were more scattered or many less points were used, the results from the different objective functions would diverge, requiring a decision as
Figure 5-28. Simultaneous fit of all data points for Run 2005. Objective function vs. $X_1$ with $X_2$ held constant at 1.0.

Location of Minima

- $F_6$
- $F_4$
- $F_5$
- $F_2$
- $F_3$
- $F_1$
which objective function should be used. Since the point-by-point analysis gave an unequivocal value, it was used for the remaining runs.

4. Urea Transport

Three runs were made with urea -C¹⁴ as the solute to be dialyzed with isotonic saline, plasma, and whole human blood as the blood-side fluid. The dialyzer was not dismantled and the same assembly and membrane were used as had been used from run 2005 with sodium chloride.

The general approach was to evaluate the urea permeability of the membrane with the aqueous solution on the blood side. With the permeability known, the effective diffusivity for diffusion in plasma and whole blood could then be determined.

a. Isotonic Saline

For dialysis of urea in isotonic saline, Run 2101, measurements were made at 25.9°C and Q_D = 617 cc/min with the following initial estimates: D = 1.41 x 10⁻⁵ cm²/sec, R_m = 20.1 min/cm, R_d = 5.5 min/cm, R_w = 25.6 min/cm and Sh_w = 2.41. The results are shown in Figure 5-29 where C* is plotted as a function of x*. The best fit of X₁ for each data point is summarized in Table 5-7.

In Figure 5-29, the last two data points show a marked deviation from the best-fit curve. These corresponded to the two lowest flow rates. With radioactive urea, the outlet blood-side solution was not pumped through the conductivity cell and the capillary tubing heat exchanger,
Figure 5-29. $C^*$ as a function of $X^*$. Run 2101, urea in isotonic saline. Best fit $Sh_w = 2.73 \pm 0.31$. 

$x^* = \frac{xD}{\nu h^2}$

$Sh_w = 2.42$

$Sh_w = 3.04$
Table 5-7

<table>
<thead>
<tr>
<th>No.</th>
<th>$x^*$</th>
<th>$C^*$</th>
<th>$X_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.119</td>
<td>.678</td>
<td>1.047</td>
</tr>
<tr>
<td>2</td>
<td>.155</td>
<td>.566</td>
<td>1.298</td>
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<td>3</td>
<td>.187</td>
<td>.509</td>
<td>1.278</td>
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<td>4</td>
<td>.219</td>
<td>.445</td>
<td>1.338</td>
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<tr>
<td>5</td>
<td>.262</td>
<td>.412</td>
<td>1.156</td>
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<td>6</td>
<td>.0942</td>
<td>.748</td>
<td>0.947</td>
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<td>7</td>
<td>.0685</td>
<td>.808</td>
<td>0.939</td>
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<td>8</td>
<td>.0407</td>
<td>.887</td>
<td>0.828</td>
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<tr>
<td>9</td>
<td>.0109</td>
<td>.927</td>
<td>2.73</td>
</tr>
<tr>
<td>10</td>
<td>.00486</td>
<td>.960</td>
<td>3.10</td>
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</table>

All data: $X_1 = 1.466 \pm 0.787 (53.7\%)$

Without points 9 and 10: $X_1 = 1.104 \pm 0.191 (17.3\%)$

resulting in a lower pressure at the blood-side inlet. At these low flow rates the pressure difference between the blood-side inlet and dialyzate inlet dropped to nearly zero which probably resulted in partial membrane collapse. Consequently these data points were not used in the analysis.

Table 5-7 shows that the two data points at the lowest $x^*$ yield highly divergent estimates of $X_1$, consistent with the sensitivity analysis in Section 5.C.5.b. These points were also discarded. The remaining data give
average estimate of \( X_1 = 1.104 \). Thus, the wall Sherwood number which best fits the data is 10.4% greater than the original estimate. Applying equation (5-217) and assuming that \( R_d \) is correct, one obtains \( \alpha = 1.136 \), or a 13.6% correction to the membrane permeability measured with the batch dialyzer. This corresponds to an estimate of 17.7 min/cm at 25.9°C. The 13.6% correction was used for all successive measurements with same membrane.

6. Plasma

Dialysis of urea in plasma. Run 2102 was performed at 25.6°C. In an attempt to reduce dialyzate pressure drop, \( Q_d \) was cut back to 394 cc/min. As a first guess, the diffusion coefficient for urea was calculated as 0.807 times the diffusion coefficient in saline, based upon the results of the stagnant diffusion measurements, yielding \( \bar{D} = 1.13 \times 10^{-5} \text{ cm}^2/\text{sec} \). Using \( k_p = 0.096 \) and \( \phi_p = 0.0792 \), \( K_{S/P} \) was calculated to be 0.984. Estimates of the other parameters were \( R_m = 17.8 \), \( R_d = 7.3 \), \( R_w = 25.1 \), and \( Sh_w = 3.15 \).

A summary of the best fit of \( X_2 \) is listed in Table 5-8, and \( C^* \) is plotted as a function of \( x^* \) in Figure 5-30. Despite the lowering of the dialyzate flow rate, the data points corresponding to the two lowest plasma flow rates again showed evidence of membrane collapse and these points were discarded.

A problem arose with the syringe pump during pumping of the plasma. The syringes employed had ground glass
Table 5-8

Urea in Plasma, Run 2102

<table>
<thead>
<tr>
<th>No.</th>
<th>X^*</th>
<th>C^*</th>
<th>X_2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.113</td>
<td>.690</td>
<td>1.161</td>
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<tr>
<td>2</td>
<td>.147</td>
<td>.601</td>
<td>1.392</td>
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<tr>
<td>3</td>
<td>.191</td>
<td>.521</td>
<td>1.337</td>
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<tr>
<td>4</td>
<td>.245</td>
<td>.408</td>
<td>1.687</td>
</tr>
<tr>
<td>5</td>
<td>.0204</td>
<td>.934</td>
<td>0.806</td>
</tr>
</tbody>
</table>

All data: \[ X_2 = 1.277 \pm 0.324 \text{ (25.4\%)} \]
Without point 4 \[ X_2 = 1.174 \pm 0.264 \text{ (22.5\%)} \]

surfaces with a very small gap between the plunger and the outer barrel. A thin film of fluid tended to flow into this gap near the front of the plunger. While perfectly satisfactory with water, the high shear rates in the gap apparently caused denaturation of the proteins because the plungers occasionally stuck to the barrel and at one point in the run they jammed tight, requiring cleaning. As a result, the plasma flow rate was not constant and an accurate measurement was impossible.

The results indicated that the diffusion coefficient which best fit the data was considerably larger than originally estimated. For example, ignoring point 4 in Table 5-8, one obtains \[ X_2 = 1.174 \], giving \[ D = 1.32 \times 10^{-5} \text{ cm}^2/\text{sec} \]. This is 0.947 times the diffusivity in saline, versus 0.807 obtained with the stag-
nant diffusion measurements. However, because of the uncertainty associated with the measured plasma flow rates, the value obtained with the stagnant measurements was assumed to be the better estimate (since it represented the average of 29 experiments), and this value was used in analyzing the data with whole blood.

c. Whole Blood

Run 2103 was made with a unit of fresh whole human blood, type O positive, with a hematocrit of 35.6. To alleviate the pumping problem, the syringes were coated with high vacuum silicone grease, and this proved successful. During pump reversals the flow was temporarily stopped and the syringes rotated in place to mix the blood which had begun to settle. At the lowest flow rates, some settling in the blood inlet header did occur, but the measured hematocrits for any single data point never deviated more than ± 1 hematocrit unit.

The diffusion coefficient of urea in whole blood was estimated from equation (4-114) with \( \theta_p = 0.807 \). \( \psi \) was calculated from the Fricke model, assuming a red cell-plasma permeability ratio of 0.04, yielding an estimate of 0.531. The diffusivity was then estimated for \( K_{WB/P} = 1.0 \), giving \( D = 0.602 \text{ cm}^2/\text{sec} \). Note that the preliminary estimate of \( D \) should have used the correct (estimated) value of \( K_{WB/P} \), but this was not included in the data reduction program. Since it was only a preliminary estimate, and the best value was fitted, this error
had no effect on the final results. Using $K_{eq} = 0.859$, $K_{S/WB}$ for 35.6 hematocrit was estimated to be 1.033. The experiment was run at 25.8°C with $Q_C = 394$ cc/min. Other estimated quantities were $R_m = 17.7$ min/cm, $R_D = 7.1$ min/cm, $R_w = 24.9$ min/cm, and $Sh_w = 6.14$. Additional details may be found in the sample computer output for run 2103 in Appendix 0.

The best fit of $X_2$ is tabulated in Table 5-9 and $C^*$ as a function of $x^*$ is plotted in Figure 5-31. The effective viscosity of blood is roughly three times that of plasma. Consequently the blood-side pressure drop was much higher and membrane collapse did not occur at the lowest flow rates.

The results yield a best fit of $X_2 = 1.020$, giving a diffusion coefficient which best fits the data of $0.614 \times 10^{-5}$ cm²/sec and a ratio of the diffusion coefficient to that in plasma of 0.542.

For a hematocrit of 35.6, the volume fraction red cells was estimated to be 0.342, for which $K_{WB/P}$ was calculated to be 0.964. From equation (4-114), one calculates $\psi = 0.523$. This is plotted in Figure 5-32, along with the results of the diffusion measurements in stagnant red cell suspensions. The data point for flowing blood is essentially indistinguishable from the stagnant results, within the limit of the experimental error.

In a recent study (79) it was shown that during laminar flow of a dilute suspension of polystyrene spheres,
Figure 5-31. $C^*$ as a function of $X^*$, Run 2103,
Urea in Whole Human Blood
Best fit $Sh_w = 6.04 \pm 1.10$

$C^* = \frac{C}{C^*}$

$X^* = \frac{xD}{\nu n^2}$

$Sh_w = 6.04$
$Sh_w = 4.94$
$Sh_w = 7.14$

--- Estimated Standard Error ---
Table 5-9

Urea in Whole Blood, Run 2103

<table>
<thead>
<tr>
<th>No.</th>
<th>X*</th>
<th>C*</th>
<th>X₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.0498</td>
<td>.757</td>
<td>1.104</td>
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<tr>
<td>2</td>
<td>.0637</td>
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<td>0.879</td>
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<tr>
<td>3</td>
<td>.0838</td>
<td>.653</td>
<td>1.005</td>
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<td>.107</td>
<td>.551</td>
<td>1.233</td>
</tr>
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<td>5</td>
<td>.143</td>
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</tr>
<tr>
<td>8</td>
<td>.0285</td>
<td>.862</td>
<td>0.792</td>
</tr>
</tbody>
</table>

All data: \( X₂ = 1.020 \pm 0.168 \) (16.4%)
Without points 4 and 8: \( X₂ = 1.022 \pm 0.141 \) (13.8%)

The rotation of the particles may significantly enhance the molecular diffusion process at sufficiently high shear rates. For parallel plates, the shear rate at the wall is given by

\[
\dot{\gamma} = \frac{6 \bar{v}}{h}
\]  \hspace{1cm} (5-218)

and the wall shear stress is

\[
\tau_w = \mu \dot{\gamma}
\]  \hspace{1cm} (5-219)

For run 2103, the average linear blood velocity ranged from about 0.0649 to 0.381 cm/sec. The channel height was 0.0536 cm, and the effective blood viscosity for 35.6 hematocrit was roughly 0.003 poise. Thus, the range of shear
Figure 5-32. Diffusivity Reduction in Red Cell Suspensions. Comparison Between Stagnant and Flowing Suspensions with Fricke Model (Oblate Ellipsoid, Axial Ratio = 4.25).
rates and shear stresses which occurred were about 7.3 to 43 sec\(^{-1}\) and 0.022 to 0.13 dyne/cm\(^2\), respectively. Clearly, within the range of these parameters, no flow-induced augmentation occurred. However, it should be noted that the shear stresses and shear rates which obtained during this study were quite low, and extrapolation of these results to much higher shear rates may not be valid.

The only comparable data in the literature, is that of Babb, et al (22). With in-vivo hemodialysis at 37°C and a hematocrit of 26, they reported an effective urea diffusivity of 1.40 \(\times\) \(10^{-5}\) cm\(^2\)/sec, compared to 1.80 \(\times\) \(10^{-5}\) cm\(^2\)/sec for saline at 37°C. The diffusivity in blood is significantly different from the value obtained in this study, even when corrected to 37°C. They used a smaller blood-side channel height, giving a lower \(Sh_W\). Consequently, their results were not a sensitive measure of diffusivity. On the other hand, their experiments were at higher shear rates, and it is conceivable that this had an effect.
CHAPTER 6

Simulation of Hemodialyzer Performance

A simulation of the performance of two currently used hemodialysers, the Kolff twin coil and the Kiil dialyzer, was carried out using the theoretical model for a flat plate dialyzer and the experimental data presented in Chapters 3, 4, and 5. The purposes of this simulation were to

1) Determine if the theoretical model and the \textit{in vitro} membrane permeability and blood diffusivity measurements obtained in the laboratory can be used to predict \textit{in vivo} clinical performance of hemodialyzers.

2) Obtain quantitative estimates of dialysance over a wide molecular weight range for which no data exists in the literature.

3) Analyze the relative blood, membrane, and dialyzate mass transfer resistances and delineate conditions where improved performance can be obtained by blood channel or membrane modification.

The approach in this simulation was to first compare predicted curves for dialysance versus flow rate with available \textit{in vitro} and \textit{in vivo} data for urea, creatinine, and uric acid. The analysis was then extended to include 1) higher molecular weight solutes, and 2) variations in membranes employed. The solutes used in the permeation studies (see Chapter 3) were employed as characteristic substances of varying size and shape. While most of them are not of specific interest for removal by the artificial kidney, it was expected that relevant
qualitative conclusions could be drawn from their predicted behavior. The membranes considered were 2.0 mil wet cellophane, 1.1 mil cuprophan, and wet gel regenerated cellulose of 2.6 and 1.1 mil thickness.

A. Theoretical Model

Both the twin coil and the Kiil dialyzers are essentially parallel plate configurations (see Appendix A). The Kiil uses large, flat sheets of membrane with a wide blood channel, while the twin coil consists of a long, narrow path defined by flattened dialysis tubing.

As discussed in Appendix A, artificial kidney performance is generally reported in terms of the dialysance, defined by

\[ D_B = Q_B \frac{(C_{B1} - C_{B0})}{(C_{B1} - C_{D1})} \]  \hspace{1cm} (A-6)

as a function of blood flow rate. From an engineering standpoint, dialysance has little intrinsic meaning. However, it is medically useful since it is a close analogue of the natural kidney clearance (see Appendix A).

To compare predicted performance with clinical data, the theoretical model from Chapter 5 and the descriptive equations of Appendix A were combined. For infinite dialyzate flow rate, it is easily shown that

\[ \frac{D_B}{Q_B} = 1 - C_b^* \]  \hspace{1cm} (6-1)
From Equation (5-41), one finds

$$C_b^* = \exp \left[ -2 \, Sh_{m,0} \, x^* \right]$$  \hspace{1cm} (6-2)

Comparison with Equations (A-13) and (A-14) yields

$$N_T = \frac{KA}{Q_B} = 2 \, Sh_{m,0} \, x^*$$  \hspace{1cm} (6-3)

where $N_T$ is the number of "mass transfer units," $K$ is the overall mass transfer coefficient based on the logarithmic mean concentration driving force and is defined by Equation (5-39), $A$ is the total mass transfer area, and $Q_B$ is the blood flow rate.

In reality, dialyzate flow rate is not infinite and dialyzate concentration varies along the flow path. To account for this, $Sh_w$ and $x^*$ were estimated from the operating parameter of the system and $Sh_{m,0}$ calculated. The resultant value of $N_T$ from Equation (6-3) was used in the appropriate equation derived in Appendix A for the particular flow geometry employed.

The Kii1 dialyzer is generally operated in co-current flow and the twin coil in cross flow. When dialyzate concentration varies, the theoretical estimate of $C_b^*$ and $Sh_{m,0}$ is not rigorously correct. For operational hemodialyzers, this variation is usually small, and consequently the error in the correction is negligible. It must be recognized that many factors exist which might lead to deviations between predicted and actual performance. These include both blood and dialyzate shunting,
distortions in the flow path, and deposition of denatured proteins and/or formed elements (white cells, platelets) on the membrane

B. Estimation of Parameters

The simulation was performed for comparison with literature data where the source articles contained sufficient information so that the necessary hemodialyzer specifications could be estimated. These are summarized in Table 6-1. Estimation of blood channel height during operation was particularly difficult and the estimates in Table 6-1 are probably good to only about 10 to 30 percent.

The studies referenced in Table 6-1 are limited to urea, creatinine, and uric acid. Additional solutes, for which permeation data was obtained in this study, were also considered. The parameters required for estimation of the diffusion coefficient in flowing blood for these solutes (see Chapter 4, Section 4 D.4) are summarized in Table 6-2. They apply to a hematocrit of 35 6, for which the urea data with flowing blood was obtained. Since the source references rarely specify the hematocrit for the data presented, this value is a reasonable estimate because most uremic patients are anemic and have hematocrits lower than normal (40-45) due to lack of erythropoietin production by the kidney.

The estimates listed in Table 6-2 were based on literature data, where available. Values of $k_p$ calculated from the experimentally measured diffusion coefficients in plasma were used, except for urea and uric acid, for which literature data
<table>
<thead>
<tr>
<th>Type</th>
<th>No. of Blood Paths</th>
<th>Area A, m²</th>
<th>Blood Path Geometry</th>
<th>Membrane</th>
<th>Wet Thickness cm x 10^4</th>
<th>Dialyzate Flow rate Qd, cc/min</th>
<th>Reference</th>
</tr>
</thead>
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<tr>
<td>4 Layer Kiil</td>
<td>8</td>
<td>1.8</td>
<td>87.4</td>
<td>Cuprohalone Pt-150</td>
<td>27.9</td>
<td>5000</td>
<td>Kiil (211)</td>
</tr>
<tr>
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<td>2.1</td>
<td>87.4</td>
<td>Cuprohalone Pt-150</td>
<td>27.9</td>
<td>5000</td>
<td>Kiil and Glover (212)</td>
</tr>
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<td>0.58</td>
<td>87.4</td>
<td>DuPont 215-PD</td>
<td>50.8</td>
<td>1000</td>
<td>Wilcox et al (438)</td>
</tr>
<tr>
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<td>1.15</td>
<td>87.4</td>
<td>DuPont 215-PD</td>
<td>50.8</td>
<td>2000</td>
<td>Freeman et al (127, 128)</td>
</tr>
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<td>1000</td>
<td>Visking Tubing</td>
<td>50.8</td>
<td>3000</td>
<td>Kolff and Hatschinger (221)</td>
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<td>1075</td>
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<td>30000</td>
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<td>1000</td>
<td>Visking Tubing</td>
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<td>13000</td>
<td>Meyer et al (285)</td>
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<td>$k_p$</td>
<td>$K_{WB/P}$</td>
<td>$K_{p/s}$</td>
<td>$K_{WB/s}$</td>
<td>$K_{s/wB}$</td>
<td>$\theta_p$</td>
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<td>------------</td>
<td>-----------</td>
<td>------------</td>
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<td>0.968</td>
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<td>0.616</td>
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<td>1.021</td>
<td>0.846</td>
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<td>0.10</td>
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<td>0.958</td>
<td>1.044</td>
<td>0.90</td>
<td>0.561</td>
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<td>0.10</td>
<td>1.028</td>
<td>0.958</td>
<td>1.044</td>
<td>0.90</td>
<td>0.561</td>
</tr>
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<td>Inulin</td>
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<td>0.107</td>
<td>1.028</td>
<td>0.957</td>
<td>1.044</td>
<td>0.883</td>
<td>0.561</td>
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<td>1.028</td>
<td>0.958</td>
<td>1.044</td>
<td>0.90</td>
<td>0.561</td>
</tr>
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<td>0.127</td>
<td>1.048</td>
<td>0.976</td>
<td>1.024</td>
<td>0.823</td>
<td>0.561</td>
</tr>
</tbody>
</table>

a. Estimates apply for: $\phi_p = 0.0792$, Hct = 35.6, $\phi = 0.342$, $\psi = 0.523$
<table>
<thead>
<tr>
<th>Solute</th>
<th>$D_{\text{saline}}$ cm$^2$/sec</th>
<th>$D_m$, cm$^2$/sec$\times 10^5$</th>
<th>$D_{\text{blood}}$ cm$^2$/sec$\times 10^5$</th>
<th>$R_d$, min/cm</th>
<th>$S_{\text{w}}$ Twin Coil with 2 mil Cellophane</th>
<th>$S_{\text{w}}$ Kiil with 1.1 mil Cuprophane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>1.81</td>
<td>2.86</td>
<td>6.02</td>
<td>0.802</td>
<td>14.0</td>
<td>16.0</td>
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<tr>
<td>Creatinine</td>
<td>1.29</td>
<td>1.54</td>
<td>3.58</td>
<td>0.533</td>
<td>17.5</td>
<td>20.0</td>
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<tr>
<td>Uric Acid</td>
<td>1.16</td>
<td>1.42</td>
<td>3.26</td>
<td>0.444</td>
<td>18.8</td>
<td>21.5</td>
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<td>1.93</td>
<td>0.331</td>
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<td>30.2</td>
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<td>Vit. B$_{12}$</td>
<td>0.379</td>
<td>0.193</td>
<td>1.01</td>
<td>0.191</td>
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<td>PEG</td>
<td>0.210</td>
<td>0.0064</td>
<td>0.11</td>
<td>0.106</td>
<td>58.9</td>
<td>67.3</td>
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<td>Inulin</td>
<td>0.215</td>
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<td>0.567</td>
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<td>0.060</td>
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<td>92.6</td>
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<td>0.00064</td>
<td>0.047</td>
<td>102.3</td>
<td>117.9</td>
</tr>
</tbody>
</table>
was employed. Where no literature or experimental data was available, the following estimates were made: $K_{eq} = 0.8$, $k_p = 0.10$, $\theta_p = 0.9$. Only for creatinine and uric acid does the estimated blood-saline distribution coefficient differ significantly from unity.

The final solute and membrane parameters for the simulation are tabulated in Table 6-3. All commercial cellophanes were assumed to be identical. Dialyzate mass transfer resistances for the twin coil were based upon the sodium chloride Wilson plot data of Leonard and Bluemle (244) (see Appendix A). The estimated urea dialyzate resistance for the Kiil dialyzer represents an educated guess which is in agreement with other investigators in the field (432a). Dialyzate flow was assumed turbulent and resistances for other solutes were scaled from the urea estimates assuming a 2/3rd power dependency on diffusivity.

C. Results and Discussion

A comparison of the theoretically predicted curves and reported data for in vitro dialysis of aqueous solutions is shown in Figure 6-1, where dialysance is plotted as a function of "blood" flow rate. In general, the predicted and literature data show excellent agreement.

Figure 6-2 compares the predicted and reported dialysance as a function of blood flow rate for in vivo hemodialysis with a 2 layer Kiil. In view of the potential errors in the experimental data and the parameter estimation, the agreement is surprisingly good. A similar plot is found in
Figure 6-3 for hemodialysis with the twin coil. The predicted curves give a reasonable representation of the data. However, considerable scatter prevents a definitive judgment.

The agreement found between the predicted curves and the reported clinical data does not constitute proof of the accuracy of the parameters estimated nor of the theoretical model. Data obtained under more controlled conditions would be required for this. However, it does show that the simulation can be used to make a rough estimate of predicted performance and permits one to simulate the effects to be expected by variations in hemodialyzer geometry and in membrane and solute parameters.

The following limitations of the simulation should be noted. It is assumed that the red cells are everywhere in chemical equilibrium with the plasma. Definitive criteria for the validity of this assumption would require an analysis, similar to that developed in Appendix F, which included the effect of the hemodialyzer membrane permeability. The other limitation is that solutes such as some of the amino acids, which are protein-bound to a large extent, or have a very high red cell plasma distribution coefficient, would give dialysance behavior outside the range of the simulation. The effect of either of these two phenomena would be to reduce the actual dialysance from that predicted.

The additional simulations were made for the twin coil and Kid dialyzers with the specifications corresponding to those of Freeman, et al. (127,128) and for hemodialysis of
blood with an hematocrit of 35.6. Fig. 6-4 illustrates the
effect of variation in the kind of membrane used on the
dialysance with the twin coil for seven different solutes
(not including PEG hepari...). The data at a blood flow rate
of 200 ml/min are plotted in Fig. 6-5 and a similar plot for
the Kiil dialyzer is shown in Fig. 6-6 for all nine solutes.
The 1.1 mil wet gel is a hypothetical membrane of the same
thickness as cuprophane. It is presently not available but
represents what might be attainable with a thin highly
swollen cellulosic membrane.

It is clear that dialysance drops off significantly
with increasing molecular weight. Making the membrane more
permeable has a proportionally greater effect on the higher
molecular weight solutes since their transport is membrane-
controlled. It is noteworthy that the data points corre-
sponding to compact spherical or elongated molecules (see
Appendix B) lie approximately in a straight line, indicating
a power-law dependence on molecular weight. The slopes of
these lines are tabulated in Table 6-4. They range from
about 0.5 for the least permeable membranes to about 0.3 for
the most permeable. This change in the molecular weight
dependence of dialysance is presumably related in a complex
way to a shift from primarily membrane-limiting to blood-
limiting behavior. The points which lie roughly on a straight
line correspond to the types of molecules which are most
likely to be found in biological systems. The lower dashed
curves correspond essentially to less compact, random coiling
Table 6-4

Logarithmic Slopes of Dialysance-Molecular Weight Relationships for Compact Molecules, from Figs. 6-5 and 6-6

<table>
<thead>
<tr>
<th>Membrane</th>
<th>Twin Coil</th>
<th>2 Layer Kiil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellophane, 2.0 mil</td>
<td>0.46</td>
<td>0.52</td>
</tr>
<tr>
<td>Cuprophan, 1.1 mil</td>
<td>0.41</td>
<td>0.46</td>
</tr>
<tr>
<td>Wet Gel, 2.6 mil</td>
<td>0.33</td>
<td>0.34</td>
</tr>
<tr>
<td>Wet Gel, 1.1 mil</td>
<td>0.31</td>
<td>0.30</td>
</tr>
</tbody>
</table>

macromolecules. The only compounds of this sort in the body might be denatured or improperly synthesized proteins. Had the curves been plotted as a function of molecular size, the relationship would have been continuous.

The results clearly show that with currently employed membranes, solutes in the molecular weight range of about 500 to 10,000 are being removed at very slow rates. Retention of such solutes, if toxic, may explain the clinical observation of neuropathy which disappears with long dialysis treatments.

Figures 6-7 and 6-8 show the relative mass transfer resistance breakdown for the twin coil and 2 layer Kiil dialyzers, respectively, at a blood flow rate of 200 ml/min and with currently used membranes. In the twin coil, the blood phase in the limiting resistance at low molecular weights. As molecular size increases, there is a crossover and the
Figure 6.1: Dialysance as a function of blood-side flow rate for dialysis of aqueous solutions.
Figure 6-2. Dialysance as a Function of Blood Flow Rate
Hemodialysis With 2 Layer Kil (127, 128)
FIGURE 6-3. DIALYSANCE AS A FUNCTION OF BLOOD FLOW RATE FOR IN VIVO HEMODIALYSIS WITH TWIN COIL.
FIGURE 6-4. EFFECT OF VARIATION IN MEMBRANE EMPLOYED AS A FUNCTION OF BLOOD FLOW RATE FOR VARIOUS SOLUTES (KOLFF TWIN COIL).
FIGURE 6-5. DIALYSANCE AS A FUNCTION OF MOLECULAR WEIGHT. FOUR DIFFERENT MEMBRANES USED WITH KOLFF TWIN COIL AT Q = 200 ML/MIN.
FIGURE 6-6. DIALYSANCE AS A FUNCTION OF MOLECULAR WEIGHT. FOUR DIFFERENT MEMBRANES USED WITH 2 LAYER KIIL AT $Q_B = 200$ ML/MIN.
Fig. 6-7 Relative Resistances for Kolff Twin Coils as a Function of Molecular Weight at $Q_B = 200$ ml/min (Visking Tubing as Membrane)
Figure 6-8: Relative resistances for 2-layer K11 as a function of molecular weight at \( Q_B = 205 \text{ mL/min} \) (Cuprophone as membrane).
Figure 6-9. Relative resistances for hollow twin coil as a function of solute molecular weight.
Figure 6.10. Relative resistances for 2-layer XIL as a function of solute molecular weight.

- Membrane (Wet Gel 1.1 mm)
- Blood
- Dialyzer
membrane becomes limiting. The relationships for the KIII dialyzer are qualitatively similar, although the blood mass transfer resistance is lower and the crossover to membrane-limiting conditions occurs at very low molecular weight.

Considerable current research is aimed at reducing membrane area and lowering the blood side mass transfer resistance by using smaller blood channels. While this will have a beneficial result in decreasing priming volume, the effect on mass transfer operation will be minimized for all but the smallest solutes. If higher molecular weight solutes need to be removed, then the results shown in Figs. 6-5 through 6-8 clearly demonstrate the need for more permeable membranes. If these are not available, dialyzers should have larger area or dialyzing time should be increased.

Although currently available wet gel cellulose may be too weak for use in clinical hemodialysis, it does represent what is attainable with highly swollen hydrophilic gels. The relative resistance breakdowns for the twin coil and KIII dialyzers with the membrane replaced by a hypothetical 1.1 mil wet gel cellulose are shown in Figs. 6-9 and 6-10, respectively. In both cases, the blood phase is the limiting transport resistance over most of the molecular weight range of interest. With such a membrane employed, further modifications in blood channel design would then be reasonable. It is suggested that additional research on such swollen gels be carried out to find a suitable hemodialysis membrane.
CHAPTER 7

Conclusions

Batch Dialyzer

1. Numerical solutions were obtained for the partial differential equations describing mass transfer from a rotating fluid to a stationary base. The results agreed with a limiting analytical solution valid near the edge of the transfer surface.

2. Experimentally measured local mass transfer coefficients at the flat bottom of a cylindrical vessel, agitated by means of an axially located turbine impeller, agreed well with the theoretically predicted values for a fluid rotating against a stationary surface except in the vicinity of the vessel wall. The data fell between the solutions for the two limiting cases of a) no velocity gradient between the impeller and the adjacent fluid, and b) the impeller replaced by a disk with boundary layer formation on both disk and stationary base between which exists an inviscid core undergoing solid body rotation.

3. Measurements of torque, local and overall mass transfer coefficients, and membrane flutter showed that above $Re = 30,000$ the membrane boundary layer is turbulent, below $Re = 20,000$ it is laminar, with a transition region possibly beginning at $Re = 20,000$ to $25,000$.

4. Combining the theoretical analysis and experimental data for a laminar boundary layer, a correlation was obtained for estimating average liquid-phase mass transfer coefficients in a batch dialyzer. With this knowledge, the true permeability of a membrane could be estimated from a single experimental
measurement with the batch dialyzer, thus eliminating the tedious repetitive measurements required in the use of a Wilson plot.

5. Extensive measurements of the sodium chloride permeability of a variety of cellulosic membranes showed that most commercial cellophanes are similar in permeation properties and that significant increases in permeation properties are attainable with never-dried, wet gel regenerated cellulose.

6. Additional permeability measurements with 14 organic solutes covering a wide range of molecular weight and conformation demonstrated a) the strong dependence of the effective diffusivity on molecular size and shape, and b) the dramatic reduction in effective diffusivity which occurs when wet gel regenerated cellulose is dried, following glycerol plasticization, in the manufacturing process for cellophane and then rewetted. The decrease in effective diffusivity is about a factor of two for small molecules but increases to more than an order of magnitude for larger molecules. For a characteristic molecular radius up to about 10Å⁺, the ratio of membrane permeability to that of an equal thickness of water is approximately constant with Avisco wet gel cellulose, but decreases significantly with increasing solute size with commercial cuprophane PT-150.

7. Additional experiments showed that

a) Pre-soaking the membrane in blood results in a slight decrease in permeability, the reduction increasing with increasing molecular size.

b) Amination of cuprophane, followed by heparinization, produces a decrease in permeability to most solutes,
amounting at most to about a 30% reduction.

**Capillary Diffusion Measurements**

8. Diffusion measurements in isotonic saline showed excellent agreement with literature data for urea and sucrose and reasonable agreement with estimated diffusivities for other organic solutes.

9. Diffusion coefficients of various organic solutes in plasma were all lower than in saline and the reduction differed from solute to solute. The quantitative results compared favorably with a theoretical model which included the effects of volume fraction proteins, solute binding by proteins, and diffusion of the solute-protein complex.

10. Urea diffusion measurements in red blood cell suspensions showed that the effective diffusivity decreases with increasing hematocrit. At normal hematocrit, about 45, the reduction from the diffusivity in plasma amounts to about 50%. Comparison of the data with a theoretical model for transport through a suspension of permeable oblate ellipsoids showed that the red cells behave as a nearly impermeable phase. This conclusion was in agreement with estimates of red cell permeability from literature data.

11. An approximate theoretical model was derived for transient diffusion in heterogeneous media with nonequilibrium between phases. The model gave quantitative criteria for the existence of phase equilibrium and showed that, for the urea experiments, the red cells and plasma were in equilibrium, but that for similar experiments with larger solutes equilibrium conditions would not
prevail.

Flat Plate Flow Dialyzer

12. Theoretical solutions were obtained for convective diffusion with laminar flow between two flat, semi-infinite semi-permeable membranes. In addition, a Leveque-type entrance region solution was developed, and an approximate expression was derived for the higher eigenvalues.

13. A new technique was developed for the determination of solute diffusivity or membrane permeability from experimental data, involving an exact fit of each data point to the model with a minimization algorithm. For this purpose, eigenvalues from the theoretical solution were fitted to high order polynomials and a "black box" computer program developed to generate theoretical results rapidly from input parameters.

14. Dye visualization flow studies with the flat plate flow dialyzer showed a flat velocity profile on the blood-side with no shunting.

15. Experimentally measured mass transfer coefficients in the dialyzate phase alone permitted evaluation of membrane permeability or solute diffusivity at all dialyzate flow rates.

16. Dialysis experiments with aqueous solutions and cupronhane gave membrane permeabilities which agreed to within 1% for sodium chloride and to within 13% for urea with results obtained with the batch dialyzer.

17. Effective diffusion coefficients of urea in flowing whole blood agreed with the theoretical model and data for diffusion
in stagnant blood, indicating that for the conditions studied (channel height 20 mils, maximum wall shear stress \( \approx 50 \text{ dynes/cm}^2 \)) no shear-induced diffusion augmentation mechanisms are operative.

**Artificial Kidney Simulation**

18. Predicted *in vitro* and *in vivo* operation of clinically used hemodialyzers compared favorably with literature data for lower molecular weight solutes.

19. Extension of the simulation to a wider spectrum of solutes showed that the blood side resistance is significant only for the lower molecular weight solutes and that the membrane resistance dominates for higher molecular solutes. Replacement of existing membranes with wet gel cellulose results in significant increases in solute removal of higher molecular weight compounds.
CHAPTER 8

Recommendations

1. The theoretical solution obtained for mass transfer from a rotating fluid to a stationary base could be extended to include:
   a) lower Schmidt number and b) ultrafiltration through the membrane. The latter aspect would yield information regarding concentration polarization in this geometry and permit studies of ultrafiltration membranes with the batch dialyzer for application to the artificial kidney or reverse osmosis for desalination.

2. Activation energies for membrane permeation should be obtained with organic solutes. In addition to gaining knowledge regarding membrane transport processes, such data would permit more accurate estimation of permeabilities for use with the flow dialyzer.

3. A complete set of phenomenological coefficients for some of the solutes and membranes studied would be helpful in a rigorous analysis of artificial kidney performance where simultaneous dialysis and ultrafiltration occur.

4. Methods of strengthening wet gel cellulose should be investigated in order to improve its potential applicability in clinical hemodialyzers.

5. In connection with (3) above, a rigorous model for transport in a flat plate device with both concentration and pressure driving forces should be developed.

6. Additional data on diffusion in flowing blood should be obtained with the batch dialyzer for a variety of hematocrits and solutes at higher shear rates and lower channel heights to determine at what point, if any, diffusion augmentation effects occur.
APPENDIX A

A Review of the Development and Performance of Hemodialyzers

Author's Note: A preliminary version of this review was published in May 1967 as a report to the Artificial Kidney-Chronic Uremia Program, National Institute of Arthritis and Metabolic Diseases in conjunction with contract PH43-66-491 from the National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare. The original review was complete through September 1966. The version presented here has been corrected for mistakes appearing in the original, and the literature search has been extended through June 1968. This section contains a separate table of nomenclature and literature citations which are independent of the remainder of the thesis.

1. Introduction

Since the first successful use of an artificial kidney by Kolff in 1943 (71), hemodialysis has matured into a lifesaving clinical technique for the maintenance of hemostasis in the case of renal failure and related pathological conditions. Because of the limited number of vessel cannulation sites, hemodialysis was originally restricted to cases of acute renal failure (148). With the introduction of permanent indwelling cannulae by Quinton, Dillard, and Scribner
in 1960, the possibility of hemodialysis for chronic renal failure over long periods of time became a reality.

The underlying principles of hemodialysis are quite simple. Blood and dialyzate solutions are circulated on opposite sides of a semipermeable membrane which permits passage of lower molecular weight solutes but restricts transfer of blood proteins and formed elements. By appropriate adjustment of the dialyzate bath composition, various solutes may be selectively removed or added to the blood to return them to their normal concentration. The removal of excess water by ultrafiltration may be accomplished by decreasing the dialyzate bath osmolality or increasing the hydrostatic pressure difference between blood and dialyzate.

The development of hemodialysis to its present state is a tribute to the ingenuity of members of the medical profession. Nevertheless, numerous problems persist in contemporary hemodialysis which limit its accessibility to the many thousands of new patients per year who would benefit from its use. Further improvements in design and performance requires a systematic study of the various facets of the problem and the application of established engineering principles to this unique separation process.

The motivation for this review is to provide an understanding of the state of the art of hemodialyzer design.
Consequently, this aspect has been emphasized in the following material. A review of the literature is presented, covering existing hemodialyzers, design considerations, and performance analyses. This is followed by an overall mass transfer analysis of hemodialyzers from published data.

2. Developments in Hemodialyzer Design

The design of suitable equipment for extracorporeal hemodialysis did not wait for the development of theories to explain the molecular transport involved or appropriate design procedures. Generally, a membrane was chosen from available materials, various dialyzing areas were evaluated for sufficient solute transfer, and mechanical support and geometrical arrangement were selected to provide the contacting area without violating the gross limitations of overall size and maneuverability, blood pressure drop, and blood priming volume. New arrangements were and still are being developed to provide alternate methods by which blood and dialyzate may be contacted across a membrane.

A brief review of significant developments in hemodialyzer design is presented here. For more detailed information on the many facets of the development and use of artificial kidneys, the reader is referred to a number of excellent reviews that have appeared (18, 42, 32, 37, 70, 148, 154).
An excellent overall review of the problems associated with the artificial kidney from an engineering viewpoint has recently been published (88).

Abel, Rowntree, and Turner (1,2) first reported on an instrument constructed in 1912 suitable for "vivi-diffusion" on dogs, which bore a marked resemblance to a 1-2 shell-and-tube heat exchanger. Blood flowed through branched 8 mm i.d. cellophane (nitrocellulose) tubes which were bathed in saline and enclosed in a larger glass tube. Hirudin was the anticoagulant. They were concerned primarily with isolating compounds normally present in blood but recognized the therapeutic potential of their technique. For the next 25 years, the lack of a dependable, reproducible membrane and a reliable anticoagulant hindered significant progress. Necheles (117) described a means of increasing the effective surface area of a peritoneal membrane and reducing blood volume by compression between metal screens. In 1937, Thalhimer (144) used a cellophane membrane in the form of seamless sausage tubing, for the first time. He also employed heparin as an anticoagulant. These two materials have remained in use up to the present.

Kolff and Berk (71) developed the first clinically successful hemodialyzer in 1943. Termed the "rotating drum" artificial kidney, it was later modified by Merrill at the Peter Bent Brigham Hospital in Boston (108, 109). It con-
sisted of a long, coiled cellophane tube, through which blood flowed by gravity, wound on a revolving drum which was partially immersed in a dialyzate bath.

The first dialyzer suitable for ultrafiltration using hydrostatic pressure was reported by Alwall in 1947 (3). A long cellophane tube was helically wrapped and compressed between two concentric cylindrical wire screens, the entire assembly being completely immersed in an agitated bath. Skeggs and Leonards, in 1948, introduced the first flat plate hemodialyzer (133), in which both blood and dialyzate, separated by a flat sheet of cellophane, flowed countercurrent to each other through shallow grooves created by two compressed corrugated rubber pads. Problems with blood coagulation resulted in subsequent modification (134) in which blood flowed between two sheets of cellophane and only dialyzate contacted the rubber pads. The average blood film thickness was reduced to the order of 0.5 mm. Any desired number of units could be connected in series of parallel.

Since 1950, many new designs have proliferated, utilizing plastic materials for construction. The Kolff Twin Coil, which is disposable and capable of mass production, evolved in 1956 (72) from earlier work of a similar design (60). It consisted of two continuously wrapped rolls of flattened cellophane tubing, 10 meters in length, through which blood flowed between two supporting layers of fiberglass screening.
.012 inches thick and spaced to allow dialyzate flow crosswise and at right angles to the flow of blood in the coil. The entire coil was submersed in a 100 liter bath and dialyzate was recirculated at high flow rates. Blood channel thickness was large, of the order of 1 mm and priming required two pints of blood. Recently, smaller versions of the Twin Coil, the Minicoil (17) and the Chronic Coil, have appeared. All require a blood pump. In 1968, a modification of the twin coil was introduced, called the Ultra-Flo 145 (38). The coil was wrapped more tightly with a polypropylene mesh material, giving a smaller blood film thickness and permitting higher ultrafiltration capability.

In 1956, the MacNeill-Collins dialyzer was described (99). It consisted of a stack of flattened cellophane tubes, 18 inches long, connected in parallel by teflon inserts and separated by nylon screens to prevent undue distensions of the blood channels which were about 0.3 mm thick. Bluemle and co-workers have shown (20) that improved performance could be attained by replacing the screens with multiple cone supports which appeared to promote turbulence and mixing at low dialyzate flows.

A new flat plate dialyzer with average blood film thickness reduced to 0.3 mm was described by Kjil (66) in 1960. Blood flowed in four parallel channels between cellophane sheets and dialysate flowed between the membrane envelope
and grooved boards of epoxy resin or polypropylene (29) about 1 meter long and one-third meter wide.

A similar flat plate device for use as an artificial kidney and lung, the Klung, was introduced in 1962 by Aletti and co-workers (49), incorporating successive layers of cellophane and oxygen-permeable membranes. Subsequent development (132, 137, 143) has concentrated on hemodialysis. Presently, the multiple cone supports of Bluemle, cited above, are employed on the blood side and an inflatable rubber bladder which serves as a pneumatic shim may be used to reduce the blood channel thickness below 0.3 mm. In 1968, the Miniklung was introduced (59), incorporating a modified flow path design to reduce the blood-side shunting which occurred with the Klung.

Another recent device, designed as both a hemodialyzer and a membrane oxygenator, was the Dialung, introduced by Esmond in 1965 (39, 40, 41, 42). It was composed of grooved, injection molded plates, 6 inches square. The plates were stacked to give the desired membrane area and blood dialyzate flowed crosswise in the grooves separated by a membrane in an arrangement somewhat similar to the original Skeggs-Leonards hemodialyzer.

All of the hemodialyzers described above have been used clinically and almost all are still in use in various parts of the world. Those most widely used in this country for
the treatment of chronic renal failure are the Kolff-Travenol Twin Coil, the two layer Kiil parallel flow dialyzer, and until a few years ago, the Skeggs-Leonards dialyzer.

In general, the coil dialyzers are most convenient because they are prepackaged, sterile, and disposable. However, they require priming with blood and high internal resistance to flow necessitates a blood pump. They usually operate at high dialyzate flow rates requiring recirculation. The flat plate dialyzers are not disposable and require considerable time for trained personnel to assemble. Although dialyzate flow rates are low, they employ a once-through operation necessitating large dialyzate makeup and storage tanks or a continuous in-line blending system. With the former, bacteria buildup over periods of time has necessitated operation at low temperature (30). The flat plate dialyzers may be operated as passive flow (pumpless) systems. In addition, their lower internal volumes require no blood for priming and they are cheaper to operate. As a result, flat plate dialyzers have proven most useful in conjunction with large dialysis centers and coil dialyzers are predominant in smaller facilities where convenience is at a premium.

In addition to the clinically used hemodialyzers, many experimental designs have been proposed, of which several
are still in development and a few have been tested in vivo on humans. Some researchers have reversed the usual approach of flowing blood inside closed conduits. Guarino and Guarino (55), in 1952, devised a system in which dialyzate solution was pumped through cellophane tubing enclosed within a glass chamber while blood flowed from the patient to the top of the chamber where it showered over the tubing and then drained from the lower chamber. No priming volume was required. Kolobow and co-workers (73) reported on a disposable hemodialyzer in which blood flowed across cellophane tubing. Dialyzate flowed inside the tubing which was internally supported by extended tubular polyethylene netting. A similar reverse coil artificial kidney using countercurrent flow was described by Smith, Gara, and Kolff in 1964, (136). Average blood film thickness was 0.5 mm. A unique design in which blood flowed in a 0.15 mm thick film on the inside of vertically mounted cellophane tubes bathed in dialyzate was presented by Leonard (90) in 1966.

Kupfer and Rosenak (75, 76), in 1959, proposed a method to increase transfer through blood. Straight cellophane tubes were internally supported by plastic rods, mounted horizontally, and immersed in dialyzate bath. Blood flowed in the narrow annular space between rod and tubing and the entire assembly was agitated. Klystra and others (70) constructed a plate type hemodialyzer in which two sheets of
cellophane were supported on mats of woven plastic filter
cloth to provide turbulence and mixing of the dialyzate.

Longmore (94, 95), in 1962, devised a hemodialyzer
consisting of plastic plates with rectangular, spiral grooves,
2 mm deep, cast into them. Sheets of cellophane were enclosed
between the plates, providing an envelope through which blood
flowed, while dialyzate circulated outside. Kuhn et al (74)
in 1957, constructed a similar unit for which he claimed the
grooves were of capillary dimensions, 0.03 mm deep. His
data, however, indicated the blood gap to be about 0.15 mm
thick. Savino (126) presented a flat plate dialyzer utiliz-
ing a single cellophane membrane between grooved plates.
However, the grooves were flared at the top providing
pseudocapillary spaces adjacent to the membrane on both
blood and dialyzate sides. Twardowski (145) has compared
the design characteristics of many existing hemodialyzers
and discussed the advantages of constructing a capillary
artificial kidney.

McDonald (105) developed, in 1964, a cylindrical hemodi-
dalyzer in which blood flowed longitudinally between two
layers of cellophane in an annular space along a cylinder.
Dialyzate flowed in grooves on the inner and outer membrane
supporting elements.

Vadot and Marion (146, 147) described a small stacked
plate type system in 1964, combining a pump-heat exchanger-
dialyzer arrangement for use on infants and small children. Craig and Stewart (33), in 1965, presented a thin film counter-current dialyzer of small area suitable for hemodialysis, reminiscent of the device of Kupfer and Rosenak. They used two concentric cylinders with a clearance of 0.5 mm. A cellophane tube was placed over the inner cylinder and the outer cylinder was rotated. Blood and dialyzate flowed longitudinally in the annular spaces between membrane and cylinders.

Sachs and Funck-Bretano (124) reported on improvements obtained in hemodialyzer performance by stretching the membrane. They also described an experimental dialyzer conceptually similar to the Kiil for use on a rat.

Bluemle and co-workers (21) presented a compact hemodialyzer in 1965, which incorporates a pleated, unsupported membrane into a very small volume. It operated by alternately pulsing blood and dialysate into the unit in a countercurrent fashion. Recently, E. F. Leonard described a similar hemodialyzer constructed out of water-proof cardboard (7, 32 page 105, 39). Bluemle earlier described a radial flow dialyzer (32, page 99) in which blood was introduced in the center and flowed outward between two plates to collecting ports. The blood flow path decreased in thickness from 0.5 mm at the center to 0.1 at the edge.

Babb and Grimsrud (8) presented a new concept in hemodialyzer
membrane support. They employed porous nickel "Foametal" to provide a rigid support in a small experimental dialyzer.

Within the past few years intensified work on equipment for saline water desalination by reverse osmosis has produced, as byproducts, several promising designs for hemodialyzers. Michaels (111) has described a module containing spacers, membranes and support backing in a spirally wrapped double sandwich. It may be envisioned as a flat plate with grooved supports wrapped similarly to the Twin Coil except that the membranes were morerigidity supported and fluid films were held to about 0.25 mm thickness (14). Blood flowed along the membrane sheets toward the center of the wrap and out the core of the unit while dialyzate flowed crosswise to the blood.

An extension of the original tubular hemodialyzer of Abel, Rowntree, and Turner to capillary dimensions was made possible by the Dow Chemical Company through the spinning of extremely fine, hollow filaments of cellulose acetate (102). While cellulose acetate is impermeable to most solutes, removal of the acetate groups by saponification improves dialysis properties. These fine capillaries may be assembled into bundles similar to a shell-and-tube heat exchanger for use as a hemodialyzer (36). Stewart et al. (140) first described a capillary artificial kidney in 1964, in which bundles of 0.055 mm i.d. fibers with 0.014 mm
wall thickness were immersed in an agitated dialyzate bath. Recent work reported by Stewart and co-workers (139) in 1966 utilized fibers of 0.16 mm i.d. They stated that the primary problems in further development of the hemodialyzer were the tendency for heparinized blood to plug the fibers and the difficulty in assembling units containing the required numbers of fibers. In 1967, Lipps, et al. (93) described a larger model employing 6000 fibers of 0.2 mm i.d. and suitable for semi-automated fabrication. Stewart, et al. (141), in 1968, presented preliminary in vivo data on a unit of 0.9 m² with 10,000 fibers and a priming volume of 135 ml.

Several new models were presented in 1968. Holtzenbein (58) reported on a new tightly wrapped, no-prime single coil, suitable for home dialysis, which employed a silicone rubber support with parallel grooves and ridges on either side and was encircled by a rigid lucite girdle to prevent coil expansion. Miller, et al. (113) described a similar device manufactured as a disposable cartridge. Lavender and Markley (80) and Lande, et al. (77, 78) presented small dialyzers using multiple, parallel flow, flat plates. Both groups described new approaches to supporting membranes and manifolding flat plate devices. Roskenbleck (122) devised a small flat plate hemodialyzer with a narrow blood channel.
With the development of more permeable membranes recently, there has been renewed interest in ultrafiltration as an adjunct to, or as a total replacement for, hemodialysis. Bluemle (19), Henderson, et al. (57), Brown and Kramer (23), Bixler, et al. (15, 16), and Dorson and Markovitz (35, 103) have all described variations on a basic theme in which water and solutes are removed simultaneously by ultrafiltration, and water and needed solutes which have been removed are added back to the blood in a make-up solution.

A novel technique was presented recently by Chang, et al (28). It involved perfusion of blood through shunts containing enzymes or detoxicants placed in semipermeable microcapsules.

An implanted artificial kidney was devised and tested on dogs by Salisbury (125) in 1958. The unit consisted of a concave plate, with up to 10 meters of collapsed cellophane tubing affixed, which was inserted into the abdominal cavity. It was perfused intermittently with dialyzate from an external reservoir containing antibiotics to prevent infection. No further work has been reported on the concept.

Operating and design parameters, from published data, for most of the hemodialyzers described above are tabulated in Table A5. The information listed includes the type of dialyzer, mode of operation (coccurrent, countercurrent,
cross flow, or well-mixed dialyzate), and membrane used, its wet thickness, and area. Under "Internal Blood Volume" and "Blood Channel Thickness" single values refer to static design values or values obtained when priming. Priming volumes refer only to the dialyzer itself and do not include associated tubing. When a range of values are given, the lower number refers to the static priming condition while the higher number refers to the dynamic conditions during which non-rigidly supported membranes distend as blood and dialyzate flow rates are increased to their maximum.

It should be pointed out at this time that much of the equipment designed for use in industrial dialysis, reverse osmosis, and as membrane oxygenators has direct application to the design of improved hemodialyzers. This equipment has been reviewed by Vromen (149), Rickles and Friedlander (121) and Buckles (25) respectively.

3. Design Considerations

Before establishing a framework for analyzing the performance of existing hemodialyzers, it is important that a number of factors be discussed. While these considerations apply to both acute and chronic renal failure, they are discussed in relation to the latter, where long term operation imposes stringent requirements.
1) Since hemodialysis involves the application of dramatic techniques to terminal patients in an emotionally charged atmosphere, many problems have arisen concerning the ethical, socio-economic, and psychological considerations (128, 130). The performance of any machine and its interaction with the patient must eventually be judged in the light of these aspects.

2) The medical and clinical basis for use of hemodialysis is still in the experimental stage (101), despite the optimism voiced by its proponents (26). While its life sustaining ability has been demonstrated, therapeutic applications for various pathological conditions are still being investigated. Furthermore, the relationship that hemodialysis will bear in the future to the alternative solution of kidney transplantation (where medical problems such as immunological response are not yet solved) is open to debate (5, 71). This situation plus the present intermediate state of development of hemodialysis equipment accounts for the ambivalence with which many authorities view the commitment of the necessary financial support for construction of large medical facilities modeled after existing hemodialysis centers (83).

3) Setting aside the medical and humanistic issues for the time being, the required design and operating characteristics for the "ideal" hemodialyzer are numerous (43, 91).
Primarily, the dialyzer must be efficient in the removal of nitrogenous and toxic products of metabolism. In addition, it must be capable of removing water from the patient and have a low internal volume and a low resistance to blood flow. The instrument should be presterilized, simple to assemble, disposable, reliable, and safe. It should give repeatable performance and produce negligible hemolysis. It should be constructed from blood-compatible, nontoxic, and nonpyrogenic materials, and it should not retain significant amounts of vital blood components, such as formed elements and various macromolecular substances. Finally, the dialyzer must be inexpensive, and along with the necessary supporting equipment it must have low maintenance costs. No hemodialyzer currently in use meets all these requirements.

4) While it is generally agreed that the removal of toxic metabolic products, which should have been removed in the urine, is the main duty of an artificial kidney, the exact nature, degree of toxicity, and the rate of production of many of these compounds are unknown (97, 154). Uremia, the pathological state associated with kidney malfunction, accompanies the retention of metabolic products, but the substances responsible for it have not yet been identified. Among the compounds whose concentrations have been found elevated during uremia are potassium ion, urea,
creatinine, uric acid, phenols, guanidines, amino acids, and various unidentified anions and high molecular weight materials. Up to 220 aromatic compounds have been identified in normal urine. Patients with uremia usually improve after hemodialysis, but it is generally impossible to correlate clinical and chemical changes, other than those chemical changes in urea and electrolytes (97). The rate of removal of urea, because it is present in the highest concentration and may be somewhat toxic, is generally used as an index of hemodialyzer efficiency, and required rates of removal for some of the low molecular weight substances have been established (81). However, it is probable that larger molecular weight compounds, more slowly dialyzed, are the significantly toxic substances (129). As such, urea removal rates may give a deceptive indication of the performance of a hemodialyzer.

5) Although rapid removal of retention products seems desirable, recent evidence indicates this is not necessarily true (43, 45). Rapid removal of solutes, particularly urea, produces various physiological and mental disturbances which have been related to the "blood-brain barrier", the mechanisms controlling concentration gradients between the brain and its surrounding environment. The slower diffusion rate of urea out of the central nervous system, as compared to the
adjacent parts of the body, during and after dialysis, produces an osmotic pressure gradient causing transport of excessive amounts of water into the central nervous system to maintain equilibrium. A quantitative basis for fixing the maximum tolerable rate of urea removal has not been established and may possibly vary between individuals (11). Thus, considering low molecular weight solutes only, further improvements in hemodialyzer design must be aimed not at increasing solute removal rates but at decreasing equipment size requirements while maintaining overall transfer rates presently employed.

4. **Overall Performance Analysis of Hemodialyzers - Previous Work**

The analysis of the overall performance of hemodialyzers has lagged behind their development and clinical use. Early work with artificial kidneys concentrated primarily on the change in urea blood concentration in the patient or animal undergoing dialysis, making comparison of various designs impossible. Wolf and co-workers (155, 156), working with the Kolff-Brigham rotary drum in 1951, defined the dialysance of a hemodialyzer as the rate of change of a substance between blood and dialyzate bath per unit blood-dialyzate concentration gradient. It is analogous to the clearance of the natural kidney, which is expressed as the rate of blood flow, in ml/min, from which a solute
is completely removed. Dialysance is useful clinically for comparison with natural kidney function, but its dependence on a large number of parameters make it of limited value in comparing the efficiency of different hemodialyzers.

Sweeney et al (142, 143) have recently defined modifications of Wolf's concept, the maximal dialysance and the relative dialysance. While a definite improvement over the original dialysance definition, they suffer from the same disadvantages. Galletti (48) recently summarized this approach.

Renkin (120), in 1956, derived an expression relating dialysance to membrane area, overall mass transfer coefficient, and blood flow rate. He implicitly assumed that all mass transfer resistance was in the membrane and that the dialyzate bath was infinite. Leonard and Bluemle (84), later showed that the overall mass transfer resistance could be broken down into blood, membrane, and dialyzate components, and they used a modified Wilson plot to determine the magnitude of the individual resistances in aqueous sodium chloride dialysis with the Twin Coil (86). They also derived the appropriate modification to Renkin's equation for a finite dialyzate flow rate in cocurrent flow, discussed the parameters influencing the resistance of each phase, and presented a method for a design optimization based upon
the constraints of internal volume, membrane width, and available pressure drop (85). Michaels recently discussed the overall mass transfer equations for other flow geometries and presented them in graphical form (112). He reviewed the factors limiting transport efficiency and suggested areas for further development.

Babb and Grimsrud (8) presented a mass transfer analysis for a parallel plate dialyzer with rigid membrane supports. They discussed the dependence of blood and dialyzate mass transfer resistances on fundamental parameters by using the results of a solution for the analogous heat transfer problem. Grimsrud and Babb (53) also performed a design optimization for an idealized parallel plate, pumpless dialyzer. They obtained quantitative values for dialysance as a function of plate spacing by making a number of simplifying assumptions and rough estimates for mass transfer coefficients. Grimsrud (52, 54) recently completed a theoretical and experimental study of the performance of a parallel plate dialyzer in the laminar flow regime. Babb and co-workers have extended Grimsrud's analysis by obtaining approximate expressions for the evaluation of membrane permeability and solute diffusivity from mass transfer rates in a flow dialyzer. They have applied their technique to in vitro (9) and in vivo (10) measurements. Wolf and Zaltzman (157) applied a simplified theoretical analysis to determine optimum geometry for both flat
plates and tubes. The limitations of these various treatments are dealt with in the body of the thesis.

Muldoon and Leonard (116) discussed the application of the Chilton-Colburn j-factor correlations for heat and mass transfer to dialyzer analysis. They compared measured heat transfer coefficients with simulated clinical mass transfer coefficients in the dialyzate phase. Miron and Leonard (113) injected tracer dyes into a Twin Coil hemodialyzer and measured outlet concentration-time curves. They related nonidealities in flow to possible geometric imperfections in the flow path and their effect on overall performance.

Macey and Wolf (100) derived a theoretical extension of the earlier expressions by Wolf et al (155) and Renkin (120) to hemodialysis with simultaneous ultra-filtration. Their results were confirmed experimentally by Barenberg and Kiley (12). Both groups concluded that under the circumstances comparable to those present in contemporary hemodialysis operation, relatively little solute is removed by ultra-filtration, and the decrease in dialysance due to ultra-filtration is of the order of 3%. However, when the artificial kidney is used to remove large quantities of water as in edema, the percent of solute removed by ultra-filtration becomes appreciable.

Yoder (160) has published a rigorous mathematical framework describing the behavior of a Twin Coil hemodialysis
system. However, his results, which are presented in the form of ten simultaneous differential equations, are not amenable to a general solution, and require insertion of a number of experimentally determined parameters.

Brian (22) recently studied the simultaneous transport of solute and solvent under pressure and concentration driving forces in a parallel plate system. Although his work was directed towards an understanding of concentration polarization in reverse osmosis desalination and his results are not directly applicable to conditions existing in hemodialysis, a similar mathematical approach may be fruitfully employed in a rigorous study of combined dialysis and ultrafiltration.

While the required mathematical models for the analysis of overall hemodialyzer performance have appeared in the artificial kidney literature (and have existed much longer in the heat transfer literature), their usefulness has not been fully appreciated and only limited and often incorrect analyses have appeared.

A few authors have reported average mass transfer coefficients calculated from Renkin's equation (68, 127) for individual dialyzers. Leonard and Bluemle (84, 86) and Bluemle et al (20) calculated overall resistances directly from their data. Someren et al (137) reported overall
permeability coefficients for a larger number of dialyzers, but their values appear low by more than an order of magnitude. Lipps (92) calculated overall coefficients for a few dialyzers from Renkin's equation and compared them with membrane permeabilities, concluding that the membrane represented only a fraction of the total mass transfer resistance. Several others have made similar conclusions (82, 112).

Sparks and Lindian (138) recently discussed the overall design problems in the artificial kidney but did not include a mass transfer analysis. Leonard (81) in 1965, presented engineering and economic considerations in a large scale hemodialysis system and concluded that the design of an efficient hemodialyzer is the most critical factor. Babb and coworkers (161) discussed the engineering aspects of artificial kidney systems. Tien (163) studied mass transfer in a flat plate hemodialyzer.

5. **Overall Hemodialyzer Mass Transfer Analysis**

An analysis of hemodialyzer performance was made by the author from published data. The purpose of this analysis was threefold: 1) To obtain a better idea of the mass transfer capabilities of the various hemodialyzer designs; 2) To obtain quantitative values for the relative mass transfer resistances of the individual phases; and, 3) To indicate directions where research is needed to further understand and improve mass transfer performance.

The mathematical basis for analysis is described below. Only solute transport due to concentration driving forces
was considered. Data involving high ultra-filtration rates were not used in the analysis.

The appropriate differential equation expressing the rate of solute transfer from blood to dialyzate through a differential area is:

$$dN = K(C_B - C_D) dA \tag{A-1}$$

Assuming that $K$ is constant over the entire area, the equation may be integrated to give:

$$N = KA \langle \Delta C \rangle_m \tag{A-2}$$

where $\langle \Delta C \rangle_m$ is an appropriate mean concentration driving force for the flow geometry under consideration and is based on the inlet and outlet concentrations. Equation (A-2) may be considered the defining equation for $K$, the average overall mass transfer coefficient based on the mean concentration difference. For the geometries of cocurrent and countercurrent flow and well mixed dialyzate, the appropriate mean concentration driving force is the logarithmic average concentration difference. It should be noted that, in general, the local overall coefficient, based on the local bulk concentration difference, is not constant, but varies along the length of the dialyzer, eventually reaching a limiting value. Thus, the average coefficient $K$ is an artificial quantity. Nevertheless, it still provides useful information when local coefficients cannot be evaluated.
The reciprocal of \( K \) may be considered the average overall mass transfer resistance, \( R \). Assuming an Ohm's law additivity of resistances, \( R \) is then the sum of the individual average mass transfer resistances. Thus:

\[
\frac{1}{K} = \frac{1}{K_B} + \frac{1}{K_M} + \frac{1}{K_D} \tag{A-3}
\]

or

\[
R = R_B + R_M + R_D \tag{A-4}
\]

The reservations concerning the constancy of \( K \) apply to both \( K_B \) and \( K_D \). In addition, the additivity of resistances is strictly true only when all conditions are maintained constant since the mass transfer coefficient is somewhat dependent upon the coefficients of the membrane and the other fluid.

From a simple material balance, it follows that:

\[
N = Q_B(C_{Bi} - C_{Bo}) = Q_D(C_{Do} - C_{Di}) \tag{A-5}
\]

The blood dialysance for a given solute is expressed by:

\[
D_B = Q_B \frac{(C_{Bi} - C_{Bo})}{(C_{Bi} - C_{Di})} \tag{A-6}
\]

The quantity \( D_B/Q_B \), denoted here by \( E \), is sometimes called the extraction ratio and is a more meaningful quantity than dialysance alone. It represents the fraction attained of the maximum solute concentration change possible if the blood were contacted with dialyzate at its inlet concentration across a membrane of infinite area, and it is directly
analogous to the effectiveness of a heat exchanger (50, page 15).

Hemodialyzer performance data is generally reported in terms of dialysance at a specific blood flow rate. Expressions must be obtained to relate dialysance to the overall mass transfer coefficient.

Let \( N_T = \frac{K_A}{Q_B} \) \( \quad \text{(A-7)} \)
and \( Z = \frac{Q_B}{Q_D} \) \( \quad \text{(A-8)} \)

Simultaneous solutions of equation (A-1), (A-2), and (A-5) through (A-8) yields the following relations for the geometrical arrangement specified:

\[
\begin{align*}
\text{Parallel (cocurrent)} & \quad E = \frac{1 - \exp[-N_T(1+Z)]}{1+Z} \quad \text{(A-9)} \\
\text{Countercurrent} & \quad E = \frac{1 - \exp[N_T(1-Z)]}{Z - \exp[N_T(1-Z)]} \quad \text{(A-10)}
\end{align*}
\]

If \( Z=1 \), \( E = \frac{N_T}{N_T+1} \) \( \quad \text{(A-11)} \)

Well Mixed Dialyzate \( \text{(Mixed transversely and laterally)} \)
\[
E = \frac{1 - \exp(-N_T)}{1 + Z[1 - \exp(-N_T)]} \quad \text{(A-12)}
\]

Similar equations for heat transfer have been presented by Kays and London (65, page 17) using an operating line-
equilibrium line plot. The parallel case was first treated in the artificial kidney literature by Leonard and Bluemle (85), Michaels (112) has recently discussed the others.

Only when \( z = 0 \), i.e., \( Q_D \) is infinite, do the above expressions reduce to the approximate relationship derived by Renkin (120).

\[
D_B = Q_B [1 - \exp(-N_T)]
\]

(A-13)

The quantity \( N_T \) is a dimensionless parameter, conveniently termed the number of hemodialyzer transfer units. It expresses the "mass transfer size" of the dialyzer and is analogous to similar expressions in heat transfer and other diffusional operations. By suitable rearrangement it may be expressed in more conventional chemical engineering nomenclature (131, page 132):

\[
N_T = \frac{K_A}{Q_B} = \frac{K_a}{G_B}
\]

(A-14)

where

- \( a \) = interfacial membrane area per unit volume of blood,
- \( L \) = length of dialyzer,
- \( G_B \) = volume flow of blood per unit time and unit cross sectional area.

For cross flow hemodialyzers, each fluid stream is assumed to be broken up into a large number of separate flow tubes for passage through the dialyzer with no cross mixing.
The effectiveness is based on the mixed mean concentration of the outlet fluids. The appropriate partial differential equations for cross flow heat transfer have been solved by Mason (104). The solution is in the form of an infinite series as follows, when converted to the appropriate nomenclature:

Let \( a = \frac{KA}{Q_B} \)  
\( \text{(A-15)} \)

and \( b = \frac{KA}{Q_D} \)  
\( \text{(A-16)} \)

Then \( E = \frac{1}{b} \sum_{n=0}^{\infty} \left[ S_n(a)S_n(b) \right] \)  
\( \text{(A-17)} \)

where \( S_n(x) = 1 - e^{-x} \sum_{m=0}^{n} \frac{x^m}{m!} \)  
\( \text{(A-18)} \)

The solution has been presented in graphical form by Kays and London (65, page 51).

Most coil dialyzers are cross flow, while flat plate and tubular devices are usually cocurrent or countercurrent. In general, for fixed values of \( N_T \) and \( Z \), \( E \) will decrease in the order countercurrent>cross flow>cocurrent>well mixed dialyzate.

To calculate \( K \) from dialysance data, equations (A-9), (A-10), (A-11), and (A-12) may be easily rearranged to give:

\[
K = \frac{-Q_B \ln \left[ 1 - \frac{D_B}{Q_B} (1 + \frac{Q_B}{Q_D}) \right]}{A \left( 1 + \frac{Q_B}{Q_D} \right)}
\]
\( \text{(A-19)} \)
Countercurrent

\[ K = \frac{Q_B}{A(1 - \frac{Q_B}{Q_D})} \ln \left[ \frac{\frac{D_B}{Q_B} \left( \frac{Q_B}{Q_D} - 1 \right)}{\frac{D_B}{Q_B} \left( \frac{Q_D}{Q_B} - 1 \right)} \right] \]  

(A-20)

when \( z = 1 \),

\[ K = \frac{Q_B \frac{D_B}{Q_B}}{A(1 - \frac{D_B}{Q_B})} \]  

(A-21)

Well-Mixed Dialyzate

\[ K = \frac{Q_B}{A} \ln \left[ \frac{\frac{D_B}{Q_B} \left( 1 + \frac{Q_B}{Q_D} - 1 \right)}{\frac{D_B}{Q_B} \frac{Q_B}{Q_D} - 1} \right] \]  

(A-22)

The procedure used in analyzing dialysance data taken from the literature was as follows. The overall mass transfer coefficient, \( K \), and its reciprocal, \( R \), were calculated from equations (A-19) through (A-22) for the appropriate geometry or read from a graph for cross flow. The overall resistance was compared with the mass transfer resistance of the membrane alone, \( R_M \), and the percentage of the overall resistance residing in the membrane calculated. These values, along with the raw data and dialyzer characteristics are tabulated in Table A5.
Published values of membrane permeability are tabulated in Table A1. The information given includes the membrane material and its commercial specification, the wet thickness, and the transport resistance for various solutes. In addition, a normalized resistance per unit wet thickness (one mil) and an effective diffusivity are tabulated. The latter, obtained by multiplying the permeability by the wet thickness, indicates the apparent solute diffusivity through an homogeneous phase equal in thickness to that of the wet membrane. The method used for measuring values of membrane permeability was a stirred batch dialyzer, except for Babb and co-workers, who used a flow dialyzer. Several investigators used a Wilson plot to correct for the fluid resistances adjacent to the membrane. Others did not. The errors associated with these measurements are discussed in the body of the thesis. For Bemberg PT-150, the data used in the mass transfer analysis were the values obtained in this study and presented in the body of the thesis. (In the original version of this review, the data of Friedman (46) and Carruba (27) were used). All other cellulosic membranes were assumed to have the same effective diffusivities as Bemberg cuprophane PT-150, and membrane resistances were calculated from the estimated wet thickness. Visking tubing was assumed to be 2.0 mils thick, wet.
Before drawing any conclusions from the analysis, it is worthwhile to discuss the reliability and accuracy limitations of the data. Most dialysance values are taken from data reported in graphical form. In addition to errors arising from reading small graphs, concentration and blood flow measurements taken under clinical conditions are usually not as accurate as those taken under controlled laboratory conditions. Most of the hemodialyzers have somewhat less membrane transfer area than that reported because of partial masking by the membrane supports. Insufficient data prevents correction for this, but it is believed to be relatively small. As blood flow rates increase, the pressure drop and dynamic holdup volume increase, and the relative blood and dialyzate dimensions may also increase. Thus, the hemodialyzers may have slightly different dimensional characteristics at various flow rates. This is particularly true of coil hemodialyzers. For some of the in vitro data where aqueous solutions are dialyzed, tap water is used as the dialyzate creating an osmotic gradient which causes water transport and a deceptively higher dialysance. Finally, different investigators working with the same hemodialyzer sometimes report different values for presumably standard characteristics like membrane area and priming volume. Either the dialyzers are in fact different, by design or by random variations in manufacture or assembly, or the methods used for measuring these simple parameters are inaccurate. Despite the above mentioned sources
of error, the calculated overall resistances show fairly good agreement, with some notable exceptions, when the same hemodialyzer is used under similar operating conditions by different investigators.

A representative sample of the values tabulated in Table A5 are summarized in Tables A2 and A3. Table A2 indicates overall and membrane resistances of clinically used hemodialyzers for urea transport at 37°C. and normal blood flow rates. In making conclusions from the data, one must consider the membrane employed and the fluid used on the "blood" side. In general, overall resistances for similar fluids vary by a factor of about two for the various dialyzers. With comparable membranes, the order of increasing resistance for the coil dialyzers is Chronic Coil<Twin Coil<Minicoil. The MacNeill-Collins and Skeggs-Leonards dialyzers give values roughly similar to the Twin Coil. Resistances for the Rotary Drum, Alwall, and Kiil dialyzers are lower while those for the Klung and Dialung are equal to or higher than the Twin Coil. For all fluids, the fractional resistance in the membrane ranges from about 15 to 50% for Visking and Dupont cellophane and about 13 to 38% for the more permeable cuprophane.

When the fluid used is changed from water to blood, the overall resistance increases significantly and the fractional resistance in the membrane decreases. This is very important
and indicates that the "blood" side resistance may increase substantially when water is replaced by blood. Thus, in vitro data taken with aqueous solutions must be analyzed in its proper perspective. The change in total resistance when going from water to blood varies with each dialyzer. It is lowest for the Kil and MacNeill-Collins, about 40%, and increases up to about 100% for the Skeggs-Leonards and Twin Coil dialyzers. This is consistent with the fact that the blood channel thickness is lowest for the Kil and MacNeill-Collins dialyzers, about 0.3 mm, and highest for the Twin Coil. An apparent exception to the bulk of the data is the low resistance with blood for the Skeggs-Leonards dialyzer reported by Freeman et al (43, 44). However, their data indicates that the priming volume of the apparatus they used, and consequently the blood channel thickness, was lower by a factor two to three than for the other Skeggs-Leonards dialyzers.

The overall and membrane resistances for experimental hemodialyzers at 37°C are tabulated in Table A.3 for various solutes and fluids. Because of the limited data available for some of the designs, their reliability may be open to question. Most of the dialyzers show lower resistances than clinically used designs. This has generally been accomplished by reducing blood and dialyzate channel dimensions, making the supports more rigid, improving mixing on the dialyzate side, minimizing shunting on the blood side, or using more
permeable membranes. A notable exception is the pleated and unsupported membrane dialyzer of Bluemle et al (21). Its high resistance is partially offset by its high surface area per unit volume. The lowest resistances are reported for the capillary and pseudocapillary type dialyzers, and for the tightly wound coil dialyzers, all characterized by a small blood channel dimension.

Although the membrane resistances for the experimental dialyzers account for a larger fraction of the total overall resistance than in the clinically used models, the percentages are mostly below 50%, indicating that the fluid phases are still the limiting resistances. A notable exception is the tightly wound cartridge coil of Miller, et al (113).

In order to obtain a more quantitative estimate of the contribution of the individual phases to the total overall resistance, the available data on the change in total resistance as a function of dialyzate flow rate at constant blood flow rate was employed by constructing a Wilson plot (153). Dialyzate flow was assumed to be turbulent, in which case \( R \) is proportional to \( (Q_D)^{-0.8} \). This assumption is not too unrealistic because the hemodialyzers for which the data was available all employed screens or cone supports on the dialyzate side to promote mixing.

A graph of \( R \) as a function of \( (Q_D)^{-0.8} \) is shown in Figure A1 for various dialyzers. Some of the lines are
curved, indicating laminar or transition flow at low \( Q_D \). A line through all the data is extrapolated to the origin (infinite \( Q_D \)), and the value for the overall resistance at the intersection with the ordinate represents the sum of \( R_M + R_B \). \( R_B \) is calculated by subtracting from this value the membrane resistance, \( R_M \). The dialyzate resistance, \( R_D \), can be determined at any \( Q_D \) directly from the graph, and \( R_B \) can be estimated at any blood flow rate by subtracting \( R_M \) and the appropriate \( R_D \) from the total resistance. To obtain values from data for which the solute was different from the data used in the Wilson plot, a new value of the dialyzate resistance was calculated by assuming that \( R_D \) is inversely proportional to the solute diffusivity to the two-thirds power, i.e.,

\[
\frac{R_{D1}}{R_{D2}} = \left( \frac{D_2}{D_1} \right)^{2/3}
\]

While this assumption is strictly valid only in completely turbulent flow, it may be advantageously used here to provide useful, though approximate, information.

The results of the above calculations are tabulated in Table A4. The various columns include design and operating characteristics for each dialyzer, raw data, and the calculated overall and component resistances and their percentage of the total resistance. For greater ease in evaluating results,
the fraction of the total resistance for the blood and membrane as a function of blood flow rate for the Twin Coil dialyzer has been plotted in Figure A2.

The calculated resistances for urea transport indicate that, under normal operating conditions in the Twin Coil dialyzer, the dialyzate resistance is very low, amounting to 3 to 15% of the total resistance. This may be attributed to the very high dialyzate flow rate and the mixing effect of the supporting screens. However, it should be noted that these values are somewhat deceptive, since observation during the actual operation of the Twin Coil discloses significant channeling and shunting of dialyzate through pathways of lower resistance to flow, so that transport does not occur equally across the entire membrane area. While $R_D$ is undoubtedly low, the blood side resistance is very high in the Twin Coil dialyzer. It amounts to from about 55 to nearly 80% of the total resistance for urea.

The relative resistance breakdown for the MacNeill-Collins dialyzer is similar to the Twin Coil. The Minicoil appears to have a higher relative blood side resistance. In the Klung, the relative blood resistance is lower because the dialyzate resistance is significantly higher, despite the use of cone supports, since the dialyzate flow rate is very low. When the blood side fluid is changed from water to blood, the blood side resistance increases about 150 to 200%
or more for the coil dialyzers and about 50 to 60% for the others.

It is clear that the blood side resistance decreases as blood flow increases. Thus, the average blood mass transfer coefficient has not reached a limiting value, even under maximum flow rate conditions, and/or the increased blood flow reduces shunting, making more membrane area effective.

The effect of changing the solute is best illustrated in Figure A2. For both uric acid and creatinine, the relative membrane resistance increases while the relative blood resistance decreases, although the change is not very large. One might logically expect that as the molecular weight of the solute increases to macromolecular magnitudes, the relative membrane resistance will increase and become the limiting factor. However, this is true only if the membrane permeability decreases faster than the liquid diffusivity, as molecular weight increases. Such a phenomenon probably occurs with cellophane, since it operates primarily by a size-selective, sieve type mechanism (79).

With the development of synthetic membranes which involve solute-polymer interaction in the transport process (98), the increase in relative membrane resistance with increasing molecular weight may occur with only some compounds or not at all.
The temperature dependence of the overall transport process is illustrated from available data in Figure A3, where the overall mass transfer coefficient is plotted as a function of reciprocal temperature on semi-logarithmic coordinates and the apparent activation energies are tabulated. The activation energy for urea transport averages about 3,300 cal/mol when water is used on the blood side and 3,800 cal/mol for blood. The values for water compare well with a value of 3,460 cal/mol between 30°C and 40°C found by Lyman (98) for urea permeating through cuprophane surrounded by two stagnant aqueous phases. When compared with the activation energy for urea diffusion in water (51, 96), 4250 cal/mol, it can be seen that the activation energy with blood on the "blood side" is closer to the activation for pure water than with water on the "blood" side. Assuming the activation energies for urea diffusion in blood and water are about equal, this observation confirms the trend noted above that the blood side resistance becomes more predominant when blood is used instead of water.

From the preceding analysis, it must be concluded that in almost all clinically used hemodialyzers for which data has been reported, the blood side mass transfer resistance is the major limiting factor in the transport of low molecular weight solutes, particularly urea. Thus, improvements in membrane permeability will have limited effects on overall
dialyzer performance for microsolute. The effect of improved membrane permeability will be larger for solutes of intermediate molecular weight (e.g. several hundred) and may be quite significant for high molecular weight substances.

Considering only the low molecular weight solutes, for which data is available, the blood side may account for as much as 75% of the overall resistance in the coil dialyzers (Twin Coil, Chronic Coil, Mini-coil). For the flat plate dialyzers (Kiil, Skeggs-Leonards, Klung), with lower blood channel thickness and lower dialyzate flow rates, the relative membrane and dialyzate side resistances become larger, but the blood side resistance is probably still of major importance.

Qualitatively, the same conclusions apply to most of the experimental hemodialyzers, although the trend in the past few years has been towards smaller blood channel dimensions and an increase in the relative membrane resistance. For the capillary, pseudo-capillary, and tightly wound coil dialyzers, the exact breakdown is unclear because of limited data. As a first guess, the blood and dialyzate resistances are probably of roughly equal magnitude.

Consequently, it is obvious that further improvements of overall mass transfer performance of hemodialyzers will necessitate developments in two areas:
1) Design improvements to minimize the fluid resistances, particularly on the blood side. To this end, a fundamental study of mass transfer in human blood will provide valuable and necessary information.

2) Data on membrane permeability and overall hemodialyzer mass transfer performance for intermediate and high molecular weight compounds. Should such compounds be membrane limited and also be toxic so that their removal is necessary, the approach to improving hemodialyzer effectiveness may be altered from that based on the analysis of low molecular weight solutes.
$Q^{-0.8}_D$ ($Q_D$ in ml/min)

OVERALL RESISTANCE R. min/cm

Symbol | Dialyzer  | Membrane | Solute in Water | $Q_{b,min}$ (ml/min) | Reference
-------|-----------|----------|-----------------|----------------------|-----------------|
  •    | Twin Coil | Visking  | NaCl            | 267                  | Leonard and Biemle (86) |
  □    | Twin Coil | Visking  | Urea            | 200                  | Meyer et al. (110)   |
  △    | MacNeill-Collins | Visking | Urea            | 300                  | McDonald and Merrill (106) |
  ●    | Minicoll  | Visking  | Urea            | 100                  | Blackmore et al. (17) |
  □    | Klung     | DuPont   | NaCl            | 200                  | Someren et al. (137)  |

$Q^{-0.8}_D$ ($Q_D$ in l/min)

FIGURE A1. WILSON PLOT FOR VARIOUS HEMODIALYZERS
Figure A2. Relative Resistances in the Twin Coil: Fraction of Total Mass Transfer Resistance for Blood and Membrane as a Function of Blood Flow Rate for the Twin Coil Hemodialyzer at 37°C
Figure A.3. Overall Mass Transfer Coefficient as a Function of Reciprocal Temperature on Semi-Logarithmic Coordinates

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<th>$\text{E}_{\text{act}}$ (cal/mole)</th>
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<td>Freeman et al (44)</td>
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$\frac{1}{T} \times 10^3 \, \text{K}^{-1}$
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Note: a Extrapolated to 37°C by assuming f = 1 constant.

b Wilson Plot not used.

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6. Nomenclature for Appendix A

A = Area, cm²
a = Specific interfacial membrane area per unit volume of blood cm²/cm³
C = Concentration, moles/cm³
D = Diffusivity, cm²/sec
D_B = Blood dialysance, cm³/min
E = Extraction ratio, D_B/Q_B, dimensionless
G = Volume flow rate per unit time and unit cross sectional area, cm³/min, cm²
L = Length, cm
K = Average mass transfer coefficient, cm/min, i.e., moles/min
     moles/cm²
     cm³
N = Mass transfer rate, moles/min
N_T = Number of mass transfer units, dimensionless
Q = Flow rate, cm³/min
R=1/K = Average mass transfer resistance, min/cm
Z=Q_B/Q_D = Ratio of blood to dialyzate flow rates, dimensionless

Subscripts
B = Blood
D = Dialyzate
M = Membrane
i = Inlet
o = Outlet
m = Mean
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APPENDIX B

Properties of Solutes Used in Permeation Studies

1. Chemical Structure and Physiological Significance

The molecular structure of the organic solutes used in the permeation experiments is illustrated in Figs. B-1 and B-2.

Sodium chloride is found throughout the human body. While its removal is not a limiting factor in the artificial kidney, it is commonly used to characterize dialysis membranes in a preliminary evaluation because of its ease of concentration measurement.

Urea is the chief final product of nitrogen metabolism, being eliminated in the urine. A normal adult man excretes about 25 to 30 gm of urea per day (401).

Creatinine is the end product of creatine catabolism and is found in the urine. The daily output is about 25 mgm per kg of body weight (401). It is an amphoteric electrolyte and is believed to dissociate as an anion under acid conditions and as a cation under alkaline conditions. The creatinine solutions used for membrane permeability measurement were found to have a pH of about 7.5. From the data of Yoshimura et al. (449), the amount of creatinine dissociated was about 0.25%.

Uric acid is the final end product of purine catabolism. It is found in the urine of all carnivorous animals and can cause the formation of urinary calculi. Crystals of the
Figure B-1. Molecular Structure of Smaller Organic Solute Molecular Weight in Parenthesis
Figure B-2. Molecular Structure of Larger Organic Solutes
Molecular Weight of Solutes Used in Parenthesis
monosodium salt (sodium urate) which deposit in the joints cause
gout. Uric acid is a weak acid with an apparent dissociation
constant in 0.15 M sodium chloride of $1.12 \times 10^{-5}$ (442). The
percentage of the acid dissociated at concentrations of $1 \times 10^{-6} \text{M}$,
1 mgm%, 30 mgm%, and 100 mgm% are 92.5%, 35.0%, 17.6%, and 4.2%,
respectively. The solubility of uric acid in water at 37°C is
0.00645 gm per 100 ml (180). The stock solution used in this
thesis, obtained from Fischer Scientific Co., contained 0.1 gm
per 100 ml water. It was prepared with 60 mg lithium carbonate
per 100 ml water. The influence of the lithium carbonate on
the permeation properties of uric acid is unknown.

Sucrose is a disaccharide which yields upon hydrolysis
equal molar quantities of glucose and fructose. It is of no
particular physiological importance in terms of the artificial
kidney, but it is useful in membrane permeability studies
because of its moderate size and accurately measured diffusion
coefficient.

Vitamin B₁₂, a cobalt coordination complex, is effective
in the treatment of pernicious anemia. Its complete structure
has been established by chemical and X-ray analysis (178, 179,
436). With a molecular formula of $C_{63}H_{88}N_{4}O_{14}PCO$, it is the
largest and most complicated nonprotein organic compound of known
structure. Although its removal is obviously not desired in the
artificial kidney, it is an excellent model compound for the
study of membrane permeability of higher molecular weight com-
ounds. Its sole drawback is its instability and tendency to
deteriorate in aqueous solution upon storage (401). Its use has
been suggested for measuring renal clearance rates (50).
Polyethylene glycol is not normally found in the human body, although some work on its removal by the kidney in rats has been reported (30). It is available in narrow molecular weight ranges and its physical properties have been fairly well defined.

Inulin is a starch-like substance which is obtained primarily from dahlia tubers or chicory roots. The structure is believed to be a chain of β-fructofuranose units joined at the 1 and 2 positions and terminated with a sucrose-type linkage to glucose. It is commonly used to measure renal clearance rates since it is completely removed from the bloodstream by the kidney. The actual compound used in this study was inulin-carboxyl C¹⁴, in which the reducing end group is replaced by a carboxyl end group labelled with C¹⁴. This should not change its properties significantly, although claims have been made that the dialysis rates of natural inulin and its radioactive derivatives are different (71).

Dextran consists of highly branched chains of glucopyranose units, joined by 1-6 linkages. Branching from the "main chain" may occur with 1-2, 1-3, or 1-4 linkages (344). It is produced by the fermentation of sucrose solutions by certain bacteria. Fractions in various molecular weight ranges are prepared by partial hydrolysis of native dextran. It has been used as a blood plasma extender (to maintain the colloidal osmotic pressure) in the treatment of shock caused by the loss of body fluids.
Heparin is a highly sulfated mucopolysaccharide consisting of α-linked, substituted anhydroglucose rings, joined at the 1-4 positions by glucosidic linkages. The most probable structure, shown in Fig. B-2, is a repeating tetrasaccharide. It is commonly available as the sodium salt, sodium heparinate. Heparin is a blood anticoagulant present in the circulatory system and is widely used medically in connection with extracorporeal circuits. Its primary drawback in membrane permeability studies is the wide molecular weight distribution in native and commercially available heparin.

All five proteins used are globular proteins which crystallize from solution. Albumin (M.W. ~66,000) is the smallest of the plasma proteins. Ovalbumin (M.W. ~45,000) is the major protein constituent (75%) of egg white from hen's eggs. Chymotripsinogen (M.W. ~23,200) is the inactive form of a group of major proteolytic enzymes. It is produced in the pancreas and carried to the intestine where it is activated by trypsin. Its main function is to hydrolyze peptide bonds during intestinal digestion of proteins. Lactoglobulin (M.W. ~35,000) is an important constituent of milk. Myoglobin (M.W. ~17,000) is an oxygen-carrying chromoprotein isolated from skeletal muscle. It is one of the few proteins for which the molecular structure has been completely elucidated.
2. **Molecular Diffusion Coefficients**

   a. **Sodium Chloride**

   Values of the diffusion coefficient of sodium chloride in aqueous solution at 25°C, as reported by several investigators (161, 406) are plotted in Fig. B-3 as a function of the square root of concentration. Over the concentration range shown (from 0 to about 0.25 moles per liter), the diffusivity is a monotonically decreasing function of concentration. At higher concentrations, the diffusivity increases (406), but this region is not of interest in this investigation. A theoretical model for diffusion of 1-1 electrolytes has been applied to sodium chloride (161). However, it is valid only at very high dilution. In order to have equations for calculating the diffusivity of sodium chloride, the data were fitted by eye to the following expressions:

   \[
   D = 1.612 - 0.8107\sqrt{c} + 1.283c \quad 0 < \sqrt{c} < 0.10 \quad (B-1)
   \]

   \[
   D = 1.5733 - 0.2817\sqrt{c} \quad 0.10 < \sqrt{c} < 0.325 \quad (B-2)
   \]

   \[
   D = 1.4888 - 0.216\sqrt{c} \quad 0.325 < \sqrt{c} < 0.70 \quad (B-3)
   \]

   Equations (B-1), (B-2), and (B-3) are shown in Fig. B-3. The agreement with measured values is generally better than 0.5%.

   b. **Organic Solutes**

   1) **Estimation of Diffusivity**

   Estimates of the diffusion coefficient were made for all the non-protein, organic solutes used in the permeation experiments. For lower molecular weight solutes for which the exact
Figure B-3. Diffusivity of NaCl as a Function of Concentration at 25°C (All Values are Differential Diffusivities)
molecular structure is known, the Wilke-Chang correlation (440) was employed:

\[ \frac{D_u}{T} = 7.4 \times 10^{-8} \cdot \frac{(X M)^{0.5}}{V_o^{0.6}} \]  

(B-4)

where

\( D \) = diffusivity of solute at infinite dilution, \( \text{cm}^2/\text{sec} \)

\( \mu \) = solution viscosity, centipoises (assumed to be that of pure water)

\( T \) = absolute temperature, \( ^o \text{K} \)

\( X \) = association parameter (2.6 for water)

\( M \) = solvent molecular weight

\( V_o \) = molal volume of solute at normal boiling point, \( \text{cm}^3 \) per g.mole

Values of \( V_o \) were estimated from the method of LeBas (440) using the tables in Perry's Handbook (318, p.14-20). The accuracy of the Wilke-Chang correlation has been estimated to be about \( \pm 10\% \) (440).

The calculations of \( V_o \) for urea, creatinine, and uric acid were straightforward. Vitamin B_{12} presented a problem because of the many interlocking, connected rings in its complex structure, as described earlier in this section. For vitamin B_{12}, \( V_o \) was calculated as follows: The appropriate contributions of all atoms corresponding to the formula \( C_{63}H_{88}N_{14}O_{14}PCo \) (assuming \( V_o \) for Co equal to 30) totalled 1637.3. From this, the values for the individual rings (four six-membered rings
and seven five-membered rings) were subtracted. In addition, the multiple ring structures were arbitrarily divided into one naphthalene-type ring and eight anthracene-type rings. Subtracting these contributions yielded 1061.8.

For compounds of high molecular weight, the correlation proposed by Polson (325) was employed. He combined the Stokes-Einstein equation with the equation for the equivalent radius of an unhydrated spherical molecule (see Section 3a, Appendix B, Estimation of Molecular Dimensions) to yield

\[ D = \left( \frac{k}{MV} \right)^{1/3} \frac{f_0}{f} \]  

(B-5)

where \( k \) is a constant dependent upon solvent viscosity and temperature, \( M \) is solute molecular weight, \( V \) is solute specific volume, \( f \) is the frictional constant per mole, and \( f_0 \) is the frictional constant for a sphere of equivalent radius. As a first approximation, Polson assumed \( V \) and the ratio \( f_0/f \) to be constant, from which he obtained

\[ D = \frac{C}{M^{1/3}} \]  

(B-6)

Evaluating \( C \) for 15 compounds ranging in molecular weight from 20 to 294,000 showed that, above about 1000 molecular weight, \( C \) was approximately constant and equal to \( 2.742 \pm 0.113(\pm 4\%) \times 10^{-5} \).

Although the original article does not specify a temperature, comparison with diffusion data tabulated elsewhere (414) indicates that the condition applies at 20°C.

The compounds used in Polson's correlation are all compact molecules for which the ratio \( f_0/f \) is relatively constant (306).
It represents a maximum estimate for the diffusivity at a given molecular weight. Significant deviations might be expected for molecules which are 1) highly hydrated, 2) highly assymetrical, or 3) random coiling.

2) Literature Data

A thorough search of the literature revealed experimentally measured diffusivities for all nine compounds except uric acid and vitamin B₁₂. Highly accurate data has been reported for urea (147, 254) and sucrose (69, 148, 253), both of which exhibit a concentration dependence. However, in the range of concentrations employed in this investigation, the solutions may be considered infinitely dilute.

Dunim (60) reported diffusivities at 37°C for urea, sucrose, creatinine, and inulin. However, his results for urea are about 20% lower and for sucrose about 8% lower, than the more accurate recent data referred to above. Thus, his diffusivities for creatinine and inulin are suspect. Furthermore, his measurements were made at high solute concentration.

Rossi et al. (349) measured diffusion coefficients of fractions of polyethylene glycol and correlated his results as

\[ D_{\text{PEG}} = 8.7 \times 10^{-5} \bar{M}_n^{-0.5} \]  \hspace{1cm} (8-7)

where \( \bar{M}_n \) is the number average molecular weight. The labelled PEG, based upon information supplied by New England Nuclear, was assumed to have a weight average molecular weight (\( \bar{M}_W \)) of 4000 (319). Mueh (290) found that the ratio of \( \bar{M}_W \) to \( \bar{M}_n \) for
PEG with a degree of polymerization of about 100 was approximately 1.1. Consequently, the samples used in this study were assumed to have a number average molecular weight of 3600.

Ingelman and Halling (126) reported diffusivities for various fractions of dextran, including a sample of molecular weight 14,000 (determined by ultracentrifugation and diffusion). Since their diffusion results indicated considerable polydispersity in the fractions, their results were assumed to apply to the 16,000 molecular weight dextran used in this study. Laurent (230) measured the diffusivity of a single fraction of heparin with 11,800 molecular weight. For all four of the higher molecular weight compounds, no estimate of the reliability of the measured values was available in the original works.

Diffusion coefficients for globular proteins have been well characterized. Values for the proteins used in this study were found in Tanford (114) and Edsall, et al. (111).

The molecular diffusion coefficients, in aqueous solution, of the solutes used in the permeation studies are tabulated in Table B-1. In addition to the estimated and literature values, the experimentally measured diffusivities of Reece (340) are included. Reece's measurements were made in collaboration with the author using the same radioactively tagged solutes as used in the permeation studies. The method of measurement and reliability of the data are discussed in the body of the thesis (see Chapter 4, Diffusion in Stagnant Plasma and Whole Blood). The last two columns of Table B-1 contain the diffusivity values used in this study and their estimated accuracy.
The measured and literature values for urea and sucrose agree to within better than 2%. Measured diffusivities for urea and creatinine were almost identical. However, within the limits of experimental error, they agree with the estimated values from the Wilke-Chang correlation, and the latter were assumed to be closer to the true value. The diffusivity of creatinine reported by Gunim (60) was discarded as being too low, for the reasons pointed out above.

The Wilke-Chang and Polson estimates for vitamin B₁₂ agree to within about 10%. Both are significantly lower than the measured value. However, the latter was discarded because of the possible deterioration of the solute upon storage in aqueous solution. The Polson estimate was selected because of the difficulty in accurately estimating \( V_0 \) and because vitamin B₁₂ is a compact, nearly spherical molecule, for which the Polson correlation should be valid.

The estimated diffusivities for PEG, inulin, and heparin are all higher than the literature values, with the measured diffusivities in between. This is consistent with the limitations on the Polson correlation, discussed above. The values used in this study for PEG and inulin were taken as the average of the literature and measured values. Since heparin is polydisperse, the average molecular weight corresponding to the measured diffusivity is not clear. Consequently, a value slightly higher than the literature data was used. The same type of estimate was made for dextran, since the difference between the measured and literature values may indicate an error in the experimental
data. The wide disparity between the measured diffusivity of
dextran and the estimated and literature values cannot be
adequately explained.

3) Estimation of Molecular Dimensions
   a. Lower Molecular Weight Solutes

   The estimation of the effective dimensions of molecules
as they exist in aqueous solution is a difficult problem. In
this section, the various methods which may be employed are
briefly reviewed and then applied to the solutes used in this
study.

   The simplest calculated size of a molecule is the equi-
   valent radius of a sphere of weight and density equal to that
   of the solute in the solid phase:

   \[ r_e = \left( \frac{3M}{4\pi \rho N_A} \right)^{1/3} \]  \hspace{1cm} (B-8)

   A more logical extension of this equation is the replacement of
density, \( \rho \), with the partial specific volume of the solute, \( \bar{v}_2 \).
Sternol and Wirtz (1969) have suggested altering equation (B-8)
with

   \[ r'_e = r_e \chi^{1/3} \]  \hspace{1cm} (B-9)

   where \( \chi \) is the "solidity" of the solid, equal to 1-\( \varepsilon \), where \( \varepsilon \) is
the porosity. For cubic close packed spheres, \( \chi = 0.74 \), and
\( \chi^{1/3} = 0.905 \).
Equation (B-8) may be criticized on the grounds that it makes no allowance for hydration in aqueous solution. The same applies to effective radii calculated from either molecular models or crystallographic studies. Electrostriction introduces an additional theoretical drawback to calculations based on the partial molal volume of the solute in aqueous solution (76).

These problems may be eliminated by replacing $\rho$ in equation (B-8) with the reciprocal of the effective hydrodynamic specific volume, $V'$, in cm$^3$ per gm of unsolvated solute (301, 356, 414). Thus

$$r = \left( \frac{3 \pi V'}{4 \pi N_A} \right)^{1/3} \quad (B-10)$$

Unfortunately, $V'$ will in general not have a predictable value.

If suitable measurements have been made on the solute of interest, the effective hydrodynamic volume may be estimated. Using the nomenclature of Tanford (414):

$$V_h = \frac{M}{N_A} (V_2 + \delta V_1^0) \quad (B-11)$$

where $V_h$ is the hydrodynamic volume of the individual molecule, $\delta$ is the number of grams of solvent associated with one gram of unsolvated solute and $V_1^0$ is the specific volume of pure solvent. A similar equation is presented by Robinson and Stokes (345) for the effective volume of a hydrated ion. With slight modification, this becomes for the total effective volume of a 1-1 electrolyte:
\[ V = (V_+ + V_- + 30h) \quad (B-12) \]

where \( V_+ \) and \( V_- \) are the volumes calculated for the cation and anion from the crystallographic radii and \( h \) is the hydration number, molecules of water per molecule of anhydrous electrolyte. Water is assumed to occupy 30 cubic angstroms per molecule. An analogous equation applies for non-electrolytes where the hydration number is known, such as sucrose (275).

An alternative approach is to evaluate an effective hydrodynamic size from viscosity or diffusivity at infinite dilution. The discussion here will be limited to the latter.

The relationship between the molecular diffusion coefficient at infinite dilution and molecular size was first derived independently and simultaneously by Einstein (113) and Sutherland (412), and is known as the Stokes-Einstein equation:

\[ D = \frac{RT}{6\pi \mu r_s N_A} \quad (B-13) \]

where \( R = \) ideal gas constant \( = 8.314 \times 10^7 \frac{\text{dyne-cm}}{\text{g mole} \degree \text{C}} \)

\( T = \) absolute temperature, \( \degree \text{K} \)

\( \mu = \) solvent viscosity, poise \( (\frac{\text{dyne-sec}}{\text{cm}^2}) \)

\( r_s = \) solvent radius, cm

\( D = \) diffusion coefficient of solute at infinite dilution, \( \text{cm}^2/\text{sec} \)

Equation (B-13) is strictly valid for the case where the solute molecule is significantly larger than the surrounding solvent.
molecules, so that the solvent acts as a continuum with a no
slip boundary condition at the surface of the solute molecule.
Sutherland (412) recognized this limitation, and he postulated
that for small molecules of solute moving against larger ones
of solvent, an effect analogous to slipping will occur.
Applying Stokes' original formula for the case of a zero
coefficient of sliding friction, he showed that \( 6\pi \) in Equation
(B-13) should be replaced by \( 4\pi \). Thus, as the size of the
diffusing particle approaches that of the solvent, the Stokes-
Einstein equation will predict too low a diffusivity for a
given particle radius, or conversely, too low a radius for
a given diffusivity. Longsworth (285) estimated that Stokes' law is valid for a solute-solvent volume ratio of 5 to 1, corre-
sponding to a radius ratio of 1.7 to 1. Friedman and Carpenter
(130) found the Stokes-Einstein relation to hold for glucose
with a molecular weight of 180. Of course, as Longsworth
points out, such fortuitous agreement may result from a com-
ensation of asymmetry and hydration on one hand and a numerical
factor less than \( 6\pi \) on the other. In light of these limitations,
it is noteworthy that Einstein used equation (B-13) in his
original paper to determine the radius and hydration of
sucrose, a molecule whose radius is only about three times
that of water.

In order to obtain better agreement between theory and
data, a number of investigators have made empirical modifications
of the Stokes-Einstein equation. Sutherland, in his original
paper, derived a relation between diffusivity in water at 16°C
and the molal volume of solute for a wide variety of compounds:
\[ V^{1/3}D \times 10^6 = 21 + \frac{220}{V^{2/3}} \]  \hspace{1cm} (B-14)

Longsworth (255) found that the product \( D V^{1/3} \) correlated with \( D \) for a dozen compounds. His data may be represented by a straight line:

\[ D V^{1/3} \times 10^6 = 1.64 \, D \times 10^6 + 23.3 \]  \hspace{1cm} (B-15)

Rearranging, and using equation (B-8), one obtains for diffusion in water at 25°C:

\[ r = 1.21 \times 10^{-8} + \frac{17.14 \times 10^{-14}}{D} \]  \hspace{1cm} (B-16)

where \( r \) is in cm.

Spernol and Wirtz (396) correlated the radius obtained with Equation (B-9), \( r_{\text{true}} \), with the radius calculated from the Stokes-Einstein Equation \( r_{\text{Stokes}} \), for 137 solute-solvent combinations as a function of the radius of the solvent molecule, \( r_L \), calculated from Equation (B-8). They defined a "micro-frictional factor of translation" (verbatim German translation), \( f_t \), denoted by

\[ f_t = \frac{r_{\text{Stokes}}}{r_{\text{true}}} \]  \hspace{1cm} (B-17)

Their data was best represented by the relation

\[ f_t = 0.16 + 0.4 \frac{r_{\text{true}}}{r_L} \]  \hspace{1cm} (B-18)
For water, Spernol and Wirtz employed $r_L = 1.92$ Å. This value is derived from equation (B-8) but differs significantly from estimates made by various experimental techniques (345). Using their value of $r_L$, and combining equations (B-17) and (B-18), one obtains a relationship between the "true" radius and the Stokes-Einstein radius for water:

$$r_{\text{true}} = -0.385 + \sqrt{0.0949 + 3.08 \frac{r_{\text{stokes}}}{0.8}}$$

(B-19)

Gierer and Wirtz (140) theoretically derived a modification to Stokes' law for the case when the fluid flowing around a spherical molecule is composed of molecules having a diameter of the same order of magnitude as the stationary sphere. Their expression for $f_t$ was

$$f_t = \frac{1}{1.5 \frac{r_L}{r_{\text{true}}} + \frac{1}{1 + \frac{r_L}{r_{\text{true}}}}}$$

(B-20)

However, the predicted $f_t$ deviated uniformly by about 20% from the data of Spernol and Wirtz.

Robinson and Stokes (345) calculated the effective radii of a homologous series of tetra-alkyl-substituted ammonium ions from the internuclear distances and Van der Waals radii. These ions are symmetrical and are believed to be unhydrated. From these estimates, they plotted a correction factor $r/r_{\text{Stokes}}$ as a function of $r_{\text{Stokes}}$. Nightingale (258) modified their correlation by omitting the point for tetramethylammonium ion and arbitrarily extrapolating the remaining data to a value of
2.69 Å (slightly less than the effective diameter of a water molecule) as \( r_{\text{Stokes}} \) goes to zero. This particular extrapolation appears to be without theoretical or empirical basis.

Schultz and Solomon (365) determined the effective hydrodynamic radii of small molecules by viscometry, assuming the Einstein relation for the viscosity of a suspension (113) to hold at molecular dimensions. They obtained good agreement between the hydrodynamic radius and the radius calculated from molecular models for radii greater than 3 Å. In addition, they obtained an empirical correction factor relating the model radius to the Stokes-Einstein radius:

\[
r = r_{\text{Stokes}} \left( 1 + \frac{0.5}{r} \right) \tag{B-21}
\]

This may be rearranged to yield the "correct" model radius as a function of the Stokes-Einstein radius, denoted by \( r_s \):

\[
r = \frac{r_s + \sqrt{r_s^2 + 2r_s}}{2} \tag{B-22}
\]

The results of the various correlations are shown in Figure B-4. The effective molecular radius is plotted as a function of the diffusion coefficient in water at 25°C. The curves illustrate the large range of estimates obtained by the various methods. The correlations of Sutherland and Longsworth (Curves 5 and 7) lie close together and are nearly parallel over the entire range plotted. For a particle size less than about 4.5 Å, they agree closely with the results
Figure B-4 Molecular Radius as a Function of Solute Diffusivity at Infinite Dilution in Water at 25°C
of Spernol and Wirtz (Curve 4). These three correlations are based on significantly more data than the other three and are considered by the author to be superior below about 4 Å. Above about 5 Å, the original Stokes-Einstein equation is probably valid to a close approximation.

The molecular radii of the smaller molecules were estimated by the various methods described above. In addition, molecular models were constructed with the appropriate atomic covalent radii and Van der Waals radii using Framework Molecular Models (Prentice-Hall, Inc., Englewood Cliffs, N. J.). Figure B-5 shows a schematic spatial representation of the Vitamin B₁₂ molecule (379), as well as the top and side view of the molecular model.

Molecular radii were calculated from the model as follows. The largest linear distance was measured. Then, the two largest dimensions in the directions perpendicular to the original measurement were obtained. Finally, the three orthogonal dimensions were averaged arithmetically.

The results of these calculations are tabulated in Table B-2, including a "best estimate" of the effective molecular radii. It should be noted from model dimensions that none of the molecules are in fact spherical. The four smallest organics could be represented as rectangular parallelepipeds with three different dimensions. However, the deviation from a spherical shape is not large. Vitamin B₁₂ is the closest to a perfect sphere.
The calculation for sodium chloride requires special mention. The various methods produce a variation in the estimate of a factor of two. Assuming that the Na\(^+\) ion and Cl\(^-\) ion diffuse together, in proximity to each other, as a single unit, then equation (B-12) may be used. However, estimates of the hydration number for sodium chloride or Na\(^+\) ion (Cl\(^-\) ion carries little, if any, associated water-molecules) reported in the literature vary by an order of magnitude (44, 83, 298, 345, 352). What is of interest is the "primary solvation," i.e. the number of solvent molecules near an ion which have lost their translational degrees of freedom and move as one entity with the ion during its Brownian motion (83). Unfortunately, different techniques of measurement yield different estimates. Since this investigation is concerned primarily with the diffusional properties of solutes, the estimate reported by Robinson and Stokes (345, p. 329) for the hydration number obtained from diffusion data, 1.1, was used. This estimate is the lowest reported in the literature and yields a calculated molecular radius of 2.4 Å. If the two ions do not diffuse as a unit, the estimate would be lower.

b. Higher Molecular Weight Substances

Macromolecular compounds in solution may be divided into three very broad categories: 1) Randomly coiled macromolecules (e.g. the majority of synthetic polymers), each coil defining an approximately spherical domain containing 98% or more solvent; 2) Macromolecules having a periodically repeating
Figure B-5. A spatial formula of vitamin B₁₂. Not to scale.
From Smith (389)
Figure B-5. Spatial Structure of Vitamin B₁₂.

b. Model - Top View

c. Model - Side View
| Solute              | M. W. | Mol Vol at NBP \(
u_0\) (440) | \(\text{cc/g-mole}\) | \(\text{Du/T}\) | \(\text{T}^\circ\) | \(\text{D}_{15}\times10^3\) | \(\text{D}_{37}\times10^3\) | \(\text{D}_{57}\times10^3\) | Val used in this Study | Estimated Accuracy |
<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Chloride (b)</td>
<td>58.45</td>
<td>61.0</td>
<td>4.297</td>
<td>1.917</td>
<td>25</td>
<td>1.612 (406)</td>
<td>2.156</td>
<td>2.16</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Urea</td>
<td>60.06</td>
<td></td>
<td></td>
<td></td>
<td>25</td>
<td>1.378 (254)</td>
<td>1.808</td>
<td>1.840</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Creatinine</td>
<td>113.1</td>
<td>117.6</td>
<td>2.898</td>
<td>1.293</td>
<td>37</td>
<td>1.08 (60)</td>
<td>1.08</td>
<td>1.215</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>168.1</td>
<td>142.0</td>
<td>2.588</td>
<td>1.155</td>
<td>37</td>
<td>1.08 (60)</td>
<td>1.215</td>
<td>1.16</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Sucrose</td>
<td>342.3</td>
<td>265.5</td>
<td>1.778</td>
<td>0.793</td>
<td>25</td>
<td>0.5209 (253)</td>
<td>0.697</td>
<td>0.711</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Vitamin B(_12)</td>
<td>1355</td>
<td>1061.8</td>
<td>0.7739</td>
<td>0.345</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG</td>
<td>4,000</td>
<td></td>
<td>0.8494</td>
<td>0.179</td>
<td>25</td>
<td>0.145 (348)</td>
<td>0.194</td>
<td>0.227</td>
<td>0.210</td>
<td>10</td>
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<tr>
<td>Insulin</td>
<td>5,200</td>
<td></td>
<td>0.5427</td>
<td>0.242</td>
<td>25</td>
<td>0.2049 (60)</td>
<td>0.205</td>
<td>0.240</td>
<td>0.215</td>
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<tr>
<td>Heparin</td>
<td>12,000</td>
<td></td>
<td>0.381</td>
<td>0.183</td>
<td>25</td>
<td>0.0745 (239)</td>
<td>0.114</td>
<td>0.159</td>
<td>0.12</td>
<td>15</td>
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<tr>
<td>Dextran</td>
<td>16,000</td>
<td></td>
<td>0.3657</td>
<td>0.166</td>
<td>20</td>
<td>0.0782 (185)</td>
<td>0.120</td>
<td>0.293</td>
<td>0.13</td>
<td>15</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>17,000</td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>0.112 (111)</td>
<td>0.171</td>
<td>0.171</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Chymotripsinogen</td>
<td>23,200</td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>0.095 (414)</td>
<td>0.145</td>
<td>0.145</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>B-Lactoglobulin</td>
<td>35,000</td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>0.0782 (414)</td>
<td>0.120</td>
<td>0.120</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Ovalbumin</td>
<td>45,000</td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>0.0776 (414)</td>
<td>0.119</td>
<td>0.119</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Albumin</td>
<td>66,000</td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>0.0594 (414)</td>
<td>0.0909</td>
<td>0.0909</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

- **a.** Tabulated diffusivities in \(\text{cm}^2/\text{sec}\). Where applicable, values refer to infinite dilution.
- **b.** See text for concentration dependence.
- **c.** Assuming \(\text{Mn} = 3600\).
- **d.** Assuming \(\text{Du/T} = \text{constant}\).


<table>
<thead>
<tr>
<th>Solute</th>
<th>M.W.</th>
<th>( \rho ) gm/cm(^3)</th>
<th>( D_{2} \times 10^{3} ) cm(^2)/sec</th>
<th>( R_{1} )</th>
<th>( R_{2} )</th>
<th>( R_{3} )</th>
<th>( R_{4} )</th>
<th>( R_{5} )</th>
<th>( R_{6} )</th>
<th>( R_{7} )</th>
<th>( R_{8} )</th>
<th>( R_{9} )</th>
<th>( R_{10} )</th>
<th>( R_{11} )</th>
<th>Dimensions from models or X-ray Crystallog. (Half Axes)</th>
<th>Best Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Chloride</td>
<td>58.45</td>
<td>2.165</td>
<td>( 1.61 ) (69)</td>
<td>2.20</td>
<td>2.00</td>
<td>1.52</td>
<td>2.27</td>
<td>2.34</td>
<td>2.88</td>
<td>3.47</td>
<td>1.91</td>
<td>2.45(a)</td>
<td>2.40(a)</td>
<td>Na(^+)=0.95 Cl(^-)=1.01</td>
<td>2.4(\pm)0.5</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>60.06</td>
<td>1.335</td>
<td>( 1.38 ) (254)</td>
<td>2.61</td>
<td>2.36</td>
<td>1.77</td>
<td>2.45</td>
<td>2.56</td>
<td>3.20</td>
<td>3.58</td>
<td>2.18</td>
<td>1.8</td>
<td>2.25</td>
<td>2.61</td>
<td>2.92(\pm)2.3(\pm)1.6</td>
<td>2.5(\pm)0.2</td>
</tr>
<tr>
<td>Creatinine</td>
<td>113.1</td>
<td>1.386 (25a)</td>
<td>( 0.996^{b} )</td>
<td>3.19</td>
<td>2.88</td>
<td>2.53</td>
<td>2.98</td>
<td>3.12</td>
<td>3.07</td>
<td>3.90</td>
<td>2.96</td>
<td>3.10</td>
<td>3.16</td>
<td>3.7(\times)3(\times)2.1</td>
<td>3.3(\pm)0.3</td>
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<tr>
<td>Uric Acid</td>
<td>160.1</td>
<td>1.893 (25a)</td>
<td>( 0.863^{b} )</td>
<td>3.28</td>
<td>2.97</td>
<td>2.83</td>
<td>3.19</td>
<td>3.33</td>
<td>4.0</td>
<td>4.0</td>
<td>3.26</td>
<td>3.30</td>
<td>3.36</td>
<td>4.8(\times)3(\times)1.9</td>
<td>3.3(\pm)0.3</td>
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</tr>
<tr>
<td>Sucrose</td>
<td>342.3</td>
<td>1.588 (255)</td>
<td>( 0.521 ) (255)</td>
<td>4.40</td>
<td>3.99</td>
<td>4.69</td>
<td>4.50</td>
<td>4.38</td>
<td>4.74</td>
<td>4.96</td>
<td>5.14</td>
<td>5.2</td>
<td>4.5</td>
<td>4.68</td>
<td>5.8(\times)5(\times)4.0</td>
<td>4.7(\pm)0.5</td>
</tr>
<tr>
<td>Vitamin B-12</td>
<td>1355</td>
<td>1.338 (389)</td>
<td>( 0.283^{c} )</td>
<td>7.38</td>
<td>6.66</td>
<td>8.62</td>
<td>7.26</td>
<td>6.07</td>
<td>8.62</td>
<td>8.62</td>
<td>9.10</td>
<td>8.7</td>
<td>7.70</td>
<td>9.5(\times)9.2(\times)7.5</td>
<td>8.5(\pm)0.5</td>
<td></td>
</tr>
</tbody>
</table>

\( a \). Where not specified, data are from Handbook of Chemistry and Physics (180).

\( b \). Calculated from Wilke-Chang correlation (440).

\( c \). Calculated from Polson correlation (225).

\( d \). Radii in Angstroms. Calculations by the following methods: \( r_{i} \), equivalent sphere; \( r_{e} \), equivalent sphere assuming cubic close packing (396); \( r_{s} \), Stokes-Einstein diffusion equation (113); \( r_{l} \), Longsworth (255); \( r_{s} \), Spernol and Wirtz (396); \( r_{s} \), Robinson and Stokes (345); \( r_{s} \), Nightingale (298); \( r_{s} \), Shultz and Solomon (369); \( r_{s} \), equivalent hydrodynamic size (368); \( r_{1s} \), average radius from molecular models; \( r_{1s} \), Sutherland (412).

\( e \). Calculated assuming hydration number of 1.1 (see text).
group (the amide group in polypeptides) by reason of which, as through hydrogen bonding, they can assume non-random conformations such as the alpha helix, or twinned helices as in collagen, leading to rod-like particles with relatively little internal solvent, having a diameter of the order of 12 Å; 3) Compact, relatively symmetrical, and relatively non-solvated macromolecular particles such as the plasma proteins, which may consist of one, two, three or more separate macromolecules having internal helical sequences linked together tightly in specific ways.

The specific conformation of any macromolecule will depend upon the solution properties of the solvent, and it may vary from one category to another as solution properties change, for example, the helix-coil transformation (414).

Over the past forty years, a number of extremely clever techniques have been developed to investigate the molecular weight and conformation of macromolecules in solution. Several excellent reviews are available on the subject (107, 121, 209, 278, 301, 306, 359, 414).

Although Stokes' law is valid for particles large compared to the size of the solvent molecules, it has generally been found that relationships derived from Stokes' law do not apply directly to molecules in categories (2) and (3) above. The deviations have been ascribed to 1) significant "hydration," 2) asymmetry, or 3) a combination of both. "Hydration" refers to a bound layer of water around the molecule, in which the water molecules are organized into semi-rigid structures by an electric double layer or by a special array of hydrogen
bonding groups. By applying several techniques to the same molecule, it is possible to estimate the magnitude of each effect. If the degree of hydration is known, the effective hydrodynamic volume may be estimated from equation (B-11). If, in addition, the degree of asymmetry or elongation is known, usually expressed as an "ellipticity" or axial ratio, a/b, estimates of the molecular dimensions may be made from the following:

As a prolate ellipsoid --

\[ V_h = \frac{4}{3} \pi ab^2 \]  \hspace{1cm} (B-23)

where \( a \) = half axis of revolution
\( b \) = half equatorial axis

As a cylindrical rod --

\[ V_h = 2\pi ab^2 \]  \hspace{1cm} (B-24)

where \( a \) = half axial length
\( b \) = cylindrical radius

Often, \( a \) and \( b \) may be estimated directly from a model of the molecule if the structure is known.

Since random coiling molecules do not have unique conformations, characteristic dimensions of these molecules must be expressed in statistical and probabilistic terms.
The most common of these are the root-mean-square end-to-end distance, \((\bar{r}^2)^{1/2}\), the root-mean-square radius of gyration \((\bar{s}^2)^{1/2}\), and the effective hydrodynamic radius, \(R_e\). For chain molecules with sufficient segments to be considered Gaussian \((121, 414)\) one finds that

\[
(\bar{s}^2)^{1/2} = \frac{(\bar{r}^2)^{1/2}}{\sqrt{6}} \tag{B-25}
\]

Furthermore, solvent immobilizing randomly coiled macromolecules behave in diffusion as an equivalent hydrodynamic sphere of radius

\[
R_e = 0.665 \bar{s}^2 \tag{B-26}
\]

The radius of gyration may be obtained directly from light scattering. In addition, the mean end-to-end distance of a solvent immobilizing coil may be obtained from intrinsic viscosity data \(\phi\) which is much easier to obtain, from the Flory-Fox relation \((122, 123)\).

\[
[\eta] = \phi \frac{(\bar{r}^2)^{3/2}}{M} \tag{B-27}
\]

\([\eta]\) = intrinsic viscosity, dL/g

\(M\) = molecular weight

\(\phi = 2.1 \times 10^{21}\)

In Equation (B-27), \((\bar{r}^2)^{1/2}\) is expressed in cm. Finally, information concerning the overall conformation of any macromolecule...
may be obtained from knowledge of the molecular weight dependence of the intrinsic viscosity.

Before discussing the size and conformation of the specific solutes, a note of caution is in order. In order to obtain dimensions from the dynamic properties of solutions, hydrodynamic theories must be used, and the results obtained will depend upon the definitions chosen. These theories are at present capable of describing the suspension behavior of only a limited number of model objects, such as spheres, ellipsoids, cylindrical rods, and random coils. The use of these theories can lead only to values which apply to the mathematical model used, not to the real particle, and their relevance to the real particle will depend upon how closely the model resembles it (301).

The estimated molecular dimensions for the larger solutes employed, in aqueous solution, are tabulated in Table B-3. The listed values include estimates appearing in the literature as well as estimates calculated from source data in the literature by the methods described above. The results are presented for two classifications: 1) as a compact and/or elongated molecule with a definite structure, and 2) as a random coiling macromolecule. Also included are estimates of the radius of an equivalent sphere and the Stokes-Einstein radius, both discussed in the previous section.

Polyethylene Glycol. PEG is a linear, non-ionic polymer which assumes a randomly-coiled conformation in aqueous solution. A molecular weight of 4,000 corresponds to about 281 chain
segments, so that Gaussian statistics should apply (121). The repeat unit is identical to polyethylene oxide, the only difference being the end groups.

Mueh (291) measured intrinsic viscosities of polyethylene glycol in water over the $M_w$ range of 240 to 35,000. Above $M_w \approx 2,000$, he found the data could be described by the relation

$$[\eta] = 1.06 \times 10^{-3} M^{0.58} \text{ dl/g} \quad \text{(8-28)}$$

For $M_w = 4,000$, $[\eta] = 0.130$. The exponent, 0.58, indicates it to be a solvent immobilizing macromolecule. Rossi (348) also measured $[\eta]$ for PEG in water. Although his log-log plot of $[\eta]$ as a function of $M_n$ is not quite linear at this molecular weight, interpolation of his data, assuming $M_n = 3,600$, yields $[\eta] \approx 0.113$. The calculated dimensions, obtained from equations (B-25) through (B-27), and shown in Table B-3, show little difference. It is noteworthy that the calculated equivalent hydrodynamic radius, $R_e$, agrees to within better than 10% with the calculated Stokes-Einstein radius obtained from diffusion data.

Bailey and Callard (24) and Shin (382) reported intrinsic viscosity - molecular weight relationships for polyethylene oxide in much higher molecular weight ranges. Extrapolation of their results to 4,000 molecular weight yields values of $[\eta]$ which are lower than the above values by about 100%. Consequently, their results were not employed.
Inulin. There is general agreement in the literature that inulin is an elongated molecule. From his diffusion measurements alone, Bunim (60) estimated that the axial ratio must be greater than 10. Pappenheimer, et al. (212) treated inulin as an ellipsoid of revolution and reported the dimensions shown in Table B-3, based upon diffusion and viscosity data. However, the source of their data and the nature of the calculations was not reported.

Phelps (320) investigated the physical properties of inulin solutions. He found $A_n$ from osmotic pressure to be 5,600 and $A_w$ from ultracentrifugation to be 7,250, which may either reflect experimental uncertainty, or a degree of polydispersity rather larger than expected for most biological polymers that have non-random conformations. Particle size and axial symmetry were characterized by sedimentation, intrinsic viscosity, partial specific volume, and diffusion data. The deviations from Stokes' law behavior (essentially the difference between $r_e$ and $r_s$) could be explained by asymmetry, yielding an axial ratio of 7, or by solvation, yielding a solvated to unsolvated radius ratio of 1.38. He proposed two steric models:

1) A flat ribbon of fructose units staggered in zig-zag pattern. If the number of fructose units is taken as 30-40 and the length per fructose unit as 3.5 A° (width 12 A°, thickness 3 A°), then the axial ratio would be in the range 9-12.
2) A helix repeating every four residues. This would have a length of 12 Å/four residues and a diameter of 12 Å, giving an axial ratio in the range 7.5 - 10. This latter postulated structure fits the facts more closely."

The dimensions in Table B-3 are based on 30 fructose units. Assuming the molecule to be a cylindrical rod, one can calculate the total effective volume per molecule from Equation (B-24). From Equation (B-11), one then obtains the hydration, \( \delta \), to be 0.58 gm H\(_2\)O/gm inulin or slightly more than five H\(_2\)O molecules per fructose ring. This represents an highly hydrated solute. Using the estimates of Pappenheimer, et al., based on diffusivity, and assuming the molecule to be ellipsoidal, one obtains about 1.5 H\(_2\)O molecules per fructose ring.

**Heparin.** The conformation of heparin in aqueous solution is not definitely known, and considerable disagreement exists in the literature. Since heparin is composed of \( \alpha-(1-4) \) linkages of glucosamine and glucuronic acid, Wolfman, et al. (441a) have suggested that heparin possesses a linkage structure related to that of amylose and may exist in a helical configuration (450). Stone (407) reported that heparin appears to exhibit a helical secondary structure, based upon optical rotatory heparin: dye complexes.

Assuming heparin to exist in the form of a tight helix, Britton (53) constructed a scale model of heparin using CPK atomic models, and twisted the model into a helix of six anhydro-glucose units per turn (407, 450). He found the helical coil repeat unit to be 8.8 Å and the diameter of the helix to be
18 Å°. The average equivalent weight of one anhydroglucose unit of sodium heparinate is calculated to be 307.2. The heparin used in this study, assumed to have a molecular weight of 12,000 (126), thus requires about 39 anhydroglucose rings, giving a length of 57.2 Å°.

Since heparin is a polyelectrolyte, its conformation would be expected to be a strong function of solution environmental conditions, such as pH, ionic strength, and temperature. Britton (53) hypothesized that at very low pH, the heparin molecule might exist in a stable helical conformation due to intramolecular hydrogen-bonding. As the pH of the solution increases, the ionization of sulfate and carboxyl groups would lead to rupture of the hydrogen bonding and electrostatic repulsion, causing the helix-coil transformation to take place. At very high pH, the heparin molecule would exist in solution as an expanded random coil.

This hypothesis appears to be contradicted by the work of Lasker and Stivala (232). They studied the physico-chemical properties of fractionated bovine heparin using sedimentation and intrinsic viscosity. At pH 2.5 in 0.5 M sodium chloride, they obtained the following intrinsic viscosity-molecular weight relationship:

\[ [\eta] = 7.85 \times 10^{-5} R_w^{0.80} \]  \hspace{1cm} (B-29)

The 0.8 exponent is that which would be expected for a solvent-immobilizing random coiling macromolecule in a good
solvent (121). Applying Equation (B-27), one obtains the dimensions listed in Table B-3. As with PEG, the calculated equivalent hydrodynamic radius shows surprisingly good (and perhaps fortuitous) agreement with the calculated Stokes-Einstein radius.

At pH 6.5 in 0.1 M NaCl, Lasker and Stivula found

\[ [\eta] = 1.75 \times 10^{-5} R_w^{0.98} \]  \hspace{1cm} (B-30)

For similar conditions, Laurent (239) obtained

\[ [\eta] = 1.58 \times 10^{-5} R_w^{1.0} \]  \hspace{1cm} (B-31)

Molecular dimensions calculated from Equation (B-27) using the \([\eta]-R_w\) relation of Laurent are tabulated in Table B-3. Although they agree closely with the previously calculated dimensions, the application of Equation (B-27) in this instance is invalid. The exponent 1.0 on molecular weight is that which would be expected for a free-draining coil in a neutral solvent (121). It indicates that at lower ionic strength, electrostatic charge effects may become more important. For a free-draining coil, the sedimentation coefficient should be independent of molecular weight. Lasker and Stivula found that it showed a marked dependence on molecular weight and thus were unable to rationalize the conformation of heparin in neutral solution at low ionic strength.

Rao and Foster (337) discussed a similar situation for the
conformation of amylose in solution, for which existing experimental results were contradictory. Various investigators have found that amylose behaves either as a helical coil or a random coil. Reviewing the large body of existing data and adding several new experiments, Rao and Foster concluded that amylose is a stiff chain molecule offering little resistance to flow within the domain of the molecule. However, as with heparin, the dependence of the sedimentation coefficient on molecular weight ruled out a completely free-draining model. They applied the wormlike chain model first introduced by Kratky and Porod (226) which has been used successfully to explain the behavior of stiff chain molecules such as cellulose and desoxyribonucleic acid. In this model, the chain direction varies continuously instead of at specific bond junctions. The flexibility of the chain is characterized by the factor q, known as the persistence length; it has a large value for stiff and rodlike chains and a small value if the chain is flexible. For this model, Benoit and Doty (227) obtained a relation for the unperturbed radius of gyration:

\[ \left( \frac{-2}{s_0^2} \right) = q \left[ \frac{2}{3} - 1 + \frac{2}{x} - 2 \left( \frac{1 - e^{-x}}{x^2} \right) \right] \]  \hspace{1cm} (B-32)

where \( x \) is the number of Porod units per molecule and is defined as

\[ x = \frac{r_{\text{max}}}{q} \]  \hspace{1cm} (B-33)
where \( r_{\text{max}} \) is the contour length. Postulating that the conformation of amylose in solution can be approximated as a relatively stiff, wormlike coil consisting essentially of an imperfect or deformed helical backbone, and using the length of the helix (as opposed to the extended molecule length) as the contour length, they obtained values of \( q \) in the range of 40 to 70 \( \text{Å} \) for molecules of known radius of gyration.

Equation (B-32) was applied to heparin, using \( q = 55 \text{ Å} \) and the dimensions of the helical coil obtained by Britton. This gave an unperturbed radius of gyration of 15.0 \( \text{Å} \). For a rigid rod \((414)\)

\[
(\frac{\lambda^2}{2})^{1/2} = (\frac{L^2}{12})^{1/2}
\]

(B-34)

where \( L \) is the length of the rod. Using Britton's dimensions again yields 16.6 \( \text{Å} \) for the radius of gyration for a 12,000 molecular weight heparin molecule as a rigid helical rod. Comparison between the two estimates indicates that the wormlike chain might not be very wormlike, i.e. relatively stiff. In this event, one would expect an exponent on the \([\eta]-M_w\) relation closer to 1.8 \((414)\). Recalculation of Equation (B-34) with persistence lengths of 30 and 10 \( \text{Å} \) yields radii of 14.0 and 11.0 \( \text{Å} \), respectively.

It should be noted at this point that both Lasker and Stivala \((232)\) and Laurent \((239)\) found commercial heparin to be highly polydisperse. The former obtained fractions ranging from 4,000 to 14,000 molecular weight, with 72% of the recovered
fractions falling between 11,000 and 13,000.

**Dextran.** Although the properties of dextran have been investigated by several workers, estimates of its conformation vary widely. Ingelman and Halling (185) estimated axial ratios for dextran fractions increasing from 17 for 14,000 molecular weight up to 100 for 3 x 10^6 molecular weight, based on diffusion, viscosity, and sedimentation measurements. However, they neglected the possibility of hydration in their calculations. For the intrinsic viscosity-molecular weight relation, they obtained an exponent of 0.34 which they could not explain. Ogston and Woods (302) recalculated their data including solvation effects and estimated axial ratios less than 10. Ogston and Woods (203) later obtained viscosity and sedimentation data from which they calculated an ellipticity of 6.9 and an effective hydrodynamic volume of 1.7 cm^3 per gm unsolvated dextran for a sample of about 20,000 molecular weight. However, they failed to observe flow-birefringence on a single sample of 5 x 10^5 molecular weight and estimated ellipticity of 4.5. The dimensions in Table B-3 are calculated for both an ellipse and a cylindrical rod. Their effective hydrodynamic volume corresponds to a solvation of about 0.09 gm water per gm unsolvated dextran. This corresponds to about 77 molecules water per molecule of dextran, or roughly one water molecule per glucose ring.

Senti, et al. (376) investigated relatively monodisperse dextran fractions in aqueous solution and evaluated the constants in the Mark-Houwink relation for intrinsic viscosity to be:
\[ [\eta] = 9.7 \times 10^{-4} R_w^{0.50} \quad (B-35) \]

The Mark-Houwink exponent, 0.50, suggests the classical semipermeable unperturbed random coil (in a theta solvent) in clear contradistinction to the models discussed above; but other evidence of theta solvent behavior is missing. They measured radius of gyration (square root of the z-average squared value) directly with light scattering and found

\[ (\frac{S_z}{s})^{1/2} = 0.6 \quad R_w^{0.43} \quad (B-36) \]

for \( M_w > 4 \times 10^5 \). Assuming this relation valid at 16,000 molecular weight, one obtains an estimate of 42.4 \( \Lambda^0 \) for the radius of gyration. It seems probable that the highest molecular weight dextrans, as bacterially synthesized, are significantly branched. Branched random coiling molecules can easily show Mark-Houwink exponents less than 0.5 even in good solvents. As the largest dextran are hydrolyzed to lower molecular species, the fragments become more linear. The square root of the z-average squared radius of gyration reflects the highest, therefore the most branched species present.

**Proteins.** All the proteins used in this investigation are globular proteins. Historically, they have been modelled as prolate ellipsoids of revolution. It is presently impossible to assign exact values to the degree of solvation for these proteins. The best estimates \(^{(306)}\) are generally in the
range of 0.1 to 0.3 grams water per gram anhydrous protein. [Compare 100 grams of solvent per gram of polymer characteristic of random coiling polymers.] Dimensions were evaluated using Equations (B-11) and (B-23) and an estimate of 0.2 gram per gram for the solvation. Axial ratios were taken from Tanford (14) who has tabulated them for this value of solvation.

The sole exception is myoglobin. Its structure has been worked out by X-ray diffraction and crystallographic techniques (209, 210). The shape is not symmetrical along any axis, and it may be characterized by three different dimensions. Also included is an outdated estimate of its dimensions as an ellipse (120). On a relative basis, the error is not very large. However, on an absolute basis, the error is significant, particularly if the 17.5 Å dimension is taken as the relevant characteristic dimension on the "short axis."

The values for albumin obtained by X-ray diffraction (257) are tentative in that other slightly different dimensions could be assigned to the molecule on the basis of the data.
<table>
<thead>
<tr>
<th>Solute</th>
<th>M. W.</th>
<th>( \rho ) g/cm(^3)</th>
<th>( \bar{v}) cm(^3)/gm</th>
<th>( \bar{D}) cm(^2)/sec</th>
<th>([n]) dl/g</th>
<th>( r_c )</th>
<th>( r_s )</th>
<th>( a/b )</th>
<th>( a )</th>
<th>( b )</th>
<th>( (\eta)^k )</th>
<th>( (R_s)^k )</th>
<th>( R_e )</th>
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<tbody>
<tr>
<td>PEG</td>
<td>4,000</td>
<td>1.204(19)</td>
<td>0.157</td>
<td>0.130(251)</td>
<td>0.113(348)</td>
<td>11.0</td>
<td>15.6±1.5</td>
<td>62.8</td>
<td>25.6</td>
<td>17.1</td>
<td>59.9</td>
<td>24.4</td>
<td>16.3</td>
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<td>Inulin</td>
<td>5,200</td>
<td>1.50(60)</td>
<td>0.601(320)</td>
<td>0.161</td>
<td></td>
<td>11.1</td>
<td>15.2±1.5</td>
<td>6.35e</td>
<td>40.0</td>
<td>6.3(312)</td>
<td>35.2</td>
<td>6.7(312)</td>
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<td></td>
<td></td>
<td></td>
<td>10.7d</td>
<td>5.25e</td>
<td>52.5</td>
<td>6.0(320)</td>
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<td>(based on viscosity)</td>
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<td></td>
<td></td>
<td>7.5g</td>
<td>45.0</td>
<td>6.0(370)</td>
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<tr>
<td>Heparin</td>
<td>12,000</td>
<td></td>
<td>0.44(239)</td>
<td>0.090</td>
<td>0.174(232)</td>
<td>0.190(239)</td>
<td>12.8</td>
<td>27.2±3.0</td>
<td>99.8</td>
<td>40.6</td>
<td>27.1</td>
<td>103</td>
<td>41.9</td>
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<tr>
<td>Dextran</td>
<td>16,000</td>
<td>0.7h(303)</td>
<td>0.097</td>
<td>15.8d</td>
<td>179</td>
<td>100.0</td>
<td>6.0(370)</td>
<td>15.6(337)</td>
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<td></td>
<td></td>
<td>3.0g</td>
<td>57.2</td>
<td>9.0(53)</td>
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<tr>
<td>Myoglobin</td>
<td>17,000</td>
<td>0.128</td>
<td>19.1</td>
<td>2.9e</td>
<td>35.0</td>
<td>12.0(120)</td>
<td>12.5±17.5±22.9(205)</td>
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<tr>
<td>Chymotripsinogen</td>
<td>23,200</td>
<td>0.721(414)</td>
<td>0.109</td>
<td>18.8</td>
<td>22.5</td>
<td>3.0e</td>
<td>39.4</td>
<td>13.2(414)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-Lactoglobulin</td>
<td>35,000</td>
<td>0.751(414)</td>
<td>0.0894</td>
<td>21.8</td>
<td>27.3</td>
<td>3.7e</td>
<td>52.7</td>
<td>14.2(414)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ovalbumin</td>
<td>45,000</td>
<td>0.748(414)</td>
<td>0.0888</td>
<td>32.3</td>
<td>27.5</td>
<td>2.5e</td>
<td>44.1</td>
<td>17.6(414)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>65,000</td>
<td>0.734(414)</td>
<td>0.0679</td>
<td>26.6</td>
<td>35.9</td>
<td>4.9e</td>
<td>77.6</td>
<td>15.8(414)</td>
<td></td>
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</tr>
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</table>

a. All dimensions in Angstroms.  
b. Assuming \( \eta = 3600 \)  
c. Based upon \( \rho \)  
d. Based upon \( \bar{v}\)  
e. Prolate ellipsoid  
f. Flat ribbon  
g. Helical cylindrical rod.  
h. Hydrodynamic specific volume.  
i. Measured by light scattering.  
j. Worm-like Purod chain.  
k. From model obtained through X-ray diffraction.
APPENDIX C

Miscellaneous Physical Properties

The following analytical approximations were employed in data reduction:

Density of Water, gm/cc

\[ \rho = 1.0033 - 2.52 \times 10^{-4} T \quad T < 30^\circ C \quad (C-1) \]

\[ \rho = 0.99576 - 3.56 \times 10^{-4} (T-30) \quad T > 30^\circ C \quad (C-2) \]

Viscosity of Water (318), poise

\[ \frac{1}{\mu} = 2.1482[(T-8.435) + \sqrt{8078.4 + (T-8.435)^2}] - 120 \quad (C-3) \]

with T in degrees C.

Diffusivity of Benzoic Acid (68)

\[ D = 18.506 \times 10^{-5} \exp[-E/RT](1 - 0.725 \sqrt{C} - 1.8C) \quad (C-4) \]

where \( E = 1615 \) cal/gmole,°K, T is in degrees K, and C is in gm moles/ℓ and is evaluated at the mean film concentration.

The solubility of benzoic in water at 25°C was assumed to be 0.02775 gm moles/ℓ, which is about the average of the values cited by Seidell (372).
APPENDIX D

Supplementary Details of Experimental Methods

1. Concentration Measurement

a. Sodium Chloride and Benzoic Acid

The concentration of both sodium chloride and benzoic acid was measured conductiometrically with a flow-through conductivity cell. The cell constant was determined by conductivity measurement of a potassium chloride solution of known specific conductance (223).

Sodium chloride concentration was calculated from the measured specific conductance using the semi-theoretical expression of Falkenhagen as given by Yortum (223). The constants for this expression, as a function of temperature, were fitted with Chebyshev Polynomials (see Appendix K). Since the equation was nonlinear, a Newton-Raphson iteration procedure was used to calculate concentration from specific conductance. The entire calculational procedure is contained in subroutine COMPAR, Table I-1, Appendix I.

The resistance of the solution measured in the conductivity cell was obtained by balancing the capacitance of the cell with a decade capacitance box. The impedance difference, \( Z \), measured by the impedance comparator with reference to a known resistance, \( R_s \), was related to the actual resistance, \( R \), by

\[
R = R_s \frac{1 + Z/2}{1 - Z/2} \quad \text{(D-1)}
\]
The conductivity of benzoic acid as a function of concentration was calibrated with a series of carefully prepared solutions. Since benzoic acid is a weak acid, the calibration curve was highly nonlinear. It was fitted with Chebyshev polynomials and concentration was calculated from the measured conductivity in analogous fashion to that described for sodium chloride.

b. Radioactive Solutes

The concentration of radioactive solutes was measured with liquid scintillation counting. This method is a proportional type of counting and its principle virtues are its high efficiency for large samples, excellent sensitivity and facility for measuring low-energy beta emitters such as $^3H$, $^{14}C$, and $^{35}S$, and ease of sample preparation compared to alternate techniques. The sample and phosphor are dissolved in the same solution. Beta radiation from sample molecules is absorbed by the surrounding solvent, and the energy is transferred to the phosphor solute which converts it to scintillations of light that are then detected by photomultiplier tubes. All samples were counted in a three channel Tri-Carb Spectrometer, Model 3375, with automatic external standardization (Packard Instrument Co., La Grange, Ill.) The mixture to be counted consists of three major components: the sample to be counted, the phosphor, and the solvent.

The basic requirements for proper sample preparation are: 1) the sample must be in good contact with the scintillator; 2) the scintillator must emit a strong flash of light; and
3) the counting mixture must be reasonably transparent to the light flashes. Severe limitations are imposed on possible phosphor-solvent combinations by the pressure of water, salts, proteins, and suspended media. Several reviews on sample preparation for liquid scintillation counting were available \((15, 94, 164, 338)\) and based upon the experience of previous investigators, the following systems were chosen

1) **Aqueous Solutions**

For aqueous solutions containing sodium chloride but no protein or blood, the solvent system described by Bray \((49)\) was employed. It does not freeze or form two phases as low as \(-8^\circ C\) and is capable of holding large quantities of water and salt solutions. The recipe is:

- 60 gm naphthalene
- 4 gm PPO \((2,5\text{-diphenyl-oxazole})\)
- 0.2 gm dimethyl POPOP \((1,4\text{-bis-[2-(4-Methyl-5-phenyloxazolyl)]-benzene})\)
- 100 ml methanol
- 20 ml ethylene glycol (ethylene glycol monomethyl ether was occasionally substituted for this) dilute to 1 & with dioxane

The standard mixture for counting was 1 ml sample in 15 ml Bray's solution placed in a 20 ml counting vial. Sample size was smaller for the capillary diffusion experiments. Occasionally, small amounts of sodium chloride precipitated out of solution, but this did not appear to influence counting rate.

With solutions containing significant amounts of unlabelled solute \((10 \text{ gm/l for inulin, heparin, and dextran})\),
considerable material precipitated when added to Bray's solution. A fraction of this, presumably, was radioactively labelled. The solids settled to the bottom of the vial, lowering the count rate and greatly increasing scatter in the data. The same phenomena was observed with lower concentrations of unlabelled uric acid. To alleviate this problem, Cab-O-Sil (fumed silica particles manufactured by Cabot Corp.), (as originally suggested by Ott, et al. (308)) was added to the Bray's solution in the ratio 0.8 g to 15 ml original solution. It served as a thixotropic gelling agent to keep the fine particles in suspension. Results with this technique were as reproducible as Bray's solution alone with no precipitated material, and although the gel was opaque, it generally produced higher efficiencies than without Cab-O-Sil.

2) Plasma and Blood

The high concentration of proteins in plasma causes precipitation of insoluble material and a nonreproducible reduction in counting rate. The presence of red blood cells causes even more difficult problems. In addition to containing labelled solute within them and interfering with the transmission of light, the intense red color of the oxy-hemoglobin complex inside the erythrocytes causes severe color quenching. If uncorrected, this is sufficient to reduce the counting rate almost completely to background levels. Some work has been done to develop techniques for counting such biological materials (43, 70, 168, 184), but these have resulted in low counting efficiencies. The method used in this thesis was an improved procedure derived from the recently published work of
Hansen and Bush (159). These authors studied a variety of materials and variations in technique and determined optimal sample composition for a variety of biological tissues. The procedure used is a modification of their technique, as follows.

The solvent-phosphor combination, referred to henceforth as toluene solution, was:

- 6 gm PPO
- 50 mgm dimethyl POPOP
- dilute to 1 l with toluene

To handle plasma or serum, a 0.2 ml sample was added to a counting vial containing 2.0 ml NCS, a new toluene-soluble quaternary ammonium base manufactured by Nuclear-Chicago. The mixture was allowed to digest at room temperature for at least six hours, or until all protein had appeared to dissolve. Then, 15 ml toluene scintillation solution was added to the vial and the mixture counted.

To count blood, a bleaching solution was first prepared by adding 6 to 7 gm Eastman Grade benzoyl peroxide to 30 ml toluene at 60°C, cooling rapidly to room temperature, and allowing the mixture to stand about one hour before filtering. This saturated solution was prepared immediately prior to use. A 0.7 ml aliquot of the benzoyl peroxide solution was added to the counting vial, followed by a 0.2 ml sample of blood and then a 2.0 ml aliquot of NCS. The mixture was digested at 40°C in an oven for three to five hours, or until all traces of precipitated blood had been dissolved. The mixture was ready
for counting after addition of 15 ml toluene scintillation solution.

All scintillation solutions were transferred with automatic glass dispersing pipettes from a 1,000 ml Erlenmeyer flask, reproducible to ± 1%. The benzoyl peroxide solution and NCS were transferred with a Minipet® repetitive syringe-type automatic dispenser, reproducible to 0.5%.

Samples to be counted were transferred with Eppendorf push-button microliter pipets with polypropylene tips. These had the advantage over glass pipets in ease of operation and the fact that with aqueous solutions, virtually no fluid adhered to the walls of the pipet after dispensing. The maximum absolute error was less than 1% and the standard deviation less than 0.3%. However, with serum, plasma, or blood, the contact angle was greater, the fluid wetted the surface and the "film" error significantly higher. The manufacturer recommended filling the pipet once, emptying, and refilling a second time, in which case 100% of the volume can be dispensed. In practice, it was found that the amount of fluid adhering to the pipet walls was not always reproducible. The procedure adopted was to fill the pipet once and dispense into the counting vial. The pipet was then refilled with distilled water and the contents slowly flushed out into the vial in an oscillatory manner. This cut the "film" error significantly, but the estimated accuracy and precision errors were still about double the magnitude estimated for aqueous solutions.
With the NCS-toluene system, it was possible to count aqueous salt solutions with very high efficiency. However, the use of NCS with many large volume aqueous samples was prohibitively expensive, so that the dioxane-based Bray's solution was retained for aqueous samples.

For the capillary diffusion measurements, a modification of the technique was employed by Reece (340). One ml of NCS was added to the counting vial, followed by about 20 μl of sample and about 100-150 μl of water rinses. Digestion was permitted to occur at room temperature for about one hour. Any samples not completely dissolved in this time were placed in an oven at 45°C until complete dissolution had occurred. Approximately 300 μl of benzoyl peroxide solution were added to the blood digests and bleaching permitted to reach completion. The standard 15 ml toluene scintillation solution was then added to all vials.

Because of small volumes used in the capillaries, relatively small absolute errors in transferring radioactive solute to the vials resulted in magnified errors on a percentage basis.

All reagents and solutions described above were stored in dark bottles at 4°C. Any final counting mixtures not placed directly in the spectrometer were stored in their vials at 4°C.

3) **Calibration of Counting Systems**

The two major problems encountered with liquid scintillation counting are 1) background counts and 2) variations in efficiency of counting. Background counts are caused by thermo-
ionic emission of the photomultiplier, cosmic rays, emissions from the glass vials, and residual phosphorescence of the glass and the solvent-phosphor mixture after exposure to light. The Packard scintillation spectrometer was designed to minimize the first two effects. The photomultiplier tubes were shielded, enclosed in a light-tight enclosure, and the entire unit maintained at constant temperature around 0-4°C. The spectrometer utilized two photomultiplier tubes and coincidence counting, so that any stray counts registered by only one circuit are disregarded. The instrument was never turned off, except for repair, and if exposed to light, the photomultiplier tubes were allowed to re-equilibrate in the dark for several days before use. All counting vials were made of special glass containing a minimum of potassium and other naturally radioactive elements. Exposure of the vials to light during preparation was unavoidable. As a result, the initial counting rate was always high and appeared to decrease exponentially with time. To obtain the true "steady state" counting rate, all samples were stored in the spectrometer for six hours or more before the final count was measured. Usually an initial determination was made, but this was always repeated at a later time.

As a result of these precautions, background counts were generally not a major problem. Background rates were measured periodically and were subtracted from the measured counting rate to yield the true value. Background count rates were generally between 25 and 40 cpm, depending upon the contents
of the counting mixture.

The quantity measured, counts per minute is equal to the number of light flashes per minute (except at very high isotope concentrations where overlapping flashes may not be registered because of the finite resolution time of the photomultiplier tubes.) This is related to the disintegrations per minute (which is proportional to concentration) by the efficiency, i.e.

\[
\text{cpm} = \text{efficiency} \times \text{dpm}
\]

(D-Z)

In practice, efficiency is always less than 100%. This is caused by three factors: 1) The solvent may not transfer all the energy from the emitted particle to the phosphor; 2) The components of the counting mixture may suppress fluorescence (chemical quenching); and 3) The compounds present may absorb the fluorescent light (color quenching). Quenching results in a decrease in the amount of light produced by each radioactive particle and thus a decrease in the height of the pulse produced by the phototube and a shift in the intensity-energy spectrum.

If the counting efficiency of all samples were identical, no correction would be needed. In practice, this did not occur, even with identical samples. This was caused by slight variations in sample makeup, spectrometer performance, and unclear or imperfect vials. In this investigation, counting vials were reused. To insure cleanliness of the vials, they were successively washed in soap and water solution, ultrasonic bath, and sulfuric acid-chromic acid cleaning solution,
followed by a distilled water rinse and two acetone rinses, after which they were dried in a vertical position. They were handled by the rims to prevent finger prints on the outside surface. The appearance of surface scratches was unavoidable.

Despite these precautions, it was necessary to correct for sample-to-sample variations in efficiency. The Packard Model 3375 spectrometer is equipped with automatic external standardization (16). In this technique, prior to counting each sample, a high activity external gamma standard is introduced into the counting chamber and counted, first alone, and then through the sample vial. The ratio of the two counts, termed the AES ratio, is related to the counting efficiency. Thus, by counting a series of vials of varying efficiency containing known amounts of radio-isotope (and therefore known dpm) one can obtain a calibration curve relating efficiency as a function of AES ratio. From the known specific activity of the radio-isotope (obtained from the supplier), the expected dpm can be calculated, since one micro Curie (µc) produces $2.22 \times 10^6$ dpm. By measuring AES ratio for each unknown sample, the efficiency may be determined and dpm calculated.

Calibrations were made for the aqueous solutions to determine the effects of: 1) water volume at fixed $^{14}C$ concentration; 2) amount of $^{14}C$ present at fixed water volume; 3) presence of sodium chloride; 4) variation of volume of Bray's solution; 5) presence of formaldehyde; and 6) use of Cab-O-Sil. The general procedure followed was to add an accurately measured quantity of radio-isotope in solution to the measured volume
of solvent-phosphor combination. Efficiency was varied by adding differing amounts of water and/or saline, producing progressively more quenched samples.

The radio-isotope solution was transferred with a Gilmont ultra-precision micrometer syringe. This instrument was calibrated with mercury, yielding an average systematic error of 0.04%, and with water, yielding an average systematic error of 0.25% and a standard deviation of ± 0.04%. Thus, the amounts added were highly accurate. However, the concentration of the radio-isotope stock solutions obtained from the supplier were known only to within ± 5%. Consequently, the measured efficiencies may contain a constant error of this amount.

All measurements using the Packard Spectrometer were made with the "$^{14}$C" button depressed for $^{14}$C and S$^{35}$ compounds and with the "$^{3}$H($^{14}$C)" button depressed for $^{3}$H. These correspond to factory pre-set amplification gain settings of 9.0% and 50% respectively, with upper and lower level discriminator settings of 50-1,000 and 50-500 respectively. In actual practice, Vitamin B$_{12}$-H$^{3}$ was sometimes counted with the "$^{3}$H" button depressed (discriminator settings of 50-1,000). It was assumed that the actual efficiencies under these conditions were equal to a constant times the calibrated values.

The results for calibrations with aqueous solutions and Bray's solution are shown in Figures D-1 and D-2. All samples contained 200 ppm formaldehyde except Vitamin B$_{12}$. Figure D-1 gives results for urea-$^{14}$C in water, isotonic saline ($\sim 0.15$M), and Vitamin B$_{12}$-H$^{3}$ in isotonic saline, all with
Figure D-1. Counting Efficiency as a Function of A.E.S. Ratio

One ml sample in 15 ml Bray's Solution

○ Urea $^{14}C$ in isotonic saline
△ Urea $^{14}C$ in distilled water
● Vitamin B-12 $^3H$ in isotonic saline
Figure D-2. Counting Efficiency as a Function of A.E.S. Ratio
One ml sample in 15 ml Bray's Solution
Bray's solution. Figure D-2 contains results for heparin-\( S^{35} \) in Bray's solution alone and Bray's plus Cab-O-Sil, and also inulin-\( C^{14} \) in Bray's plus Cab-O-Sil.

The data were fitted to polynomials using a least-squares procedure (see Appendix K) which determines the best degree polynomial to represent the data. The results are tabulated below, where \( Y \) is the efficiency and \( X \) is the AES ratio.

\[
\begin{align*}
\text{Urea-}C^{14}(\text{water}) + \text{Bray's} \\
Y = -0.10890 + 1.9506X - 1.0055X^2 \\
\text{Urea-}C^{14}(\text{saline}) + \text{Bray's} \\
Y = -0.97865 + 4.6886X - 3.2059X^2 \\
\text{Vitamin} B_{12}-H^{3}(\text{saline}) + \text{Bray's} \\
Y = -0.61690 + 2.27293X - 1.54491X^2 \\
\text{Heparin-}S^{35}(\text{saline}) + \text{Bray's} \\
Y = -0.67264 + 3.67168X - 2.46644X^2 \\
\text{Heparin-}S^{35}(\text{saline}) + \text{Bray's and Cab-O-Sil} \\
Y = -0.67264 + 3.67168X - 2.24073X^2 \\
\text{Inulin-}C^{14}(\text{saline}) + \text{Bray's and Cab-O-Sil} \\
Y = -0.99692 + 4.80640X - 3.10262X^2
\end{align*}
\] (D-3) (D-4) (D-5) (D-6) (D-7) (D-8)

The curves plotted in Figures D-1 and D-2 were calculated from the fitted polynomials. With the exception of the scattered data for heparin-\( S^{35} \) in Bray's alone, the curves agree with the data to within several tenths of one percent. The results for urea-\( C^{14} \) were assumed to be representative of
all C\textsuperscript{14} compounds in Bray's alone, and the results for inulin-C\textsuperscript{14} were assumed to be representative of all C\textsuperscript{14} compounds in Bray's solution plus Cab-O-Sil.

The relatively short half life of heparin-S\textsuperscript{35} (\(\sim 86.7\) days) required correction of the measured counts for the variation in specific activity during the counting period. Denoting \(a_0\) as the specific activity at some base time (e.g., the start of counting), \(a\), the specific activity at time \(t\), in days, is given by

\[
a = a_0 e^{-kt}
\]  \hspace{1cm} (D-9)

where \(k = \frac{\ln 2}{t_{1/2}}\) \hspace{1cm} (D-10)

\(t_{1/2}\) = half time

For all other radio-isotopes used the half time is measured in thousands of years and requires no correction.

For the toluene-based system, calibrations were made using water and blood. With water, a stock solution was prepared containing 5 \(\mu\)c urea-C\textsuperscript{14}, 5 ml isotonic saline and 30 ml NCS. This was added to 15 ml toluene scintillation solution in amounts ranging from 0.05 ml to 3.50 ml, using the micrometer syringe. The composition of calibration samples using blood are tabulated in Table D-1. The basic approach was to add a fixed amount of urea-C\textsuperscript{14} to each sample and vary the amount of solubilized and bleached blood-NCS-benzoyl peroxide mixture added to 15 ml toluene solution.
TABLE D-1
Sample Composition for Blood Urea-C¹⁴ Calibration

Overall ratios:

NCS volume (ml) = 15xblood volume + 0.8
Benzoyl Peroxide volume = 5xblood volume

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Blood Volume, ml (60 Hct)</th>
<th>NCS Volume, ml</th>
<th>Saturated Benzoyl Peroxide Solution, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.35</td>
<td>6.05</td>
<td>1.75</td>
</tr>
<tr>
<td>2</td>
<td>0.30</td>
<td>5.30</td>
<td>1.50</td>
</tr>
<tr>
<td>3</td>
<td>0.20</td>
<td>3.80</td>
<td>1.00</td>
</tr>
<tr>
<td>4</td>
<td>0.15</td>
<td>3.05</td>
<td>0.75</td>
</tr>
<tr>
<td>5</td>
<td>0.10</td>
<td>2.30</td>
<td>0.50</td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>1.55</td>
<td>0.35</td>
</tr>
<tr>
<td>7</td>
<td>0.02</td>
<td>1.10</td>
<td>0.10</td>
</tr>
<tr>
<td>8</td>
<td>0.01</td>
<td>0.95</td>
<td>0.050</td>
</tr>
<tr>
<td>9</td>
<td>0.005</td>
<td>0.875</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Add to each: 1) 0.1 ml isotonic saline containing 0.2μC (2.0μC/ml)

2) 15 ml toluene scintillation solution

Duplicates of each sample tested.

Background samples (with 15 ml toluene scintillation sol'n)
1) Blank
2) 1.0 ml NCS + 0.35 ml Benzoyl Peroxide
3) No.(2) + 0.02 ml Blood (50 Hct) + 0.8 ml Water
4) 2.0 ml NCS + 0.7 ml Benzoyl Peroxide
5) No.(4) + 0.2 ml Blood (50 Hct)
The various background samples tested ranged between 30 to 40 cpm.

The calibration results for water and blood are shown in Figure D-3. The data span a very wide range, from almost zero efficiency for large blood samples to around 85% for small water samples. Fortunately, the water data begins where the blood data ends so that both may be correlated together. The polynomial least squares best fit is:

\[
\text{Urea-}^{14}\text{C in Saline or Blood and Toluene Solution (AES)} \\
y = 0.02740 + 0.84919x + 0.98768x^2 - 0.95787x^3 \quad (D-11)
\]

The curve plotted in Figure D-3 was calculated from Equation D-11. At high AES ratios, the fit is quite good and the efficiencies high. This region corresponds to saline, plasma, and small volumes of blood. At higher volumes of blood, AES ratio and efficiency drop to very low values. Furthermore, all sensitivity is lost below an AES ratio of 0.1 and relative errors are very high. Consequently, to count the larger blood volumes required with the flat plate flow dialyzer (without using dangerously high activity levels), an alternate counting procedure was required. It should be noted, however, that the counting mixture actually used with unknown samples had a different makeup from that used in the calibration, yielding higher ratios and efficiencies.

To obtain higher counting efficiencies, it was necessary to raise the amplification gain above that corresponding to the factory pre-set "$^{14}\text{C}$" button. In addition, the Channels
Figure D-3. Calibration Curve for Urea C-14 in Toluene & NCS (AES)

Water (Background=30)
Blood & Benzoyl Peroxide (Background=40)
Ratio technique of calibration correlation was employed (14, 170). This method is capable of providing greater sensitivity at low efficiency. Two channels are required; a channel for determination of counting efficiency, covering the overall pulse height-energy spectrum, and a channel for monitoring quenching, covering only the lower portion of the spectrum. The measured efficiency obtained from the first channel is then correlated with the ratio of the count rate in the two channels.

The procedure followed was to pick an amplification gain setting and vary the upper level discriminator of the second channel, keeping the first channel fixed at 50-1,000 and the lower level of the second channel at 50. At each set of conditions, the calibration curve was generated, and the optimum curve selected as those conditions which yielded the highest efficiencies for large blood samples while still maintaining a monotonic increase over the entire range, i.e., no maximum. This procedure was repeated for a variety of amplification gains, and the overall "best" conditions were found to be 20% gain and 150 upper level discriminator on the second channel.

The results are shown in Figure D-4, where efficiency is plotted as a function of Channels Ratio minus 1.0. The data is also plotted as a function of AES ratio at a gain of 20%, and the superiority of the Channels Ratio method at low efficiency is evident. The best fit polynomial was found to be:
Figure D-4. Calibration Curve for Urea C-14 (in Blood) in Toluene & NCS (Channels Ratio)

Efficiency as a Function of:

- Channels Ratio Minus 1.0
  - Gain = 20%
  - Discriminator Settings
    - 50-1000
    - 50-150

- AES Ratio Gain 20% (50-1000)
Urea-C\textsuperscript{14} in Blood and Toluene Solution (Channels Ratio)

\[ Y = -0.04556 + 1.09093X - 0.71201X^2 + 0.16565X^3 \quad (D-12) \]

where \( Y \) = efficiency
\[ X = \text{Channels Ratio} - 1.0; \left(\frac{-50-1,000}{50-150}\right) \text{ at 20\% gain.} \]

The AES correlation, Equation D-11, was used for the capillary blood and plasma diffusion measurements, and the channels ratio correlation, Equation D-12, was used for the flat plate flow dialyzer blood and plasma studies.

From the measured counts per minute and the calculated efficiency, the activity (disintegrations per minute) may be determined from Equation D-2. This can be related to the actual concentration if the specific activity is known. This is usually unnecessary since the concentration of tracer may be expressed simply as dpm per unit volume.

2. Equipment Drawings and Photographs

Figure D-5 is a drawing of a single chamber of the batch dialyzer. Figures D-6, D-7, and D-8 are detailed drawings of the flat plate flow dialyzer inlet endplate, outlet endplate, and body plates, respectively. The two pieces of apparatus were designed by the author and fabricated by Moore Manufacturing Co., Peabody, Massachusetts. The batch dialyzer seal and bearing assembly was designed and fabricated, according to the author's specifications, by the A.W. Chesterton Co., Everett, Massachusetts. Figure D-9 contains photographs of the primary pieces of equipment used in this study.
3. Equipment and Materials Specification

Table D-2 lists the nominal concentration of radioactive solutes employed. Tables D-3 and D-4 contain materials and equipment specifications. Equipment calibrations were as follows:

**Moyno Pump**

\[ Y = -59.74 + 22.95X - 0.01288X^2 \]  \hspace{1cm} (D-13)

where \( Y \) = flow rate, cc/min and \( X \) = potentiometer setting, percentage of full speed

**Impeller Speed (Batch Dialyzer)**

\[ Y = -41.7 + 8.347X \]  \hspace{1cm} (D-14)

where \( Y \) = impeller speed, rpm, and \( X \) = potentiometer setting, percentage of full speed.

The syringe pump calibration is given in Table D-5.
a. Batch dialyzer - single chamber

b. Batch dialyzer partially assembled for operation

Figure D-4. Equipment Photographs
c. Model of single batch dialyzer chamber for torque studies

d. Microphotograph of nickel foametal

Figure D-4. Equipment Photographs
c. Assembled flat plate flow dialyzer (without spacers)

Figure D-4. Equipment Photographs
Figure D-5. Batch Dialyzer - Single Chamber Assembly
DIALYZER INLET ENDPLATE - ONE PIECE

FIGURE D-6
DIALYZER OUTLET ENDPLATE - ONE PIECE

Figure D-7
Figure D-8 FLAT  PLATE DIALYZER BODY - TWO PIECES
TABLE D-2  
Nominal Concentration of Radioactive Solutes Used in Membrane Permeation Studies

<table>
<thead>
<tr>
<th>Solute</th>
<th>Activity µc/ml</th>
<th>Concentration mg/ml</th>
<th>Molarity x 10^4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>10</td>
<td>0.14</td>
<td>2.3</td>
</tr>
<tr>
<td>Creatinine</td>
<td>10</td>
<td>0.64</td>
<td>5.1</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>10</td>
<td>0.79</td>
<td>4.6</td>
</tr>
<tr>
<td>Sucrose</td>
<td>10</td>
<td>1.02</td>
<td>3.0</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>20-60</td>
<td>0.016-0.05</td>
<td>0.011-0.033</td>
</tr>
<tr>
<td>PEG</td>
<td>10</td>
<td>23.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Inulin</td>
<td>10</td>
<td>7.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Heparin</td>
<td>5-20</td>
<td>110</td>
<td>9.2</td>
</tr>
<tr>
<td>Dextran</td>
<td>10</td>
<td>4.0</td>
<td>0.24</td>
</tr>
</tbody>
</table>

a. Tabulated values apply to batch dialyzer. Maximum variation up to twice tabulated value. For plasma and blood studies in flow dialyzer, concentrations ~10 times higher. For stagnant diffusion in plasma and blood, concentrations ~50 to 100 times higher.
### TABLE D-3

**Specification and Source of Supply of Radioactive Solut es**

<table>
<thead>
<tr>
<th>Solute</th>
<th>Mol. Wt.</th>
<th>Radio-chemical Purity</th>
<th>Specific Activity</th>
<th>Catalogue Number</th>
<th>Lot Number</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea-C(^{14})</td>
<td>62.1</td>
<td>&gt; 99%</td>
<td>4.24 mC/mM</td>
<td>NEC-108</td>
<td>361-117</td>
<td>NEN</td>
</tr>
<tr>
<td>Creatinine-4-C(^{14})</td>
<td>115.4</td>
<td></td>
<td>1.75 mC/mM</td>
<td>C-191</td>
<td>62-71-5</td>
<td>TL</td>
</tr>
<tr>
<td>Uric Acid-2-C(^{14})</td>
<td>170.1</td>
<td></td>
<td>2.0 mC/mM</td>
<td>9954</td>
<td>--</td>
<td>CBC</td>
</tr>
<tr>
<td>Sucrose-C(^{14})</td>
<td>344.3</td>
<td>&gt; 99.5%</td>
<td>3.36 mC/mM</td>
<td>NEC-100</td>
<td>292-093</td>
<td>NEN</td>
</tr>
<tr>
<td>Vitamin B(_{12})-H(^{3}) (Cyanocobalamin)</td>
<td>1356</td>
<td>&gt; 97%</td>
<td>1.3 mC/mg</td>
<td>TRA-112</td>
<td>109112 (Batch 6)</td>
<td>NC</td>
</tr>
<tr>
<td>Polyethylene-1,2-C(^{14})-Glycol</td>
<td>~4000</td>
<td></td>
<td>0.43 mC/gm</td>
<td>NEC-473</td>
<td>301-73</td>
<td>NEN</td>
</tr>
<tr>
<td>Inulin-Carboxyl-C(^{14})</td>
<td>5000-5500</td>
<td></td>
<td>1.32 mC/gm</td>
<td>NEC-164</td>
<td>334-090</td>
<td>NEN</td>
</tr>
<tr>
<td>Heparin-S(^{35}) (Sodium Salt)</td>
<td>10000-12000 (140-150 U.S.P. units/mg)</td>
<td>~0.75 mC/gm(^{c})</td>
<td>S94321</td>
<td>78005</td>
<td>CBC</td>
<td></td>
</tr>
<tr>
<td>Dextran-Carboxyl-C(^{14})</td>
<td>15000-17000</td>
<td></td>
<td>2.49 mC/gm</td>
<td>NEC-218A</td>
<td>96-162A</td>
<td>NEN</td>
</tr>
</tbody>
</table>

---

**Notes:**

a. Mol. wt. for PEG and higher-information obtained from supplier.


c. Activity continually decreased because of short half-life of S-35 (~86.7 days)
<table>
<thead>
<tr>
<th>Protein</th>
<th>Source</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoglobin</td>
<td>Pentex, Inc. Kankakee, Illinois</td>
<td>IX Cryst (Horse Heart) Code PP1362</td>
</tr>
<tr>
<td>α-Chymotripsinogen A</td>
<td>Sigma Chemical Co. St. Louis, Missouri</td>
<td>6X Cryst (Bovine Pancreas) Typells Salt-free 26.5 units/mg after Trypsin activation to Chymotripsin Lot 378-0570-1</td>
</tr>
<tr>
<td>Beta Lactoglobulin</td>
<td>Pentex, Inc.</td>
<td>3X Cryst Purity&gt;95% Code PP0166 Lot 38</td>
</tr>
<tr>
<td>Ovalbumin (Egg Albumin)</td>
<td>Sigma Chemical Co.</td>
<td>Grade V: Salt-free Crystallized and Lyophilized Electrophoretic Purity ~99% Lot 678-8091</td>
</tr>
<tr>
<td>Albumin</td>
<td>Merck Sharp &amp; Dohme West Point, Pennsylvania</td>
<td>Albumisol $^R$ No. 4553 Normal Serum Albumin (Human) Contains 12.5 gm normal human serum albumin in 250 cc of buffered diluent, approx. iso-osmotic with whole plasma. Stabilized with 0.004M sodium caprylate and 0.004M sodium acetyltryptophanate.</td>
</tr>
<tr>
<td>Equipment</td>
<td>Model</td>
<td>Manufacturer</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>AC Tachometer</td>
<td>508A</td>
<td>Hewlett-Packard Co. Palo Alto, Calif.</td>
</tr>
<tr>
<td>Frequency Counter</td>
<td>5211B</td>
<td>Hewlett-Packard Co. Palo Alto, Calif.</td>
</tr>
<tr>
<td>Step-Function Speed Reducer</td>
<td>00140</td>
<td>Inso Corp. Groton, Mass.</td>
</tr>
<tr>
<td>Variable Speed Motor</td>
<td>Model STE 230T-1B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Model STE 232T-1E</td>
<td></td>
</tr>
<tr>
<td>Moyno Pump</td>
<td>SSQ-1L2</td>
<td>Robbins and Meyers Co. Springfield, Ohio</td>
</tr>
</tbody>
</table>
Table D-5

<table>
<thead>
<tr>
<th>Gear Box Setting</th>
<th>Flow Rate cc/min (Pot = 100)</th>
<th>Pot Setting</th>
<th>Flow Ratio to Pot = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>112.4</td>
<td>10</td>
<td>0.325</td>
</tr>
<tr>
<td>2</td>
<td>45.8</td>
<td>20</td>
<td>0.388</td>
</tr>
<tr>
<td>3</td>
<td>23.1</td>
<td>30</td>
<td>0.474</td>
</tr>
<tr>
<td>4</td>
<td>11.4</td>
<td>40</td>
<td>0.545</td>
</tr>
<tr>
<td>5</td>
<td>5.79</td>
<td>50</td>
<td>0.616</td>
</tr>
<tr>
<td>6</td>
<td>2.29</td>
<td>60</td>
<td>0.718</td>
</tr>
<tr>
<td>7</td>
<td>1.15</td>
<td>70</td>
<td>0.782</td>
</tr>
<tr>
<td>8</td>
<td>0.578</td>
<td>80</td>
<td>0.857</td>
</tr>
<tr>
<td>9</td>
<td>0.228</td>
<td>90</td>
<td>0.919</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>110</td>
<td>1.123</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>1.251</td>
</tr>
<tr>
<td></td>
<td></td>
<td>130</td>
<td>1.349</td>
</tr>
</tbody>
</table>

The volumes of the batch dialyzer chambers were

Left hand side \( V = 231.4 \text{ cc} \)

Right hand side \( V = 234.2 \text{ cc} \)

The volume of the external circuit (added to volume of right hand chamber) was 4.3 cc for discrete sampling (radioactive solutes) and 6.4 cc for continuous monitoring (sodium chloride).
APPENDIX E

Protein Composition of Plasma and Its Influence on Diffusion

The concentration of proteins in normal human serum is tabulated in Table E-1. The composition data is taken primarily from the compilation by Schultzze and Heremans (367). Values tabulated are the reported ranges. The mean value was assumed to be the average of the extremes, except for fibrinogen. A fairly complete tabulation is also given by Altman and Dittmer (6). Specific values for individual compounds differ from the two sources. However, the total protein concentration, about 8.27 gm/100 ml plasma, obtained by adding all the values presented by Altman and Dittmer, is very close to the 8.22 gm/100 ml obtained by adding the values in Table E-1. This value is significantly higher than the estimate presented in Guyton (839) of 7.3 gm/100 ml plasma (albumin - 4.5 gm%, globulins - 2.5 gm %, fibrinogen - 0.3 gm %). It is possible that Guyton's tabulation does not include the lipoproteins or the lipid portion thereof, since subsubtraction of the lipoprotein concentration from the estimated total in Table E-1 yields about 7.36 gm %. The values of Schultzze and Heremans (367) were used since they represent the most recent and complete tabulation. Their nomenclature was also used, although it differs from other sources (6, 335).

The obstruction factor, \( \hat{\alpha} \), was interpolated from the magnitudes derived by Wang (431), where axial ratio was known. The axial ratio was estimated from the charts presented by
Oncley (306) using the known values of \( f/f_0 \) and assuming an hydration of 0.2 gm water per gm anhydrous protein. Where \( f/f_0 \) was not known, \( \tilde{a} \) was assumed equal to 1.6, (except for the lipoproteins, which are believed to be spherical (120), and for which \( \tilde{a} \) was set equal to 1.5). Since \( \tilde{a} \) for prolate ellipsoids ranges from 1.5 for spheres to 1.67 for infinite rods, the maximum error associated with this estimate is about 6%, and the actual error is probably considerably less.

The effective volume fraction of each hydrated protein was calculated from

\[
\phi = C_p \left( \tilde{V}_p + \frac{H}{d_0} \right) \tag{D-1}
\]

where \( H \) is the hydration, gm/gm, \( d_0 \) is the density of water (taken to be 1.0 gm/cc), and the other symbols are defined in Table D-1. The density of protein-bound water is probably different from that of pure water. However, this error will be small compared to the uncertainty in the value used for hydration. Wang's original estimate (431) of the hydration of albumin was 0.18 gm/gm and Oncley (305) estimated hydrations ranging from 0.1 to 0.3 gm/gm for a variety of proteins. Consequently, a value of 0.2 gm/gm was used for all the plasma proteins with the idea that deviations from this figure would tend to cancel out. The largest error would probably be associated with the lipoproteins because of their high lipid content.

The influence of each of the plasma proteins in reducing the rate of diffusion through the solution was assumed to be additive, whereupon one obtains for the total effect of all
proteins

\[ \bar{\alpha}_\phi = \sum \bar{\alpha}_{\phi_i} \]  \hspace{1cm} (D-2)

The upper and lower bounds on \( \bar{\alpha}_\phi \) were calculated from the extremes of protein concentration tabulated.
<table>
<thead>
<tr>
<th>Albumin</th>
<th>69,000</th>
<th>3500-4500</th>
<th>0.733</th>
<th>4.9</th>
<th>1.615</th>
<th>3.132</th>
<th>6.027</th>
<th>6.781</th>
<th>5.274</th>
<th>1.29</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>61,000</td>
<td>28-35</td>
<td>(0.733)</td>
<td></td>
<td>(1.615)</td>
<td>0.430</td>
<td>0.048</td>
<td>0.053</td>
<td>0.042</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protein</th>
<th>Mol. %</th>
<th>Conc. in Normal Plasma mg/100 ml</th>
<th>Specific Vol (20°C)</th>
<th>Relative Density</th>
<th>A 1+</th>
<th>A 2+</th>
<th>Mean Vol.</th>
<th>Diffusion Reduction (Hydrated)</th>
<th>Diffusion Reduction (Upper Bound)</th>
<th>Diffusion Reduction (Lower Bound)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>1.55</td>
<td>0.087</td>
<td>0.140</td>
<td>0.277</td>
<td>0.072</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>1.16</td>
<td>0.228</td>
<td>0.644</td>
<td>0.547</td>
<td>0.439</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>44,100</td>
<td>75-100</td>
<td>0.675</td>
<td>12</td>
<td>1.653</td>
<td>0.077</td>
<td>0.127</td>
<td>0.145</td>
<td>0.106</td>
<td>1.7b</td>
<td></td>
</tr>
<tr>
<td>Transferrin</td>
<td>45,000</td>
<td>210-500</td>
<td>0.646</td>
<td>(1.6)</td>
<td>0.300</td>
<td>0.481</td>
<td>0.677</td>
<td>0.284</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein</td>
<td>14-35</td>
<td>(0.7)</td>
<td>0.023</td>
<td>0.036</td>
<td>0.050</td>
<td>0.020</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XI</td>
<td>100,000</td>
<td>30-190</td>
<td>0.766</td>
<td>(1.6)</td>
<td>0.116</td>
<td>0.170</td>
<td>0.294</td>
<td>0.046</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XII</td>
<td>160,000</td>
<td>27-39</td>
<td>0.72</td>
<td>(1.6)</td>
<td>0.011</td>
<td>0.049</td>
<td>0.058</td>
<td>0.040</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>820,000</td>
<td>220-380</td>
<td>0.735</td>
<td>6.5</td>
<td>1.63</td>
<td>0.211</td>
<td>0.457</td>
<td>0.579</td>
<td>0.264</td>
<td>1.43</td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>5-20-10⁴</td>
<td>150-230</td>
<td>-1.02</td>
<td>(1.5)</td>
<td>0.232</td>
<td>0.348</td>
<td>0.421</td>
<td>0.275</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>49,000</td>
<td>8(6)</td>
<td>(0.7)</td>
<td>(1.6)</td>
<td>0.077</td>
<td>0.012</td>
<td>0.012</td>
<td>0.012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>41,000</td>
<td>4(6)</td>
<td>(0.7)</td>
<td>(1.6)</td>
<td>0.024</td>
<td>0.006</td>
<td>0.006</td>
<td>0.006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>62,700</td>
<td>9(6)</td>
<td>0.70(35)</td>
<td>(1.6)</td>
<td>0.008</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>3.2×10⁵</td>
<td>200-440</td>
<td>-1.06</td>
<td>(1.5)</td>
<td>0.454</td>
<td>0.681</td>
<td>0.832</td>
<td>0.529</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>90,000</td>
<td>200-320</td>
<td>0.725</td>
<td>5.8</td>
<td>1.625</td>
<td>0.341</td>
<td>0.491</td>
<td>0.301</td>
<td>1.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>35</td>
<td>(0.7)</td>
<td>(1.6)</td>
<td>0.031</td>
<td>0.050</td>
<td>0.050</td>
<td>0.050</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>80,000</td>
<td>80-100</td>
<td>(0.7)</td>
<td>(1.6)</td>
<td>0.081</td>
<td>0.130</td>
<td>0.144</td>
<td>0.115</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>20-25</td>
<td>(1.0)</td>
<td>(1.6)</td>
<td>0.021</td>
<td>0.033</td>
<td>0.036</td>
<td>0.029</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>160,000</td>
<td>1200-1800</td>
<td>0.739</td>
<td>5.8</td>
<td>1.625</td>
<td>1.409</td>
<td>2.289</td>
<td>2.747</td>
<td>1.831</td>
<td>1.38</td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>10⁴</td>
<td>75</td>
<td>(0.7)</td>
<td>(1.625)</td>
<td>0.068</td>
<td>0.110</td>
<td>0.110</td>
<td>0.110</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>100</td>
<td>(0.7)</td>
<td>(1.625)</td>
<td>0.096</td>
<td>0.146</td>
<td>0.146</td>
<td>0.146</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>341,000</td>
<td>200-400</td>
<td>0.723</td>
<td>18</td>
<td>1.66</td>
<td>0.268</td>
<td>0.444</td>
<td>0.919</td>
<td>0.306</td>
<td>2.34(4)</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>6726-9210</td>
<td>Mean=9210</td>
<td>7.922</td>
<td>12.69</td>
<td>15.34</td>
<td>10.32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Data obtained from Schulte and Heremans (267) unless specified otherwise.

b. For lipoproteins specific densities are given instead of partial specific volumes.
A Model for Transient Diffusion in Heterogeneous Media With Non-Equilibrium Between Phases

A relatively simple, approximate, mathematical model was derived to describe transient diffusion in heterogeneous media for the condition that the phases are not at thermodynamic equilibrium. Only one dimensioanal diffusion and two phases are considered, a continuous phase, A, and a dispersed phase, B, but the model may be generalized to more complex cases. The diffusion coefficients are assumed to be constant and independent of concentration. The purposes in deriving the model were to obtain 1) quantitative criteria for the existence of equilibrium between phases, and 2) a rough quantitative estimate of the departure from equilibrium when such criteria are not met.

The problem presents formidable mathematical difficulties and a rigorous solution may be impossible to obtain. The author has been unable to find any attempt in the literature to solve the general transient problem. In the model considered here, use is made of existing solutions for steady-state, equilibrium transport in a medium comprising a continuum and a dispersed phase. A rigorous treatment for this case, except at infinite dilution, also does not exist, but substantial progress has been made for a number of limiting cases (see Section 4.B.1, Diffusion in Heterogeneous Media). For clarity, the model is developed first for steady-state, equilibrium conditions and then extended to the more complex situation. In what follows,
\( D_A = \text{diffusivity of solute in phase A} \)

\( D_B = \text{diffusivity of solute in phase B} \)

\( C_a = \text{concentration of solute in phase A} \)

\( C_b = \text{concentration of solute in phase B} \)

\( C_T = \text{concentration in total volume of phases A and B} = (1-\phi) C_a + \phi C_b \)

\( \phi = \text{volume fraction of dispersed phase B} \)

**Case 1. Homogeneous phase A**

\[
J = -D_A \frac{dC_T}{dx} \quad (F-1)
\]

\[
= -D_A \frac{dC}{dx} \quad (F-2)
\]

**Case 2. Impermeable Phase B dispersed in phase A**

\[
J = -D^o_{\text{eff}} \frac{dC_T}{dx} \quad (F-3)
\]

\[
= -D_A \frac{\psi^o}{1-\phi} \frac{dC_T}{dx} \quad (F-4)
\]

\[
= -D_A \frac{\psi^o}{1-\phi} \frac{dC_a}{dx} \quad (F-5)
\]

The superscript "o" refers to the fact that phase B is impermeable, i.e., \( D_B = C_B = 0 \). \( \psi(1-\phi) \) may be termed the "obstruction" factor or the "shape" factor (91); it is the ratio between the effective diffusivity in the suspension (when the driving force is based on the concentration calculated from the total volume of phases A and B) and the free liquid diffusivity in A. The reciprocal of this factor is often referred to as the tortuosity (354) when
considering diffusion through a solid matrix containing pores. It includes the effects of tortuous pores (a diffusion path greater than the straight line distance between two points) and varying pore cross-sectional area. Denoting \( \varepsilon \) as the porosity and \( \tau \) as the tortuosity one often finds eqn (F-5) expressed with \( \psi = \varepsilon / \tau \). In the present context, \( \psi \) may also be considered to be related to the distortion in the concentration field caused by the presence of phase B, resulting in a reduced effective concentration gradient. For this case, \( \psi^e \) is a function of the shape and volume fraction of phase B, but independent of size (according to all theoretical treatments to date) as long as the characteristic dimension of the dispersed particles is small compared to the overall dimensions of the volume considered.

Case 3. Permeable Phase B Dispersed in Phase A

\[
J = -D_{\text{eff}} \frac{dC_T}{dx} = -D_{\text{eff}} \frac{K_{T/A}}{K_{f/A}} \frac{dC_A}{dx} \quad (F-6)
\]

\[
= -D_A \frac{\psi}{K_{f/A}} \frac{dC_T}{dx} = -D_A \psi \frac{dC_A}{dx} \quad (F-7)
\]

where, in general, \( K_{T/A} = C_T/C_A \) at equilibrium. This formulation is similar to Case 2, except that \((1-\psi)\) has been replaced by an equilibrium distribution coefficient, and \(\psi^e\) has been replaced by a more general function, \(\psi\), where

\[
\psi = \psi(\text{shape}, \text{volume fraction}, K_{eq}D_B/D_A) \quad (F-8)
\]

The third factor in the parentheses requires explanation. The gradient of concentration does not, in general, measure the net
force acting in a diffusional process. Such a measure is often taken as the gradient in chemical potential. Thus, at a point in the $i^{th}$ phase,

$$J_i = -D_i \frac{dC_i}{dx}$$

$$-D_i C_i \frac{du_i}{dx}$$

Consequently, for equal chemical potential driving forces, the ratio of the flux in phases A and B is

$$\frac{J_B}{J_A} = \frac{C_B D_B}{C_A D_A}$$

Thus, $\psi$ is a function of $C_A D_A / C_B D_B$. If a Henry's law type relation governs the sorption in each phase, then at equilibrium

$$D_{eq} = K_{B/A} = \frac{C_B}{C_A}$$

resulting in the expression in eqn. (F-8). The equilibrium distribution or partition coefficient, $K_{eq}$, is also the ratio of the activity coefficients in each phase. It is possible to relate the concentrations at equilibrium to that in a third phase, $C_e$, external to the heterogeneous media, as done by Higuchi and Higuchi (175). In this case,

$$\frac{J_A}{J_B} = \frac{K_a D_A}{K_b D_B} = \frac{P_A}{P_B}$$

where $K_a = \frac{C_a}{C_e}$
\[ K_b = \frac{C_b}{C_e} \]

i.e., the ratio of the fluxes is equal to the ratios of the permeabilities. Of course, more complex expressions than eqn (F-12) may be applicable, such as a nonlinear relation. In using any of the theoretical formulations for \( \psi \), eqn. (F-11) is the correct expression to apply in analogy to the intrinsic transport property ratio. This has been recognized by some of the investigators concerned with diffusion in heterogeneous media \((91, 175)\), but it has not always been applied correctly, particularly with reference to diffusion in blood \((57)\). The problem arises because for other physical situations where LaPlace's equation applies, e.g., magnetism, dielectric effects, electrical and thermal conductivity, the measured transport property is associated with the correct driving force, and the situation analogous to different concentrations in phases A and B at equilibrium does not occur.

In this treatment, the particular mathematical description of the functional dependence of \( \psi \) is left in general terms. Several theoretical formulations exist in the literature, and in the absence of definitive experimental verification of any model for the general problem, the choice is arbitrary.

In order to describe the transient, nonequilibrium situation, two equations will be used, one for each phase, describing diffusion in parallel in each phase and coupled by a term describing solute transfer between phases. A schematic diagram of this is shown in Fig. F-1a. The effective diffusion constants must be defined so as to account for the dispersion of B in A. Furthermore, the
a. Diffusion processes in parallel with interchange between phases

Case 1. Homogeneous Phase A
Case 2. Impermeable Phase B Dispersed in Phase A
Case 3. Permeable Phase B Dispersed in Phase A
\[
\frac{K_{eqB}}{D_A} < 1
\]

b. Distortion of diffusion paths caused by presence of phase B

Figure F-1. Schematic Model for Diffusion in Heterogeneous Media
parallel model must reduce, in the limit, to the appropriate equations presented above for each case.

First, consider steady-state diffusion in terms of a parallel model.

\[ J_A = -D_A \frac{dC_a}{dx} \]  
\[ = -D_A \psi_A \frac{dC_a}{dx} \]  
\[ J_B = -D_B \frac{dC_b}{dx} \]  
\[ = -D_B \psi_B \frac{dC_b}{dx} \]

The total flux is given by

\[ J_T = J_A(1-\phi) + J_B \phi \]

\[ = -D_A \psi_A (1-\phi) \frac{dC_a}{dx} \frac{dC_a}{dx} \]

\[ = - \left[ D_a \psi_A(1-\phi) + D_B \psi_B \phi \left( \frac{dC_b}{dx} \right) \right] \frac{dC_a}{dx} \]

Furthermore,

\[ C_T = (1-\phi) C_a + \phi C_b \]

\[ = \left[ 1-\phi + \phi \left( \frac{C_b}{C_a} \right) \right] C_a \]

The quantity in brackets equals \( K_{T/A} \) at equilibrium. Consequently, eqn. (F-20), which is expressed in terms of the concentration
in phase A alone, may be rearranged in terms of the total concentration in both phases:

\[
J_T = - \left\{ \frac{D_a \psi_A^*(1-\phi) + D_B \psi_B^* \phi \left( \frac{\partial C_b}{\partial C_a} \right)}{1 + \phi \left[ \frac{C_b}{C_a} - 1 \right]} \right\} \frac{dC_T}{dx} \quad (F-23)
\]

At equilibrium, assuming a Henry's Law-type relationship,

\[
\frac{dC_b}{dC_a} = \frac{C_b}{C_a} = K_{eq} \quad (F-24)
\]

The starred variables, \( \psi_A^* \) and \( \psi_B^* \), are not related to quantities previously defined for case 1 or case 2. At first glance, one may be tempted to let \( \psi_A^* = \psi^* \) and \( \psi_B^* = 1 \), but that this is incorrect is shown in Fig. F-1b. The diffusion path in A is altered from the case where B is impermeable and the diffusion path in B is different from that in homogeneous B. Further, such a substitution in eqn. (F-23) does not reduce to case 2 \((K_{eq} = 0, D_B = 0)\).

The problem at hand is to determine \( \psi_A^* \) and \( \psi_B^* \). In a few published solutions such as Higuchi and Higuchi (175). The problem is formulated in a fashion analogous to that given here, and explicit, though approximate, expressions are available for both quantities. These authors show that \( \psi_A^* \) and \( \psi_B^* \) are independent of concentration for a linear equilibrium ratio. However, although both \( D_a \) and \( D_b \) are assumed independent of concentration, the apparent or effective diffusivity defined by eqn (F-23) will be concentration dependent if the \( C_a-C_b \) equilibrium relationship is nonlinear. In some treatments, however, a final expression for \( D_{eff} \) or \( \rho \) is presented and quantities associated with \( \psi_A^* \)
and \( \psi_B^* \) may not be directly extracted. In this case, it is possible to force the parallel model to fit the overall expression, eqn. (F-7), by proper selection of \( \psi_A^* \) and \( \psi_B^* \). Comparing eqns. (F-7) and (F-23), it is required that

\[
D_{\text{eff}} = \frac{D_A \psi_A^*(1-\phi) + D_B \psi_B^* \phi K_{\text{eq}}}{1 + \phi(K_{\text{eq}} - 1)} \tag{F-25}
\]

or

\[
\psi = \frac{D_{\text{eff}} \psi_A^*(1-\phi) + \frac{K_{\text{eq}} D_B}{D_A} \psi_B^* \phi}{1 + \phi(K_{\text{eq}} - 1)} \tag{F-26}
\]

Now, assume that \( \psi_B^* = 1 \). The resulting expression for \( \psi_A^* \) is

\[
\psi = \frac{K_{\text{eq}} D_B}{D_A} \phi
\]

\[
\psi_A^* = \frac{1 - \phi}{1 - \phi} \tag{7-27}
\]

By using this expression in eqn. (F-23), with \( \psi_B^* = 1 \), the parallel model of eqns. (F-15) and (F-17) agree with eqn. (F-7).

The use of eqn. (F-27), with \( \psi_B^* = 1 \), in eqn. (F-23) yields the correct result for the total flux. However, neither \( \psi_A^* \) nor \( \psi_B^* \), defined this way, correspond to a physically meaningful quantity. As a result, eqns. (F-15) and (F-17) will not give the correct value for the fluxes through phases A and B, respectively. On the other hand, the assumption becomes more reasonable for phase B much less permeable than phase A, since the contribution from the flux through B becomes small and the error inconsequential. With the use of this assumption, one is now able to write the transient equations with a parallel model.
the equations for transient diffusion (Fick's second law) with equilibrium between phases from the parallel model results in an effective diffusivity identical with that in eqn. (F-23). This is true whether the driving force is expressed in terms of the concentration in Phases A, B, or the total volume, in contradistinction to the steady-state case. The fact that the same expression for $D_{\text{eff}}$ based on $C_T$ is obtained for the transient case indicates that at equilibrium the values of $\psi$ derived for the steady-state case may be applied. Presumably, the same would hold true for a system changing slowly enough to be at a pseudo-steady-state condition. This conclusion has also been made by Higuchi and Higuchi (175).

In formulating the transient, nonequilibrium model, it is assumed that the concentrations in phases A and B are a function of $x$ and $t$ only. This implies that the particles are small enough with respect to the volume element considered that at any point, $x$, they may be characterized by a single concentration inside phase B surrounded by a uniform concentration in phase A. This approximation is strictly valid only when the particle size becomes vanishingly small.

Transient diffusion without equilibrium between phases may now be expressed in terms of the parallel model as follows:

$$(1-\phi) \frac{\partial C_A}{\partial t} - k_b s \phi (C_b - C_{b\text{eq}}) = D_A \psi_t (1-\phi) \frac{\partial^2 C_A}{\partial x^2}$$

(F-28)
\[
\phi \frac{\partial C_B}{\partial t} + k_b s(\phi (C_b - C_{beq})) = D_B \psi_B^t \phi \frac{\partial^2 C_B}{\partial x^2}
\]  \hspace{1cm} (F-29)

where

- \( k_b \) = mass transfer coefficient for interchange between phases A and B
- \( s \) = specific area of dispersed particles, phase B
- \( C_{beq} = f(C_a) \) = concentration in phase B which is in equilibrium with \( C_a \).

The superscript \( t \) denotes that the effective diffusion coefficients may be time-dependent (as well as concentration dependent if the equilibrium expression is nonlinear).

Clearly, a rigorous solution of this problem is impossible since the functional form of \( \psi_A^t \) and \( \psi_B^t \) is unknown. If the departure from equilibrium conditions is small, then to a first approximation one can assume that \( \psi_A^t = \psi_A^* \) and \( \psi_B^t = \psi_B^* \).

This leads to a set of equations which can be solved, in principle. A nonlinear equilibrium relationship would require numerical solution. However, if eqn. (F-24) holds, and one lets \( \psi_B^* = 1 \) and uses eqn. (F-27) for \( \psi_A^* \), eqns. (F-28) and (F-29) reduce to a set of linear, simultaneous partial differential equations:

\[
\frac{\partial C_A}{\partial t} + k_b s\left(\frac{\phi}{1-\phi}\right)(C_b - K_{eq} C_A) = D_A \psi_A^* \frac{\partial^2 C_A}{\partial x^2}
\]  \hspace{1cm} (F-30)

\[
\frac{\partial C_b}{\partial t} + k_b s(C_b - K_{eq} C_A) = D_B \frac{\partial^2 C_b}{\partial x^2}
\]  \hspace{1cm} (F-31)

Amundson and co-workers (10, 11, 335) have considered a similar set of equations for heat transfer in terms of the solid-fluid
interactions in fixed and moving beds, with the diffusion term in eqn. (F-29) 1) removed (phase B well mixed) and 2) replaced by a term describing radial conduction within a spherical particle surrounded by fluid at constant temperature, such that, in the nomenclature used here, \( C_b = C_b(r,x,t) \). However, these investigators did not consider the problem of estimation of the effective bed conductivity.

At equilibrium, the interphase transport terms drop out and the use of steady-state expressions for \( \psi_A^* \) and \( \psi_B^* \) is more clear-cut. Consequently, the solution to this set of equations, subject to the appropriate boundary conditions, can give definitive quantitative criteria for the existence of equilibrium between phases so long as the assumptions inherent in the model are physically meaningful. In addition, if \( \psi_A^* \) and \( \psi_B^* \) are a reasonable approximation to \( \psi_A^t \) and \( \psi_B^t \), the solution may be used to estimate roughly 1) the degree of departure from equilibrium, and 2) the rate of change of departure from equilibrium.

Before obtaining a complete solution, one may obtain a rough estimate of the conditions required for equilibrium. If \( D_B \) is small enough so that the diffusion term may be dropped from eqn (F-31), the characteristic time for transport between phases is obtained from

\[
\frac{\Delta C_b}{t_1} = k_B s (K_{eq} C_a - C_b) \quad (F-32)
\]

If, in addition

\[
\Delta C_b \sim K_{eq} C_a - C_b \quad (F-33)
\]
then,

\[ t_1 \sim \frac{1}{k_b s} \]  

(F-34)

The characteristic time for diffusion across length L is

\[ \frac{\Delta C_a}{t_2} = D_{\text{eff}} \frac{\Delta C_a}{L^2} \]  

(F-35)

or \[ t_2 \equiv \frac{L^2}{D_{\text{eff}}} \]  

(F-36)

One would expect equilibrium to occur if \( t_2 \gg t_1 \)

or \[ \frac{L^2 k_b s}{D_{\text{eff}}} \gg 1 \]  

(F-37)

The equations (F-30) and (F-31) were solved for the case of a plane sheet of heterogeneous material and thickness 2L, initially of uniform concentration with phases A and B in equilibrium, which is suddenly immersed in an infinite bath of different concentration with its surfaces kept at constant concentration. The boundary conditions are

\[ t = 0 \quad -L < x < +L \quad C_a = C_{a_1} \]  

\[ C_b = C_{b_1} = K_{\text{eq}} C_{a_1} \]  

(F-38)

\[ t > 0 \quad x = L \quad C_a = C_{a_0} \]  

\[ C_b = C_{b_0} = K_{\text{eq}} C_{a_0} \]  

(F-39)

\[ x = 0 \quad \frac{\partial C_a}{\partial x} = 0 \]  

\[ \frac{\partial C_b}{\partial x} = 0 \]  

(F-40)
The set of equations and boundary conditions may be made dimensionless by the following transformation of variables. Let

\[ A = \frac{C_a - C_{a_0}}{C_{a_1} - C_{a_0}} \]  \hspace{1cm} (F-41)

\[ B = \frac{C_b - C_{b_0}}{C_{b_1} - C_{b_0}} \]  \hspace{1cm} (F-42)

\[ Z = \frac{X}{L} \]  \hspace{1cm} (F-43)

\[ \Theta = \frac{D_A t}{L^2} \]  \hspace{1cm} (F-44)

\[ K_1 = \frac{k_b s L^2 \Theta K_{eq}}{D_A \psi_A^* (1-\phi)} \]  \hspace{1cm} (F-45)

\[ K_2 = \frac{k_b s L^2}{D_A \psi_A^*} \]  \hspace{1cm} (F-46)

\[ K_3 = \frac{D_B}{D_A \psi_A^*} \]  \hspace{1cm} (F-47)

Then, eqns. (F-30) and (F-31) and boundary conditions (F-38) through (F-40) become

\[ \frac{\partial A}{\partial \Theta} - K_1 (B-A) = \frac{\partial^2 A}{\partial Z^2} \]  \hspace{1cm} (F-48)

\[ \frac{\partial B}{\partial \Theta} + K_2 (B-A) = K_3 \frac{\partial^2 B}{\partial Z^2} \]  \hspace{1cm} (F-49)

\[ \Theta = 0 \quad -1 < Z < +1 \quad A = B = 1 \]  \hspace{1cm} (F-50)

\[ \Theta > 0 \quad Z = 1 \quad A = B = 0 \]  \hspace{1cm} (F-51)
\[ Z = 0 \quad \frac{\partial A}{\partial Z} = \frac{\partial B}{\partial Z} = 0 \quad (F-52) \]

This system of equations may be solved by separation of variables. Assume a solution of the form

\[ A = F_a(\theta) \, G_a(Z) \quad (F-53) \]

\[ B = F_b(\theta) \, G_b(Z) \quad (F-54) \]

Substitution for \( A \) and \( B \) in eqns. (F-48) and (F-49) and division by \( A \) and \( B \), respectively, leads to

\[ \frac{F_a'}{F_a} - K_1 \left[ \left( \frac{F_b}{F_a} \right) \frac{G_b}{G_a} \right] - 1 = \frac{G_a''}{G_a} \quad (F-55) \]

\[ \frac{F_b'}{F_b} + K_2 \left[ 1 - \left( \frac{F_a}{F_b} \right) \frac{G_a}{G_b} \right] \right] = K_3 \frac{G_b''}{G_b} \quad (F-56) \]

With the equations in this form, it cannot be proven a priori that either \( F_i'/F_i \) or \( G_i''/G_i \) is equal to a constant. However, if the diffusion term is left out of the second equation, then \( G_a''/G_a \) may be proven constant, as follows. Equation (F-56) becomes

\[ \frac{F_b'}{F_b} = K_2 \left[ 1 - \left( \frac{F_a}{F_b} \right) \frac{G_a}{G_b} \right] \quad (F-57) \]

LHS = constant or \( f(\theta) \)

\[ \neq f(Z) \]

Therefore, RHS = constant or \( f(\theta) \) only since \[ \frac{F_a}{F_b} = \text{constant or } f(\theta) \]

and \[ \frac{G_a}{G_b} = \text{constant or } f(Z) \]
Consequently, $G_a/G_b$ must be constant. Similar reasoning with eqn. (F-55) shows that $F_b/F_a$ is constant. It will be assumed that this holds for the complete set of equations. If the solution obtained by making this assumption satisfies the differential equation, then it is a unique solution, since the equations are linear. Thus, assume

$$\frac{G''}{G_a} = -\lambda^2$$

(F-58)

for which the solution is

$$G_a = C_1 \cos \lambda Z + C_2 \sin \lambda Z$$

(F-59)

Applying the boundary conditions yields

$$C_2 = 0$$

(F-60)

$$\lambda_n = \left(\frac{2n+1}{2}\right) \pi \quad n = 0, 1, 2, \ldots$$

(F-61)

If eqn. (F-50) holds, then by the above reasoning

$$\frac{G''_b}{G_b} = -\mu^2$$

(F-62)

$$G_b = C_3 \cos \mu Z + C_4 \sin \mu Z$$

(F-63)

Since $G_b$ is subject to the same boundary conditions as $G_a$,

$$C_4 = 0$$

(F-64)

$$\nu_n = \lambda_n = \left(\frac{2n+1}{2}\right) \pi \quad n = 0, 1, 2, \ldots$$

(F-65)

Substitution of these results into eqns. (F-55) and (F-56), and assuming that $G_a$ and $G_b$ are related by a constant, $G_b/G_a = \alpha$, yields
\[ \frac{F_b'}{F_a} - K_1 \left[ \frac{F_b}{F_a} - 1 \right] = -\lambda_n^2 \quad (F-66) \]

\[ \frac{F_b'}{F_b} + K_2 \left[ 1 - \frac{F_a}{\alpha F_b} \right] = -K_n^2 \lambda_n^2 \quad (F-67) \]

Solving eqn. (F-66) for \( F_b \) and differentiating with respect to \( \theta \) leads to

\[ F_b = \frac{1}{\alpha K_1} \left[ F_a' + (\lambda^2 + K_1) F_a \right] \quad (F-68) \]

\[ F_b' = \frac{1}{\alpha K_1} \left[ F_a'' + (\lambda^2 + K_1) F_a' \right] \quad (F-69) \]

Substitution into eqn. (F-60) for \( F_b \) and \( F_b' \) yields

\[ F_a'' + \left[ \lambda^2 + K_1 + K_2 + K_3 \lambda^2 \right] F_a' + \left[ K_2 \lambda^2 + K_3 \lambda + K_1 K_3 \lambda^2 \right] F_a = 0 \quad (F-70) \]

The solution to this ordinary differential equation is

\[ F_a = C_5 e^{m_1 \theta} + C_6 e^{m_2 \theta} \quad (F-71) \]

where

\[ m_1, m_2 = -\frac{(\lambda^2 + K_1 + K_2 + K_3 \lambda^2) \pm \sqrt{(\lambda^2 + K_1 + K_2 + K_3 \lambda^2)^2 - 4(K_2 \lambda^2 + K_3 \lambda + K_1 K_3 \lambda^2)}}{2} \quad (F-72) \]

and \( \lambda \) is given by eqn. (F-61)

Solving for \( F_b \) from eqns. (F-68) and (F-71) gives

\[ F_b = \left( \frac{\lambda^2 + K_1 + m_1}{K_1} \right) \frac{C_5}{\alpha} e^{m_1 \theta} + \left( \frac{\lambda^2 + K_1 + m_2}{K_1} \right) \frac{C_6}{\alpha} e^{m_2 \theta} \quad (F-73) \]
Hence the solutions to the set of equations and boundary conditions are

\[ A = \left\{ A_{1n} e^{\theta_1} + A_{2n} e^{\theta_2} \right\} \cos \lambda_n Z \quad (F-74) \]

\[ B = \left\{ B_{1n} \left( \frac{\lambda^2 + K_1 + m_1}{K_1} \right) e^{\theta_1} + B_{2n} \left( \frac{\lambda^2 + K_1 + m_2}{K_1} \right) e^{\theta_2} \right\} \cos \lambda_n Z \quad (F-75) \]

where \( B_{in} = \frac{A_{in}}{\alpha} \)

Since the differential equations are linear, the most general solution may be obtained by superposition:

\[ A = \sum_{n=0}^{\infty} \left\{ A_{1n} e^{\theta_1} + A_{2n} e^{\theta_2} \right\} \sin \lambda_n Z \quad (F-76) \]

\[ B = \sum_{n=0}^{\infty} \left\{ B_{1n} \left( \frac{\lambda^2 + K_1 + m_1}{K_1} \right) e^{\theta_1} + B_{2n} \left( \frac{\lambda^2 + K_1 + m_2}{K_1} \right) e^{\theta_2} \right\} \cos \lambda_n Z \quad (F-77) \]

Let \( \beta_1 = \frac{\lambda^2 + K_1 + m_1}{K_1} \) \quad (F-78)

\[ \beta_2 = \frac{\lambda^2 + K_1 + m_2}{K_1} \] \quad (F-79)

Applying the initial conditions,

\[ A_0 = 1 = \sum_{n=0}^{\infty} \left( A_{1n} + A_{2n} \right) \cos \lambda_n Z \quad (F-80) \]

\[ B_0 = 1 = \sum_{n=0}^{\infty} \left( -\frac{\beta_1}{\alpha} A_{1n} + \frac{\beta_2}{\alpha} A_{2n} \right) \cos \lambda_n Z \quad (F-81) \]
Equation (F-70) and the boundary conditions are of the Sturm-Liouville type, and thus the functions \( \cos \left( \frac{(2n+1)\pi Z}{2} \right) \) are orthogonal with respect to each other with a weighting function of unity. Multiplying both sides of eqns. (F-80) and (F-81) by \( \sin \left( \frac{(2m+1)\pi X}{2} \right) \) and integrating yields

\[
\begin{align*}
A_{1n} + A_{2n} &= \frac{\beta_1}{\alpha} A_{1n} + \frac{\beta_2}{\alpha} A_{2n} = \int_0^1 \cos \left( \frac{(2n+1)\pi Z}{2} \right) \frac{dZ}{(2n+1)\pi} = \frac{4(-1)^n}{(2n+1)\pi} = R \\
\end{align*}
\]

(F-82)

Thus,

\[
A_{1n} + A_{2n} = R
\]

(F-83)

\[
\begin{align*}
\beta_1 A_{1n} + \beta_1 A_{2n} &= \beta_1 R \\
\frac{\beta_1}{\alpha} A_{1n} + \frac{\beta_2}{\alpha} A_{2n} &= R
\end{align*}
\]

(F-84)

(F-85)

Subtracting eqn. (F-85) from eqn. (F-84), rearranging, and combining with eqn. (F-83) yields

\[
\begin{align*}
A_{1n} &= \frac{\beta_2 - \alpha}{\beta_2 - \beta_1} = \frac{\lambda^2 + m_2 + K_{1}(1\alpha)}{m_2 - m_1} \\
A_{2n} &= \frac{\alpha - \beta_1}{\beta_2 - \beta_1} = \frac{\lambda^2 + m_1 - K_{1}(\alpha-1)}{m_2 - m_1}
\end{align*}
\]

(F-86)

(F-87)

Substitution of \( A_{1n} \) and \( A_{2n} \) into the initial condition for \( B_{1n} \), eqn. (F-81), shows that it can only be satisfied for \( \alpha = 1 \).

The complete solution for \( A \) and \( B \) is thus
\[ A = \frac{4}{\pi} \sum_{n=0}^{\infty} \frac{(-1)^n}{(2n+1)} \left\{ \left[ \frac{(2n+1)^2}{2} \pi^2 + m_2 \right] e^{m_1 \theta} - \left[ \frac{(2n+1)^2}{2} \pi^2 + m_1 \right] e^{m_2 \theta} \right\} \cos \left( \frac{2n+1}{2} \right) \pi Z \]

\[ B = \frac{4}{\pi} \sum_{n=0}^{\infty} \frac{(-1)^n}{(2n+1)} \left\{ \left[ \frac{(2n+1)^2}{2} \pi^2 + K_1 + m_1 \right] \left[ \frac{(2n+1)^2}{2} \pi^2 + m_2 \right] e^{m_1 \theta} - \left[ \frac{(2n+1)^2}{2} \pi^2 + K_1 + m_2 \right] \left[ \frac{(2n+1)^2}{2} \pi^2 + m_1 \right] e^{m_2 \theta} \right\} \cos \left( \frac{2n+1}{2} \right) \pi Z \]

where \( m_1 \) and \( m_2 \) are given by eqn. (F-72). Substitution of these expressions for \( A \) and \( B \) into the original differential equations shows that the solution does satisfy the differential equations and boundary conditions. Consequently, the assumptions made in obtaining the solution are legitimate. The average values of \( A \) and \( B \) may be determined by integrating eqns. (F-88) and (F-89) over \( Z \) from 0 to 1, in which case the cosine distance term drops out and the numerical coefficient becomes \( 8/(2n+1)^2 \pi^2 \).

From the definition of \( A \) and \( B \), eqns. (F-41) and (F-42), the actual concentrations are

\[ C_a = A(C_{a_1} - C_{a_0}) + C_{a_0} \quad \text{(F-90)} \]

\[ C_b = B(C_{b_1} - C_{b_0}) + C_{b_0} \]

\[ = K_{eq}(C_{a_0} - C_{a_0}) + K_{eq} C_{a_o} \quad \text{(F-92)} \]
Using these expressions, and the boundary conditions, eqns. (F-38) and (F-39), one may define a relative deviation from equilibrium in phase B as

$$\Delta_B = \frac{C_b - C_{b0}}{C_{b_{eq}} - C_{b0}} = \frac{A}{B} \quad (F-93)$$

This quantity represents the ratio of the actual dimensionless concentration in phase B to that which would occur if phase B were always in equilibrium with phase A. At equilibrium, $\Delta_B$ equals unity. The "excess" nonequilibrium portion of the dimensionless concentration is given by

$$\Delta^* = \frac{C_b - C_{b_{eq}}}{C_{b_{eq}} - C_{b0}} = \frac{B}{A} = 1 \quad (F-94)$$

and the fraction of the total dimensionless concentration in phase B which is in excess of the equilibrium value is

$$\Delta_B = \frac{C_b - C_{b_{eq}}}{C_b - C_{b0}} = 1 - \frac{A}{B} \quad (F-95)$$

Similar quantities may be defined in terms of the solute concentration in the total volume:

$$\Delta_T = \frac{C_T - C_{T0}}{C_{T_{eq}} - C_{T0}} = 1 + \left( \frac{\phi}{1 + \phi} \right) \frac{B}{A} K_{eq} \quad (F-96)$$
\[
\Delta_T = \frac{C_T - C_{T_{eq}}}{C_{T_{eq}} - C_T} = \frac{\left(\frac{\phi}{1+\phi}\right) K_{eq} \left(\frac{B}{A} - 1\right)}{1 + \left(\frac{\phi}{1+\phi}\right) K_{eq}}
\]  

(F-97)

\[
\Delta_T = \frac{C_T - C_{T_{eq}}}{C_T - C_{T_{eq}}} = \frac{\left(\frac{\phi}{1+\phi}\right) K_{eq} \left(1 - \frac{A}{B}\right)}{1 + \left(\frac{\phi}{1+\phi}\right) K_{eq}}
\]  

(F-98)

The equilibrium criteria is \( B = A \), and evaluation of this and the other quantities defined above requires evaluation of eqns. (F-88) and (F-89) for as many terms as are needed. However, both \( A \) and \( B \) are the same function of \( Z \), so this may be neglected. Further simplification is obtained by considering intermediate to long dimensionless times, where only the first term in the summation is necessary. Then

\[
A = A_1 e^{m_1 \phi} + A_2 e^{m_2 \phi}
\]  

(F-99)

\[
B = \beta_1 A_1 e^{m_1 \phi} + \beta_2 A_2 e^{m_2 \phi}
\]  

(F-100)

and \( \lambda = \frac{\pi}{2} \)

Simplification in evaluating \( m_1 \) and \( m_2 \) is obtained by noting that, for \( x \ll 1 \)

\[
\sqrt{1 - x} = 1 - \frac{x}{2}
\]  

(F-101)

Let us consider certain limiting cases:

1) \( K_1 = K_2 = K_3 = 0 \)

The solution for \( B \) breaks down under these conditions because \( K_1 \) is in the denominator for \( \beta_1 \) and \( \beta_2 \).
2) Same as (1) except \( \lambda^2 \gg K_1 \neq 0 \)

\[
m_1 \sim 0 \quad m_2 \sim -(\lambda^2 + K_1)
\]

\[
A_1 \sim \frac{1}{1 + \frac{\lambda^2}{K_1}} \quad A_2 \sim \frac{1 + \frac{K_1}{\lambda^2}}{1 + \frac{K_1}{\lambda^2}}
\]

\[
\beta_1 \sim 1 + \frac{\lambda^2}{K_1} \quad \beta_2 \sim 0
\]

Then,

\[
A = \frac{1}{1 + \frac{\lambda^2}{K_1}} e^\Theta + \frac{1}{1 + \frac{K_1}{\lambda^2}} e^{-(\lambda^2 + K_1)\Theta} \quad \left( \frac{\lambda^2}{K_1} + 0 \right) e^{-\lambda^2 \Theta}
\]

\[
B = \left( 1 + \frac{\lambda^2}{K_1} \right) \frac{1}{1 + \frac{\lambda^2}{K_1}} e^\Theta + (0) \frac{1}{1 + \frac{K_1}{\lambda^2}} e^{-(\lambda^2 + K_1)\Theta} = 1
\]

Consequently, \( A \) decays towards zero but \( B \) remains about constant. This is the extreme nonequilibrium case, since \( B/A \rightarrow \infty \) as \( \Theta \rightarrow \infty \)

3) \( K_1 + K_2 \gg \lambda^2, K_3 = 0 \)

\[
m_1 \sim -\frac{K_2 \lambda^2}{\lambda K_1 + K_2} \quad m_1 \sim -(K_1 + K_2)
\]

\[
A_1 \sim 1 \quad A_2 \sim -\frac{K_1 \lambda^2}{K_1 + K_2}
\]

\[
\beta_1 \sim 1 + \frac{\lambda^2}{K_1 + K_2} \quad \beta_2 \sim 1 + \frac{\lambda^2}{K_1} -(K_1 + K_2)
\]

Thus,

\[
\left| A_1 e^{m_1 \Theta} \right| \gg \left| A_2 e^{m_2 \Theta} \right|
\]

and

\[
\left| \beta_1 A_1 e^{m_1 \Theta} \right| \gg \left| \beta_2 A_2 e^{m_2 \Theta} \right|
\]
Consequently, one finds for $\Delta_B$

$$\frac{B}{A} \approx \beta_1 \approx 1 + \frac{\lambda^2}{K_1 + K_2} \tag{F-102}$$

and the requirement for equilibrium, $\Delta_B' \approx 0$, is

$$K_1 + K_2 \gg \lambda^2 = \frac{\pi^2}{4} \approx 2.5 \tag{F-103}$$

When only one term in the summation is required, $B/A$ is independent of time. This will not be true, however, for short times.

Substituting for $K_1$ and $K_2$ yields

$$\left[ \frac{k_b S L^2}{D_A \psi_A} \right] \left[ 1 + \frac{\phi}{(1 + \phi) K_{eq}} \right] \gg 2.5 \tag{F-104}$$

For the particular case where $\phi = 0.5$, $K_{eq} = 1$, this reduces to

$$\frac{k_b S L^2}{D_A \psi_A} \gg 1.25$$

which is remarkably similar to the requirements defined by eqn. (F-37). However the solution to the eqns. allows one to define more quantitatively the criteria for equilibrium.

For $\Delta_B' < 0.1$,

$$K_1 + K_2 > 25 \tag{F-105}$$

and for $\Delta_B' < 0.01$,

$$K_1 + K_2 > 250 \tag{F-106}$$

4) $K_1 + K_2 + K_3 \lambda^2 \gg \lambda^2$
As in case (3), one finds that the first term predominates.

\[ m_1 \approx -\frac{\lambda^2 (K_2 + K_3 \lambda^2 + K_1 K_3)}{K_1 + K_2 + K_3 \lambda^2} \]

\[ \beta_1 \approx 1 + \frac{\lambda^2 (1 + K_3)}{K_1 + K_2 + K_3 \lambda^2} \]

For equilibrium,

\[ K_1 + K_2 + K_3 \lambda^2 \gg \lambda^2 (1 + K_3) \]

or

\[ K_1 + K_2 \gg \lambda^2 (1 + K_3) - K_3 \lambda^2 = \lambda^2 \]

Consequently, the requirements for equilibrium are the same as for case (3) and are independent (to a first approximation, at least) of the value of \( K_3 \), as long as \( K_1 + K_2 \gg \lambda^2 \).
APPENDIX G

Mass Transfer from a Rotating Fluid to a Stationary Surface-Limiting Analytical Solutions

Four analytical solutions to the general problem are developed in this Appendix. They apply for specific limiting conditions: the leading edge of the mass transfer surface with a developing concentration boundary layer and high Schmidt number (constant concentration and constant flux boundary conditions); the region far from the surface; and a turbulent boundary layer with high Schmidt number. The specific formulation of these solutions was due to Professor K. A. Smith.

1. Leading Edge Solution, Constant Concentration at Wall

From Section 3.C.4, the equation for convective diffusion in axially symmetric flow is

\[ V_r \frac{\partial c}{\partial r} + V_z \frac{\partial c}{\partial z} = D \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial c}{\partial r} \right) + \frac{\partial^2 c}{\partial z^2} \right] \]  \hspace{1cm} (G-1)

with

\[ V_r = r \omega F(\zeta) \]  \hspace{1cm} (G-2)

\[ V_z = \sqrt{\nu \omega} H(\zeta) \]  \hspace{1cm} (G-3)

\[ \zeta = z \sqrt{\frac{\omega}{\nu}} \]  \hspace{1cm} (G-4)

Near the wall, \( F \) and \( H \) may be approximated as

\[ F(\zeta) = F(0) + F'(0) \zeta + \frac{1}{2} F''(0) \zeta^2 + \ldots \]  \hspace{1cm} (G-5)

\[ H(\zeta) = H(0) + H'(0) \zeta + \frac{1}{2} H''(0) \zeta^2 + \frac{1}{6} H'''(0) \zeta^3 + \ldots \]  \hspace{1cm} (G-6)
From the velocity boundary conditions, \( F(o) = H(o) = 0 \), and from Bodewadt (1331), \( H'(o) = 0 \). Thus

\[
F(\zeta) = F'(o) \zeta + \ldots \tag{G-7}
\]

\[
H(\zeta) = \frac{1}{2} H''(o) \zeta^2 + \ldots \tag{G-8}
\]

From continuity, eqn. (3-39), \( 2F = -H' \). Consequently

\[
2F' = -H'' \tag{G-9}
\]

and \( H = -F'(o) \zeta^2 + \ldots \tag{G-10} \)

Using only the first term approximations for \( F \) and \( H \), and defining

\[
\Theta = \frac{C-C_W}{C_W-C_W} \tag{G-11}
\]

eqn. (G-1) becomes

\[
r \omega F'(o) \zeta \frac{\partial \Theta}{\partial r} - \sqrt{\omega} F'(o) \zeta^2 \frac{\partial \Theta}{\partial z} = D \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial \Theta}{\partial r} \right) + \frac{\partial^2 \Theta}{\partial z^2} \right] \tag{G-12}
\]

After considerable experimentation with various relationships, the following similarity transformation was adopted. Let \( \Theta = f(\xi, r) \), where

\[
\xi = \left[ \frac{\omega}{D^2 \nu} \right]^{1/6} \frac{Z}{[\ln \left( \frac{b}{r} \right)]^a} \tag{G-13}
\]

\[
= \left( \frac{\omega}{\nu} \right)^{1/2} \left( \frac{\nu}{D} \right)^{1/3} \frac{Z}{[\ln \left( \frac{b}{r} \right)]^a} \tag{G-14}
\]

\[
= \frac{\zeta \text{ Sc}^{1/3}}{[\ln \left( \frac{b}{r} \right)]^a} \tag{G-15}
\]

where the constant \( a \) is to be determined later. Evaluating the derivatives in eqn. (G-12) yields
\[
\frac{\partial \theta}{\partial r} = \frac{a\xi}{r \ln\left(\frac{b}{r}\right)} \frac{\partial \theta}{\partial \xi} \tag{G-16}
\]

\[
\frac{\partial \theta}{\partial z} = \frac{\sqrt{\frac{\omega}{\nu} \text{Sc}^{1/3}}}{\left[\ln\left(\frac{b}{r}\right)\right]^a} \frac{\partial \theta}{\partial \xi} \tag{G-17}
\]

\[
\frac{a^2 \theta}{\xi z^2} = \frac{\frac{\omega \text{Sc}^{2/3}}{\left[\ln\left(\frac{b}{r}\right)\right]^a}}{\frac{\partial \theta}{\partial \xi} \frac{\partial^2 \theta}{\partial \xi^2}} \tag{G-18}
\]

\[
\frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial \theta}{\partial r} \right) = \frac{a}{r^2 \left[\ln\left(\frac{b}{r}\right)\right]^z} \left[ (a+1) \xi \frac{\partial \theta}{\partial \xi} + a \xi^2 \frac{\partial^2 \theta}{\partial \xi^2} \right] \tag{G-19}
\]

Substituting eqns. (G-16) through (G-19) into eqn. (G-12), expressing \( \xi \) in terms of \( \xi \), and dividing by \( \omega \left[\ln\left(\frac{b}{r}\right)\right]^{a-1} / \text{Sc}^{1/3} \) yields

\[
a F'(0) \xi^2 \frac{\partial \theta}{\partial \xi} - F'(0) \left[\ln\left(\frac{b}{r}\right)\right] \xi^2 \frac{\partial \theta}{\partial \xi} = \left[\ln\left(\frac{b}{r}\right)\right]^{-3a+1} \frac{\partial^2 \theta}{\partial \xi^2} \tag{G-20}
\]

\[
+ \left( \frac{a r^2}{\nu} \text{Sc}^{2/3} \right) \frac{1}{\left[\ln\left(\frac{b}{r}\right)\right]^{1+a}} \left[ (a+1) \xi \frac{\partial \theta}{\partial \xi} + a \xi^2 \frac{\partial^2 \theta}{\partial \xi^2} \right]
\]

Setting \( a = 1/3 \) causes the logarithmic expression for the first term on the right-hand side to become unity.

Up to this point, the only limitation on eqn. (G-20) is that it applies near the wall where the velocities may be approximated as a linear function of distance. However, in terms of developing an analytical solution, eqn. (G-20) presents only a small advantage over eqn. (G-1). In order to obtain an ordinary total differential equation, the following restrictions are necessary:
1) Radial diffusion is neglected. This requires that
\[ \frac{\omega r^2}{v} \text{Sc}^{1/3} \left[ \ln \left( \frac{b}{r} \right) \right]^{4/3} \gg 1. \]
2) The solution is restricted to the leading edge (outer radial portion) of the mass transferring surface, for which \( \ln \left( \frac{b}{r} \right) \ll 1 \), i.e., roughly the outer 10 per cent of the surface. Combining this restriction with (1) above results in the requirement \( \text{Re} \cdot \text{Sc}^{2/3} \gtrsim 100 \), where \( \text{Re} = \frac{\omega b^2}{v} \).

Equation (3-20), subject to the above restrictions, becomes
\[ \frac{d^2 \theta}{d \xi^2} - \frac{1}{3} F'(\theta) \xi^2 \frac{d \theta}{d \xi} = 0 \]  
\( (G-21) \)

with boundary conditions
\[ \xi = 0 \quad \theta = 0 \]  
\( (G-22) \)
\[ \xi = \infty \quad \theta = 1 \]  
\( (G-23) \)

Substituting \( p = \frac{d \theta}{d \xi} \) into eqn. (G-21) and integrating yields
\[ \frac{d \theta}{d \xi} = A \exp \left[ \frac{F'(\theta)\xi^3}{9} \right] \]  
\( (G-24) \)

Integration of eqn. (G-24), noting that \( F'(\theta) \) is negative \( (46) \) gives
\[ \theta = A \int_0^\xi \exp \left[ \frac{F'(\theta)\xi^3}{9} \right] d \xi \]  
\( (G-25) \)

and
\[ A = \int_0^\infty \exp \left[ \frac{F'(\theta)\xi^3}{9} \right] d \xi = \left( -\frac{F'(\theta)}{9} \right)^{1/3} \frac{3}{\Gamma(\frac{1}{3})} \]  
\( (G-26) \)

Of primary interest are the mass transfer coefficients.
The local coefficient is defined by
\[
\dot{n} = k_x (C_w - C_\infty) = -D \frac{\partial C}{\partial z} \bigg|_{Z=0} = -D (C_\infty - C_w) \frac{\partial \Theta}{\partial z} \bigg|_{Z=0} \quad (G-27)
\]

From eqns. (G-17), (G-24), and (G-26),

\[
\frac{\partial \Theta}{\partial z} \bigg|_{Z=0} = \frac{\partial \Theta}{\partial z} \bigg|_{Z=0} = \left( \frac{-F'(\Theta)}{9} \right)^{1/3} \frac{3}{\Gamma(\frac{1}{3})} \frac{\sqrt{\omega}}{\ln(\frac{D'}{r})} \quad (G-28)
\]

From eqn. (G-27)

\[
k_x = D \frac{\partial \Theta}{\partial z} \bigg|_{Z=0} \quad (G-29)
\]

Combination of eqns. (G-28) and (G-29) and rearrangement results in

\[
\left( \frac{k_x}{\omega b} \right) \left( \frac{v}{D} \right)^{2/3} = \frac{3}{\Gamma(1/3)} \left( \frac{-F'(\Theta)}{9} \right)^{1/3} \left( \frac{v}{\omega b} \right)^{1/2} \frac{1}{\ln(\frac{D'}{r})} \quad (G-30)
\]

From Bodewadt (46) \( F'(\Theta) \approx -0.94197 \), and eqn. (G-30) becomes

\[
St_x \ Sc^{2/3} = 0.528 \ Re^{-1/2} \frac{1}{\ln(\frac{D'}{r})} \quad (G-31)
\]

where \( St_x \) is the local Stanton number.

For application to the batch dialyzer with the impeller replaced by a disk, the appropriate velocity beyond the boundary layer on the stationary base is \( \gamma w \), where \( \omega \) is the angular velocity of the disk and \( 0 < \gamma < 1 \). Consequently, \( \omega \) must be replaced by \( \gamma w \). This results in eqn. (G-31) being multiplied by \( \gamma^{1/2} \).

Further developments of the solution were made using one additional term in the expansions for the velocity components. The incremental change in the calculated mass transfer correlation, however, was negligible.
The average mass transfer coefficient is obtained by integrating the local mass transfer coefficient across the transport surface. Hence,

$$k_m = \int_0^b \frac{2\pi r k_x dr}{\pi b^2}$$  \hspace{1cm} (G-32)

and

$$\left( \frac{k_m}{\omega b} \right) Sc^{2/3} = \frac{3}{\Gamma(1/3)} \left(-\frac{F'(0)}{9}\right)^{1/3} Re^{-1/2} \int_0^b \frac{r}{b} \left[\ln \left( \frac{b}{r} \right) \right]^{1/3} d\left( \frac{r}{b} \right)$$  \hspace{1cm} (G-33)

Let  \hspace{1cm} \ln \left( \frac{b}{r} \right) = \mu  \hspace{1cm} (G-34)

$$\frac{b}{r} e^\mu$$  \hspace{1cm} (G-35)

$$\frac{r}{b} = e^{-\mu}$$  \hspace{1cm} (G-36)

Then

$$2 \int_0^1 \frac{r}{b} \left[\ln \left( \frac{b}{r} \right) \right]^{1/3} d\left( \frac{r}{b} \right) = 2 \int_0^\infty \frac{-e^{-2\mu}}{\mu^{1/3}} d\mu$$  \hspace{1cm} (G-37)

$$= \int_0^\infty 2^{1/3} \frac{e^{-2\mu}}{(2\mu)^{1/3}} d(2\mu)$$  \hspace{1cm} (G-38)

$$= 2^{1/3} \Gamma \left( \frac{2}{3} \right)$$  \hspace{1cm} (G-39)
Finally,

\[ \text{St}_m \frac{Sc^{2/3}}{\Gamma(1/3)} = \frac{3(2)^{1/3} \Gamma(2/3)}{\Gamma(1/3)} \left( \frac{-F'(0)}{9} \right)^{1/3} \text{Re}^{-1/2} \]  

\[ = 1.706 \text{ Re}^{-1/2} \]  

(G-40)

(G-41)

In view of the limitations on the solution, one would not expect the predicted average Stanton number to give a good representation of the actual physical situation.

2. **Leading Edge Solution, Constant Flux at Wall**

The differential equations are the same as before, but the boundary conditions for the axial direction become

\[ Z = 0 \quad -D \frac{\partial C}{\partial Z} = \dot{h}_0 \]  

(G-42)

\[ Z = \infty \quad C = C_\infty \]  

(G-43)

As before, let

\[ \xi = \left[ \frac{\omega^3}{D^2uv} \right]^{1/6} \frac{Z}{\left[ \ln \left( \frac{b}{r} \right) \right]^{1/3}} \]  

(G-13)

In addition, assume a solution of the form

\[ C - C_\infty = \frac{\dot{h}_0}{D} \left[ \frac{D^2uv}{\omega^3} \right]^{1/6} \left[ \ln \left( \frac{b}{r} \right) \right]^{1/3} f(\xi) \]  

(G-44)

\[ = \frac{\dot{h}_0}{D} \frac{Z}{\xi} f(\xi) \]  

(G-45)
Hence, the boundary conditions become
\[ \xi = 0 \quad -\frac{\partial f}{\partial \xi} = 1 \quad \text{(G-46)} \]
\[ \xi = \infty \quad f = 0 \quad \text{(G-47)} \]

From eqns. (G-13) and (G-44), the partial derivatives in the original differential equation become
\[ \frac{\partial c}{\partial r} = \frac{1}{3} \frac{\eta}{D} \left[ \frac{D^* v}{\omega^2} \right]^{1/6} \left[ \ln \left( \frac{b}{r} \right) \right]^{-2/3} \left[ -\frac{f}{r} + \frac{\xi}{r} f \right] \quad \text{(G-48)} \]
\[ \frac{\partial c}{\partial z} = \frac{\eta}{D} f' \quad \text{(G-49)} \]
\[ \frac{\partial^2 c}{\partial z^2} = \frac{\eta}{D} f'' \left[ \frac{\omega^2}{D^* v} \right]^{1/6} \left[ \frac{1}{\ln \left( \frac{b}{r} \right)} \right]^{1/3} \quad \text{(G-50)} \]

As before, the radial diffusion term is neglected. Substitution of eqns. (G-48) through (G-50) into eqn. (G-12), followed by rearrangement yields
\[ \frac{F'(0)}{3} \left[ -f + \xi f' \right] - F'(0) \xi^2 \left[ \ln \left( \frac{b}{r} \right) \right] f' = f'' \quad \text{(G-51)} \]

Dropping the term containing the logarithmic factor, which limits the solution to \( \ln(b/r) < 1 \), yields
\[ f'' - \frac{F'(0)}{3} \xi^2 f' + \frac{F'(0)}{3} \xi f = 0 \quad \text{(G-52)} \]

Let \( A = -\frac{F'(0)}{3} \). Dividing eqn. (G-52) by \( A \xi \), differentiating with respect to \( \xi \), and then multiplying by \( A \xi^2 \) gives
\[ \xi f''' + (A \xi^3 - 1) f'' = 0 \quad \text{(G-55)} \]

Now, let \( \chi = \left( \frac{A}{3} \right)^{1/3} \xi \)
\[ Q = \frac{d f(E)}{d \xi} = f' \quad \text{(G-55)} \]
Noting that
\[
\frac{d^{n+1}f(\xi)}{d\xi^{n+1}} = \frac{d^n}{dx^n} \left[ \frac{d}{d\xi} \right]^n \tag{G-56}
\]
one obtains upon substitution of eqn. (G-56) and (G-54) into (G-53):
\[
Q'' + (3\chi^3 - 1) Q' = 0 \tag{G-57}
\]
with boundary conditions
\[
\begin{align*}
\chi &= 0 \quad Q = 1 \tag{G-58} \\
\chi &\to \infty \quad Q \to 0 \tag{G-59}
\end{align*}
\]
While the second boundary condition does not follow explicitly from eqn. (G-47), as \(\xi \to \infty, f \to 0 \) implies \( f' \to 0 \).

Equation (G-57) and associated boundary conditions have been solved by Brid (36a), and the solution to the same equation is discussed in more detail in Appendix M, Section 1. Integrating eqn. (G-54), one obtains
\[
\int_0^\infty df(\xi) = -f(\xi) = \frac{d\xi}{dx} \int_\chi^\infty Q(x) \, dx = \tag{G-60}
\]
\[
= \left( \frac{\Lambda}{3} \right)^{-1/3} \int_\chi^\infty Q(x) \, dx \tag{G-61}
\]
of primary interest here is \( f(0) \), which is given by
\[
f(0) = \left( \frac{\Lambda}{3} \right)^{-1/3} \frac{1}{\Gamma(\frac{2}{3})} = \frac{-F'(0)}{9} \left( \frac{1}{\Gamma(\frac{2}{3})} \right) \tag{G-62}
\]
From eqns. (G-28) and (G-44), and noting that \( C = C_W \) at \( \xi = 0 \), one finds the local mass transfer coefficient to be
\[ k_x = \frac{n_0}{c_w - c_\infty} = \frac{D}{\tau(0)} \left( \frac{1}{\ln\left(\frac{b}{r}\right)} \right)^{1/3} \left( \frac{\omega^3}{D^2 \nu} \right)^{1/6} \quad (G-63) \]

which upon rearrangement yields

\[ \left( \frac{k_x}{\nu} \right)^{2/3} = \frac{1}{\tau(0)} \left( \frac{\nu}{\omega^3} \right)^{1/2} \frac{1}{\left[ \ln\left(\frac{b}{r}\right) \right]^{1/3}} \quad (G-64) \]

or

\[ St_x \cdot Sc^{2/3} = 0.638 \cdot Re^{-1/2} \frac{1}{\left[ \ln\left(\frac{b}{r}\right) \right]^{1/3}} \quad (G-65) \]

The ratio of the mass transfer coefficients for the constant flux case to that of the constant concentration case is simply

\[ \frac{r(\frac{1}{3})}{r(\frac{2}{3})} \frac{1}{3} = 1.209 \quad (G-66) \]

This ratio applies to both local and average mass transfer coefficients. It is noteworthy that the same ratio occurs with the constant flux and constant concentration Leveque-type solutions for transport in a conduit (see Section 4.C.3).

3. "Far Field" Solution

The two previous solutions are restricted to the developing concentration boundary layer at the leading edge and high Schmidt number. It is instructive to examine the nature of the concentration field far from the surface, and in particular near the axis of symmetry. Beyond the momentum boundary layer, the radial velocity is negligible and the axial velocity is constant. Radial
convection may be ignored and axial diffusion is assumed small compared to axial convection. Hence, eqn. (G-1) becomes

\[ V_z \frac{\partial C}{\partial z} = D \frac{1}{r} \frac{\partial}{\partial r} (r \frac{\partial C}{\partial r}) \]  

(G-67)

with boundary conditions

\[ Z = -\infty \quad C = 0 \]  

(G-68)

\[ r = 0 \quad \frac{\partial C}{\partial r} = 0 \]  

(G-69)

\[ r = \infty \quad C = 0 \]  

(G-70)

Let

\[ \Theta = \frac{C - C_w}{C_w - C_\infty} \]  

(G-71)

\[ V_z = \sqrt{\nu \omega} H(\infty) \]  

(G-72)

From Bodewadt (46), \( H(\infty) = 1.35 \). Note that \( \Theta \) is defined differently from the first two solutions, eqn. (G-11).

Eqn. (G-67) is thus

\[ \sqrt{\nu \omega} H(\infty) \frac{\partial \Theta}{\partial z} = D \frac{1}{r} \frac{\partial}{\partial r} (r \frac{\partial \Theta}{\partial r}) \]  

(G-73)

Eqn. (G-73) may be changed to a total differential equation by using a similarity transformation of the form

\[ \Theta = \frac{A}{Z} g(n) \]  

(G-74)

where

\[ n = \left( \frac{\nu \omega}{D^2} \right)^{1/4} \frac{r}{Z^{1/2}} \]  

(G-75)

\[ = \left( \frac{\nu}{C} \right)^{1/2} \left( \frac{\omega r^2}{\nu} \right)^{1/2} \]  

(G-76)

and \( A \) is a constant to be determined. Substitution for \( \Theta \) in
eqn. (G-73) followed by rearrangement yields

\[ g'' + \left[ 1 + \frac{H(\omega) \eta}{2} \right] g' + H(\omega) g = 0 \]  
\( G-77 \)

which reduces to

\[ \frac{dn}{d\eta} \left[ \frac{1}{n} g' \right] + \frac{H(\omega)}{2} \frac{d}{d\eta} \left[ n^2 g \right] = 0 \]  
\( G-78 \)

with boundary conditions

\[ \eta = 0 \quad g' = 0 \]  
\( G-79 \)

\[ \eta = \infty \quad g = 0 \]  
\( G-80 \)

The solution to eqn. (G-78) is given by

\[ g = A \exp \left[ -\frac{H(\omega)}{4} n^2 \right] \]  
\( G-81 \)

Hence,

\[ \Theta = \frac{A}{Z} \exp \left[ -\frac{H(\omega)}{4} \frac{Sc \omega r^2}{\zeta} \right] \]  
\( G-82 \)

The total mass transfer rate is equal to the flux through a plane perpendicular to the Z-axis. Hence.

\[ N = V_z \int_0^\infty (C-C_\infty) 2\pi r \ dr \]  
\( G-83 \)

\[ = \sqrt{n} \omega H(\omega) (C_w - C_\infty) \int_0^\infty \Theta \ 2\pi r \ dr \]  
\( G-84 \)

\[ = \sqrt{n} \omega H(\omega) (C_w - C_\infty) \pi \int_0^\infty \frac{A}{Z} \exp \left[ -\frac{H(\omega)}{4} \frac{Sc \omega r^2}{\zeta} \right] d(r^2) \]  
\( G-85 \)

\[ = 4\pi A D (C_w - C_\infty) \]  
\( G-86 \)

Thus,

\[ A = \frac{\dot{N}}{4\pi D (C_w - C_\infty)} \]  
\( G-87 \)
and the far field solution becomes

\[ C - C_\infty = \frac{N}{4\pi D} \exp \left[ -\frac{H(\infty) \, Sc \, \omega r^2}{4 \, \zeta \, \nu} \right] \]  \tag{G-88}

From the results of the leading edge solution, the average mass transfer coefficient for high Sc, defined by

\[ N = k_m \pi b^2 (C_w - C_\infty) \]  \tag{G-89}

is assumed to be of the form

\[ \left( \frac{k_m}{\omega b} \right) Sc^{2/3} = B \left( \frac{\nu}{\omega b^2} \right)^{1/2} \]  \tag{G-90}

where B is a constant. If one solves eqn.(G-90) for \( k_m \), substitute this relation into eqn.(G-89), and uses the resulting expression for \( N \) in eqn.90, one obtains

\[ 0 = \frac{B \, \nu^{1/2} \, Sc^{-2/3} \omega^{1/2} b^2}{4 \, \pi \, \nu} \exp \left[ -\frac{H(\infty) \, Sc \, \omega r^2}{4 \, \zeta \, \nu} \right] \]  \tag{G-91}

\[ = \frac{B \, \Re \, Sc^{1/3}}{4 \, \zeta} \exp \left[ -\frac{H(\infty) \, Sc \, \omega r^2}{4 \, \zeta \, \nu} \right] \]  \tag{G-92}

In the region around the axis of symmetry (small r) the exponential term drops out and

\[ \Theta \left|_{r=0}^{\infty} = \frac{B \, \Re \, Sc^{1/3}}{4 \, \zeta} \right. \]  \tag{G-93}

Since B/4 is of order unity, one may estimate the magnitude of dimensionless axial distance, \( \zeta \), required to attain a given value of \( \Theta \) along the Z axis. For typical conditions of operation of the batch dialyzer, \( \Re \sim 10^4 \), \( Sc \sim 10^3 \). Defining the edge of
the concentration boundary layer as $\Theta \sim 0.01$, one finds
\[ \frac{10^6 \ 10^4}{10^{-3}} \sim 10^7 \]  \hspace{1cm} (G-94)

This exceedingly large order of magnitude for the concentration boundary layer thickness indicates that the concentration along the Z-axis drops very slowly with increasing distance.

The exponential term in eqn. (G-91) may be rewritten as
\[ \exp \left[ - \frac{H(\infty)}{4} \frac{\text{Sc} \ \text{Re}}{\zeta} \left( \frac{r}{D_r} \right) \right] \approx \exp \left[ - \frac{\text{Sc} \ \text{Re}}{\zeta} \left( \frac{r}{D_r} \right) \right] \]  \hspace{1cm} (G-95)

For $\zeta \ll \text{Sc} \ \text{Re}$, the pre-multiplier of the dimensionless radial distance is very large, indicating that $\Theta$ drops off very sharply away from the Z-axis. Except in the immediate vicinity of the Z-axis, $\Theta$ is essentially zero.

The far field solution is valid for the following conditions:
1) $V_r \sim 0$. Therefore, $\zeta \gg 1$
2) $V_z \frac{\partial \Theta}{\partial z} \gg D_r \frac{\partial^2 \Theta}{\partial z^2}$, or roughly, $\zeta \text{Sc} \gg 1$
3) $\Theta < 1$. Therefore, from eqn. (G-93), $\zeta > \text{Re} \ \text{Sc}^{1/3}$
4) The system is at steady state.

The latter requirement, while implicit in the solution, is noteworthy because near the Z-axis very long dimensionless times would be required for the concentration field to propagate all the way out. During the transient of the far field, the concentration field near the surface would already have reached steady state.

4. **Turbulent Boundary Layer**

Although it is not possible to solve for the concentration field for a turbulent boundary layer, the desired mass transfer
relationships may be obtained from the turbulent momentum and mass transport analogies. The Chilton-Colburn (274) analogy may be expressed as

\[
\frac{k_x S c^{2/3}}{U} = \frac{f}{2} = \frac{\tau_o}{\rho U^2}
\]  

(G-96)

Here, \( U \) is defined such that near \( y = 0 \), \( u = U(z, \delta)^{1/7} \). \( U \) is a hypothetical free stream velocity which is not equal to \( r \omega \). The wall shear stress, \( \tau_o \), may be obtained from the results of Schultz-Grunow (360) as discussed in Section 3.C.3. Using the same nomenclature as in the body of the thesis, one finds

\[
\tau_o = 0.0225 \rho U^2 \left( \frac{v}{U \delta} \right)^{1/4}
\]  

(G-97)

Hence

\[
\frac{k_x S c}{U} = 0.0225 \left( \frac{v}{U \delta} \right)^{1/4}
\]  

(G-98)

where

\[
\delta^{1/4} = \chi^{1/10} \nu^{1/20} \beta^{-1/20} \alpha^{3/20} D
\]  

(G-99)

\[
U = r \beta \sqrt{1 + \alpha^2}
\]  

(G-100)

\[
\alpha = \chi^{9/10} \nu^{1/5} \beta^{8/5} C
\]  

(G-101)

\[
\chi = 1 - \frac{r}{b}
\]  

(G-102)

\[
C = \sum_{n=0}^{\infty} c_n \chi^n
\]  

(G-103)

\[
D = \sum_{n=0}^{\infty} d_n \chi^n
\]  

(G-104)
The coefficients $c_n$ and $d_n$ are given in eqns. (3-93) and (3-94), respectively; $\beta = \gamma \omega$ is the inviscid core angular velocity.

Combining eqns. (G-98) through (G-104) yields

\[
\frac{k}{b \beta} \text{Sc}^{2/3} = 0.0225 \left(1 + \alpha^2\right)^{3/8} \frac{\nu^{1/5} r^{3/4}}{\beta^{1/5} b^{23/5} \chi^{1/10} D} \tag{G-105}
\]

\[
= 0.0225 \left(1 + \alpha^2\right)^{3/8} \left(\frac{\nu}{\beta b^2}\right)^{1/5} \left(1 - \chi\right)^{3/4} \chi^{1/10} D \tag{G-106}
\]

or

\[
\text{St}_x \text{Sc}^{2/3} = 0.0225 \text{Re}^{-1/5} \left(1 + \alpha^2\right)^{3/8} \left(1 - \chi\right)^{3/4} \chi^{1/10} D \tag{G-107}
\]

The correlation for the average mass transfer coefficient is obtained by integrating eqn. (G-107) over the total mass transfer area. Thus,

\[
\text{St}_m = \frac{\int_0^b \text{St}_x 2\pi r dr}{\pi b^2} \tag{G-108}
\]

\[
= 2 \int_0^1 \text{St}_x \left(\frac{r}{b}\right) d\left(\frac{r}{b}\right) \tag{G-109}
\]

\[
= \int_0^1 \text{St}_x \left(1 - \chi\right) d\chi \tag{G-110}
\]

and

\[
\text{St}_m \text{Sc}^{2/3} = 0.0450 \text{Re}^{-1/5} \int_0^1 \left(1 + \alpha^2\right)^{3/8} \left(1 - \chi\right)^{7/4} \chi^{1/10} D \tag{G-111}
\]

The integral in eqn. was broken up into two parts:

\[
\int_0^1 = \int_0^0.02 + \int_0^{0.02} \tag{G-112}
\]
The second term, covering the inner 98% of the radius was integrated numerically on a digital computer using Simpson's rule. The first term was integrated analytically. For \( x \) close to zero, 
\[(1+\alpha^2)^{3/8} \approx 1, \quad (1-x)^{7/4} \approx 1 - 7/4x, \quad \text{and} \quad D = d_0 + d_1x, \]
where \( d_0 = 0.8554 \) and \( d_1 = 1.063 \). Thus,

\[
\int_0^{x_1=0.02} \frac{(1+\alpha^2)^{3/8} (1-x)^{7/4}}{x^{1/10} D} dx \approx \int_0^{0.02} \left[ \frac{x^{-1/10}}{d_0 + d_1 x} - \frac{7/4x^{9/10}}{d_0 + d_1 x} \right] dx \\
\approx 0.0323 \tag{G-113}
\]

The numerical integration yielded a value of 0.6066. Combining the two terms and substituting into eqn. (G-113) gives

\[
St_m Sc^{2/3} = 0.0285 \, Re^{-1/5} \tag{G-114}
\]

The mass transfer results have the same limitations as the original solution of the fluid dynamic problem, i.e., they are not accurate beyond roughly the outer one-third of the transport surface.
APPENDIX H

Mass Transfer from a Rotating Fluid to a Stationary Surface -

Numerical Solution

1. Formulation of the Problem

The equation for convective diffusion in axially symmetric flow is

\[ \nu_r \frac{\partial c}{\partial r} + \nu_z \frac{\partial c}{\partial z} = D \left( \frac{\partial^2 c}{\partial z^2} + \frac{\partial^2 c}{\partial r^2} + \frac{1}{r} \frac{\partial c}{\partial r} \right) \]  \hspace{1cm} (H-1)

The problem of interest is that of a finite circular area of radius \( b \) which is transferring mass to or from the surrounding fluid. The boundary conditions are

\[ z = 0 \quad 0 \leq r \leq b \quad c = c_w \] \hspace{1cm} (H-2)

\[ z = \infty \quad \text{all } r \quad c = c_\infty \] \hspace{1cm} (H-3)

\[ \text{all } z \quad r = 0 \quad \frac{\partial c}{\partial r} = 0 \] \hspace{1cm} (H-4)

\[ z > 0 \quad r = \infty \quad c = c_\infty \] \hspace{1cm} (H-5)

The first boundary condition assumes a constant concentration at the wall. The third boundary condition is due to symmetry about the \( z \)-axis. The second and fourth boundary conditions assume a constant ambient concentration at infinite distance from the surface in all directions.

The problem is put in dimensionless form by the following transformations:

\[ x = \frac{r}{b} \] \hspace{1cm} (H-6)

\[ \zeta = z \frac{w}{\nu} \] \hspace{1cm} (H-7)
\[ \theta = \frac{c - c_\infty}{c_w - c_\infty} \]  
\[ V_r = r\omega F(\zeta) \]  
\[ V_z = \sqrt{\nu} H(\zeta) \]

where the velocity component functions \( F \) and \( H \) are known functions of \( \zeta \) (46). The equation becomes

\[ x \frac{\partial \theta}{\partial x} + H \frac{\partial \theta}{\partial \zeta} = \frac{1}{Sc} \left[ \frac{\partial^2 \theta}{\partial \zeta^2} + \frac{1}{Re} \left[ \frac{\partial^2 \theta}{\partial x^2} + \frac{1}{\partial x} \right] \right] \]  

with boundary conditions

\[ \zeta = 0 \quad 0 \leq x \leq 1 \quad \theta = 1 \]  
\[ \zeta = \infty \quad \text{all } x \quad \theta = 0 \]  
\[ \text{all } \zeta \quad x = 0 \quad \frac{\partial \theta}{\partial x} = 0 \]  
\[ \zeta > 0 \quad x = \infty \quad \theta = 0 \]  

In order to solve eqn. (H-11) numerically over a finite region, it is necessary to assume that the second and fourth boundary conditions are satisfied at some finite value of \( \zeta \) and \( x \), respectively. Equations (H-13) and (H-15) become

\[ \zeta = \zeta_\infty \quad \text{all } x \quad \theta = 0 \]  
\[ \zeta > 0 \quad x = 1 \quad \theta = 0 \]  

The procedure used was to solve the problem with successively larger values of \( \zeta_\infty \) until the concentration field near the wall, and thus the local mass transfer coefficients, did not change significantly with increasing \( \zeta_\infty \). The results of the "far field" solution in Appendix G showed that this method would give a good representation of the physical situation over the
entire region except in the immediate vicinity of the z-axis. Setting $x = 1$ for the outer radial boundary condition was equivalent to neglecting radial diffusion beyond the edge of the transfer surface. This led to some inaccuracy in the immediate region of the leading edge; various techniques employed to improve the procedure are discussed later. Finally, since the region close to the surface was of primary importance but the region of integration extended out to $z = \infty$, a transformation of variables was employed to expand the near-wall region. The particular formulation was

$$
\zeta = e^{py} - 1 \quad (H-18)
$$

or

$$
y = \frac{1}{p} \ln (\zeta + 1) \quad (H-19)
$$

The boundary condition of eqn. (H-16) was changed to

$$
y = 1 \quad \text{all } x \quad \Theta = 0 \quad (H-20)
$$

Hence

$$
p = \ln (\zeta_{\infty} + 1) \quad (H-21)
$$

With this transformation, the equations and boundary conditions in x-y space become

$$
x F \frac{\partial \Theta}{\partial x} + \frac{H}{p \exp(py)} \frac{\partial \Theta}{\partial y} = \frac{1}{Sc} \left[ \left( \frac{1}{p \exp(py)} \right)^2 \frac{\partial^2 \Theta}{\partial y^2} + \frac{1}{Re} \left( \frac{\partial^2 \Theta}{\partial x^2} + \frac{1}{\Theta} \frac{\partial \Theta}{\partial x} \right) \right] \quad (H-22)
$$

$$
y = 0 \quad 0 \leq x \leq 1 \quad \Theta = 1 \quad (H-23)
$$

$$
y = 1 \quad \text{all } x \quad \Theta = 0 \quad (H-24)
$$

$$
0 < y < 1 \quad x = 0 \quad \frac{\partial \Theta}{\partial x} = 0 \quad (H-25)
$$

$$
y > 0 \quad x = 1 \quad \Theta = 0 \quad (H-26)
$$
Equation (H-22) was solved by iterating the transient to the steady state. In addition, the following shorthand nomenclature was employed.

\[ \alpha(y) = F(y) \]  \hspace{1cm} (H-27)

\[ \beta(y) = \frac{H(y)}{p \exp(py)} \] \hspace{1cm} (H-28)

\[ \gamma(y) = \frac{1}{\text{Sc} \ [p \exp(py)]^2} \] \hspace{1cm} (H-29)

\[ \delta = \frac{1}{\text{Sc} \ \text{Re}} \] \hspace{1cm} (H-30)

Thus, the equation to be solved numerically becomes

\[ \frac{\partial \Theta}{\partial t} + \alpha(y) \frac{\partial \Theta}{\partial x} + \beta(y) \frac{\partial \Theta}{\partial y} = \gamma(y) \frac{\partial^2 \Theta}{\partial x^2} + \delta \left[ \frac{\partial^2 \Theta}{\partial x^2} + \frac{1}{x} \frac{\partial \Theta}{\partial x} \right] \] \hspace{1cm} (H-31)

2. Numerical Solution

Equation (H-31) was solved numerically using the alternating difference implicit procedure (ADIP) of Peaceman and Rachford (317). All derivatives were expressed as central finite differences. At each time-step, the equation was solved first explicitly in \( y \) (forward difference) and implicitly in \( x \) (backward difference); then the procedure was reversed. An initial progression of increasing time steps was employed to prevent instability from occurring and the solution was continued until \( \Theta \) at all points on the grid converged to a time invariant value within a prescribed tolerance.

The finite difference expressions employed were as follows.
\[ x = (i-1) \Delta x \quad 1 \leq i \leq I + 1 \]  \hspace{1cm} (H-32)

\[ y = (j-1) \Delta x \quad 1 \leq j \leq J + 1 \]  \hspace{1cm} (H-33)

\[ t = (n-1) \Delta t \]  \hspace{1cm} (H-34)

\[ \frac{\partial \theta}{\partial t} = \left( \theta_{i,j,n+1} - \theta_{i,j,n} \right) / \Delta t \]  \hspace{1cm} (H-35)

Then, at the appropriate time level \((n\ or\ n+1)\),

\[ a(y) x \frac{\partial \theta}{\partial x} = a_j \left[ x_{i+1/2} \left( \theta_{i+1,j} - \theta_{i,j} \right) + x_{i-1/2} \left( \theta_{i,j} - \theta_{i-1,j} \right) \right] / 2 \Delta x \]  \hspace{1cm} (H-36)

\[ b(y) \frac{\partial \theta}{\partial y} = \left[ b_{j+1/2} \left( \theta_{i,j+1} - \theta_{i,j} \right) + b_{j-1/2} \left( \theta_{i,j} - \theta_{i,j-1} \right) \right] / 2 \Delta y \]  \hspace{1cm} (H-37)

\[ \frac{\partial^2 \theta}{\partial x^2} = \left( \theta_{i+1,j} - 2 \theta_{i,j} + \theta_{i-1,j} \right) / \Delta x^2 \]  \hspace{1cm} (H-38)

\[ \frac{1}{x} \frac{\partial \theta}{\partial x} = \left[ \frac{1}{x_{i+1/2}} \left( \theta_{i+1,j} - \theta_{i,j} \right) + \frac{1}{x_{i-1/2}} \left( \theta_{i,j} - \theta_{i-1,j} \right) \right] / 2 \Delta x \]  \hspace{1cm} (H-39)

The axial diffusional term is more properly expressed as

\[ \gamma(y) \frac{\partial^2 \theta}{\partial y^2} = \frac{1}{Sc} \psi(y) \left[ \frac{\partial}{\partial y} \psi(y) \frac{\partial \theta}{\partial y} \right] \]  \hspace{1cm} (H-40)

where

\[ \psi(y) = \frac{1}{\mu \exp(\beta y)} \]  \hspace{1cm} (H-41)
Then
\[ \psi(y) \frac{\partial}{\partial y} [\psi(y) \frac{\partial \theta}{\partial y}] = \psi_j \left[ \psi_{j+1/2} \frac{\partial \theta}{\partial y} |_{j+1/2} - \psi_{j-1/2} \frac{\partial \theta}{\partial y} |_{j-1/2} \right] / \Delta y \]
\[ \text{(H-42)} \]
\[ = \psi_j \left[ \psi_{j+1/2} (\theta_{1,j+1} - \theta_{1,j}) / \Delta y - \psi_{j-1/2} (\theta_{1,j} - \theta_{1,j-1}) / \Delta y \right] / \Delta y \]
\[ \text{(H-43)} \]

At \( x = 0 \), the term \([1/\times) \partial \theta / \partial x]\) is indeterminate. Applying L'Hopital's rule to the entire radial diffusion term (231) one finds
\[ \lim_{x \to 0} \left( \frac{\partial^2 \theta}{\partial x^2} + \frac{1}{x} \frac{\partial \theta}{\partial x} \right) = \frac{\partial^2 \theta}{\partial x^2} = 4(\theta_{1,j+1} - \theta_{1,j}) / \Delta x^2 \]
\[ \text{(H-44)} \]
since \( \theta_{1,j+1} = \theta_{j+1} \) by reflection. In addition, the radial convection term was written for the 1 + 1/4 point and is given by
\[ \alpha(y) \times \frac{\partial \theta}{\partial x} = \alpha_j \times 1+1/2 \left( \theta_{1,j+1} - \theta_{1,j} \right) / 2 \Delta x \]
\[ \text{(H-45)} \]

When the finite difference formulations are substituted into eqn. (H-31) at the appropriate time levels, \( n \) and \( n+1 \), there results for each slice during a pass across the finite difference grid a set of simultaneous linear algebraic equations which form a tri-diagonal matrix. These were solved by an algorithm attributed to Thomas (231).

In addition to solving for the concentration field, \([\partial \theta / \partial y]_{y=0}\) was evaluated in order to calculate mass transfer coefficients. The method used was the so-called "1/4-point" technique, attributable to Professor P. L. T. Brian (51), in which the finite
difference approximations are written for one-half of the first grid slice in from the boundary \((y=0, j=1)\), i.e., an average for \(j\) and \(j+1/2\). This is equivalent to making a mass balance about \(j+1/4\) over the first half grid slice. Using this approach and noting that \(\alpha(y) = (\partial\Theta/\partial x) = 0\) at \(y = 0\), one obtains for \(j = 1\).

\[
\alpha(y) \times \frac{\partial \Theta}{\partial x} \bigg|_{j+1/4} = \frac{1}{2} \left[ \alpha_j \times \frac{\partial \Theta}{\partial x} \bigg|_0 + \alpha_{j+1/2} \times \frac{\partial \Theta}{\partial x} \bigg|_{j+1/2} \right] = \frac{\alpha_{j+1/2} \times \frac{\partial \Theta}{\partial x} \bigg|_{j+1}}{4} \tag{H-46}
\]

\[
= \frac{\alpha_{j+1/2}}{8 \Delta x} \left[ x_i + 1/2 (\Theta_{i+1,j+1} - \Theta_{i,j+1}) + x_i - 1/2 (\Theta_{i,j+1} - \Theta_{i-1,j+1}) \right] \tag{H-47}
\]

Similarly,

\[
\delta \left[ \frac{\partial^2 \Theta}{\partial x^2} + \frac{1}{4} \frac{\partial \Theta}{\partial x} \right]_{j+1/4} = \frac{\delta}{4} \left[ \frac{\partial^2 \Theta}{\partial x^2} + \frac{1}{4} \frac{\partial \Theta}{\partial x} \right]_{j+1} \tag{H-48}
\]

Since \(\beta(0) = 0\),

\[
\beta(y) \frac{\partial \Theta}{\partial y} \bigg|_{j+1/4} = \frac{1}{2} \beta_{j+1/2} \frac{\partial \Theta}{\partial y} \bigg|_{j+1/2} = \beta_{j+1/2} (\Theta_{i+1,j+1} - \Theta_{i,j})/2 \Delta y \tag{H-49}
\]

\[
\frac{\psi(y)}{Sc} \frac{\partial}{\partial y} \left[ \frac{\psi(y)}{\partial y} \right]_{j+1/4} = \frac{\psi_{j+1/4}}{Sc} \left\{ \frac{\psi_{j+1/2} \frac{\partial \Theta}{\partial y} \bigg|_{j+1/2}}{\Delta y/2} - \frac{\psi_j \frac{\partial \Theta}{\partial y} \bigg|_j}{\Delta y/2} \right\} \tag{H-50}
\]

\[
= \frac{2\psi_{j+1/4} \psi_{j+1/2}}{Sc \Delta y^2} (\Theta_{i+1,j+1} - \Theta_{i,j}) - \frac{2\psi_{j+1/4} \frac{\partial \Theta}{\partial y} \bigg|_{y=0}}{\rho \Delta y \frac{\partial}{\partial y} \bigg|_{y=0}} \tag{H-51}
\]
Equations (H-46) through (H-51) are substituted into eqn. (H-31) without the transient term and $[\partial \Theta / \partial y]_{y=0}$ is evaluated from the steady-state concentration values one slice in from the boundary. From eqn. (H-18),

$$\frac{\partial \Theta}{\partial z} \bigg|_{\zeta=0} = \frac{1}{p} \frac{\partial \Theta}{\partial y} \bigg|_{y=0}$$  \hspace{1cm} (H-52)

The local mass transfer coefficient is defined by

$$\dot{m} = k_x (c_w - c_\infty) = -D \frac{\partial c}{\partial z} \bigg|_{z=0}$$  \hspace{1cm} (H-53)

and

$$\frac{\partial c}{\partial z} \bigg|_{z=0} = (c_w - c_\infty) \sqrt{\frac{\omega}{v}} \frac{\partial \Theta}{\partial \zeta} \bigg|_{\zeta=0}$$  \hspace{1cm} (H-54)

Consequently,

$$k_x = -D \sqrt{\frac{\omega}{v}} \frac{\partial \Theta}{\partial \zeta} \bigg|_{\zeta=0}$$  \hspace{1cm} (H-55)

and

$$\frac{k_x}{\omega b} \left( \frac{\omega b^2}{v} \right)^{1/2} = -\frac{\partial \Theta}{\partial \zeta} \bigg|_{\zeta=0}$$  \hspace{1cm} (H-56)

or

$$St_x Sc Re^{1/2} = -\frac{\partial \Theta}{\partial \zeta} \bigg|_{\zeta=0}$$  \hspace{1cm} (H-57)

From the analytical leading edge solution for high Sc (see Appendix G) and the results for a rotating disk in a stagnant fluid for both high and low Sc (394), one might expect a correlation of the form
\[ St_x \frac{Sc^{2/3}}{Re^{1/2}} = -\frac{1}{Sc} \frac{\partial \theta}{\partial \zeta} \bigg|_{\zeta=0} = f(x) \text{ only} \quad (H-58) \]

for very high Sc and

\[ St_x \frac{Re^{1/2}}{Sc} = -\frac{1}{Sc} \frac{\partial \theta}{\partial \zeta} \bigg|_{\zeta=0} = f(x) \text{ only} \quad (H-59) \]

for very low Sc. Both quantities on the right-hand sides of eqns. (H-58) and (H-59) were calculated. These were essentially trial forms for the correlation. Eqn. (H-58) proved successful for high Sc, while eqn. (H-59) was not successful for low Sc. From pure intuitive physical reasoning, one would actually expect eqn. (H-59) not to hold for the problem studied here. Although it was originally intended to investigate a wide Sc range, the bulk of the useful results were restricted to the high Sc case.

The average mass transfer coefficients were obtained by integrating the slope at the wall across the face of the mass transfer surface. For the high Sc case, this leads to

\[ St_m \frac{Sc^{2/3}}{Re^{1/2}} = -2 \frac{Sc}{Sc^{1/3}} \int_0^1 \frac{\partial \theta}{\partial \zeta} \bigg|_{\zeta=0} \, dx \quad (H-60) \]

The integration was carried out numerically using Simpson's rule and Newton's 3/8th rule (17).

At \( x=0 \), \( k_x \) is infinite, and the numerical solution provides no estimate of the value. Initially, \( k_x \) was linearly extrapolated to \( x=0 \) from the values for the two adjacent grid points. This was later discarded in favor of a more accurate approach. \( St_x \frac{Sc^{2/3}}{Re^{1/2}} \) was calculated from the leading edge solution
of Appendix G,

\[ St_x \cdot Sc^{2/3} \cdot Re^{1/2} = \frac{0.528}{[\ln(b/r)]^{1/3}} \]  

(G-31)

These values were compared with the numerical solution and the grid points where they crossed determined. The point at which the two solutions crossed, \( x_1 \) (generally \( x_1 \approx 0.95 \)), was calculated by linear interpolation between the adjacent grid points. For \( 0 \leq x \leq x_1 \), the numerical solution was integrated, and for \( x_1 \leq x \leq 1 \), eqn. (G-31) was integrated, and the values from the two integrations were added. Integration of eqn. (G-31) was accomplished as follows. For \( b/r = 1 \),

\[ \ln \left( \frac{b}{r} \right) = \frac{b}{r} - 1 = \frac{1}{x} - 1 = x \]  

(H-61)

and

\[ \int_{x_1}^{1} \frac{1}{[\ln(b/r)]^{1/3}} \cdot d\left( \frac{r}{b} \right) = \int_{0}^{x_1} \frac{x^{1-1/3}}{(1+x)^{3}} \cdot dx \]  

(H-62)

Repeated integration by parts yields

\[ \int_{0}^{x_1} \frac{x^{1-1/3}}{(1+x)^{3}} \cdot dx = 1.5 \cdot \frac{x_1^{2/3}}{(1+x_1)^{3}} + 2.7 \cdot \frac{x_1^{5/3}}{(1+x_1)^{6}} + 4.05 \cdot \frac{x_1^{8/3}}{(1+x_1)^{9}} + \ldots \]  

(H-63)

The discussion thus far has been limited to a constant concentration boundary condition at the wall. The second case of interest is replacement of the wall by a membrane. In the batch dialyzer, the fluid dynamic conditions are identical on either side of the membrane. Assuming constant physical properties in all phases and identical liquid phase mass transfer
coefficients on either side of the membrane, the system becomes symmetrical about the plane through the center of the membrane, and the concentration in this plane is constant.

The first boundary condition, eqn.(H-2), must be replaced by

$$z = 0 \quad 0 \leq r \leq b \quad -D \frac{\partial c}{\partial z} = 2p_m (c_m - c_o) \quad (H-64)$$

where $p_m$ is the permeability of the membrane, based upon its full thickness, $c_m$ is the concentration in the center plane of the membrane multiplied by the external solution-membrane distribution coefficient, and $c_o$ is the liquid phase concentration at the membrane surface. Let

$$\Theta = \frac{c - c_m}{c_m - c_\infty} \quad (H-65)$$

$$\Theta_o = \frac{c_o - c_\infty}{c_m - c_\infty}$$

$$\xi_w = \frac{2p_m}{D \sqrt{\frac{W}{V}}} \quad (H-67)$$

Then

$$-D \frac{\partial \Theta}{\partial z} \bigg|_{z=0} = 2p_m (1-\Theta_o) \quad (H-68)$$

$$\frac{\partial \Theta}{\partial \xi} \bigg|_{\xi=0} = -S_h \frac{1-\Theta_o}{(1-\Theta_o)} \quad (H-69)$$

$$\frac{\partial \Theta}{\partial y} \bigg|_{y=0} = -p S_h \frac{(1-\Theta_o)}{(1-\Theta_o)} \quad (H-70)$$
For the permeable wall boundary condition, a new set of finite difference approximations were employed for \( y = 0 \) \( (j = 1) \). Since \( (i) = 0 \), it was necessary to write the radial convection term at the \( j + 1/4 \) point. At time level \( n \) (explicit) the radial convection term was written as in eqn. (H-47), involving only \( j + 1 \) terms. For the implicit solution, time levels \( n \) and \( n + 1 \) were employed for the \( j \) and \( j + 1 \) terms, respectively. Thus,

\[
\frac{a_{j+1/2}}{2} \frac{\partial \Theta}{\partial x} \bigg|_{j+1/2} = \left[ \frac{a_{j+1/2}}{2} \frac{\partial \Theta}{\partial x} \bigg|_{j,n+1} + \frac{1}{2} \frac{\partial \Theta}{\partial x} \bigg|_{j+1,n} \right]
\]

where the \( \partial \Theta / \partial x \) expressions are formulated as before. When marching across the grid in the \( y \) direction and solving the equations at the \( j \) level, information at the \( j+1 \) grid points is not yet available at the \( n+1 \) time level, and the \( n \) time level values must be used to maintain a tridiagonal matrix. Eqn. (H-71) was intuitively considered a better approximation than leaving out the information from the \( j+1 \) points entirely. The axial convection term was expressed as in eqn. (H-49). The radial diffusion term was written as usual (at the \( j \) level), and the axial diffusion term was expressed as in eqn. (H-5i) with \( \partial \Theta / \partial y \bigg|_{y=0} \) replaced by eqn. (H-70).

With the boundary conditions for \( x=0 \) and \( y=1 \) described above, stable solutions were attained over only about two-thirds of the finite difference grid. Instabilities occurred in the region of large \( x \) and large \( y \), where \( \Theta \) decays to its
smallest value. Depending upon the value of \( \zeta \) employed, these instabilities either oscillated (positive-negative) or were amplified to large negative numbers, finally spreading over most of the grid. While the source of these instabilities was never clear, it was believed related to the axial convection term becoming large with respect to the axial diffusion term (408).

The far field solution in Appendix G showed that along the z-axis, the length scale for diffusion was very large and the concentration virtually constant at \( \Theta \sim 1 \) for the values of \( \zeta \) employed in this study. Away from the z-axis, \( \Theta \) dropped sharply and was virtually constant at \( \Theta \sim 0 \). Consequently, based upon these results, two changes were made in the boundary conditions. First, the boundary condition at \( x = 0 \) was replaced by \( g = 1 \). While this tended to stabilize the region near the axis of symmetry, it had little effect elsewhere. Secondly, the far field boundary condition was replaced by

\[
y = 1 \quad \text{all } x \quad \frac{\partial \Theta}{\partial y} = 0 \quad (H-72)
\]

This gave surprising improvement over the whole grid. Instabilities were completely eliminated, although small negative numbers did appear in some portions of the grid where \( \Theta \geq 10^{-3} \). Consequently, eqn.\( (H-72) \) was used for the far field boundary condition, replacing eqn.\( (H-24) \), and all results reported in this study were obtained with this boundary conditions, regardless of the boundary conditions on the other faces of the grid.
Using eqn. (H-72) it was necessary to write finite difference expressions for \( y = 1(J = J + 1) \). The radial terms remained the same as for the interior of the grid and were evaluated at \( j \). The axial terms were evaluated at \( j - 1/4 \) and are given by

\[
\beta(y) \frac{\partial \psi}{\partial y} \bigg|_{j-1/4} = \beta_{j-1/2} \left( \Omega_{i,j - 1} - \Omega_{i,j-1} \right) / 2\Delta y \tag{H-73}
\]

\[
\psi(y) \frac{\partial^2 \psi}{\partial y^2} \bigg|_{j-1/4} = -\frac{2\psi_{j-1/4}}{\Delta y^2} \psi_{j-1/2} \left( \Omega_{i,j} - \Omega_{i,j-1} \right) \tag{H-74}
\]

The imposed boundary condition at \( x = 1, \Omega = 0 \), resulted in some error being propagated into the first one or two axial slices, requiring matching with the analytical leading edge solution. Preliminary attempts were made to modify this boundary condition to give a more realistic representation of the physical situation. The boundary condition was first changed to \( \partial \Omega / \partial x = 0 \), but the numerical values did not significantly change. Next, the grid was extended five radial slices past \( x = 1 \), and insulated boundary conditions imposed on the additional surface. This led to instabilities in the added region which propagated past the leading edge. Further experimentation along these lines was terminated, although it was never verified whether the instabilities were intrinsic in the finite difference method used, or were caused by the formulation of the individual approximations at the extended boundary or unknown errors in the program. A suggested alternative
approach to solve the problem would be to transform the radial coordinate in order to expand the leading edge region, in a similar manner to that employed for the axial coordinate.

Convergence of the steady-state solution was tested by standard procedures. Grid size was varied in both directions independently with the number of grid points ranging from 25 by 25 to 100 by 300. A 50 by 50 grid was judged to give highly accurate results over most of the region of interest except at the leading edge. The convergence criteria usually employed for the attainment of steady state was a relative change of one part in $10^4$. Under these conditions the values of $0$ near the surface ($y=0$) converged to nearly one part in $10^5$. The steady-state solution propagated upwards during the transient, and the number of iterations required to reach steady state over the entire grid depended upon $C_w$ and $Sc$, generally ranging between 40 and 150.

3. **Computer Program**

Table H-1 contains a listing of the computer program for the numerical solution. It was written in Fortran 4 and was run on the IBM 360/65. The large main program calls three subroutines: YCAL calculates all coefficients which are a function of $y$. It contains the velocity components $F$ and $H$ from the solution developed by Bodewadt (46). PROFIL calculates the concentration profiles from the steady-state concentration field, and XMATCH performs the matching of the numerical and leading edge solutions.
Table H-2 is a sample printout of the steady-state solution on a 50 by 50 grid for $\text{Sc} = 10^3$ and $\text{Re} = 10^4$. Successive columns tabulate $\Theta$ as a function of $y$ and $\zeta$ (labeled $z$) for increasing values of $x$. The solution corresponds to $\zeta_\infty = 0.93$. Increasing $\zeta_\infty$ did not alter the concentrations near boundary at all, although the far field values changed slightly.

The steady-state concentration field is followed by an analysis of the slope at the wall ($y=0$). Successive columns tabulate $x$, $\Theta/\Theta_y$, $\Theta/\Theta_\zeta$, $(\Theta/\Theta_\zeta)/\text{Sc}$, $(\Theta/\Theta_\zeta)/\text{Sc}^{1/3}$, and $x(\Theta/\Theta_\zeta)$. The next two columns show 1) the fraction of the total mass transfer rate which occurs in the circular region of radius $x$, and 2) the ratio of the local mass transfer coefficient to the average value. The average quantities are shown at the bottom.

The next section shows the concentration profiles (the value of $\zeta$) as a function of $x$ at which $\Theta = 0.01$, 0.20, 0.50, and 0.80. These quantities are also multiplied by $\text{Sc}$ and $\text{Sc}^{1/3}$.

The following page compares the numerical solution with various analytical solutions generated during the course of the study. Of primary interest are the columns labeled $(\Theta/\Theta_\zeta)/(\text{Re}^{1/2}\text{Sc}^{1/3})$, the numerical solution, and ANAL3, the equivalent quantity from the analytical leaded edge solution of Appendix G.

The last page is a reenact of the first analysis of the slope at the wall. Here, however, the corrected average values contain the matched analytical solution, and the fractional transport and relative mass transfer coefficient ratio have been recalculated on this basis.
Table H-1. Program Listing, Finite Difference Equations for Mass Transfer in the Batch Dialyzer (PDEMTBD)
Table H-2. Sample Output for FDEMHD
(Sc = 10³, Re = 10⁴, 50 x 50 Grid)

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**STEADY STATE SOLUTION**

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**Table H-2 (continued)**

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**AVERAGE GRADIENT IN X  =  -7.610174**  
**DIVIDED BY SC  =  -0.007660**  
**DIVIDED BY SC+1/3  =  -0.766219**  
**AVE GRADIENT IN /SC+1/3  =  -0.761001**  
**DIVIDED BY SC  =  -0.007660**  
**DIVIDED BY SC+1/3  =  -0.766219**
APPENDIX I

Data Reduction for the Batch Dialyzer

1. Overall Approach

The analysis of all data from the batch dialyzer was performed with computer programs written in Fortran 4 for the IBM 360/65. Input data consisted of primary variables and equipment readings.

Concentrations in each chamber were calculated from the impedance comparator measurements and settings for sodium chloride or counting rates and efficiencies, for radioactive solutes (see Appendix D). The natural logarithm of the dimensionless concentration as a function of time was fitted to a straight line with a least squares procedure, and the overall mass transfer coefficient, \( K_o \) obtained from eqn.(3-18). The liquid phase mass transfer coefficients were calculated from eqns.(3-146) and (3-136) and the membrane permeability evaluated from eqn.(3-2). A complete error analysis was performed for each run.

2. Sodium Chloride

Since the diffusivity of sodium chloride in water is concentration-dependent, it was necessary to estimate a time-mean average film concentration for the liquid on each side of the membrane. The diffusivity at infinite dilution was used for the initial estimate of the liquid phase mass transfer coefficient. Then, the average film concentration in each chamber was calculated from
\[
\bar{c}_{1f} = \frac{\bar{c}_1 + \bar{c}_{1s}}{2} \quad (I-1)
\]
\[
\bar{c}_{2f} = \frac{\bar{c}_2 + \bar{c}_{2s}}{2} \quad (I-2)
\]

where
\[
\bar{c}_{1s} = \bar{c}_1 - \bar{c}_1 - \bar{c}^* \Delta c_0 \left( \frac{k_0}{k_f} \right) \quad (I-3)
\]
\[
\bar{c}_{2s} = \bar{c}_2 + \bar{c}^* \Delta c_0 \frac{k_0}{k_f} \quad (I-4)
\]
\[
\Delta c_0 = (c_1 - c_2)_{t=0} \quad (I-5)
\]
\[
\bar{c}_1 = \left[ \bar{c}^* \Delta c_0 + c_{20} + \left( \frac{V_1}{V_2} \right) c_1^0 \right] / \left( 1 + \frac{V_1}{V_2} \right) \quad (I-6)
\]
\[
\bar{c}_2 = \left( \frac{V_1}{V_2} \right) (c_1^0 - \bar{c}_1) + c_{20} \quad (I-7)
\]
\[
c^* = \frac{(c_1 - c_2)_0}{(c_1 - c_2)_t} \quad (I-8)
\]
\[
\bar{c}^* = \frac{1}{\xi} \int_0^t c^* \, dt = (1 - c^*) / \left[ K_0 \ A \left( \frac{1}{V_1} + \frac{1}{V_2} \right) \right] \quad (I-9)
\]

The bar refers to time-mean values, and the subscript \( \text{a} \) refers to liquid concentrations at the membrane surface.

In the iterative process to calculate the liquid phase mass transfer coefficients (see Section 3.D.2), \( \bar{c}_{1f} \) and \( \bar{c}_{2f} \) were continually reevaluated.

3. **Discrete Sampling of Radioactive Solutes**

In order to account for removal of samples during the run and replacement by solution with no tracer, a modification
of eqn. (3-18) was derived. The sampling process was assumed to occur as follows. At \( t_m \), a sample of volume \( V_r \) and concentration \( c_{1m} \) is instantaneously removed from the external circuit sample port. Immediately following this, at time \( t_m^+ \), the sample is instantaneously replaced by a solution of volume \( V_r \) and concentration \( c_r \). The resulting concentration in chamber 1 is denoted by \( c'_{1m} \). Assuming that no concentration change due to permeation occurs during the sampling and replacement interval, i.e., \( t_m^+ = t_m \), then a mass balance on chamber 1 yields

\[
V_1 c'_{1m} = V_1 c_{1m} - V_r c_{1m} + V_r c_r
\]

or

\[
c'_{1m} = c_{1m} + \frac{V_r}{V_1} (c_r - c_{1m})
\]  \hspace{1cm} (I-10)

At time \( t_{m+1} \), another sample is taken from chamber 1 of concentration \( c'_{1m+1} \). The concentration in chamber 2 at \( t_{m+1} \) is obtained from a mass balance, since the total mass in the system at \( t_{m+1} \) is the same as at \( t_m^+ \). Thus,

\[
V_1 c_{1m+1} + V_2 c_{2m+1} = V_1 c'_{1m} + V_2 c_{2m}
\]

or

\[
c_{2m+1} = c_{2m} + \frac{V_1}{V_2} (c'_{1m} - c_{1m+1})
\]  \hspace{1cm} (I-12)

Over the time interval \( t_m \) (more properly \( t_m^+ \)) to \( t_{m+1} \), eqn. (3-18) may be written as
\[
\ln \frac{(c_{1m+1} - c_{2m+1})}{(c'_{1m} - c_{2m})} = -KA \left( \frac{1}{V_1} + \frac{1}{V_2} \right) (t_{m+1} - t_m) \quad (I-14)
\]

Summation over \( n \) time intervals leads to
\[
\sum_{m=0}^{m=n} \ln \frac{(c_1 - c_2)}{(c'_{1m} - c_{2m}) t_{m+1}} = -KA \left( \frac{1}{V_1} + \frac{1}{V_2} \right) t_n \quad (I-15)
\]

Plotting the summation term of each value of \( m \) versus \( t_m \) should lead to a straight line on a semilogarithmic plot. For the first sample, \( c'_{1m} = c_{1m} \) since no replacement solution has yet entered the system.

4. **Time Lag in Concentration Measurement**

The response of the system to a step change in concentration in the chamber being sampled was evaluated experimentally by injecting an aliquot of concentrated saline into one stirred chamber. The recorder trace showed an induction period of about 20 seconds followed by a sigmoidal approach to a new constant value, lasting about 20 seconds. The sigmoidal response was due to axial Taylor dispersion in the external circuit tubing and the induction period represented the time required for the fluid to traverse the distance from the chamber outlet to the conductivity cell. Consequently, the concentration measured had a built-in lag of about 40 seconds. To account for this, zero time was taken as one minute after the run was started and all times were referred to this pseudo-starting point. Since the initial mass added to the system was known, the concentrations in each chamber
could be calculated at zero time.

5. Error Analysis

A complete statistical analysis was obtained from the least-squares test straight line calculation. For almost all runs, correlation coefficients were generally 0.999° and the standard deviation of the slope of the semi-log plot, $s$, was usually less than one percent of the absolute value of the slope. From the equations presented in Chapter 3, the following relations were derived for estimating the standard deviation or variance of each quantity of interest. From eqn.(3-18)

$$\left( \frac{\sigma_{K_0}}{K_0} \right)^2 = \left( \frac{\sigma_S}{S} \right)^2 + \left( \frac{\sigma_A}{A} \right)^2 + \left( \frac{\sigma_V}{V} \right)^2$$  \hspace{2cm} (I-16)

Let $B$ be the exponent of the Schmidt number in eqn.(3-135) and $n$ the impeller speed in rpm, then

$$\left( \frac{\sigma_{k_f}}{k_f} \right)^2 = \left( \frac{\sigma_A}{A} \right)^2 + (\ln Sc)^2 \sigma_B^2 + (\ln Re)^2 \sigma_C^2 + (1-B)^2 \left( \frac{\sigma_D}{D} \right)^2$$

$$+ (B-c)^2 \left( \frac{\sigma_V}{V} \right)^2 + \left( \frac{\sigma_I}{n} \right)^2 \left( \frac{\sigma_n}{n} \right)^2 + (2c-1)^2 \left( \frac{\sigma_b}{b} \right)^2$$  \hspace{2cm} (I-17)

$$\sigma_{P_m}^2 = \sigma_{K_0}^2 + 4\sigma_{k_f}^2$$  \hspace{2cm} (I-18)

Estimates of the variances required for these equations were obtained from the experimental results or from repeated measurements of primary variables. For the diffusivity, the estimates tabulated in Appendix B were employed. All estimates
were permanently built into the computer program.

6. Computer Program Listings and Sample Output

Tables I-1 and I-3 contain program listings for sodium chloride (SCPBD) and radioactive solute (RSPBD) analyses. Each program is followed by a sample output, in Tables I-2 and I-4, which contains a complete analysis of the data.

For SCPBD, MAIN calls five subroutines, RECORD (not listed) converts recorder data to impedance difference measurements. COMPAR converts impedance difference to absolute concentration (see Appendix D) and calculates the log of the dimensionless concentration. LSQ performs the least-squares analysis. MCALC and TCALC are dummy subroutines for calculating weighting coefficients and altering the sample times.

All input is done with NAMELIST. Input variables for SCFD are as follows: RUN = run no.; RPM = impeller speed; TEMP = temperature, °C; AMOUNT, FULL, SCALE, RS = recorder deflection, recorder units for full-scale deflection, impedance comparator scale, and reference resistance; UNITS, RSTART = same as AMOUNT and RS, for initial concentrated solution; N = no. of data points; CONDW = conductivity of distilled water; VOLA, VORB = V₁, V₂, cc; TIME = sample times, min; CONST = conductivity cell constant; T99 = Student t factor for 99% confidence limits; TSTART, TLAG, DELT = initial time, time lag for conductivity measurement, and time increment for samples; WETMIL = membrane wet thickness, mil.
Table I-1 (continued)

<table>
<thead>
<tr>
<th>Column 1</th>
<th>Column 2</th>
</tr>
</thead>
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<tr>
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</tr>
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<td>Data 7</td>
<td>Data 8</td>
</tr>
<tr>
<td>Data 9</td>
<td>Data 10</td>
</tr>
</tbody>
</table>

... (continued)
Table I-2. Sample Output for SCPBD, Run 186 (Cuprophone)

**PERFORMANCE EVALUATION**

**Run No. = 186.2**

| TIME (HRS) | VELOCITY (m/s) | PRESSURE (bar) | TEMPERATURE (°C) | VOLUME (cm³) | CONCENTRATION (ppm) | DENSITY (g/cm³) | SURFACE (m²) | AREA (m²) | FLOW (m³/h) | EFFICIENCY (%) | AIRFLOW (m³/h) | ENERGY (kWh) | POWER (W) | TEMPERATURE (°C) | PRESSURE (bar) | VELOCITY (m/s) | CONCENTRATION (ppm) | DENSITY (g/cm³) | SURFACE (m²) | AREA (m²) | FLOW (m³/h) | EFFICIENCY (%) | AIRFLOW (m³/h) | ENERGY (kWh) | POWER (W) |
|------------|----------------|----------------|------------------|-------------|---------------------|-----------------|-------------|-----------|-------------|----------------|----------------|----------------|--------------|----------|----------------|----------------|----------------|----------------|----------------|-------------|-----------|-------------|----------------|----------------|----------------|----------|
Table I-4. Sample Output for RSPBD, Run 512 (Urea-Cuprophane)

**PEeRMAE PERPCAPABILITY EVALUATION**

**ACTIVE SCHEME**

**RUN NO. = 512.1**

**VOLR = 231.0**

**VCLB = 236.3**

**L = 6**

**COMP = 7**

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<th>TIME</th>
<th>CPM</th>
<th>APS</th>
<th>EPP</th>
<th>DPP</th>
<th>VCLB</th>
<th>CENCA</th>
<th>CENCP</th>
<th>CONCA</th>
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<td>0.8784</td>
<td>2307.9</td>
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<td>0.3029E-05</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
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<td>507.8</td>
<td>0.5454</td>
<td>0.8258</td>
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<td>0.3739E-05</td>
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<td>0.4459E-05</td>
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<td>1.00</td>
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<td>0.1014E-05</td>
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<td>1.50</td>
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<td>0.5481</td>
<td>0.8258</td>
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<td>0.2190E-05</td>
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<td>2.00</td>
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<td>0.8258</td>
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<td>0.3947E-05</td>
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<td>0.5481</td>
<td>0.8258</td>
<td>456.5</td>
<td>1.00</td>
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<td>0.3947E-05</td>
<td>0.3947E-05</td>
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<td>0.8258</td>
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<td>0.3739E-05</td>
<td>0.3947E-05</td>
<td>0.3947E-05</td>
</tr>
</tbody>
</table>

**RATIO**

**PERCENT CONFIDENCE LIMITS**

**INTERCEPT: 0.2450237E-02**

**SLOPE: 0.0115835E-01**

**VARIANCE OF B: 0.1304151E-02**

**PERМEABILITY(CPM/CH): 0.9332E+03**

**RATIO: 0.1269E-01**

**RPE BASED ON MEMBRANE RADIUS: 20582.**

**CHAMBER A**

**TIME MEAN BULK CONC MOLES/LITTER: 2E+05**

**CHAMBER B**

**TIME MEAN SURFACE CONC MOLES/LITTER: 1E+05**

**MEAN H2O MEMBRANE CONC: 1E+04**

**DIFFUSIVITY: 0.1042E-04**

**TOTAL LIQUID**

**VALUE**

**VARIANCE**

**ST DEV**

**PCC**

**TOTAL LIQUID**

**MEMBRANE**

**PERM CP/MCH**

**SHELF**

**DIFF RATIO**
Sample output from run 186 (Cuprophone) is shown in Table I-2. The program first prints the input data, calculated concentration, c*, ln c* and the values calculated from the straight line fit. This is followed by a statistical analysis from the least-squares procedure. The lower part of the output contains the surface and film concentrations and diffusivities in each chamber, followed by a complete summary of the results. The value of each parameter is followed by its variance, standard deviation, per cent standard deviation, and upper and lower 99% confidence limits.

The radioactive solute analysis, RSPBD, is similar to SCPBD. MAIN calls three subroutines. PERM calculates efficiencies, concentrations (dpm/ml), and c*. LSQ is the same as described above. DIFFUS calculates estimated diffusion coefficients and their variances (see Appendix B). Input data different from SCPBD are: COMPD = compound number (see listing); VOLR, CR = V_r, c_r; METHOD = 1, sample from concentrated side, = 2, sample from dilute side; CPM = measured counts per minute; AES = AES ratio (see Appendix D); VOLS = sample volume; BKGD = background count rate; CAB = 0, Bray's solution alone = 1, Bray's plus Cabosil (see Appendix D).

The output for run 512 (urea-cuprophone) is given in Table I-4. Except for some obvious modifications, it is identical with the general format for SCPBD.
APPENDIX J

Batch Dialyzer Permeability Measurements with Organic Solutes

Summary of Results

Table J-1 contains a complete summary of the batch dialyzer permeability measurements with radioactively labeled organic solutes. All runs were made at about 37°C. Column headings are self-explanatory. Columns labeled "S.D." refer to the estimated standard deviation of the quantity in the preceding column. The following column contains the standard deviation expressed in terms of percentage (see Appendix K).

The tabulated results contain one residual error of small consequence. The standard deviation of the ratio of the effective membrane diffusivity to the free liquid diffusivity (second from last column) was calculated assuming $\sigma_D = 0.05D$. More properly, the estimates of $\sigma_D/D$ in Appendix B should be used.

The first eleven runs were made with sampling from the concentrated chamber. The semilogarithmic plot of dimensionless concentration as a function of time was quite scattered and the calculated permeabilities relatively inaccurate. All successive runs were made with sampling from the dilute chamber.

The first set of runs indicated that significant adsorption occurred with inulin, heparin, and dextran. This was confirmed by adsorption experiments in a single dialyzer chamber. Subsequently, these compounds were run in the presence of 10 gm/l unlabeled solute. The effect of concentration on membrane permeability was evaluated with the other solutes. Table J-2 contains a complete summary of the concentration of
unlabeled solutes employed in the permeability measurements. A number of permeability measurements with cuprophane were repeated. Generally the repeat measurements showed high reproducibility. At first, stock solutions were reused repeatedly. However, with several compounds, notably vitamin B\textsubscript{12}, and, to a lesser extent sucrose, permeability increased with successive measurements. Using a fresh solution of vitamin B\textsubscript{12} with the same membrane, the initial permeability measurement was reproduced. It was concluded that the radioactive tracer solute degraded with time. Consequently, the vitamin B\textsubscript{12} stock solution was never reused more than twice. The other solutes were used three or four times. Heparin permeability increased rapidly at first and then leveled off with successive measurements. This was attributed to the polydispersity of heparin (see Appendix B). As a general rule, with the exception of heparin, the first measured permeability for a particular solute-membrane combination was taken to be the correct measurement. These are the values reported in Chapter 3.

All saponified cellulose acetate membranes (Du Pont CA148) were tested for acetyl content. The original membranes contained 39\% (about 2.4 out of a maximum possible 3 acetate groups per anhydroglucose unit). After treatment, they all contained 0 ± 1\% acetyl content. The first series of membranes tested gave extraordinarily high permeabilities. A recheck of the preparation procedure showed that these membranes had been improperly rinsed. It is believed that overexposure to dilute caustic solution (several days) resulted in complete breakdown of the cellulose

<table>
<thead>
<tr>
<th>Membrane Code</th>
<th>Equiv./ml Wet</th>
<th>1.04 ml Wet</th>
</tr>
</thead>
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<td>534.9</td>
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<td>1.07</td>
</tr>
<tr>
<td>535.0</td>
<td>200.0</td>
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<td>1.07</td>
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</table>

**Membrane Ang A Taversch Wt:** 3.01, 2.49 Wt Wt

crystalline regions and scission of the glucose chains, resulting in gross holes which permitted convective transport through the membrane. A careful rinsing procedure (four consecutive changes of distilled water) were employed for the final set of data (runs 579-585).
**TABLE J-2**

Concentration of Unlabeled Organic Solutes Employed in Permeability Measurements

(All runs in isotonic saline)

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<thead>
<tr>
<th>Run</th>
<th>Solute</th>
<th>Conc. gm/kg</th>
<th>Run</th>
<th>Solute</th>
<th>Conc. gm/kg</th>
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</thead>
<tbody>
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<td>512</td>
<td>Urea</td>
<td>10</td>
<td>545</td>
<td>Dextran</td>
<td>10</td>
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<tr>
<td>513</td>
<td>Creatinine</td>
<td>10</td>
<td>547</td>
<td>Dextran</td>
<td>10</td>
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<td>514</td>
<td>Uric Acid</td>
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<td>550</td>
<td>Heparin</td>
<td>10</td>
</tr>
<tr>
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<td>Sucrose</td>
<td>10</td>
<td>551</td>
<td>Heparin</td>
<td>10</td>
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<td>Vit B₁₂</td>
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<td>554</td>
<td>Heparin</td>
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<td>PEG</td>
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<td>Heparin</td>
<td>10</td>
<td>594</td>
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<td>10</td>
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</table>

All other runs were made with tracer solute alone.
APPENDIX K

Error Analysis and Curve Fitting

1. Error Analysis

Throughout this study, the error in quantities calculated from experimental data was estimated by a propagation of error analysis (287). Consider a quantity \( F \) calculated from several measured variables:

\[
F = f(x_1, x_2, \ldots, x_n)
\]  

Associated with each \( x_i \) is a known or estimated variance of that parameter, \( \sigma_{x_i}^2 \). Then the variance in \( F \) is given by

\[
\sigma_F^2 = \sum_{i=1}^{n} \left( \frac{\partial F}{\partial x_i} \right)^2 \sigma_{x_i}^2
\]  

where \( \sigma_F \) is the estimated standard deviation associated with multiple calculated values of \( F \) or the estimated standard error for a single value of \( F \). Where possible, values estimated from Equation (K-2) were compared with experimentally derived quantities from multiple sets of measurements and the higher value was used. Estimates of the various \( \sigma_{x_i} \) were made from repeated measurement of experimental variables.

The standard deviation corresponds to a confidence interval of about \( \pm 68\% \) for a Gaussian distribution. Additional confidence intervals were obtained by multi-
plying the standard deviation by the appropriate "Student" t-factor. For n experimental measurements, the t-factor for n-2 degrees of freedom was employed. When only a single set of data was available, in the use of Equation (K-2) for example, the t-factor for an infinite number of measurements was used.

Often, estimated errors were reported as the "percent standard error" (for a particular confidence limit) defined by

\[ \% \text{ standard error} = \pm 100 \frac{\sigma_f}{F} \]  

(K-3)

The error analysis for the capillary diffusion measurements is discussed in the text of the thesis. For the other experimental investigations, the error analysis was incorporated directly into the computer programs used for data reduction, and these may be found in their respective appendices.

2. Curve Fitting
   a. Linear Relationships

Linear relationships were fitted to the "best" straight line by a least-squares procedure. A general computer program was written to calculate the least-squares straight line for non-uniformly weighted data. The equations given by Bacon (23) were employed in modified form, similar to that given by Hickley, Sherwood, and Reed (287). In the latter reference, however, Equations (2-108) to (2-110) are incorrect and each should be multiplied by the weighted estimate of the variance similar to Equation (2-91).
In general, weighting coefficients were set equal to the reciprocal of the variance of each data point. Where this information was unavailable, the weighting coefficients were set equal to unity. The least-squares straight-line analysis is part of the program for data reduction with the batch dialyzer.

b. Nonlinear Relationships

Two methods were used to fit nonlinear relationships: 1) Chebyshev polynomials and 2) power series polynomials fitted with a least-squares procedure.

The Chebyshev polynomial approximation used corresponded to the following:

\[ y = \sum_{n=0}^{m} C_n T_n(x) \]  
(K-4)

where \( T_0(x) = 1 \)
\( T_1(x) = x \)
\( T_2(x) = 2x^2 - 1 \)

with higher-order terms generated by the recurrence relation

\[ T_{n+1}(x) = 2x T_n(x) - T_{n-1}(x) \]  
(K-5)

The coefficients, \( C_n \), were obtained with SHARE program number 1260 (SOFCHEB) obtained from the M.I.T. Computation Center Library. The program was written in FORTRAN 2 and required equally spaced data for the independent variable, \( x \).

To simplify use of these polynomials, the Chebyshev polynomial coefficients were originally converted to power
series coefficients, \( D_n \), corresponding to the relation

\[
y = \sum_{n=0}^{m} D_n x^n
\]  \hspace{1cm} (K-6)

by adding coefficients of like powers of \( x \) in Equation (K-4). At a later stage of the thesis, a subroutine was added to the IBM Scientific Subroutine Package library which permitted direct evaluation of Chebyshev polynomials, given the coefficients \( C_n \), and evaluation of the power series coefficients was discontinued.

A Chebyshev polynomial approximation has the property that it minimizes the maximum deviation between the tabulated data points and the fitted polynomial over the entire interval. The SHARE program used automatically increased the degree of the approximation in successive calculations (up to a specified maximum) until this maximum deviation reached a minimum. In this way, the degree of the Chebyshev approximation yielding the optimum fit was obtained.

The least-squares polynomial regression employed was taken from the sample program descriptions in the IBM Scientific Subroutine Package manual (17) written in FORTRAN 4. The main program, POLRG, was written as a subroutine and modified to permit up to 20th degree polynomials. The SSP subroutines used were GDATA, ORDER, MINV, and MULTR. When necessary calculations were performed in double precision arithmetic (14 significant decimal digits). The program incorporated an automatic procedure similar to the Chebyshev program. Powers of the independent variable were generated
to calculate polynomials of successively increasing degrees. When there was no reduction in the residual sum of squares between two successive degrees of polynomials, the program terminated, yielding the best-fit polynomial.

The least-square procedure minimizes the squares of the residuals summed over all data points. Empirical comparison of fitted polynomials using both procedures with various types of data indicated a better overall fit for a given degree, particularly at the ends of the interval, with the Chebyshev polynomials. Consequently, this procedure was employed when equally-spaced data were available. In the latter stages of this thesis, the M.I.T. Computation Center no longer supported FORTRAN 2. Rather than rewrite the Chebyshev program, which was fairly complex, the least-squares procedure was used for all data.

3. Fitting Asymptotic S-Shaped Curves

In various phases of this study, it was necessary to fit smooth data defined over the interval zero to infinity. This included fluid-side Sherwood numbers and eigenvalues as a function of wall Sherwood number. A typical graph of the data to be fitted is shown in Figure K-1a. Initial attempts to fit such a curve with least-squares or Chebyshev polynomials produced relatively poor results because of the existence of an asymptotic value of y for x = ∞.

A superior fit was obtained by transforming the data, as follows. The data was plotted as y = f(Z) - f(log x), producing the curve shown in Figure K-1b. The midpoint on
Figure K-1. Fitting Asymptotic S-Shaped Curves
the $y$-axis, $\bar{y}$, was calculated as the mean of the two asymptotic values, and the corresponding value on the $Z$-axis, $\bar{Z}$, was obtained by either graphical interpolation or calculated if an analytical expression relating $y$ to $Z$ was available. Next, the data was normalized about $(\bar{Z}, \bar{y})$ over the intervals $\pm 1$ on the $y$-axis and $\pm \infty$ on the $Z$-axis.

The final transformed data is shown in Figure K-1c. It may be noted that the curve looks qualitatively like the function $\tanh (X)$. If this holds exactly, then the derived relationship is simply $Y = \tanh X$. In general, this is not true, so that a polynomial approximation is required, of the form

$$Y = B_0 + \sum_{n=1}^{N} B_n \, \left[ \tanh X \right]^n \quad (K-7)$$

where

$$Y = \frac{y - \bar{y}}{y(\infty) - \bar{y}} \quad (K-8)$$

$$\bar{y} = \frac{y(\infty) + y(o)}{2} \quad (K-9)$$

$$X = Z - \bar{Z} \quad (K-10)$$

$$Z = \log x \quad (K-11)$$

Finally, once the polynomial fit of $Y$ is obtained, $y$ can be calculated for a given $x$ from
\[ y = Y [y(\infty) - \bar{y}] + \bar{y} \]  \hspace{1cm} (K-12)

Using this procedure, it was possible to obtain extremely high accuracy in the fit of \( y \) as a function of \( x \). This was particularly necessary in fitting the eigenvalues for the parallel plate dialyzer theoretical model.
APPENDIX L

Derivation of Expansion Coefficients for Modified Graetz Solution

The equation of interest, eqn. (5-57), may be written as

\[
\frac{d^2 Y_m}{dy^2} + \beta_m^2 (1 - 4y^2) Y_m = 0 \quad (L-1)
\]

with boundary conditions

B.C. 1 \quad y = 0 \quad \frac{dY_m}{dy} = 0 \quad (L-2)

B.C. 2 \quad y = \pm 1/2 \quad \frac{dY_m}{dy} = \pm Sh_w Y_m \quad (L-3)

It is desired to evaluate the definite integrals in the expression

\[
A_m = \frac{\int_{-1/2}^{1/2} (1-4y^2) Y_m \, dy}{\int_{-1/2}^{1/2} (1-4y^2) Y_m^2 \, dy} \quad (L-4)
\]

For simplicity, note that, for even functions (as required by B.C. 2)

\[
\int_{-1/2}^{1/2} Z \, dx = 2\int_{0}^{1/2} Z \, dx \quad (L-5)
\]

The numerator of eqn. (2-4) may be determined by rearranging eqn. (L-1). Thus

\[
\int_{0}^{1/2} (1 - 4y^2) Y_m \, dy = -\frac{1}{\beta_m^2} \int_{0}^{1/2} \frac{d^2 Y_m}{dy^2} \, dy \quad (L-6)
\]
\[
\int_0^{1/2} y_m \left. \frac{\delta}{\delta y} \left[ \frac{\partial y_m}{\partial \beta_m} \right] \right|_{y} \, dy + 2\beta_m \int_0^{1/2} \omega(y) \, y_m^2 \, dy
+ \beta_m^2 \int_0^{1/2} \omega(y) \left[ \frac{\partial y_m}{\partial \beta_m} \right] \, y_m \, dy = 0 \tag{L-13}
\]

The first term in eqn. (L-13) may be integrated by parts.

Let
\[
\int_0^{1/2} y_m \left. \frac{\delta}{\delta y} \left[ \frac{\partial y_m}{\partial \beta_m} \right] \right|_{y} \, dy = \int_a^b u \, dV \tag{L-14}
\]

where

\[
u = y_m \tag{L-15}
\]

\[
du = \frac{\partial y_m}{\partial y} \, dy \tag{L-16}
\]

\[
dV = \left[ \frac{\partial}{\partial y} \left( \frac{\partial y_m}{\partial \beta_m} \right) \right] \, dy \tag{L-17}
\]

\[
V = \frac{\partial}{\partial y} \left( \frac{\partial y_m}{\partial \beta_m} \right) \tag{L-18}
\]

Then
\[
\int_a^b u \, dV = uv \bigg|_a^b - \int_a^b v \, du \tag{L-19}
\]

\[
= \left[ y_m \left\{ \frac{\partial}{\partial y} \left( \frac{\partial y_m}{\partial \beta_m} \right) \right\} \right]^{1/2} \int_0^{1/2} \left[ \frac{\partial}{\partial y} \left( \frac{\partial y_m}{\partial \beta_m} \right) \right] \, \frac{\partial y_m}{\partial y} \, dy \tag{L-20}
\]

Integrating the second term in eqn. (L-20) by parts, let

\[
u = \frac{\partial y_m}{\partial y} \tag{L-21}
\]

\[
du = \frac{\partial}{\partial y} \left[ \frac{\partial y_m}{\partial y} \right] \, dy \tag{L-22}
\]
\[-695-\]

\[= - \frac{1}{\beta_m^2} \int_0^{1/2} \frac{d}{dy} \left( \frac{d}{dy} Y_m \right) dy \quad \text{ (L-7)}\]

\[= - \frac{1}{\beta_m^2} \frac{d}{dy} Y_m \bigg|_{y=1/2} \quad \text{ (L-8)}\]

From B.C. 2,

\[\frac{d Y_m}{dy} \bigg|_{y=1/2} = - Sh_w Y_m(1/2) \quad \text{ (L-9)}\]

Thus,

\[\int_0^{1/2} (1 - 4y^2) Y_m dy = \frac{Sh_w Y_m(1/2)}{\beta_m^2} \quad \text{ (L-10)}\]

Integration of the denominator is more complex. The treatment here is analogous to that of Lundberg, et al. (260). Let \((1-4y^2)\) be denoted by \(\omega(y)\). Differentiating eqn.(2-1) with respect to \(\beta_m\) yields

\[\frac{\partial}{\partial \beta_m} \left[ \frac{\partial}{\partial y} \left( \frac{\partial Y_m}{\partial y} \right) \right] + 2\beta_m \omega(y) Y_m + \beta_m^2 \omega(y) \frac{\partial Y_m}{\partial \beta_m} = r \quad \text{ (L-11)}\]

The order of partial differentiation of the first term may be reversed to give

\[\frac{\partial}{\partial y} \left[ \frac{\partial}{\partial y} \left( \frac{\partial Y_m}{\partial \beta_m} \right) \right] + 2\beta_m \omega(y) Y_m + \beta_m^2 \omega(y) \frac{\partial Y_m}{\partial \beta_m} = 0 \quad \text{ (L-12)}\]

Multiplying by \(Y_m\) and integrating over \(y\), one obtains
\[ \text{d}V = \frac{\partial}{\partial y} \left( \frac{\partial y_m}{\partial \beta_m} \right) \text{d}y \quad \text{(L-23)} \]

\[ V = \frac{\partial y_m}{\partial \beta_m} \quad \text{(L-24)} \]

Thus,
\[ \int_0^{1/2} \frac{\partial}{\partial y} \left( \frac{\partial y_m}{\partial \beta_m} \right) \frac{\partial y_m}{\partial y} \text{d}y = \left[ \frac{\partial y_m}{\partial y} \frac{\partial y_m}{\partial \beta_m} \right]_0^{1/2} \left[ \frac{\partial y_m}{\partial y} \frac{\partial y_m}{\partial \beta_m} \right]_0^{1/2} - \int_0^{1/2} \frac{\partial y_m}{\partial \beta_m} \frac{\partial}{\partial y} \left( \frac{\partial y_m}{\partial y} \right) \text{d}y \quad \text{(L-25)} \]

Combining eqns. (L-20) and (L-25) yields
\[ \int_0^{1/2} y_m \frac{\partial}{\partial y} \left( \frac{\partial y_m}{\partial \beta_m} \right) \text{d}y = \left[ y_m \frac{\partial}{\partial y} \frac{\partial y_m}{\partial \beta_m} \right]_0^{1/2} - \left[ \frac{\partial y_m}{\partial \beta_m} \frac{\partial y_m}{\partial y} \right]_0^{1/2} \]

\[ + \int_0^{1/2} \frac{\partial y_m}{\partial \beta_m} \frac{\partial}{\partial y} \left( \frac{\partial y_m}{\partial y} \right) \text{d}y \quad \text{(L-26)} \]

Substitution of eqn. (L-26) into eqn. (L-13) gives
\[ 2\beta_m \int_0^{1/2} \omega(y) y_m^2 \text{d}y = \left[ \frac{\partial y_m}{\partial y} \frac{\partial y_m}{\partial \beta_m} \right]_0^{1/2} - \left[ y_m \frac{\partial}{\partial y} \frac{\partial y_m}{\partial \beta_m} \right]_0^{1/2} \]

\[ - \int_0^{1/2} \frac{\partial y_m}{\partial \beta_m} \left\{ \frac{\partial}{\partial y} \left( \frac{\partial y_m}{\partial y} \right) + \beta_m^2 \omega(y) y_m \right\} \text{d}y = 0 \quad \text{(L-27)} \]

The quantity in brackets in the third term is identical with eqn. (L-1) and thus the integral vanishes. The order of differentiation in the second term may be interchanged. Then, noting that \( \partial y_m / \partial y = 0 \) at \( y = 0 \) from the first boundary condition and that this condition is invariant with changes in \( \beta_m \).
one finds

\[ 2\beta_m \int_0^{1/2} \omega(y) Y_m^2 \, dy = \frac{\partial Y_m}{\partial y} \left| \begin{array}{c} \frac{\partial Y_m}{\partial \beta_m} \\ \end{array} \right|_{y=1/2} - Y_m \frac{\partial}{\partial \beta_m} \left( \frac{\partial Y_m}{\partial y} \right) \right|_{y=1/2} \]

(L-28)

From the second boundary condition, note that

\[ \frac{dY_m}{dy} \bigg|_{y=1/2} = -Sh_w \dot{Y}_m(1/2) \]  \hspace{1cm} (L-29)

and

\[ Y_m(1/2) = -\frac{1}{Sh_w} \frac{dY_m}{dy} \bigg|_{y=1/2} \]  \hspace{1cm} (L-30)

Consequently,

\[ \frac{\partial}{\partial \beta_m} \left( \frac{\partial Y_m}{\partial y} \right) \bigg|_{y=1/2} = -\frac{dSh_w}{d\beta_m} Y_m(1/2) - Sh_w \frac{\partial Y_m(1/2)}{\partial \beta_m} \]  \hspace{1cm} (L-31)

and

\[ Y_m \frac{\partial}{\partial \beta_m} \left( \frac{\partial Y_m}{\partial y} \right) \bigg|_{y=1/2} = - Y_m^2(1/2) \frac{dSh_w}{dC_m} + \frac{\partial Y_m}{\partial y} \bigg|_{y=1/2} \frac{\partial Y_m(1/2)}{\partial \beta_m} \]  \hspace{1cm} (L-32)

Finally, combination of eqns. (L-28) and (L-32) yields the desired relationship:

\[ \int_0^{1/2} (1-4y^2) Y_m^2 \, dy = \frac{Y_m^2(1/2)}{2\beta_m} \frac{dSh_w}{d\beta_m} \]  \hspace{1cm} (L-33)

Consequently,

\[ A_m = \frac{2Sh_w}{Y_m(1/2) \beta_m \frac{dSh_w}{d\beta_m}} \]  \hspace{1cm} (L-33)
APPENDIX M

Entrance Region Solutions for Flat Plate Dialyzer

1. Perturbation Analysis

In the entrance region of the dialyzer, where the concentration boundary layer is small with respect to the half width of the dialyzer, the velocity may be assumed to be a linear function of the distance from the wall and proportional to the velocity gradient at the wall. Thus, eqn.(5-2) may be written

\[ V_0 y \frac{\partial c}{\partial x} = D \frac{\partial^2 c}{\partial y^2} \quad (M-1) \]

where for flat plates

\[ V_0 = \frac{6v}{h} \quad (M-2) \]

with boundary conditions

B.C.1 \( x = 0 \) \ all \( y \) \( c = c_i \) \quad (M-3)

B.C.2 \ all \( x \) \( y \to \infty \) \( c \to c_i \) \quad (M-4)

B.C.3 \ all \( x \) \( y = 0 \) \( D \frac{\partial c}{\partial y} = k_w(c_w - c_o) \) \quad (M-5)

Here \( y \) refers to the distance from the wall. Using the dimensionless variables defined by eqns.(5-10), (5-11) and (5-23), the differential equation and third boundary condition may be restated as

\[ 6y^* \frac{\partial c^*}{\partial x^*} = \frac{\partial^2 c^*}{\partial y^{*2}} \quad (M-6) \]

B.C.4 \ all \( x^* \) \( y^* = 0 \) \( \frac{\partial c^*}{\partial y^*} = Sh_w(c_w - c_o) \) \quad (M-7)
For constant concentration (247) and constant flux (36a) boundary conditions, a similarity transformation of the form,

\[ Y = y \left( \frac{V_o}{9 \times D} \right)^{1/3} \quad (M-8) \]

\[ \equiv Ay^* x^{-1/3} \quad (M-9) \]

where A is a constant, may be employed to reduce eqn. (M-6) to a second order ordinary differential equation which is readily solved. Such a classical Leveque-type transformation, however, does not apply here because it does not satisfy the third boundary condition.

A solution to eqn. (M-6) and its boundary conditions was obtained for "near constant flux" conditions by perturbing the constant flux solution. The specific formulation of the perturbation analysis was due to Professor K. A. Smith. In it, one assumes the form of the solution to be

\[ c = c_i + (c_i - c_o) [\varepsilon f(\xi) + \varepsilon^2 f_2(\xi) + \ldots] \quad (M-10) \]

where

\[ \varepsilon = \left( \frac{K_wh}{D} \right)^{1/3} \left( \frac{xD}{6\bar{V}h^2} \right) \quad (M-11) \]

\[ = 6^{-1/3} \text{Sh}_w x^{1/3} \quad (M-12) \]

and

\[ \xi = y \left( \frac{6\bar{V}}{xDh} \right)^{1/3} \quad (M-13) \]

\[ = 6^{1/3} y^* x^{-1/3} \quad (M-14) \]

\( \xi \) is identical with Y defined by eqn. (M-8) except for a
constant. A perturbation solution of this type will be valid for $\epsilon \ll 1$, or $Sh_{\infty}^{1/3}, \ll 1$.

Substituting eqn. (M-10) into eqn. (M-6), and considering only the first two terms, yields

$$6y^* \left[ \frac{\partial \epsilon}{\partial x^*} f_1 + \epsilon f_1' + 2\epsilon \frac{\partial f_2}{\partial x^*} + \epsilon^2 f_2'' \frac{\partial \epsilon}{\partial x^*} \right]$$

$$= \left[ \epsilon f_1'' \left( \frac{\partial \epsilon}{\partial y^*} \right)^2 + \epsilon^2 f_2'' \left( \frac{\partial \epsilon}{\partial y^*} \right)^2 \right]$$

(M-15)

where primes denote differentiation with respect to $\xi$. Since

$$\frac{\partial \epsilon}{\partial x^*} = \frac{\epsilon}{3x^*}$$

(M-16)

$$\frac{\partial \epsilon}{\partial x} = - \frac{\epsilon}{3x^*}$$

(M-17)

$$\frac{\partial \epsilon}{\partial y^*} = 6^{1/3} x^{-1/3}$$

(M-18)

one obtains

$$6y^* \left[ \frac{\epsilon}{3x^*} f_1 + \epsilon f_1' \left( - \frac{\epsilon}{3x^*} \right) + 2\epsilon \left( \frac{\epsilon}{3x^*} \right) f_2 + \epsilon^2 f_2'' \left( \frac{\epsilon}{3x^*} \right) \right]$$

$$= 6^{2/3} x^{-2/3} \left[ \epsilon f_1'' + \epsilon^2 f_2'' \right]$$

(M-19)

Noting that

$$\frac{6y^*}{6^{2/3} x^{-2/3} \cdot \frac{1}{3x^3}} = \frac{1}{3} \xi$$

(M-20)

eqn. (M-19) simplifies to

$$\frac{1}{3} \xi \left[ f_1 - \xi f_1' + \xi \left( 2f_2 - \xi f_2' \right) \right] = f_2'' + \epsilon f_2''$$

(M-21)
or
\[
\left[ f_1'' + \frac{1}{3} \xi^2 f_1' - \frac{1}{3} \xi f_1 \right] + \xi \left[ f_2'' + \frac{1}{3} \xi^2 f_2' - \frac{2}{3} \xi f_2 \right] = 0
\]  
(M-22)

Thus, one obtains a second order ordinary differential equation for both \( f_1 \) and \( f_2 \):

\[
f_1'' + \frac{1}{3} \xi^2 f_1' - \frac{1}{3} \xi f_1 = 0
\]  
(M-23)

\[
f_2'' + \frac{1}{3} \xi^2 f_2' - \frac{2}{3} \xi f_2 = 0
\]  
(M-24)

with boundary conditions

\[
\xi \to \infty \quad f_1 \to 0
\]  
(M-25)

\[
\xi \to \infty \quad f_2 \to 0
\]  
(M-26)

From the third boundary condition, eqn. (M-7), one obtains, upon substitution of eqn. (M-10)

\[
(c_1 - c_0) \left. \frac{\partial f}{\partial y} \right|_{y = 0} = Sh_w \left( c_1' + (c_1 - c_0) \right)
\]

\[
\left. \left[ \epsilon f_1 + \epsilon^2 f_2 \right] \right|_{y = 0} = 0
\]  
(M-27)

or

\[
\frac{\epsilon}{Sh_w} \left. \frac{\partial \xi}{\partial y} \right|_{y = 0} = 1
\]  
(M-28)

Since

\[
\frac{\epsilon}{Sh_w} \left. \frac{\partial \xi}{\partial y} \right|_{y = 0} = 1
\]  
(M-29)

eqn. (M-28) yields

\[
\left[ f_1'(o) - 1 \right] + \epsilon \left[ f_2'(o) - f_1(o) \right] = 0
\]  
(M-30)
and the second boundary condition on \( f_1 \) and \( f_2 \) is

\[
\xi = 0 \quad f_1'(0) = 1 \quad (M-31)
\]
\[
\xi = 0 \quad f_2'(0) = f_1(o) \quad (M-32)
\]

If eqn. (M-23) is divided by \( \xi \), differentiated with respect to \( \xi \), then multiplied by \( \xi^2 \) and rearranged, one finds

\[
\xi f_1'''' + (\frac{1}{3} \xi - 1) f_1'' = 0 \quad (M-33)
\]

Letting

\[
\chi = g^{-1/3} \xi \quad (M-34)
\]

\[
Q(\chi) = \frac{d f_1(\xi)}{d \xi} = f_1' \quad (M-35)
\]

yields

\[
\chi Q'' + (3\chi^3 - 1)Q' = 0 \quad (M-36)
\]

with

\[
\chi = 0 \quad Q = 1 \quad (M-37)
\]
\[
\chi = \infty \quad Q = 0 \quad (M-38)
\]

This is precisely the equation obtained by Bird (360) for the constant flux case, for which the solution is

\[
Q = \frac{3}{\Gamma(2/3)} \int_{\chi}^{\infty} xe^{-x^3} \, dx \quad (M-39)
\]

\[
= \frac{\Gamma(2/3, \chi^3)}{\Gamma(2/3)} \quad (M-40)
\]

where \( \Gamma(2/3, \chi^3) \) is an incomplete gamma function. Finally, integrating eqn. (M-35) gives
\[
\int \frac{f_1(\xi)}{f_1(\xi)} \, df_1(\xi) = - f_1(\xi) = \int_{\chi}^{\chi_{\infty}} Q(x) \, dx = 9^{1/3} \int_{\chi}^{\infty} Q(x) \, dx \quad (M-41)
\]

and

\[
f_1(\xi) = - 9^{1/3} \int_{9^{1/3} \xi}^{\infty} Q(9^{-1/3} \xi) \, d(9^{-1/3} \xi) = - \frac{3(9^{1/3})}{\Gamma(2/3)}
\]

\[
\int_{9^{-1/3} \xi}^{\infty} \left[ \int_{9^{-1/3} \xi}^{\infty} (9^{-1/3} \xi) e^{-3 \xi^3} \, d(9^{-1/3} \xi) \right] \, d(9^{-1/3} \xi) \quad (M-42)
\]

Using Bird's solution, one obtains

\[
f_1(\xi) = - 9^{1/3} \left[ \frac{9^{-1/3} \xi^{1} e^{-3 \xi^3}}{\Gamma(2/3)} - 9^{-1} \xi^{3} \left( 1 - \frac{\Gamma(2/3, 9^{-1/3} \xi^{3})}{\Gamma(2/3)} \right) \right] \quad (M-43)
\]

At \( \xi = 0 \),

\[
f_2'(0) = f_1(0) = - \frac{9^{1/3}}{\Gamma(2/3)} \approx - 1.536
\]

It is clear from this analysis that the \( f_1 \) term alone in eqn. (M-10) corresponds to a Leveque type constant-flux solution for a parallel plate channel. Consequently, the \( f_2 \) term is a first order correction to the constant flux solution for finite, non-zero \( Sh_w \). The analogy with Bird's formulation may be seen more clearly by defining a dimensionless concentration using only the \( f_1 \) term in eqn. (M-10) as

\[
\theta = \frac{c - c_i}{Sh_w(c_i - c_0)} = 6^{-1/3} \chi^{1/3} f_1(\xi) \quad (M-45)
\]
which is analogous to Bird's eqn. (23) and leads to the relationships shown in eqns. (M-41) to (M-44).

An analytical solution to \( f_2 \) could not be readily obtained. Therefore, the differential equation (M-24) was integrated numerically. The equation of interest may be written as

\[
y'' + \frac{1}{3} x^2 y' - \frac{2}{3} x^2 y = 0
\]  
(M-46)

with boundary conditions

\[
X = 0 \quad y' = \frac{9^{1/3}}{r(\frac{2}{3})}
\]
(M-47)

\[
X = \infty \quad y = 0
\]
(M-48)

Let \( y_1 \equiv y \equiv f_2 \)

\[
y_2 \equiv y'
\]
(M-49)
(M-50)

Equation (M-46) becomes

\[
\frac{dy_2}{dx} + \frac{1}{3} x^2 y_2 - \frac{2}{3} x y_1 = 0
\]
(M-51)

\[
\frac{dy_1}{dx} - y_2 = 0
\]
(M-52)

with boundary conditions

\[
X = 0 \quad y_2 = -\frac{9^{1/3}}{r(\frac{2}{3})}
\]
(M-53)

\[
X = \infty \quad y_1 = 0
\]
(M-54)

The set of equations and boundary conditions (M-51) through (M-54) was integrated numerically using Hamming's modified predictor-corrector method for the solution of general
initial-value problems. The integration was performed on the IBM 360/65 digital computer in double precision using subroutine DHPCG from the IBM Scientific Subroutine Package (17). It is a fourth-order method which uses a fourth-order Runge-Kutta procedure for adjustment of the initial increment and for computation of the starting values. The solution was checked by altering 1) the initial increment and 2) the accuracy criterion which causes bisection of the x increment if not met.

To obtain the true solution to the differential equations, it was necessary to start with the correct initial condition for \( y_1 \), which was unknown. A trial and error procedure was used. Several values for \( y_1(0) \) were guessed and the solutions calculated. From the behavior at large \( x \), new guesses were made. The procedure was repeated until the solution for \( y_1 \) at \( x = 25 \) asymptoted to \( \pm 10^{-4} \). To obtain five significant digits in \( y_1(0) \), approximately 40 evaluations were required.

The solutions for \( f_1 \) and \( f_2 \) are shown in Fig. M-1. Since both initial values for \( f_1 \) were known, the solution for \( f_1 \) was also calculated numerically, although eqn.(M-43) could have been used. The initial condition for \( f_2 \) was found to be

\[
f_2(0) = 2.0842.
\]

The local Sherwood numbers were evaluated as follows. For the overall mass transfer coefficient,

\[
D \frac{\partial c}{\partial y} \bigg|_{y=0} = k_{x,0} (c_1 - c_0) \quad (M-55)
\]
or
\[ Sh_{x, o} = \frac{k_x, o h}{D} = \frac{1}{(c_1 - c_0)} \left. \frac{\partial c}{\partial y} \right|_{y^* = 0} \]

Now, from eqn. (M-10)
\[ \left. \frac{\partial c}{\partial y} \right|_{y^* = 0} = (c_1 - c_0) \left. \frac{\partial \xi}{\partial y} \right|_{y^* = 0} \varepsilon \left[ f_1'(0) + \varepsilon f_2'(0) \right] \]

Thus,
\[ Sh_{x, o} = \left. \frac{\partial \xi}{\partial y} \right|_{y^* = 0} \varepsilon \left[ f_1'(0) + \varepsilon f_2'(0) \right] \]

\[ = (6^{1/3} x^{*-1/3}) \left( 6^{-1/3} Sh_w x^{1/3} \right) \left[ 1 - 6^{-1/3} Sh_w x^{1/3} \frac{9^{1/3}}{\Gamma(2/3)} \right] \]

\[ = Sh_w \left[ 1 - 6^{-1/3} \frac{9^{1/3}}{\Gamma(2/3)} Sh_w x^{1/3} \right] \]

\[ = Sh_w \left[ 1 - 0.8453 \right] \]

As expected, the overall Sherwood number tends to \( Sh_w \) as \( x^* \) tends to zero. For \( Sh_w = 0 \), \( Sh_{x, o} = 0 \).

The fluid-side mass transfer coefficient is defined by
\[ D \left. \frac{\partial c}{\partial y} \right|_{y = 0} = -k_{x, f} (c_1 - c_w) \]

and
\[ Sh_{x, f} = \frac{k_{x, f h}}{D} = \frac{1}{c_1 - c_w} \left. \frac{\partial c}{\partial y} \right|_{y^* = 0} \]

\( c_w \) is evaluated at \( y = 0 \). Thus,
\[ c_1 - c_w = c_1 - \left( c_1 + (c_1 - c_0)[\varepsilon f_1'(0) + \varepsilon^2 f_2'(0)] \right) \]

\[ = (c_1 - c_0) \left[ \varepsilon f_1'(0) + \varepsilon^2 f_2'(0) \right] \]
Combining eqns. (M-57), (M-63), and (M-65) gives

\[ Sh_{x,f} = \frac{\frac{\partial E}{\partial y} \epsilon [f_1'(o) + \epsilon f_2(o)]}{[\epsilon f_1(o) + \epsilon^2 f_2(o)]} \]

\[ = \frac{\frac{\partial E}{\partial y} [f_1'(o) + \epsilon f_2'(o)]}{f_1(o) + \epsilon f_2(o)} \]  

(M-66)

(M-67)

\[ = -6^{1/3} x^{-1/3} \left[ 1 - 6^{-1/3} Sh_w x^{*1/3} \frac{g^{1/3}}{\Gamma(2/3)} \right] \]

\[ - \frac{g^{1/3}}{\Gamma(2/3)} + 6^{-1/3} Sh_w x^{*1/3} (2.0842) \]

(M-68)

\[ = 1.817 x^{-1/3} \left[ 1 - 0.8453 Sh_w x^{*1/3} \frac{1.5361 - 1.147 Sh_w x^{*1/3}}{1.5361} \right] \]  

(M-69)

The expression for \( Sh_{x,f} \) may be simplified. Factoring \( f_1(o) \) from the denominator of eqn. (M-67) yields

\[ Sh_{x,f} = -\frac{1}{f_1(o)} \frac{\partial E}{\partial y} \frac{f_1'(o) + \epsilon f_2'(o)}{1 + \epsilon \frac{f_2(o)}{f_1(o)}} \]  

(M-70)

Since \( f_1(o) \) and \( f_2(o) \) are of order unity, and \( \epsilon \ll 1 \),

\[ \frac{1}{1 + \epsilon \frac{f_2(o)}{f_1(o)}} \leq 1 - \epsilon \frac{f_2(o)}{f_1(o)} \]  

(M-71)
Thus,
\[
Sh_{x,f} = -\left[ \frac{1}{f_1'(0)} \frac{\partial \xi}{\partial y} f_1'(0) + \varepsilon f_2'(0) \right] \left[ 1 - \varepsilon \frac{f_2(o)}{f_1(o)} \right]
\]  \hspace{1cm} (M-72)

The term in brackets is
\[
f_1'(0) + \varepsilon f_2'(0) - \varepsilon f_1'(0) \frac{f_2(o)}{f_1(o)} - \varepsilon^2 f_2'(0) \frac{f_2(o)}{f_1(o)}
\]  \hspace{1cm} (M-73)

Dropping the term of order \( \varepsilon^2 \) and substituting for the other terms from eqns. (M-31) and (M-32) yields
\[
Sh_{x,f} = -\frac{1}{f_1(o)} \frac{\partial \xi}{\partial y} \left[ 1 + \varepsilon \left( f_1(0) - \frac{f_2(o)}{f_1(o)} \right) \right]
\]  \hspace{1cm} (M-74)

\[
= -\frac{\Gamma(\frac{2}{3})}{\Gamma(\frac{1}{3})} 6^{1/3} x^{-1/3} \left[ 1 + 6^{-1/3} \frac{\Gamma(\frac{1}{3})}{\Gamma(\frac{2}{3})} \frac{9^{1/3}}{9^{1/3}} + \frac{2.0482}{9^{1/3}} \frac{\Gamma(\frac{2}{3})}{\Gamma(\frac{1}{3})} \right]
\]  \hspace{1cm} (M-75)

\[
= 1.1829 x^{-1/3} \left[ 1 - 0.1116 Sh_w x^{1/3} \right]
\]  \hspace{1cm} (M-76)

\[
= 1.1829 x^{-1/3} - 0.1320 Sh_w
\]  \hspace{1cm} (M-77)

From eqn. (M-77) several conclusions may be drawn:

1) For \( Sh_w = 0 \), \( Sh_{x,f} \) is given by the constant flux expression.

2) At sufficiently small \( x* \), \( Sh_{x,f} \) approaches the constant flux value for any \( Sh_w \).

3) As \( x* \) increases from a very low value, \( Sh_{x,f} \) for successively lower values of \( Sh_w \) will "peel off" the constant flux curve.
2. *Boundary-Layer Analysis*

Grimsrud and Babb (153,154) developed a Karman-Polhausen-type boundary-layer analysis for a parallel plate dialyzer. They assumed that the concentration profile could be expressed as a polynomial of the form (assuming $c_0 = 0$):

$$c = c_i \left[ A + B \frac{Y}{\delta} + C \left( \frac{Y}{\delta} \right)^2 + E \left( \frac{Y}{\delta} \right)^3 \right]$$

(M-78)

where $\delta$ is the concentration boundary layer thickness, which is a function of $x^*$ and $Sh_w$, and $A$, $B$, $C$, and $E$ are functions of $Sh_w$ and $\delta$.

The reader is referred to the original works for details of the derivation. Of interest here is a comparison of the solution with the model developed in this study. Grimsrud and Babb found the solution for $c$ to be, for $y \leq \delta$:

$$c = c_i \left[ \frac{3D + 3k_w y - k_w \frac{y^3}{\delta^2}}{3D + 2k_w \delta} \right]$$

(M-79)

Consequently,

$$\frac{\partial c}{\partial y} \bigg|_{y=0} = c_i \frac{(3k_w)}{3D + 2k_w \delta}$$

(M-80)

and

$$c_i - c_w = c_i \left[ 1 - \frac{3D}{3D + 2k_w \delta} \right]$$

(M-81)

Using the Sherwood number definitions from eqns. (M-56) and (M-63), one obtains
\[ Sh_{x,0} = \frac{3 k_w h}{3D + 2k_w \delta} \]  \hspace{1cm} (M-82)

\[ = \frac{k_w h}{D} \left[ \frac{1}{1 + \frac{2}{3} \left( \frac{k_w h}{D} \right) \frac{\delta}{h}} \right] \]  \hspace{1cm} (M-83)

\[ = Sh_w \left[ \frac{1}{1 + \frac{2}{3} Sh_w (\frac{\delta}{h})} \right] \]  \hspace{1cm} (M-84)

and

\[ Sh_{x,f} = \frac{3 k_w h}{2k_w \delta} = \frac{1}{\frac{2}{3} (\frac{\delta}{h})} \]  \hspace{1cm} (M-85)

It should be noted that the overall Sherwood number defined by eqn. (M-84) is different from that used by Grimsrud and Babb (154, eqn. (38)) which is based on the concentration driving force \((c_b - c_o)\). Their result may be expressed as

\[ Sh_{x,0} = \frac{k_{x,o} h}{D} = \frac{6}{\eta a^4 + \frac{3\eta a^3}{5} + 2\eta + 3K} \]  \hspace{1cm} (M-86)

where

\[ y = \frac{\delta}{a} = 2 \frac{\delta}{h} \]  \hspace{1cm} (M-87)

\[ K = \frac{D}{k_w a} = \frac{2}{Sh_w} \]  \hspace{1cm} (M-88)

However, for \( y \ll 1 \), eqn. (-86) reduces to eqn. (M-85), which is reasonable since then \( c_b \approx c_i \). From eqn. (M-86), one may calculate the fluid-side Sherwood number directly as

\[ \frac{1}{Sh_{x,f}} = \frac{1}{Sh_{x,0}} - \frac{1}{Sh_w} \]  \hspace{1cm} (M-89)
Thus,
\[
Sh_{x,f} = \frac{6}{\frac{n^6}{8} + \frac{3n^3}{5} + 2n}
\]  \hspace{1cm} (M-90)

which reduces to eqn. (M-85) for small \(n\).

In order to use these equations, it is necessary to know the \(Sh_w\) and \(x^*\) dependence of \((\delta/h)\). Grimsrud and Babb found this to be
\[
4x^* = \frac{xD}{V_{a^2}} = -\frac{n^6}{32} + \left[8 - \frac{5}{4} K\right] \frac{n^3}{60} + \left[9 K + \frac{4fK^2}{16}\right] \frac{n^2}{60}
\]
\[
- \left[\frac{27K^2 + 235K}{16}\right] \frac{n}{60} + \left[81K^2 + \frac{405K^4}{16}\right] \frac{\ln(\frac{2n+3K}{3K})}{120}
\]  \hspace{1cm} (M-91)

The denominator "4" in the second term was missing from their paper (154) but was included in Grimsrud's original derivation (153).

Fig. M-2 contains a plot of \(\delta/h\) as a function of \(X^*\) for \(Sh_w = 10^{-1}\) and \(10^{-2}\), calculated from eqn. (M-91). For \(Sh_w = 10^{-1}\), one finds for \(x^* \gg 10^{-4}\),
\[
\delta = c x^{1/3}
\]  \hspace{1cm} (M-92)

where the coefficient \(c\) was evaluated numerically for \(\delta/h \sim 10^{-2}\) \((x^* \sim 4.15 \times 10^{-7})\), yielding \(c = 1.3592\). Substituting into eqns. (M-84) and (M-85) gives
\[
Sh_{x,0} = Sh_w \left[\frac{1}{1 + 0.9061 Sh_w x^{1/3}}\right]
\]  \hspace{1cm} (M-93)
\[
\approx Sh_w \left[1 - 0.9061 Sh_w x^{1/3}\right]
\]  \hspace{1cm} (M-94)

and
\[
Sh_{x,f} = 1.1104 x^{-1/3}
\]  \hspace{1cm} (M-95)

Thus, the boundary layer analysis yields an expression for \(Sh_{x,0}\)
Figure M-2. Entrance Region Solutions for Local Sherwood Number

\[ \frac{Sh_x}{k_x h} = \frac{XD}{V h^2} \]

From Eqn. (M-90)
Boundary Layer Analysis

\( Sh_w = 10^1 \)
\( Sh_w = 10^2 \)

\( \frac{Sh_x}{k_x h} \) for
- Const. Conc.
- Const. Flux.

from Leveque-type Solution

\( \frac{s}{h} \) from Eqn. (M-91)

\( Sh_w = 10^1 \)
\( Sh_w = 10^2 \)

(7 Eigen Values)
quite similar to the perturbation analysis, eqn. (M-61), with a slight difference in the constant. However, the expression for \( \text{Sh}_{x,f} \) is significantly different for the two analyses. Whereas from the perturbation analysis \( \text{Sh}_{x,f} \) tends towards the constant flux solution as \( x^* \) decreases, the boundary layer analysis does not produce this behavior. For \( \text{Sh}_w = 10^2 \) the slope of the \( \delta/h \) vs. \( x^* \) plot differs from 1/3. This is not surprising, since the "near constant flux" condition does not apply.

In Fig. M-2, several additional quantities are plotted, including the Leveque-type solutions for constant concentration and flux boundary conditions, \( \text{Sh}_{x,f} \) for \( \text{Sh}_w = 10^{-1} \) and \( 10^2 \) from the boundary layer analysis, eqn. (M-90), and \( \text{Sh}_{x,f} \) from eqn. (5-89) using seven eigenvalues for \( \text{Sh}_w = 10^{-1}, 10^2, \) and \( 10^3 \).

At \( x^* = 2 \times 10^{-3} \), the eigenvalue solutions for high and low \( \text{Sh}_w \) are approaching the constant concentration and constant flux Leveque-type solutions, respectively. The boundary layer analysis, however, deviates considerably from the "true" eigenvalue analysis. Consequently, attempting to match the boundary layer analysis with the eigenvalue solution at this or higher values of \( x^* \), as suggested by Grimsrud (153) will lead to erroneous results.

As \( x^* \) decreases, \( \text{Sh}_{x,f} \) for \( \text{Sh}_w = 10^{-1} \) and \( 10^{-2} \) from the boundary layer analysis appear to be converging. However, the curve for \( \text{Sh}_w = 10^{-1} \) does not tend towards the constant flux line, as expected from the perturbation analysis. The latter solution gives a \( \text{Sh}_{x,f} \) curve which is not visually different from the constant flux line over the entire \( x^* \) range plotted. This means
that for low $\text{Sh}_w$ the effects of a parabolic velocity profile become important before the influence of the non-zero $\text{Sh}_w$ becomes apparent. For $\text{Sh}_w = 10^2$, the perturbation analysis is not valid within the plotted range.

3. Asymptotic Expression for Higher Eigenvalues

An alternative to a solution valid only in the entrance region is to evaluate as many eigenvalues and eigenfunctions as are required. However, as discussed in Section 5.C.2, the higher eigenvalues require increased significant digits and more lengthy intermediate calculations. The practical limit, using 14 significant digits on the IBM 360/65 computer, was about the first seven or eight eigenvalues. For the higher eigenvalues, an asymptotic expression was obtained following the method of Sellars, Tribus, and Klein (374) which is valid as the eigenvalues become very large.

For large $\beta$ and $y^*$ close to one-half, Cess and Shaffer (64) applied the technique of Sellars; et al. (374) and derived the asymptotic solution for the eigenfunctions for a semi-infinite channel:

$$\psi(\xi) = a \xi^{1/2} \left[ A J_{1/3}(f(\xi)) - B J_{-1/3}(f(\xi)) \right] \quad (M-100)$$

where

$$a = \frac{2}{3} (\lambda \pi)^{1/2} \quad (M-101)$$

$$A = \sin\left(\frac{\lambda \pi}{4} - \frac{1}{12}\right) \quad (M-102)$$

$$B = \sin\left(\frac{\lambda \pi}{4} - \frac{5}{12}\right) \quad (M-103)$$

$$\xi = 1 - \frac{v}{a} = 1 - 2y^* \quad (M-104)$$

$$\lambda = \frac{1}{2} \beta \quad (M-105)$$
\[ f(\xi) = \frac{\lambda \sqrt{B}}{3} \xi^{3/2} \]  

(M-106)

and \( J_p(x) \) is the Bessel function of the first kind of order \( p \).

Note that their equation is based upon the half-channel height, \( a \), as the characteristic length.

To obtain an expression for the eigenvalues, the wall boundary condition, eqn.(5-59), is applied. Thus,

\[ -\frac{1}{Y(0)} \frac{dY(y^*)}{dy^*} \bigg|_{y^*=\frac{1}{2}} = Sh_w \]  

(5-59)

or

\[ \frac{2}{Y(0)} \frac{dY(\xi)}{d\xi} \bigg|_{\xi=0} = Sh_w \]  

(M-107)

Hence,

\[ \frac{1}{Y(0)} \frac{dY}{a\xi} \bigg|_{\xi=0} = \frac{1}{2} Sh_w \]  

(M-108)

The Bessel functions may be expressed as

\[ J_p(x) = \sum_{K=0}^{\infty} \frac{(-1)^K x^{p+2K}}{K! \Gamma(p+K+1)} \]  

(M-109)

Using only the first term, which is sufficient for \( \xi = 0 \) or \( f(\xi) \) close to zero yields

\[ J_p(x) \approx \frac{x^p}{2^p \Gamma(p+1)} \]  

(M-110)

and

\[ J_{-p}(x) \approx \frac{2^p x^{-p}}{\Gamma(1-p)} \]  

(M-111)
Consequently

\[ Y = \frac{2}{3} (\lambda \pi \xi)^{1/2} \left[ \frac{A}{\Gamma\left(\frac{4}{3}\right)} \left( \frac{\lambda \sqrt{8}}{6} \xi^{3/2} \right)^{1/3} - \frac{B}{\Gamma\left(\frac{2}{3}\right)} \left( \frac{\lambda \sqrt{8}}{6} \xi^{3/2} \right)^{-1/3} \right] \]

and

\[ Y(0) = - \frac{2}{3} (\lambda \pi)^{1/2} \frac{B}{\Gamma\left(\frac{2}{3}\right)} \left( \frac{\lambda \sqrt{8}}{6} \right)^{-1/3} \]

The derivative term is given by

\[ \frac{dY}{d\xi} = \frac{1}{3} (\lambda \pi)^{1/2} \xi^{-1/2} \left[ A J_{1/3}(f(\xi)) - B J_{-1/3}(f(\xi)) \right] \]

\[ + \frac{2}{3} (\lambda \pi \xi)^{1/2} \left[ A \frac{d}{d\xi} \left( J_{1/3}(f(\xi)) \right) - B \frac{d}{d\xi} \left( J_{-1/3}(f(\xi)) \right) \right] \]

Noting that

\[ \frac{d}{dx} [J_D(\gamma x)] = -\gamma J_{p+1}(\gamma x) + \frac{D}{x} J_p(\gamma x) \]

one obtains

\[ \frac{d}{d\xi} [J_{-1/3}(f(\xi))] = \frac{3}{2} \xi^{1/2} \left[ - \frac{\lambda \sqrt{8}}{3} J_{4/3}(f(\xi)) - \frac{1}{3\xi^{3/2}} J_{1/3}(f(\xi)) \right] \]

\[ \frac{d}{d\xi} [J_{-1/3}(f(\xi))] = \frac{3}{2} \xi^{1/2} \left[ - \frac{\lambda \sqrt{8}}{3} J_{2/3}(f(\xi)) - \frac{1}{3\xi^{3/2}} J_{-1/3}(f(\xi)) \right] \]

Substituting eqns. (M-116) and (M-117) into eqn. (M-114) and using the series expressions for the Bessel functions, yields
\[ \frac{dV}{d\xi} \bigg|_{\xi=0} = \frac{2}{3}(\lambda \pi)^{1/2} \frac{A}{\Gamma(\frac{4}{3})} \left( \frac{\lambda \sqrt{\beta}}{6} \right)^{1/3} \]  

(M-118)

Finally, the desired relationship is obtained by combining eqns (M-113) and (M-118) with eqn. (M-108) to give

\[ \frac{1}{2} Sh_w = -\frac{\sin(\frac{\lambda \pi}{4} - \frac{\pi}{12}) \Gamma(\frac{2}{3})}{\sin(\frac{\lambda \pi}{4} - \frac{5\pi}{12}) \Gamma(\frac{4}{3})} \left( \frac{\lambda \sqrt{\beta}}{6} \right)^{2/3} \]  

(M-119)

Substituting \( \lambda = \frac{1}{2} \beta \) yields

\[ Sh_w = -2 \frac{\sin\left(\frac{\beta \pi}{8} - \frac{\pi}{12}\right)}{\sin\left(\frac{\beta \pi}{8} - \frac{5\pi}{12}\right) \Gamma\left(\frac{4}{3}\right)} \left( \frac{\beta \sqrt{\beta}}{12} \right)^{2/3} \]  

(M-120)

For \( Sh_w = 0 \), the sin term in the numerator must be zero, and hence

\[ \beta_m = 8(m-1) + \frac{2}{3} \]  

(M-121)

Similarly, for \( Sh_w = \infty \), the denominator must go to zero, which is satisfied for

\[ \beta_m = 8(m-1) + \frac{10}{3} \]  

(M-122)

For intermediate values of \( Sh_w \), the eigenvalues may be represented by an expression of the form

\[ \beta_m = 8(m-1) + f(m, Sh_w) \]  

(M-123)

According to eqn. (M-120), \( f(m, Sh_w) \) will be between 2/3 and 10/3 for all \( m \) and \( Sh_w \).
From eqn. (M-120), \( f(m, Sh_w) \) was calculated and the results are shown in Fig. M-3 for \( m \) equal to 1, 7, 50, and 100. The "true" value of \( f(m, Sh_w) \), obtained from the direct modified Graetz-type solution (see Sec. 4.C.2) is also plotted. It is clear that \( f(m, Sh_w) \) is a function of \( m \), i.e., the shape of the \( \beta_m - Sh_w \) relationship changes with \( m \). As \( m \) increases, \( f(m, Sh_w) \) tends towards the constant flux value, \( 2/3 \). In the limit, for very large \( m \) (\( \beta_m \to \infty \)), the eigenvalues approach the value for \( Sh_w = 0 \). This is also shown by rearranging eqn. (M-120):

\[
\frac{\sin \left( \frac{\beta \pi}{8} - \frac{\pi}{12} \right)}{\sin \left( \frac{\beta \pi}{8} - \frac{5\pi}{12} \right)} = - (\text{const}) \frac{Sh_w}{\beta^{2/3}} \quad (M-124)
\]

As \( \beta \to \infty \), the right-hand side tends to zero (unless \( Sh_w \to \infty \)), and \( f(m, Sh_w) \approx \frac{2}{3} \).

For the first eigenvalue, the asymptotic expression gives a poor estimate. As \( m \) increases, the value calculated from the asymptotic expression and the true value converge. As illustrated in Fig. M-3, for \( m = 7 \) the agreement is relatively good, and the asymptotic value may be used for \( m > 7 \) with reasonably good accuracy, the error decreasing as \( m \) increases. Of course, the nonlinear form of eqn. (M-120) requires an iterative technique to find \( \beta_m \) for a specified \( Sh_w \).

With \( \beta_m \) now determined for \( m > 7 \), it remains to derive a suitable asymptotic approximation for \( A_m \) and \( B_m \). From eqn. (5-71),

\[
A_m = \frac{2 \ Sh_w}{\beta_m Y_m \left( \frac{1}{2} \right) \frac{d Sh_w}{d \beta_m}} \quad (5-71)
\]
Figure W-3. $f(m, S_{H_w})$ as a function of $S_{H_w}$ for various values of $m$.

Asymptotic value for large $m$

True value from Graetz-type solution

$m = 1$
$m = 7$
$m = 50$
$m = 100$

$S_{H_w} = \frac{k_{\omega h}}{D}$
\( Y_m(\frac{1}{2}) \) is equivalent to \( Y(o) \) given by eqn. (M-113). Differentiating eqn. (M-120) yields

\[
\frac{dS_{h_w}}{d\beta} = -2 \frac{r(\frac{2}{3})}{r(\frac{4}{3})} \left( \frac{\sqrt{8}}{12} \right)^{2/3} \left\{ \frac{-2}{3} \beta^{1/3} \sin \left( \frac{\beta \pi}{8} - \frac{\pi}{12} \right) \sin \left( \frac{\beta \pi}{8} - \frac{5\pi}{12} \right) \right. \\
+ \frac{\beta^{2/3}}{8} \left[ \sin \left( \frac{\beta \pi}{8} - \frac{5\pi}{12} \right) \cos \left( \frac{\beta \pi}{8} - \frac{\pi}{12} \right) - \sin \left( \frac{\beta \pi}{8} - \frac{\pi}{12} \right) \cos \left( \frac{\beta \pi}{8} - \frac{5\pi}{12} \right) \right] \right\} \\
\sin^2 \left( \frac{\beta \pi}{8} - \frac{5\pi}{12} \right)
\]

(M-125)

The numerator in brackets may be simplified to

\[
\sin \left( \frac{\pi}{12} - \frac{5\pi}{12} \right) = -\sqrt{3}/2
\]

since

\[
\sin (x - y) = \sin x \cos y - \sin y \cos x
\]

(M-126)

Further, \( S_{h_w} \) may be factored out of the first term to yield

\[
\frac{dS_{h_w}}{d\beta} = \frac{2}{3} \frac{S_{h_w}}{\beta} + \frac{\pi}{4} \frac{r(\frac{2}{3})}{r(\frac{4}{3})} \left( \frac{\beta \sqrt{8}}{12} \right)^{2/3} \frac{\sqrt{3}}{2}
\]

(M-127)

With this relationship, both \( A_m \) and \( B_m \) may be calculated directly, once \( \beta_m \) is determined, from eqns (5-71) and (5-73).
APPENDIX N

Flat Plate Dialyzer: Generation of Theoretical Solution for Specified $x^*$ and $Sh_w$

A computer program was written to numerically evaluate the solution to the theoretical model discussed in Section 5.C.1. for specified values of $x^*$ and $Sh_w$. Specifically, the quantities of interest were the bulk mixing-cup concentration and the various Sherwood numbers.

The program may be considered as a self-contained "black box." One specifies $x^*$ and $Sh_w$ as input parameters and obtains all desired information as output. The program was written with two major uses in mind: 1) Evaluation of membrane (or wall) permeability and/or solute diffusivity from experimental data, and 2) simulation of hemodialyzer performance. For both applications, the program must be efficient and rapid to minimize computer costs. In addition, for the analysis of experimental data, it is desirable that the error associated with the theoretical solution be insignificant with respect to the error associated with the experimental data. In this study, the most accurate concentration measurements, those made for sodium chloride with the conductivity cell and impedance comparator, were good to about 0.1 per cent. On this basis, the accuracy required of the theoretical solution for the dimensionless bulk concentration, $C_b^*$, was arbitrarily set at 0.01 per cent.
1. **Calculation of Eigenvalues**

The first, and most difficult, aspect in obtaining the theoretical solution is the calculation of the eigenvalues. Two criteria must be established: 1) How many eigenvalues are required? and 2) What accuracy is needed for each?

a. **Accuracy Requirements**

In collaboration with the author, Stroeve (409) evaluated the theoretical solution over a wide range of Sherwood numbers and dimensionless lengths for one to seven eigenvalues. From his results, the eigenvalue requirements were established.

The number of eigenvalues required for 0.01% accuracy in $C_b^*$ is shown in Fig. N-1 as a function of $x^*$ and $Sh_w$. The same criteria applies for $5 \leq Sh_w \leq \infty$. Below $Sh_w = 10^{-2}$, two eigenvalues are required for $10^{-4} < x^* < 10^{-3}$ and four for $10^{-5} < x^* < 10^{-4}$.

Stroeve's results were available only at discrete values of $x^*$ and $Sh_w$, resulting in the box-like appearance of Fig. M-1. In reality, the curves separating each successive eigenvalue are smooth. Consequently, the requirements shown are on the safe side.

As $Sh_w$ decreases at constant $x^*$, the number of eigenvalues required decreases. This is reasonable, since as $Sh_w$ tends to zero, $C_b^*$ tends to 1.0, and the errors caused by neglecting higher eigenvalues decreases. Such a conclusion is true only for the requirement of fixed accuracy in the dimensionless concentration. If one requires a fixed
accuracy in the log-mean fluid-side Sherwood number, for example, Stroeve (409) found that the number of eigenvalues needed are invariant with $\text{Sh}_W$ and depend only on $x^*$. The required number for all $\text{Sh}_W$ is the same as that for $\text{Sh}_W = \infty$. As an extreme illustration of this point, consider the case of low $\text{Sh}_W$ and low $x^*$, for which one might find $C_b^* = 0.9999$ with many eigenvalues. Using only one eigenvalue, one might calculate $C_b^* = 0.9998$. Both values would be within the 0.01 per cent accuracy requirement for $C_b^*$. However, the calculated overall log-mean Sherwood number would be twice as large for the second case, and the fluid-side value would be in even greater error. Stroeve has considered in more detail the eigenvalue requirements for fixed Sherwood number accuracy. For the purposes of interest here, the more lenient requirements depicted in Fig. N-1 are satisfactory.

The second important criterion, the accuracy required for each eigenvalue, was evaluated by a rough error analysis. An accuracy of 0.01% in $C_b^*$ requires, at most, that the coefficients $B_m$ in Equation (5-65) be accurate to 0.01%, the most important coefficient, of course, being $B_1$. This requirement is more stringent than requiring that the exponential term meet the same condition. By perturbing the eigenvalues slightly from their "true" value (to about eight significant digits, as tabulated by Stroeve (409) and noting the effects on $B_m$ and $C_b^*$, the accuracy requirement for the eigenvalues was judged to be about one part in 20,000 to one
Figure N-1 Number of Eigen Values Required for 0.01 % Accuracy in $C_b^*$ as a Function of $X^*$ and $Sh_w$. (The Limits of the Seventh Eigen Value Were Not Evaluated.)
part in 50,000, or about $\pm 1$ in five significant figures. This conclusion was verified by computational experiments.

b. Direct Evaluation

For a given wall Sherwood number, one desires to have the required number of accurate eigenvalues. However, as discussed in Section 5.C.2., the nonlinear nature of the solution permits one only to assume a value of $\zeta_m$ and then calculate the corresponding $\text{Sh}_W$ from Equations (5-74), (5-75), and (5-78). To circumvent this problem, alternative procedures are required.

Initial attempts were made with Stroeven's procedure (403) of formulating the equations as a minimization problem (See Section 5.C.2.). For more than two eigenvalues, this method consumed a great deal of computer time and was economically impractical. Fitting the $\beta_m - \text{Sh}_W$ data directly with a least-square polynomial did not yield sufficient accuracy. Evaluation of the roots of Equation (5-80) with a Newton-Raphson iterative procedure was unstable and did not converge.

The technique finally adopted was to fit the first seven eigenvalues with polynomials, after transforming the $\beta_m - \text{Sh}_W$ relationship. A computer program was written to generate values of $\text{Sh}_W$ for a series of values of $\beta_m$. The data was then transformed according to the method described in Appendix K for fitting asymptotic S-shaped curves. The transformed data was fitted to a least-squares polynomial. All calculations were performed in double precision on the
IBM 360/65.

The results of these curve fittings are shown in Table N-1 for the first seven eigenvalues. The nomenclature is similar to that used in Appendix K, with the following differences

\[ y = \beta_m (EIGEN) \]
\[ x = Sh_w (SHW) \]
\[ m = NUMDEG \]
\[ \bar{y} = EIGENZ \]
\[ \bar{z} = ZZ \]
\[ X = \gamma \]
\[ \tanh X = X \]

Where a "C" is added to the end of the name of a variable, it indicates the value calculated from the fitted polynomial.

Of primary interest here are columns two, five, and six, containing \( Sh_w \), \( \beta_m \) and \( \beta_m \) calculated from the polynomial. Examination of the tables reveals an excellent fit, generally exceeding the accuracy criterion defined above, except for very low \( Sh_w \) and for the first eigenvalue over its entire range.

The first eigenvalue required an 18th degree polynomial, the second eigenvalue at 15th degree polynomial, and all subsequent eigenvalues a 10th degree polynomial. All coefficients and constants required for the polynomials may be found in the subroutine BNFIT listed in Table N-2 at the
end of this appendix. The eigenvalues are calculated from the last two executable statements in subroutine GUESS. These statements are essentially equivalent to Equations (K-7) and (K-12) in Appendix K.

It is noteworthy in Table N-1 that the accuracy of the fit improves as the eigenvalue number increased. As expected for high degree polynomials, the fitted estimates tend to oscillate about the true values. The error, however, is generally restricted to form the fourth to the seventh significant digit.

Because of the importance of the first eigenvalues, it was necessary to employ a minimization technique to obtain sufficient accuracy in its evaluation. The value calculated from the fitted polynomial was used as a first guess. Since it was accurate to about three to four significant figures, the number of objective function evaluations for five figure accuracy was not large.

2. **Computer Program**

The computer program is listed in Table N-2. It consists of an executive subroutine, THEORY, and six additional subroutines. Communication with an external program is done through the argument list in THEORY. No input/output is performed anywhere in the program. The program is set up to handle a vector of values of \( x^* \) for a single value of \( Sh_W \).

First, the constants and coefficients are calculated in BNFIT. Subroutine GUESS then determines the number of
eigenvalues required for the smallest value of \( x^* \), according to the criteria described above, and calculates the eigenvalues. A more accurate estimate for the first eigenvalue is made in MAXIN, which contains a golden section optimization algorithm. The objective function is evaluated in OBJF. Subroutine MAXIN is a modification of a program originally written by Stroeve (27). The coefficients \( a_n \) for each eigenvalue are calculated in OBJFX. All remaining quantities needed for the solution are calculated in TERMX. Finally, \( C_b^* \) and the various Sherwood numbers \( Sh_{x,0}^* \), \( Sh_{x,f} \), \( Sh_{m,0} \), and \( Sh_{m,f} \) are calculated at the end of THEORY. The working formulas for the program are given in Section 5.C.2.

The program contains a number of built-in error tolerances to determine when various procedures and infinite summations should be terminated. These tolerances were determined to meet the overall accuracy requirements by empirical evaluation. The golden-section minimization is terminated when the interval of uncertainty is less than TOL, which is set at \( 10^{-5} \). The calculation of \( a_n \) in OBJF and OBJFX is stopped when the absolute value of the relative change in the calculated \( Sh_w \) (see Equation (5-78)), produced by the inclusion of \( a_{n+1} \), is less than \( 10^{-6} \), or when \( a_n \) is less than \( 10^{-20} \). This then sets the maximum number of terms for subsequent infinite summations performed in TERMX. These, however, are terminated if the absolute value of the relative change in \( B_m \) in two successive calculations is less
than BTOL1, which is set at $5 \times 10^{-5}$. BTOL2 is a residual tolerance used during debugging but is redundant in the present version.

The accuracy of the final calculated numbers may be modified by alteration of the error tolerances. Higher accuracy would also require an optimization for all the required eigenvalues. If lower accuracy can be accepted, the optimization for the first eigenvalue may be removed.

For usage of the program, the following points should be noted:

1) The entire program is written in double precision; thus, all arguments in the external calling program must be of like type.

2) As shown, the listing contains type declarations for all double precision library functions, as required by the FORTRAN 4 WATFOR compiler. It may be necessary to remove them for other compilers.

3) The external calling program must contain a labelled COMMON called START containing the marker ISTART initialized to an integer not equal to unity. The first time through THEORY, ISTART is set to unity and subsequently BNFIT is bypassed. This is done to eliminate the unnecessary repetitive call to BNFIT if $S_{H_W}$ does not change. However, if $S_{H_W}$ is changed, ISTART must be re-initialized.

The variables in the argument list for THEORY have the following meaning:
\[ SHW = Sh_w \]
\[ XSTAR = x^* \]
\[ EIGEN = \beta_m \]
\[ BN = B_n \] (polynomial coefficients)
\[ NUMEIG = m \] (no. of eigenvalues)
\[ NUMDEG = n \] (polynomial degree for each eigenvalue)
\[ OBJF = \left| Sh_w - Sh_{wc} \right| \]
\[ SHWC = Sh_{wc} \] (Sh_w calculated from Equation (5-79))
\[ AM = A_m \]
\[ BM = B_m \]
\[ ADD = \frac{\partial y_m}{\partial y^*} \Big|_{y^* = 1/2} \]
\[ NUMX = \text{no. of values of } x^* \text{ inputted} \]
\[ CSTART = c_{b^*} \]
\[ SHOLN = Sh_{m,0} \]
\[ SHBLN = Sh_{m,f} \]

SHZLOG, A1, A2 = constants for polynomial fit of \( \beta_m \)
\[ NUMIT = n \] (highest subscript of \( a_n \) used before summation terminated)

all variables except \( SHW, NUMEIG, \) and \( NUMX \) are arrays. Although \( Sh_{x,0} \) and \( Sh_{x,f} \) are calculated (SHOLC and SHBLOC), they are not included in the argument list.

In its final form, the program was compiled under the FORTRAN H compiler with OPT=2 (highest optimization). The execution time on an IBM 360/65 for the entire program for a
### Table H-1

#### Calculated and Fitted Eigenvalues as a Function of Sh_w

<table>
<thead>
<tr>
<th>Sh_w</th>
<th>I</th>
<th>J</th>
<th>X</th>
<th>EIGEN</th>
<th>EIGENC</th>
<th>Y</th>
<th>YC</th>
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</thead>
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<td>0.0000000000</td>
</tr>
</tbody>
</table>

### Notes
- Sh_w: Stratified Sherwood Number
- EIGEN, EIGENC: Eigenvalues
- X: Independent variable
- Y, YC: Dependent variables
Table N-1 (continued)

<table>
<thead>
<tr>
<th>i</th>
<th>Smh</th>
<th>r</th>
<th>Eigen</th>
<th>Eigen</th>
<th>v</th>
<th>t</th>
</tr>
</thead>
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<td>0.700046258000</td>
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<td>0.894998874200</td>
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<td>0.700046258000</td>
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<td>0.894998874200</td>
<td>0.634763721400</td>
<td>0.700046258000</td>
<td>0.700046258000</td>
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<td>0.107310454900</td>
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<td>0.634763721400</td>
<td>0.700046258000</td>
<td>0.700046258000</td>
</tr>
</tbody>
</table>

- **Columns:**
  - i: Row index
  - Smh: Some value
  - r: Some value
  - Eigen: Eigenvalue
  - t: Some value
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<th>Y</th>
<th>Z</th>
</tr>
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Table N-1 (continued)

**Table Note:**
- First row indicates column headers.
- Second row contains header values.
- Data follows with specified columns for each row.

**Header Values:**
- X, Y, Z represent the respective column headers for each row.

**Data Format:**
- Values are presented in a tabular format with three columns for X, Y, Z respectively.

**Table Dimensions:**
- The table spans across multiple rows and columns, detailing specific values for each X, Y, Z combination.
Table N-1 (continued)

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<th>y</th>
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<th>P(x,y)</th>
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<td>F(T)</td>
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Table N-1 (continued)
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single value of $S_{hW}$ was about 0.1 second for three eigenvalues, 0.16 seconds for four eigenvalues, and 0.25 seconds for five eigenvalues. These times were independent of the number of $x^*$ values used.
APPENDIX O

Data Reduction for the Flow Dialyzer

1. Overall Approach

The analysis of all data from the flow dialyzer was performed with computer programs written in FORTRAN 4 for the IBM 360/65. The input to these programs consisted primarily of the necessary equipment settings and readings. All primary variables such as concentrations and flow rates were calculated with the equipment calibrations presented in Appendix D. Since the solutes employed were the same as those used with the batch dialyzer, common features of the analysis, already discussed in Appendix I, will not be repeated.

The general approach was as follows. The dimensionless concentration was calculated from the inlet and outlet concentrations, with the dialyzate concentration assumed constant (and equal to zero for all experiments performed). Linear flow velocities were calculated and diffusion coefficients estimated. Then $x^*$, $R_d$, and $S_c$ were calculated. The dialyzate mass transfer coefficient was estimated from Equation (5-210). The effective diffusion coefficient in Cuprophan PT-150 was estimated from the results of the batch dialyzer measurements, using an equation of the form

$$ D_m = D_{m_0} \exp (-E/RT) $$  \hspace{1cm} (0-1)
For sodium chloride, $D_{m_0} = 1.112 \times 10^{-3}$ and $E/R = 1790.4$. Urea permeabilities were measured at $37^\circ C$ only. As a reasonable approximation for estimation at other temperatures, the activation energy for sodium chloride was used, with $D_{m_0} = 9.25 \times 10^{-4}$. From the measured thickness, membrane permeabilities and resistances were estimated. Finally, the wall mass transfer coefficient was estimated from Equation (5-8) and $Sh_w$ calculated. From the estimated $x^*$ and $Sh_w$, $C_t^*$ was calculated for comparison with experimental values.

2. Sodium Chloride

Since the diffusivity of sodium chloride in water is dependent upon concentration, it was necessary to estimate a mean concentration on both the blood side and dialyazate side. The dialyazate outlet concentration was calculated from a material balance. The "film" concentrations were first approximated as the average of the inlet and outlet bulk concentrations. After calculation of the various mass transfer coefficients, the log-mean average fluid concentration in the "film" and at the membrane-fluid interfaces were calculated from the following Equations:

\[ \text{Let } \bar{C}_b = C_{b_1} + \Delta C_{1n} \]  \hspace{1cm} (0-2)

\[ \frac{C_{b_1} - C_b}{\Delta C_{1n}} = \frac{1}{n} \left( \frac{1}{C^*} \right) \]  \hspace{1cm} (0-3)
Then

\[ C_{w_b} = \frac{C_b}{k_{m,b}} - \frac{k_{m,0}}{k_{m,b}} \Delta C \ln \]

\[ C_{b_f} = \frac{C_b + C_{w_b}}{2} \]

and

\[ C_{w_d} = C_{d_1} + \frac{k_{m,0}}{k_{m,d}} \Delta C \]

\[ C_{d_f} = \frac{C_{d_1} + C_{w_d}}{2} \]

where the mass transfer coefficients are the log-mean average values and the subscripts b, d, and w refer to blood-side, dialyzate, and membrane-fluid interface, respectively. Diffusion coefficients were evaluated at their respective average film concentrations, \( C_{b_f} \) and \( C_{d_f} \).

3. Error Analysis

From the equations used in handling the experimental data, the following relations were derived for estimating the standard error or variance of each quantity of interest.

\[
\left( \frac{\sigma_{D_m}}{D_m} \right)^2 = \left( \frac{\sigma_{D_0}}{D_0} \right)^2 + \left( \frac{E}{RT} \right)^2 \left( \frac{\sigma_T}{T} \right)^2 + \left( \frac{1}{T_0} - \frac{1}{T} \right)^2 \sigma^2_{E/R} \]

(0.7)
\[
\left( \frac{\sigma_v}{v} \right)^2 = \left( \frac{\sigma_D}{D} \right)^2 + \left( \frac{\sigma_h}{h} \right)^2 \quad (0-8)
\]

\[
\left( \frac{\sigma_V}{V_d} \right)^2 = \left( \frac{\sigma_Q}{Q_d} \right)^2 + \left( \frac{\sigma_w}{w} \right)^2 + \left( \frac{\sigma_h}{h} \right)^2 \quad (0-9)
\]

\[
\left( \frac{\sigma_k}{k_d} \right)^2 = \left( \frac{\sigma_a}{a} \right)^2 + b^2 \left( \frac{\sigma_V}{V_d} \right)^2 + (b-1)^2 \left( \frac{\sigma_h}{h_d} \right)^2 + \left( \frac{1}{3} - b \right) \left( \frac{\sigma_V}{V} \right)^2 + \left( \frac{2}{3} \right) \left( \frac{\sigma_D}{D} \right)^2 + (1 - \text{Re}_d)^2 \sigma_b^2 \quad (0-10)
\]

\[
\left( \frac{\sigma_K}{k_w} \right)^2 = \left( \frac{k_w}{k_m} \right)^2 \left( \frac{\sigma_P}{p_m} \right)^2 + \left( \frac{k_w}{k_d} \right)^2 \left( \frac{\sigma_k}{k_d} \right)^2 \quad (0-11)
\]

\[
\left( \frac{\sigma_{ShW}}{Sh_w} \right)^2 = \left( \frac{\sigma_k}{k_w} \right)^2 + \left( \frac{\sigma_h}{h} \right)^2 + \left( \frac{\sigma_D}{D} \right)^2 \quad (0-12)
\]

\[
\left( \frac{\sigma_C}{C^*} \right)^2 = \left( \frac{\sigma_c}{C} \right)^2 + \left( \frac{\sigma_c}{C_f} \right)^2 \quad (0-13)
\]

\[
\left( \frac{\sigma_x}{x^*} \right)^2 = \left( \frac{\sigma_x}{x} \right)^2 + \left( \frac{\sigma_D}{D} \right)^2 + \left( \frac{\sigma_V}{V_b} \right)^2 + 2 \left( \frac{\sigma_h}{h_b} \right)^2 \quad (0-14)
\]

\[
\left( \frac{\sigma_k}{k_m,0} \right)^2 = \left( \frac{\sigma_Q}{Q_b} \right)^2 + \left( \frac{\sigma_w}{w} \right)^2 + \left( \frac{\sigma_x}{x} \right)^2 + \left[ \frac{1}{\ln \left( \frac{C^*}{C} \right)} \right]^2 \left( \frac{\sigma_C^*}{C^*} \right)^2 \quad (0-15)
\]
\[
\left( \frac{\sigma_{Sh_{m},0}}{Sh_{m},0} \right)^2 = \left( \frac{\sigma_{k_{m},0}}{k_{m},0} \right)^2 + \left( \frac{\sigma_{h}}{h} \right)^2 + \left( \frac{\sigma_{D}}{D} \right)^2
\]  \hspace{1cm} (0-16)

\[
\sigma_{k_{m},f}^2 = \sigma_{k_{m},0}^2 + \sigma_{p,ln}^2
\]  \hspace{1cm} (0-17)

\[
\left( \frac{\sigma_{Sh_{m},f}}{Sh_{m},f} \right)^2 = \left( \frac{\sigma_{k_{m},f}}{k_{m},f} \right)^2 + \left( \frac{\sigma_{h}}{h} \right)^2 + \left( \frac{\sigma_{D}}{D} \right)^2
\]  \hspace{1cm} (0-18)

In order to calculate the relations given in eqns. (0-7) to (0-18), the following estimates for the standard deviations of primary variables were used. They were obtained from repeated measurements of each variable and/or from least-squares straight line analyses.

\[
\sigma_{E/R} = 340
\]  \hspace{1cm} (0-19)

\[
\frac{\sigma_{D_{m_0}}}{D_{m_0}} = 0.091
\]  \hspace{1cm} (0-20)

\[
\frac{\sigma_{t_m}}{t_m} = 0.05
\]  \hspace{1cm} (0-21)

\[
\frac{\sigma_{a}}{a} = 0.113
\]  \hspace{1cm} (0-22)

\[
\frac{\sigma_{b}}{b} = 0.0232
\]  \hspace{1cm} (0-23)

\[
\frac{\sigma_{Q_D}}{Q_D} = 0.5 + 0.01
\]  \hspace{1cm} (0-24)
\[
\frac{\sigma_w}{w} = 0.0185 \text{ (blood side)} \tag{0-25}
\]
\[
\frac{\sigma_w}{w} = 0.01 \text{ (dialyzate side)} \tag{0-26}
\]
\[
\frac{\sigma_v}{v} = 0.001 \tag{0-27}
\]
\[
\frac{\sigma_D}{D} = 0.05 \tag{0-28}
\]

The remaining quantities were fed in as input data. For sodium chloride, \(\sigma_c/c = c_{c_1}/c_i = 0.003\). For urea, multiple measurements were made for each data point, and the actual standard deviations used. As a rough rule of thumb, \(\sigma_c/c\) was about 0.0075 for aqueous solutions, 0.0125 for plasma and 0.02 for blood.

The error analysis was calculated for each data point. After the best fit of \(X_1\) or \(X_2\) was evaluated, the actual experimental value of \(\sigma_D/D\) or \(\sigma_{p_m}/P_m\) was used.

4. **Evaluation of \(X_1\) or \(X_2\)**

The experimentally measured \(C^*\) and the estimates of \(x^*\) and the average \(S_{h_w}\) for the run corresponding to

\[
x^* = \frac{X_1 x_D}{V h^2} \tag{5-137}
\]
\[
S_{h_w} = \frac{X_1 k_{wh}}{X_2 D} \tag{5-138}
\]
with $X_1 = X_2 = 1.0$, were fed into the optimization program. Then the value of $X_1$ or $X_2$, with the other held constant, which fitted each data point to the theoretical solution was found with a Golden Section minimization technique. After all $X_1$ or $X_2$ were evaluated, the average was calculated and the correction to $D$ or $P_m$ determined. The original data were then reanalyzed with the best-fit value of $D$ or $P_m$ and the best-fit theoretical quantities generated.

5. Computer Program Listings and Sample Output

Tables O-1, O-3, and O-5 contain listings of the computer programs used for the analysis of experimental data from the flow dialyzer with sodium chloride (SCFD), radioactive solutes (RSFD), and for the evaluation of $X_1$ and/or $X_2$ by the optimization technique, respectively. Each listing is followed by a sample printout, in Tables O-2, O-4, and O-6, which contains a complete analysis of the data.

Each program consists of a main program and several subroutines. For SCFD, MAIN calls five subroutines. RECORD (not listed) converts recorder data to impedance measurements. CMPRFD converts impedance difference to absolute concentrations and calculates $C^*$ (similar to COMPAR in Appendix I). PUMPS calculates the blood-side flow rate, $Q_b$, from the syringe pump settings and estimates $\sigma_{Q_b}/Q_b$. DIFF calculates the diffusivity as a function of concentration. THEORY calculates the theoretical solution for the estimated $X^*$ and $Sh_w$ (see Appendix N).

All input is done with NAMELIST. Input variables for SCFD are as follows: RUN = run no; N = no. data pts.;
TEMPC = conductivity cell temperature, °C; TEMPB = dialyzer temperature; ISTEP, IRATE = syringe pump-gear setting and percentage of full speed; POT = Myno pump setting, percentage of full speed; RS, AMOUNT, SCALE, FULL, UNITS, RSTART = recorder and impedance comparator readings, same as described in Appendix I for program SCPBD, with the latter two parameters referring to initial dialyzate concentration; L, W, HB = length, width, and height of blood-side channel mass transfer section, cm; HD, WD = height and width of dialyzate channel, cm; TWET = wet membrane thickness, mil; FACTOR, WMULT, BMULT = correction factors to alter $Q_B$, $P_m$, and $D$ (blood-side) as calculated by program; PCCONI, PCCONC = $\sigma_{C_i}/c_i$ and $\sigma_{C}/c$. All data relating to individual data points are fed in as arrays.

The output from SCFD is shown for 2005 with the best-fit estimate of membrane permeability ($WMULT = 1.020$). The program first prints the input data, calculated bulk concentrations, and $C^*$. The second section consists of three rows of estimated parameters and quantities calculated from the data, such as mass transfer coefficients, resistances, and Sherwood numbers. The nomenclature is generally consistent with that used in the body of the theses. The prefix SD means the estimated standard deviation (or standard error). The suffixes LN and B refer to overall log-mean and blood-side log-mean, respectively. RBFRA, RMFRAC, and RDFRAC are the relative mass transfer resistances in the blood-side, membrane, and dialyzate phases. Where unspecified, all units are in the cgs system. The numbers beneath several of the columns are
averages for all data points. The third section contains parameters calculated for the theoretical solution, including $B_n$, $Sh_w$ (calculated from Equation (5-78), $A_m$, and $B_m$. This is followed by a comparison between the theoretical and experimental results. The suffix T refers to the theoretical quantity. In addition to that shown in Table 0-2, the program calculates additional points for plotting the theoretical curves, as well as theoretical results corresponding to the upper and lower $Sh_w$ estimates.

RSFD is similar to SCFD. It requires three subroutines, PUMPS, DIFFUS (similar to subroutine of same for batch dialyzer analysis), and THEORY. Only MAIN is listed. The input variables are the same as SCFD, with the concentration measurement parameters deleted and the following additions: $X = AES$ ratio or channels ratio minus one, depending upon counting mixture (see Appendix D); CPM = measured counts per minute; BKGD = background count rate; VOLS = sample volume, ml; DPM = disintegrations per minute; ICALC $= 1$, use DPM data as is, $\neq$. calculate DPM: $= 0$, Bray's solution, $= 2$, toluene solution with AES ratio, $= 3$, toluene solution with channels ratio (see Appendix D); XX, FZX $= X$, F(Z,X) in Equation (4-71); DMZERO $= D_0 \cdot DPLAS = \theta_P$; ISOLV $= 1$, aqueous solution, $= 2$, plasma, $= 3$, blood; HCT = hematocrit; PCDB = $\sigma_D/D$; EACTR = $- E/R$, for membrane. The program calculates the blood-side: dialyzate equilibrium distribution coefficient for the particular blood-side fluid, determined by ISOLV. As presently written, this calculation is for urea only.
The sample printout in Table 0-4 is for run 2103.2 with whole blood. With the exception of the different concentration parameters, the output is similar to that for SCFD. THETA is the diffusivity reduction factor, \( \psi \). Both SCFD and RSFD punch cards for use as input to OPTIM.

The optimization program, OPTIM, is a condensed version of a program written by Stroeve (27) for a n-dimensional optimization. The main program contains two methods, either of which gives identical results for a one-dimensional problem. MAIN calls FMC which, for the unconstrained optimization of interest here, calls MAXMIN where a golden section minimization is performed. The objection function, \( F_s = \sum (C_s - C_{s*})^2 \), is evaluated in VALUE which calls THEORY to calculate \( C_{s*} \). SETUP initializes various program control parameters and reads in most of the data. Input data using conventional format are as follows: read by MAIN-METHOD = method to be used, (1 or 2); MAXIT = maximum number of overall iterations (1 or 2 sufficient); IPRINT = interval of printing intermediate results; read by SETUP = \( X(1), X(2) = \) initial guess for \( X_1 \) and \( X_2 \) (1.0); TOL = maximum value of objective function or difference in successive values of \( X_1 \) or \( X_2 \) for overall convergence (set at 0.0001); TOL2 = fractional interval of uncertainty for golden section convergence (set at 0.0001); RUN = run no; NUMX = no. of data points; SHW = \( Sh_w \); XSTAR, CSTAR = \( x^*, C^* \) for an individual data point; ICODE = 1, evaluate \( X_1 \) and \( X_2 \), = 2 evaluate \( X_1 \) only, = 3 evaluate \( X_2 \) only.

The output from OPTIM in Table 0-6 is for a single data point from run 2103.2. The program prints out successive values
Table 0-1
Program Listing, Sodium Chloride Flow Dialyzer (SCFD) Analysis
Table 0-2
Sample Output for SCFD, run 2005.0

SODIUM CHLORIDE MASS TRANSFER AND PERMEABILITY MEASUREMENTS IN FLOW DIALYZER

\[ B_1 = 0.2789 \quad B_2 = 60.25 \quad B = 0.3286 \quad \text{LINFIN} = 126.32 \]

ORIGINAL CONCENTRATION ON DIALYZATE SIDE = 0.0

RUN NO. = 2005.0

\[ N = 18 \quad L = 5.08 \quad WD = 5.08 \quad W = 5.08 \]

UNITS = 0.0

\[ \text{RESTART} = 0.0 \quad \text{CONDW} = 0.18E-05 \quad \text{TEMP} = 24.95 \]

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<th>POT</th>
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Table 0-3. Program Listing, Radioactive Solute Flow Dialyzer (RSFD) Analysis

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**Note:** The program listing appears to be a listing of a program related to the flow of radioactive solutes in a dialyzer. The content is not clearly transcribed due to the nature of the image.
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### Comparison of Theoretical Solution with Experimental Data Run 2105.20

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Table 0-5

Program Listing for Evaluation of $X_1$ and $X_2$ by Optimization (OPTIM)

- 760 -
Table 0-5 (continued)

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TOTAL NUMBER OF FUNCTION EVALUATIONS: 150,500
### Table 0-6

**Sample Output for OPTIM**

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**PARAMETERS FOR THEORETICAL SOLUTION**

<table>
<thead>
<tr>
<th>Eigenvalues Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

**EIGENVALUES SHOWN**

<table>
<thead>
<tr>
<th>Eigen</th>
<th>SHMC</th>
<th>AN</th>
<th>HM</th>
<th>ACO</th>
<th>NMR</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>2.679210</td>
<td>5.566311</td>
<td>1.142714</td>
<td>0.488826</td>
<td>-1.447930</td>
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<tr>
<td>2</td>
<td>7.045497</td>
<td>0.057567</td>
<td>0.75574</td>
<td>0.75594</td>
<td>-0.000000</td>
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</tbody>
</table>

**WALL PERMEABILITY FACTOR = 1.00000**
**DIFFUSIVITY FACTOR = 4.1013**

**ORIGINAL SHMC = 0.487268**
**NEW SHMC = 5.566311**
**RATIO = 0.0094**
of $F_1$, $X_1$, and $X_2$ during the minimization. Typically, about 40 evaluations of $F_1$ were required. After the final values are printed, the best fit of the theoretical solution to the experimental datum point is given.
Numbers in parentheses refer to the equation where each parameter is defined. Additional variables, particularly those employed within mathematical derivations, are defined where first used in the text.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>impeller radius; activity; half channel height</td>
</tr>
<tr>
<td>$a_n$</td>
<td>eqn.(5-74)</td>
</tr>
<tr>
<td>A</td>
<td>area</td>
</tr>
<tr>
<td>$A_m$</td>
<td>expansion coefficient, eqn.(5-63)</td>
</tr>
<tr>
<td>b</td>
<td>membrane or cylindrical vessel base radius</td>
</tr>
<tr>
<td>$B_m$</td>
<td>expansion coefficient, eqn.(5-66)</td>
</tr>
<tr>
<td>c</td>
<td>concentration</td>
</tr>
<tr>
<td>C</td>
<td>concentration</td>
</tr>
<tr>
<td>$C^*$</td>
<td>local dimensionless concentration, eqn.(5-9); bulk mixing cup average dimensionless concentration (when referring to experimental data)</td>
</tr>
<tr>
<td>$C_b^*$</td>
<td>bulk mixing cup average dimensionless concentration</td>
</tr>
<tr>
<td>$C_M$</td>
<td>dimensionless moment coefficient</td>
</tr>
<tr>
<td>d</td>
<td>diameter</td>
</tr>
<tr>
<td>$d_i$</td>
<td>impeller diameter</td>
</tr>
<tr>
<td>D</td>
<td>molecular diffusion coefficient</td>
</tr>
<tr>
<td>$D_{eff}$</td>
<td>effective diffusivity</td>
</tr>
<tr>
<td>$D_B$</td>
<td>dialysance</td>
</tr>
<tr>
<td>E</td>
<td>activation energy</td>
</tr>
<tr>
<td>F</td>
<td>objective function, eqns.(5-141) to (5-146); erythrocyte membrane-plasma distribution coefficient</td>
</tr>
</tbody>
</table>
\( F(z,x) \)  eqn. (4-71)

\( h \)  channel height

\( J \)  mass transport rate per unit area

\( k \)  mass transfer coefficient; distribution coefficient, eqn. (4-2)

\( k',k_p \)  distribution coefficients, eqns. (4-1) and (4-3)

\( K \)  mass transfer coefficient; distribution coefficient

\( K_{eq} \)  red cell - plasma distribution coefficient

\( K_{x/y} \)  distribution coefficient between phases \( x \) and \( y \)

\( L \)  length

\( L_p,L_{pd},L_d \)  phenomenological coefficients

\( M \)  turning moment or torque; molecular weight; Fricke model parameter, eqn. (4-76)

\( n \)  angular velocity (rpm)

\( \dot{N} \)  mass transport rate per unit area

\( \dot{N} \)  mass transport rate

\( N_A \)  Avogadro's number

\( N_T \)  number of transfer units

\( P \)  permeability

\( Q \)  flow rate

\( R \)  mass transfer resistance; ideal gas constant

\( \text{Re} \)  Reynolds number

\( s \)  axial gap, impeller to chamber base; specific area

\( Sc \)  Schmidt number

\( Sh \)  Sherwood number

\( Sh_w \)  wall Sherwood number

\( St \)  Stanton number
\( t \)  
\( \text{time; thickness} \)

\( u \)  
\( \text{resultant of radial and circumferential velocity components} \)

\( U \)  
\( \text{hypothetical free stream resultant velocity} \)

\( v \)  
\( \text{velocity} \)

\( \overline{v} \)  
\( \text{average velocity; partial specific volume} \)

\( V \)  
\( \text{velocity; volume; volume fraction} \)

\( V_* \)  
\( \text{frictional velocity} \)

\( w \)  
\( \text{channel width} \)

\( W \)  
\( \text{weighting coefficient; weight fraction} \)

\( x \)  
\( \text{axial coordinate; length; dimensionless radial coordinate} \)

\( x^* \)  
\( \text{dimensionless length} \)

\( X_1, X_2 \)  
\( \text{correction factors for } k_w \text{ and } D, \text{ respectively} \)

\( y \)  
\( \text{transverse coordinate; dimensionless axial coordinate} \)

\( Y \)  
\( \text{eigenfunction} \)

\( z \)  
\( \text{axial coordinate; saturation} \)

\( \alpha \)  
\( \text{solubility; ratio of radial to circumferential velocity} \)

\( \overline{\alpha} \)  
\( \text{parameter for estimating } \psi, \text{ eqn.}(4-59) \)

\( \beta \)  
\( \text{eigenvalue; inviscid core angular velocity} \)

\( \gamma \)  
\( \text{ratio of inviscid core to disc velocity; activity coefficient} \)

\( \delta \)  
\( \text{boundary layer thickness} \)

\( \zeta \)  
\( \text{dimensionless axial coordinate} \)

\( \eta \)  
\( \text{boundary layer thickness} \)

\( \Theta \)  
\( \text{dimensionless concentration; angle between circumferential and resultant velocity components} \)
\( \mu \) viscosity
\( \rho \) density
\( \sigma \) standard deviation
\( \tau \) shear stress
\( \phi \) volume fraction (generally red cells)
\( \phi_p \) volume fraction proteins in plasma
\( \psi \) permeability reduction ratio
\( \omega \) angular velocity

SUBSCRIPTS

\( a \) average; phase A; component a
\( a_o \) arithmetic average, overall
\( a_f \) arithmetic average, fluid-side
\( A \) phase A
\( b \) blood; phase B; component b; bulk mixing cup average
\( B \) blood; phase B
\( c \) constant concentration boundary condition; cellulose
\( d \) dialyze
\( D \) dialyze
\( e \) equivalent
\( eff \) effective
\( f \) fluid
\( i \) initial; inlet
\( m \) membrane; log-mean; eigenvalue number
\( m_f \) log-mean, fluid-side
\( m_o \) log-mean, overall
\( o \) overall; initial; outlet; total; maximum
p  plasma
P  plasma
r  radial
s  solution; saline
t  at time t; theoretical
w  wall
x  local; cross-sectional
x,f  local, fluid-side
x,o  local, overall
z  axial
φ  circumferential
1  chamber 1
2  chamber 2
∞  asymptotic value; infinite distance from wall
Note: Appendix A contains a separate and independent set of literature citations. This tabulation applies to the remainder of the thesis.


42. Bluemle, L. W., Jr., Syracuse Univ, Syracuse, N.Y., Personal Communication, Jan. 23, 1968.


104. Doolan, P. D., in Reference 82, p. 115.


BIOGRAPHICAL NOTE

The author, Clark Kenneth Colton, was born in New York City on July 20, 1941, the first of two children of Mr. and Mrs. Sidney Colton. After obtaining his primary education in New York City, he moved to Maplewood, New Jersey, where he attended Columbia High School, from which he graduated in 1959.

The author entered the School of Chemical Engineering at Cornell University in 1959 and was awarded a B. Ch. E. degree in 1964. During this time he was supported by McMullen Regional and Proctor and Gamble Scholarships and was elected to Tau Beta Pi. While at Cornell, the author met the former Ellen Ruth Brandner, whom he married in June 1965.

In September 1964, the author commenced graduate study at M.I.T. and passed the doctoral qualifying examinations in May 1965. He has held appointments as both a research and teaching assistant and has received a National Institute of Health Predoctoral Fellowship. At the Massachusetts Institute of Technology he was elected to the Society of Sigma Xi and Phi Lambda Upsilon.

The author has spent four summers as a research engineer for Thiokol Chemical Corp., Standard Oil Co. of California, and DuPont de Nemours and Co., and has served as a part-time consultant to Monsanto Research Corp. He
has accepted appointment as Assistant Professor of Chemical Engineering at M.I.T. upon completion of his thesis.

Other Publications by the Author


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