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Ultrafiltration of Blood: Effect of Hematocrit on Ultrafiltration Rate

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Rates of ultrafiltration of bovine blood of various hematocrits were measured in ultrafilters of hollow-fiber type. The results were analyzed by the gel-polarization model. The mass transfer coefficient k for the back-diffusion of protein molecules away from the gel layer, which controls the ultrafiltrate flux, increases with the cube root of the shear rate at the membrane surface. At a given shear rate, it increases and then decreases with increasing hematocrit. A working equation for predicting k is proposed.

INTRODUCTION

The artificial kidney utilizing ultrafiltration of blood was first proposed by Henderson (1967). It has advantages over the conventional hemodialysis system in that it removes middle molecular toxins as well as toxins of lower molecular weights, the rate of water removal from the body fluid can be more easily controlled, and it can possibly be made more compact. Some experimental data on ultrafiltration of blood have been reported by Blatt *et al.* (1970), by Porter (1972), and recently by Colton *et al.* (1975). Kozinski and Lightfoot (1972) compared their data on ultrafiltration of bovine serum albumin solutions with analytical and numerical predictions, demonstrating the effects of protein-concentration-dependent viscosity and diffusivity. Colton *et al.* (1975) performed experiments of ultrafiltration of blood and plasma solutions. They observed some variation of ultrafiltrate flux with hematocrit and explained the variation by the increase in the effective solute diffusivity due to secondary flows induced by movements of red cells and by the damping-out of such augmentation mechanism by particle–particle interactions at higher red cell volume fractions.

The present work was intended to study in particular the effect of the hematocrit on the ultrafiltrate flux and to obtain a practical working equation for the ultrafiltrate flux for the design of clinical blood ultrafilters.

APPARATUS AND PROCEDURE

The flow sheet of the experimental apparatus is shown in Fig. 1. Bovine blood, stored in a jacketed and temperature-controlled reservoir at atmospheric pressure,

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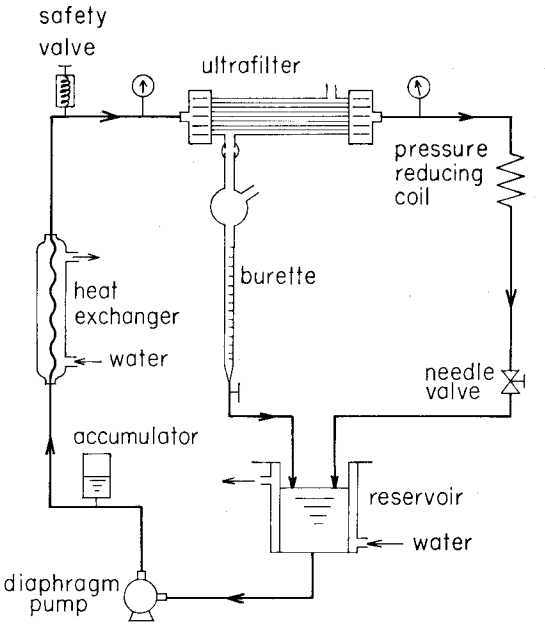

FIG. 1. Schematic diagram of experimental apparatus.

was supplied through a diaphragm pump, an accumulator for reducing pulsation, and a heat exchanger, into the tube side of an ultrafilter at 37°C. The ultrafilters used were the hollow-fiber type (HDX1 or H1DP10) manufactured by Amicon Company, containing 1000 hollow fibers, 16 cm in length and 200 μm in i.d., with a total filtering area of 1000 cm^2. The retentate was reduced in pressure through a pressure-reducing coil and a needle valve to be recycled to the reservoir. The nominal cutoff molecular weight was 10,000. The ultrafiltrate, which was at atmospheric pressure, was also recycled to the reservoir through a burette for the determination of its flow rates. The retentate side pressure was measured by two Bourdon gauges attached to the tubings leading to and from the ultrafilter.

In most experiments, bovine blood, defibrinated by the procedure reported by Yoshida and Ohshima (1966) and stored in a refrigerator, was used within 1 or 2 days after slaughter. Heparinized blood was also used in some runs but did not give results different from those with defibrinated blood, as will be discussed later. Low-hematocrit blood was prepared by diluting a whole-blood sample with serum obtained by centrifuging whole blood for 30 min at 20,000g. Serum solutions of low protein concentrations were prepared by diluting serum with physiological sodium chloride solution. Samples of whole blood and serum solutions were filtered with sterilized cotton gauze before use.

A series of ultrafiltration runs, with samples of the same serum protein concentration and of varying hematocrit values, was performed with a single ultrafilter. Before use, the ultrafilter was rinsed with 20 liters of tap water and then with 1 liter of physiological NaCl solution, and after use, with 2 liters of NaCl solution, 20 liters of water, and finally with 2.5% formaline solution. It was kept wet for

possible reuse, but was never used for more than two series of runs. A reused ultrafilter gave exactly the same results as a new ultrafilter except that it gave a slightly lower ultrafiltrate flux for water. When one ultrafilter was used twice, samples of a higher protein concentration were tested in the second series of runs. All the experiments were performed at 37°C.

The gauge after the ultrafilter indicated slightly lower pressure than the gauge before the ultrafilter. The upstream pressure was regarded as the transmembrane pressure difference. The flow rate of the ultrafiltrate was determined with a graduated cylinder and a stopwatch. Concentration of serum proteins was obtained by measuring the refractive index of a sample. The hematocrit was measured by the standard method using a centrifuge. Hemolysis was determined by measuring the concentration of free hemoglobin by the standard cyan-met hemoglobin colorimetric method.

BACKGROUND OF INTERPRETATION

According to the gel-polarization model (Blatt *et al.*, 1970), the limiting resistance to the flow of ultrafiltrate is in the gel layer dynamically formed on the membrance, which is assumed to have a gel concentration C_G and is free to vary in thickness or porosity. The ultrafiltrate flux J becomes independent of the transmembrane pressure differences above a certain threshold pressure difference, since the resistance of the gel layer adjusts itself until the transport of membrane-retained solutes to the membrane surface due to the bulk flow of the ultrafiltrate becomes equal to the back-diffusive transport of the solute.

The steady-state balance of the solute over a liquid element of differential thickness parallel to the membrane gives

$$JC = D(dC/dx), \tag{1}$$

where D and C are the diffusivity and the concentration of the retained species,

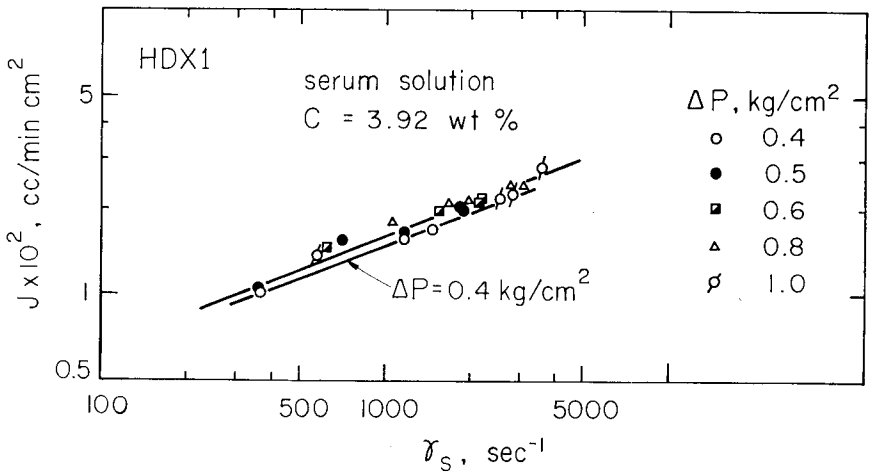

FIG. 2. Logarithmic plot of filtrate flux vs wall shear rate; protein concentration: 3.92%.

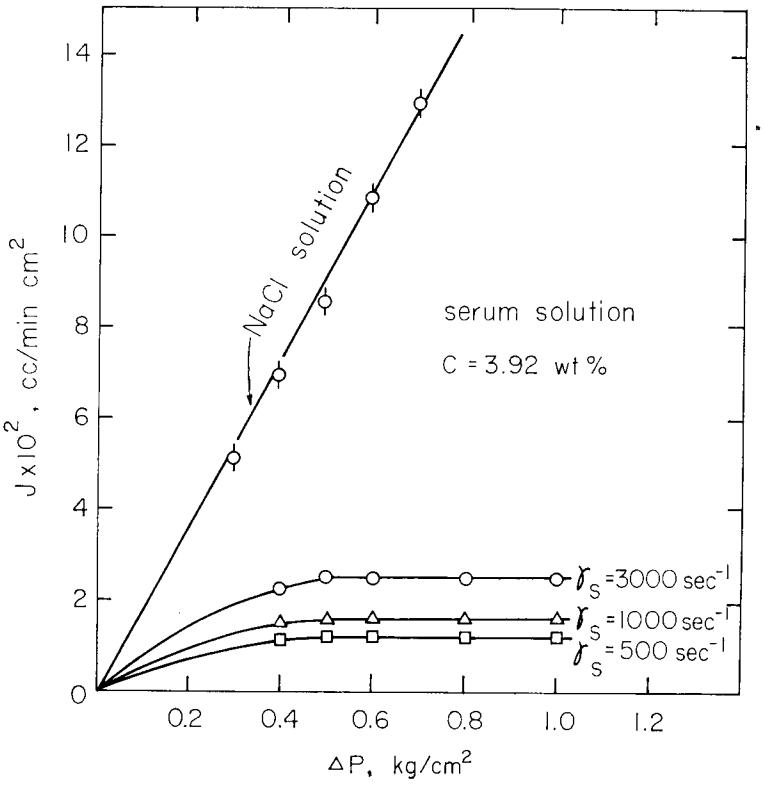

FIG. 3. Filtrate flux plotted against transmembrane pressure with wall shear rate as parameter.

and x the distance from the gel layer surface. Integration of Eq. (1) between the limits $C = C_G$ and $C = C_B$ and the simple film theory of mass transfer give

$$J = \frac{D}{\Delta x} \ln \frac{C_G}{C_B} = k \ln \frac{C_G}{C_B}, \tag{2}$$

where Δx is the effective thickness of the boundary layer over which the concentration varies, k is the local mass transfer coefficient, which should be a function of various fluid properties, the channel diameter (thickness), and the fluid velocity along the membrane. The difference between the local and the length-averaged values of k can be neglected, which seems justifiable for flow in tubes several hundred diameters long such as those used in the present experiments. If laminar flow and fully developed parabolic velocity profile are assumed, the shear rate at the tube surface γ_s is given by

$$\gamma_s = -(du/dr)_{r=R} = 4U/R, \tag{3}$$

where u is the local fluid velocity, r the distance from the tube axis, U the average fluid velocity over the entire cross section of the tube, and R the tube radius.

Colton *et al.* (1975) have shown that the length-averaged mass transfer coeffi-

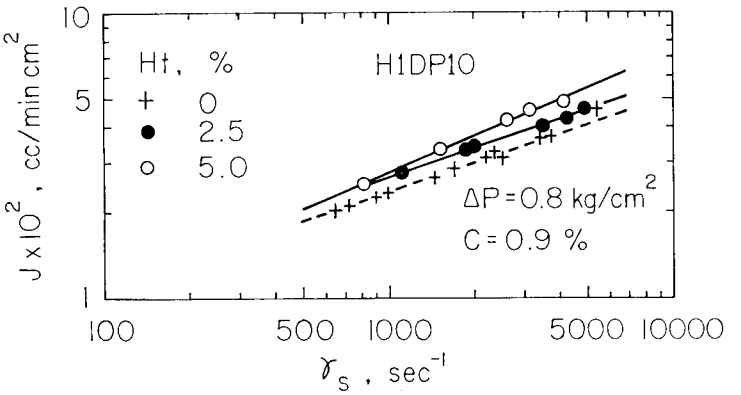

FIG. 4. Logarithmic plot of filtrate flux vs wall shear rate; protein concentration: 0.9%.

cient k is given by

$$k = 48.4[(\gamma_s/L)D^2]^{\frac{1}{3}}, \tag{4}$$

where L is the length of the hollow fiber. They attributed variation of the filtrate flux with the hematocrit by the variation of the effective values of D, as mentioned earlier.

The equation for k by Kozinski and Lightfoot (1972), based only on their data with albumin solutions, is more complicated by the inclusion of a correction factor, which accounts for the variation of diffusivity and viscosity with protein concentration and which generally does not depart greatly from unity.

It might be pointed out here that blood is a heterogeneous suspension with red cells, impermeable for protein diffusion, occupying substantial fraction of the total volume. It would be inappropriate to apply to such a system theories developed for diffusion in a single homogeneous phase. Also, if the problem is limited to the ultrafiltration of blood, if seems cumbersome and unnecessary to use in

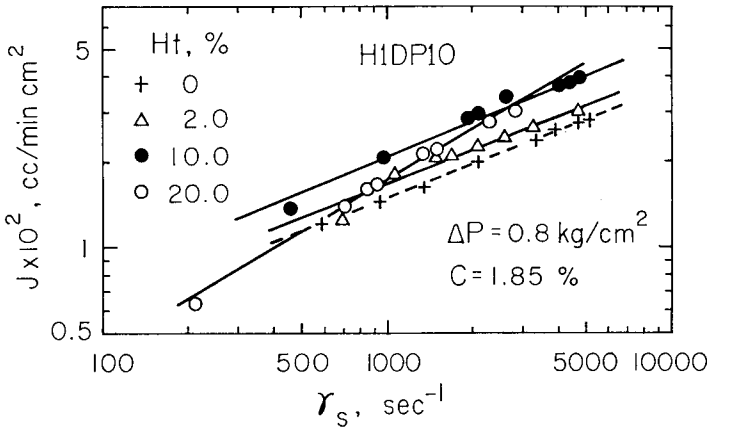

FIG. 5. Logarithmic plot of filtrate flux vs wall shear rate; protein concentration: 1.85%.

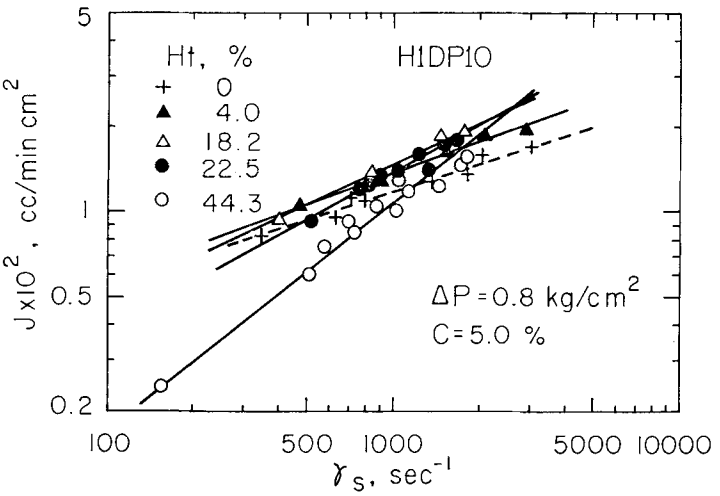

FIG. 6. Logarithmic plot of filtrate flux vs wall shear rate; protein concentration: 5.0%.

a working equation for k the effective diffusivity, which should be a complicated function of the protein concentration, hematocrit, and the flow conditions.

RESULTS AND DISCUSSION

No significant difference was seen among data with blood from different animals.

Figure 2 shows a logarithmic plot of the filtrate flux J vs the wall shear rate γ_s for ultrafiltration of a serum solution with a protein concentration of 3.92 wt%. Although the transmembrane presusre ΔP was varied from 0.4 to 1.0 kg/cm², values of J were independent of ΔP for ΔP of 0.5 to 1.0 kg/cm². The flux was slightly lower for ΔP of 0.4 kg/cm².

The relationship between J and ΔP is clearly shown in Fig. 3, in which values

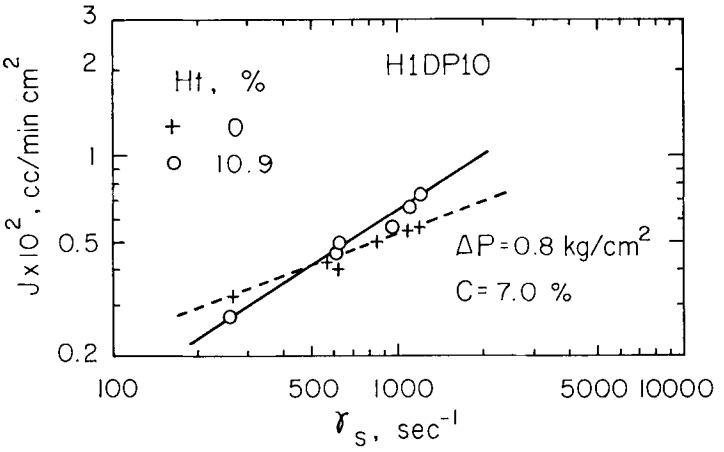

FIG. 7. Logarithmic plot of filtrate flux vs wall shear rate; protein concentration: 7.0%.

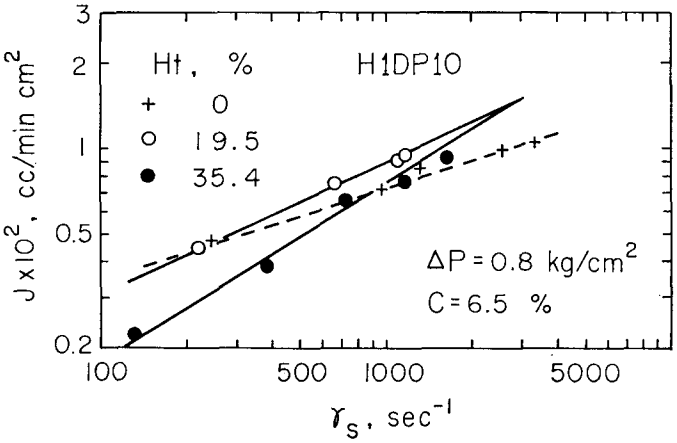

FIG. 8. Data with heparinized blood; logarithmic plot of filtrate flux vs wall shear rate; protein concentration: 6.5%.

of J are plotted against the transmembrane pressure ΔP with the shear rate γ_s as the parameter, based on the same data as shown in Fig. 2. Data for pure physiological NaCl solution are shown by the straight line in Fig. 3, which indicates that in this case the flow resistance is solely in the membrane itself.

Figure 4 shows a logarithmic plot of the filtrate flux against the wall shear rate at a transmembrane pressure of 0.8 kg/cm² for ultrafiltration of a serum solution and diluted blood, both with a serum protein concentration of 0.9 wt%. Hematocrits of blood were 2.5 and 5.0%. It is seen that the filtrate flux for a given value of the wall shear rate increases slightly with the hematocrit.

Figures 5 to 7 are figures similar to Fig. 4 for the data with serum solutions and diluted blood of varying hematocrits and of different serum protein concentrations of 1.85, 5.0, and 7.0 wt%, respectively. These figures show that variation of the filtrate flux with the hematocrit at a given wall shear rate is not simple and straightforward.

All the above data were obtained with defibrinated blood or serum solutions. Figure 8 shows the data with heparinized blood. The variation of the filtrate flux with the hematocrit is similar to the variations shown in Figs. 4 to 7. The results agree with those with defibrinated blood, as will be shown later.

Equation (2) suggests that if values of filtrate flux with solutions of various concentrations at a given shear rate are plotted against the logarithm of the bulk concentration C_B, a straight line with a negative slope k would be obtained provided that C_G does not vary (Porter, 1972). Figure 9 shows such plots based on the data for serum solutions of various protein concentrations which are represented by the broken lines in Figs. 4 to 7. The points in Fig. 9 were obtained by cross plots from Figs. 4 to 7, at four shear rates indicated in the figure. The protein concentration in the entering serum solution was taken as C_B. The four straight lines converge at a point on the abscissa, giving *a* C_G value of 20 wt%. This point should represent the concentration of the gel layer C_G, since according to Eq. (2),

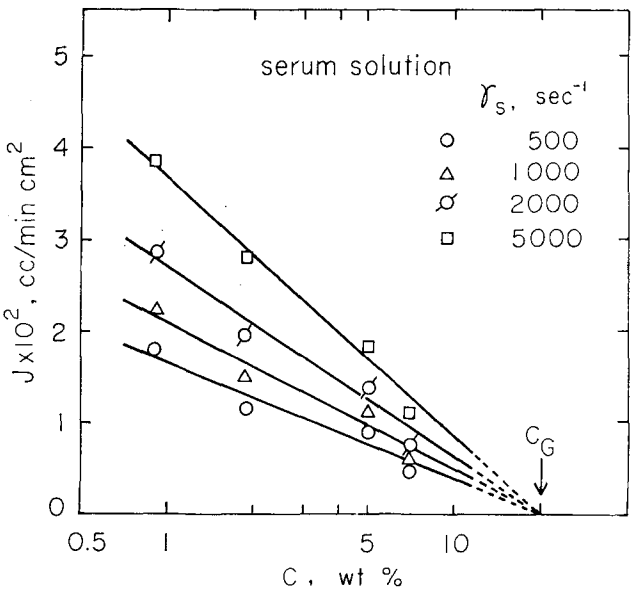

FIG. 9. Filtrate flux with serum solutions vs logarithm of protein concentration with shear rate as parameter.

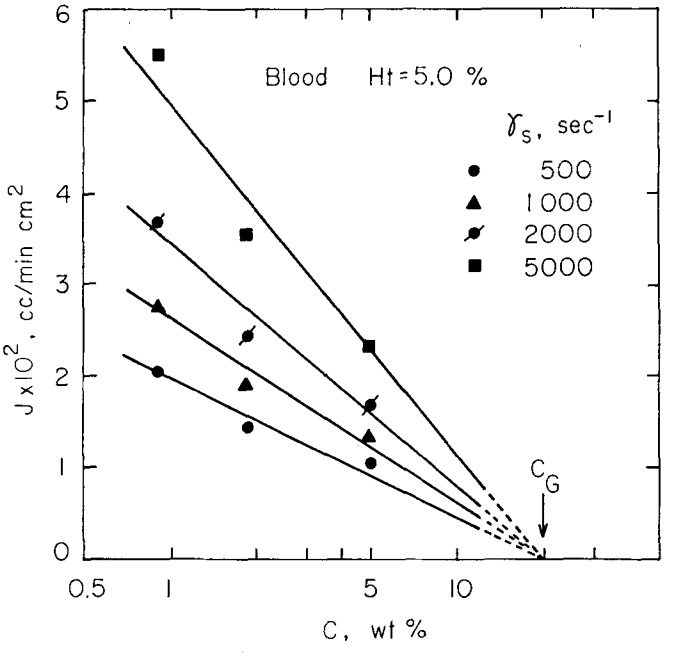

FIG. 10. Filtrate flux with blood (Ht = 5.0%) vs logarithm of protein concentration with shear rate as parameter.

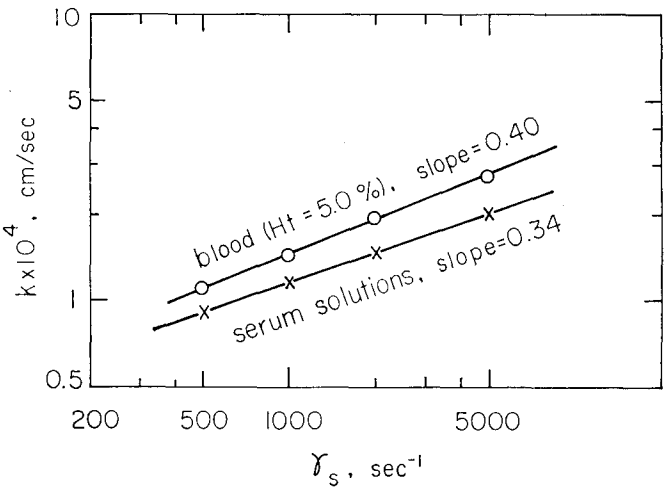

FIG. 11. Logarithmic plot of mass transfer coefficients in serum solution and blood (Ht = 5.0%) vs wall shear rate.

the flux should become zero if C_B, the concentration of the bulk of stream, were equal to C_G.

Figure 10 shows, as another example, a graph similar to Fig. 9, obtained from the data for blood of a hematocrit of 5.0% by cross plots from Figs. 4 to 6, i.e., by drawing a J vs Ht curve for each of three protein concentrations with the shear rate as the parameter, reading off values of J at Ht of 5.0% and plotting the J values against the logarithms of protein concentrations. Again the straight lines obtained converge at a point on the abscissa, giving the same value of C_G as in Fig. 9. Similar graphs, not shown here, were obtained for other hematocrit values.

The slopes of the straight lines in Figs. 9 and 10 give the values of the mass transfer coefficient k. Figure 11 shows k values thus obtained for serum solution and blood (Ht = 5.0%) from Figs. 9 and 10, respectively, plotted against the wall shear rate. The mass transfer coefficients for blood (Ht = 5.0%) and serum solution increase with the shear rate raised to the 0.4 and 0.34 powers, respectively. The latter value agrees with the exponent of $\frac{1}{3}$ on the fluid velocity in Eq. (4).

Variation of the mass transfer coefficient k with the hematocrit and the wall shear rate may be, at least partially, due to variation of the effective diffusivity D. However, in a working equation for the design of blood ultrafilters, it seems more convenient not to include D, since the fluid in question is limited to blood, but to include a correction factor $f(Ht \cdot \gamma_s)$ which accounts for the variation of D. The following empirical equation, with the data for serum solutions as the basis, was obtained from the data of the present experiments, which covered the ranges of the Reynolds number from 0.13 to 17.0 and the hematocrit of 0 to 44.3 and a temperature of 37°C.

$$k = 3.03 \times 10^{-5} f(Ht \cdot \gamma_s)(\gamma_s/L)^{\frac{1}{3}}. \tag{5}$$

Although the present experiments were performed with only one length of the

capillary, the length of the channel or capillary, L ,was included in Eq. (5), and the exponent of $-\frac{1}{3}$ on L was assumed in view of Eq. (4) and the Graetz-type semitheoretical equation (see, e.g., Bird *et al.*, 1960) for the heat transfer in laminar flow. According to Eq. (5), k should vary with the tube diameter to the $-\frac{1}{3}$ power, since γ_s is inversely proportional to the tube diameter by Eq. (3). This diameter dependence of k agrees with the Graetz equation.

The correction factor $f(Ht \cdot \gamma_s)$, which by definition is unity for serum solutions, accounts for the variation of D with the hematocrit and the wall shear rate. The effect of the protein concentration per se on D was neglected in view of our data. Values of $f(Ht \cdot \gamma_s)$, determined by comparing all the experimental values of the flux with calculations by Eqs. (2), (3), and (5), are plotted in Fig. 12 as a function of Ht with the wall shear rate as the parameter. No data points can be shown in the figure, since the curves were obtained by cross plotting. It is seen that $f(Ht \cdot \gamma_s)$ is greater with increasing wall shear rate, but, at a given wall shear rate, it increases, reaches a maximum, and the decreases with increasing hematocrit. Such complicated variation of $f(Ht \cdot \gamma_s)$ could be explained as follows.

Red blood cells suspended in plasma would promote turbulence in the bloodstream, especially at higher wall shear rates, which in turn would increase the effective diffusivity and hence the mass transfer coefficient k. However, at higher hematocrits, $f(Ht \cdot \gamma_s)$ would decrease, since the masking or barrier effect by red

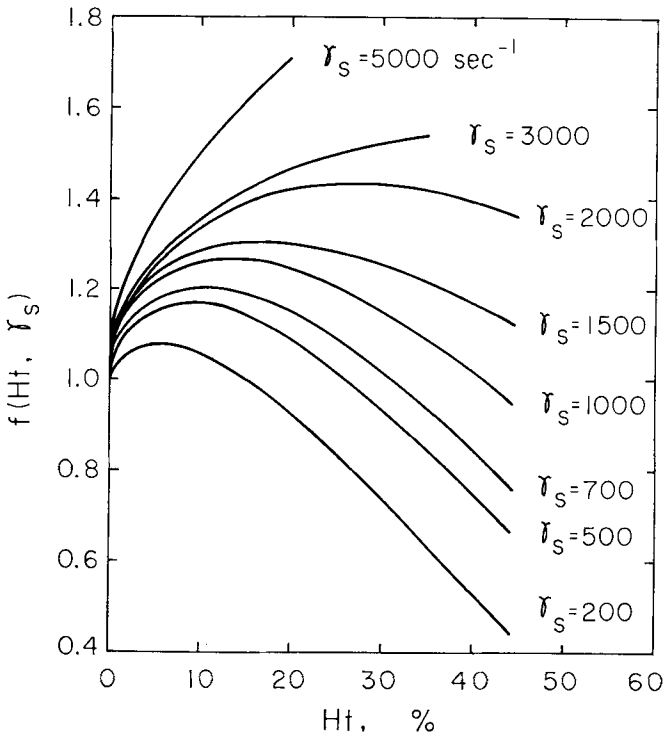

FIG. 12. Variation of $f(Ht \cdot \gamma_s)$ with hematocrit and wall shear rate.

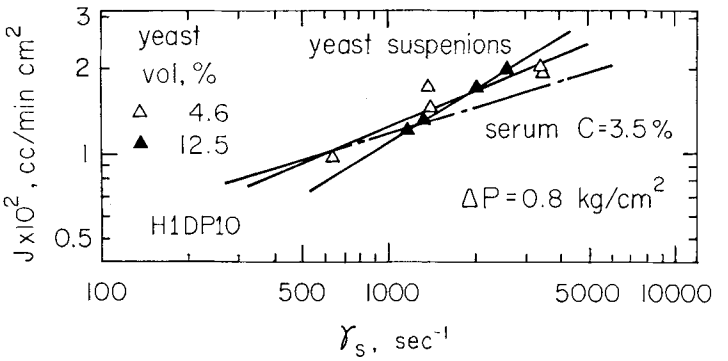

FIG. 13. Logarithmic plot of filtrate flux vs wall shear rate; suspensions of yeast cells in serum solution.

blood cells would outweigh the turbulence-promoting effect. Since protein molecules cannot diffuse through red cells, the fractional area available for the back-diffusion of protein molecules away from the membrane surface should decrease with increasing fraction of red blood cells.

To confirm that such variation of the flux or the mass transfer coefficient is due to the presence of red blood cells, experiments were performed with suspensions of yeast cells in serum. The yeast used was dried baker's yeast manufactured by Oriental Yeast Company, Japan. Although the yeast cell is not disk-shaped like the red blood cell, its size is roughly that of a red blood cell, i.e., several micrometers. The hydrodynamic behavior of yeast cells suspended in serum

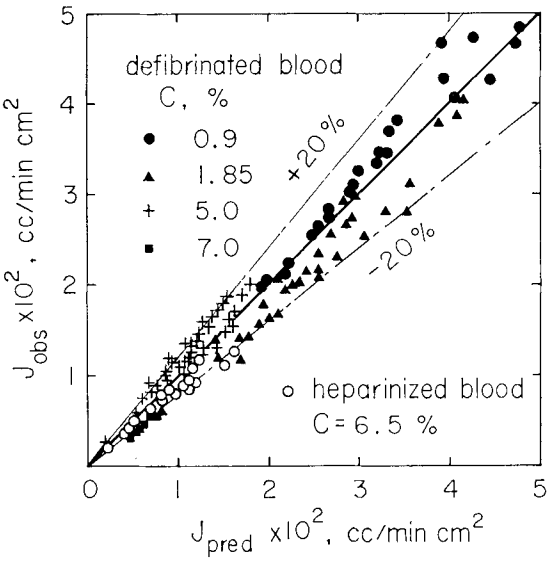

FIG. 14. Comparison between observed and predicted values of ultrafiltrate flux; all data with defibrinated and heparinized blood.

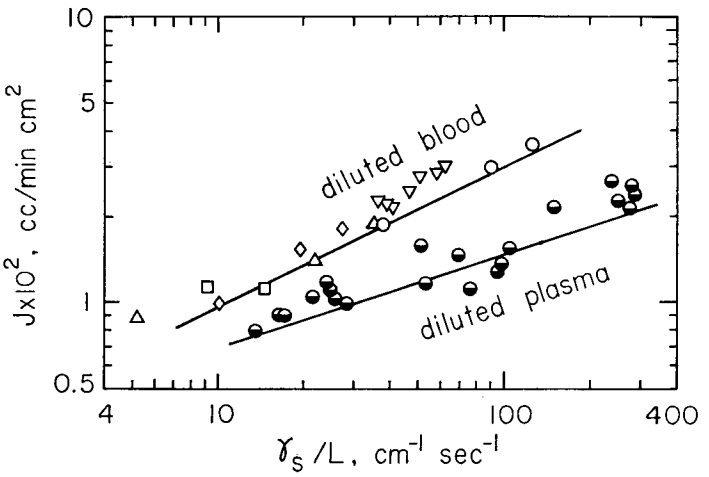

FIG. 15. Data of Colton *et al.* compared with calculation by Eq. (5).

would simulate that of red cells in blood. Figure 13 shows a logarithmic plot of the filtrate vs the wall shear rate with two yeast suspensions of different yeast concentrations. The variation of the filtrate flux with the yeast concentration is, at least qualitatively, quite similar to that with the hematocrit, which seems to justify our interpretation of the variation of the filtrate flux with the hematocrit.

The usefulness of Eq. (5) in conjunction with Fig. 12 is demonstrated by Fig. 14, in which all of our observed values of the filtrate flux with defibrinated as well as heparinized blood of various protein concentrations and hematocrits are compared with the values predicted by Eqs. (2) and (5) and Fig. 12. The agreement between the observed and predicted values is within 20%, which seems sufficient for design purposes.

Comparison with the data of Colton *et al.* (1975) is made in Fig. 15, in which all of their data, with tube diameters from 193 to 328 μm and tube lengths from 16.5 to 31.8 cm, are replotted from Fig. 3 of their paper. The two solid lines in Fig. 14 represent values calculated by Eq. (5) with use of Fig. 12. Fair agreement of Eq. (5) with the data of Colton *et al.* seems to indicate general applicability of the equation.

The rate of hemolysis in the whole experimental apparatus, including the pump, and the pressure reducing coil was measured by recirculating whole blood through the apparatus at flow rates corresponding to those in ultrafiltration runs. For example, the hemoglobin concentration in the plasma increased from 20.96 to 24.32 mg/dl in 2 hr, i.e.; the hourly increase in the hemoglobin concentration was approximately 3 mg/dl, which seemed well under the allowable limit.

CONCLUSIONS

The ultrafiltrate flux in the ultrafiltration of blood can be estimated by use of a simple empirical equation [Eq. (5)] for the coefficient for back-diffusion of

protein molecules away from the gel layer formed on the membrane surface by concentration polarization of proteins in the plasma. The equation does not include the effective protein diffusivity per se, but it includes a correction factor, which, in effect, accounts for the variation of the effective diffusivity with the hematocrit and the wall shear rate.

NOMENCLATURE

C	Protein concentration (g/cm^3)
D	Diffusivity of protein molecules in plasma (cm^2/sec)
J	Flux of ultrafiltrate (cm^3/cm^2 sec, or cm^3/cm^2 min)
f	Function
Ht	Hematocrit (%)
k	Mass transfer coefficient for back-diffusion of protein molecules from gel layer (cm/sec)
L	length of flow channel or capillary (cm)
P	pressure (kg/cm^2)
U	average fluid velocity over channel cross section (cm/sec)
u	local fluid velocity (cm/sec)
R	radius (cm)
r	distance from axis of capillary (cm)
x	distance from surface of gel layer (cm)
γ	shear rate (sec^{-1})

Subscripts

B	Bulk of liquid
G	Gel layer
s	Membrane surface

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