THE FLOW OF SICKLE-CELL BLOOD IN THE CAPILLARIES

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ABSTRACT Oxygen tension levels and red cell velocities for the flow of sickle-cell blood in the capillaries are determined by using the Krogh model for oxygen transport and lubrication theory for the cell motion. The coupling and interaction between these arises from the red cell compliance, which is assumed to vary with the oxygen concentration. Microsieving data is used to establish an upper bound for this relationship. Calculations are carried out for a range of capillary sizes, taking into account the rightward shift of the oxyhemoglobin dissociation curve and the reduced hematocrit of sickle-cell blood, and are compared to, as a base case, the flow of normal blood under normal pressure gradient. The results indicate that under normal pressure gradients the oxygen tensions and cell velocities for sickle blood are considerably higher than for normal blood, thus acting against the tendency for cells to sickle, or significantly change their rheological properties, in the capillaries. Under reduced pressure gradients, however, the concentrations and velocities drop dramatically, adding to the likelihood of such shape or flow property changes.

INTRODUCTION

The clinical symptomology of sickle-cell disease is primarily a manifestation of abnormal events in the capillaries. In this paper we look at some aspects of the flow of sickle-cell disease blood through the capillaries in order to elucidate the interplay of mechanisms at work.

Sickle blood (blood from persons with sickle-cell anemia) is known to undergo rheological changes and shape changes if the oxygen level falls low enough. If, as oxygen is released by the red blood cells, the oxygen tension falls to low levels in the capillaries, the following sequence of events may occur (1). Rheological changes increase blood viscosity, which leads to a decrease in velocity of flow, leading to the release of more oxygen. This latter effect is due not only to the lower velocity but also to the increase in hydrogen ion concentration of tissue and blood, which shifts the oxygen dissociation curve so as to enhance further the unloading of oxygen from the hemoglobin. There follows a further increase in viscosity, hence a further decrease in velocity, and so on. The potential end result of this "vicious cycle" is a static mass of sickled cells lodged in the capillaries, blocking circulation.

Clearly, the oxygen tension levels in the capillary, which initiate this cycle, are of critical importance. Sickle blood has a number of characteristics and properties that would tend to lower oxygen tensions in the capillary. Among the more important of these are: (*a*) impaired oxygen-carrying capacity stemming from the rightward shift of the oxyhemoglobin dissociation curve and subnormal oxygenation in the lungs; (*b*) a tendency to rheological and shape changes, which can increase blood viscosity and therefore decrease velocity of blood flow; and (*c*) a lower oxygen-carrying capacity due to a reduced hematocrit, so that more oxygen per

red cell must be given up to satisfy tissue demands. There are, however, aspects of these same characteristics that tend either to maintain high oxygen tensions in the capillary or to mitigate against the consequence of low oxygen levels. The rightward shift of the oxyhemoglobin dissociation curve makes it possible for small decreases in oxygen concentration to liberate sufficient oxygen to meet tissue requirements. The much lower hematocrit of sickle-cell blood (25–30% vs. the normal value of ~48%) decreases the resistance to flow of such blood in the capillary and therefore leads to dramatically higher than normal transit velocities of the cells for a given pressure gradient. (A measure of the effectiveness of this compensatory mechanism is that there is little difference between the viscosity of completely deoxygenated sickle blood at a hematocrit of 25% and that of fully oxygenated normal blood at a hematocrit of 50%.) These higher cell velocities tend to keep oxygen tensions high because there is less time available for oxygen to be released. Finally, because the rheological and shape changes to which sickle cells are susceptible require a finite time, even if the tensions fall to low values, the cells, particularly since they move faster than normal cells, may exit the capillary before significant changes of this kind occur. Thus the actual oxygen levels and velocities of flow in the capillary depend on the interplay of these opposing tendencies.

The primary purpose of this paper is to incorporate all of these characteristics of sickle blood into a model of capillary flow and oxygen transport. We shall show which way the balance falls, and how it is affected by changes in flow conditions and/or sickle blood properties.

To analyze the problem of oxygen concentration in the capillary bed we employ the Krogh model (2). In this model a single capillary is assumed to be the sole supplier of oxygen to a surrounding annulus of tissue. Solutions must be obtained simultaneously for the blood velocity and for the oxygen concentration in the capillary and in the tissue. The blood velocity is determined from a lubrication theory of red cell motion in a capillary (3–6). The key elements of the analysis are that the oxygen concentration depends on the velocity of flow whereas the velocity depends on the overall concentration in the capillary. Although there are many Krogh-type studies of transport in the capillaries in which the first of these dependencies is taken into account, it is the introduction of the second, providing as it does a feedback mechanism, that distinguishes the approach taken here from previous studies.

The manner in which the dependence of the velocity of flow on the overall oxygen concentration is calculated clarifies and eliminates a paradox in the vicious cycle (1) of sickle-cell disease. According to the vicious cycle, the fall of oxygen concentration as the cells move down the capillary leads to an increase in viscosity and a consequent decrease in cell velocity. However, since blood is effectively incompressible, one cannot reconcile a difference in velocities at the proximal and distal ends with the principle of conservation of mass flow through the capillary.

Although rheological changes in red cells due to reduced oxygen tensions occur very rapidly (7), shape changes of the red cells, which might be expected to more dramatically affect their passage through the capillary, occur more slowly, over times larger than the normal transit times of cells across a capillary. The transit times calculated as part of the present analysis can be used as a guide to the kinds and magnitudes of the sickling changes in the cells that might be expected under different physiological conditions.

The only previous work that has attempted a quantitative investigation of the interaction

between oxygen transport and the dynamics of red cell motion for sickle blood is that of Lomen and Gross (8). Although in spirit their work is close to that presented here, their analysis leads to misleading conclusions about the flow of sickle blood. We discuss this fully at the end of the Discussion.

MATHEMATICAL MODEL

We use the Krogh cylinder model and consider the transport of oxygen only. Cylindrical polar coordinates x, r, θ are used (Fig. 1), but it is assumed throughout that the problem is axially symmetric, so there is no θ dependence. The tissue element and the capillary are taken to be concentric cylinders of radii r_t and r_c, respectively, and of length L.

The problem of oxygen transport can be formulated either in terms of the oxygen concentration, c, or the partial pressure, Po_2, of oxygen in equilibrium with a solution at concentration c. These two quantities are related by Henry's law, $c = \alpha Po_2$, where α is the solubility constant. Throughout this paper Po_2 will be in units of millimeters of Hg, and c will be in some appropriate set of units, such as a volume fraction.

We now separately consider the capillary and tissue regions, assuming that steady-state conditions prevail.

Tissue Region: $r_c \leq r \leq r_t$

We assume that oxygen moves through the tissue by molecular diffusion only and is then consumed by metabolism. Previous studies of oxygen diffusion and transport using the Krogh model demonstrate that axial diffusion is negligible in the tissue region surrounding the capillary (9). To simplify the subsequent analysis we shall assume that the metabolic rate is constant, equal to A (rate of consumption of oxygen per unit volume of tissue). This approximation and simplification plus the assumption of steadiness reduce the equation governing the concentration of oxygen in the tissue to the form

$$D^t\left(\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r}\right) = A, \tag{1}$$

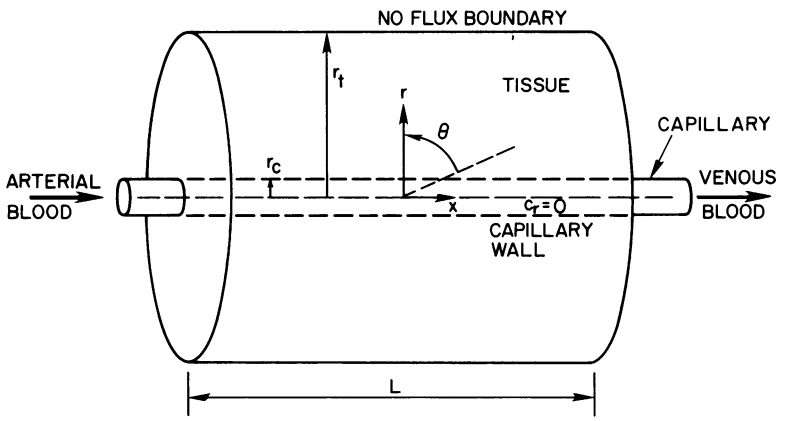

FIGURE 1 Krogh cylinder model and coordinate system.

where D^t is the (radial) diffusivity of oxygen in the tissue. (Whenever the need arises to distinguish values in the tissue from that in the blood, we shall use t for the former and b for the latter, either as subscript or superscript.)

Capillary Region: $0 \leq r \leq r_c$

The equation determining the oxygen concentration c in the capillary represents a balance between convection, diffusion, and production. As for the tissue region, other studies with the Krogh model indicate that in the capillary axial diffusion of oxygen is usually negligible compared to axial convective transport (9). In assuming further that in the capillary axial velocities are much greater than radial velocities, we can write the oxygen balance equation for the capillary, approximately, as

$$u\frac{\partial c}{\partial x} = D^b\left(\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r}\right) + d(c), \tag{2}$$

where u is the axial velocity, D^b is the (radial) oxygen diffusivity in blood, and d represents the production of oxygen due to the dissociation of oxyhemoglobin in the red blood cells.

The kinetics of the oxyhemoglobin dissociation process are very rapid compared to diffusion rates. The equilibrium state depends on the oxygen partial pressure of plasma external to the red blood cells and the carbon dioxide partial pressure. We shall assume that this state exists at every instant and that the fraction of oxygen bound to hemoglobin is always in equilibrium with the oxygen content of the plasma. Then $d(c) = -N(Ds/Dt)$, where N is the oxygen-binding capacity of blood and s is the fractional saturation (Fig. 2). The fractional saturation is assumed to be related to the concentration by the Hill equation, $s = K\mathrm{Po}_2^n/(1 + K\mathrm{Po}_2^n)$, where K is a constant depending on the ionic strength and pH of the hemoglobin solution and n is also a constant lying in the range of 2.5 ~ 2.7.

The Hill equation lacks the theoretical foundation of the Adair intermediate compound equation (10) and fails to represent adequately the saturation curve at its ends. The Hill equation is in fact reasonably successful within the range of 20–98% saturation, that part of the dissociation curve of main physiological interest. It is considerably simpler in form and

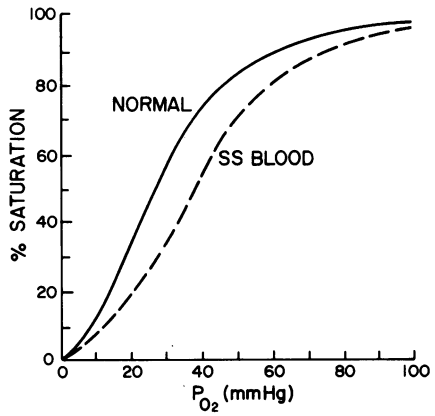

FIGURE 2 Oxygen dissociation curves of human normal hemoglobin and hemoglobin from individuals with sickle-cell anemia.

easier to work with. Moreover, since the constant K is equal to $(Po_2)_{50}^{-n}$, where $(Po_2)_{50}$ is the value of Po_2 at which the hemoglobin is 50% saturated, for the Hill equation, unlike the Adair equation, the rightward shift of the dissociation curve for sickle blood can be directly related to a change in just one constant. This facilitates comparisons between normal and sickle blood.

Using Henry's law, the Hill equation can be written in terms of c as

$$s = \frac{K'c^n}{1 + K'c^n}, \tag{3}$$

where $K' = K/\alpha^n$.

Eq. 2 may now be written

$$u\frac{\partial}{\partial x}(c + Ns) = D^b\left(\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r}\right), \tag{4}$$

or

$$u\left(1 + \frac{nNK'c^{n-1}}{(1 + K'c^n)^2}\right)\frac{\partial c}{\partial x} = D^b\left(\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r}\right). \tag{5}$$

Boundary Conditions

Continuity of oxygen flux at the capillary-tissue interface requires that

$$D^b\frac{\partial c}{\partial r}\bigg|_{\substack{r=r_c \\ \text{blood}}} = D^t\frac{\partial c}{\partial r}\bigg|_{\substack{r=r_c \\ \text{tissue}}}. \tag{6}$$

If we assume that the capillary wall offers negligible resistance to the diffusion of oxygen, then the oxygen partial pressure is continuous across the capillary wall, or since $c = \alpha Po_2$,

$$\frac{c}{\alpha_b}\bigg|_{\substack{r=r_c \\ \text{blood}}} = \frac{c}{\alpha_t}\bigg|_{\substack{r=r_c \\ \text{tissue}}}, \tag{7}$$

where α_b is the solubility of oxygen in blood, and α_t the solubility of oxygen in the surrounding tissue. (If the capillary wall offers resistance to diffusion, Eq. 7 must be replaced by another expression.)

Symmetry at the axis of the capillary requires that

$$\frac{\partial c}{\partial r}\bigg|_{r=0} = 0. \tag{8}$$

By assumption, the edge of the tissue cylinder, r_t, is chosen so that there is no flux of oxygen beyond this radius, therefore

$$\frac{\partial c}{\partial r}\bigg|_{r=r_t} = 0. \tag{9}$$

Boundary conditions Eqs. 6–9 apply for all x.

Probably the most physically realistic conditions at the proximal and distal ends of the

capillary would be specification of either concentration or axial flux at each end, i.e., for $0 \leq r < r_c, r_c < r \leq r_t$,

$$c \text{ at } x = 0 \text{ and}$$

$$\text{at } x = L, \tag{10 a, b}$$

or

$$\frac{\partial c}{\partial x} \text{ at } x = 0 \text{ and}$$

$$\text{at } x = L. \tag{11 a, b}$$

Eqs. 1 and 5 are to be solved subject to the boundary and end conditions Eqs. 6–8 and either Eq. 10 or 11. The equations and conditions are coupled to the fluid mechanics of the capillary blood flow through the appearance of the axial flow velocity u in the convective transport term of Eq. 5.

SOLUTIONS

Tissue

Eq. 1 is to be solved subject to boundary conditions Eqs. 7 and 9. (Note that Eq. 1 does not explicitly involve x; thus end conditions Eq. 10 or 11 cannot be imposed.) The solution is

$$c(x, r) = \frac{A}{4D^t}(r^2 - r_c^2) - \frac{A}{2D^t} r_t^2 \ln \frac{r}{r_c} + \frac{\alpha_t}{\alpha_b} c_b|_{r_c}. \tag{12}$$

Note that $c_b|_{r_c}$, the capillary oxygen concentration evaluated in the blood at the edge of the capillary, is still unknown and must be determined from matching with the capillary solution. It is this term alone which contributes the x dependence to c for the tissue because the first two terms on the right-hand side of Eq. 12 are independent of x.

From Eq. 12 and the boundary conditions Eq. 6 we readily obtain

$$\left.\frac{\partial c_b}{\partial r}\right|_{r=r_c} = \frac{A}{2r_c D^b}(r_c^2 - r_t^2), \tag{13}$$

a constant independent of x.

Capillary

Eq. 5 is nonlinear because of the second term in parentheses on the left-hand side; it is therefore impossible to solve in closed form. A well-known and often used technique for treating equations in which the nonlinearity appears as in Eq. 5 is to linearize them by making an approximation in which the coefficient of $\partial c/\partial x$ and the x variable are replaced by the introduction of a new independent variable. If, in the definition of this new independent variable, the coefficient of $\partial c/\partial x$ is evaluated at some particular value of r, rather than taken to be a constant, the method is known as the "modified Oseen approximation" (11). Both the coefficient and the new axial variable are determined as part of the solution.

Adopting this modified Oseen approach we set

$$\frac{dx}{d\xi} = u\left(1 + \frac{nNK'\hat{c}^{n-1}}{(1 + K'\hat{c}^n)^2}\right), \tag{14}$$

where $\hat{c}$ is the value of c evaluated at some appropriately defined value of r or is some other appropriately chosen characteristic value of c. (The choice of the right-hand side of Eq. 14 will be discussed more fully later.) Since the second term is always positive, the right-hand side of Eq. 14 is finite and greater than zero for $u > 0$; therefore Eq. 14 can always be solved for $x(\xi)$, and this transformation is one to one between x and ξ. Eq. 5 can now be written

$$\frac{\partial c}{\partial \xi} = D^b \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right). \tag{15}$$

The solution of this equation will be a function $c(\xi, r)$. Eq. 14 will determine, with the known $\hat{c}(\xi)$, the transformation $x = x(\xi)$. This relation together with $c(\xi, r)$ determines the solution $c(x, r)$ to the original problem.

Eq. 15 is solved subject to boundary conditions Eqs. 8, 13, and 10 *a*. In particular, for this last condition, we assume that $c = c_0(r)$ is the specified inlet profile at $\xi = 0$. (Note that conditions at $x = L$ cannot be imposed because the omission of axial diffusion in the equation for the capillary has changed the equation from elliptic to parabolic). The solution is

$$c(\xi, r) = \frac{A}{r_c^2}(r_c^2 - r_t^2)\left(\xi + \frac{r^2}{4D^b}\right) + k_1 + \sum_{\lambda_m} A_m e^{-\lambda_m^2 D^b \xi / r_c^2} J_0\left(\lambda_m \frac{r}{r_c}\right), \tag{16}$$

where the sum on the right-hand side is over all λ_m, the positive roots of $J_1(\lambda_m) = 0$, and k_1 and the A_m are constants, given in term of the profile at $\xi = 0$, by the expressions

$$k_1 = \frac{2}{r_c^2}\int_0^{r_c} c_0(r) r\, dr - \frac{A}{8D^b}(r_c^2 - r_t^2), \tag{17 a}$$

$$A_m = \frac{2}{r_c^2 J_0^2(\lambda_m)}\int_0^{r_c} r c_0(r) J_0\left(\lambda_m \frac{r}{r_c}\right) dr - \frac{A(r_c^2 - r_t^2)}{\lambda_m^2 D^b J_0(\lambda_m)}. \tag{17 b}$$

The tissue solution, Eq. 12, involves the unknown value $c_b|_{r_c}$. Determining this from Eq. 16 we obtain the final form of the tissue concentration

$$c(\xi, r) = \frac{A}{4D^t}(r^2 - r_c^2) - \frac{A}{2D^t} r_t^2 \ln\frac{r}{r_c} + \frac{\alpha_t}{\alpha_b}\left\{\frac{A}{r_c^2}(r_c^2 - r_t^2)\left(\xi + \frac{r_c^2}{4D^b}\right) + k_1 + \sum_{\lambda_m} A_m e^{-\lambda_m^2 D^b \xi / r_c^2} J_0(\lambda_m)\right\}. \tag{18}$$

Eqs. 16 and 18 for the capillary and tissue oxygen concentrations, respectively, are not sufficient to determine the axial variation until we determine the transformation from ξ to x. We shall turn to this shortly; first, we note some properties of the solutions already obtained.

PROPERTIES OF THE SOLUTIONS

First, we note that the infinite sums on the right-hand side of Eqs. 16 and 18 are spatial transient terms that effect the transition between arbitrary initial concentration profiles at $\xi = 0$ and the universal fully developed profiles far downstream. (The length of this transition or

developing region will be evaluated below.) These sums decay as $\xi \rightarrow \infty$ and do not contribute to the far downstream solution.

The average value of the concentration across the capillary cross section is defined as

$$c_{av} = \frac{1}{\pi r_c^2} \int_0^{r_c} c(\xi, r) 2\pi r dr. \tag{19}$$

From Eq. 16 we find that

$$c_{av} = \frac{A}{8D^b}(r_c^2 - r_t^2) + \frac{A}{r_c^2}(r_c^2 - r_t^2)\xi + k_1. \tag{20}$$

If we substitute for k_1, Eq. 17 *a*, in Eq. 20, we can write c_{av} as

$$c_{av} = (c_{av})_{\xi=0} - A\left(\frac{r_t^2}{r_c^2} - 1\right)\xi. \tag{21}$$

Thus c_{av} decreases linearly with increasing ξ from its initial value at $\xi = 0$.

The second term in the parentheses on the left-hand side of Eq. 5 represents the contribution to the local oxygen concentration from oxygen carried bound in oxyhemoglobin and liberated locally. We need to know how important this contribution is compared to the oxygen that is convected in dissolved unbound form. For normal blood for the range of oxygen tensions, 20 mm Hg $\leq P_{O_2} \leq$ 95 mm Hg

$$5.7 \leq \frac{nNK'c^{n-1}}{(1 + K'c^n)^2} \leq 194. \tag{22}$$

(We note that P_{O_2} = 95 mm Hg is the normal tension at the arterial end of a capillary, whereas P_{O_2} = 40 mm Hg is the normal venous end value.) The maximum value in this inequality occurs at approximately P_{O_2} = 20 mm Hg, whereas the minimum value occurs at P_{O_2} = 95 mm Hg. Thus

$$\frac{nNK'c^{n-1}}{(1 + K'c^n)^2} \gg 1 \tag{23}$$

except possibly near the arterial end of the capillary. These estimates for normal blood depend on the value of $(P_{O_2})_{50}$, the value of oxygen tension at which the blood is half-saturated, or $c = 0.5$. Sickle blood has a higher $(P_{O_2})_{50}$ than normal blood; in particular, $(P_{O_2})_{50}$ is shifted from ~25 mm Hg for normal blood to ~40 mm Hg for sickle blood. However, the value of N is less for such blood. The effect of these changes is to increase the lower bound in Eq. 22 from 5.7 to about 8.5, so that inequality (Eq. 23) is even stronger for sickle blood.

Apart from the linear terms in ξ, the solutions for the capillary and the tissue, Eqs. 16 and 18, depend on ξ only through the spatial transient terms appearing in the infinite sums. To estimate how important these terms are, we note that the first few roots of $J_1(\lambda_m) = 0$ are λ_m = 3.832, 7.016, 10.173, . . . ; thus the leading term in the sum behaves like $\exp(-\lambda_m^2 D^b \xi / r_c^2)$, where $\lambda_m = 3.832$. This term will be $O(1)$ when $\lambda_m^2 D^b \xi / r_c^2 = O(1)$, or $\xi =$

$O(r_c^2/14.24\ D^b)$. If, for purposes of estimation, we take $dx/d\xi \approx 80\ u$ = constant[1] so that $x \approx 80\ \mu\xi$, then in terms of x this estimate is equivalent, nondimensionally, to $x/r_c \approx O[(80\ ur_c)/14.25\ D^b]$. Taking as typical values for a capillary $r_c = 5\ \mu$m, $u = 300\ \mu$m/s, and $D^b = 1{,}000\ \mu$m^2/s, this yields $x/r_c \approx O(8)$. Thus the spatial transients, because of the entrance concentration profile, decay within a distance of the order of at most 10 capillary radii.

For sickle blood, for $0 \leq Po_2 \leq 95$ mm Hg, the maximum value of $N\,ds/dc$ occurs at $Po_2 \approx 30$ mm Hg and has approximately the value 72, so the above estimate of the distance for the spatial transients to decay applies to sickle blood also.

Eqs. 16 and 18 represent the solutions for oxygen concentration in the capillary and tissue as a function of ξ and r. To obtain the solutions in the physical plane we must solve Eq. 14. Before considering the question of how to determine the velocity u, let us consider some deductions immediately derivable from Eq. 14.

It follows immediately from Eq. 14 that $x > u\xi$, with the amount that x exceeds $u\xi$ depending on the magnitude of the oxyhemoglobin term.

Let us now consider the situation for sickle blood. The rightward shift of the hemoglobin saturation curve in sickle-cell anemia (Fig. 2) means that at higher oxygen concentrations, near the arterial end of the capillary, values of $N ds/dc$ are higher for sickle blood than for normal blood. This behavior can be shown quantitatively as follows: For the higher values of c that occur very near the arterial end, both for normal and sickle blood, $K'c^n \gg 1$, so $N ds/dc \approx nN/K'c^{n+1}$. It then follows that for a fixed high value of c,

$$\left.\frac{\left(\frac{ds}{dc}\right)_{s-c}}{\left(\frac{ds}{dc}\right)_{\text{normal}}}\right|_{\text{fixed } c} = \frac{N_{s-c}}{N_{\text{normal}}}\,\frac{K'_{\text{normal}}}{K'_{s-c}}.$$

This ratio is about 1.4. (Because n is fairly large (2.5 ~ 2.7), the validity of this particular approximation decreases rapidly as c decreases.) The effect then of the rightward shift is to make x bigger than the equivalent x for normal blood. Thus the rightward shift of the hemoglobin saturation curve is beneficial at least in that it means a given oxygen tension occurs further down the capillary. On the other hand, any decrease in u will tend to counterbalance the effect of a larger slope ds/dc, and tend to make $dx/d\xi$ smaller. Thus u plays a critical role in determining oxygen tension levels in the capillary. The determination of u is discussed in the next section.

DEPENDENCE OF FLOW UPON OXYGEN CONCENTRATION

We begin by considering more carefully what the velocity u represents.

In the Krogh model, the fluid under consideration is regarded as a single component homogeneous fluid. Thus, in applying the model with blood as the fluid, the fact that blood is a suspension of red cells (and other particulates) is overlooked, and physical parameters and

[1]This is a very conservative estimate, since 80 is the maximum value of the factor in parentheses on the right-hand side of Eq. 14 for 40 mm Hg $\leq Po_2 \leq$ 95 mm Hg and occurs at 40 mm Hg.

flow characteristics are assigned values which represent the behavior of the fluid as a whole. Our earlier discussion of the magnitude of the convective terms on the left-hand side of Eq. 5 made it clear that oxygen is transported mainly bound in oxyhemoglobin. Inasmuch as it then follows that the primary agents responsible for oxygen transport are the red blood cells, it is reasonable to interpret u appearing in Eqs. 5 and 14 as the red cell velocity, and we shall do so from this point on.

We now need to determine, for sickle blood, how the red cell velocity varies with oxygen tension levels. Experimental flow studies of sickle blood, for example filtration experiments, such as those of Messer and Harris (7) or Usami et al. (12), or viscometric studies, such as Usami et al. (13) and Roselli (14), cannot readily be interpreted in terms of red cell flow in the capillaries. There is, however, a theoretical model for such flow, assuming red cells move down the capillary in the so-called parachute shape. This theory, which assumes the existence of a thin lubricating film between each cell and the capillary wall, was introduced by Lighthill (3), refined by Fitz-Gerald (4, 5), and recently corrected by Tözeren and Skalak (6). As shown in the Appendix, it leads to the following relationship between the velocity u, the (hydrostatic) pressure drop across the red cell Δp, and the compliance β of the red cell,

$$\Delta p = \left[\left(\frac{E^*}{A^{*1/k}}\right)\left(\frac{\mu u}{(\kappa r_c)^{1/2}}\right)^{1/k} r_c^{\frac{k-2}{k}}\right]\beta^{\frac{1-k}{k}}. \qquad (24, \text{also A.4})$$

(The other quantities appearing are defined in the Appendix.)

As indicated earlier, conservation of mass requires that the mass flow velocity be constant along the capillary. Just above, u was taken to represent the red cell velocity. Since red cells and plasma have approximately the same density, the mass flow velocity and red cell velocity are identically the same only if the plasma and red cells move at the same velocity. In fact, the plasma in the capillary on the average moves slower than the cells. However, the difference in velocities is small enough (3, 4), perhaps at most a few percent, so that it will be neglected here. Henceforth, then, no distinction will be made between the red cell velocity and the mass flow velocity. This velocity should depend only on the total distribution of concentration and not on any particular local value. The manner in which this dependence is determined is described in the Calculations section.

In using this model here, we are assuming that the lubrication model applied to sickle cells enjoys roughly the same domain of validity as it does for normal cells. This could only be expected to be true for such cells when they are either fully oxygenated, and therefore relatively underformed, or if, at lower oxygen tensions, they have had insufficient time to grossly change from the discoid shape. This is probably not a stringent condition. The underlying premise of this study is that the sickle cells entering the capillary are oxygen-saturated and of normal shape, and changes that occur do so in response to falling oxygen tension along the capillary. The processes that are initiated by low oxygen tension and lead to gross configurational changes of the cell would probably take longer than the normal residence time of the sickle cell in the capillary. It has been observed experimentally that properties reflecting the rheological state of the cell change before there are any noticeable changes in shape. For example, Messer and Harris (7) observed changes in filterability within 0.12 s of sudden deoxygenation of blood from patients with sickle-cell disease, long before any noticeable shape changes.

Decreasing oxygen concentration with distance down the capillary will alter the properties of both the internal contents and the membrane of a red cell. In particular, it is well known that the hemoglobin within the cell undergoes, under sufficiently low oxygen tensions, a series of chemical and physical transformations leading to a gel and ultimately to a crystalline structure. What happens to the red cell membrane under the same conditions is not so well understood, although there is evidence that it becomes less flexible. The combined effect of both these changes is to make the cell more rigid and less flexible, characteristics which make themselves felt at the macroscopic level in terms of increased viscosity (13) and decreased filterability (7, 12). We do not yet know how to assign to the internal hemoglobin and the red cell membrane their separate contributions to the overall increased rigidity. On the other hand, only the red cell compliance β enters the expression for the pressure[2] drop across each cell, Eq. 24. In Lighthill's lubrication model, β is defined as the modulus of elastic compliance of the rim membrane and enters the mathematical formulation in the linear elastic relation between the pressure in the lubrication film and the radial displacement of the membrane. As long as the hemoglobin within the cell is, and remains, a viscous Newtonian fluid, and hence has no elastic response, it plays no role in determining the instantaneous elastic behavior of the cell membrane when subjected to a localized external pressure force. It may, however, seem inappropriate to use a relationship between u, Δp, and β alone to account for the decrease of velocity of a sickle cell in a capillary when this decrease may be due both to decreased elastic compliance of the membrane and to changes in the internal hemoglobin. Discussions in the literature suggest that in the presence of reduced oxygen tension the SS-hemoglobin[3] within a cell becomes more viscous, and that this increased viscosity makes the cell more rigid and leads to a decrease of cell velocity. Two difficulties arise immediately, however, if one attempts to make this association between increased hemoglobin viscosity and decreased cell velocity. First, after the cell membrane has reached an equilibrium configuration the only state of the fluid within the cell consistent with the assumption of steady flow is a state of uniform rest (15). Motion of the interior fluid is caused by the distortions to which the cell is subjected if it must deform to enter the capillary. However, these "entry" motions decay very rapidly. Second, even if there is motion of the interior fluid, all theoretical (16, 17) and experimental (18) investigations of liquid-filled membranes or droplets moving in narrow tubes indicate that the velocity of such objects becomes nearly independent of internal viscosity when it exceeds a small multiple, 5 or so, of the viscosity of the external medium. Thus, because the ratio of hemoglobin viscosity to plasma viscosity for a normal cell is about 5, the effect of increasing hemoglobin viscosity upon the cell velocity is minimal.

If, on the other hand, the gelation and crystallization of SS-hemoglobin within the cell cause it to exhibit some elastic properties, however, small, then these will alter the elastic response of the cell to external pressure. The sickling of the hemoglobin may also lead to

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[2]Throughout the remainder of the article, pressure, whenever it appears without a modifier, will be assumed to refer to hydrostatic pressure. Since the oxygen level is primarily specified in terms of concentration c, rather than partial pressure Po_2, there should be no ambiguity in using this abbreviated terminology.

[3]SS-hemoglobin is the designation for the hemoglobin found in the red cells of individuals who are homozygous for the gene responsible for hemoglobin S (HbS) production, and therefore have sickle-cell disease. Individuals heterozygous with respect to this gene have sickle-cell trait; the hemoglobin in their red cells is a mixture of hemoglobin A (HbA) and hemoglobin S and is denoted by the symbol AS. Normal hemoglobin is denoted by AA.

interactions with the membrane (19) that affect the elastic response of the cell. We may think of β in the u-Δp-β relation above, therefore, as representing either one or both of these other effects in addition to changes in the membrane compliance itself under reduced oxygen tension.

We come now to the relatioship between β and c. A good deal of recent work has attempted to describe the kinetics of part or all of the processes that take place between the initial deoxygenation of SS-hemoglobin and the final crystalline state (20–22). A wide gap, however, separates our understanding of these processes from our ability to predict the variation of macroscopic rheological behavior with oxygen concentration. Our considerations will therefore necessarily be *ad hoc* and speculative. We do hope that the principal features and characteristics of the problem will emerge even with the use of primitive relationships.

We shall assume that β and c are related by

$$\frac{\beta}{\beta_0} = \left(\frac{c}{c_0}\right)^j, \tag{25}$$

where j is some positive constant, β_o is the compliance of a normal cell, assumed constant, and $c_o = 28.5 \times 10^{-4}$ ml 0_2/ml plasma, the concentration at the arterial end of the capillary. (This expression is assumed to hold only for those values of c found in the capillaries, so the perhaps unrealistic behavior as $c \rightarrow 0$ implied by Eqs. 24 and 25, namely that $u \rightarrow 0$, is not encountered.) Eq. 25 may be regarded as an *ad hoc* representation of the expected relationship between compliance and concentration over the narrow ranges of values of both these quantities in the capillaries. Greater justification for this particular choice is given below.

The value $j = 0$ in Eq. 25 represents those cases where compliance and concentration are not coupled, or cases where, although they are coupled, and perhaps even strongly, the characteristic time or times for significant sickling changes are so large that in fact the compliance changes little. It would be useful if we could obtain a reasonable upper bound for j. As suggested earlier, there appears to be nothing available in the literature which directly relates to this quantity. This leads us to make a speculative argument as follows. According to Fitz-Gerald (4) β is inversely proportional to S, the "resistance to bending." Thus, instead of a β-c relationship, we can write a resistance-concentration relationship, of the form

$$\frac{S}{S_o} = \left(\frac{c}{c_o}\right)^{-j} = \left(\frac{Po_2}{(Po_2)_o}\right)^{-j}, \tag{26}$$

where $(Po_2)_o$ is the value of Po_2 when the cells are fully oxygenated. Fig. 4 shows on a log-log plot the solid curve shown in Fig. 3 as the best fit by Usami et al. (12) to their data, obtained by microsieving, on the relationship between relative resistance and Po_2. (The circled points in Fig. 4 are points read off their solid curve; the solid curve in Fig. 4 represents our best fit to these points.) If one interprets their (nondimensional) R as being equivalent to S/S_o, then Fig. 4 should represent the relationship given in Eq. 26. Excluding the 30 mm Hg point, because it lies near the lowest values of Po_2 encountered in our calculations and occurs in our work near the distal end of the capillary, and specifying a power-law relation between R(or S/S_o) and Po_2, which we see from Fig. 4 is a good approximation to the other points, we find that $j = 2.0$ represents the best fit with a very high significance ratio. This suggests that $j = 2$ may be a

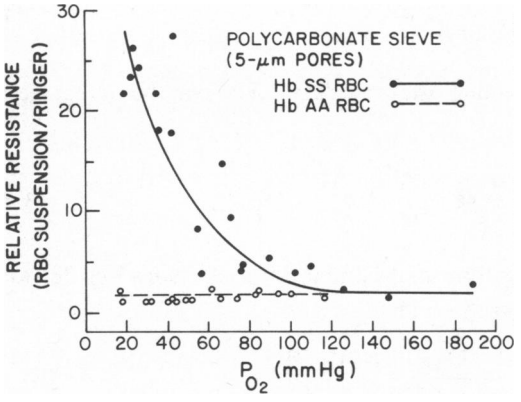

FIGURE 3

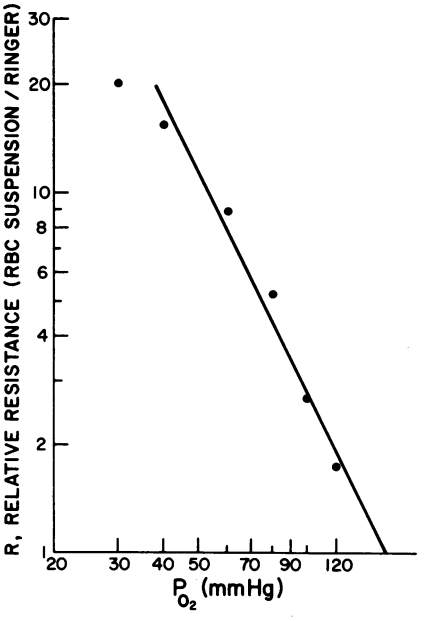

FIGURE 4

FIGURE 3 Relationship between relative resistance and Po_2. (From Usami et al. [12].)
FIGURE 4 Log-log plot of relationship between relative resistance and Po_2 (replot of Fig. 3; solid circles are points read off solid curve of Fig. 3).

reasonable upper bound for this parameter. That this value of j is an upper bound stems from the fact that, in the Usami et al. (12) miscrosieving experiment, at each specified Po_2 the HbSS blood was allowed sufficient time to equilibrate with the oxygen tension. If one assumes a finite lag time between deoxygenation and the effects resulting therefrom, then one should expect that, in the capillary flow an expression of the form in Eq. 26 with $j = 2$ will predict resistance higher than that to be expected at any instantaneous value of Po_2. Thus the equilibrium expression of Eq. 26 with $j = 2$ should represent an upper bound for S and therefore a lower bound for β at any value of Po_2 (or c). Therefore, we will carry out calculations for $0 \leq j \leq 2$, covering the range between the case where compliance and concentration are uncoupled up to the equilibrium coupling case.

CALCULATIONS

Before presenting the final forms of the equations we introduce nondimensional variables. It is convenient to nondimensionalize the independent variables using as the characteristic velocity the (constant) velocity of a normal red cell u_o and a typical capillary length l. (Thus l/u_o is the time it takes a normal red cell to traverse the capillary of length l.) Nondimensional x and ξ are then defined by

$$\bar{x} = \frac{x}{l}, \quad \bar{\xi} = \left(\frac{u_o}{l}\right)\xi. \tag{27}$$

For the sample calculations to be reported in this paper, we have used for $\hat{c}(\xi)$ the average

value of c across the capillary, Eq. 21. In nondimensional form $\hat{c}(\xi)$ can be written

$$c_{av}(\bar{\xi}) = a - b\bar{\xi} = \hat{c}(\bar{\xi}), \tag{28}$$

where $a = (c_{av})_{\xi=0}$ and $b = A(r_t^2/r_c^2 - 1)l/u_o$.

Using the definition of s and Eq. 28, Eq. 14 can be rewritten nondimensionally as

$$\frac{d\bar{x}}{d\bar{\xi}} = \frac{u}{u_o}\left(1 + N\frac{ds}{d\hat{c}}\right) = \frac{u}{u_o}\left(1 - \frac{N}{b}\frac{ds}{d\bar{\xi}}\right). \tag{29}$$

Since u has been assumed to be constant along the capillary, this can be integrated immediately, to yield

$$\bar{x} - \frac{u}{u_o}\frac{N}{b}s(0) = \frac{u}{u_o}\left(\bar{\xi} - \frac{N}{b}s(\bar{\xi})\right), \tag{30}$$

assuming that $\xi = 0$ when $x = 0$. Substituting for s and eliminating $\hat{c}(\xi)$ using Eq. 28, we obtain the final form of the transformation between ξ and x

$$\bar{x} = \frac{u}{u_o}\left[\bar{\xi} + \frac{N}{b}\left\{s(0) - \frac{K'(a - b\bar{\xi})^n}{1 + K'(a - b\bar{\xi})^n}\right\}\right]. \tag{31}$$

Since, from this point on, only $s(c)$, and not its slope, appears in the analysis, the use of the Hill equation, whose slope departs first from the true dissociation curve, rather than the Adair equation, becomes an even better approximation.

We shall concern ourselves here only with the average value of c across the capillary; henceforth, whenever c appears, it is to be interpreted as c_{av}. That this is not an unreasonable approximation is supported by the numerical results of Reneau et al. (9), which indicate that the $c(\xi, r)$ profile, at least for the normal case, is very flat over most of the cross section of the capillary. Thus, from this point on, c and $\hat{c}$ are equivalent quantities. Also, since from now on, only the concentration in the blood appears, c is to be interpreted as having the units milliliter O_2/milliliter plasma.

At this point we shall describe the broad outlines of the solution procedure and the philosophy underlying it. Our primary aim is to compare the sickle with the normal case. The base normal case assumes that, at the arterial end of the capillary, P_{O_2} = 95 mm Hg, and at the venous end, P_{O_2} = 40 mm Hg. The characteristic velocity u_o, introduced above, is taken to be the actual normal red cell velocity, the actual length of the capillary is then determined by solving Eqs. 28 and 31 simultaneously. For an assumed hematocrit, the total (hydrostatic) pressure drop across the capillary for the normal case is calculated by adding the contribution from the intervening plasma regions to the sum of the pressure drops across each cell. This total (hydrostatic) pressure drop is assumed to have the same value for the sickle case. Underlying this is the more fundamental assumption that the pressure drop across the capillaries is primarily controlled by factors external to the capillaries, such as the state of dilatation of the arterioles, and further, that under normal conditions the capillary pressure drop is the same for the sickle cell-diseased individual as for the normal.

The calculation for the sickle case is begun by choosing a value of u, the (constant) sickle cell velocity. (The capillary length is that calculated above for the normal case.) The oxygen

concentration and the total (hydrostatic) pressure drop across the capillary for this case are then calculated. If this calculated total pressure drop is not equal to that for the normal case we choose another value for u and repeat the entire calculation. This iteration on u is carried out until the total pressure drop for the sickle case agrees (to a specified accuracy) with the normal value (which remains unchanged throughout the iteration). In this way we determine the velocity of the sickle cells. Thus, the oxygen concentration in the capillary affects the cell velocity through its effect upon the pressure gradient available to drive the cells. As part of the solution we also determine the concentration c along the capillary, the comparison of this quantity for both the normal and sickle cases being one of our principal interests.

The second major part of the calculation consists of observing the effect of decreasing (hydrostatic) pressure drop across the capillary upon the flow in the sickle-cell case. The normal case is dropped, the pressure drop is systematically decreased by 5% increments, and the solution is obtained for each such case. Because of the complex interaction between Δp, u, and c, u decreases by an amount much different from 5% for each case. We continue decreasing the pressure drop by 5% increments until we reach the case for which the pressure drop has been decreased by 50%, unless at some earlier point the solution predicts a zero value of u, in which event the calculation terminates.

Returning now to the details of the calculation, we note first that we can identify c_o (appearing in Eq. 25) with $(c_{av})_{\xi=0}$. For normal blood, both have the value 28.5×10^{-4} (corresponding to $Po_2 = 95$ mm Hg). For a variety of reasons, the oxygen concentration of sickle blood at the arterial end of the capillary is usually low (23), normally between 21.0 and 27.0×10^{-4} (70 mm Hg $\leq Po_2 \leq$ 90 mm Hg). For sickle blood we have used the value $c_o = (c_{av})_{\xi=0} = 25.5 \times 10^{-4}$ ($Po_2 = 85$ mm Hg), a value at the high end of this range. There are a number of constants appearing in Eqs. 28 and 31 which must be specified before the integration can proceed. In lieu of better information, the constant A is assigned the value 5×10^{-4} ml 0_2/ml-s, the value of oxygen metabolism in the brain. There is considerable question regarding an appropriate value for r_t and how this quantity varies from tissue to tissue. For the sample initial calculations we use $r_t = 10\, r_c$, which lies well within the range of extreme values represented in the literature. For n we use the value $n = 2.7$. (At a pH of 7.35, n for sickle cell blood is closer to 3.0, rather than this normal blood value 2.7 [24]. However, using the value 2.7 causes the percent saturation for sickle cell blood to differ from the actual value by a maximum of 4% at any physiological value of c and generally much less than this amount.) The oxygen-binding capacity of blood, N, is usually taken to have the value 0.2 ml 0_2/ml blood. We use this value for normal blood; for sickle-cell blood, we use this value reduced by the ratio of the sickle cell to the normal hematocrit. The quantity K' can be represented as $K' = [\alpha(Po_2)_{50}]^{-n}$ = milliliter plasma/milliliter 0_2. Because of the rightward shift of the hemoglobin saturation curve in sickle-cell anemia, K' is different for normal and sickle blood. For normal blood $K' = 2.32 \times 10^8$. For sickle blood, using the value $(Po_2)_{50} = 40$ mm Hg, $K' = 7.70 \times 10^7$. (We use for the solubility constant, $\alpha = 3 \times 10^{-5}$ ml 0_2/ml plasma $-$ mm Hg.)

The only constants which have not yet been assigned values are r_c, l, and u_o. We carry out calculations separately for the three capillary radii $r_c = 3.5$, 3.0, and 2.5 μm. For typical normal red cell velocity we take $u_o = 500$ μm/s; we set $l = 600$ μm. However, as indicated above, there is no a priori way of knowing if, at this arbitrarily chosen value of l, the value of c

will be 1.20×10^{-3} (or $Po_2 = 40$ mm Hg), the oxygen concentration at the venous end of the capillary under normal conditions. Calculation of the actual capillary length will be described below.

Consistent with our earlier discussion we write Eq. 25 in the form $\beta/\beta_o = (\hat{c}/c_o)^j$, where $c_o = (c_{av})_{\xi=0}$. According to Fitz-Gerald (4), for the normal cell, $\beta = r_c^2/15S = \beta_o$, where S is the "resistance to bending" and is ~0.0185 dyn/cm; thus we can write $\beta = (r_c^2/15S)\,(\hat{c}/c_o)^j$. If this is substituted in Eq. 24 we obtain

$$\Delta p = \left[\left(\frac{E^*}{A^{*1/k}}\right)\left(\frac{\mu u}{(\kappa r_c)^{1/2}}\right)^{1/k} r_c^{-1}\right](15S)^{\frac{k-1}{k}}\left(\frac{\hat{c}}{c_0}\right)^{\frac{j}{k}(1-k)}. \tag{32}$$

Since we expect values of $(\kappa r_c)^{1/2}$ to be close to unity (3, 4), we use this value throughout the calculations. Eq. 32 is the final form of the expression used for the calculation of the pressure drop across each cell. In this form it applies only to sickle blood; for normal blood we use this same expression with the $\hat{c}/c_o$ term missing, and with u set equal to u_o.

The calculation of the total pressure drop across the capillary must include the sum of the drops across all the individual cells and the contribution from the plasma regions separating cells. We assume that the plasma behaves as a Newtonian fluid and that the flow is Poiseuille, so the pressure change across each such region of length Δz is given by

$$\frac{\Delta p}{\Delta z} = \frac{8\mu}{r_c^2}(u_{av})_p = \frac{8\mu}{r_c^2}u, \tag{33}$$

where $(u_{av})_p$ is the average velocity in the plasma regions. The equality of the last two parts of this equation results from our approximation that the average velocity and the red cell velocity are the same. In making this equivalence, we are neglecting the effect of plasma leakback (3, 4, 6), which is responsible for the average plasma velocity being less than the red cell velocity. However, the difference between these is generally <10%. Moreover, the contribution of the plasma regions to the total pressure drop is at least one order smaller than that of the cells, so any small error in the former is further mitigated.

To calculate the total pressure drop due to the cells and intervening plasma, we must determine the number of cells and plasma regions in the capillary. In doing so we must take into account the major difference in hematocrit between normal blood and sickle-cell blood. We use the value $H = 0.45$ for the former and $H = 0.25$ for the latter. (H represents fractional hematocrit, i.e., the ratio of the volume of red cells to the total blood volume, rather than the more traditional percentage hematocrit, for which the values would be 45% and 25%, respectively.) We also take into account that the volume of a cell remains constant. If V_{RBC} is the volume of a red cell (assumed to be the same value for normal and sickle blood), then the number of cells $\hat{N}$ in a capillary of length L is given by

$$\hat{N} = \left(\frac{\pi r_c^2 L}{V_{RBC}}\right)H. \tag{34}$$

If we assume, crudely, that each cell is approximately a right circular cylinder of height w, then $w = V_{RBC}/\pi r_c^2$. (The value 1×10^{-10} cm^3 has been used for V_{RBC} [25].) The total pressure

drop across all the plasma regions is then given by

$$\hat{N}\Delta p = \frac{8\mu}{\pi r_c^4}\hat{N}V_{\mathrm{RBC}}\left(\frac{1}{H} - 1\right)u. \tag{35}$$

We assume that the true capillary length (L) is that at which, with the constant velocity u_o, the oxygen concentration in the normal case reaches the specified value $\hat{c}(L) = 1.20 \times 10^{-3}$ at the venous end. The procedure in this case is as follows: we solve Eq. 28 for $\bar{\xi}_L$, the value of $\bar{\xi}$ at which this value of $\hat{c}(L)$ is reached,

$$\bar{\xi}_L = \left(\frac{u_0}{l}\right)\frac{(c_{\mathrm{av}})_{\bar{\xi}=0} - \hat{c}(L)}{A\left(\frac{r_t^2}{r_c^2} - 1\right)}. \tag{36}$$

Having determined $\bar{\xi}_L$, we then evaluate Eq. 31, using values of the constants appropriate for the normal case, for this value $\bar{\xi}_L$ and thus determine a corresponding $\bar{x}_L$. This now determines $x_L = l\,\bar{x}_L = L$, the actual length of the capillary.

We now describe the solution procedure in detail. We begin by choosing a value of u. With $\bar{\xi}_L$ and $\bar{x}_L$ calculated, the transformation between $\bar{\xi}$ and $\bar{x}$ for both the normal and sickle cases is determined from Eq. 31, in which the different values of K' are used for the two cases, and in the normal case u/u_o is set identically equal to one. Eq. 28 is then used to calculate $\hat{c}(\bar{\xi})$ for $0 \le \bar{\xi} \le \bar{\xi}_L$ and, through the transformation, as a function of the normal and sickle cell $\bar{x}$. With the assumed values of normal and sickle fractional hematocrit the number of cells in the capillary of length L for the two cases is calculated. Next the total pressure drop across the plasma regions for both cases is calculated using Eq. 35. At this point in the numerical work it is convenient to rescale $\bar{x}$ so that it lies between 0 and 1 not in the initially assumed length l, but in the capillary of actual length L. Defining this new variable by X, this is accomplished by setting $X = \bar{x}/\bar{x}_L$. Next the location of the center of each red cell is determined for each case, assuming one cell has just fully entered the capillary and one just fully exited, from the expression

$$X_{\mathrm{RBC}}^{(r)} = (r - 1)\frac{1}{\hat{N}} + \frac{1}{2}\frac{w}{L}, \quad r = 1, 2, \ldots, \hat{N}, \tag{37}$$

where $X_{\mathrm{RBC}}^{(r)}$ denotes the center of the rth cell. We now interpolate among the tabulated values of $\hat{c}(\bar{\xi})$ and the transformation $\bar{x} = \bar{x}(\bar{\xi})$ to find the value of $\hat{c}$ at the points $X_{\mathrm{RBC}}^{(r)}$ for the normal and sickle cases. Eq. 32 is then used to calculate the pressure drop across each cell for the normal and sickle cases. (For the normal case, with Eq. 32 modified as described below that equation, Δp is the same across each cell; for the sickle case Δp is different for each cell because $\hat{c}$ is.) The total pressure drop due to all the cells is then obtained for both cases by summation over the $\hat{N}$ cells of all these individual pressure drops. The final total pressure drop across the entire capillary for both cases results from adding this total cell pressure drop to the total pressure drop across all the plasma regions calculated above.

This series of calculations is carried out for three capillary radii, $r_c = 2.5$, 3.0, and 3.5 μm, and for each of these radii, for $j = 0$, 0.2, 0.5, 1, and 2.

RESULTS AND DISCUSSION

We recall that the calculation was begun with a nominal assumed capillary length of $l = 600$ μm, and that the actual length was determined in the course of the calculation. This length, which is independent of r_c, turns out to be 457 μm. The values of the normal total pressure drop across the capillary, denoted by ΔP, for the three capillary radii considered are:

$$(\Delta P)_{\text{total}} = \begin{cases} 1.04 \times 10^4 \text{ dyn/cm}^2 = 7.88 \text{ mm Hg for } r_c = 3.5\mu\text{m} \\ 1.24 \times 10^4 \text{ dyn/cm}^2 = 9.30 \text{ mm Hg for } r_c = 3.0\mu\text{m}. \\ 1.50 \times 10^4 \text{ dyn/cm}^2 = 11.25 \text{ mm Hg for } r_c = 2.5\mu\text{m}. \end{cases} \quad (38)$$

Fig. 5–7 show c vs. X ($0 \leq x \leq L$), i.e., the concentration along the entire length of capillary, for the three capillary radii and various choices of j and reduced pressure gradients. (In these and subsequent figures $n\%\Delta P$ represents $n\%$ of the pressure gradient of the equivalent normal case.) In choosing the j and pressure gradients shown we have attempted to illustrate "typical" as well as extreme cases.

We can see from Figs. 5–7 that, for some of the cases when the pressure gradient across the capillary in the sickle case is the same as in a normal capillary, the 0_2 concentration generally remains somewhat above that in a normal capillary, however strong the coupling of the compliance of the red cells with the 0_2 concentration. i.e., whatever the value of j. For the three capillary radii, in fact, the lowest concentration for any $j \leq 1$ at the distal end is 1.39×10^{-3} or about 46 mm Hg, as against 1.2×10^{-3} or 40 mm Hg for the normal case. Thus, in these cases the effects of the rightward shift of the oxyhemoglobin dissociation curve and the higher cell velocity overwhelm any detrimental rheological changes. Maintaining high

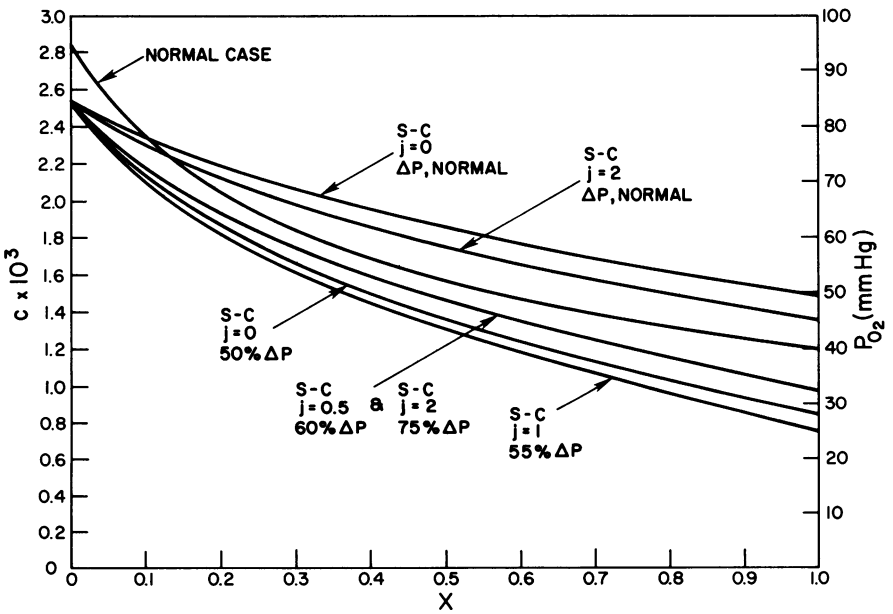

FIGURE 5 Oxygen concentration variation with (nondimensional) distance along capillary for a number of values of j and total pressure drop across the capillary (capillary radius, $r_c = 3.5 \times 10^{-4}$ cm).

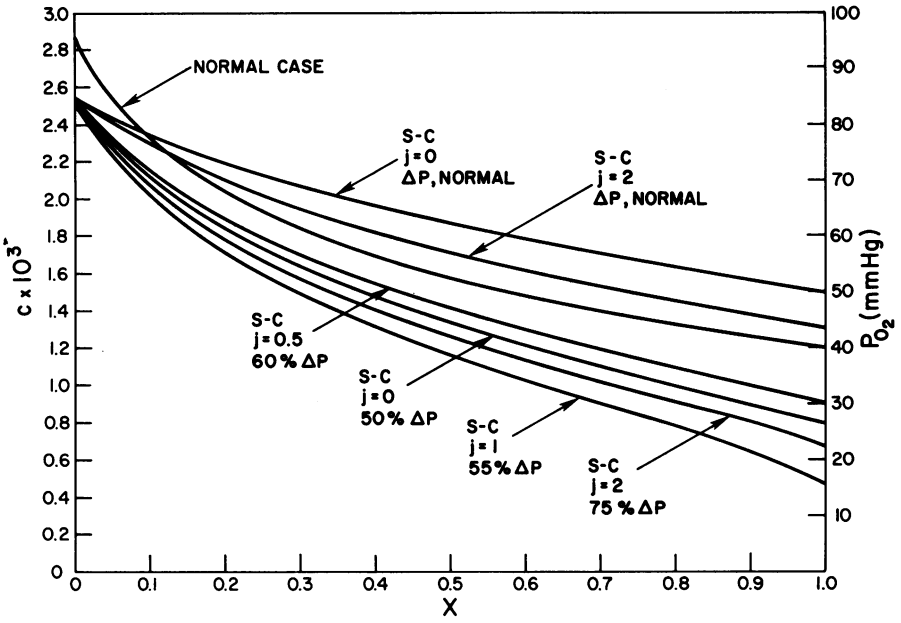

FIGURE 6 Oxygen concentration variation with (nondimensional) distance along capillary for a number of values of j and total pressure drop across the capillary (capillary radius, $r_c = 3.0 \times 10^{-4}$ cm).

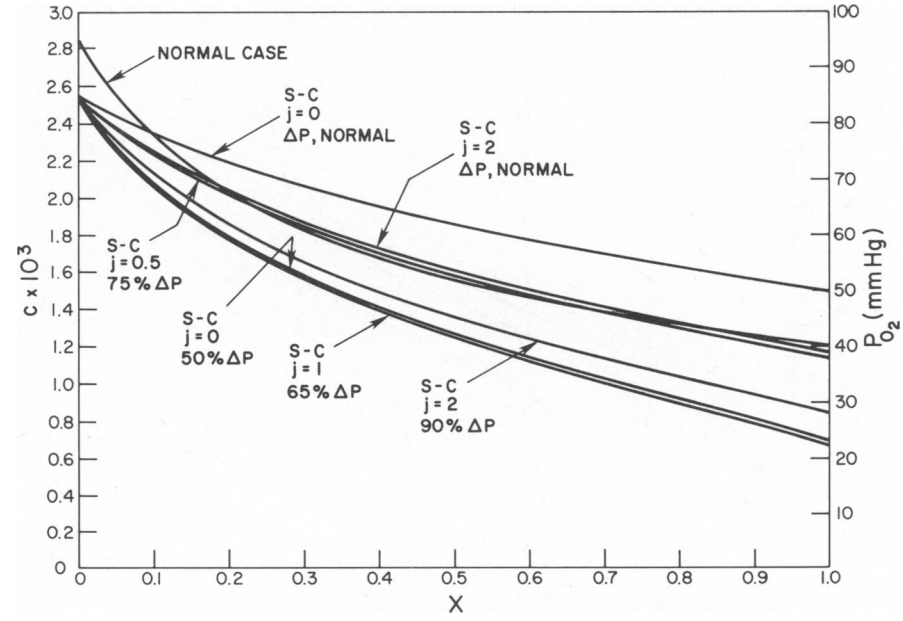

FIGURE 7 Oxygen concentration variation with (nondimensional) distance along capillary for a number of values of j and total pressure drop across the capillary (capillary radius, $r_c = 2.5 \times 10^{-4}$ cm).

concentration levels has at least two beneficial, interactive, consequences: (*a*) there is little tendency for the cells to begin undergoing the sickling process; and (*b*) their velocity of passage through the capillary remains so high that even if sickling begins there is little time for it to progress very far before the cells exit. We shall discuss this latter point in some further detail later.

The same statement about the concentration remaining near or above the normal case applies for any j for slight reductions (say up to 10–15%) in total pressure drop. For larger pressure reductions, for any value of j, the situation changes dramatically, and the concentration levels fall below the normal, and in the case of very large values of these parameters, very considerably below. Thus, for large pressure reductions with some minimum coupling between concentration and cell compliance, the combined and coupled effects of lessened cell velocity and compliance overwhelm the rightward shift of the oxyhemoglobin dissociation curve.

Fig. 8–10 show, for the three capillary radii and a number of values of j, the variation of u/u_o (the ratio of the velocity of sickle cells under conditions of reduced driving pressure to the velocity of normal cells subject to normal pressure gradients) with pressure drop. We note that at normal pressure the cell velocities for all the cases considered are between 1 and 1.7 times the velocity of a normal cell; this result is a direct consequence of the difference in hematocrits. We note further that for any value of j there is a steep decrease in cell velocity with decreasing pressure drop. The nonlinearity of the relationship between u and ΔP (unlike for example, Poiseuille flow) is obvious in these figures. Thus, for example, a halving of ΔP results in a velocity decrease by a factor of two to three or more. The early termination of some of the curves in these figures reflects situations for which the next 5% decrease in ΔP would lead to stagnation of the flow, and so indicates flows whose velocity has decreased by even larger factors. Although most of the curves in Figs. 8–10 exhibit similar behavior, the steepness of the $j = 2$ curves for the 3.0- and 2.5-μm capillaries (Fig. 9) is striking; for the

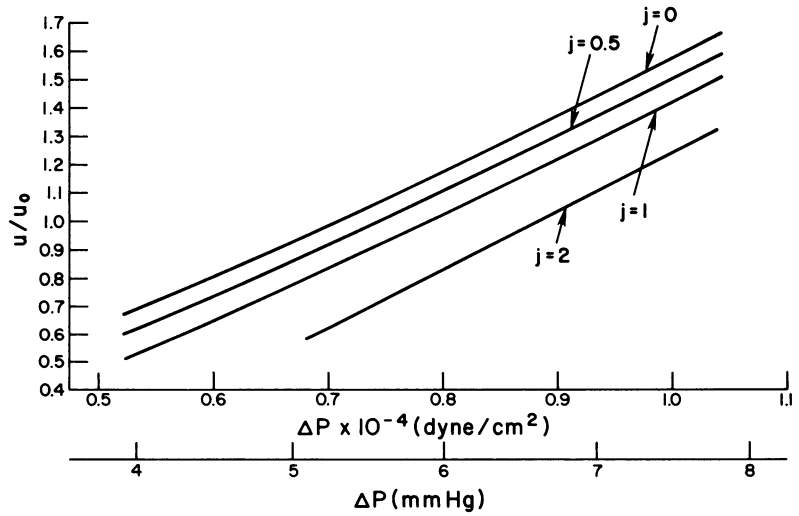

FIGURE 8 Variation of red cell velocity with total pressure drop across capillary for a number of values of j (capillary radius, $r_c = 3.5 \times 10^{-4}$ cm).

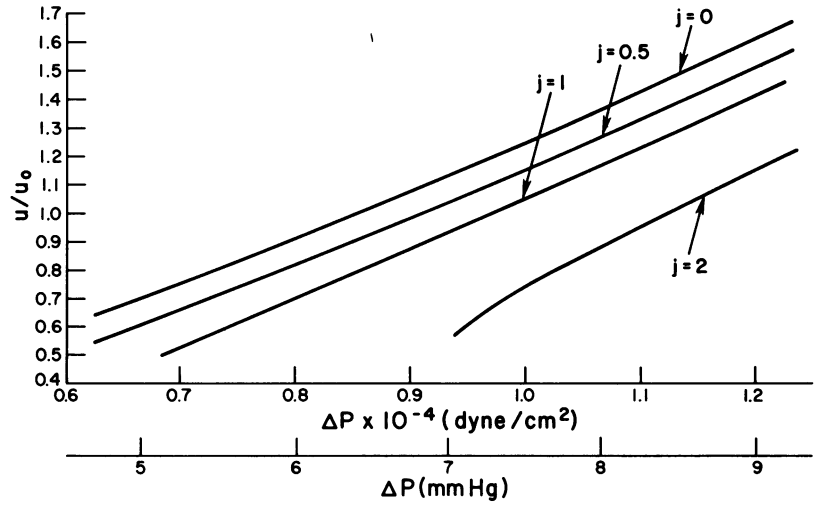

FIGURE 9 Variation of red cell velocity with total pressure drop across capillary for a number of values of j (capillary radius, $r_c = 3.0 \times 10^{-4}$ cm).

2.5-μm capillary, for example, a decrease of 10% in pressure drop results in a 35% decrease in velocity.

Usami et al. (12) used a microsieving or filtration technique to study the deformability of sickle cells as a function of oxygen tension. Their principal results are summarized in Fig. 3. The ordinate, relative resistance, is defined as the ratio of the pressure necessary to force a HbSS red blood cell suspension through a polycarbonate sieve with micropores 5 μm in diameter to the pressure necessary to force a cell-free Ringer solution through the sieve at the same flow rate. Usami et al. identify a P_{O_2} of 80 mm Hg as the value below which a noticeable

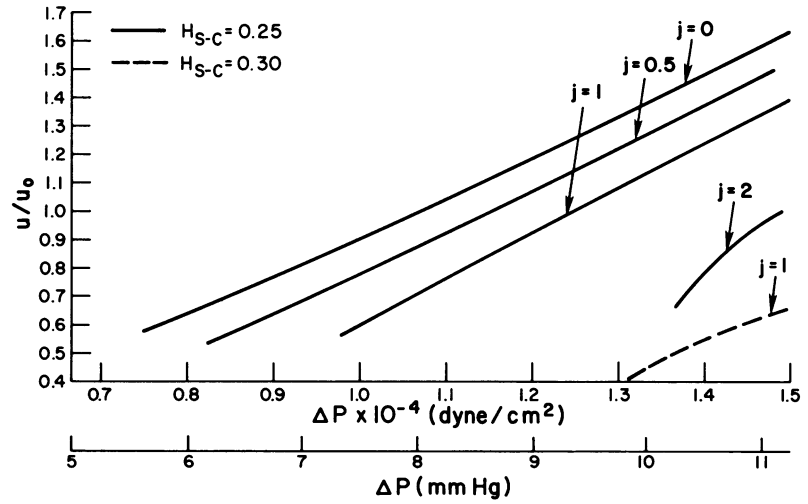

FIGURE 10 Variation of red cell velocity with total pressure drop across capillary for a number of values of j (capillary radius, $r_c = 2.5 \times 10^{-4}$ cm).

increase in the relative resistance R becomes evident. Fig. 3 illustrates the rapid increase in R that occurs as Po_2 is reduced below this value. Earlier work by this same group of investigators (13) had suggested that 60 mm Hg was the critical value of Po_2 below which significant rheological changes occurred. However, this was based on measurements of apparent viscosity in a coaxial cylinder viscometer. Although measurements in such a device would undoubtedly be influenced by changes in the deformability of HbSS erythrocytes, measurements in a filtration experiment would appear to be more sensitive to deformability changes. That is, in the latter experiment, much of the resistance to flow probably results from the necessity to distort individual red cells to enable them to enter the narrow pores, and thus, although it cannot definitely be inferred from the data, much of the pressure increase with deoxygenation may be due to the increasing resistance of the cell membranes to configurational changes. Since it is just this latter effect that is most relevant to the present analysis, 80 mm Hg appears to be the more appropriate determinant of the onset of cell deformability changes.

From the solutions obtained one may readily determine for each case the point in the capillary at which Po_2 has decreased to a value of 80 mm Hg (or a concentration value of 2.4×10^{-3}). Then, with the value of red cell velocity u appropriate to the case, it is possible to calculate the time that the red cells will remain in the capillary, after reaching this value, before exiting. The significance of this time, which we shall call *residence time,* is as a measure of the time available for morphological and rheological changes associated with sickling to occur. Short residence times are advantageous, since even if the concentration falls to low values, it is quite possible that little change will occur in the deformability of the cell during its transit through the capillary. Figs. 11–13 show, for the three capillary radii and a

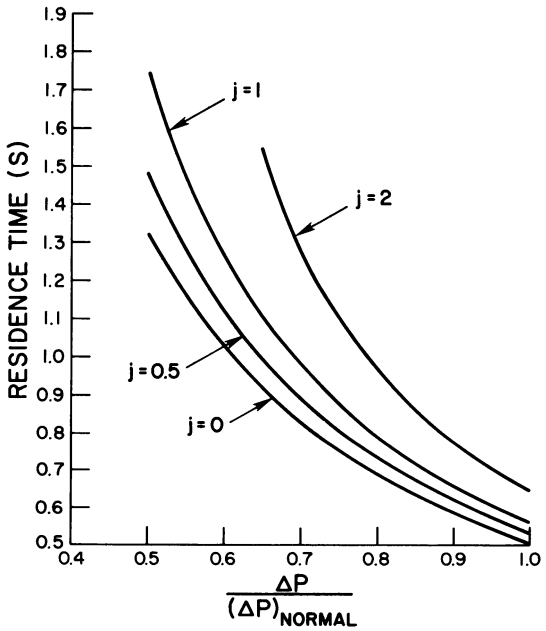

FIGURE 11 Residence times of red cells at oxygen tensions below 80 mm Hg as a function of (nondimensional) total pressure drop across capillary for various values of j (capillary radius, $r_c = 3.5 \times 10^{-4}$ cm).

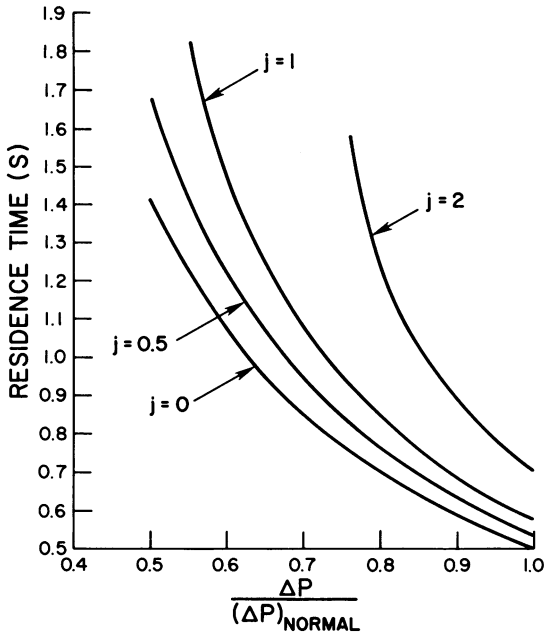

FIGURE 12 Residence times of red cells at oxygen tensions below 80 mm Hg as a function of (nondimensional) total pressure drop across capillary for various values of j (capillary radius, $r_c = 3.0 \times 10^{-4}$ cm).

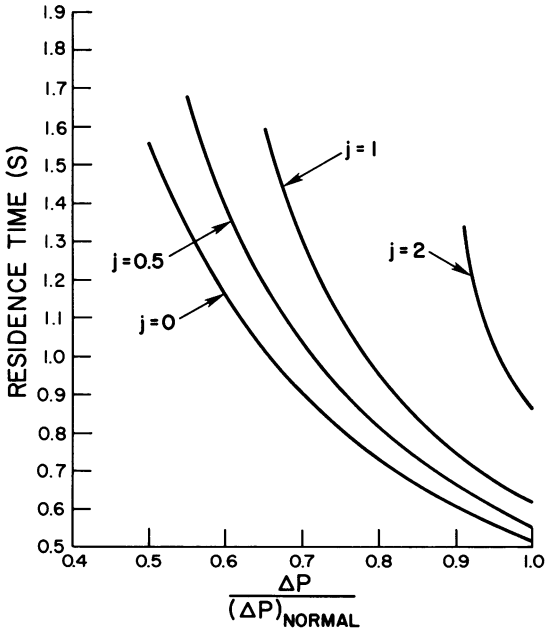

FIGURE 13 Residence times of red cells at oxygen tensions below 80 mm Hg as a function of (nondimensional) total pressure drop across capillary for various values of j (capillary radius, $r_c = 2.5 \times 10^{-4}$ cm).

number of values for j, the variation of residence time with pressure drop across the capillary (this latter quantity is made nondimensional with respect to the pressure drop in the normal case). For all three capillary radii, the time for a normal cell at the normal pressure level to transit the entire length of capillary is 0.915 s. All the curves show a very steep rise as ΔP decreases. This is evident even for low values of j and becomes quite remarkable for larger j. For the cases illustrated in these figures, over the pressure range shown, the residence times increase by a factor of two to more than three. The larger times are comparable to and in some cases exceed the times quoted in the literature for significant rheological changes to occur in sickle cells.

It was noted earlier that the oxygen concentration of sickle blood entering the capillary is usually low (23), lying in the range $21.0–27.0 \times 10^{-4}$ (70 mm Hg $\leq P_{O_2} \leq$ 90 mm Hg). In all the calculations reported thus far, a value at the high end of this range, 25.5×10^{-4} (P_{O_2} = 85 mm Hg), was used. To see the effect of a lower entrance value of concentration, we have run a case (r_c = 2.5μm, j = 1.0) for the value $(c_{av})_{\xi=0} = 22.5 \times 10^{-4}$ (P_{O_2} = 75 mm Hg). The variation of c as a function of distance along the capillary is shown in Fig. 14 for the normal case and sickle blood at normal and reduced pressure drop. A comparison of the curves in Fig. 14 with the corresponding ones in Fig. 7 shows that they are qualitatively the same, although the curves in Fig. 14 are less steep so that the differences in concentration between the cases in these two figures are much less at the distal end of the capillary than at the proximal end. The corresponding velocities differ only slightly.

Since the lower hematocrit of sickle blood plays such a major role in these results, we have also run the r_c = 2.5 μm, j = 1 case with a slightly higher hematocrit, $H_{S\text{-}C}$ = 0.30. At normal pressure drop the values c vs. x for this case are essentially indistinguishable from those for the

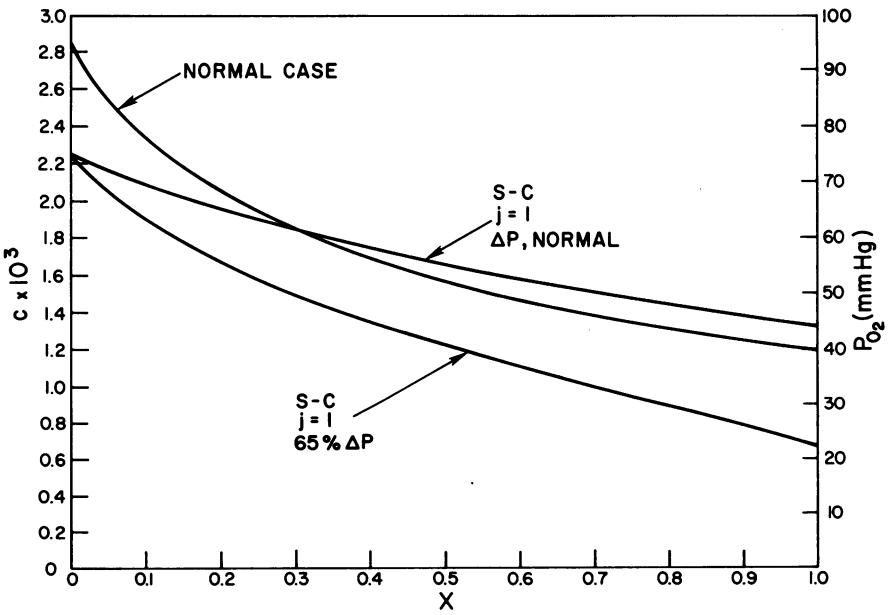

FIGURE 14 Oxygen concentration variation with (nondimensional) distance along capillary for sickle cell $(c_{av})_{\xi=0} = 2.25 \times 10^{-3}$ ($r_c = 2.5 \times 10^{-4}$ cm, j = 1).

corresponding case with $H_{S\text{-}C} = 0.25$. With the pressure drop reduced 35%, the concentration along the capillary is everywhere lower for the higher hematocrit, reaching a maximum difference at the distal end of 7.7 mm Hg. As might be expected, the velocities for this case are much lower (see Fig. 10).

At the end of the Introduction we referred to the differences between this investigation and that of Lomen and Gross (8). We are now in a position to comment in more detail about these. First, Lomen and Gross do not take into account the major difference between the hematocrits of sickle and normal blood; this leads to their predicting values of cell velocity and oxygen concentration along the capillary very much lower than those found here. Second, Lomen and Gross use exclusively the Po_2-cell deformability relationship suggested by the Usami et al. (12) experiments. As discussed earlier, the use of this data (corresponding to our $j = 2$) under the nonequilibrium conditions likely to prevail in the capillaries will probably overestimate the effect of this relationship. Third, Lomen and Gross assume that the clearance of each cell, a crucial parameter in the lubrication theory of red cell motion (3, 4), has a constant value along the capillary. However, since β, the compliance, is different at different points in the capillary one would also expect the clearance of each cell to be different. Fourth, Lomen and Gross use the lubrication theory of Lighthill-Fitz-Gerald to calculate the relationship between resistance to flow and cell compliance. Our work uses values calculated (30) from the corrected theory by Tözeren and Skalak (6). Finally, Lomen and Gross carry out all their calculations assuming the cell velocity is constant, and present graphs of the variation of resistance with entering Po_2 level for different values of cell velocity. This is the inverse of what would occur physiologically. It is unlikely that there is a physiological control mechanism which maintains constant cell velocity. Given that the major resistance to arterial flow occurs in the microcirculation, and that the controls at this level (arteriole dilatation, etc.) directly affect pressure drop across the capillaries, it is more physiologically relevant to vary pressure drop and determine its effect upon Po_2 concentration and cell velocity, as done in the present investigation. The net effect of all these differences between the two investigations is to change the results and conclusions significantly. Thus, while the figures in Lomen and Gross show resistance ratios (of sickle to normal blood) larger than one, and by implication suggest that the flow of sickle blood is always sluggish and subjected to low oxygen concentration levels, our results indicate that under many conditions sickle blood may flow at velocities, and be subjected to Po_2 concentrations, much higher than the normal, due to the interplay between the various detrimental and compensating factors that characterize sickle blood.

CONCLUSIONS

Our results show that under normal pressure conditions the combination, for sickle cells, of a rightward shift in the oxyhemoglobin dissociation curve and a much lower hematocrit is very effective in maintaining higher than normal oxygen concentration along the entire length of capillary, and red cell velocities one to more than one-and-a-half times larger than for normal cells under the same pressure drop. Both of these effects are beneficial, tending to keep the red cells away from the threshold of oxygen tensions that mark the beginning of the sickling process, and moving so rapidly that little time is available for this process to proceed very far in any case. The same trends in concentration and cell velocity hold under moderate decreases in pressure gradient.

The picture changes dramatically if the pressure gradient across the capillary, driving the cells, decreases by larger amounts. Velocity is impeded, permitting more oxygen to be released from the cells, thereby bringing the concentration level to much lower levels, which in turn further decreases the velocity of flow. The severity of these changes depends on the magnitude of the pressure gradient decrease, the capillary radius, and the degree of coupling between compliance and concentration.

These results suggest that the feedback interaction between oxygen concentration and velocity of flow throught the capillary can be important for sickle blood. This mechanism, leading to stasis or near-stasis of flow, is often cited as the so-called "vicious cycle" of sickle-cell anemia. What remains unclear in such discussions is whether the red cells are slowed for a sufficiently long enough time for a significant part of the sickling process to be completed, and why sickle-cell crisis, which would seem the result of the mechanism above causing blockage of flow through large numbers of capillaries, occurs only rarely. The present results indicate that under ordinary conditions there is little reason to expect cells to undergo any further sickling changes while traversing the systemic capillaries. However, under abnormal or unusual circumstances involving decreased arteriole-venule pressure differences, conditions conductive to sickling obtain and residence times become large enough to allow significant changes in the cells to occur before they exit the capillaries.

Although the calculated hydrostatic pressure drops across the capillaries (see Eq. 38) are about three times that experienced by Poiseuille flow with viscosity equal to that of plasma, they are considerably lower than the values usually given in the literature for capillary bed pressure drop (26, 27), although there is very large scatter in the data (28). A number of factors may be responsible for, or play a role in, this discrepancy:

(*a*) Within the lubrication theory gross simplications or inadequate knowledge may contribute to incorrect quantitative predictions. Probably the most important of these is the use of a simple linear elastic theory to model the complex elastic response of the red blood cells. Moreover, the compliance β appearing in this simple theory, or the elastic constants required if one attempted a more accurate modeling, vary over very wide ranges (15).

(*b*) Recent in vivo studies suggest that the values for hydrostatic pressure drop across individual capillaries may be less than those traditionally quoted (29), or that these latter values may be abnormally high due to the plugging of capillaries by leukocytes due to shock (30).

(*c*) Since all the sickle cases are compared to the flow of normal blood, we are in effect using Eq. 24, the only place where lubrication theory enters the analysis, to calculate the ratio

$$\frac{(\Delta p)_{s-c}}{(\Delta p)_{\text{normal}}} = \left(\frac{u_{s-c}}{u_{\text{normal}}}\right)^{1/k} \left(\frac{\beta_{s-c}}{\beta_{\text{normal}}}\right)^{\frac{1-k}{k}}. \tag{39}$$

Although absolute values of pressure drop are quoted they play no essential role in the calculations. The values of the exponent $(1 - k)/k$ are such that the dependence of the ratio of pressure drops on the erythrocyte compliance is weak. The dependence on the velocity predicted by Eq. 24 is supported by a substantial measure of observational evidence (31). In fact, there is much to affirm the status of lubrication theory as "the most convincing theoretical model of red cell motion in narrow capillaries" (28), and to accept

its principal predictions about the dependence of pressure drop on certain critical parameters.

In summary, possible inadequacies in the prediction of hydrostatic pressure drop across the capillaries arise from deficiencies in our theoretical and experimental knowledge about the flow of erythrocytes in the capillaries and not from the present analysis, nor should they invalidate, qualitatively, any of the results or predictions derived from it.

A number of effects have been omitted from the analysis. Among the more important are the following: (*a*) the finite times associated with sickling changes; (*b*) decreased deformability of sickle cells due to past sickling-unsickling history (19), aging (1), or, more generally, the apparent lessened deformability, in comparison to normal cells, of HbSS cells even when fully oxygenated (32); (*c*) the influence of mean corpuscular hemoglobin concentration on the degree to which decreasing oxygen levels lead to sickling and concomitant changes in the rheological properties of the cells; and (*d*) the influence of changes in pH. Efforts are currently under way to incorporate some of these factors into the analysis.

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APPENDIX

In this Appendix we shall use the Lighthill-Fitz-Gerald (3-5) lubrication theory of red cell flow in the capillaires, with the recent correction due to Tözeren and Skalak (6), to derive a relation between the velocity of a red cell u, the pressure drop across the cell Δp, and the compliance of the cell β. Fig. 15, based on new calculations of the corrected lubrication theory by Aroesty et al. (33), will be used to obtain the required relationship. We first recall the

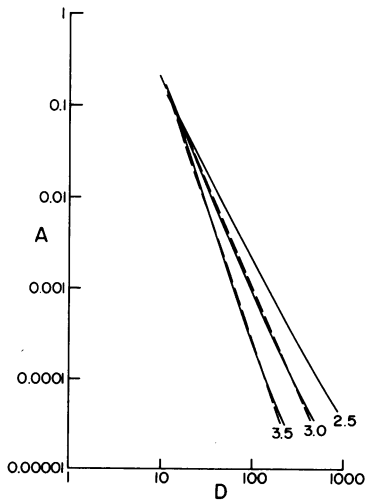

FIGURE 15 Variation of velocity parameter A with resistance parameter D according to lubrication theory of capillary flow.

following definitions introduced in the theory:

$$A \equiv \frac{\mu U \beta}{r_c^2 (\kappa r_c)^{1/2}}$$

$$D \equiv \frac{[p(-g) - p(g)] r_c (\kappa r_c)^{1/2}}{\mu U} \tag{A1}$$

$$E \equiv \frac{\beta}{r_c} [p(-g) - p(g)],$$

where β and r_c are as already defined, U is the velocity of the pellet (or red cell), μ is the plasma viscosity, $p(g)$ is the pressure ahead of the pellet and $p(-g)$ that behind it, and κ is the curvature of the gap profile at the point of contact with the tube (or capillary) under the reference pressure p_o.[4] The solid curves in Fig. 15 show the variation of A with D for a deformable red cell for several tube or capillary radii (assuming a red cell of standard dimensions). Inasmuch as, to a good approximation, these curves are straight lines in this log-log plot (the broken lines in Fig. 15 show explicitly the straight line approximations used), we can write, approximately, $A \propto D^{k'}$, where k' is a (different) constant for each value of r_c. According to Eq. A.1, $E = AD$, so this proportionality can be rewritten as $A \propto E^k$, where $k = k'/(k' + 1)$. Finally, because of the common point of intersection in Fig. 15, we can set

$$A = \left(\frac{A^*}{E^{*k}}\right) E^k, \tag{A.2}$$

where the asterisk denotes values of A and E at the intersection point. From Fig. 15 we find these values to be $A^* = 7.49 \times 10^{-2}$, $E^* = 1.079$. and the values of the exponent k to be

$$k = \begin{cases} 1.52 \text{ for } r_c = 3.5\ \mu m \\ 1.78 \text{ for } r_c = 3.0\ \mu m \\ 2.22 \text{ for } r_c = 2.5\ \mu m. \end{cases} \tag{A.3}$$

Substituting for A and E in Eq. A.2 using the definitions given in Eq. A.1 we obtain

$$\Delta p = \left[\left(\frac{E^*}{A^{*1/k}}\right)\left(\frac{\mu u}{(\kappa r_c)^{1/2}}\right)^{1/k} r_c^{\frac{k-2}{k}}\right] \beta^{\frac{1-k}{k}}, \tag{A.4}$$

where $\Delta p = p(-g) - p(g)$ is the pressure drop across the red cell. (Note we use u rather than U in the text for red cell velocity.)

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[4]The reference pressure p_o is defined as that pressure which will deform the pellet just sufficiently for it to fit the tube; it depends both on the clearance and the properties of the pellet.

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