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ABSTRACT

A simplified model of diffusion of inflammatory products, controlled by shear dependent permeability of the endothelium, is proposed to account for the localisation of a medial gap (caused by tissue breakdown) at a bifurcation apex, the endothelial barrier being intact at this stage. For the later stage where the artery wall is broken, a diffusion boundary layer model is proposed which predicts that, in a particular case, the diffusion flux through the break is about 400 times larger than the flux which would exist if the wall was intact at that point, and at least 40 times the downstream flux for a shear stress of 300 dynes/cm^2.

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ARTERIOSCLEROSIS; ARTERIES; BLOOD; ENDOTHELIUM; MASS TRANSFER; DIFFUSION; PARTICLES

CONTENTS

1. INTRODUCTION

Mass transfer of plasma substances between the arterial wall and intraluminal blood is believed to play an important role in the atherosclerotic process. In addition, the localisation of atherosclerosis to regions where the blood flow is disturbed (e.g. at vessel branches and bends) suggests an important coupling of wall mass transfer with fluid dynamical factors (e.g. shear stress).

Caro, Fitz-Gerald and Schroter [1971] reported that early atherosclerotic development occurs in regions which experience relatively low shear. They explained these results by proposing a simplified model of mass diffusion for which the diffusional boundary layer offers the major resistance to diffusion; but at the same time they recognised the possible importance of wall permeability.

Subsequent experimental studies by Caro and Nerem [1973] and Caro [1973] revealed that the diffusion boundary layer could not be rate-controlling as had been previously assumed, but that the greatest resistance to mass transfer occurs at the endothelium and is shear-dependent. A similar conclusion was reached by Fry [1972] who found that the endothelial surface possesses a very high diffusion resistance which is sensitive to variations in wall shear stress, turbulent flow and wall stretch. Evidence for the importance of fluid dynamic forces has been reviewed by Patel *et al.* [1974].

Recently, Tucker *et al.* [1975] traced the development of a lesion across the tip of the bifurcation apex of a 600 micron diameter artery of the rat lung; (the stagnation point at the tip is, of course, a region of locally low shear). As a result of tissue breakdown acting from the outer aspect of the artery wall, the elastic coats were first broken in the form of an arrowhead (medial gap) directed towards the lumen. Later, as a further result of the formation of a cleft through the wall, interchange between tissue fluid and blood occurred.

In this paper an explanation for the formation of the medial gap at the apex is proposed, based on the transport of inflammatory products to the blood from within the tissue at the bifurcation angle. During the early development, the endothelial barrier is still intact; the diffusion boundary layer cannot be rate-controlling during this phase. It may, however, be of major importance near the apex once the wall is broken since, clearly, the endothelial barrier does not exist at such a point.

2. ANATOMIC CONSIDERATIONS

Experimental results, when rats inhaled microparticulate markers that were histologically identifiable, have shown that materials deposited in the alveolar regions are cleared with the flow of lung liquid to perivascular,

peribronchial sheaths. Dusts then accumulated in lymphatic nodules which formed on the bronchial bifurcations and were thence excreted to the airways through the bronchial walls. Because the bronchi and arteries are paired throughout their distributions, the lymph nodes are adjacent to and encroach upon the bifurcations of the arteries. [Tucker *et al.* 1973].

Small vessels, which are part of the bronchial rete supplying the bronchial wall, run through the substance of the node and pass close to the bifurcation apex of the artery. The perivascular space surrounding these minute vessels provides a pathway by which products of inflammatory reaction in the node might pass to the loose, connective tissue surrounding the pulmonary artery.

The tissue layers of the arterial wall undergo progressive breakdown from the outer (adventitial) aspect along a line across the tip of the flow divider. Cells containing marker particulates pass into the arterial blood stream where an actual breach of all layers of the wall has been formed. [Tucker *et al.* 1975]. An illustration of a lymph node and its associated wall lesion is given in Figure 1.

3. TRANSPORT PROCESSES

Transport of material between the lymph node and the blood before the breaking of the artery wall involves the following stages:

(i) transport of material from the lymph node to the outer surface of the artery wall. (This process can take place both by diffusion and convection (bulk flow). Bulk flow in the tissue along the bronchial rete, and diffusion in the interstitial fluid space surrounding the artery may be important in bringing inflammatory material close to the wall near the apex);

(ii) transfer of matter across the outer surface of the artery wall. (The diffusion resistance in this stage may be associated with the solubility of the species or chemical reactions at the interface);

(iii) diffusion through the artery wall to the endothelium;

(iv) mass transfer across the endothelial barrier. (This process may also involve the conversion of material from one form to another. The diffusion resistance here depends on the wall shear stress (see below)); and

(v) movement through a diffusion boundary layer in the blood.

Experimental work by Caro and Nerem [1973] on an isolated artery using

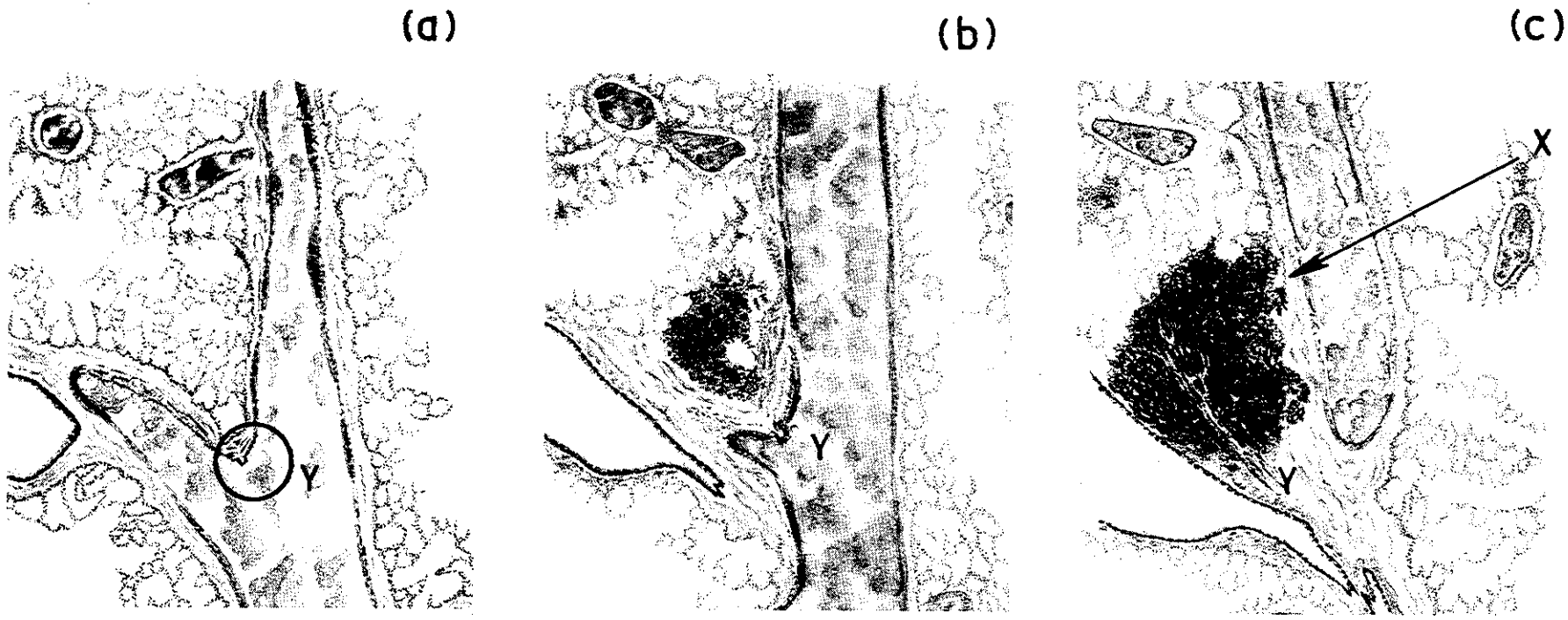

Figure 1 (a), (b), (c) are three successive sections (with the bronchus behind (c)) of a branched blood vessel showing a lymph nodule (X) and its associated wall lesion (Y) at the tip of the flow divider. [After Tucker *et al.* 1975].

labelled cholesterol, eliminated the diffusion boundary layer as a significant source of diffusion resistance; the concentration difference through this boundary layer is therefore negligible. Subsequent work by Caro [1973] revealed a substantial increase in flux with increase of wall shear stress, although the mechanism relating these two quantities is unknown. Caro [1973] observed that this is inconsistent with the artery wall being rate limiting and he concluded that movement is controlled by processes at the endothelial barrier. However, the possibility of significant concentration differences in the wall in conjunction with a shear-dependent flux which is controlled by the blood-wall interface cannot be ruled out.

The above experimental work applies to an intact artery wall. Once the artery wall is breached, diffusion is no longer limited by the wall or the interface at that point and the diffusion boundary layer may become a significant source of resistance there.

4. MASS TRANSFER WITH WALL INTACT

Figure 2 is a two-dimensional representation of the region near the arterial flow divider. The wall shear near the stagnation point S is, of course, low; whereas downstream of S it is relatively high. The actual variation in wall shear with distance along the wall from S will depend on surface geometry and on incident flow. Qualitatively, shear rises to a peak and then falls away downstream. If the downstream geometry is such that separation occurs, then the shear becomes zero at that point. However, it is the rising portion of the curve which occurs near the apex that is of interest here.

We make the following assumptions for a simplified two-dimensional model of diffusion near the apex:

(i) that the combination of convection and diffusion in the tissue spaces is enough to maintain a uniform concentration of inflammatory material in the tissue near the artery wall at the apex;

(ii) that diffusion is limited only by transport across the inner and outer surfaces of the artery wall and by transport across the artery wall itself, i.e. resistance in the diffusion boundary layer is negligible; and

(iii) that the longitudinal flux is locally uniform. If transport within the wall is by passive diffusion, this assumption corresponds to the case $\partial^2 C/\partial X^2 << \partial^2 C/\partial Y^2$ (where X and Y are longitudinal and normal coordinates respectively). This assumption is likely to be valid since the ratio of wall

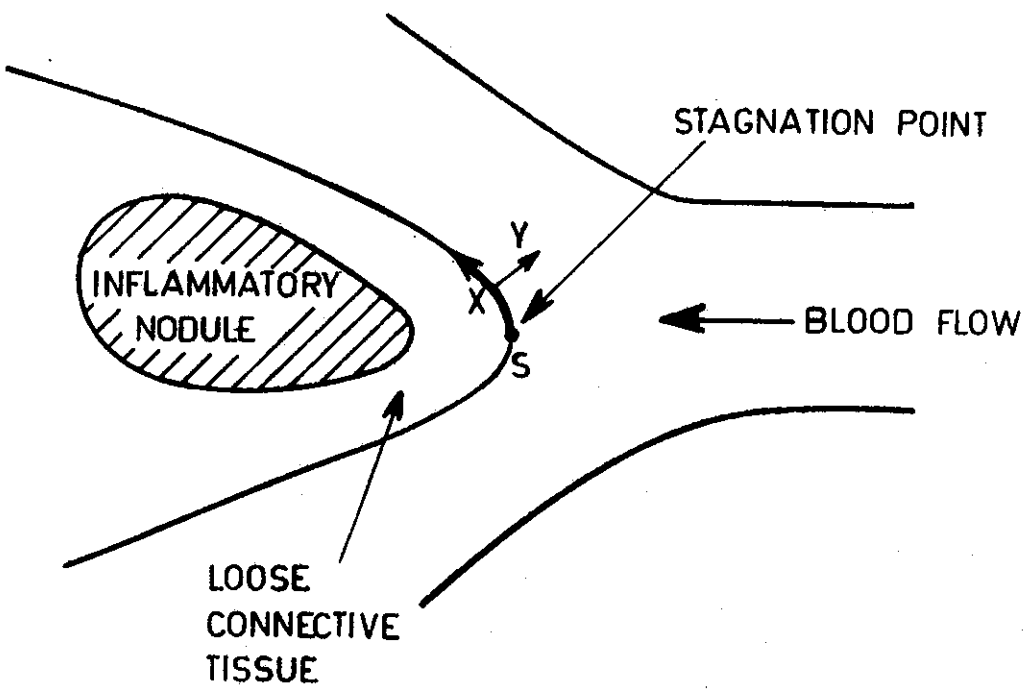

Figure 2 Two-dimensional representation of region near the arterial flow divider

thickness to the longitudinal length scale (radius of curvature) is small. For the artery studied by Tucker *et al.* [1975], this ratio is about 0.06, based on wall thickness of 15 microns and radius of curvature of 250 microns.

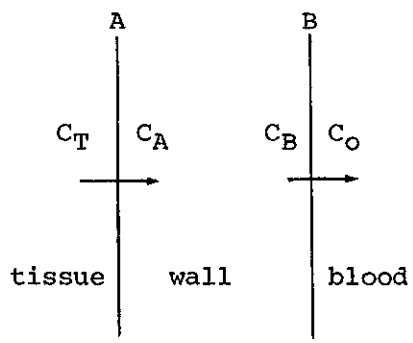

Figure 3 A Diffusion Pathway Across a Wall Segment

In Figure 3 which illustrates the diffusion pathway across a wall segment, C_T is the concentration of diffusing material in the tissue near the artery wall, C_A and C_B are concentrations in the wall at surfaces A and B respectively, and C_o is the concentration in blood. Concentration C_T is chosen to be constant and the permeability (h) of surface B is taken to be an increasing function of wall shear.

Now the flux at A is given by

$$(\text{flux})_A = h_A\ (C_T - C_A) \tag{1}$$

where h_A is the permeability of surface A. We represent the flux through the wall by

$$(\text{flux})_w = h_w\ (C_A - C_B) \tag{2}$$

where h_w is the effective permeability of the wall.

In addition, the flux at B is given by

$$(\text{flux})_B = h(C_B - C_o) \quad . \tag{3}$$

In general, h_A and h_w will depend on concentration and on location upon the artery. However in the absence of information concerning these parameters we take them to be constant. This assumption may be valid at least before the development of significant erosion of the artery wall.

By continuity $(\text{flux})_A = (\text{flux})_w = (\text{flux})_B$ and from equations 1, 2 and 3 we have

$$\text{flux} = H\ (C_T - C_o) \tag{4}$$

where

$$\frac{1}{H} = \frac{1}{h_A} + \frac{1}{h_w} + \frac{1}{h} \quad . \tag{5}$$

Since C_T and C_o are taken to be constant, we see that the flux, as well as the permeability h, increases with increasing wall shear stress. Therefore by

equation 1, C_A decreases with increasing wall shear. This result, together with equation 2, shows a similar variation in C_B. Concentrations C_A and C_B are therefore greatest at the stagnation point and decrease with distance from S as expected. If we assume that a sufficiently high wall concentration of inflammatory products results in degradation of wall tissue, then we have a mechanism which can account for the location of the medial gap at the apex. The same mechanism can be used to account for the development of medial gaps at other sites of low shear, e.g. on the lateral walls (see Stehbens [1972] p.65). In addition, $C_A > C_B$; this is consistent with a breakdown of the wall which begins first at surface A.

Under our hypothesis, factors determining the width of the medial gap include the longitudinal variation of concentration ($\partial C/\partial X$), the relationship between the degree of tissue breakdown and concentration, and the time over which the process has been active. The gradient $\partial C/\partial X$ depends on the rate at which wall shear varies over the nose region of the flow divider. Since the concentration is greatest near S, we propose that degradation of wall tissue occurs there first over an initial width which depends on the concentration threshold for tissue breakdown, and that this width increases with time at a rate which depends on $\partial C/\partial X$ (and hence, the longitudinal gradient of wall shear).

Caro's result [Caro 1973] indicates that uptake of cholesterol by the artery wall can increase by a factor of ten as wall shear stress increases through a physiological range of zero to about 300 dynes/cm^2. Under conditions of elevated blood flow, peak shear stress may become larger still, perhaps even in excess of 400 dynes/cm^2 when the endothelial surface becomes damaged [Fry 1968].

Estimates of wall shear rates in the circulation [Whitmore 1967] indicate that shear increases with distance into the periphery. That is, $\bar{U}/L$ increases even though the Reynolds number $Re = \bar{U}L/\nu$ decreases, where $\bar{U}$ is the mean velocity through a vessel of diameter L.

Further, Caro *et al.* [1971] noted that the work of Fitz-Gerald [1969] indicates that wall shear rate in the capillaries may be some 5 to 10 times greater than Whitmore's value for the aorta.

In the high Reynolds number case, Davidson [1978] has indicated, from an asymptotic analysis of plane stagnation point flow, that as the curvature at the apex increases, the general trend is for wall shear stress at a point near S to increase. That is, the wall shear stress increases more sharply from zero with increasing distance from S, the effect increasing as the angle of

branching becomes more acute. Zamir and Roach [1973] also find that shear near the apex is higher at small bifurcation angles.

We conclude that, in both large and peripheral arteries, the wall shear stress and hence wall concentration may vary significantly over longitudinal distances (from S) of similar order to the radius of curvature, the effect being more pronounced at small angles of branching. (It is interesting to note that medial gaps are observed to be more frequent in this case (Stehbens [1972], p.65).)

5. MASS TRANSFER WITH WALL BROKEN

As mentioned earlier, the diffusion boundary layer in the blood may be a significant part of the diffusion process in regions where the artery wall has been broken. In the large arteries where the Reynolds number is high, an estimate of the diffusion boundary layer thickness (δ) in relation to the thickness of the hydrodynamic boundary layer (δ_h) can be obtained. Caro *et al.* [1971] take the region along the flow divider as equivalent to flow past a flat plate, and observe that, in such a case (see Bird *et al.* [1960], p.607), with diffusion between wall and fluid, together with no chemical reaction and large Schmidt number Sc, we have

$$\delta/\delta_h = Sc^{-1/3} \qquad (6)$$

where $Sc = \nu/D$, and ν is the kinematic viscosity of the fluid and D is the diffusion coefficient of the species. We shall see later that equation 6 also applies near the stagnation region. Following Caro *et al.* [1971], we assume that the diffusing material (cholesterol in their case) is transported in association with plasma protein and has the same diffusion coefficient $D = 10^{-7}cm^2s^{-1}$; so that $Sc = 3 \times 10^5$ and $\delta/\delta_h \approx 0.015$.

When $\kappa\delta_h$ is small (κ is surface curvature), the hydrodynamic boundary layer thickness in plane stagnation point flow (see, for example, Schlichting [1955], p.72) is given by

$$\delta_h/L = 2.4/Re^{\frac{1}{2}} \qquad (7)$$

where L is the length scale and Re is the Reynolds number. Using equations 6 and 7 we find that for the aortic bifurcation, the diffusion boundary layer thickness at the stagnation point is approximately 15 μ, based on a diameter of 15 mm and Reynolds number of 1500. Wall shear is greater in the peripheral vessels, so δ is probably smaller there.

The width of the gap in the artery wall at the apex may vary considerably. In the artery studied by Tucker *et al.* [1975] the gap width is of similar order to δ. However, an example of a gap spanning almost the entire width of the apex may be found in Stehbens [1972], p.63. In this example, the term

$\partial^2 C/\partial X^2$ in the diffusion equation can be ignored near S, resulting in an equation of the boundary layer type. However, for the narrower gap widths considered here, terms corresponding to both tangential and normal diffusion must be retained.

5.1 Stagnation Point Models

(a) Flow

The flow near the gap must first be described for use in the convection-diffusion equation. We assume that the flow which impinges on the stagnation point S (see Figure 2) is plane, steady and symmetric. In addition to the incident flow, a flow from tissue to blood occurs through the orifice at S against the opposing transmural pressure gradient. This active secretion is presumably promoted by the general flow of interstitial fluid (against the direction of blood flow, towards the bifurcation apex) in the sheath of loose connective tissue surrounding the artery. However, the magnitude of this flux is unknown. We therefore ignore it completely except to note that the total orifice flux predicted from the convection-diffusion equation in part (b) (Section 5) will be underestimated.

Average blood velocity and vessel diameter at the bifurcation are chosen as our reference speed ($\bar{U}$) and reference length (L) respectively, and the Reynolds number (Re) is based on $\bar{U}$ and L. In the following, all variables are dimensionless.

We use a curvilinear coordinate system (X,Y) made up of straight lines normal to the surface of the flow divider and curves parallel to the surface. X denotes the distance along the surface from the stagnation point and Y is the distance normal to the surface. The stagnation point S has coordinates (0,0).

Let U and V be the velocity components in the X and Y directions respectively. Since S is a stagnation point, U and V have the following asymptotic forms for small X and Y:

$$U = BXY \quad , \quad V = -\tfrac{1}{2}BY^2$$

where B is a constant. When Re is large, and for a point lying well within the usual hydrodynamic boundary layer, B is $O(Re^{\frac{1}{2}})$.

(b) Convection-Diffusion

The convection-diffusion equation for material diffusing in a fluid (blood) is

$$U \cdot \nabla C^* = \frac{1}{Pe} \nabla^2 C^* \qquad (9)$$

where $C^*(X,Y)$ is the concentration and $Pe = \bar{U}L/D$ is the Peclet number which, in our case, is large. Let $C = (C^* - C_o)/(C_T - C_o)$ where C_T is the concentration

in tissue and at the gap, and C_o is the concentration in the blood outside the diffusion boundary layer.

In terms of tangential and normal coordinates (X,Y) equation 9 becomes

$$\frac{U}{h}\frac{\partial C}{\partial X} + V\frac{\partial C}{\partial Y} = \frac{1}{hPe}\left[\frac{\partial}{\partial X}\left(\frac{1}{h}\frac{\partial C}{\partial X}\right)+\frac{\partial}{\partial Y}\left(h\frac{\partial C}{\partial Y}\right)\right] \qquad (10)$$

where $h = 1 + K(X)Y$, and K is the surface curvature.

We choose the following boundary conditions on the body surface

$$\left.\begin{aligned} C(X,0) &= 1 \quad , \quad -a \leq X \leq a \\ \left(\frac{\partial C}{\partial Y}\right)_{Y=0} &= 0 \quad , \quad |X|>a \end{aligned}\right\} \qquad (11)$$

We have taken the gap width at S to be 2a and have assumed that the flux through the intact wall adjacent to the gap is much smaller than the gap flux.

The diffusion boundary layer (sublayer) is very thin, as indicated earlier, and lies deep within the hydrodynamic boundary layer. We therefore follow the usual procedure in such cases by replacing U and V in equation 10 by their asymptotic forms within the sublayer (see, for example, Frank-Kamenetskii [1969], p.280). Since the gap width is taken to be of similar order to the diffusion boundary layer thickness, we require U and V for both X and Y→0 as in equation 8.

As discussed earlier, the complete diffusion equation must be used in the region near the gap. In this region both diffusion terms are important and balance the convective terms. Using equation 8, in equation 10, we find that this region can be given by $\zeta = X/\Delta$, $\eta = Y/\Delta$ where ζ and η are O(1);

$$\Delta = B^{-1/3}\,Pe^{-1/3} = B^{-1/3}\,Re^{-1/3}\,Sc^{-1/3} \quad . \qquad (12)$$

Now δ/L is $O(\Delta)$. When equation 7 is satisfied and B is $O(R^{\frac{1}{2}})$ when Re is large, δ does indeed have the order indicated by equation 6.

Taking only the dominant terms in equation 10 for large Sc yields

$$\zeta\eta\,\frac{\partial C}{\partial \zeta} - \frac{1}{2}\eta^2\frac{\partial C}{\partial \eta} = \frac{\partial^2 C}{\partial \zeta^2} + \frac{\partial^2 C}{\partial \eta^2} \quad . \qquad (13)$$

Further downstream ($\zeta\to\infty$) we expect equation 13 to be of typical boundary layer type with $\frac{\partial^2 C}{\partial \zeta^2} \approx 0$. We therefore choose

$$\frac{\partial^2 C}{\partial \zeta^2} \to 0 \quad , \quad \zeta\to\infty \qquad (14)$$

and $C\to 0$, $\eta\to\infty$.

If we take $a = \Delta$ in equation 11, then the boundary conditions become

$$\left.\begin{aligned} &C(\zeta,0)= 1 \quad , \quad -1 \leq \zeta \leq 1 \\ &\frac{\partial C}{\partial \eta} = 0 \quad , \quad |\zeta|>1 \\ &\frac{\partial^2 C}{\partial \zeta^2} \to 0 \text{ as } \zeta\to\infty \quad ; \quad C\to 0 \text{ as } \eta\to\infty \end{aligned}\right\} \quad . \qquad (15)$$

We require to solve equation 13 subject to boundary conditions 15. An analytical solution is not readily available and the equation must be solved numerically.

The time dependent, conservative form of equation 13 is

$$\frac{\partial C}{\partial t} + \frac{\partial}{\partial \zeta}(\zeta \eta C) - \frac{\partial}{\partial \eta}\left(\frac{1}{2}\eta^2 C\right) = \frac{\partial^2 C}{\partial \zeta^2} + \frac{\partial^2 C}{\partial \eta^2} \quad . \tag{16}$$

This equation is solved using a Dufort-Frankel leapfrog differencing scheme (see, for example, Roache [1976], p.61) and the required solution of equation 13 is the steady state solution of equation 16. A mesh spacing $h = 0.1$ was chosen and a time step (Δt) was taken such that $\frac{\Delta t |U|_{max}}{h} < 1$. Calculations were first continued until the difference in C between successive iterations ($|\Delta C|$) was less than 0.0001. The average concentration gradient $\left(\frac{\partial C}{\partial n}\right)$ at the gap was found to be 0.873. Subsequent iteration until $|\Delta C| < 0.00001$ yielded a change in $\left(\frac{\partial C}{\partial n}\right)$ of about 0.1 per cent. An error of similar magnitude was also found for the finite size taken for the computational region.

Caro [1973] has found a diffusion velocity (V_{wall}) into the artery wall of 1.455×10^{-7} cm s^{-1} for cholesterol at zero shear. Our calculated diffusion velocity (V_{gap}) through the gap is given by $\frac{D}{L\Delta}\frac{\partial C}{\partial n}$ cm s^{-1}. Taking $L\Delta \approx 0.0015$ cm (the order of the diffusion boundary layer thickness at the aortic bifurcation) we have, in this case, $\frac{V_{wall}}{V_{gap}} \approx 0.0024$. This result indicates that as expected, it is indeed valid to assume that the flux through the intact wall is much less than the flux through the gap.

6. CONCLUSIONS

A simplified model of diffusion, controlled by shear dependent permeability of the endothelium, is proposed to account for the localisation of the medial gap at a bifurcation apex. During formation of the lesion, the elastic coats are broken down forming a wedge directed toward the lumen. The model accounts for the preferential breakdown of wall tissue at the stagnation point and for the direction of the breakdown.

After the wall is broken, a diffusion boundary layer model is used to predict the diffusion flux through the break in the wall. Assuming that the gap width is equal to twice the value of an estimate of the diffusion boundary layer thickness (δ) based on the aortic bifurcation, the flux (quite apart from bulk flow by secretion) is about 400 times that which would exist if the wall was intact at that point, and at least 40 times the flux downstream of the stagnation point (based on a downstream stress of 300 dynes/cm^2). In the more peripheral arteries we expect δ to be smaller than the aortic value so that predicted flux ratios may be even greater in this case.

The author wishes to thank Dr. A. D. Tucker for many valuable discussions during the course of this work.

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