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SOME THEORETICAL CONSIDERATIONS CONCERNING THE INTERCHANGE OF METABOLITES BETWEEN CAPILLARIES AND TISSUE

INGRAM BLOCH
THE UNIVERSITY OF CHICAGO

The author's previous treatment of diffusion of oxygen from an idealized capillary is made more exact; the treatment here is valid for any substance which diffuses between blood and tissue, though the physical situation is still somewhat idealized. A general equation is derived but not solved.

Then follows an approximate treatment of the case in which all capillaries within a certain sphere have ceased to flow; conditions are discussed under which cells at the center of this sphere will die.

In an earlier paper (Bloch, 1941), the author presented an approximate treatment of the problem of diffusion of oxygen from a capillary. The present paper contains a formulation of the exact problem of diffusion of any substance from or into a capillary.

We shall again consider a circular cylindrical capillary of length l, whose axis is to be the ζ-axis, so that $\zeta = 0$ at the arteriole and $\zeta = l$, at the venule. $r(P)$ will be the distance of point P in the tissue from the ζ-axis; r_0 will be the radius of the capillary, and v the velocity of the blood-flow. D and h will denote, respectively, the tissue diffusion coefficient and the capillary permeability of the substance under consideration, while $Q(P)$ will be the rate of production of the substance in gm/cc sec at point P in the tissue. r_0 and h are assumed to be constant.

I. The case of oxygen: For consideration of oxygen, we shall need to define some more quantities:

$c_0(\zeta)$ = concentration, in gm cm^{-3}, of oxygen dissolved in the blood.

$c_1 = c_0(0)$, $c_2 = c_0(l)$, $c'(\zeta)$ = concentration, in gm cm^{-3}, of oxygen in the tissue immediately outside the capillary wall.

$x_0(\zeta)$ = concentration, in gm per cm^3 of blood, of removable oxygen in oxyhemoglobin.

$x_1 = x_0(0)$, $x_2 = x_0(l)$, $T_0(\zeta) = x_0(\zeta) + c_0(\zeta)$, $T_1 = x_1 + c_1$, $T_2 = x_2 + c_2$, $c(P)$ = concentration, in gm cm^{-3}, of oxygen at point P in the tissue.

$$\sigma = -\frac{1}{4\pi}\left(\frac{\partial c}{\partial r}\right)_{r=r_0}. \tag{1}$$

From material balance (Bloch, 1941), we have the following expression:

$$-vr_0\frac{dT_0}{d\zeta} = 2h[c_0(\zeta) - c'(\zeta)] = 8\pi D\sigma. \tag{2}$$

Also we know that the diffusion equation may be used in the tissue:

$$\nabla^2 c = -\frac{Q}{D}.$$

The diffusion equation may be otherwise stated; the capillaries in the volume V' of tissue will make a contribution to $c(P)$ which will be given by the sum of several surface integrals, each of which is taken over the surface of one capillary; added to this sum will be a volume integral, which represents the effect of tissue metabolism within volume V':

$$c(P) = \sum_{i \text{ in } V'}\left\{\int\int_{S_i}\frac{\sigma(\zeta_i)\,dS_i}{\rho(p_i,P)}\right\} + \int\int\int_{V'}\frac{Q(P')\,dV'}{4\pi D\rho'(P',P)}. \tag{3}$$

Here S_i is the surface of the i-th capillary: $\rho(p_i,P)$ is the distance from P to p_i, the general point on S_i, and $\rho'(P',P)$ is the distance from P to P', the general point in V'. Equation (3) is a special case of the general solution of Poisson's equation (MacMillan, 1936).

Bloch (1941) gave a brief discussion of the effect of other capillaries on concentration of a metabolite at a point in the region of supply of some particular capillary. The only conclusion reached was that, in general, this effect could not be neglected. It will, however, be evident that distant capillaries will have less effect at points immediately outside the surface of some particular capillary than at points nearer the boundary of the region of supply. Hence, we shall set up equation (3) for $c'(z)$, and shall neglect all terms but the first in the summation. The z-axis is to be taken coincident with the ζ-axis, but whereas ζ is defined only for points within the capillary and on its surface, z is defined only for points in the tissue. Thus $c'(\zeta)$ and $c'(z)$ are logically distinct, but physically identical.

Equation (2), combined with equation (3) set up as proposed above, will still require one more relation to make the problem determinate. This relation may be most conveniently obtained by consideration of the equilibrium between dissolved oxygen and oxyhemoglobin, which consideration should lead us to an expression for $x_0(c_0)$.

$x_o(c_o)$ having been found, equation (3) for $c'(z)$ can be solved, and the quantities $c'(\zeta)$, $c_o(\zeta)$, $x_o(\zeta)$, $T_o(\zeta)$, and $\sigma(\zeta)$ will all be determined. Then this value of $\sigma(\zeta)$ can be substituted in each term of equation (3), which substitution, combined with a reasonable assumption about $Q(P)$, will reduce the problem of determining $c(P)$ in the field of n equivalent capillaries to that of evaluating the integrals. If, on the other hand, we prefer not to make any assumptions about $Q(P)$, we can use H. D. Landahl's expression for $Q(c)$ (Rashevsky, 1940) in the volume integral, in which case $c(P)$ will be the solution of an integral equation. Thus, by the use only of the approximation involved in dropping all but one of the terms in the summation in equation (3) when solving for $c'(z)$, we shall be able, in principle, to obtain an expression for $c(P)$.

Bloch (1941) gives a discussion of the equilibrium between oxygen and oxyhemoglobin, in which it is pointed out that x_o will depend not only on c_o, but also on concentration of CO_2 and on the time lag in dissociation of oxyhemoglobin. It has seemed expedient to neglect the time lag, and to determine the relationship between x_o and c_o and CO_2 concentration by reference to data in L. J. Henderson, (1928, p. 130). The curves here show y, percentage of hemoglobin oxidized, as a function of u, pressure of dissolved oxygen in millimeters of mercury. The parameter of the family of curves is w, pressure of CO_2; since its effect is slight (if w and u are expressed in mm Hg $(du/dw)_y \cong 1/4$ per cent mm^{-1} $(dy/dw)_u \cong 2/3$ per cent mm^{-1}), we have set $y(u,w) = y(u,$ average $w)$. $y(u)$ may be fairly well represented in the significant range of u (from 20 to 80 mm) by a parabola:

$$y = \alpha_2 u^2 + \alpha_1 u + \alpha_0$$

where $\alpha_2 = -2.18 \times 10^{-2}$, $\alpha_1 = 3.24$, and $\alpha_0 = -27.3$.

To get $x_o(c_o)$, one must get $x_o(y)$ and $u(c_o)$. Both these relationships are simple proportionalities.

$$x_0 = \frac{x_s}{100} y = My \tag{4}$$

where x_s is the concentration of oxygen in HbO_2(gm cm^{-3} of blood) when Hb is 100% oxidized, and $M \equiv x_s/100$.[1] Also, u is proportional to c_o:

$$u = Nc_0 .$$

[1] It may be of interest here to note that anemia will be characterized by a low value of the quantity x_s. Perhaps in the future it will be possible to investigate anemia from this point of view.

Hence we have

$$x_0 = My = M(\alpha_2 u^2 + \alpha_1 u + \alpha_0) = M(\alpha_2 N^2 c_0^2 + \alpha_1 N c_0 + \alpha_0). \quad (5)$$

Since $T_0 = x_0 + c_0$,

$$T_0 = c_0 + M(\alpha_2 N^2 c_0^2 + \alpha_1 N c_0 + \alpha_0) = \gamma_2 c_0^2 + \gamma_1 c_0 + \gamma_0 \quad (6)$$

the γ's being defined in terms of the α's and N by equation (6).

Now we are able to combine equations (2), (3) and (6) into a single equation in one unknown.

First, since we shall be manipulating only the surface integral in equation (3), we shall substitute A for the volume integral. We have

$$c'(P) = \int_s \int \frac{\sigma(\zeta)\, dS}{\rho(p,P)} + A$$

or

$$c'(z) = \int_0^{2\pi} d\Theta \int_0^l \frac{r_0 \sigma(\zeta)\, d\zeta}{\sqrt{2r_0^2(1 - \cos\Theta) + (z-\zeta)^2}} + A \quad (7)$$

where Θ is the angle between the radii vectores to the points p and P. Only one angle appears in the integrand because σ is assumed to be a function of ζ only.

From equation (2) we learn that

$$\sigma(\zeta) = -\frac{vr_0}{8\pi D} \frac{dT_0}{d\zeta} \quad (8)$$

and that

$$c'(\zeta) = c_0(\zeta) + \frac{vr_0}{2h} \frac{dT_0}{d\zeta}. \quad (9)$$

Equation (6) gives us another expression for $dT_0/d\zeta$:

$$\frac{dT_0}{d\zeta} = (2\gamma_2 c_0 + \gamma_1) \frac{dc_0}{d\zeta}. \quad (10)$$

If we substitute in (8) and (9) the value of $dT_0/d\zeta$ given in (10), and substitute the resulting expressions for $c'(\zeta)$ and $\sigma(\zeta)$ in (7), we get

$$c_0(z) + \frac{vr_0}{2h} [2\gamma_2 c_0(z) + \gamma_1] \frac{dc_0}{dz}$$
$$= \int_0^{2\pi} d\Theta \int_0^l -\frac{vr_0^2}{8\pi D} [2\gamma_2 c_0(\zeta) + \gamma_1] \frac{dc_0}{d\zeta} \quad (11)$$
$$\times \frac{d\zeta}{\sqrt{2r_0^2(1 - \cos\Theta) + (z-\zeta)^2}} + \int\int_{V'}\int \frac{Q(P')\, dV'}{4\pi D \rho'(P',P)}.$$

Equation (11) will, in principle, give us $c_0(\zeta)$, from which we can readily obtain $c'(\zeta)$, $\sigma(\zeta)$, $T_0(\zeta)$, and $x_0(\zeta)$. If we put the value of $\sigma(\zeta)$ thus derived into equation (3), we will have a determinate expression for $c(P)$. Therefore the present desideratum is the solution of (11). Unfortunately, however, equation (11) is of a form which is, so far as is known, not soluble. Hence we shall have to confine ourselves to an incomplete discussion of the solution.

First, it is evident that, since $O \leqq z \leqq l$, there will, for every choice of $P(z)$, be one point in the range of integration in (11) at which the integrand will become infinite. That this singularity will not make the integral become infinite can, however, be shown by the following argument: Consider a small circle, of radius δ, fitted to the surface of the capillary with its center at the point $P(z)$. If δ is sufficiently small; we may approximate the integration over the interior, η, of this circle by integration of a constant $\bar{\sigma}$, the average value of σ in the neighborhood of P, over a circular region of a plane; as δ approaches zero, this approximation becomes exact; for any $\delta > 0$, the singularity in the integrand occurs within the circle, so that there will be no singular points encountered in integrating over such of the capillary surface S as lies outside η. Now, if ε denotes the distance from the center of the circle to the general point in η, our integral becomes

$$\int_0^{\delta} \frac{\bar{\sigma} \cdot 2\pi\varepsilon}{\varepsilon} d\varepsilon = \int_0^{\delta} 2\pi\bar{\sigma} d\varepsilon = 2\pi\bar{\sigma}\delta.$$

This quantity obviously approaches zero as δ approaches zero, so that, as δ approaches zero, the integration over $S - \bar{\eta}$ approaches a finite limit; it is evident that the singularity at P does not make the integral diverge.

II. The case of glucose: The problem of the diffusion of glucose is simpler than that of oxygen because glucose experiences no buffering so,

$$c_0(\zeta) \equiv T_0(\zeta), \quad x_0(\zeta) \equiv 0.$$

For this reason, the equation corresponding to equation (11) is

$$c_0(z) + \frac{vr_0}{2h}\frac{dc_0}{dz} = \int_0^{2\pi} d\Theta \int_0^{l} \frac{-vr_0^2 \frac{dc_0}{d\zeta} d\zeta}{8\pi D\sqrt{2r_0^2(1-\cos\Theta)+(z-\zeta)^2}} + A. \quad (12)$$

The same argument as that given for the case of oxygen applies here and shows that the singularity in the integrand does not make the integral diverge.

III. Other cases: It will be seen that other metabolites will behave either like oxygen or like glucose; we shall denote the types of substances exhibiting these two types of behavior as types I and II, respectively, type II being, as we have seen, a special case of type I.

A. Non-buffered substances: All non-buffered substances behave like glucose, and hence belong to type II. Therefore equation (12) applies to their concentrations in the blood, and its solution will enable us to compute all other unknown quantities.

B. Buffered substances: In the general case of buffering, the substance will exist in several forms, in some of which, the "mobile" forms, it can pass through the capillary wall and in the rest of which, the "immobile" forms, it cannot. Let us denote by $c_0(\zeta)$ the total concentration, in gm per cc of blood, of the substance in mobile form, by $x_0(\zeta)$ its total concentration in immobile form, and, as for oxygen, by $T_0(\zeta)$ the sum $c_0(\zeta) + x_0(\zeta)$; let $c(P)$, $x(P)$, and $T(P)$ be the corresponding concentrations at point P in the tissue. Let us assume we know x as a function of c (x_0 as a function of c_0) when the forms are at equilibrium.

We are treating a steady state, so we assume the existence of equilibrium between mobile and immobile forms in the tissue, and, in accordance with the treatment of oxygen, neglect any time lag there may be in the transition between the two forms in the blood.

It will be seen that buffering in the tissue will manifest itself by influencing the production integral in equation (3). But, since we are dealing with the case in which exactly as much of the substance goes from the mobile form to the immobile form as goes the other way, at any point in the tissue, it is evident that buffering in the tissue has no effect on the value of Q, and hence introduces no change in our problem.

Buffering in the blood will manifest itself exactly as it did in our treatment of oxygen. σ will be defined in the same way, and equations (2), (3), and (7) will be unchanged. The steps between equation (7) and equation (11) will be essentially the same as before, except that, in general, we shall not have x_0 as a quadratic function of c_0.

$$\frac{dT_0}{d\zeta} = \frac{d}{d\zeta}\left[x_0(c_0) + c_0\right] = \left[\frac{dx_0}{dc_0} + 1\right]\frac{dc_0}{d\zeta};$$

$\left[\frac{dx_0}{dc_0} + 1\right]$ will be known: let us denote it by $\phi(c_0)$. Hence, from equations (8) and (9)

$$\sigma(\zeta) = -\frac{vr_0}{8\pi D}\phi(c_0)\frac{dc_0}{d\zeta} \tag{13}$$

$$c'(\zeta) = c_0(\zeta) + \frac{vr_0}{2h}\phi(c_0)\frac{dc_0}{d\zeta}. \tag{14}$$

The generalized version of equation (11) will thus be

$$c_0(z) + \frac{vr_0}{2h}\phi(c_0)\frac{dc_0}{dz} = \int_0^{2\pi} d\Theta \int_0^{l} -\frac{vr_0^2}{8\pi D}\frac{\phi(c_0)\frac{dc_0}{d\zeta}\,d\zeta}{\sqrt{2r_0^2(1-\cos\Theta)+(z-\zeta)^2}} + A. \tag{15}$$

It will be evident that equations (12) and (14), for general substances of types II and I respectively, will hold whether the substances are being produced or consumed in the tissue, since the sign of Q does not affect the validity of equations (2), (3), or (7), from which the later equations are derived. Actually, also, equation (12) is a special case of equation (15), in which $\phi(c_0) \equiv 1$.

Thus the solution of equation (15) will determine the behavior of any metabolite in its passage between blood and tissue.

IV. Since the solution of equation (15) presents seemingly insurmountable difficulties, we shall derive an expression which should enable us to find, approximately, the effect of distant capillaries.

First, because we are interested in the concentration at a point far from a capillary, we shall treat the capillary as a line segment of length l, omitting the integration with respect to Θ in equation (3). In accordance with this change, we must replace σ, productivity per unit area, by λ, productivity per unit length. It will be seen that

$$\lambda = 2\pi r_0 \sigma. \tag{16}$$

Hence, if we denote by $c_i(P)$ the contribution to $c(P)$ made by the i-th capillary, and by $A(P)$ the effect at P of production in the tissue, as in equations (7), (12), (15), we have

$$c(P) = \sum_i c_i(P) + A(P). \tag{17}$$

The quantity $c_i(P)$ will be given by the following equation:

$$c_i(P) = \int_0^{l_i} \frac{\lambda(\zeta_1)\,d\zeta_i}{\rho(\zeta_i,P)} = 2\pi r_0 \int_0^{l_i} \frac{\sigma(\zeta_i)\,d\zeta_i}{\sqrt{r_i^2+(z_i-\zeta_i)^2}}. \tag{18}$$

Determination of $\sigma(\zeta)$ requires the solution of equation (15) or an equivalent equation, in which can not be used the line-segment ap-

proximation of this section, since the equation applies to a point adjoining the surface of the capillary. For this reason, we shall investigate the form of $c(P)$ for two simple forms of σ, assumed given.

From equation (2) we note that, if $\sigma(\zeta)$ is a polynomial of degree K, $T_0(\zeta)$ is a polynomial of degree $K+1$. In particular, if $\sigma(\zeta)$ is a constant, $\sigma(\zeta) = \sigma_0$, we have $T_0(\zeta)$ a linear function of ζ,

$$T_0(\zeta) = T_1 + \frac{T_2 - T_1}{l}\zeta$$

and

$$\sigma = \sigma_0 = \frac{vr_0}{8\pi D}\frac{T_1 - T_2}{l}. \tag{19}$$

Also, if σ is linear, T_0 is quadratic:

$$T_0(\zeta) = T_0 + \mu_1\zeta + \mu_2\zeta^2$$

and

$$\sigma(\zeta) = -\frac{vr_0}{8\pi D}(\mu_1 + 2\mu_2\zeta) \tag{20}$$

In the case of quadratic $T_0(\zeta)$ [equation (20)], we have not enough facts at our disposal to evaluate the coefficients μ_1 and μ_2, but if $T_0(\zeta)$ is linear [equation (19)], all coefficients are determined. It will be seen later that this linear form is the most useful.

If $\sigma(\zeta)$ is constant, equation (19) tells us its value is $\frac{vr_0}{8\pi D}\frac{T_1 - T_2}{l}$. Thus, from equation (18), we have, dropping the subscripts and performing the integration,

$$c(r,z) = \frac{vr_0^2(T_1 - T_2)}{4Dl}\log\frac{\sqrt{r^2 + (z-l)^2} + l - z}{\sqrt{r^2 + z^2} - z}. \tag{21}$$

If T_0 is quadratic and σ linear, as in equation (20), so that

$$\sigma(\zeta) = -\frac{vr_0}{8\pi D}(\mu_1 + 2\mu_2\zeta),$$

then integration gives

$$c(r,z) = -\frac{vr_0}{8\pi D}\left\{2\mu_2[\sqrt{r^2 + (z-l)^2} - \sqrt{r^2 + z^2}] + [2\mu_2 z + 1]\,\mu_1\log\frac{\sqrt{r^2 + (z-l)^2} + l - z}{\sqrt{r^2 + z^2} - z}\right\}. \tag{22}$$

When one is dealing with an actual capillary, T_0 and σ cannot be linear and constant, respectively, since expression (21) is sym-

metric about the plane $z = l/z$, while linearity of T_0 implies asymmetry in c_0 and in c', hence in $c(P)$, if permeability, h, is assumed constant. However, in treating the case of many capillaries, oriented at random, we shall assume that for each capillary with a given orientation there is another at the same distance with opposite orientation, and shall use equation (21) to express the effect of one capillary.

Distance in this case will be the distance from the central point of the capillary:

$$R = \sqrt{r^2 + (z - \frac{l}{z})^2},$$

or, if

$$z - \frac{l}{z} = Z, R = \sqrt{r^2 + Z^2}.$$

We shall set $r = Z$ on the average. Now equation (21) becomes

$$c(R)\left(= c(r, Z)\right) = \frac{vr_0^2(T_1 - T_2)}{4Dl} \times \log \frac{\sqrt{R^2 - \frac{lR}{\sqrt{2}} + \frac{l^2}{4}} - \frac{R}{\sqrt{2}} + \frac{l}{2}}{\sqrt{R^2 + \frac{lR}{\sqrt{2}} + \frac{l^2}{4}} - \frac{R}{\sqrt{2}} - \frac{l}{2}} \tag{23}$$

Since we are interested only in the effects of distant capillaries, we shall assume l is small compared with R and shall hence subtract $\frac{1}{8}l^2$ from the radicands in both numerator and denominator of equation (23), thus making the radicands perfect squares. Now it is easy to integrate $c(R)$ over the volume between $R = R_1$ and $R = R_2$. This integration will give us an expression for contributions to concentration at point P of all capillaries lying between two spherical surfaces of radii R_1 and R_2, respectively, with their centers at P. $R_2 > R_1$. What we are doing here is treating these capillaries as a producing/consuming continuum rather than as discrete producing/consuming bodies; we shall obtain $\sum c_i(P)$ [see equation (17)] for the case in which all capillaries within a sphere of radius R_1 have ceased to flow. if the tissue has radius R_2.

$$\sum_i c_i(P) = \frac{\pi n v r_0^2 (T_1 - T_2)}{3Dl} \left\{ R_2^3 \log \frac{R_2 + \frac{1}{2}l}{R_2 - \frac{1}{2}l} + \frac{l^3}{8} \log \frac{R_2^2 - \frac{l^2}{4}}{R_1^2 - \frac{l^2}{4}} - R_1^3 \log \frac{R_1 + \frac{1}{2}l}{R_1 - \frac{1}{2}l} + \tfrac{1}{2}l(R_2^2 - R_1^2) \right\}. \tag{24}$$

Here n is the number of capillaries per cubic centimeter between R_1 and R_2. $A(P)$ will be given by the following integration:

$$A(P) = \frac{Q}{4\pi D} \int_0^{R_2} \frac{4\pi R^2}{R}\, dR = \frac{Q}{2D} R_2^2. \tag{25}$$

Thus, by combining equations (24) and (25) in accordance with equation (17), we obtain

$$c(P) = \frac{\pi n v r_0^2 (T_1 - T_2)}{3Dl} \left[R_2^3 \log \frac{R_2 + \frac{1}{2}l}{R_2 - \frac{1}{2}l} - R_1^3 \log \frac{R_1 + \frac{1}{2}l}{R_1 - \frac{1}{2}l} + \frac{l^3}{8} \log \frac{R_2^2 - \frac{l^2}{4}}{R_1^2 - \frac{l^2}{4}} + \tfrac{1}{2}l(R_2^2 - R_1^2) \right] + \frac{Q}{2D} R_2^2. \tag{26}$$

Equation (26), then, enabling us, as it does, to calculate concentration in a region whose capillaries are not flowing, should be susceptible to experimental verification.

An assumption which must be made concerning tissue is that, if equivalent capillaries are uniformly distributed, n per unit volume, throughout tissue, each capillary produces/consumes exactly one n-th as much of any metabolite as is consumed/produced in a unit volume of tissue. This must be true if the tissue is in a steady state.

If, as in the case we are considering, the capillaries inside a sphere of radius R_1 are not flowing, then capillaries at distances from the center not much greater than R_1 will have to supply/consume some of the material that normally would have been supplied/consumed by the capillaries inside the sphere. For this reason they will have values of σ greater in absolute magnitude than the average value for the whole tissue; hence equation (26) is not accurate, since σ in fact should be a function of R and so should have been included in the integrand. This correction we shall neglect.

Whatever may be the correction to σ for the closer capillaries, it will be seen that the more distant capillaries will be less affected by the absence of capillaries within the sphere of radius R_1; as R approaches infinity, the correction approaches zero, so that capillaries at infinite distance from P will each produce/consume exactly as much material as is consumed/produced in one n-th unit volume of tissue at infinite distance. Hence,

$$\lim_{R_2 \to \infty} \frac{dc(P)}{dR_2} = 0. \tag{27}$$

Application of equation (27) to equation (26) will give us a relation between Q and $(T_1 - T_2)$ in terms of the other quantities involved:

$$\lim_{R_2 \to \infty} \frac{\pi n v r_0^2 (T_1 - T_2)}{Dl} \left[R_2 \log \frac{R_2 + \frac{l}{2}}{R_2 - \frac{l}{2}} \right] + \frac{Q}{D} = 0, \tag{28}$$

whence

$$\frac{\pi n v r_0^2 (T_1 - T_2)}{D} R_2 + \frac{Q}{D} R_2 = 0$$

or

$$\pi v r_0^2 (T_1 - T_2) = -\frac{Q}{n}. \tag{29}$$

Equation (29) is identical with the relation between Q and $(T_1 - T_2)$ obtained by a different method.

If blood is flowing with velocity v in a capillary of radius r_0, then the volume of blood passing a given point per unit time is $\pi r_0^2 v$. Then, if the concentration of some substance is T_1 at the entering end of the capillary and T_2 at the other end, the blood entering per unit time contains a mass of the substance equal to $T_1 \pi r_0^2 v$, while the mass contained in the blood leaving per unit time is $T_2 \pi r_0^2 v$. Hence, in unit time, the blood loses $(T_1 - T_2)\pi r_0^2 v$, or gains $(T_2 - T_1)\pi r_0^2 v$, mass units. Now, if there are n capillaries per unit volume of tissue, and if we assume each capillary to produce/consume as much of the substance as is consumed/produced by a volume $1/n$ of tissue, then

$$(T_1 - T_2)\pi r_0^2 v = -\frac{Q}{n} \tag{30}$$

if Q is production per unit volume of tissue. Equation (30) is seen to be identical with equation (29). This fact does not constitute a verification of our assumption that σ is constant, since the assumptions leading to equations (29) and (30) are equivalent for any $\sigma(\zeta)$, and thus must lead to the same equation. Hence the identity of (29) and (30) merely indicates that the error introduced in the approximation used in integrating equation (23) vanishes as R approaches infinity.

If we now substitute for Q in equation (26) its value as given by equation (29), we obtain

$$c(P) = \frac{\pi n v r_0^2 (T_1 - T_2)}{3Dl}\left[R_2^3 \log \frac{R_2 + \frac{1}{2}l}{R_2 - \frac{1}{2}l} - R_1^3 \log \frac{R_1 + \frac{1}{2}l}{R_1 - \frac{1}{2}l} + \frac{l^3}{8} \log \frac{R_2^2 - \frac{1}{4}l^2}{R_1^2 - \frac{1}{4}l^2} - \frac{1}{2} l R_1^2 - \frac{3}{2} l R_2^2 \right]. \tag{31}$$

It is now possible to obtain an expression for concentration at any point $\mathcal{P}$ at distance $\mathcal{R}$ from point P, if $\mathcal{R} < R_1$ and if we assume the field within the sphere of radius R_1 about P is spherically symmetrical. This comes from solution of the diffusion equation

$$\nabla^2 c = -\frac{Q}{D}$$

whose solution for this case is

$$c(\mathcal{R}) = \frac{\pi n v r_0^2 (T_1 - T_2)}{3Dl}\left[R_2^3 \log \frac{R_2 + \frac{1}{2}l}{R_2 - \frac{1}{2}l} - R_1^3 \log \frac{R_1 + \frac{1}{2}l}{R_1 - \frac{1}{2}l} + \frac{l^3}{8} \log \frac{R_2^2 - \frac{1}{4}l^2}{R_1^2 - \frac{1}{4}l^2} - \tfrac{1}{2} l R_1^2 - \frac{3}{2} l R_2^2 + \tfrac{1}{2} l \mathcal{R}^2 \right]. \tag{32}$$

All the foregoing treatment has been carried through on the assumption that Q is constant. Whether or not this will in general be true is difficult to say; Landahl has, however (Rashevsky, 1940), obtained relations between concentration and consumption for glucose and oxygen, respectively. These relations show that, as concentration of either of these substances outside a cell increases, the cell's consumption of this substance approaches an asymptotic value $-Q^*$. It is possible to define in each case a value c^* of external concentration such that Q may be considered equal to Q^* if and only if $c > c^*$. It seems also reasonable to assume that metabolism of other substances depends upon the metabolism of oxygen and glucose in such a way that if oxygen and glucose concentrations, denoted by C and C' re-

spectively, are greater than their critical values, C^* and C'^*, all productions and consumptions are constant, provided the constants of the cells in the tissue do not change. Hence, our treatment is valid if and only if $C \geqq C^*$ and $C' \geqq C'^*$. In Rashevsky, 1940, we find expressions for C and C':

$$C = \chi \frac{Q}{Q^*} + \frac{\xi Q}{Q^* - Q} \tag{33}$$

$$C' = \chi \frac{Q'}{Q'^*} + \frac{\xi' Q'}{Q'^* - Q'}. \tag{34}$$

Here Q, Q^*; Q', Q'^* are consumption and critical consumption of oxygen and glucose, respectively. ξ, ξ', χ, χ' are constants given in Rashevsky, 1940; my χ is Rashevsky's ζ. These constants depend, in particular, upon the nature of the cells in the tissue.

Now we set

$$\begin{aligned} C^* &= \chi + \xi \\ C'^* &= \chi' + \xi'. \end{aligned} \tag{35}$$

These are the values of C and C' at which the straight lines tangent to the $C(Q)$ and $C'(Q')$ curves, respectively, at the origin, intersect the lines $Q = Q^*$ and $Q' = Q'^*$. They seem reasonable values for C^* and C'^*.

If we now substitute for T_1, T_2, D the values $\mathcal{T}_1$, $\mathcal{T}_2$, $\mathcal{D}$; $\mathcal{T}_1'$, $\mathcal{T}_2'$, $\mathcal{D}'$ for the special cases of oxygen and glucose, respectively, and substitute for $c(P)$ in equation (31) the values of C^* and C'^* from equation (35), we obtain

$$\begin{aligned} \chi + \xi = \frac{\pi n v r_0^2 (\mathcal{T}_1 - \mathcal{T}_2)}{3\mathcal{D} l} \Bigg[& R_2^3 \log \frac{R_2 + \tfrac{1}{2}l}{R_2 - \tfrac{1}{2}l} \\ & - R_1^3 \log \frac{R_1 + \tfrac{1}{2}l}{R_1 - \tfrac{1}{2}l} + \frac{l^3}{8} \log \frac{R_2^2 - \tfrac{1}{4}l^2}{R_1^2 - \tfrac{1}{4}l^2} - \tfrac{1}{2} l R_1^2 - \frac{3}{2} l R_2^2 \Bigg]. \\ \chi' + \xi' = \frac{\pi n v r_0^2 (\mathcal{T}_1' - \mathcal{T}_2')}{3\mathcal{D}' l} \Bigg[& R_2^3 \log \frac{R_2 + \tfrac{1}{2}l}{R_2 - \tfrac{1}{2}l} \\ & - R_1^3 \log \frac{R_1 + \tfrac{1}{2}l}{R_1 - \tfrac{1}{2}l} + \frac{l^3}{8} \log \frac{R_2^2 - \tfrac{1}{4}l^2}{R_1^2 - \tfrac{1}{4}l^2} - \tfrac{1}{2} l R_1^2 - \frac{3}{2} l R_2^2 \Bigg]. \end{aligned} \tag{36}$$

These equations give the conditions that concentrations of oxygen and glucose, respectively, are as low as they can be if metabolism is to

remain constant as concentration changes. If R_1^* and $R_1'^*$ are the values of R_1 for which these two equations are true, then the smaller of these is the radius of the largest sphere of capillaries whose ceasing to flow will not decrease metabolic rate at any point of the tissue.

If we divide each equation (36) by the (positive) coefficient in front of the brackets on the right side, we get two equations, in each of which the quantity on the right side is the same decreasing function of R_1. Hence, $R_1^* < R_1'^*$ if

$$\frac{3\mathcal{D}l(\chi + \xi)}{\pi n v r_0^2 (\mathcal{T}_1 - \mathcal{T}_2)} > \frac{3\mathcal{D}'l(\chi' + \xi')}{\pi n v r_0^2 (\mathcal{T}_1' - \mathcal{T}_2')} \tag{37}$$

or if

$$\frac{\mathcal{D}(\chi + \xi)}{\mathcal{T}_1 - \mathcal{T}_2} > \frac{\mathcal{D}'(\chi' + \xi')}{\mathcal{T}_1' - \mathcal{T}_2'}.$$

Thus we see that if the inequality (37) is true, oxygen is the critical substance in maintenance of asymptotic metabolism; otherwise, glucose is the critical substance.

Once we have discovered whether or not inequality (37) is true, we know which of the equations (36) to solve for R_1. It is to be expected that when R_1 exceeds this value, the metabolism of the cells in the center of the sphere of non-flowing capillaries will considerably slow down, and in some tissues, notably in brain and in striated muscle, the cells may begin to die.

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LITERATURE

Bloch, I. 1941. "Some Preliminary Considerations Concerning Concentration of Oxygen in Tissue." *Bull. Math. Biophysics*, 3, 121-126.

Henderson, L. J. 1928. *Blood—A Study in General Physiology*. New Haven: Yale University Press.

MacMillan, W. O. 1936. *Theoretical Mechanics: The Theory of the Potential*. New York and London: McGraw Hill.

Rashevsky, N. 1940. *Advances and Applications of Mathematical Biology*. Chicago: University of Chicago Press.