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Percutaneous absorption: transport in the dermis

W. John Albery *, Richard H. Guy ** and Jonathan Hadgraft ***

* *Department of Chemistry, Imperial College, London SW7 2AY (U.K.);* ** *School of Pharmacy, University of California; San Francisco, CA 94143 (U.S.A.);* and *** *Department of Pharmacy, University of Nottingham, Nottingham NG7 2RD (U.K.)*

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Summary

Results are presented for the percutaneous absorption of 3 different esters of nicotinic acid from circular patches; the values of the diffusion coefficients and triggering concentrations for visible erythema are in good agreement with previous work. For methyl nicotinate the radial spread of the erythema has been followed as a function of time; the results are shown to fit a radial diffusion equation. However, the value of the diffusion coefficient is found to be a thousand times larger than the expected value for molecular diffusion. A model is presented in which the radial transport is caused by uptake in the capillaries. Reasonable values are found for the rate constants describing uptake and for the geometry of the capillaries. This geometry is shown to be close to the optimum for efficient transport to and from the dermis.

Introduction

In this paper we report the results of experiments in which we have studied the percutaneous absorption of 3 different esters of nicotinic acid. These compounds produce a noticeable erythema after penetrating the epidermis. We have studied the radial spread of the erythema produced by methyl nicotinate. From analysis of the rate of spread we can measure the rate of radial diffusion and of uptake by the capillary system.

* To whom correspondence should be addressed.

Materials and Methods

Experimental details have been given previously (Albery and Hadgraft, 1979b). The radial spread was measured at suitable time intervals by outlining the erythematous area on the subject's arm with a felt-tip pen. At the end of the experiment, when about 6 "contours" had been recorded, the arm was photographed in a fixed position with respect to the camera. The area on the photograph was measured by tracing each contour on to graph paper and counting the squares. The conversion of the photographic area to the area on the original skin was achieved by photographing graph paper in position on the arm.

Theory

Previous work (Albery and Hadgraft, 1979b) has shown that there is no significant barrier to transfer through the epidermis from kinetic barriers at phase boundaries. This simplifies the theoretical treatment of the transport through the epidermis. On the other hand, we now have to include the transport in the dermis. The model we use is illustrated in Fig. 1. Transport through the epidermis is described by Fick's second law

$$\frac{\partial c}{\partial t} = D_E \cdot \frac{\partial^2 c}{\partial z^2} \tag{1}$$

where c is the concentration of the diffusion species and D_E is the diffusion coefficient in the epidermis. This equation holds for the area under the patch ($r < r_0$). The boundary conditions for Eqn. 1 are as follows. Firstly, on the surface of the skin, while the patch is applied, we have:

$$\text{at } z = 0 \quad \text{and } 0 < t < t_1, \quad c = c_0 = Kc_\infty \tag{2}$$

where K is the partition coefficient between the patch and the epidermis and c_∞ is

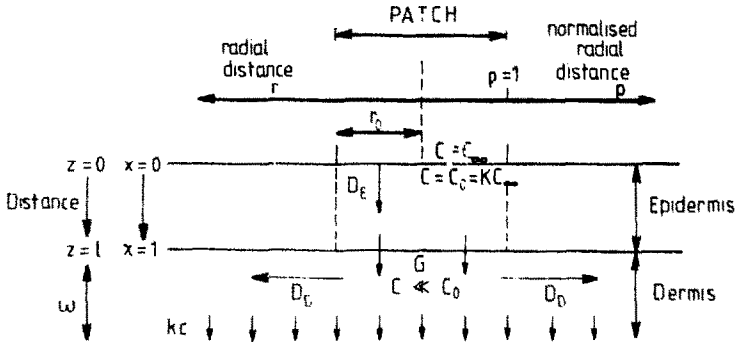

Fig. 1. Model and notation for transport from a circular patch through the epidermis and with radial transport in the dermis.

the concentration of ester in the patch. This boundary condition takes no account of depletion in the external phase. This can be important when vehicles of high viscosity are used (Albery and Hadgraft, 1979b) but can be ignored in the present work when only aqueous solutions are employed. Secondly, after the patch is removed we have

at $z = 0$ and $t > t_1$, $(\partial c/\partial z)_0 = 0$

Thirdly, at the inside edge of the epidermis we have:

at $z = \ell$ $c \simeq 0$.

This boundary condition assumes that removal by transport in the dermis and the circulatory system is rapid compared to transport across the epidermis. This assumption is justified by experiment (Katz and Poulsen, 1971) and is also confirmed by analysis of our results (see below).

Fourthly, at the start of the experiment we have for all values of z:

at $t = 0$, $c = 0$.

We express Eqn. 1 in dimensionless variables:

$$\frac{\partial u}{\partial \tau} = \frac{\partial^2 u}{\partial \chi^2} \tag{3}$$

where $u = c/c_0$, $\tau = tD_E/\ell^2$, and $\chi = z/\ell$.
The boundary conditions become:

at $\tau = 0$ $u = 0$
at $\chi = 1$ $u = 0$
at $\chi = 0$

for $\tau_1 > \tau > 0$ $u = 1$ (4)

and for $\tau > \tau_1$, $(\partial u/\partial \chi)_0 = 0$ (5)

In the dermis we assume that the distance, w, between the epidermis and the circulatory system is small enough for the concentration to be uniform. The processes occurring are therefore the supply of material from the patch the diffusive transport in the radial direction and the removal by the circulatory system. The differential equation is therefore:

$$\frac{\partial c}{\partial t} = D_D\left(\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\cdot\frac{\partial c}{\partial r}\right) + G - kc \tag{6}$$

where D_D is the diffusion coefficient in the dermis, k is a first-order rate constant

describing removal by the circulatory system, and G describes the supply of material from the patch of radius r_0.

For $r < r_0$,

$$G = \frac{aD_E}{w}\left(-\frac{\partial c}{\partial z}\right)_{z=\ell} = \frac{aD_E c_0}{w\ell}\left(-\frac{\partial u}{\partial \chi}\right)_1$$

and for $r > r_0$, $G = 0$

The parameter a describes the fractional area of the interstitial channels through which the ester diffuses compared to the total area of the dermis (Albery and Hadgraft, 1979b).

Expressing Eqn. 6 in dimensionless variables we obtain:

$$\frac{\partial v}{\partial \tau} = Q\left(\frac{\partial^2 v}{\partial \rho^2} + \frac{1}{\rho}\cdot\frac{\partial v}{\partial \rho}\right) - \left(\frac{\partial u}{\partial \chi}\right)_1 - \kappa v \tag{7}$$

where

$$v = wu/\ell a = wc/\ell c_0 a$$

$$Q = D_D \ell^2 / D_E r_0^2 \tag{8}$$

$$\rho = r/r_0 \tag{9}$$

$$\kappa = k\ell^2/D_E \tag{10}$$

The boundary conditions are:

at	$\tau = 0$	$v = 0$
at	$\rho = 0$	$\partial v/\partial \rho = 0$
as	$\rho \to \infty$	$v \to 0$.

The problem in solving Eqn. 3 with boundary conditions (4) and (5) is the change in boundary condition when the patch is removed at $t = t_1$. In our previous treatment (Albery and Hadgraft, 1979a) we used a double Laplace transform to solve the equation. In this work we proceed by first solving Eqn. 3 for $t < t_1$ with the appropriate boundary condition (4). We then find an equivalent boundary condition to Eqn. 5 in $(\partial u/\partial \chi)_0$ rather than in u_0. With the use of the step function we can express the boundary condition at $\chi = 0$ in terms of $(\partial u/\partial \chi)_0$ for all values of t and this means that we do not have to use the double Laplace transform technique.

Hence solving Eqn. 3 with boundary condition (4) we obtain the Laplace transform:

$$(\partial \bar{u}/\partial \chi)_0 = -s^{-1/2}\coth(s^{1/2}) \simeq -s^{-1/2}$$

The approximation is justified since $\tau_1 \ll 1$ (Albery and Hadgraft, 1979b). We then invert the transform to obtain the combined boundary condition:

$$(\partial u/\partial \chi)_0 = -f = -(\pi\tau)^{-1/2}[1 - U(\tau - \tau_1)] \tag{11}$$

where the step function,

$$U(\tau - \tau_1) = 0 \quad \text{for } \tau < \tau_1$$

$$= 1 \quad \text{for } \tau > \tau_1$$

Now solving Eqn. 3 with boundary condition (11) we obtain for the supply of material to the dermis:

$$(\partial \bar{u}/\partial \chi)_{\chi=1} = -\bar{f} \cdot \operatorname{sech}(s^{1/2}) \tag{12}$$

For experiments where the patch is removed and the time, t_2, for erythema to appear under the patch is measured we can ignore the Q terms in Eqn. 7. Hence the accumulation of the drug under the patch to reach the triggering level is given by

$$v_E = -\int_0^{\tau_2}[(\partial u/\partial \chi)_{\chi=1} - \kappa v]d\tau' \tag{13}$$

where $v_E = n_E/\ell K c_\infty \alpha$ and n_E $(= c_E w)$ is the number of moles per unit area required to trigger the erythema.

From Eqns. 12 and 13

$$v_E = L^{-1}_{\tau=\tau_2}\bar{f}\operatorname{sech}(s^{1/2})/(s+\kappa) \simeq \frac{4}{\pi}\int_0^{\tau_1}\frac{(\tau_2-\lambda)^{1/2}\exp\left[-0.25(\tau_2-\lambda)^{-1}\right]}{\lambda^{1/2}\left[1+4\kappa(\tau_2-\lambda)^2\right]}d\lambda \tag{15}$$

We have used the convolution integral to invert the transform. However, because of the step function, U, in the expression for f in Eqn. 11 we replace the upper integration limit τ_2 with τ_1; for $\tau > \tau_1$ the integrand is zero. We have also used the following approximation, which holds for $\tau_2^2 \ll 1$,

$$L^{-1}\frac{\operatorname{sech}(s^{1/2})}{s+\kappa} \simeq L^{-1}\frac{2\exp(-s^{1/2})}{s+\kappa} \simeq \frac{4\tau^{1/2}\exp(-\frac{1}{4}\tau)}{\pi^{1/2}(1+4\kappa\tau^2)}$$

Consideration of the integrand in Eqn. 15 shows that for $\tau < 1$ the exponential term is always small but that it has its maximum value when $\lambda \to 0$. For larger values of λ the exponential term reduces the size of the integrand so much that its contribution to the integral is negligible. Hence writing

$$-\frac{1}{4(\tau_2-\lambda)} \simeq -\frac{1}{4\tau_2} - \frac{\lambda}{4\tau_2^2} - \cdots$$

we obtain

$$v_E \simeq \frac{4\tau_2^{1/2}\exp(-0.25/\tau_2)}{\pi(1+4\kappa\tau_2^2)}\int_0^{\tau_1}\frac{\exp(-\lambda/4\tau_2^2)}{\sqrt{\lambda}}d\lambda$$

$$= \frac{8\tau_2^{3/2}\exp(-0.25/\tau_2)\,\mathrm{erf}(\tau_2^{1/2}/2\tau_2)}{\pi^{1/2}(1+4\kappa\tau_2^2)} \qquad (16)$$

If we take $\tau_1 = \tau_2$, which corresponds to not removing the patch, then, since $\tau \ll 1$, the erf term is unity. With $\kappa = 0$, Eqn. 16 then reduces to our previous result (solution IA, of Table 1, Albery and Hadgraft, 1979a) for this case:

$$v_E = 8\pi^{-1/2}\tau_2^{3/2}\exp(-0.25/\tau_2)$$

On the other hand if we take $1 \gg \tau_2^2 \gg \tau_1^2$ then

$$v_E \simeq \frac{4\tau_2^{1/2}\exp(-0.25/\tau_2)\tau_1^{1/2}}{\pi(1+4\kappa\tau_2^2)} \qquad (17)$$

This equation (with $\kappa = 0$) is then the same result as we obtained previously (solutions P3 and P1 of Table 3, Albery and Hadgraft 1979a). The advantage of the new treatment is that we do not have to make any assumptions about the relative size of τ_1 and τ_2. In this work we have also taken into account the removal of the ester by the circulatory system (the term in $\kappa\tau_2^2$). By contrast our previous work contained two effects not considered here—the kinetics of interfacial barriers and the depletion of the external phase.

Next we turn to the radial diffusion. We take the Laplace transform of Eqn. 7 and write

$$(s+\kappa)\bar{v}_n = Q(\partial^2\bar{v}_n/\partial\rho^2 + \rho^{-1}\partial\bar{v}_n/\partial\rho) \qquad (18)$$

where for $\rho < 1$, $(r < r_0)$, $n = 1$

and $\bar{v} = \dfrac{(\partial\bar{u}/\partial\chi)_1}{s+\kappa} - \bar{v}_1$

while for $\rho > 1$, $(r > r_0)$, $n = 2$

and $\bar{v} = \bar{v}_2$

The solutions to Eqn. 18 are modified Bessel functions of order zero (Abramowitz and Stegun, 1965b). They are shown in Fig. 2. In order to fulfill the boundary conditions

$$\bar{v}_1 = AI_0(q\rho)$$

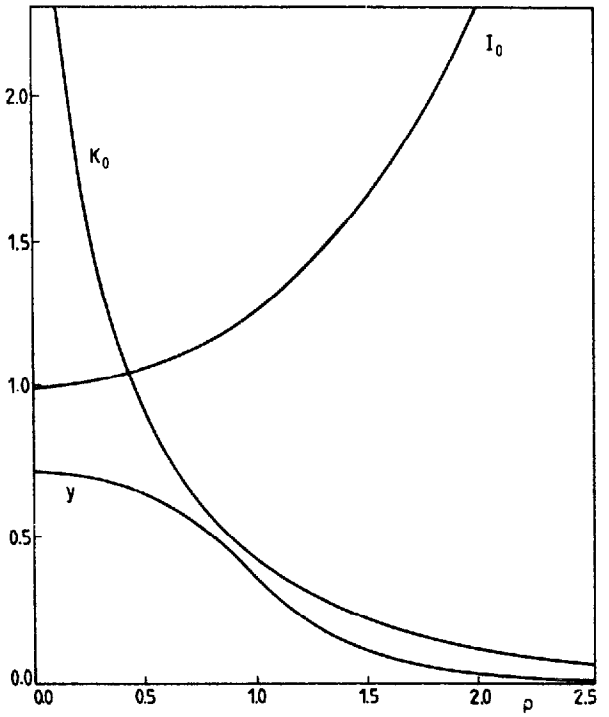

Fig. 2. Plot of the Bessel functions $I_0(\rho)$ and $K_0(\rho)$ together with a typical plot of Eqns. 19 and 20 with $q = 2$ plotted with y as defined in Eqn. 21.

while $\bar{v}_2 = BK_0(q\rho)$

where $q = (s + \kappa/Q)^{1/2}$

and A and B are constants.

The constants are found by matching the values of $\bar{v}_n$ and $(\partial\bar{v}_n/\partial\rho)$ at $\rho = 1$. Hence we obtain for

$$\rho < 1, \quad \bar{v} = \frac{(-\partial\bar{u}/\partial\chi)_1}{s + \kappa}[1 - qI_0(q\rho)K_1(q)] \tag{19}$$

while for

$$\rho > 1, \quad \bar{v} = \frac{qI_1(q)K_0(q\rho)}{(s + \kappa)}\left(-\frac{\partial\bar{u}}{\partial\chi}\right)_1 \tag{20}$$

Fig. 2 also shows a typical plot for $q = 2$ of the radial variation of $\bar{v}$ plotted as y where

$$y = \frac{(s + \kappa)\bar{v}}{(-\partial\bar{u}/\partial\chi)_1} \tag{21}$$

For $\lambda > 2$ (Abramowitz and Stegun, 1965b)

$$\lambda I_0(\lambda)K_1(\lambda) \simeq \lambda I_1(\lambda)K_0(\lambda) \simeq \tfrac{1}{2}$$

Thus the concentration on the edge of the patch is one-half that at the centre, because material is being lost from the edge by radial diffusion. This factor of 1/2 is a difference between these experiments, where the patch is removed and the time for erythema to develop is measured for the place where the patch was, and those experiments, where the patch remains in place and the time is measured for a halo of erythema to develop around the patch. In the latter case v_E is given by Eqn. 16 with the factor of 8 replaced by 4.

At greater radial distances, assuming $\tau^2 \ll 1$, which leads to $s^2 \gg 1$ and $q^2 \gg 1$, we can replace the Bessel functions by their asymptotic forms for large argument (Abramowitz and Stegun, 1965b) and so obtain (for $\rho > 1$)

$$\bar{v}_E \simeq \rho^{-1/2} L^{-1} \bar{g} \cdot \bar{f} \tag{22}$$

$$\text{where } \bar{g} = \frac{\exp\left[-s^{1/2} - (\rho_E - 1)(s+\kappa)^{1/2}/Q\right]}{(s+\kappa)} \tag{23}$$

As described in Appendix 1, the transform is inverted by first inverting $\bar{g}$ and then using the convolution theorem. We obtain.

$$v_E = \frac{4}{(\pi\rho_E)^{1/2}} \cdot \frac{F(\zeta, \theta)}{\gamma^{3/2}} \cdot \exp[-\gamma H(\zeta, \theta)] \operatorname{erf}\left[\frac{\tau_1^{1/2} H(\theta/\zeta)}{2\tau_E}\right] \tag{24}$$

where

$$F(\zeta, \theta) = \frac{(\zeta^2 - 1)^{3/4}}{\zeta^{1/2}(\zeta^3 + \theta)^{1/2}}$$

$$H(\zeta, \theta) = \frac{1 + \theta(2\zeta^2 - 1)/\zeta}{4(\zeta^2 - 1)^{1/2}}$$

$$\tau_1 = \gamma^{-1}(\zeta^2 - 1)^{1/2}(1 + \theta/\zeta)$$

$$\gamma = 2\kappa^{1/2} \tag{25}$$

$$\text{and } \theta = (\rho_E - 1)/Q^{1/2} \quad \text{at } \rho = 1, \theta = 0$$

and Eqn. 24 reduces to Eqn. 16 apart from the factor of 2 which describes the radial diffusion at the edge of the patch.

Results and Discussion

Continuous application

Experiments in which the ester was applied continuously were carried out for methyl, *n*-butyl and hexyl nicotinate. For these experiments the κ-term is negligible (see below) and hence we can use the simple Eqn. 16 with the factor of 4 rather than 8 to allow for radial depletion at the edge of the patch. Substituting for $\tau_1 = \tau_2$ and for v_E from Eqn. 14 we find

$$\log(c_\infty t_2^{3/2}) = \log\left(\frac{n_E}{a\ell}\right) - \log\left[\frac{4K}{\pi^{1/2}} \cdot \left(\frac{D_E}{\ell^2}\right)^{3/2}\right] + \frac{\ell^2}{4 \times 2.303\, D_E t_2} \tag{26}$$

where we have neglected the term in $1 + 4\kappa\tau_2^2$; this approximation is justified below.

The results of the experiments are plotted in Fig. 3 and are collected together in Table 1. Each of the points in Fig. 3 is the mean of at least 12 separate experiments. In calculating $n_E/a\ell$ we have estimated K from the measured values for the partition of the esters between water and isopropyl myritate K_{IPM}, corrected by a factor of 6 (Albery and Hadgraft, 1979b):

$$K = 6K_{IPM} \tag{27}$$

We assume that these esters diffuse by the intercellular rather than the transcellular route (Albery and Hadgraft, 1979b). That is the ester diffuses in the channels round the keratinized cells rather than through the cells. For this route we estimate (Albery and Hadgraft, 1979b) that

$$\ell/\text{mm} = 0.34, \tag{28}$$

and that the fractional area occupied by the channels, a, is given by

$$a = 7 \times 10^{-3} \tag{29}$$

The results in Table 1 show that despite a 50-fold change in K the 3 esters give similar triggering concentrations. Furthermore, the diffusion coefficient of each ester in the interstitial channels parallels that for each ester in IPM; the epidermal diffusion coefficients are slower by a factor of 25.

Our previous results (Albery and Hadgraft, 1979b) for methyl nicotinate gave $D_E = 37\ m^2 \cdot Ts^{-1}$, and $n_E = 40\ pmol \cdot cm^{-2}$. Considering that these results were obtained with JH they are in good agreement with those in Table 1. Our results also agree with those of Stoughton et al. (1960) who found, using direct injection, that $n_E \sim 10\ pmol \cdot cm^{-2}$ and that n_E was insensitive to the different alkyl groups.

Pulse experiments

Experiments in which the patch is applied for a time t_1 and erythema subsequently appears in the place where the patch was at time t_2 were carried out for

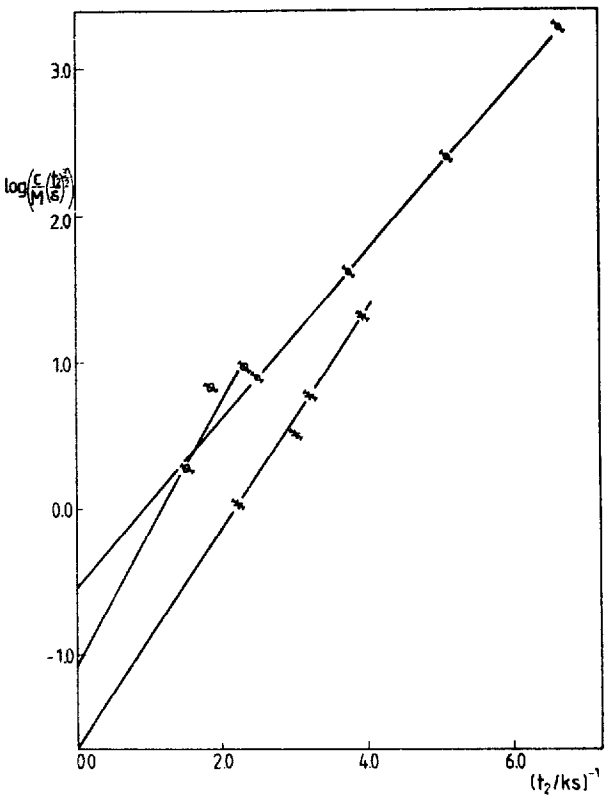

Fig. 3. Plots of Eqn. 26 for experiments with continuous application of nicotinate esters: ○, methyl; ×, n-butyl; □, hexyl.

methyl nicotinate with $c_\infty = 93.8$ mM. The results are reported in Table 2; each result for t_2 is the mean of 12 separate experiments. Using the value of D_E/l^2 determined from the continuous application experiments in Table 1 we calculate v_E.

TABLE 1

RESULTS FOR CONTINUOUS APPLICATION EXPERIMENTS

Ester	Methyl	n-butyl	hexyl
$(D_E/\ell^2)/ks^{-1}$ [a]	0.190	0.142	0.122
K [b]	20	230	430
$n_E/al/\mu M$ [c]	36	80	33
$D_E/m^2\ Ts^{-1}$ [d]	22	17	14
$D_{IPM}/m^2\ Gs^{-1}$	0.51	0.43	0.40
$10^2 D_E/D_{IPM}$	4.3	3.8	2.9
$n_E/pmol\ cm^{-2}$ [d]	9	19	8

[a] Calculated from gradients of plots in Fig. 3.
[b] From Eqn. 27.
[c] Calculated from intercepts of plots in Fig. 3.
[d] Calculated using values in Eqn. 28 and 29.

TABLE 2

RESULTS FOR PULSED EXPERIMENTS FOR METHYL NICOTINATE

t_1/s	t_2/s	$10^5 v_E$
20	244 ± 16	14.5
30	212 ± 16	6.3
60	215 ± 14	9.4
120	209 ± 10	6.4
180	218 ± 7	9.1
	mean·····	9.1 ± 1.5

from Eqn. 16. Reasonably constant values are found. From Eqn. 14 we find

$$n_E = 41 \text{ pmol} \cdot \text{cm}^{-2} \tag{30}$$

This value is in reasonable agreement with that in Table 1. These results therefore confirm Eqn. 16 and the theoretical description of diffusion in the patch area.

Radial diffusion experiments

The area, A, of the erythematous region is measured as described in the experimental section. The area is assumed to be circular with an average radius, r_E. The dimensionless parameter, ρ_E, can then be calculated:

$$\rho_E = \frac{r_E}{r_0} = \frac{1}{r_0} \cdot \sqrt{\frac{A}{\pi}}$$

where r_0 is the radius of the patch. In Table 3 and Figs. 4, 5 and 6 we report the experimental results.

In Eqn. 24 we can use the values of v_E and D_E/l^2 from the experiments with continuous application. There are then only the two unknowns which describe radial diffusion and removal by the circulatory system, respectively:

$$Q = D_D \ell^2 / D_E r_0^2 \tag{31}$$

$$\gamma = 2\kappa^{1/2} = 2k^{1/2} \ell D_E^{-1/2} \tag{32}$$

Taking values of Q, the corresponding value of γ can be calculated for each experimental point. A successful fit of the experimental data to Eqn. 24 is indicated by a constant value of γ for the different experimental points in a series; typical results are shown in Fig. 7.

For values of Q less than those given in Table 3 (Q_{min}), no fit can be found to Eqn. 24 for many of the experimental points and the remaining values of γ are more dispersed. For values of Q greater than Q_{min} reasonable fits (as shown in Fig. 7) can

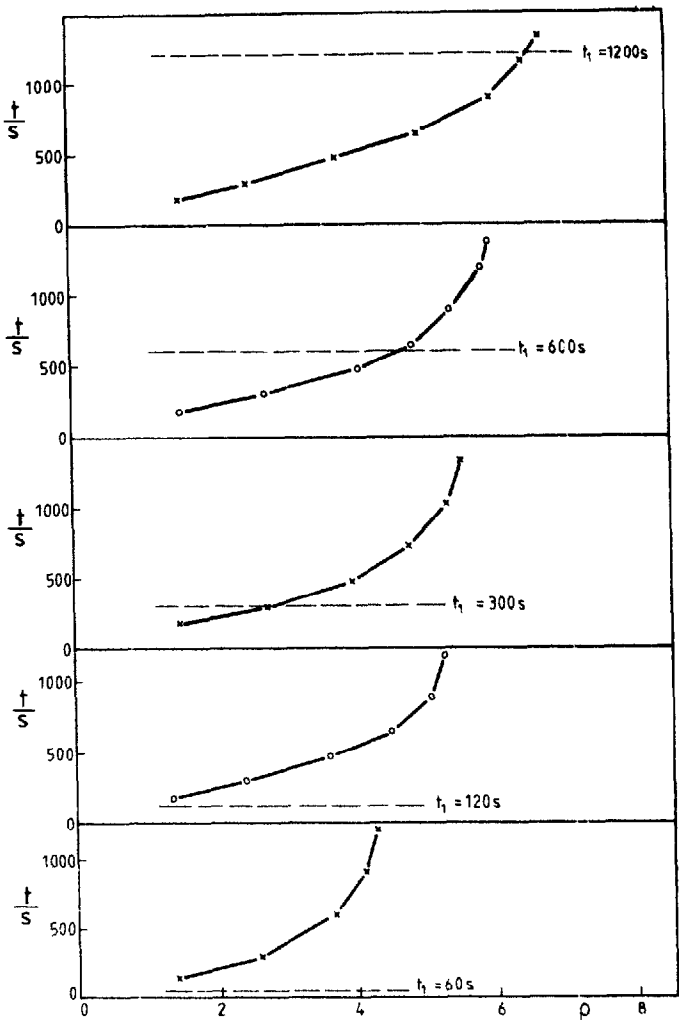

Fig. 4. Results for radial spread of erythema from methyl nicotinate for different values of t_1 — Series I.

be found; there is no significant variation in the standard deviation for γ for different values of Q. In Fig. 8 we show the values of log γ plotted against log Q. Q varies with the size of the patch and in Fig. 8 we have also plotted the data for the experiments of Series I shifted by 0.41 log units, which corresponds to the radius

TABLE 3

RESULTS FOR RADIAL DIFFUSION EXPERIMENTS

Series	Fig.	c_∞/mM	r_0/cm	Q_{min}
I	4	290	0.313	50
II	5	93.8	0.500	10
III	6	1020	0.500	10

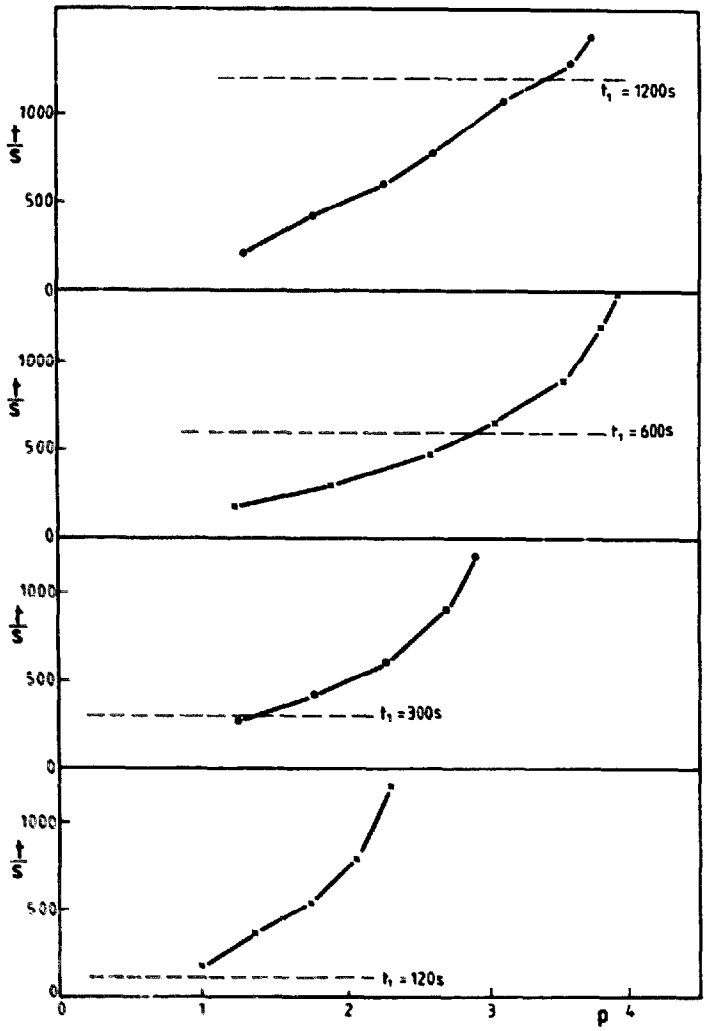

Fig. 5. Results for radial spread of erythema from methyl nicotinate for different values of t_1 — Series II.

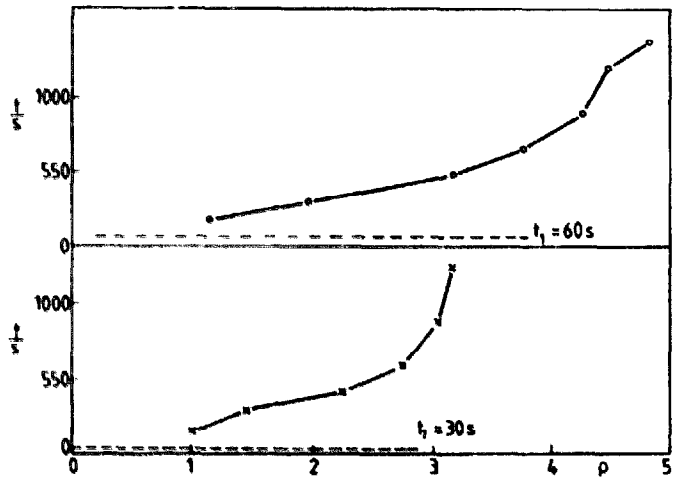

Fig. 6. Results for radial spread of erythema from methyl nicotinate for different values of t_1 — Series III.

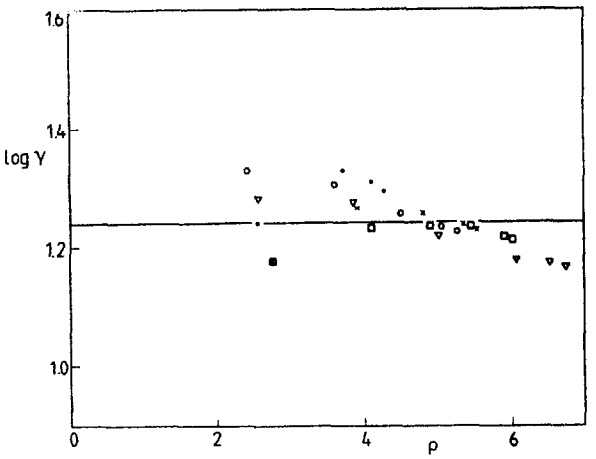

Fig. 7. Typical analysis of the Series I results using, in this case, Q = 50 and Eqn. 24. The values of t_1/s are as follows: ●, 30; ○, 60; × 300; □, 600; ▽, 1200. The value of log γ is 1.24 ± 0.05.

ratio squared $(0.50/0.31)^2$. It is satisfactory that when this is done the values of log γ as a function of log Q from Series I are in good agreement with those from Series II and III. The same factor can be applied to Q_{min} in Table 3 reducing it from 50 to 20, which is in reasonable agreement with the other two values. Although the data can be fitted by any pair of values of γ and Q in Fig. 8, we shall show below that the

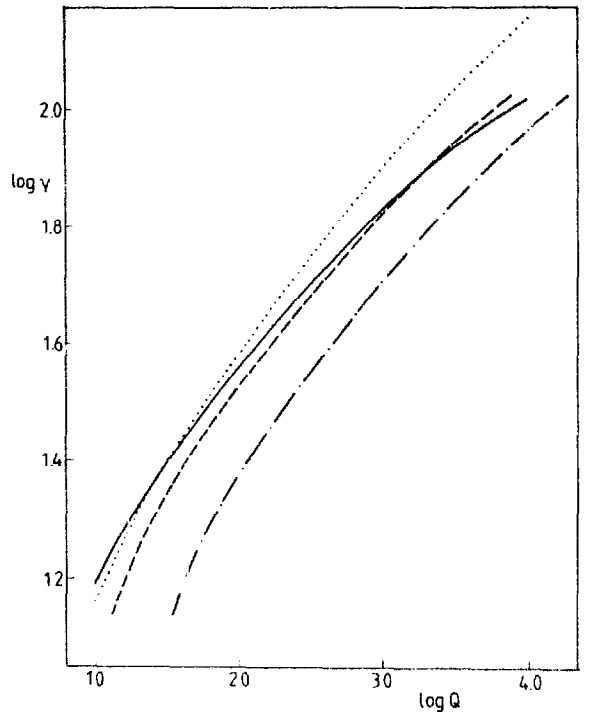

Fig. 8. Results for log γ plotted against log Q: Series I, - · - · -; Series II, ———; Series III, - - - -. The remaining dotted line (· · · · ·) shows Series I plotted with (log Q − 0.41) to allow for the smaller radius.

most plausible values are the smallest:

$$\gamma \simeq 10 \tag{33}$$

$$Q \simeq 10 \tag{34}$$

The removal by the capillary system

From Eqns. 32 and 33 and the value of D_E/ℓ^2 in Table 1 we find that k, the first-order rate constant for the removal of methyl nicotinate for the dermis by the capillary system, is

$$k = 5 \times 10^{-3}\ s^{-1} \tag{35}$$

This value is in good agreement with results from a totally different type of experiment, in which radioactive phosphate was injected intracutaneously (Helde and Seeberg, 1953). The average value of k for 10 subjects was $k = 10^{-3}\ s^{-1}$. Hence we can conclude that the lifetime of the ester in the dermis is 3–10 min. The agreement between the values of k is why we take γ to be as low as possible. Higher values of γ would lead to implausibly larger values of k.

We can now estimate that the $(1 + 4\kappa\tau_2^2)$ term in Eqn. 16 and 17 is only about 1.10. For the penetration of the epidermis the removal by the capillary system is relatively unimportant since it only removes the ester that has actually reached the dermis. Hence the κ-term is in the pre-exponential part of the expression. On the other hand, for the radial diffusion in the dermis there is continuous removal of the diffusing ester and so κ (or γ) appears in the exponential term in Eqn. 24.

The size of the radial diffusion coefficient

From Eqns. 31 and 34, and with the value of D_E/l^2 from Table 1 and $r_0 = 0.5$ cm we obtain

$$D_D = 5 \times 10^{-4}\ cm^2 \cdot s^{-1} \tag{36}$$

This value is almost a thousand times larger than the expected value for a dermal diffusion coefficient. Since no fit to the data can be obtained with a significantly lower value of Q, we conclude that the process which transports the ester in a radial direction is much more efficient than ordinary diffusion. This conclusion in fact does not depend on the detailed mathematical analysis. For $D_D \sim 10^{-6}\ cm^2 \cdot s^{-1}$ and a radial distance of 1 cm the characteristic time would be 10^6 s or 10 days as opposed to times of the order of 10 min.

The capillary diffusion model

The more efficient radial transport process must involve the capillaries and we now present a model in which the ester partitions into the capillaries, is then carried radially outwards and then re-enters the dermis. The model is illustrated in Fig. 9

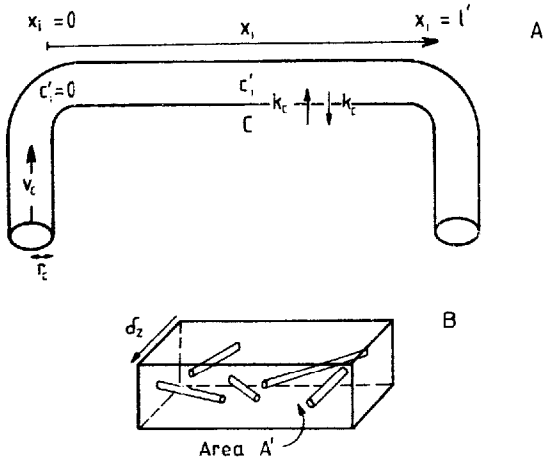

Fig. 9. Capillary diffusion model. Fig. 9A shows the i^{th} capillary loop. Fig. 9B shows a thin slice through the dermis with randomly oriented capillaries.

where we have only considered diffusion in the dermis in one dimension, z. The basic differential equation for transport in the capillary is

$$\frac{\partial c'_i}{\partial t} = k_c(c - c'_i) - v_c \cdot \frac{\partial c'_i}{\partial x} \tag{37}$$

where c'_i is the concentration inside the capillary; c is the concentration in the adjoining dermis; v_c is the velocity of flow of the blood in the capillary; x_i describes the distance along the capillary from when it entered the dermis; k_c describes the rate of transfer between the dermis and the capillary; and we have assumed a partition coefficient between the dermis and the blood of unity. The first-order rate constant k_c can be related to a heterogeneous interfacial transfer rate constant k′ by considering the capillary diagram in Fig. 9.

$$\pi r_c^2 k_c c'_i = 2\pi r_c k' c'_i$$

$$\text{or} \quad k_c = 2k'/r_c \tag{38}$$

where r_c is the radius of the capillary.

Next we define the characteristic distance, x_c, for the establishment of equilibrium in the capillaries

$$x_c = v_c/k_c$$

and we write

$$\phi_i = x_i/x_c$$

Eqn. 37 then becomes:

$$\frac{\partial c'_i}{\partial \phi_i} + c'_i = c - \frac{1}{k_c} \cdot \frac{\partial c'_i}{\partial t} \simeq c \tag{39}$$

The approximation is justified because as we shall show below $k_c t \gg 1$; it is equivalent to the steady-state approximation often used in chemical kinetics. With the approximation we can integrate Eqn. 39 to obtain

$$c_i' = \exp(-\phi_i)\int_0^{\phi_i} c \cdot \exp(\phi_i')\,d\phi_i' \tag{40}$$

where we have used the boundary condition that c_i' equals zero when the capillary enters the dermis ($\phi_i = 0$).

For a thin slice of dermis of width δz and cross-sectional area A′ (Fig. 9)

$$\delta z\, A'(\partial c/\partial t) = -\sum_{i=1}^{i=n} 2\pi r_c \delta z k'(c - c_i') \tag{41}$$

where $n = A'n'$, and n' is the number of capillaries per unit area. We now define α the ratio of the area of capillaries to that of the dermis

$$\alpha = n'\pi r_c^2 \tag{42}$$

Then substitution from Eqns. 38, 40 and 42 into Eqn. 41 gives

$$\begin{aligned}\frac{\partial c}{\partial t} &= -\frac{\alpha k_c}{n}\sum_{i=1}^{i=n}(c - c_i') \\ &= -\frac{\alpha k_c}{n}\sum_{i=1}^{i=n} c - e^{-\phi_i}\int_0^{\phi_i} c e^{\phi_i} d\phi_i' \\ &= -\frac{\alpha k_c}{n}\sum_{i=1}^{i=n}\left[e^{-\phi_i}c - \sum_{j=1}(-1)^j(1 - e^{-\phi_i})x_c^j(\cos\theta_i)^j\frac{\partial^j c}{\partial z^j}\right]\end{aligned} \tag{43}$$

where the second sum is obtained by repeated integration by parts.

$$\begin{aligned}\text{Now } \sum_{i=1}^{i=n}(\cos\theta_i)^j &= \int_0^{2\pi}(\cos\theta_i)^j d\theta_i/2\pi \\ &= 0 \quad \text{if j is odd} \\ &= \frac{\Gamma(j/2 + \frac{1}{2})}{\Gamma(j/2+1)\Gamma(\frac{1}{2})} \quad \text{if j is even}\end{aligned} \tag{44}$$

For a network of randomly oriented capillaries we have replaced the summation with integration. The terms with odd values of j in Eqn. 44 vanish. For instance, if there was a linear concentration gradient, the random capillaries achieve no net transport because there is cancellation between material arriving from the richer

regions and material being lost to the poorer regions. Turning to the terms with even values of j each successive term is multiplied by x_c^2. If z were to be replaced by ρ then the multiplier would be $(x_c/r_0)^2$. Furthermore, the coefficient from the cos function in Eqn. 44 decreases as j increases. So providing $x_c < r_0$, we take just the first term in the series.

Then, as shown in Appendix 2,

$$\sum_{i=1}^{i=n} \exp(-\phi_i) = (n\, x_c/\ell')[1 - \exp(-\ell'/x_c)] \tag{45}$$

and substitution into Eqn. 43 gives

$$\frac{\partial c}{\partial t} = -kc + D_D \partial^2 c/\partial z^2 \tag{46}$$

where

$$k = \frac{\alpha v_c}{\ell'}\left[1 - \exp\left(-\frac{\ell'}{x_c}\right)\right] \tag{47}$$

and

$$D_D = \frac{1}{2}\alpha v_c x_c\left[1 - \frac{x_c}{\ell'}\left\{1 - \exp\left(-\frac{\ell'}{x_c}\right)\right\}\right] \tag{48}$$

Hence the capillary diffusion model yields a kinetic diffusion equation of the same form as Eqn. 6 where k and D_D are related to the geometry, kinetics and flow rate of the capillary system. The ratio of distances x_c/ℓ' plays an important part. If x_c is smaller than ℓ' then for most of its length in the dermis the capillary blood is equilibrated with the material in the dermis. If, on the other hand, x_c is greater than ℓ' then equilibrium is not achieved. In Table 4 we give approximate expressions for k and D_D.

Taking each case in turn, for $x_c > \ell'$, k is simply given by the rate at which material is transferred from the dermis across the capillary wall. On the other hand, when $\ell' > x_c$ for constant α the rate constant decreases with ℓ'. This is because the larger ℓ' can only be achieved by having fewer capillaries. Since each capillary is

TABLE 4

APPROXIMATIONS FOR k AND D_D FROM EQNS. 47 AND 48

	$\ell' < x_c$	$\ell' > x_c$
	Non equilibrated	Equilibrated
k	$\alpha v_c/x_c = \alpha k_c$	$\alpha v_c/\ell'$
D_D	$\frac{1}{4}\alpha v_c \ell'$	$\frac{1}{2}\alpha v_c x_c = \frac{1}{2}\alpha v_c^2/k_c$

equilibrated, it is more efficient to have a larger number of shorter capillaries. When $x_c > l'$, "diffusion" requires as large a value of l' as possible in order to allow exchange. On the other hand when $x_c < l'$ then D_D depends on x_c. This is because the capillary blood arriving at any point contains information about the dermal concentration at a distance of the order of x_c away. The larger this distance the more efficient is the mixing process. Hence we find that the smaller the interfacial rate constant the larger is the "diffusion" coefficient. Returning to Eqns. 47 and 48 we can combine them in the following two ways:

$$y = \frac{kD_D}{(\alpha v_c)^2} = \frac{1}{2}\frac{x_c}{\ell'}\left[1 - \exp\left(-\frac{\ell'}{x_c}\right)\right]\left[1 - \frac{x_c}{\ell'}\left\{1 - \exp\left(-\frac{\ell'}{x_c}\right)\right\}\right] \tag{49}$$

and

$$y' = \frac{D_D}{kx_c\ell'} = \frac{1}{2}\left[\frac{1}{1 - \exp\left(-\frac{\ell'}{x_c}\right)} - \frac{x_c}{\ell'}\right] \tag{50}$$

Plots of y and y′ as functions of ℓ'/x_c are shown in Fig. 10. It can be seen that y passes through a maximum when x_c and ℓ' are of comparable size, while y′ only varies between $\frac{1}{4}$ and $\frac{1}{2}$.

Results for capillary parameters

From the maximum of 0.125 in Fig. 10 and the results in Eqns. 35 and 36 we find that

$$\alpha v_c > 2(2kD_D)^{1/2} = 4.5 \times 10^{-3}\ \mathrm{cm \cdot s^{-1}} \tag{51}$$

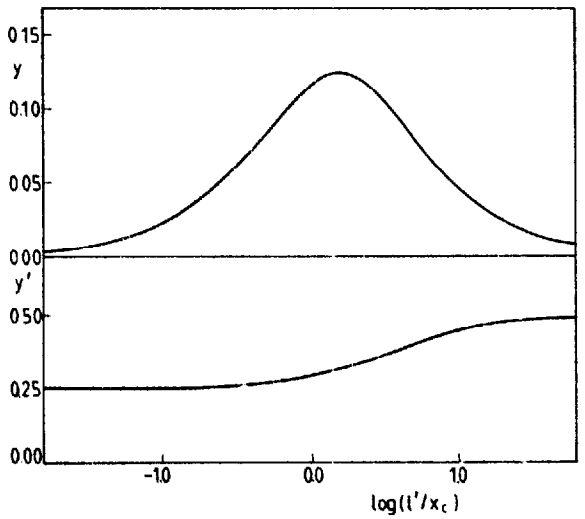

Fig. 10. Plots of y and y′ according to Eqns. 49 and 50.

Now (Champion et al., 1971) α is about 0.1 and v_c has been found to be about 10^{-2} cm · s^{-1}. Using these values αv_c is a little smaller than the value in Eqn. 51. However, of all the subjects tested in our experiments so far, RHG has the fastest response time and so the value in Eqn. 51 is entirely reasonable. However, it does suggest that y is close to its maximum value and this in turn means that

$$x_c \simeq \ell' \tag{52}$$

Furthermore, these results provides further confirmation of the choices of low values of γ and Q in Fig. 8. A choice of higher values would have led to a larger value in Eqn. 51. Using the plot of y′ in Fig. 10, we can now write

$$x_c \simeq \ell' = (0.3\, kD_D)^{1/2} = 0.6 \text{ cm} \tag{53}$$

Considering that the dermis is about 0.2–0.3 cm thick (Katz and Poulsen, 1971), a value of ℓ' which is 2–3 times the thickness of the dermis seems to us to be entirely plausible and to provide further confirmation of our model and analysis.

We can now calculate results for k_c and for the interfacial transfer rate constant k′:

$$k_c = v_c/x_c = 10^{-1}\ s^{-1}$$

$$k' = \tfrac{1}{2} r_c k_c = 2 \times 10^{-4}\ \text{cm} \cdot s^{-1}$$

where we have used (Rothman, 1954) $r_c = 4 \times 10^{-3}$ cm. The result for k_c means that in the radial diffusion experiments where t > 100 s, $k_c t$ is > 10 and this justifies the approximation in Eqn. 39. The result for k′ is an order of magnitude less than the equivalent rate for the transfer of methyl nicotinate from water to isopropyl myristate, (Albery et al., 1976). However, one would expect that the transfer through the capillary wall would be slower than that through a liquid–liquid interface.

It is interesting that our analysis shows that x_c is approximately equal to ℓ'. In Fig. 11 we plot the variation with ℓ'/x_c of k, the overall rate constant for removal of material from the dermis, and k/n_c the efficiency of a single capillary loop. The

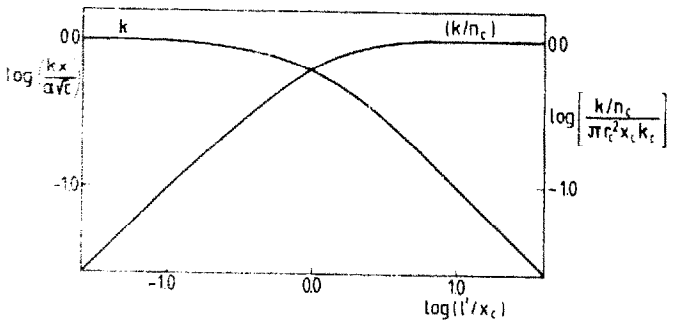

Fig. 11. Plots against ℓ'/x_c of k from Eqn. 47, and of k/n_c the efficiency of each loop from Eqn. 55.

expression for k is the same as Eqn. 47. The number of loops per unit volume is given by

$$n_c = n'/\ell' \tag{54}$$

Substitution in Eqn. 47 gives for the efficiency

$$\log\left[\frac{(k/n_c)}{\pi r_c^2 x_c k_c}\right] = 1 - \exp\left(-\frac{\ell}{x_c}\right) \tag{55}$$

For ℓ' much smaller than x_c, k is constant but the efficiency of each capillary loop is small. This is because the blood returns before it has equilibrated. For ℓ' much larger than x_c the blood equilibrates so the efficiency is constant but k falls as the number of capillary loops fall. Note that the limiting efficiency for a single loop is k_c operating on the cylinder $\pi r_c^2 x_c$, which is also equal to $\pi r_c^2 v_c$. Hence the optimum arrangement, as found in this work is to have $x_c \simeq \ell'$ giving a value of k close to the maximum with each channel close to its maximum efficiency. Under these conditions the blood in each capillary loop spends just enough time in the dermis for it to become equilibrated with its surroundings.

Appendix 1

This appendix describes the inversion, $L^{-1}\,\bar{g}\,\bar{f}$ in Eqn. 22 where $\bar{f}$ and $\bar{g}$ are given by Eqns. 11 and 23, respectively. To invert $\bar{g}$ we start with the two inverse transforms (Roberts and Kaufman, 1966):

$$L^{-1}\exp(-s^{1/2}) = \exp(-0.25/\tau)/2\pi^{1/2}\tau^{3/2}$$

and

$$L^{-1}\frac{\exp-\left[\theta(s+\kappa)^{1/2}\right]}{s+\kappa} = \exp(-\kappa\tau)\,\mathrm{erfc}\left(\frac{\theta}{2\tau^{1/2}}\right)$$

$$\simeq \frac{2\tau^{1/2}}{\pi^{1/2}\theta}\exp\left(-\kappa\tau - \frac{\theta^2}{4\tau}\right)$$

where $\theta = (\rho - 1)/Q^{1/2}$, and in using the approximation for the complimentary error function (Abramowitz and Stegun, 1965a) we have assumed $\theta^2 > \tau$. Next we use the convolution theorem for inverting $\bar{g}$:

$$g = \int_0^\tau \frac{1}{\pi\theta}\frac{\lambda^{1/2}}{(\tau-\lambda)^{3/2}}\exp(-y)\,d\lambda \tag{56}$$

where $y = \kappa\lambda + \theta^2/4\lambda + 0.25/(\tau - \lambda)$

Inspection of y shows that when λ tends to zero and when λ tends to τ y is very large. Hence for these values of λ the integrand is very small and because of the $\exp(-y)$ term, for intermediate values of λ it passes through a sharp maximum corresponding to the minimum value of y. The integral in Eqn. 56 is therefore mainly determined by the value of the integrand near this minimum value of y. Hence we can obtain a good approximation for g by expanding the integrand around its maximum value at the minimum value of y. We write

$$y \simeq y_m + \tfrac{1}{2}C(\lambda - \lambda_m)^2 \ldots$$

where

$$y_m = \kappa\lambda_m + \theta^2/4\lambda_m + 0.25/(\tau - \lambda_m), \tag{57}$$

$$\left(\frac{\partial y}{\partial \lambda}\right)_{\lambda=\lambda_m} = 0 = \kappa - \frac{\theta^2}{4\lambda_m^2} + \frac{1}{4(\tau - \lambda_m)^2} \tag{58}$$

and

$$C = \left(\frac{\partial^2 y}{\partial \lambda^2}\right)_{\lambda=\lambda_m} = \frac{\theta^2}{2\lambda_m^3} + \frac{1}{2(\tau - \lambda_m)^3} \tag{59}$$

We can replace λ with λ_m in the pre-exponential function in Eqn. 56 because the maximum in the integrand is so sharp. Hence

$$g \simeq \frac{1}{\pi\theta} \cdot \frac{\lambda_m^{1/2}}{(\tau - \lambda_m)^{3/2}} \cdot \exp(-y_m) \int_{-\lambda_m}^{\tau - \lambda_m} \exp\left[-\tfrac{1}{2}C(\lambda - \lambda_m)^2\right] d(\lambda - \lambda_m) \tag{60}$$

$$\simeq \left(\frac{2\lambda_m}{\pi C}\right)^{1/2} \cdot \frac{\exp(-y_m)}{\theta(\tau - \lambda_m)^{3/2}}$$

The Gaussian integral is calculated by replacing the integration limits with $\pm\infty$. This is justified because for $\tau \ll 1$

$$C\lambda_m^2 \gg 1 \text{ and } C(\tau - \lambda_m)^2 \gg 1$$

The physical reason why this approximation works is illustrated in Fig. 12. The exponential term in the convolution integral samples that part of the pre-exponential term which is mainly responsible for the erythema. At values of λ less than λ_m very little material has arrived at ρ. At values of λ greater than λ_m more material is arriving but will not have time to reach ρ before the erythema is triggered. In Eqn. 57 for y_m the first two dermal terms describe the radial diffusion and the loss to the circulatory system. The third term describes the effect of the epidermal barrier.

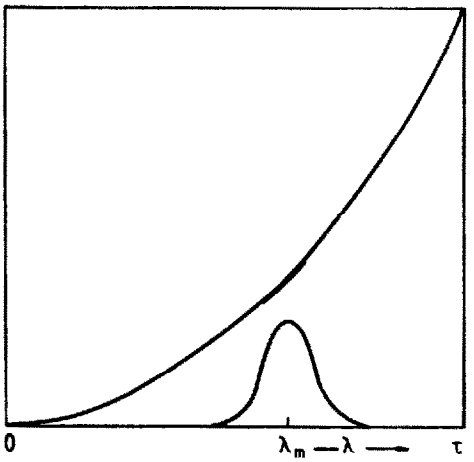

Fig. 12. Diagram to show how one has only to evaluate the integrand in Eqn. 56 near its maximum value. The monotonic curve represents the non-exponential part; the Gaussian samples this function near the minimum value of y.

Considering the simple case where $\kappa = 0$, one can see from Eqn. 58 that if θ is large, corresponding to slow dermal diffusion, then λ_m is close to τ; the θ-term dominates the expression for y. On the other hand, if θ is small corresponding to rapid dermal diffusion (or ρ close to unity) then λ_m is close to zero; the epidermal term dominates y_m.

Returning to Eqn. 22 we convolute $\bar{g}$ with $\bar{f}$ using the same approach as used in Eqn. 15. Hence

$$v_E = \frac{1}{\rho^{1/2}} \int_0^{\tau_1} \frac{g(\tau_2 - \lambda)}{\pi(\lambda)^{1/2}} d\lambda$$

$$= \frac{1}{\rho^{1/2}} \int_0^{\tau_1} \left(\frac{2\lambda_m}{\pi C} \right)^{1/2} \cdot \frac{\exp(-y_m)}{\theta(\tau_2 - \lambda_m - \lambda)^{3/2} \pi \lambda^{1/2}} d\lambda$$

where

$$y_m = \kappa\lambda_m + \theta^2/4\lambda_m + 0.25/(\tau_2 - \lambda_m - \lambda)$$

By definition $\partial y_m/\partial\lambda_m = 0$ and hence y_m is smallest when λ is smallest. As with Eqn. 56 we approximate the integrand for λ close to zero writing

$$y_m \simeq y_{m,\tau_2} + \lambda/4(\tau_2 - \lambda_m)^2 \ldots$$

and we obtain

$$v_E = \frac{2}{\theta} \left[\frac{2\lambda_m}{\pi C \rho (\tau_2 - \lambda_m)} \right]^{1/2} \exp(-y_{m,\tau_2}) \operatorname{erf} \left[\frac{\tau_1^{1/2}}{2(\tau_2 - \lambda_m)} \right]$$

In this equation C, λ_m and y_m are described by Eqns. 57–59. Defining the new variables,

$$\gamma = 2\kappa^{1/2} \text{ and } \xi^2 = 1 + 4\kappa(\tau_2 - \lambda_m)^2$$

we obtain finally the result in Eqn. 24.

Appendix 2

In this appendix we work out the sum $\sum_{i=1}^{i=n} \exp(-\phi_i)$ to obtain the result in Eqn. 45. There are n capillaries randomly distributed with respect to the distance x_i after they reached the surface between the value of $x_i = 0$ (just reached the surface) and $x_i = \ell'$ (just about to leave the surface). Thus the element for each capillary is ℓ'/n or in terms of ϕ_i, $\delta\phi = \ell'/nx_c$. Hence we may write

$$\delta\phi \sum_{i=1}^{i=n} \exp(-\phi_i) \simeq \int_0^{\ell'/x_c} \exp(-\phi_i) d\phi_i$$

giving

$$\sum_{i=1}^{i=n} \exp(-\phi_i) = \frac{nx_c}{\ell'}\left[1 - \exp\left(\frac{\ell'}{x_c}\right)\right]$$

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