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THE SIGNIFICANCE OF THE DISTRIBUTION RATIOS OF NON-ELECTROLYTES BETWEEN PLASMA AND THE INTRA-OCULAR FLUID

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IN a recent paper Kinsey and Grant (1942) have discussed the problem of the penetration of a dissolved substance from the blood into the aqueous humour, and have reached the conclusion that at equilibrium the concentrations of the substance considered, electrolyte or non-electrolyte, will not be equal in both fluids when there is a flow of aqueous humour away from the anterior chamber by some drainage channel, *e.g.*, Schlemm's Canal. On the basis of this conclusion they state: "... it follows that unless definite proof is forthcoming to show that there is no flow out of the anterior chamber, it appears that the ultrafiltration hypothesis can account for equilibrium ratios less than 1 and therefore need not be discarded because of experimental findings of such ratios."

In view of the importance which has hitherto been attached to the distribution ratios of dissolved substances in blood and tissue fluids in determining whether these fluids are secretions or not, it is important that the theoretical basis of this contention should be

critically examined. Thus the acceptance of the modern views of urine formation depends to a large extent on the demonstration by Richards and his co-workers that the glomerular fluid contains a number of non-electrolytes, urea, glucose, etc., in the same concentrations as those found in plasma.

Kinsey and Grant consider the case of a dissolved substance whose concentration in the blood is maintained by injection at a fixed level, C_1 , and assume that it enters the aqueous humour by ultrafiltration, presumably by a passage of filtrate from arterial capillaries associated by a corresponding removal of the diluted filtrate into venous capillaries. If this process took place the differential equation¹ for penetration would be:

$$\frac{dA}{dt} = k_2(C_1 - C_2) \quad \dots\dots\dots(1)$$

where A = amount of substance present in aqueous humour,

C_2 = concentration² in aqueous at a given time t_1

k_2 = coefficient of transfer from blood to anterior chamber.

Superimposed on this process they conceive of a drainage of aqueous humour from the anterior chamber via. e.g., Schlemm's Canal; so that Equation (1) is modified to become:

$$\frac{dA}{dt} = k_2(C_1 - C_2) - k^1 C_2 \quad \dots\dots\dots(1a)$$

where k^1 = coefficient of transfer out of anterior chamber by flow.

Substituting $C_2 = A/V$, where V is the volume of aqueous humour;

$$V \frac{dC_2}{dt} = k_2 C_1 - (k_2 + k^1) C_2 \quad \dots\dots\dots(2)$$

which on integration between the limits $t=0$ and $t=t_1$ gives:

$$C_2 = \frac{k_2}{k_2 + k^1} C_1 \left[1 - e^{-\left(\frac{k_2 + k^1}{V}\right) t_1} \right] \quad \dots\dots\dots(3)$$

The authors then proceed to state that equilibrium³ will occur when $t=\infty$, whence the condition for equilibrium³ is:

$$\frac{C_2}{C_1} = \frac{k_2}{k_2 + k^1} \quad \dots\dots\dots(4),$$

i.e., at equilibrium³ C_2/C_1 is less than unity when flow out of the anterior chamber takes place.

Foot-note¹.—The same equation would apply if simple diffusion without ultrafiltration were the sole process of penetration.

Foot-note².—We may note here a rather confusing mathematical notation. C_2 is defined as the concentration at a given time t_1 , i.e., it is a definite value of the variable and therefore its differential coefficient in respect to time should be zero, yet in Equation (2) it quite clearly has a finite value. It was thought by the authors to be a printer's error, but it will be noted that on integrating Equation (2) between the limits $t=0$ and $t=t_1$, C_2 has been given the definite value at t_1 .

Foot-note³.—The term "equilibrium" is out of place here; apparently the authors envisage a "steady state."

The error in this argument follows from the integration of Equation (2) at constant volume; if V is to remain constant the fluid lost from the anterior chamber must be replaced by fluid from the blood, *i.e.*, by more ultrafiltrate, and this will clearly increase the rate of increase of A , the amount of substance in the aqueous humour, by a factor: $k^1 C_1$. Hence Equation (1a) should be:

$$\frac{dA}{dt} = k_2(C_1 - C_2) - k^1 C_2 + k^1 C_1$$

$$= (k_2 + k^1)(C_1 - C_2) \dots\dots\dots (5)$$

On substituting $C_2 V$ for A and integrating we obtain from (5)

$$\frac{C_1 - C_2}{C_1} = - \left(\frac{k_2 + k^1}{V} \right) t \dots\dots\dots (6)$$

which gives, as a limiting condition when $t = \infty$, $C_1 = C_2$, *i.e.*, equal concentrations of the dissolved substance in blood and aqueous humour.

It may be argued that the fluid which replaces the aqueous humour lost via Schlemm's Canal is free from the particular dissolved substance considered, so that $k^1 C_1$ is equal to zero in Equation (5); this however, is at variance with the original assumption as to the mechanism whereby the substance enters the aqueous humour, *viz.* by ultrafiltration. It is also at variance with the known facts and theory of ultrafiltration at low filtration pressures (*vide e.g.*, Ingraham, Lombard and Visscher, 1933); thus, if the concentration of the penetrating substance in the plasma is 0.01M the production of a fluid free from this substance would require a filtration pressure of about 180 mm. Hg over and above the 25 mm. Hg necessary to counterbalance the colloid osmotic pressure. Moreover, if it is assumed that this replacement fluid is free from the particular substance considered, there is no reason why it should not be free from the other constituents of the blood plasma, *i.e.*, why it should not be pure water; the filtration pressure necessary to separate water from plasma is of the order of 4 atmospheres.

Davson and Quilliam (1940) have treated the same problem of the penetration of a dissolved substance into the aqueous humour, assuming that the process is one of simple diffusion and not one of ultrafiltration, and ignoring the effects of drainage by Schlemm's Canal. The fundamental equation set up on the basis of Fick's Law by these authors is similar to Equation (1), which has been derived on the basis of a fluid exchange hypothesis; if, therefore, allowance is made for drainage, replaced by filtration from the blood, Equation (6) should be appropriate, so that the permeability constants of Davson and Quilliam become composite. However, in view of the experimental errors in permeability measurements of this nature, it appears to the authors that elaborate theoretical treatments of the process are academic at the present moment.

For those readers to whom a mathematical argument has no appeal, the general problem with which this note deals may be stated thus: If the concentration of a given substance, say urea, is higher in the blood than in the aqueous humour, the system, plasma-aqueous humour, is not in equilibrium and hence diffusion of urea should take place into the aqueous humour until the equilibrium condition⁴ of equal concentrations in the two fluids is achieved. Kinsey and Grant admit that this would happen in the absence of drainage and secretory activity. However, they claim that as soon as drainage occurs the concentrations become different, *i.e.*, the system is no longer in equilibrium so far as urea is concerned, as defined thermodynamically. Now the second Law of Thermodynamics states that a system of this kind can only be maintained at a non-equilibrium position by the continued performance of work on it. Drainage of fluid away from the anterior chamber is not capable of performing the necessary work on the system, so that in the absence of secretory activity the concentration differences claimed by Kinsey and Grant are excluded by the second Law.

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THE DETECTION AND SIGNIFICANCE OF MELANOPHORE EXPANDING SUBSTANCE IN URINE AND BLOOD WITH SPECIAL REFERENCE TO RETINITIS PIGMENTOSA*

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Introduction

VERTEBRATES show two striking examples of pigment migration. One is migration of pigment within the skin melanophores of chromatically active cold-blooded vertebrates. The other is

Foot-note⁴.—The condition for equilibrium is that the chemical potentials are equal on both sides of the membrane; assuming that the activity coefficients are equal in the two fluids, for a non-electrolyte this is equivalent to stating that the concentrations must be equal.

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