CHAPTER II

THEORY

When ^{131}I-AA was injected intravenously, the particles were phagocytized by the R.E. cells lining the blood vessel and principally by the Kupffer cells of the liver and the reticular cells of the spleen (Stiffel et al, 1970). The blood clearance of colloid has been found to follow an exponential function of the time (Benacerraf et al,1957).

$$C_t = C_0 \ 10^{-Kt} \qquad .....(1)$$

Where C_0 and C_t are the concentration of the particles in the blood at zero time and at time t respectively, the constant K which measures the rate of phagocytosis of colloids by the R.E.S. has been called "phagocytic index" (Biozzi, Benacerraf and Halpern, 1953; Biozzi, Benacerraf, Stiffel et al, 1957). The value of this phagocytic index, (K) could be calculated from

$$K = \frac{\log C_1 - \log C_2}{t_2 - t_1} \qquad .....(2)$$

Where C_1 and C_2 are the concentration at time t_1 and t_2 respectively. It appears that the value of K is inversely proportional to the dose of colloid injected (D), this relationship may be represented by an equation

$$K \times D = \text{constant} \qquad .....(3)$$

The value of D may be replaced by the initial blood concentration (C_0) because $\frac{D}{\text{blood volume}} = C_0$ and the value of blood volume is a physiologic constant. The equation (3) becomes

$$K \times C_0 = b \qquad (b \text{ is a constant})$$

The introduction of ^{131}I-AA has enabled us to attain two different aims. A practical one is the ability to study R.E. function in man because of the relative harmlessness of ^{131}I-AA, a theoretical one is the establishment of the limits the validity of the fundamental equation (3).

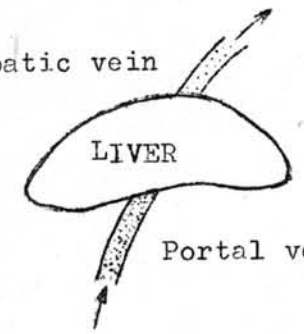
This last achievement was possible because the high degree of sensitively of detection of the radiotracer ^{131}I permit the study of blood clerance of very small doses of colloid. From these experiments, it appears that below a certain dose of colloid called "critical dose" the rate of blood clearance reaches a constant maximum value (K_{max}) and becomes independent of the dose injected (Fig. 2).

The "critical dose" can be calculated from the following formula:

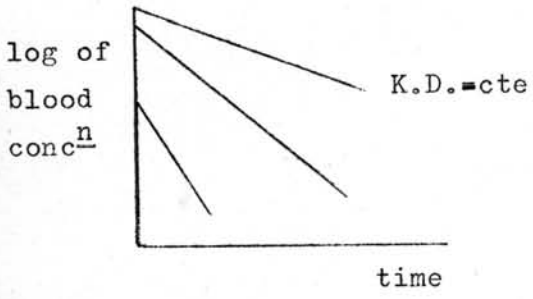
$$\text{critical dose} = \frac{K \times D}{K_{max}} \qquad \ldots\ldots(4)$$

With doses above the "critical dose", the concentration of particles entering the liver via the portal vein is such that they cannot be completely cleared by a single passage through the organ. Consequently, a certain concentration of particles leaves

Blood clearance of amounts of colloid above the "CRITICAL DOSE"



C = colloid - concentration

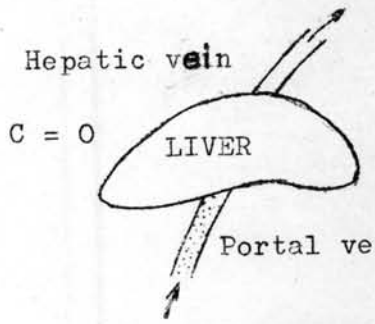


K dose dependent

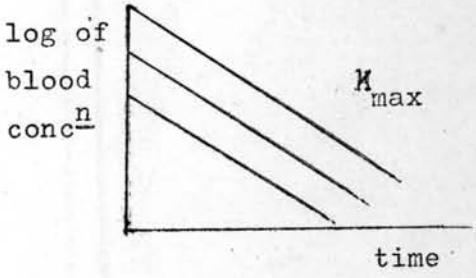
Limiting factor : the R.E.S. phagocytic function

K = Phagocytic Index

Blood clearance of amounts of colloid below the "CRITICAL DOSE"



C = colloid - concentration



K_{max} dose independent

Limiting factor : the liver blood flow

Fig. 2 Schematic physiologic meaning of the kinetics of blood clearance of ^{131}I-AA injected intravenously at doses above and below the "critical dose".

(Biozzi and Stiffel, 1965)

through the hepatic veins. The rate of blood clearance is then determined by the phagocytic activity of R.E. cells. Below the "critical dose", the concentration of particles entering the liver is so low that they are totally phagocytized in a single passage through the liver. The rate of blood clearance is then no longer dependent on the phagocytic activity of the R.E. cells but only on the amount of blood filtered by the liver (liver blood flow). The critical dose has a very intersting implication as being a measure of the maximal physiologic capacity of the Kupffer cells relative to liver blood flow. It represents a physiologic constant characteristic of each animal species (Benacerraf, Biozzi, Halpern et al, 1957; Benacerraf, Biozzi, Cuendet et al, 1955; Benacerraf, Bilbey, Biozzi et al, 1957).

In this range, the plasma clearance is dependent only upon the blood flow through the liver, for the liver absorbs almost 100 per cent of the injected dose. Under this condition, the constant K, expressed in natural logarithms (K_e) per minutes represents the fraction of the total blood volume which is cleared of colloid in this time. This volume would correspond to the liver blood flow of the colloid that was fixed in the liver if an efficiency of clearance was 100 per cent. Since the Kupffer cells phagocytize about 85-95 per cent of the colloid, the liver blood flow measured by the K_e is called "sinusoidal liver blood flow".

$$\text{Sinusoidal liver blood flow} = K_e \times \text{blood volume} \quad \ldots.(5)$$

It has been demonstrated that the phagocytic index, K,

measured with the same dose of colloid showed a wide variation among animals, due to individual differences in the size of the liver and spleen. The corrected phagocytic index (α) which measures the phagocytic function per constant weight of the liver and spleen is used to correct this discrepancy. The correct phagocytic index (α) is calculated from a formula

$$\alpha = \sqrt[3]{K} \times \frac{W}{W_{ls}} \qquad \ldots\ldots(6)$$

Where W is the body weight and W_{ls} is the weight of liver and spleen.

The phagocytic activity of the R.E.S. may therefore be expressed by two indices:

(1) The "phagocytic index" (K) which measures the total phagocytic function of the R.E. cells lining the blood vessels.

(2) The "corrected phagocytic index" (α) which express the R.E. cell activity per unit of weight of liver and spleen.

The index α, shows a smaller standard deviation than the corresponding K and is very useful for detecting slight variations in the phagocytic function of the R.E.S. (Stiffel, 1958).