The Disappearance of K$^{42}$ from the Nonuniformly Mixed Circulation Pool in Dogs

By C. W. Sheppard, R. R. Overman, W. S. Wilde, and W. C. Sanghen

The disappearance of injected labeled substances which disappear rapidly from the circulation is discussed theoretically and tested in experiments with injected K$^{42}$ in the dog. Comparing the inflow and outflow from a capillary bed, using semilogarithmic plots of label concentrations, events upstream are repeated downstream but displaced in time by the amount of the mean circulation time between the points of observation. Downward displacement occurs owing to the intervening loss of material, and smearing of the time relations is produced by the dispersing action of variable path lengths in the capillary labyrinth. For the circulation as a whole, the time relations consist of the sum of a periodic component and an aperiodic component. The periodic component is governed by the mixing relations in a virtual circulation whose architecture approximates that of the real circulation. Extrapolating the aperiodic component to zero time yields the volume of dilution of the injected material in the virtual circulation, providing that injection and sampling points are close together. When the points are separated, correction must be made for time delay and loss of label between. The initial slope is governed not only by the mean rate of exchange of injected substance with the tissues but also by the mean circulation time.

The problem of simultaneous mixing and disappearance of materials quickly injected into the circulation is currently engaging the attention of physiologists with a wide variety of research interests. The usual assumption of a uniformly mixed circulation pool will obviously be valid when the time for a detectable amount of label to disappear is quite large compared with a mean circulation time. In practical situations, this has been assumed of necessity, but little criticism of the assumption has appeared. Nevertheless, uniform mixing does not hold for deuterium oxide and more recently other substances have been found such as colloidal gold in the dog and labeled potassium in the rabbit for which the assumption definitely fails and the interrelated processes of mixing and disappearance must be considered together. In this communication, we wish to outline some of the principal features of a theoretic inquiry into the problem of the kinetics of rapidly disappearing substances and to present the results of some preliminary experimental tests of the theory using injected K$^{42}$ in the dog.

**Experimental Methods**

The experimental part of the research consisted of a series of observations in dogs of the fluctuating plasma radioactivity following sudden injection of radioactive K$^{42}$. In order to obtain high resolution of the rapid events in the time-concentration curves, it is essential that the radioactivity be introduced into the vascular system in a volume which is small relative to the blood volume, and nearly instantaneously. In these experiments 3 to 4 mEq. of K containing the K$^{42}$ in 0.8 cc. of solution was introduced into the unexposed left jugular vein as rapidly as possible from a 1 cc. tuberculin syringe through a 20-gage needle. Rapid serial blood sampling of dogs under Nembutal anesthesia (dose, 35 mg. per kilogram) was accomplished by cannulation of arteries or veins with polyethylene tubing and direct bleeding into heparinized, thick-walled, centrifuge tubes. Except where otherwise stated, arterial samples were obtained from the cannulated right common carotid by passing the centrifuge tubes (held in a row in lucite blocks) under the outflow which was controlled by a hemostat. Under these conditions 1 to 3 cc. of blood could be obtained at
intervals as close as two seconds if desired. Venous sampling was usually done by rapidly interchanging syringes, and then delivering the blood into the centrifuge tubes. Usually simultaneous arterial and venous sampling required at least four people, two collecting and two recording the time by stopwatch. In experiments involving simultaneous arterial and jugular sampling, the right jugular was cannulated toward the head and the arterial samples were taken from the more accessible right femoral artery, rather than the common carotid. Previous experiments showed that there was a time lag of less than three seconds between the two arterial sites, and the spatial congestion resulting from three simultaneous operations around the head was avoided.

In experiments involving hepatic vein sampling, no attempt was made to eliminate blood from regions below the liver. This portion of the flow probably made a large contribution to the time relations at this site. Samples were obtained through a cardiac catheter introduced through the exposed right jugular vein. A similar procedure was adopted in sampling renal vein blood except that mass ligatures were tied around the abdominal aorta and vena cava just posterior to the renal veins immediately before injection. Where the catheter was used, its location was subsequently verified at autopsy in all cases.

The length and flow rate of the catheter was such that samples from deep locations taken through it were delayed often by several seconds. It was usually possible, however, to estimate the sampling delay times within one to two seconds. It should be noted that to avoid losing resolution of rapid events by the smearing effect of laminar flow in the catheter, its volume should be small relative to the volume of sample. With a catheter, 35 cm. long by 3 mm. inner diameter, such as we selected to insure adequate flow rates, the volume is comparable to the sample volume and so this requirement was not well met. Increasing the sample size could not be permitted without disturbing the circulation. It is thus quite possible that the time relations for samples from deep-lying venous sites had lost some of their finer details. This objection may also be raised in any experiments where blood is taken from a vessel via lengthy tributary.

Prior to counting, samples were centrifuged at high speed, and 0.1 to 0.5 cc. aliquots of plasma were pipetted into 1 inch diameter by ½ inch deep metal cups. The proteins were precipitated by dropwise addition of 10 percent trichloracetic acid and the samples were dried under an infrared heat lamp. Radioactivity was determined with a Tracerlab automatic sample changer and Autoscaler. The radiochemical purity of the isotope was the same as in the experiments of Walker and Wilde. The total amount of blood removed seldom exceeded 15 per cent of the calculated blood volume and the most important features of the experimental curves were delineated before this much hemorrhage had occurred. Since the penetration of the isotope into the cellular components of the blood is slow, the activity of 1 cc. of blood is all in the plasma and the disappearance is transcapillary.

Experimental Results

As Walker and Wilde have stated, the expression of the plasma activities in cts./sec./ml. blood

\[
\text{cts./sec. injected Gm. body weight}
\]

(their P* unit) provides a good basis for intercomparison between different rabbits. We have found this also to be the case in our experiments in dogs. A synthesis of the carotid arterial curves found in seven dogs, injected in the jugular vein, is shown in figure 1. Since the distance from the injection point to the right atrium is not great, a fairly sharp pulse of the label was thus produced at the atrium which can be taken as an arbitrary origin. In this case observations were not made at the origin so that the time relations underwent additional smearing by the effect of the heart and lungs. Observations made, as they were, on blood from the carotid artery should closely reflect the situation in the aorta, since the volume of the sampling tube was small. For events early in time an aperiodic quasi-exponentially declining curve is observed with
three rapidly damped, but clearly discernible, superimposed periodic oscillations.

When serial samples of blood were taken simultaneously from different points in the circulation, events upstream were repeated downstream but delayed in time. The attenuation due to intervening loss of tracer from the circulation appeared as a downward displacement when logarithmic ordinates were used. The downstream curves were also demonstrably smeared relative to those taken upstream. The most illustrative example from several points of view occurred in an animal in which the circulation through the right carotid had been interrupted in an unsuccessful experiment a week previously. Figure 2 shows the simultaneous activity–time relations in the left femoral artery and vein.

The reason for the notch in the curves is not well established, but, since in this early experiment difficulty was encountered in the injection, it is thought to be due in part to failure to inject the material cleanly into the vein. The situation is fortuitous, however, for demonstrating the repetition principle, since the notch serves particularly well to show the decreased resolution after passage of the wave of activity through the capillaries of the leg. Although possibly greater for the second than for the first wave, the mean retardation in the time relations on the venous side is about 20 seconds which is definitely longer than in any of our other experiments. (In this animal the blood flow in the leg was very sluggish and some of the venous samples could be obtained only by massage.) The downward displacement of the venous curve was also quite large, which enables a better demonstration of the principle but represents a greater than normal rate of potassium movement from the blood in the leg.

The repetition principle is well illustrated under less artifactitious conditions in figure 3 where simultaneous samples were taken in the carotid artery and jugular vein of a normal animal. Here, after the oscillatory portion is complete, the two curves practically coincide because the horizontal and vertical displacements return the downsloping portion of the venous curve into coincidence with the arterial.

That arterial and venous curves such as those in figure 3 represent the sum of a periodic and an aperiodic component can be better realized from a consideration of the mixing curves for some substance which disappears slowly from the blood if at all. Here it is a familiar fact that following the completion of the waves of

![Fig. 1. Composite arterial curve. The combined observations on seven dogs were pooled and averaged. The ordinate is the logarithm of the relative activity per cubic centimeter of carotid blood measured in units of activity per cubic centimeter divided by activity per gram of animal. Note the periodic and aperiodic components. The first maximum represents the appearance of the injected material after passage through the lung. The second is the return of the injected slug after one circulation followed by a recognizable third wave.](image1)

![Fig. 2. Experimental verification of the repetition principle, for samples in femoral artery and vein. Note the horizontal and vertical displacements and the loss of resolution of the venous curve relative to the arterial. Logarithmic ordinates are the same as in figure 1, • = femoral artery, O = femoral vein.](image2)
circulatory mixing a flat plateau is reached which can be extrapolated back to zero time yielding the volume of dilution of the injected material. The aperiodic portion is a constant, and the periodic portion adds to or subtracts from this, being rapidly damped out after a few oscillations. When the substance is disappearing while it is being mixed, the aperiodic portion is no longer constant but declines monotonically. In the theoretic section it will be shown that it is initially nearly straight on semilogarithmic coordinates, so that a linear extrapolation to zero time can still be attempted and some consideration given to the physiologic significance of the slope and zero intercept of the resulting line. Where the departure from linearity is initially not too great, some improvement may be gained by resolving the semilogarithmic plot into two components in the same manner as that employed in analyzing the decay of a mixture of radioactive isotopes. Figure 4 shows a series of observations made at various points in the canine circulation. Both the hepatic and renal samples were obtained through a long catheter and have been corrected for time delay in sampling. Since the venous curves were obtained on different animals, it was also necessary to displace them until their arterial curves coincided with the composite arterial curve, a portion of which is included for comparison. During the first minute or so in each case a straight line can be passed through the oscillations, although it is recognized that the process is somewhat difficult to do accurately. The principal uncertainty arises from the complicating effects of the oscillations and early departure from linearity caused at least in part by backflow of the label from extravascular pools, which seems to begin at about 60 to 80 seconds. Nevertheless, to the extent the experimental error permits verification, the slope of this early portion of the aperiodic (phase) solution appears to be very similar in all curves including the arterial. Figure 3 also provides a good illustration for samples taken simultaneously in the carotid artery and jugular vein.

Although the slopes are alike, the zero intercepts (for example, \( I_1 \) and \( I_2 \) in figure 4) are not, the biggest deviation occurring in the hepatic vein curve. For the arterial curves in rabbits, Walker and Wilde investigated the intercept values in relation to plasma volumes obtained by more conventional methods in animals of the same uniform stock. They made use of the fact that, when their \( P^* \) unit is employed, the reciprocal of the initial intercept multiplied by 1000 gives the initial volume...
of dilution directly in cubic centimeters per kilogram. To obtain good agreement it was necessary to assume that the time delay between injection and observation points just compensated for the effect of the small amount of $K^{42}$ lost in the lungs. In our experiments (table I) the mean value of 35.7 cc. per kilogram for the "plasma volume" was obtained by the same type of extrapolation procedure using the same system of units. A tangent was drawn to the slowly declining residual exponential and the initial values were subtracted, the resulting data being replotted, the best straight line being drawn through the oscillations. To correct for the A-V time delay, we assumed that the mean delay through the pulmonary circuit was slightly greater than the time of the first maximum of the arterial curve, usually between 8 and 10 seconds. The linear extrapolation through the initial oscillations was then displaced to the left by this amount, the resulting intercepts yielding plasma volumes of about 45 cc. per kilogram. This value is still below commonly accepted plasma volumes for the dog, which are about 55 cc. per kilogram.

Table I also shows values of cardiac output for dogs computed from the $K^{42}$ data by the method of Hamilton and co-workers. Although there are no independent determinations by a separate method the results are entirely reasonable.

**Discussion**

When a small amount of labeled material is suddenly injected into a large vessel of the circulation it will soon become separated into a very large number of practically infinitesimal elementary portions or slugs which will follow different paths or "flow circuits" through the circulation. It is the variable mean velocities and lengths of these flow circuits with resulting variable traversal times which causes these elements of the label to become dispersed in time, and which causes the remarkably efficient process of circulatory mixing. The principal dispersion which first acts in the large vessel is the variation in velocity between the various faster and slower lamellae of laminar flow. As the label proceeds downstream, the dispersal increases tremendously as the arborization of the circulatory system proceeds into the smaller vessels and capillaries. A further action occurs in a few places in the circulation where turbulence may occur. Thus, on one passage around the vascular system, so much dispersion occurs that only two or three additional recirculations are required to produce essentially complete homogenization, provided that the labeled material does not disappear from the blood.

Coincident with mixing, however, many substances will be lost from the circulation perhaps as the result of exchange with extravascular pools, perhaps by one-way movement (mass transfer), or both. For certain substances, such as $K^{42}$, which disappear very rapidly there will at times be a marked gradient of radioactivity downstream (which at particular locations may be quite large) so that circulatory mixing and actual disappearance of the label from the blood stream are interrelated. Although the spatial and temporal variations in concentration of the label will occur in all vessels large and small, it will be in the large vessels where the time relations will be particularly important, since these will generally be the sites of injection and observation.

These effects are analyzed mathematically in the theoretic section. The first step is to
relate the specific activity as a function of time at two arbitrary points along a single flow circuit, taking into account the variable flow velocity and exchange rate between the points. We consider the dispersing effects produced by passage through the circulatory labyrinth from a statistical point of view. Considering in a similar fashion the statistical distribution of the mean exchange rates for the various flow circuits we establish the general equation for circulatory mixing with disappearance and show that it can be related to the equation for mixing of a nondisappearing substance. The kinetics of mixing and equilibrium concentration, however, are for a virtual circulatory labyrinth rather than for the true one, the difference between the real and virtual circulation increasing as the spread in mean exchange rates of the flow circuits increases.

The principal conclusions of the analysis are:

1. During the period immediately following the sudden injection of a small quantity of labeled material into the circulation, events upstream are repeated downstream but delayed by the mean transit time between the injection and sampling points. A reduction in scale, that is, a downward movement of the semilogarithmic plot, occurs determined by the mean value of the exchange rates in the intervening space. Progressive smearing of the time relations occurs, due to the dispersing action of the variable circulatory paths.

2. For the circulation as a whole, the relation between specific activity (or the concentration of circulating isotope) and time has two slightly interrelated components, periodic and aperiodic (fig. 5). The periodic component is the result of mixing in the virtual circulation. Its form will depend on the rapidity of the original injection, on the over-all dispersing action of the virtual vascular tree, and on the rate of blood flow. The aperiodic component will be a quasi-exponential function whose initial rate of decline is determined primarily by the over-all mean rate of exchange \( \bar{\phi} \) between the circulation and the tissues, plus an added constant \( \alpha \) which is a measure of the effect of circulation rate or mean circulation time \( \bar{t} \) on the kinetics of disappearance of the label. The latter effect is small if there is only a small spread in the exchange rates of the individual circulatory paths, but becomes important as the distribution of exchange rates includes larger deviations from the over-all mean.

By these considerations it is shown that the injected material will move initially as a wave through the circulation, become rapidly suppressed and broadened, and will quickly return on itself, the combined waves soon merging into a distribution of activity such that the concentration, although not uniform around the circuit, declines everywhere by the same fraction in a given interval of time.

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**Fig. 5.** The periodic and aperiodic components of the theoretic time relations for a substance which disappears rapidly while being mixed in the circulation. The ordinate represents the logarithm of the specific activity or of the radioactivity per cubic centimeter. For the latter quantity, if \( I \) is the amount injected and \( V \) the blood volume, the zero extrapolation of the aperiodic component yields the blood volume dilution \( I/V \). Observations are assumed to be close to the point of injection.

3. If observations are made of radioactivity per cubic centimeter of blood close to the site of injection, the extrapolated ordinate intercept value for the aperiodic component (fig. 5) should theoretically be close to the blood volume dilution, that is, the amount of label injected divided by the freely circulating blood volume. A large spread of exchange rates will alter this intercept only slightly. If observations are made downstream, a correction of the intercept must be made for the mean transit time and loss of tracer by exchange with or disappearance into intervening extravascular pools. If the mean properties of the vascular
system between the two points of observation are the same as those of the circulation as a whole, the two displacements bring the aperiodic portions and the extrapolated intercepts back into coincidence.

The experimental results are in satisfactory agreement with the theoretic analysis with the possible exception of the blood volume dilutions which are definitely too low. The difference could be explained readily by assuming that 20 per cent of the plasma mixes more slowly than the rest, being included nevertheless in the dye volumes as usually measured.19 Such a large magnitude for this effect has been questioned14 but the idea of a slowly mixing plasma fraction, whether of large or small volume, is scarcely questioned. Part of the difference may be due to the fact, as shown in the theoretic section, that the volume of the virtual circulation is slightly less than the true volume. Nevertheless, we must also consider the uncertainty in making the initial extrapolation in the presence of the oscillations. This difficulty will remain until more precise information is available as to the relative courses of the initial periodic and aperiodic portions of \( a(t) \). Recently Overman12 has reported that, in the dog, intercepts obtained with \( K^{42} \) when corrected for pulmonary circulation time give results which are in good agreement with intercepts obtained with the dye T-1824. It is of interest that very little potassium can be lost in the lung of the dog, since, if correction were required for such an effect, the resulting blood volume would be even lower than before. The smallness of the loss of \( K^{42} \) in the lung is further borne out in the reasonable cardiac outputs which were obtained. Overman12 has more recently compared cardiac outputs determined simultaneously with \( K^{42} \) and dye and with Na24 and dye. The three indicators yield identical values for cardiac output, but occasionally the potassium dosage required at a distance from the reactor is toxic and affects all output determinations equally. The mean value of the cardiac outputs when combined with a typical dye volume of 55 cc. per kilogram yields a mean circulation time of about 45 to 50 seconds. Typical intervals observed between the first and second arterial waves (fig. 1) were not over 20 to 30 seconds in length. After making liberal allowance for the fact that the distribution in circulatory traversal times is strongly skewed, the results are still in better accord with the low value of 45 cc. per kilogram for the plasma volume of the freely circulating blood.

The slopes of the initial portions of the arterial curves were quite uniform with the exception of one experiment (experiment IX) which was definitely anomalous. The results are given in the fifth column of table 1. Lacking a knowledge of \( \alpha \) the results yield only a lower limit to the over-all mean exchange rate \( \beta \) of about 8 per cent of the total circulating \( K \) per second. This represents roughly between two and four times the cardiac output in units of the plasma volume per second, two to four times \( 1/\tau \). If we arbitrarily chose a value of 3 and if we could accept the value \( \alpha = -1.45 \) calculated in the theoretic section for a rectangular distribution as being representative, then \( \beta \) would be approximately 15 per cent per second, the lower rate of disappearance being due in part to the inability of the circulation to deliver the isotope fast enough to the tissues. The coincidence of the extrapolated intercepts of the carotid artery and jugular vein curves in figure 3 indicates a general similarity in the properties of their common vascular bed to those of the over-all circulation. Such a similarity evidently cannot be assumed in the case of the hepatic curve in figure 4 since its intercept \( I_2 \) is considerably less than the intercept \( I_1 \) for the arterial curve. The depression of the hepatic intercept would be even greater if it were not for the dilution by the nonhepatic outflow from the lower extremities and other sites. We thus conclude that there is a greater than average initial disappearance of \( K^{42} \) from the liver and gut, which is the region drained by the hepatic outflow. For the renal curve, the interpretation is complicated by the disturbance caused by the ligatures which were applied in an attempt to eliminate the dilution of the renal outflow by blood from other channels. An admitted further source of difficulty is the uncertainty in comparing curves...
obtained by necessity in different animals, even though they are brought to an approximate common time scale.

The movement of tracer after its initial localization is much more difficult to describe mathematically. From the qualitative point of view, however, the initial distribution of tracer will not persist, since the terminal condition is reached only when uniform specific activity is achieved throughout the entire system. Consequently, following the initial nonuniform distribution of label, which is controlled by circulatory factors and individual exchange rates, there must be an over-all backflow out of the initial depots and into the over-all body pools as a whole. Among the controlling factors will be the relative size of the extravascular pools. There may well be situations in which these pools are actually relatively small and in which backflow of the label from them into the circulation will ensue considerably earlier in time than elsewhere. One such area of the body may be the lung. Since the effect is small in any event, a possible approximate method of taking this into account might be to include among the circulatory paths some extravascular ones. In this case, however, the success of the method will depend on how much the distribution of extravascular paths will be affected by the preceding intravascular time relations since these two situations are now mutually dependent.

**THEORETIC SECTION**

The notation is as follows.

Let $S$ be the labeled material ($K$ in the present case)

$t = \text{time}$

$x = \text{distance along a flow circuit}$

$a(x, t) = \text{specific activity of } S \text{ in the circuit at point } x \text{ and time } t, \text{(cts./min./mEq.)}$

$a_d(t) = \text{specific activity as a function of time at } x = 0$

$a(0) = \text{mean specific activity or concentration of a small initial slug or portion of activity injected at } x = 0$

$\Delta t = \text{mean duration of the injection}$

$a_d(t) = \text{specific activity upstream, at point 1}$

$\tau = \text{transit time from 0 to } x, \text{i.e., } \int_0^x \frac{dx}{V}$

$\tau_L = \text{transit time for a flow circuit taken around the entire circulation}$

$\bar{\tau} = \text{arithmetic mean of all } \tau_L \text{'s for an entire circulatory system (also the time for one complete plasma volume to pass through the heart)}$

$\check{\tau} = \text{arithmetic mean of all } \tau_L \text{'s for the virtual circulation}$

$p(x) = \text{exchange rate at } x, \text{this is the fraction of the amount of substance in the circuit exchanging per unit time between the circuit and its surroundings}$

$p(x) = \text{exchange rate at } x, \text{this is the fraction of the amount of substance in the circuit exchanging per unit time between the circuit and its surroundings}$

$\rho(x) = \text{exchange rate at } x, \text{this is the fraction of the amount of substance in the circuit exchanging per unit time between the circuit and its surroundings}$

$\rho_0 = \text{mean value of } \rho \text{ between 0 and } x \text{ and taken as a function of } \tau, \text{i.e.,}$

$\rho = \text{mean value of } \rho \text{ taken around an entire closed circuit}$

$\bar{\rho} = \text{grand arithmetic mean of all } \rho \text{'s for an entire circulatory system}$

$\kappa = \text{difference of any given } \bar{\rho} \text{'s for an entire circulatory system}$

$G(\tau_L) = \text{modified kernel function which when}$
multiplied by the normalizing function, gives the distribution of traversal times all the way around the virtual circulation

\[ \Gamma(\theta) = \text{distribution of traversal times in portions of the virtual circulation, i.e., taken between two points 1 and 2} \]

\[ e^{\mu t} = \text{normalizing function} \]

\[ \alpha/\tau = \text{correction term which must be added to } \beta \text{ because of circulation rate effects in the disappearance of } K^* \]

\[ f(t) = \text{specific activity variations with time for a nondisappearing isotope in the actual circulation} \]

\[ \psi(t) = \text{specific activity variations with time for a nondisappearing isotope in the virtual circulation} \]

We first consider the problem of the disappearance of label by exchange between an external pool and a single flow circuit whose lateral dimensions are sufficiently small that all properties are uniform throughout its cross section.

The partial differential equation which relates \( a \) to \( x \) and \( t \), allowing for variable exchange rates at different points, and variable velocities and backflow of the label from the external pools is

\[ \frac{\partial a}{\partial t} = -\rho(x)\Delta a - \frac{\partial}{\partial x} (aV). \quad (1) \]

A solution of this equation is quite complicated, since two simultaneous partial differential equations must be solved. Actually, \( \rho \) and \( V \) are not constant, and \( \Delta a \) depends on all the external space coordinates. These difficulties are avoided if we consider events sufficiently early in time so that no return flow of the label occurs from outside into the circuit. This approximation will be of practical use for all cases such as the disappearance of \( K^* \) where a large external pool exists to dilute the label so that the returning element has negligible specific activity over a fairly large initial interval \( (\Delta a = a) \). Another advantage of the approximation is that, whether the label leaves by exchange or mass transfer, the situation is unaltered, \( \rho(x) \) being in either case the fractional rate of decline of activity in the flow circuit by either or both processes.

Using the approximation, then, the equation is

\[ \frac{\partial a}{\partial t} = -\rho(x)a - V(x) \frac{\partial a}{\partial x}. \quad (2) \]

The solution of equation 2 gives a relation between the specific activity as a function of time \( t \) at some point \( x \) and the time dependent specific activity at some arbitrary origin \( (x = 0) \) upstream. The relation includes the time delay \( \tau \) and the mean exchange rate \( \rho:\) between the points. It can be derived by standard procedures such as the method of Laplace transforms.

For \( t \) greater than \( \tau \) it can be verified by substitution, that

\[ a(x, t) = a_0 \left( t - \frac{\tau}{V} \exp \left( -\frac{\tau}{V} \int_0^x \rho(x)dx \right) \right) \]

\[ = a_0 (t - \tau) e^{-\rho a} \quad (3) \]

This solution predicts an interesting repetition principle which is best illustrated when the ordinate scale is the logarithm of \( a(x, t) \). If upstream at \( x = 0 \) the time relation is \( a_0(t) \) a similar relation will occur downstream at \( x \). However, the curve will be displaced horizontally to the right on the abscissa scale by the traversal time \( \tau = \int_0^t \frac{\rho(x)dx}{V(x)} \) and vertically downward on the ordinate scale by the reduction parameter \( \frac{\rho(x)dx}{V(x)} = \rho_m \tau \) which is determined by the total exchange effects occurring between the two points. The mean exchange rate \( \rho_m \) is expressed as the fractional rate of exchange of the labeled element contained in the circuit between the points. The intervening loss of tracer is thus determined by the product of the mean exchange rate between the two points and the time which is required for the fluid to traverse the intervening distance.

The repetition principle does not hold for times less than \( \tau \) since the effects upstream have not yet had sufficient time to be manifest at the downstream observation point. During the interim period the effect of any activity distribution which may be present in the intervening region between the two points will be
observed downstream. In the present analysis we will be concerned only with the case where, at the beginning of the observations \((t = 0)\), there is no initial activity between the two points, and thus this portion of the solution will be zero.

In considering the manner in which the movement of label from the circulation proceeds it is evident that the rate at which the label leaves a given point in a flow circuit is unaffected by the concentrations or the movements in other circuits, even though the label may frequently pass through the neighboring circuits on its way to the periphery (as would occur in diffusion movements in regions of laminar flow). However, the movements can produce a redistribution within the vessel, which to a sufficiently good approximation, can be included as a small part of the overall randomization.

Since there will be variable traversal times \(\tau\) and mean exchange rates \(\rho_m\) we introduce these effects into the analysis by a method employed by Stephenson. Before considering the general case, it will be convenient, first, to consider the effect of connecting two branch circuits of equal flow but different parameters in parallel. In this case the specific activity or activity per unit amount of labeled material \(S\) (for example, potassium) in the outflow will be the sum of the activities per second contributed by each circuit, divided by the total amount of \(S\) per second. Thus the result is the weighted mean of two expressions of the type in equation 3, the weighting factor for a given branch being the fraction of the flow in that branch. For any number of circuits in parallel we merely add together the sum of such expressions, one for each circuit, multiplied by its fraction of flow. Two summations will actually be required, one for each parameter. In order to obtain the equivalent expression for a very large number of small branch circuits, we proceed formally from the sum to its infinite equivalent, the integral, employing two functions \(F(\tau)\) and \(\phi(\rho_m)\) which resemble typical distribution functions of the type encountered in statistical analysis. Of the total fluid passing a given point per unit time, \(F\) and \(\phi\) are the fractions in a given class interval of \(\tau\) and \(\rho_m\) respectively.

It is assumed on fairly satisfactory grounds that the simultaneous distribution of \(\tau\) and \(\rho_m\) (that is, the fraction of the flow through the bed which has both a time delay between \(\tau\) and \(\tau + d\tau\), and also a mean exchange between \(\rho_m\) and \(\rho_m + d\rho_m\)) is equal to the product of the individual distributions \(F(\tau)\) and \(\phi(\rho_m)\). The two distributions are thus assumed to be independent. A more complete analysis shows that this requirement is actually not essential but merely makes for simplification in the material which follows. We note that

\[
\int_0^{\infty} F(\tau) d\tau = \int_0^{\infty} \phi(\rho_m) d\rho_m = 1.
\]

The functions are thus said to be "normalized."

Taking these various factors into account, if the activity in the inflow of a capillary bed as a function of time is \(a(t)\), the relation at the outflow is

\[
a_2(t) = \int_0^{\infty} \left\{ \int_0^{t} F(\tau) \phi(\rho_m) a_1(t - \tau) e^{-\rho_m \tau} d\tau \right\} d\rho_m.
\] (4)

The upper limit of \(t\) on the integration over the \(\tau\) variable arises because no circuit whose \(\tau\) is greater than \(t\) has had time to make its influence felt at the outflow. As \(t\) becomes progressively greater the integral will embrace a larger and larger portion of \(F(\tau)\) as more circuits become involved. Finally, at some ultimate time all portions of the intervening bed will be included. If the system initially contains labeled material, an additional term must be included to account for the transient effect of activity between points 1 and 2 at the beginning of the experiment. Our present analysis will not require an inclusion of this effect.

Since equation 4 applies to any two points in the circulation connected by a set of flow circuits, it can be applied immediately to the circulation as a whole. In establishing the relation it is necessary to distinguish between the first circulation and recirculations. It will be convenient to consider the case in which, starting with no initial activity in the circulation, a sharp initial pulse of activity is injected...
at the origin. Theoretically, the height is infinite and the temporal extent or spread infinitesimal, so that the resulting finite area is $a(0)d\tau$. Actually, both the height and spread will be finite but in close approximation to the theoretic situation. We will thus use the theoretic $dt$ and the practical $\Delta t$ in this connection without any real distinction. Now it has been emphasized that the repetition principle will not apply for any flow circuit until the time exceeds the traversal time for the circuit. For the present case the correction for the amount between the two points degenerates to an added term, which accounts for the return of the smeared out pulse at the origin upon one circulation. Having once arrived, the repetition principle will then automatically insure the repeated arrival of the repeatedly smeared out pulse on all future recirculations. When applied to a population of flow circuits the time relation at the origin, say in the right atrium, is obtained by solving the integral equation

$$a(t) = a(0)F(t)dt \int_0^\infty \phi(\tau)e^{-\lambda_1 \tau} d\tau$$

the first term on the right being the effect of the first circulation and the second the effect of all recirculations.

It is not necessary to solve this equation but rather to relate it to the equation of mixing of a nondisappearing substance, that is,

$$f(t) = a(0)F(t)dt + \int_0^t F(\tau)L(t - \tau) d\tau,$$

When expressed this way $F(\tau)$ is called the "kernel" of the equation.

The relation between equations 5 and 6 may be achieved if in equation 5 we make the substitution

$$a(t) = \psi(t)e^{-\lambda_1 t}\int_0^\infty \phi(\tau)e^{\lambda_1 \tau} d\tau$$

obtaining

$$\psi(t) = a(0)G(\tau)e^{\lambda_1 \tau} dt$$

whose kernel, $G(\tau)e^{\lambda_1 \tau}$, is normalized if we impose the relation

$$\int_0^\infty G(\tau)e^{\lambda_1 \tau} d\tau = 1.$$

This equation serves as a defining relation for $\alpha$ which is a measure of the effect of circulation rate on the movement of label from the circulation.

Although equation 8 has the same form as equation 6 it has a different kernel and thus yields different mixing kinetics.

Fig. 6. Effect of alteration of the kernel (see text); the periodic component is altered so that the relations are those for a virtual vascular system whose distribution of traversal times is given by $G(\tau)e^{\lambda_1 \tau}$ instead of $F(\tau)$. Dotted lines are for the altered, solid lines for the unaltered kernel. Note slight alteration of the equilibrium plateau. Relations as indicated are schematic only.

Physically, the effect may be regarded as an effective distortion of the true vascular architecture of the real circulation into an altered fictitious architecture of a virtual circulation (fig. 6). The mixing of a nondisappearing substance in this altered system would be given by $\psi(\tau)$ rather than $f(\tau)$, and the distribution of traversal times by $G(\tau)e^{\lambda_1 \tau}$ rather than by $F(\tau)$. From elementary considerations it can be shown that

$$G(\tau) = F(\tau) \int_\tau^\infty e^{\lambda_1 \tau} \psi(\tau) d\tau$$

$$= F(\tau) \left[ 1 + \frac{\lambda_1}{2} (-1)^a \frac{\lambda_1^n}{n!} \right]**
where the \( \kappa_n \) are the various moments of \( \phi(x) \) about \( \bar{x} \) (i.e., \( \int_{-\infty}^{\infty} \phi(x) \kappa_n \, dx = \kappa_n \)). If the moments are all small, that is, if the spread of the \( \bar{x} \) is not great then

\[
G(\tau_\varepsilon) \to F(\tau_\varepsilon), \ \psi(t) \to f(t) \text{ and } \alpha \to 0.
\]

In the case of transcapillary exchange of isotopes such as K\(^{42} \), since the individual paths through the circulation are likely to be quite devious, there should be an averaging effect so that all paths may have, to some extent, an equal opportunity for rapid or slow exchange due to the purely random way in which they encounter the various tissues. To this extent the mean exchange rates will tend to be alike. Nevertheless, the existence of shunts in the circulation is recognized. Even though exchange in the shunts may be less than in the capillaries, such bridges as those occurring between arterioles and venules may be sufficiently well woven into the capillary fabric to minimize the scattering (broadening) of the \( \phi \) function. Larger shunts between small arteries and veins can exclude blood from the capillaries and may, in this way, contribute to the broadening. Certain organs will also receive more K\(^{42} \) than others. At present we cannot assess these various effects very well. To the extent that they are active, there will undoubtedly be some spread of the exchange rates \( \bar{x} \) about the mean value.

The analysis of a hypothetic distribution of \( \bar{x} \) and \( \tau_\varepsilon \) will suggest that a large variation indeed will actually be required before the effects of disappearance and mixing will become seriously interrelated. The situation where \( \bar{x} \) and \( \tau_\varepsilon \) are both given by broad rectangular functions of unit area ranging from 0 to twice the arithmetic mean is fairly easy to treat. For the rabbit,\(^4 \) the disappearance of K\(^{42} \) is such that \( \bar{x} \) is roughly equal to 1/\( \tau_\varepsilon \). Under these conditions \( \alpha \) can be shown to be only about \(-0.2 \) and the difference between the true and virtual circulation is only on the verge of becoming important. For \( \bar{x} \tau_\varepsilon = 3 \) however \( \alpha = -1.45 \) and becomes more extreme as \( \bar{x} \tau_\varepsilon \) increases. Calculations for other more difficult types of distributions will be reserved for a separate communication. Although a proof is lacking that \( \alpha \) is invariably negative, in the majority of cases this will be so.

In summary, we conclude that the equation of combined circulatory mixing and capillary exchange (equation 5) can be related to mixing alone by expressing \( \alpha(t) \) as the product of two factors. One is an exponentially declining function which in the first approximation is determined by the mean exchange rate \( e^{-\bar{x} \tau_\varepsilon} \) and the other a function which is a solution of the mixing equation for a nonexchangeable substance. In the higher approximation a more exact solution can be obtained by introducing a constant \( \alpha \) (probably small and negative) in the exponent which is a measure of the amount by which the effect of circulation rate enters. This solution is

\[
\alpha(t) = \psi(t) e^{-(\bar{x} \tau_\varepsilon + \alpha t)}.
\]

Where \( \psi(t) \) is a solution of the mixing equation for a nondisappearing substance in an altered or virtual circulation which differs slightly from the true one. Since \( \alpha \) is probably small, the exponential exchange rate term is not very sensitive to changes in mean circulation time. The effect of circulation rate, would of course, be greater if the spread in individual mean exchange rates were greater than we believe at present.

**Extrapolation to the Blood Volume Dilution.**

In the case where the exchange rate is either zero or very small compared with the circulation times, it is intuitively obvious that the aperiodic portion of the solution will yield the blood volume dilution, when the semilogarithmic plot is extrapolated back to zero time. Thus, if \( C \) is the concentration of K in the vascular space, whose volume is \( V \), \( I \) is the activity injected, \( \alpha(0) \) is the mean specific activity at the injection point during the injection, \( Q \) is the number of milliequivalents per second of labeled material (total K) flowing past the site, \( \Delta t \) is the mean duration of the injection, and \( \tau_\varepsilon \) is the mean circulation time, that is, the time for a complete volume of blood
to circulate once, we have for the extrapolated intercept

$$A_0 = I/CV = \frac{a(0)Q\Delta t}{\pi Q} = a(0)\Delta t/\tau.$$  (11)

Now for the case of rapid disappearance, since the exponential term in \(a(t)\) is initially unity, the zero intercept will be determined by the intercept of \(\psi(t)\) which is the solution of the equation of mixing for the virtual circulation. Not only will the kinetics be somewhat different but also the mean circulation time \(\bar{\tau}\) for the virtual circulation. Nevertheless, the change will not be very great. For the rectangular distributions in \(\beta\) and \(\tau_c\), where \(\beta = 1/\bar{\tau}\) and where \(\alpha\) was \(-0.2\), \(\bar{\tau}\) is 5 per cent greater than \(\bar{\tau}\). For \(\beta = 3/\bar{\tau}\), however, \(\bar{\tau}/\bar{\tau}\) is 1.12. Thus we may expect the blood volume obtained from the extrapolation to be definitely lower by a few per cent. At present, and lacking further information concerning the actual form of \(\phi(\beta)\) and \(F(\eta)\), it is not possible to calculate the exact amount of the effect; we may merely recognize its existence.

The reason for the uniformity in slope and variability of intercepts for observations taken at different points might seem on intuitive grounds to arise from the fact that the exchange across the vessel walls is so generalized or the mixing so fast relative to exchange, that no particular portion of the circulation emerges to govern the over-all kinetics. No point can lose activity at a greater or smaller fractional rate, since it is governed by the supply from upstream and must fall into step with it. Local increases or decreases in exchange rate will thus appear as reductions or magnifications in the scale of \(a(t)\), that is, as changes in initial intercept when plotted on semilogarithmic coordinates.

A concrete illustration of the principle can be obtained from equation 4 which relates the time relations at point 1, that is, the right atrium, to those at some arbitrary point downstream (point 2) which may or may not include all circuits. Inserting for \(a_1\) the previously derived relation \(a_1 = \psi_1(t)e^{-\beta \tau} + \alpha^0\), and \(a_1 = \psi_1(t)Ae^{-\beta t}\), we find that the two exponentials cancel if \(k = \beta + \alpha/\bar{\tau}\), yielding

$$\psi_2(t) = \frac{1}{A} \int_0^t \psi_1(t - r)\Gamma(r) \, dr.$$  (12)

As in the case of equation 5, we have converted an equation for a disappearing substance into the equation for a nondisappearing substance with an altered kernel. Because the exponential factors are the same in both cases, the slopes on the semilogarithmic plot will be the same. When normalized by the factor \(A\), the equation describes the redistribution or "smearing" of the time relations imposed at the origin but observed at the downstream location. As before, the kernel \(\Gamma(\tau)\) is altered somewhat from that for a nondisappearing substance and becomes the equivalent kernel for a "virtual" distribution of intervening paths. The difference in this case from the previous one is that here the requirement that \(a_1\) and \(a_2\) be the same function is not imposed and so the normalization can be achieved through the multiplying constant \(A\). This constant will determine the initial intercept of the aperiodic portion of the solution. In general, \(A\) will not be unity and so the intercepts of the various aperiodic solutions for the different points in the circulation will not coincide.

\(A\) will be unity, in general, whenever the capillary bed between the two points of observation has the same average properties as the over-all circulation. A comparison of the properties can be made through the two kernel functions \(\Gamma(\tau)\) and \(G(\tau)e^{-\beta \tau}\). Here, if the local bed and the general circulation have the same exchange properties, the distributions of the exchange rates will be identical. However, in the case of the traversal times, those for the over-all circulation would be greater than for the local bed in the ratio of the mean values for the two cases. As long as the ratio \(\tau/\bar{\tau}\) is unaltered, since \(\tau\) is merely a variable of integration the value of \(\alpha\) which serves to normalize the \(G(\tau)\) for the over-all circulation will normalize the kernel for the local bed. This is true provided that \(\Gamma(\tau)\) is derived from \(G(\tau)e^{-\beta \tau}\) by a simple extension of all traversal times by the same ratio.
Summary

Immediately following the sudden jugular injection of K\textsuperscript{42} in the dog the plasma levels in the carotid artery follow a rapidly declining quasi-exponential aperiodic curve with three superimposed periodic oscillations. When observations are made at two different points events upstream are repeated downstream with time delay, attenuation due to intervening loss of tracer from the circulation and loss of resolution due to the distribution of traversal times of the various elements of label between the two points. The aperiodic portions of the curves tend to be parallel with different intercepts. Reasonable values of cardiac output are obtained by analysis of the first circulation wave by the Stewart-Hamilton method. The loss of isotope in the lung is therefore small. The extrapolated zero intercepts of the aperiodic portion of the arterial curves when corrected for time delay yield initial volumes of dilution significantly lower than accepted plasma volumes for dogs.

Theoretic analysis of the problem shows that the integral equation for simultaneous mixing and disappearance of label can be reduced to the equation of mixing in a virtual circulatory pool without disappearance. The initial slopes of the aperiodic portions of the plasma curves are determined partly by the over-all mean exchange rate of K with the various extravascular pools and partly by a constant a which represents the effect of circulation rate. The constant depends on the spread of the individual exchange rates for the various flow circuits.

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