Compound Interest Laws and Disappearance of Tracers from the Circulation

Injecting indicators into the right heart and recording curves of arterial blood concentration as a function of time is a familiar physiologic maneuver which yields important information. More recently it has become evident that curves for substances, such as K4', which disappear very rapidly from the circulation are amenable to analysis and are potentially richer in information than "non-disappearing" substances such as T1824. A really comprehensive study of such disappearance curves, when disappearance is so rapid as to be interrelated with mixing, requires advanced mathematics. Nevertheless, considerable understanding of some basic points can be achieved from elementary considerations involving the use of a special kind of compound interest in which the rate is negative and interest is compounded continually.

In ordinary compound interest, bank accounts accrue by a series of jumps, the magnitude of the jump being proportional to the amount in the account at the time that interest is credited. If the intervals between jumps were made vanishingly small the interest would be continuously compounded and at any time the deposits would be growing steadily in proportion to the amount present. In other words, the percentage growth rate would be constant. It is characteristic of such a law of growth that if the amount be expressed as a fraction of the initial amount, the logarithm of this fraction grows linearly from 0 in proportion to the interest rate multiplied by the time elapsed since the account was set up. Substances injected into the circulation should disappear according to a similar law if they are well mixed in the blood. The rate, of course, is negative since material is being lost rather than gained. Irrespective of the process of removal, the loss rate is constant percentwise because, if two units are injected rather than one, both units disappear independently and the total rate is doubled, the percent rate being unchanged. A plot on semi-log paper of the percentage remaining should yield a straight line with a downward slope.

Nevertheless, experimental results now familiar to all show that semi-log plots are far from linear. By assuming a single uniformly mixed extravascular pool, attempts have been made to correct for back-flow of tracer, using mathematic technics known to work in simple two-compartment systems; but the curvature remained and was accepted as real. Non-uniformity of extravascular mixing and the problem of excretion has been approached by introducing multiple extravascular compartments, including one for the extravascular environment. With loss of tracer into several compartments at different rates, curved semi-log plots were theoretically predicted and verified, but the same theoretic curvatures could usually be obtained for several alternative hypothetical models of the system under study. It was rarely possible to obtain high experimental precision; kinetics calculated for four or five compartments often gave no better fit than a three-compartment assumption under conditions where a larger number of compartments should be expected. Nevertheless, experiments in this field have not been unproductive. Irrespective of their lack of sharp resolution, many instances of gross alterations in disappearance curves were seen in pathologic situations. Furthermore, in some cases ad hoc assumptions could be made within which data could be tentatively reconciled with theoretic predictions.

Attempts to refine the theories of tracer experiments in which heterogeneous mixing was a problem have directed increasing attention to mixing processes in the circulatory compartment. We know that, under certain conditions, the rate of blood flow can influence the rate at which injected substances vanish and hence the corresponding slope of the disappearance curve. When an organ is perfused...
from a stirred reservoir at relatively low rates of flow, material may be cleared from the blood as fast as it reaches the tissue; blood flow is an over-all rate-limiting step. The disappearance of colloidal Au\textsuperscript{198} from the circulation can be roughly described similarly by imagining the main circulation to be the stirred reservoir and the splanchnic circulation to be the perfusion circuit from which the colloidal particles are nearly quantitatively removed by the reticuloendothelial cells in the liver and spleen.\textsuperscript{9}

In the disappearance of colloidal Au\textsuperscript{198} and of K\textsuperscript{42} there are obviously large arteriovenous differences in concentration of isotopes. Does this mean that arteriovenous differences in general introduce "circulation rate effects" into the kinetics of disappearance? Is the vanishing of K\textsuperscript{42} affected drastically by circulation rate? Certainly if the arteriovenous difference were independent of circulation rate, then the conclusion would be tenable. Actually, as will be shown, at least one situation can occur where, despite large arteriovenous differences, there is no "circulation effect" on the loss of labeled material from the blood. With varying circulation rate the arteriovenous difference changes inversely so as to just cancel the effect of disappearance on the kinetics. Thus arteriovenous differences per se are only part of the story so far as "circulation rate effects" are concerned.

Since large arteriovenous differences occur early while the effects of backflow and interaction with environmental pools are small, it is sufficient to consider only the outgoing movement of injected material. If a single small slug of tracer is injected into the heart it will be dispersed into many small masses, each of which goes around the circulation by one of a great many possible paths. Upon returning to the heart, these masses are recombined and a new dispersal occurs in random fashion for a new circulatory trip. We can gain some understanding of the situation by considering first only two paths, later generalizing to include a practically infinite number.

For one of the closed paths alone, in the absence of other paths, the amount left in a slug, after a given interval of time, does not depend on the number of circuits per minute made by the slug, just as the money in the bank under continuous compounding would not depend on how frequently one consulted with the banker but only on the elapsed time of the account. Certainly, on its path through the vascular labyrinth, material is lost in a variable manner depending on the local loss rates at various points; the observer can only see the over-all mean effect for the entire trip. For K\textsuperscript{42} much of the loss might occur by initial diffusion from minute vessels and sinusoids, but the picture is still incomplete. Other processes will determine local rates for some injected substances, such as phagocytosis for colloids. These processes will be constant so long as local conditions are. Doubling the circulation rate will reduce the loss by half on the requisite logarithmic scale, since the time spent in each locality is halved. However, for the same time interval, the number of circulations is doubled so the net loss is the same as before. Of course, the change in circulation rate might cause the rates of loss at various loci to change. There is also a small component of loss of small molecules in the isolated canine limb which occurs by filtration.\textsuperscript{10} But this represents a change in the rate of extravascular transport and not a fictitious one caused by intravascular "circulation rate effects." Of course it should be realized that the distribution of the material among the extravascular pools may be influenced by circulation rate.

The independence is also preserved if the interest rates of the two banks are the same even if the banks are visited at different times. With a common interest rate it makes no difference in which bank the money is and funds can be shifted back and forth at will. In the two circuit model, then, changes in circulation rate will not alter the kinetics of disappearance provided the loss rates in the two branches are alike. The same would be true for the actual circulatory labyrinth if the loss rates were homogeneous. Thus one situation can be imagined where there could be large arteriovenous differences but no "circulation rate effect."

Certainly there is some heterogeneity in the loss rates of various paths in the actual circulation. Varying the circulation rate will affect.
the disappearance kinetics to some extent, since there is certainly a spread in the circulation times. In such a case the aortic redistribution of the slugs affects the ultimate fate of the injected material. The rate at which these redistributions occur is altered with changes in circulation rate. This situation is particularly extreme with colloidal Au\textsuperscript{198} where 20–30 per cent of the disappearance rates through the splanchnic circulation are essentially infinite whereas the remainder are 0. In the case of K\textsuperscript{2} the individual rates are probably clustered about some central value. Even with a rather large spread there should not be a large rate effect.\textsuperscript{2} More precise statements await better knowledge concerning the actual distribution of disappearance rates.

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EDITORIAL NOTICE

The deadline for receipt of complete, acceptable manuscripts for the September issue is June 14, 1957. Contributors are urged to read carefully the information contained on the masthead page.
Editorials: Compound Interest Laws and Disappearance of Tracers from the Circulation

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