"Why is the cardiotonic action so specific in therapeutic use?". One answer might be that cardiac muscle is continuously active whereas other muscles are less so. When cardiac muscle is quiescent, it is appreciably less sensitive to digoxin or ouabain (Sanyal & Saunders, 1958; Walker & Weatherall, 1964).

Similar experiments have now been performed with skeletal muscle. Isolated phrenic nerve-diaphragm preparations from guinea-pigs have been set up in Krebs-Henseleit solution and stimulated alternately directly and through the phrenic nerve, usually at 1 Hz. When digoxin or ouabain (2 μg/ml) was applied with continuing stimulation contractions diminished and no response to direct or indirect stimulation was detectable after 20–25 min. When stimulation was stopped from the moment of adding glycoside until 30 min later, normal or enlarged responses occurred on resuming stimulation, and paralysis set in over the next 5–20 min. Thus, the inactive preparation was still apparently unaffected by the glycoside at a time when the active preparation had become entirely unresponsive. Further experiments suggest that at lower rates of stimulation failure of response occurs more slowly; that is, in diaphragm, as in cardiac muscle, sensitivity depends on the rate of contraction.

A possible explanation is that failure results directly or indirectly from accumulation of sodium in the tissue when sodium transport is impaired by the glycoside. The entry of sodium is greatly increased by each stimulus, so that tissue stimulated continuously is more susceptible than quiescent tissue. As long as contractions are not too frequent, sodium can be extruded despite some impairment of the pump. But in physiological conditions the frequency and continuity of contraction of the heart makes it more susceptible than any skeletal muscle to effects of cardiac glycosides.

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Quantitative treatment of the distribution of drugs after intravenous injection

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The effect of a drug probably depends on its concentration in the tissue in which it acts. Antibacterial activity may well relate closely to concentrations in plasma, because diffusion occurs fairly rapidly between plasma and extracellular fluids and infecting bacteria are on the whole extracellular. But the effectiveness of drugs acting on specific organs, for example cardiac glycosides, is likely to relate to the concentration in that organ, or some part of it, rather than to the concentration in plasma. It would therefore be useful to predict the concentration of a drug in different organs at various times after giving single or repeated doses. Reliable predictions would add to the understanding of pharmacological responses, and also would allow more accurate therapeutic use. To make such predictions, rates of transfer between plasma and tissues or components of tissues must be estimated. The whole body can be regarded as a very complex system of many compartments, and some sort of simplified model is essential. In Teorell's (1937a, b) classical papers, only four compartments (site of administration, blood, tissues, excreta) were used, and complete equations using first order kinetics were shown to describe blood concentrations quite well. Extension of Teorell's equations to

allow for tissues with several different rates of uptake leads to appallingly heavy algebra. Also Teorell did not present any means of estimating rate constants from experimental observations. More recent treatments have not overcome this problem, despite much ingenuity and mathematical sophistication.

Suppose a drug is injected intravenously into an animal, and the animal is killed some minutes later and the amount of drug in various organs is estimated. If the uptake by tissues is slow compared with the rate of mixing in the circulation, movement of drug back from tissues to plasma can be ignored, and the concentration of drug in plasma during the period is approximately

$$C_t = C_o\, e^{-k_1 t}$$

where C_t is the concentration at time t, C_o the concentration at zero time (=dose/plasma volume) and k_1 a constant given by the slope of the line relating log C to time. The rate constant of uptake of drug by any tissue can then be calculated from the amount taken up by the tissue and the plasma concentration over the period.

Suppose other animals are injected with the same dose, and killed hours later and estimations of drug are made on tissues and excreta. Suppose variation between individual animals is small enough to be ignored. By using the uptake rate constants already calculated together with all other observations, the return rate constants (that is, for transfer from tissue to plasma) can readily be estimated.

The amount of drug which can be accounted for at any time by adding together all the known estimates is usually less than the dose given. The missing material either has been eliminated by metabolism or excretion, or is in tissues which have not been analysed and from which it later returns to the circulation. The total quantity of missing material is known by difference, and it can be included in alternative calculations by assuming either elimination or storage or an arbitrary partition between the two fates.

When constants have been calculated in these ways, complete model systems are set up, from which expected concentrations in all tissues considered can be computed at any required time. Differences between computed and observed values can readily be obtained, and the sums of squared deviations for different models used as a measure of goodness of fit.

In spite of, or more probably because of, the large number of approximations and assumptions, quite good predictions can be made in this way. With suitable data it is clear that missing material is either all eliminated or all retained, or intermediately, and the estimates provided are continually suitable for testing experimentally.

Examples will be shown of computed results applied to published data, and on-line calculation from experimental data will be shown.

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