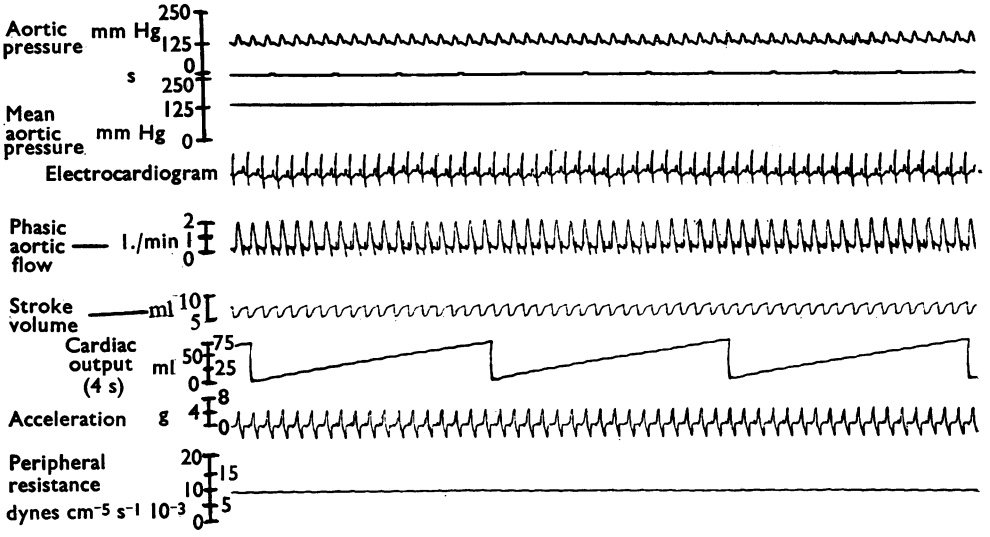

FIG. 1. Recording from a dog anaesthetized with chloralose.

Peripheral vascular resistance (excluding coronary circulation). Mean aortic pressure and mean aortic flow were derived by passing the respective pulsatile signals through a " leaky " integrating operational amplifier. Resistance was computed by dividing pressure by flow using a " multiplier-divider " (Philbrick/Nexus Research). The system was calibrated by calculating peripheral resistance for various values of pressure and flow (Kaneko, Page & McCubbin, 1964); the relationship between resistance and pen deflection (V/cm) was linear.

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The response of stimulated and quiescent phrenic nerve diaphragm preparations to digoxin and ouabain

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The action of cardiac glycosides on the heart appears to involve inhibition of an adenosine triphosphatase and of active sodium transport. However, these effects are widespread and are not confined to cardiac muscle; the membrane adenosine triphosphatase of the heart is not particularly sensitive to the glycosides, and the glycosides are not particularly concentrated in heart muscle. The question arises,

"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