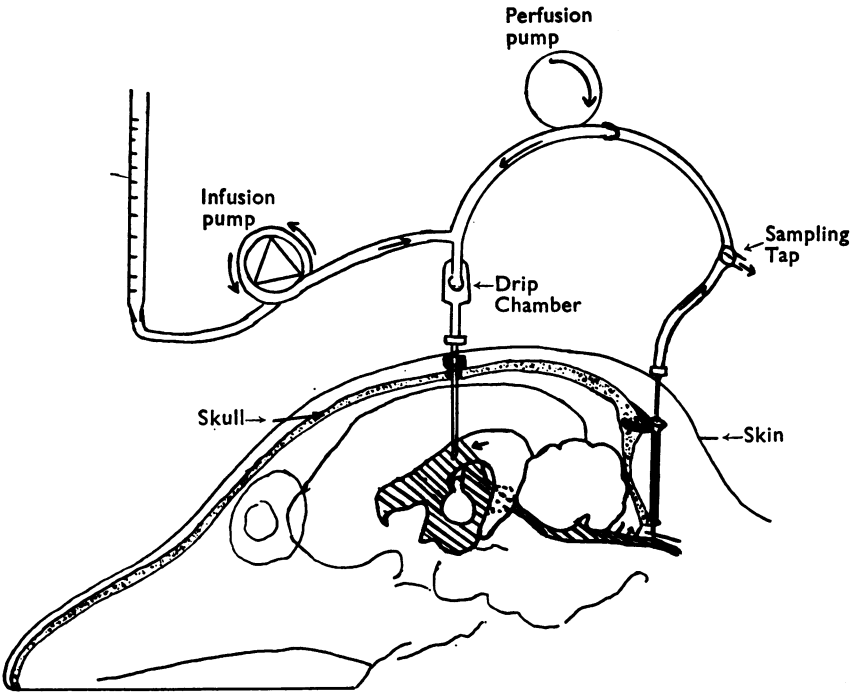

FIG. 1. A recirculatory perfusion system of the cerebral ventricular system of the dog.

Perfusion experiments of this type in conscious unrestrained dogs can be undertaken at intervals of two weeks without any subsequent ill effects.

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An action of ouabain to promote smooth muscle contraction unrelated to membrane ATPase inhibition

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A concentration of 10^{-3} M ouabain causes contracture of uterine muscle isolated in a modified Krebs bicarbonate solution (Daniel & Robinson, 1960) and maintained at 17°–19° C. In 1964, Daniel proposed that this contracture was due to inhibition of membrane ATPase.

It has been shown that smaller concentrations (10^{-5} to 5×10^{-4} M) of ouabain potentiate the responses of the isolated rat uterus to a variety of agonists. Furthermore, the potentiation of any one agonist by ouabain is not prevented by the antagonists of the others. Both the contracture produced by the higher concentrations of ouabain and the potentiation of the responses to other agonists produced by the lower concentrations are, however, prevented by low doses of a number of complexing agents (8 hydroxyquinoline, 1 : 10 phenanthroline, ATP, and other nucleotides).

Like ouabain, $ZnCl_2$ (10^{-4} M) causes potentiation of the responses of the uterus to the same agonists, and in higher concentrations will produce contracture. Furthermore,

these effects of zinc and ouabain are mutually additive, and those of the zinc, like those of the ouabain, are prevented by the same complexing agents. Phenanthroline is preferentially soluble in lipids, whereas the sulphonated derivative is preferentially soluble in water. Because the former is a much more effective antagonist of the ouabain contracture than is the latter, it is concluded that its site of action is separated from the bath fluid by a lipid membrane.

In 1964 Daniel showed that concentrations of ouabain sufficient to produce contracture also caused downhill ion movements of sodium and potassium. Concentrations of ouabain or of zinc, sufficient to cause potentiation of responses to other agonists, however, do not cause these downhill ion movements or inhibition of a sodium activated membrane ATPase, nor does the ouabain cause net movements of Ca or Mg.

The present data indicate clearly a relationship between the contractures and the potentiations produced by zinc and ouabain which is inconsistent with either being caused by inhibition of membrane ATPase. Both zinc and ouabain contractures and potentiations are inhibited by concentrations of adrenaline which are without effect on responses to acetylcholine. As adenyl cyclase is inhibited by zinc (Sutherland, Rall & Menon, 1962) and by ouabain (Ho, Jeanrenaud, Posternak & Renold, 1967), whilst it is activated by adrenaline (Sutherland & Rall, 1957), it is possible that these effects of ouabain and zinc are caused by inhibition of this enzyme, which, in turn, affects internal calcium release and contracture.

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Sodium maleate-induced potentiation of the penicillamine effect on the urinary mercury excretion

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Sodium maleate, which produces metabolic changes in the renal cells, has been shown to decrease the kidney mercury content and to increase the urinary mercury excretion, the lowest effective dose being 100 mg/kg s.c. (Clarkson & Magos, 1967). As it is a thiol reagent, experiments were carried out on albino rats to see whether sodium maleate modified the effect of some known thiol complexing agents on the urinary excretion of mercury.

It was found that sodium maleate enhanced the effect of *d*-penicillamine, and to a lesser extent that of *N*-acetyl-penicillamine, but, if anything, slightly decreased the effect of 2,3-dimercaptopropanol. Sodium maleate, 25 mg/kg daily s.c. given on the sixth and seventh days after the administration of 100 μg Hg (as labelled $HgCl_2$), potentiated the effect of *d*-penicillamine (35.8 mg/kg I.M. twice a day), resulting in a urinary excretion of