lytic or sympatholytic action of ethyl yohimbine it seems reasonable to believe that they act directly upon smooth muscle components and not upon ephinephrine-receptors in the vascular musculature.

The belief that epinephrine-receptors are not stimulated by angiotonin gains support by the failure of this substance to produce salivary flow or mydriasis in those cats which salivated profusely after epinephrine and cervical sympathetic nerve faradization.

The results of our vascular experiments confirm those reported by other workers[5] in that this hypertensive agent is unlike epinephrine. In their investigations a dioxane derivative, F 933, was employed as the sympatholytic agent and their angiotonin equivalent was known as pepsitensin which seems to be similar to the "hypertensin" of Braun Menendez and his co-workers.[6]

*Conclusions.* 1. Angiotonin (Page) has a true pituitrin-like action. 2. It contracts smooth muscle directly and not through the medium of adrenergic neural vasoconstrictor components. 3. Its action is not reversed by ethyl yohimbine as is that of epinephrine. 4. It exhibits no vasodilating action such as is characteristic of small doses of epinephrine. 5. It does not nullify the adrenolytic or sympatholytic action of ethyl yohimbine. 6. It has no effect upon cholinergically or adrenergically controlled salivation or pupillary responses.

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## Effect of Insulin, Glucose, and Glucose and Insulin on the Rate of Metabolism of Ethyl Alcohol.

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Reports in the literature are not in agreement concerning the effect of insulin on the rate of metabolism of ethyl alcohol. Numerous reports indicate that insulin has no effect on the rate of metabolism of this substance.[1-7] Many reports claim, on the other hand, that insulin or insulin and glucose increase the rate of oxidation of ethyl alcohol.[3,8-14]

The conflicting reports in the literature, the fact that insulin or insulin and glucose have been used clinically in the treatment of acute alcoholism, and the theoretical unlikelihood that insulin would be so lacking in specificity

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of action have led us to reinvestigate this problem.

In general, much of the published work may be criticized on the basis of the short time over which observations were made. And the clinical evidence is not well controlled in view of the poor state of nutrition often seen in patients with alcoholic intoxication serious enough to require hospitalization. In addition, some of the published work failed to show a study of the capacity of the animal or intoxicated man to oxidize alcohol over a control period with alcohol alone from the beginning to disappearance of the alcohol from the blood. Furthermore, much of the experimental work and all of the clinical work was done following the ingestion of alcohol by mouth. The variability of absorption rate in any animal and in different animals could cause apparent differences in the rate of disappearance of the alcohol from the blood. This would be true particularly when observations were made over only a few hours' time.

*Methods.* All studies were made on dogs which had been on a diet of Purina Dog Chow 2 or more days and then fasted 15 or more hours before the administration of alcohol in both the control and the experimental group which received insulin. These were carried out initially following administration of 3 cc

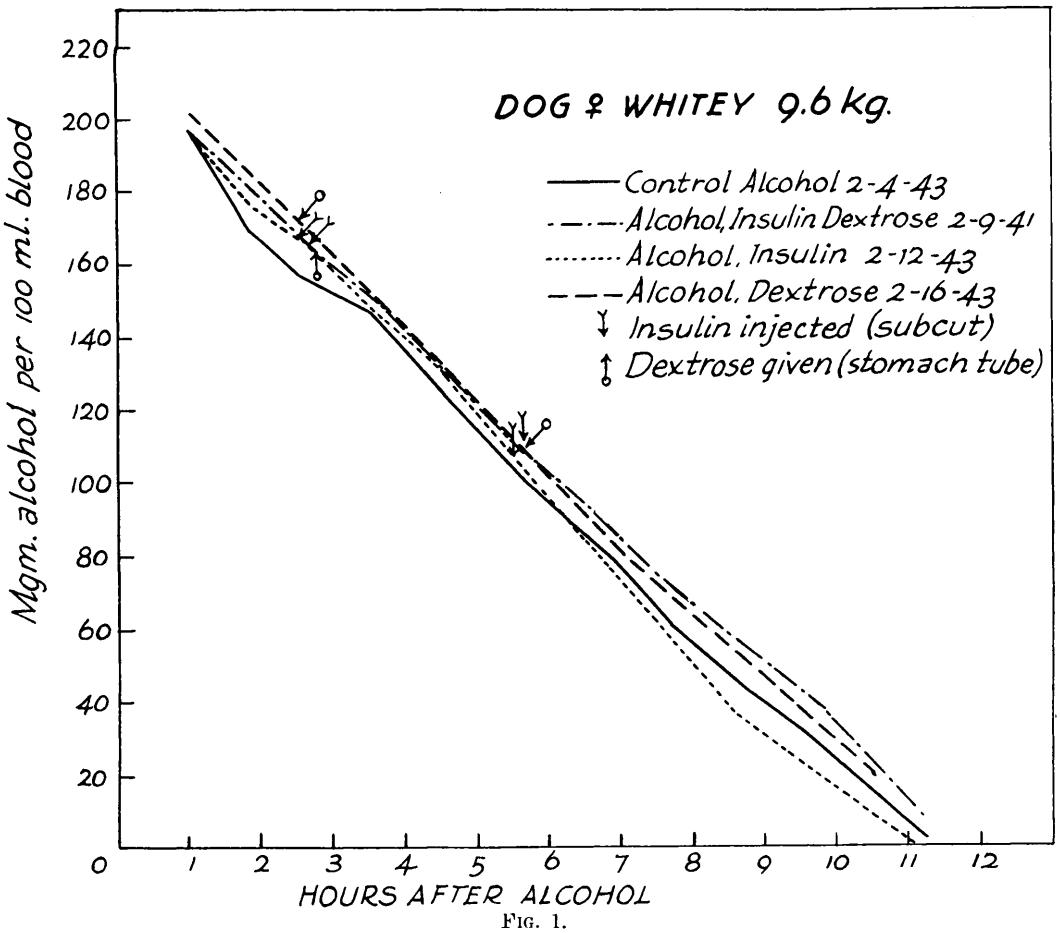


FIG. 1.

This shows the rate of disappearance of ethyl alcohol from the blood of a dog after intravenous administration of 20% ethyl alcohol, the total amount of which was 2 cc of absolute ethyl alcohol per kilo of weight, under the 4 conditions of alcohol alone, alcohol plus insulin, alcohol plus dextrose, alcohol plus insulin and dextrose. The dextrose was given in the amount of 3 g per kilo of weight as a 33⅓% solution. The dates upon which the 4 different experiments were done are indicated.

of ethyl alcohol per kilo by stomach tube. The alcohol was diluted to 20% strength by volume. The blood alcohol levels were so variable and the disappearance curves were so irregular that we concluded this to be an unsatisfactory method of giving the alcohol. We injected, therefore, ethyl alcohol intravenously in amounts of 2 cc per kilo in 20% strength. About 5 minutes were required for the injections. This method of administration gave disappearance curves that were smooth and reproducible in all animals in which it was repeated. About 11 hours were uniformly required for the complete disappearance of the alcohol from the blood.

Six dogs were subjected to the following experiments, usually in this sequence: (a) rate of disappearance of alcohol alone, (b) rate of disappearance of alcohol after the subcutaneous injection of one unit of regular insulin per kilogram. This dose was repeated after 3 hours, (c) rate of disappearance of alcohol after administration of 3 g of glucose per kilo by stomach tube as a 33⅓% solution, (d) rate of disappearance of alcohol plus insulin, as indicated in (b), plus glucose, as indicated in (c). In other words, 24 experiments were done on 6 dogs. In each instance 45 to 60 minutes were allowed to elapse following intravenous injection of alcohol to insure uniform distribution in the body. Blood specimens for alcohol analysis were then drawn at three-quarter- to one-hour intervals until the alcohol had practically disappeared. This was almost uniformly approximately 11 hours after injection of the alcohol. Estimations of alcohol in the blood were made according to a combination of the methods of Harger[15] and Heise.[16] The oxidation and titration were done by the former method and the distillation was accomplished by the latter method slightly modified. Combination of the two methods has been previously employed by Ewing.[17]

*Results.* The results and procedures of 4 experiments on one dog are shown graphically in Fig. 1. The results of the same types of experiments on 5 other dogs were practically identical. There is also evidence from some of our other experiments that the state of nutrition of the animal has some influence on the rate at which ethyl alcohol is metabolized. It is suggested on this basis that the general treatment of intoxicated patients with fluids and glucose, rather than the insulin, is responsible for the apparent increased rate of disappearance of ethyl alcohol from the blood of intoxicated man. It is further suggested that the correction of dehydration which is usually associated with severe intoxication may have a "diluting" effect on the alcohol of the body fluids and in this way give rise to an apparent increased rate of disappearance from the blood.

*Conclusions.* There is no evidence from 24 experiments in 6 dogs that insulin, glucose, or insulin plus glucose increases the rate of metabolism of ethyl alcohol.

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