SPECIAL ARTICLES

THE EFFECTS OF ALCOHOL AS INFLUENCED BY BLOOD SUGAR[1]

IT has long been recognized that when alcohol is taken by mouth the presence of food in the stomach influences its effects. The action of the food is purely physical; it dilutes the alcohol and slows its absorption so that the concentration of alcohol in the blood does not rise as high as it would if the stomach were empty and the absorption rapid. The observations that we have now to report introduce another similar, but heretofore unrecognized, factor. We find that the increase of sugar in the blood, which follows a meal, greatly lessens the pharmacological effect of alcohol that has been absorbed. Our investigation has been made chiefly on rats, but we have evidence that men react similarly.

Our results were obtained by determining the concentration of alcohol in the blood required to produce definite effects at various concentrations of blood sugar. This was death from respiratory failure in the case of experimental animals. To obtain valid results in any study of the relation between the concentration of alcohol in the blood and the resulting effects, it is necessary to take into consideration the factors that control the distribution of alcohol in the body. Failure to do so has led to many misinterpretations in work of this kind. The factors that control the distribution of alcohol are essentially the same as those which I established for ethyl ether.[2]

The intoxicating and lethal effects of alcohol arise from its action on the brain. The concentration of alcohol in the brain depends upon that in the blood reaching the brain and the rate of circulation through the brain. The effects of alcohol correspond precisely to the concentration of alcohol in the jugular blood leaving the brain and are independent of the concentrations, higher or lower, that may be found in blood drawn from other parts of the body.

Complete equilibrium throughout the body, following intraperitoneal injection of a single large dose of alcohol in a rat, may take more than an hour; short of this equilibrium wide differences may exist in the venous blood drawn from various parts of the body, due largely to differences in rate of local circulation. Thus following the injection into a rat of 20 mg of alcohol per gram, a fatal dose, blood drawn from the jugular vein at the moment of death had 9.4 mg per cc, that from the femoral vein 6.3 mg per cc, the right heart 16.0 mg and the arterial 15.8 mg. We have found, however, that, regardless of excess of the dose given or of the time required to cause death by respiratory failure or of the concentration in the blood from the heart or peripheral veins, that in the jugular vein of fasting rats (blood sugar 0.1 per cent.) is at the moment of death always 9.0 to 9.8 mg per cc. The concentration of alcohol in the jugular blood thus affords a basis for comparison in the study of the influence of variation in blood sugar upon the lethal concentration of alcohol. It is one that is not influenced when the equilibrium of alcohol in the body is incomplete.

For confirmation of our determinations we have made measurements of dosage as well as concentrations. To do so it was necessary to develop a technique of administration by which a nearly complete equilibrium could be maintained throughout the body. Small but uniform doses of alcohol were administered intraperitoneally every 5 minutes over a period of several hours. Under the condition thus induced and maintained the concentration in the blood in all parts of the body is virtually uniform. Thus three measurable factors, time, dose and blood concentration, can be accurately determined. For the lethal effect of alcohol all three factors were found to be constant but constant only when the concentration of sugar in the blood is also constant.

The toxicity of alcohol is influenced inversely by the concentration of sugar in the blood. Thus when the blood sugar is reduced by prolonged fasting to 0.07 per cent. the lethal concentration in the blood is 8.0 mg per cc of blood; when the blood sugar is 0.1 per cent., as following a short fast, the lethal concentration is 20 per cent. higher, that is, 9.5 mg per cc. When the blood sugar is raised to 0.2 per cent. by forcing sugar the lethal concentration is 50 per cent. higher than that during starvation, that is, 12.0 mg per cc of blood. The amounts of alcohol that were administered under our technique to obtain these values are respectively 6.5, 7.75 and 11.0 mg per gram of rat. For intermediate values of blood sugar the lethal concentration of alcohol and the dose fall correspondingly between these limits. Very high concentrations of sugar, far beyond normal possibilities, obtained by injection of sugar do not increase the protective action and in some cases diminish it.

Similar experiments carried out with ethyl alcohol and with ether, which unlike ethyl alcohol are not appreciably burned in the body, showed that the concentration of sugar in the blood does not influence the lethal concentration of these substances. The presumption is therefore that the modifying effects of sugar upon the action of alcohol is in some way connected with the combustion of alcohol in the tissues.

The alcohol used in these experiments was commercial spirits, common grain alcohol. We have made additional tests with highly purified alcohol and with

[1] Read before the National Academy of Sciences, Washington, D. C., April 26, 1937.

[2] H. W. Haggard, *Jour. Biol. Chem.*, 59: 737–802, 1924.

some beverage alcohols. The lethal concentration in the blood is the same for all we have tested, but there is considerable difference as between alcohol from various sources in the dose required to produce this concentration, a fact suggesting a difference in the rate of oxidation.

Our observation that the concentration of blood sugar influences the pharmacological effects of alcohol may offer some explanation of the alleged idiosyncrasies in human reactions to alcohol. It affords a new factor that must be taken into consideration in any experimental study of the pharmacology of alcohol. Our technique of determining doses under conditions of equilibrium affords a method of making precise quantitative measurement of the toxicity of alcohols from various sources.

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THE OPERCULAR APPROACH TO THE PITUITARY[1]

SURGICAL techniques for the removal of the pituitary gland of teleosts have been described by Parker[2] in the catfish, *Ameiurus,* and by Matthews[3] in the killifish, *Fundulus.* These techniques are not quite satisfactory in experiments to be carried on over long periods of time, inasmuch as the operated animals survived only for a short time; the catfish surviving only two days, and the killifish several weeks. A new approach to the teleost hypophysis whereby tissue injury is reduced to a minimum has been worked out by the author with more satisfactory results.

(1) THE CATFISH

Parker's method of hypophysectomy consisted in making a U-shaped cut through the gular membrane from the opercular opening on one side to that on the opposite side of the animal, so that the lower jaw was completely separated from the gills. Having accomplished this initial opening, the operation was completed by puncturing a hole in the parasphenoid and sniping off the gland. This method involves a two-inch incision which may be avoided in the following manner. The catfish is wrapped in a wet cloth and placed on its back under a binocular microscope. The mouth is held open by five retractors, and an incision about two to three millimeters in length is made through the mucous membrane covering the parasphenoid bone. A trephine drill is then introduced under the operculum and between the first and second gill arches. One merely lifts the operculum and gently separates the first from the second gill arch. This procedure exposes a wide natural cavity, and the drill may now be inserted directly perpendicular to the roof of the mouth. The hypophysis can be seen through the bone as a small yellow spot. A hole (1.5 mm in diameter) is drilled through the bone, the gland sucked up in a pipette, and the wound closed by a single suture through the mucous membrane. The operation can be performed virtually without the loss of a single drop of blood and need not take over three minutes. The animal is returned to a tank of running tap water and survives for many months. Within a week, the suture disappears and the cut membrane heals over completely.

(2) THE KILLIFISH

Matthews's method of hypophysectomy involved a sub-oral route, since he first made a V-shaped incision through the branchiostegal membrane with the base of the V at the tip of the tongue. The tongue was then pulled sufficiently ventral to expose the region of the pituitary. My operations with the sub-oral route proved unsatisfactory mainly because of the size of the initial incision, and the necessary cutting of a large blood vessel running along the ventral surface of the lower jaw. These two difficulties may be avoided by the opercular approach. The fish, first immobilized by immersion in cracked ice, is placed on its left side under an operating microscope. The operculum is elevated and held by a single retractor. The first and second gill arches are separated, thus exposing a wide space directly below which the hypophysis is located. A three-millimeter incision is made through the epithelial membrane slightly lateral to the mid-line in order to avoid a median artery. A hole is drilled with a trephine drill (1 mm in diameter) and the gland sucked up in a pipette. The wound is not closed by a suture because of the proximity of the median artery, but the circular piece of bone excised by the drill may be replaced to close the wound. The operation may be performed within five minutes and if done with sufficient care is a totally bloodless operation. The animal is placed in salt water for a day and then transferred to running tap water, as Matthews recommends, or it may be placed directly in tap water at room temperature.

This approach to the pituitary gland under the operculum and between the first and second gill arches may prove satisfactory for other teleost fishes.[4]

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[1] Aided in part by a grant from the National Research Council Committee on Problems of Sex administered by F. L. Hisaw.

[2] G. H. Parker, *Jour. Exp. Zool.,* 69: 199, 1934.

[3] S. A. Matthews, *Biol. Bull.,* 64: 315, 1933.

[4] Smith, Burr and Ferguson (*Endocrin.,* 19: 409, 1935), describe an orbital approach for hypophysectomy in the goldfish. These authors state, however, that their operative procedure involves enucleation of the right eye, severe traumatization of the interorbital plates, invariable rupture of an artery, blind groping for the hypophysis, traumatization of the hypothalamus and successful extirpation in one of seventeen cases.