A series of studies were made upon the rate of oxidation, simultaneously and under identical conditions, of α-methyl glucoside, β-methyl gentiobioside, *Leuconostoc mesenteroides* dextran (*7*) and *Leuconostoc dextranicum* dextran (*6*). In all cases the rate of reaction was almost identical and the equivalent for the first two substances agreed closely with the calculated value. *L. mesenteroides* dextran was found to have an equivalent of 204, i.e., 1.25 × theory. Thus from 5 glucose units only four yield formic acid or, in other words, 1 unit in five is engaged in side branching. This evidence indicates a structure:

$$G^1 - {}^6G^1 - {}^6G^1 - {}^6G^1 - {}^6G^1 - \\ {}^4| \qquad \text{(I)}$$

[G represents a glucopyranose unit and the superscripts, the points of attachment] proposed by Fowler *et al.* (*4*) on the basis of methylation studies, by which it was shown that the molecule consists entirely of glucopyranose units. The following partly methylated sugars were isolated: 2 : 3 dimethyl methyl glucoside, (one part 22.6%), 2 : 3 : 4 : trimethyl methyl glucoside (three parts 57.9%) and 2 : 3 : 4 : 6 : tetramethyl methyl glucoside (one part 19.6%).

On the constitution of the dextran from *L. dextranicum*, there has been some divergence of opinion (*2, 3, 6*) concerning the significance of the amounts of tetramethyl and dimethyl methyl glucosides obtained from the hydrolyzed methylated polysaccharide. Evans and Hibbert (*2*) suggested that the quantity of dimethyl sugar was excessive, due to incomplete methylation of the material. Fairhead, Hunter, and Hibbert (*3*) identified in their hydrolyzate, 2 : 3 : 4 : trimethyl methyl glucoside (four parts, 90%), and a dimethyl methyl glucoside (one part, about 10%). Peat, Schlücterer and Stacey (*6*) detected 0.23% of 2 : 3 : 4 : 6 : tetramethyl methyl glucoside in their material in addition to 2 : 3 : 4 : trimethyl methyl glucoside (four parts, 90%) and 2 : 3 : dimethyl methyl glucoside (one part, about 10%).

By periodate exidation, the equivalent of this dextran was 187, i.e., 1.15 × the theoretical value. This would indicate that at least one glucose residue in eight is engaged in branched chain formation, and this is in accord with the structure II proposed from the methylation data.

$$G^6 - {}^1G^6 - {}^1G^6 - {}^1G^6 - {}^1G^6 - {}^1G^6 - {}^1G^6 - {}^1G \\ {}^4| \qquad \text{(II)}$$

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The Potentiating Effect of Glucose and Its Metabolic Products on Barbiturate Anesthesia

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In July 1944, we studied shock from hemorrhage, using a large number of dogs, most of them anesthetized with pentobarbital sodium (nembutal) given intravenously early in the morning. The dogs were then bled and various procedures carried out on them during the day. Most of these dogs recovered slowly from the anesthetic in the evening. On one occasion, when we were about to inject glucose (10 ml of a solution of 50 g glucose dissolved in 100 ml of water) intravenously, the dog suddenly came out of anesthesia. The animal responded normally when spoken to and tried violently to get off the table. It was with difficulty that the intravenous injection of glucose was made. Instantly the dog relaxed, going into deep sleep and complete anesthesia exactly as after an injection of a barbiturate. The result was so striking that when the dog again recovered suddenly, an hour later, a fresh glucose solution was injected. This produced the same effect, that is, immediate sleep and anesthesia which, however, lasted only 45 min. The dog then went through this cycle of sudden awakening and then immediate sleep and anesthesia after an injection of glucose. The duration of sleep after each glucose injection was 1 hr, 45 min, 30 min, 20 min, 10 min, and 5 min, respectively. Then further injection of glucose produced no sleep, the dog remaining awake and, if anything, hyperexcitable.

In several dogs similar results were seen, but others treated in the same way recovered slowly from the anesthetic and did not go to sleep again after glucose was injected.

This observation was reported to the Office of Scientific Research and Development Committee on Shock, but the work they had been supporting was discontinued and considerable time passed before it was taken up again.

At first we associated this phenomenon with shock, or the extremely high temperatures which occurred in our dogs at this time, when the temperature of our laboratory was well over 100° F. Later, in studying approximately 100 dogs, shock and artificially produced high temperature were eliminated as factors producing the reaction, and it was found that a small percentage of normal dogs given pentobarbital sodium or hexobarbital soluble (evipal) reacted to the subsequent intravenous injection of glucose on awakening, as our shocked dogs did. An occasional dog reacted as strikingly as our first dog. Others reacted little or not at all to the injection of glucose. Because we were unable to reproduce this reaction at will, its study was greatly hindered.

[1] Funds for carrying on this work were kindly supplied by the Mallinckrodt Chemical Works.

Finally, in 1948, guinea pigs were tried, using hexobarbital intraperitoneally as the anesthetic. On awakening, the animals were given glucose, also intraperitoneally. Practically 100% of the guinea pigs responded with a return to sleep after awakening from hexobarbital, when 1 ml of glucose solution was injected intraperitoneally. Rats do not behave in the same way; rabbits and hamsters do, but with more delay in the onset of anesthesia after glucose.

As yet we have not developed an accurate quantitative method for studying this reaction. Guinea pigs were given a dose of hexobarbital intraperitoneally, 0.20–0.25 ml of a 2% solution per 100 g of pig. They went to sleep in about 2 min and slept for about 45 min but varied considerably in time of awakening. When the pig was definitely awake and responded to stimulation, but before it could run around, glucose, or whatever substance was being studied, was given intraperitoneally. The pig usually responded instantly or within 5 min, and went to sleep on its side. It would at first respond slightly to a pinch of the foot by squealing, but more violently if the back of the neck was pinched. After 5 min, there might be no reaction of any sort after pinching the foot or neck. In about 45 min, the pig woke up and often could be put to sleep by a second dose of glucose. If too long a time passed before the second injection was made, there was no response.

At present our best criterion of effect from the injection of a given substance is the return to sleep and anesthesia after awakening from the hypnotic. The duration of sleep is too variable for quantitative work unless large numbers of animals are used. After hexobarbital over 30 pigs have responded to the intraperitoneal injection of 1 ml of 50% glucose and only a rare pig has failed to respond, although the degree of response varies. They have responded well to the injection of 5% glucose in doses of as much as 10 ml in a 500-g pig and as little as 1.25 ml or approximately 12 mg/100 g of pig. The injection of glucose alone causes no sleep or anesthesia.

That this is not an osmotic effect is shown by the fact that solutions of sucrose, as well as of sodium chloride of the same tonicity, do not produce such an effect. We have obtained this reaction to glucose after hexobarbital, narconumal, seconal sodium, and pentothal sodium; but have obtained no such reaction to glucose after ether, chloral, or chloralose. We have found that intermediary products of glucose metabolism such as hexose diphosphate, lactate, pyruvate, succinate, and fumarate, as well as malonate, and the water extract of both brewer's and baker's yeast produce the same effect, some more strongly than glucose. Sucrose, as already stated, produces no such effect; arabinose only a slight effect; and galactose and levulose a definite effect, but less than glucose.

To observe this reaction, inject a guinea pig intraperitoneally with a 2% solution of hexobarbital soluble (0.25 ml/100 g of pig). This will cause sleep for about 45 min to an hour. When the pig wakes up and responds well to pinching, but before it can run, inject 2 ml of 50% sodium lactate (Mallinckrodt) (0.1 ml is effective). This has consistently produced such a pronounced depression that there is no doubt about the result. The same reaction is produced regularly in dogs by lactate, malonate, or succinate.

As far as we are aware, the observations given here have not been reported before, although the literature on the relationship between glucose and its metabolic products to anesthesia is enormous and sometimes conflicting. Our results in dogs show very wide variation in response to glucose after barbiturate anesthesia; the great difference of reaction in animal species might account for this. Our results are qualitative only, excessively large doses having been given at times to insure a reaction of an active substance. The effect of each compound used has, however, been controlled by injection of a corresponding amount of the substance in a normal animal without anesthetic; such injection has in no case produced depression.

After this article had been written, it was found that, although the duration of hexobarbital anesthesia did not seem to be greatly changed by the simultaneous administration of glucose or its degradation products, in the few experiments tried, these substances greatly affected the dose of hexobarbital necessary to produce anesthesia, lowering it roughly from 0.15 ml of 2% hexobarbital solution to 0.01 ml when 2 ml of 50% sodium lactate was given at the same time. The potentiating effect of glucose was striking, but less than that of lactate. Pigs which showed no response to a subanesthetic dose of hexobabital went to sleep at once after the injection of glucose or lactate.

It would therefore appear that we have been dealing with a potentiation of barbiturate anesthesia by glucose and its metabolic degradation products and that the return to a state of hypnosis or anesthesia after waking from barbiturate sleep is probably due to a potentiating effect of these substances on the subanesthetic level of barbiturate in the blood.

Detailed reports of our work will be published later.