# Original Articles

## CAUSES OF HYPERGLYCÆMIA DURING OPERATION*

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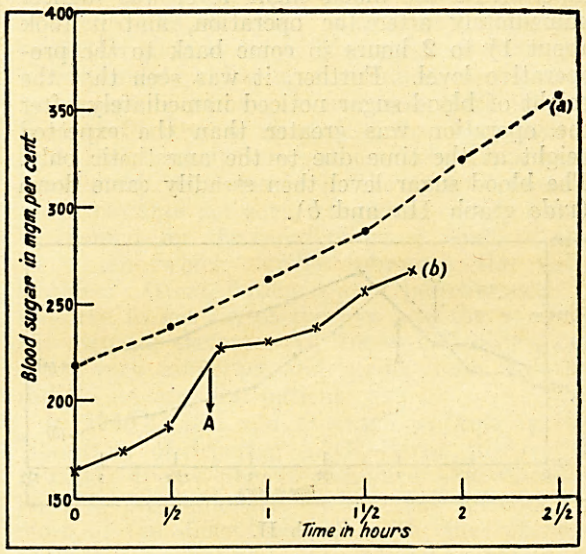
ADRENALINE hyperglycæmia is a physiological response at times of emergency. Blum (1901) was the first to note that adrenaline produces glucosuria. The immediate source of sugar of the blood is the liver glycogen.

A rise in blood sugar has been observed during surgical operations under anæsthesia. Cantarow and Gehret (1931) attributed the rise of the blood sugar level to the increased hepatic glycogenolysis, due either to the direct action of the anæsthetic used, or to increased hydrogen ion concentration associated with ether anæsthesia. Swan (1911) and Atkinson and Ets (1922) had shown that ether anæsthesia is always associated with hyperglycæmia in normal animals. Minnitt (1932) showed that a much greater hyperglycæmia was produced by ether than by nitrous oxide, and in a number of cases the blood sugar which was normal before anæsthesia rose to more than 200 mg. per cent after the operation. He showed that the blood sugar rose by variable but definite increments, and that it was much higher at the end of the operation than at the beginning; after the operation was finished there was a fall. He showed that in one of his cases the blood sugar was 178 mg. per cent after 5½ hours and 111 mg. per cent after 48 hours. He showed that the rise of blood sugar was irrespective of the method of anæsthesia, and obtained a rise of blood sugar with local and spinal anæsthesia as well. He concluded that the anæsthetic, or something associated with the operation if performed under a local anæsthetic, by stimulating adrenal bodies produced hypersecretion of adrenaline into the system. The production of hyperglycæmia by anæsthetics, whatever might be its cause, has been proved beyond doubt.

Now, the question is whether all the rise of blood sugar during operation can be accounted for by the anæsthetic used. This investigation has been undertaken with a view to ascertaining the exact cause or causes of the rise of blood sugar which is always found at the end of the operation. In order to study this matter it was considered desirable to use an anæsthetic which would give a uniform and steady result when given in accurate doses, and whose effect would last for a fairly long time, at least till the experiments were over, because it has been shown by De (1946) that the rise of the blood sugar varies directly with the depth of anæsthesia. It was, therefore, decided to use urethane, 2 gm. per kilo body-weight of the animal, by the intramuscular route in every case except where otherwise stated. Cats were used in these experiments, and all operations were done three hours after the administration of urethane, when the animals were definitely anæsthetized.

Urethane anæsthesia produced a progressive and steady rise of blood sugar; a typical curve has been shown in graph I(*a*). The rise of blood sugar was, in every case, practically linear all through, except towards the end when the rise was more sharp in some of the cases. This rise, due to the anæsthesia, naturally complicated the determination of other possible factors, which also might be responsible for the rise of blood sugar. In order to determine the exact rôle of the operative interference on the blood sugar, it was, therefore, decided to perform two series of experiments which involved both simple and extensive operative interference. In the first series, three hours after the injection of urethane, samples of blood were drawn from the femoral vein of cats at 15-minute intervals, with the least possible operative interference, to determine the level of the rise of blood sugar during that period. These results, when plotted, indicated the level of the rise of blood sugar due to urethane only, and prolongation of this line practically indicated the level of the blood sugar at the particular moment. Then several operative measures




Graph I.

(*a*)—Hyperglycæmia under urethane.
(*b*)—Urethane anæsthesia. Effect of operation on the blood sugar level.
A—Period for operation. Note the rise in blood sugar level.

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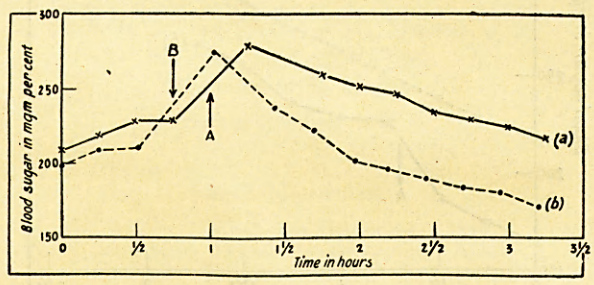
such as opening the femoral vein, putting in the tracheal cannula, exposing the carotids, etc., were done in the same animal. The blood sugar of the sample taken immediately after the operation was observed to be always higher than the expected blood sugar at that time due to urethane anæsthesia only (*vide* graph I*b*).

In the second series of experiments, preparations were made in which the steady rise of blood sugar normally seen under urethane was avoided. Anæsthetized cats were decerebrated at a low level in order to destroy the posterior hypothalamic nucleus, or decerebrated behind the level of this nucleus (De, 1946) or completely transected at the upper cervical region in order to produce hypoglycæmia after the operation. These procedures themselves involved a fairly extensive operative interference on the top of the anæsthetic used. It was noticed that though the blood sugar dropped after this operation, yet it did not come to the pre-operative level immediately. In all these experiments the blood sugar level was highest immediately after the operation, and it took about 1½ to 2 hours to come back to the pre-operative level. Further, it was seen that the height of blood sugar noticed immediately after the operation was greater than the expected height at the time due to the anæsthetic only. The blood sugar level then steadily came down (*vide* graph II*a* and *b*).

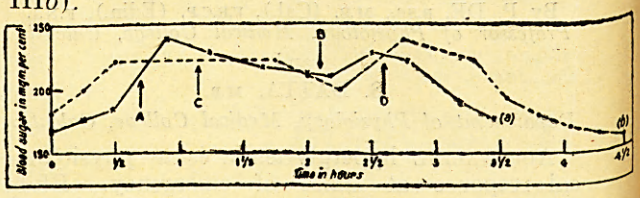



Graph II.

(*a*)—Blood sugar level in spinal preparation done under urethane.
A—Period for operation. Note the rise of the blood sugar level.
(*b*)—Blood sugar level in decerebration at the colliculo-mamillary plane done under urethane.
B—Period for operation. Note the rise of blood sugar level.

In both these series of experiments, the 'excess' rise of blood sugar above the expected rise due to the anæsthetic must be attributed to factors other than the anæsthetic used. Can this 'excess' rise be due to the stimulation of the sympathetic and liberation of adrenaline?

Experiments were therefore performed in animals in which the sympathetic activity and the hyperglycæmic action of adrenaline were abolished with ergotoxine. In cats anæsthetized with urethane 10 mg. of ergotoxine were injected intravenously in repeated small doses. Such cats showed a fall of blood sugar after ergotoxine but when decerebration was done at the colliculo-mamillary plane described by De (1946) on such ergotoxinized animals, a rise of blood sugar was still observed immediately after the decerebration, though this rise was less than that observed in similar experiments done without ergotoxine. This rise was followed by a steady and persistent fall (*vide* graph III*b*).




Graph III.

(*a*)—Blood sugar level after spinal preparation.
A—Period for operation.
B—Left femoral vein opened and right axillary region dissected.
(*b*)—Blood sugar level after decerebration at the colliculo-mamillary plane in ergotoxinized cat under urethane.
C—10 mg. of ergotoxine injected in 75 minutes.
D—Period for decerebration.

The next question was to determine whether the peripheral nervous mechanism had any influence on the production of the hyperglycæmia due to operative interference. The spinal cord was transected at the level of the upper cervical region under chloroform and ether anæsthesia so as to remove the influence of the higher centres. In these animals operative measures, such as opening the femoral vein and dissection in the axillary region, after the effects of the previous operation of spinal transection had passed off, produced a transitory rise of blood sugar, after about 20 to 25 minutes. No rise of blood sugar was observed immediately after the operation (*vide* graph III*a*). A similar but more transient and smaller rise was produced in the ergotoxinized animals after similar operation following decerebration at the colliculo-mamillary plane.

*Discussion.*—A rise of blood sugar has always been observed after operations under general anæsthesia (De, 1946). The effects of fright, anxiety, emotional excitement, etc., before the anæsthesia, being so well known, have not been considered here. It has been shown in graph I(*a*) that urethane produces a steady rise of blood sugar, the rise being more or less linear in character throughout, except towards the end, when the rise is more sharp. So the 'excess' rise of blood sugar above that due to anæsthesia must be attributed to some cause or causes other than that of anæsthesia. It has been observed in experiments cited before (graph II*a* and *b*) that any operative interference under general anæsthesia produces a greater rise of blood sugar than that due to anæsthesia alone. So the cause of this 'excess' rise must, therefore, be attributed either to the effect of the operation or to some other cause.

The operation itself stimulates the nerve endings at the site of the operation and supplies an impulse by which the centre is reflexly stimulated to liberate adrenaline which produces a high blood sugar. Also it has been observed that in ergotoxinized cats, decerebration produces a smaller rise of blood sugar immediately after the operation. It is known that ergotoxine inhibits the sympathetic activity and abolishes the hyperglycæmic action of adrenaline, and also it has been observed that ergotoxine produces a fall of blood sugar in urethanized cats. Therefore, the difference in the rise of blood sugar observed between these two experiments, done with and without the administration of ergotoxine, must be due to the stimulation of the sympathetic nerve endings at the site of the operation. Any rise that is noticed after ergotoxine cannot be due to reflex secretion of adrenaline, but must be due to a cause or causes other than anæsthesia or stimulation of sympathetics from the operative interference.

Now, the question resolves itself into one of finding out the cause of the rise of blood sugar noticed after the operation following ergotoxine. In experiments on spinal cats, it has been shown that any operative interference in these animals is followed by small transient rise of blood sugar which appears after a fairly long latent period (graph III*a*). A similar but smaller rise of blood sugar after a fairly long latent period has been observed in ergotoxinized cats when the same operations were performed, following decerebration at the colliculo-mamillary plane. This long latency precludes the possibility of its being reflex in origin, and favours the idea that it is possibly metabolic in nature. The high blood sugar that has been observed in Minnitt's case after 5½ hours and 48 hours also suggests that it is due to metabolic disturbance.

It therefore appears clear that all the rise of blood sugar observed after operation should not be attributed to effects of the anæsthesia alone, but that the operative interference itself plays a fair part in it.

*Summary.*—The rise of blood sugar immediately after the operation is due to (*a*) the effect of the anæsthesia, (*b*) the stimulation of the sympathetic nerve endings due to the operative interference and (*c*) the metabolic activity.

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## PHENIODOL : A NEW DYE FOR CHOLECYSTOGRAPHY

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IN the year 1924 Graham and Cole were able to visualize the gall-bladder for the first time by the intravenous injection of tetrabromophenolphthalein. Soon after this, iodine was substituted for bromine as the former has nearly twice the atomic weight of the latter. Later, the acid sodium salt of tetraiodophenolphthalein was found to be the best, and its oral administration for cholecystography has been the method of choice until very recently.

The results obtained with tetraiodophenolphthalein show a very high degree of accuracy. Unfortunately, this dye produces unpleasant symptoms in some patients, and since 90 per cent of the dye is eliminated by the gastro-intestinal tract it very often obscures the gall-bladder by its presence in the hepatic flexure. Some patients get severe diarrhœa which is accompanied by the production of wind in the large gut which further obscures the gall-bladder. Great patience and perseverence is required to get rid of the dye and the wind in the hepatic flexure. All these difficulties are often very annoying and tiring both to the radiologist and the patient.

In 1940 Dohrn and Diedrich working in the laboratory of Schering A. G., Berlin, discovered a new dye—a-phenyl-(4-hydroxy-3:5-di-iodophenyl) propionic acid—which has surmounted most of the difficulties met with the phenolphthalein compound. The Germans called it 'Biliselectan.' As soon as papers giving information about this compound reached the allied countries, experiments were made and details perfected in the manufacture of this compound. The Medical Research Council gave it the official name of 'Pheniodol.' In the United States of America it has been named 'Priodax.' It is a white odourless powder, soluble in alkali, ether, alcohol and acetone, but insoluble in water. It is very bitter to the taste, but this bitter taste can be masked. It is sold as pheniodol powder, pheniodol meal and pheniodol sugar-coated granules, and in U.S.A. as priodax tablets. This dye is given by the oral route only. Most of it is excreted by the kidneys.

I have used this dye in 35 patients. Only four patients complained of a bitter burning taste and this also only on interrogation. Two patients vomited after pheniodol. Both were very weak and emaciated. Sixteen patients showed a very mild diarrhœa usually with a