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THE ADRENALS AND ANÆSTHETIC HYPERGLYCÆMIA.

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The object of this work was to indicate the rôle of the adrenal glands in increasing the blood sugar p.c. (glycæmic response) during anæsthesia. Elliott [1912] stated that all the ordinary conditions of anæsthesia with ether, chloroform, and urethane were attended by exhaustion of adrenaline. Rogoff and Stewart [1920] from a large series of experiments and Burn [1915] from adrenalectomy experiments during anæsthesia claimed that the hyperglycæmia associated with anæsthetization in cats was not dependent on the adrenals. Macleod [1926] wrote in favour and Evans, Tsai and Young [1931] cited four experiments indicating their connection in the course of their work on liver glycogen. A general objection, however, can be taken to conclusions based entirely on the results of operations on the adrenals, the adrenal medullas or their nerve supply on the ground that the animals so treated were not normal or were largely incapable of showing the usual reactions of intact animals to anæsthetics.

Methods.

Three methods were used, operative, indirect and comparative, to determine the glycæmic response to anæsthetics in rabbits fed on the standard laboratory diet. The open method of anæsthetization was preferred. The aim was to select rabbits which took the anæsthetic well, and those animals were discarded which resisted and struggled during one or two trial inductions.

Operative method.

A series of thirty rabbits of about 1·5 kg. was prepared by two-stage aseptic operations under open etherization which aimed at decreasing or immobilizing the available adrenaline by double adrenalectomy (ten), unilateral adrenalectomy with contra-lateral medulliadrenalectomy or

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denervation and decapsulation (ten), and double medulliadrenalectomy or double denervation and decapsulation (ten). These three groups of rabbits have been designated A.A., A.M. and M.M. respectively. The interval between operations was not less than 14 days.

The glands were exposed through the lumbar extra-peritoneal route and removed after ligation of the blood vessels.

Medulliadrenalectomy was carried out by curetting or cauterizing the medulla after puncturing the gland with the scalpel point. Curettage was ultimately the method of choice, as in one or two cases the cortex had apparently been damaged by heat—as judged by the after-history of the animals. From the beginning of etherization to skin suturing occupied about 30 min. as a rule. There was no sepsis in the series. The essential point in post-operative treatment was to keep the animals warm, but precautions against exposure to cold were necessary only for a few weeks at night during the cool season in India.

The glycæmic response to open etherization was determined during the post-absorptive period (16 hours' fast) by repeated tests at intervals of several days (4 or 5) before operation. Blood samples for sugar estimation [Hagedorn and Jensen, 1923] were taken from the marginal ear vein before etherization, after induction (5 to 7 min.) and at end of 30 min. surgical anæsthesia. Blood-sugar records for the operations were also made.

Weight records were kept throughout and blood concentration was studied by specific gravity readings (chloroform and benzene method), r.b.c. counts and Hb p.c. determinations (colorimetric method). Notes on the cardiac action and rate were made, as determined by palpation during the experimental anæsthesia.

Results (Fig. 1). During surgical etherization for 30 min. the increase in blood sugar was invariably greatest in the intact rabbit, slightly less after the first and least after the second operation.

The glycæmic response of those A.A. rabbits with signs of adrenal insufficiency was noticeably small, and very small 2 or 3 days before death.

The glycæmic response of the A.A. rabbits which survived for long periods in good health was slightly less than for the A.M. and M.M. groups.

The fasting blood-sugar level was low (40–60 mg./100 g.) in those rabbits with signs of adrenal insufficiency.

In the remaining groups of double operated rabbits the average fasting blood-sugar level was about 85–90 mg./100 g. as compared with 105–115 mg./100 g. for the intact animals.

Further differentiation of the A.M. and M.M. groups was not justified, as the difference in the average fasting levels of intact and single operated rabbits was small and less than the "probable error" obtained on statistical investigation.

In the A.A. rabbits which died of adrenal insufficiency the loss of weight was progressive and averaged 20 p.c. at death. In the other

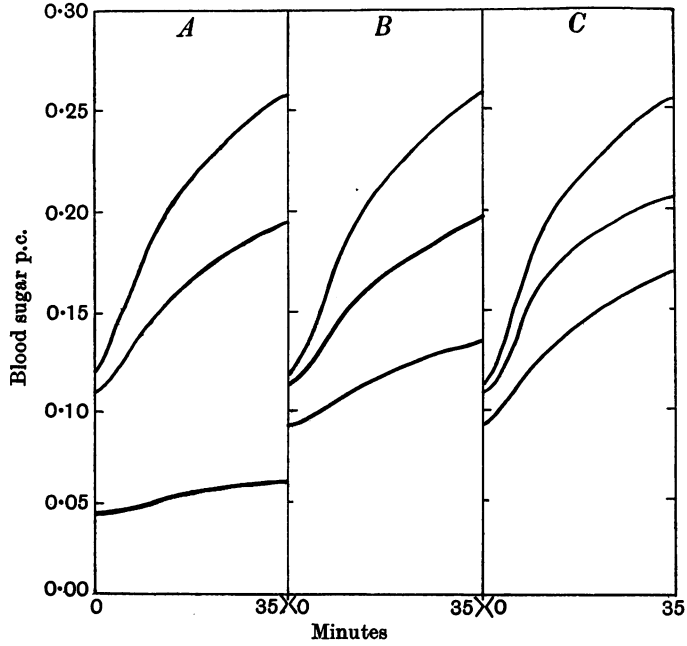

Fig. 1. Effect of ether anæsthesia on blood sugar. Ether begun at 0 min. Uppermost lines in *A*, *B*, *C* are for intact, middle for single operated and lowest for double operated rabbits. *A* = A.A. rabbits which developed signs of adrenal insufficiency. Each graph is mean of six experiments on three rabbits. *B* = A.A. rabbits which survived without signs of adrenal insufficiency. Mean of fourteen experiments on seven rabbits. *C* = A.M. and M.M. rabbits. Mean of forty experiments on twenty rabbits.

groups the weight decreased slightly after the operations but remained more or less steady thereafter.

Discussion. Some but not all A.A. rabbits showed signs of adrenal insufficiency. This was clear from results in a series of thirty rabbits adrenalectomized by the above two-stage method and retained for observations summarized elsewhere [Reid, 1932]. Three died within a day or two after the second operation, probably from extrinsic causes, nine died between the 9th and 17th days, and eighteen were living more

than 30 days after the second operation, apparently in good health. Therefore 60 p.c., or if we exclude deaths within a day or two, 66 p.c. survived for long periods. This result may be correlated with Kojima's [1929] detection of accessory adrenal tissues in 70 p.c. of normal rabbits, although the number of our rabbits (thirty) is small.

Adrenal insufficiency was shown by a steady fall in weight, hæmoconcentration, slow and feeble heart action during etherization and low blood-sugar level. Four rabbits from the operated groups were killed for liver glycogen estimation. It seemed from these few results that continued fall in body weight after the second operation indicated low liver glycogen. Muscle glycogen was not studied. Weight records were relied upon as an index of the general well-being of the operated animals.

Results got from rabbits which showed early or, after a few days, obvious signs of adrenal insufficiency are not admissible owing to the presence of disturbed general or carbohydrate metabolism, indicated by the decreasing body weight and fasting blood-sugar level. As M.M. rabbits survived for long periods apparently in normal health, it seems that the adrenal cortex is concerned with general and, indirectly at any rate, with carbohydrate metabolism.

Results are admissible from A.A. rabbits surviving for long periods apparently in good health, but the possible influence of decreasing the available cortical tissue by operation must be considered. This point is met by results from M.M. experiments. But the decreased glycæmic response of these rabbits might still be due partly to decrease of those circulatory and other adjustments normally seen in anæsthetized intact rabbits.

In the A.A. rabbits with signs of adrenal insufficiency the heart rate during anæsthesia was easily counted on palpation, and was much less than for the normal anæsthetized animals. Our data from the other double-operated rabbits indicated some decrease as compared with the normal during anæsthesia. If we postulated even a moderate decrease, this might explain partly the decreased glycæmic response. Accurate data were not available, in our form of experiments, on the effect of variations in the general and liver circulations of intact animals in increasing the blood sugar during a period of active glycogenolysis. In the course of later experiments on dogs the increases in blood sugar p.c. and pulse rate were found to be approximately contemporaneous during and after anæsthetization with ether or chloroform.

With the usual anæsthetic dose of amytal, on the other hand, blood sugar p.c. and pulse rate remained more or less steady, and Murphy

and Young [1932] found least fall in liver glycogen with amytal of the anæsthetics tried. Another factor that occurred to us as having some relation to the circulation through the liver was the respiratory rate. The action of the respiratory muscles appeared weak in A.A. rabbits with slight signs of adrenal insufficiency, but not in the other groups. The relation of this to the decreased glycæmic response in the former is doubtful. In one dog the resting respiratory rhythm was halved during amytalization and doubled during etherization. It would be difficult to determine what effect variations in respiratory rhythm had on the liver circulation in the intact animal and consequently *per se* on blood sugar p.c. under different experimental conditions.

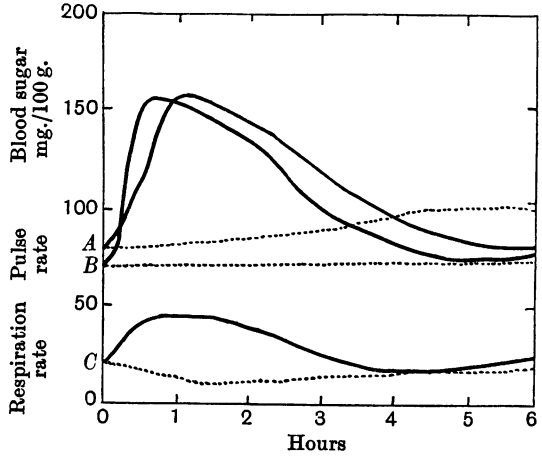

Fig. 2. Effect of ether (solid lines) and amytal (broken lines) on blood sugar (mg./100 g.) (*A*), pulse rate per min. (*B*), and respiration rate per min. (*C*). Etherization, begun at 0 min., lasted 1·5 hr. Amytal at 0 min. Mean of eight experiments on dogs.

It should not be understood that the above is put forward here as accounting for the different effects of ether and amytal, but as an indication of factors to be considered in assessing the results of anæsthetics on blood sugar p.c. in intact and operated animals.

In cases of interference with medulliadrenal function Britton, Calvery and Geiling [1928] have shown that the complete suppression of adrenaline secretion by evacuation of the medulla in cats resulted in a marked increase in sensitivity to insulin injection, although the hepatic glycogen reserves were maintained at practically normal levels. Such increased sensitivity to insulin offers a possible explanation, but perhaps not a likely one, of the decreased glycæmic response to anæsthetics

obtained in the operated groups, if an increased insulinæmia is postulated as occurring during anæsthesia or in association with the rise in blood sugar. In view of the above considerations further tests were made on intact animals in the indirect and comparative methods.

A preliminary conclusion is made that the adrenals play a part in producing anæsthetic hyperglycæmia.

Indirect method.

The indirect method consisted in using combinations of anæsthetics or narcotics. It comprised the study of the glycæmic response of normal and amytalized animals to (1) ether, (2) morphine narcosis, (3) adrenaline. Most of the experiments under (1) were done on dogs. Chloroform was also used instead of ether in both rabbits and dogs.

(1) The concentration of ether and optimal respiratory rate necessary to maintain surgical anæsthesia by the "Ideal" respiration pump were determined for normal tracheotomized animals of nearly the same weight as those used for the remaining experiments. Dogs were nearly 10 kg. and rabbits 1·5 kg.

The glycæmic response to ether was determined during 2 hr. surgical anæsthesia in eight dogs and two rabbits by repeated tests. After a week's interval amytal (B.D.H. Ltd.) was injected intraperitoneally (dog 60 mg. per kg.; rabbit 50–80 mg. per kg.). After anæsthetization in 10–30 min. tracheotomy was done and ether administered for 2 hr.

(2) The minimal subcutaneous dose of morphine sulphate to produce in 1 hour an increase of at least 100 mg./100 g. in the blood sugar was decided for each rabbit. This varied between 10–20 mg. per kg. for different animals in the series used. After the usual interval the rabbit was anæsthetized by amytal and morphine given in the requisite dose for that animal. Tracheotomy and artificial respiration by pump were begun at the earliest sign of depression of the respiratory centre, if necessary. In some cases artificial respiration by hand was sufficient.

(3) Adrenaline (Parke, Davis & Co.) was used subcutaneously (0·15 mg. per kg.) in rabbits.

The alkali reserve of the blood was determined in sixteen dogs during ether chloroform and amytal anæsthesia by van Slyke's method [1922].

Results (Figs. 3 and 4). Amytal inhibits partly the hyperglycæmia occurring normally in ether or chloroform anæsthesia in rabbits and dogs.

Amytal checked the normal glycæmic response to morphine more than that to ether or chloroform.

Amytal did not prevent adrenaline hyperglycæmia of the normal order.

The alkali reserve was decreased during ether or chloroform anæsthesia but not with amytal.

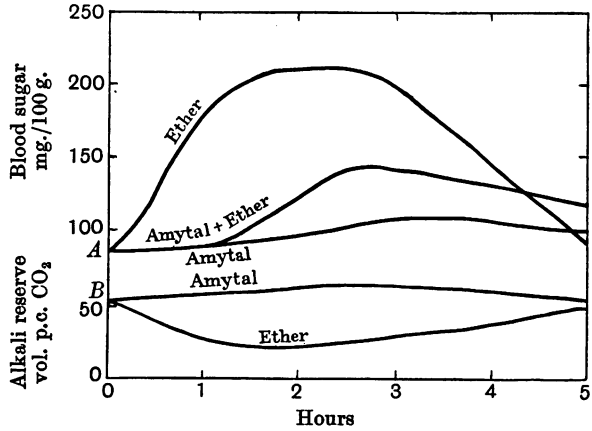

Fig. 3. *A*, Effect of ether, amytal and ether, amytal on blood sugar (mg./100 g.). Mean of eight experiments on dogs. Ether at 0 hr. for 2 hr. Amytal at 0 hr. and ether at 1 hr. for 2 hr. Amytal for 0 hr. *B*, Alkali reserve of blood (vol. CO_2 p.c.). Mean of eight experiments.

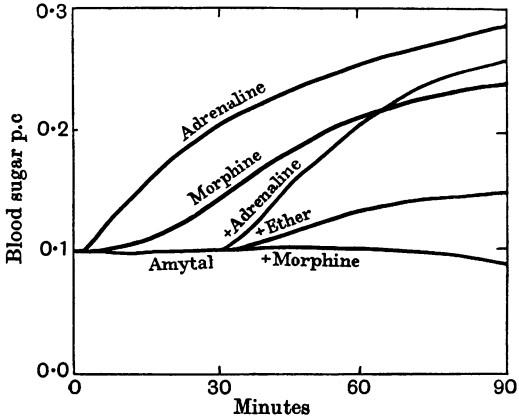

Fig. 4. Effects of adrenaline, morphine, amytal and adrenaline, amytal and ether, amytal and morphine on blood sugar. Adrenaline, morphine at 0 min., amytal at 0 min., followed by adrenaline and ether, morphine at 30 min. Mean of eight experiments on rabbits.

Discussion. Rogoff and Stewart [1922] admitted that the adrenals were directly concerned in morphine hyperglycæmia (confirmed by us) and were unable to correlate the size of the increase in blood sugar p.c. with the liver glycogen content of their intact and surviving adrenal-

ectomized animals. It is clear from our results that an amytalized rabbit showed adrenaline hyperglycæmia of the usual order. Since the glycæmic response to morphine was of negligible amount in the amytalized animal, it seemed probable that amytal inhibited the usual adrenalinæmia after morphine and, *a priori*, with ether or chloroform anæsthesia. The small decrease in liver glycogen in the course of 10–30 min. after amytal in anæsthetic dose [Evans, Tsai and Young, 1931] could not account for the markedly decreased glycæmic response to ether or chloroform.

As regards evidence of the presence of adrenaline in the blood the effect of serum from anæsthetized dogs was tried on rabbits' intestine suspended in a modified Tyrode solution in the Burn-Dale bath. Buckmaster and Gardner [1910] found that the concentration of chloroform in the blood of dogs was 0·03–0·04 p.c. after 1 hour's anæsthesia. To a known volume of bathing fluid was added a fixed amount of (*a*) normal dog's serum, (*b*) normal dog's serum plus 0·03 p.c. chloroform, (*c*) amytalized dog's serum, (*d*) anæsthetized (chloroform) dog's serum. The bathing fluid was changed after each addition of (*a*), (*b*), (*c*) or (*d*). Several experiments were done, the additions of serum not always being made in the same order. The slight definite decrease of tone and of the intestinal contractions was always more marked for (*d*) than for (*a*), (*b*) or (*c*). This result was suggestive, although the addition of dog's serum to rabbit's intestine introduced complicating factors.

Apart from their effects on blood sugar p.c., morphine and amytal differed in that the former caused a rise in body temperature of 1°–2° F. in many rabbits in the course of an hour, while the body of an amytalized rabbit under similar conditions (not on a hot plate) tended to cool.

Morphine hyperglycæmia was obtained in intact rabbits without very deep narcosis and without the struggling and disturbed respiration often associated with the induction period of ether. This suggests that hyperglycæmia could occur in anæsthesia probably through an adrenalinæmia not necessarily associated with the concomitant struggling and disturbance of respiration of the induction period.

Correlation between the rise of body temperature and blood sugar was lacking in the rabbits examined.

Comparative method.

Rabbits of approximately the same weight were given 0·15 mg. adrenaline per kg. body weight in the post-absorptive state and the glycæmic response noted at 10 and 60 min. If the increase in blood sugar was small, the same amount of adrenaline was injected after several days

in divided doses at different sites to eliminate the possibility of variation in the absorption rate. Two groups of rabbits were made, one showing a well-marked rise of at least 150 mg./100 g. and another showing a comparatively small rise of less than 100 mg./100 g. in blood sugar. Their blood-sugar increase to etherization was determined according to the usual routine.

Result (Fig. 5). The anæsthetic glycæmic response was greater in the group of rabbits which had shown previously a large increase in blood sugar in response to adrenaline than in the group less sensitive to adrenaline.

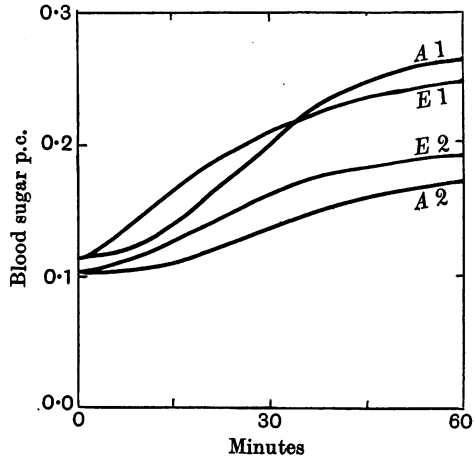

Fig. 5. Effect of ether (*E* 1; *E* 2) at 0 min. on blood sugar of two groups of rabbits which showed large and small adrenaline hyperglycæmias (*A* 1; *A* 2 respectively). Each graph is the mean of six experiments.

Discussion. The above result is taken as confirming that the adrenals take part in increasing blood sugar during surgical anæsthesia. Bose [1930], quoting the results of experiments by Acton and Bose on the alleged deterioration of insulin in India, stated that in rabbits of the same species but of different colours adrenaline caused a much larger increase in the blood sugar of the albino variety (Himalayan) than in either the black (Himalayan) or brown (Belgian hare) variety. The average increase in blood sugar in 1 hour after 0·15 mg. adrenaline was 146 mg./100 g. for ten albinos and 41 mg./100 g. for six Belgian hare rabbits. The actual increases in mg./100 g. noted by us were 88, 145, 123, 167, 66, 147 (mean 123) for six albinos and 57, 80, 143, 147, 58, 106 (mean 102) for six Belgian hare rabbits. The rabbits were chosen at random from the two species. This result suggests not that the sensitivity

of rabbits to adrenaline could be gauged by their colour, but that, in studying the relationship of the adrenals to experimental hyperglycæmias, clearer results would emerge from using animals proved sensitive to adrenaline injection from the size of the blood-sugar increase.

Summary.

1. The part played by the adrenal glands in increasing the blood sugar during 30 min. surgical anæsthesia has been investigated by three methods, operative, indirect and comparative. Rabbits mainly and, for some observations, dogs were used.

2. The anæsthetic glycæmic response of operated rabbits was less than for intact animals and markedly so for the double operated animals.

3. Points for consideration in regard to conclusions based only on results from operative methods have been indicated.

4. In the indirect method combinations of anæsthetics were used, *e.g.* amytal and morphine, amytal and ether or chloroform.

5. Amytal inhibited the usual hyperglycæmia occurring in ether or chloroform anæsthesia and in morphine narcosis, but not following subcutaneous injection of adrenaline.

6. In the comparative method the blood-sugar increase of anæsthetized rabbits sensitive to adrenaline has been compared with that for rabbits less sensitive and found to be greater.

7. The advisability of using animals sensitive to adrenaline in studies on the relationship of the adrenals to experimental hyperglycæmia has been indicated.

8. It is concluded that the adrenals are concerned partly in increasing the blood sugar during 30 min. surgical anæsthesia with ether or chloroform.

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