appendicitis was ultimately proved in cases in which our contributing doctors had sent the patients into the hospital with that diagnosis. In children the symptoms may vary rapidly, and many such cases appeared to have little the matter by the time they reached hospital, but when operated upon I nearly always found the appendix grossly and unmistakably diseased. Often the child will appear to be quite well and to have nothing but a little remaining tenderness over the appendix, and yet the appendix may be perforated and surrounded by pus.

In old people the peritoneum seems to lose its powers of natural resistance, and I am again satisfied that we should not postpone an operation because a patient probably suffering from appendicitis is aged. We should rather say that advancing age is a factor which prompts early operation. No one with any experience will overlook the fact that in the aged there are special difficulties in diagnosis: bowel growths, diverticulitis, and even prostatic mischief have not infrequently misled.

When appendicitis is a complication of pregnancy it demands early operation. The course of the pregnancy will seldom be interrupted by such intervention, and, in any event, whatever the risk so far as that is concerned, it is probably much less than the risk of a recrudescence of the disease nearer term, during labour, or immediately after. In my own experience I have only once had a patient abort, and I feel sure that was due to delayed intervention rather than to the actual intervention itself. The same applies to patients with heart disease, asthma, and pulmonary infections. In such cases local anaesthesia will often enable us to carry out life-saving operations with little anxiety.

I think we must admit that there may be a variation in the virulence of appendicitis, not only at different ages and in varying circumstances, but from time to time, depending perhaps on the seasonal variation in the organismal invasions of the gastro-intestinal tract. I was persuaded that in Northumberland there was some difference as between the country people leading a healthy open-air life and the town-dwellers, and I am quite prepared to hear that these differences are met with in other parts of the country. But these possibilities do not affect the general rule as to the necessity of prompt operative intervention.

The difficulty about all the plans which countenance delay in the surgical treatment of appendicitis is that they are apt to be abused, for the public and a certain section of the profession are only too ready to find an excuse for adopting any treatment other than operation. It is for this reason that I am afraid of any attempt at differentiation as between the cases which ought to be treated immediately by operation and those which may be left to a more convenient season.

Murphy used to deplore what he called "epidemics of so-called conservatism" in dealing with appendicitis, and I have myself often pointed out that the recurring advocacy of a waiting policy or delayed operation has almost invariably been followed by a wave of increased mortality.

Conclusion

Irrespective of interesting academic problems, I think it is essential that we should recognize that any acute condition of the appendix ought to be treated by operation without delay. I do hope that as the result of this discussion the message may once again go forth to the profession with no uncertain voice that appendicitis means operation, and that the earlier the operation the better the chance for the patient.

CARBOHYDRATE METABOLISM IN ANAESTHESIA: A REVIEW *

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The production of surgical anaesthesia by the administration of ether or chloroform is accompanied by various metabolic changes, among which may be mentioned a rise of blood cholesterol (Reicher, 1908 ; Ducceschi, 1919 ; Mahler, 1926), a rise of blood fat (Bloor, 1914), increased blood phosphate (Marenzi and Gerschman, 1934), a diminution of blood potassium (Marenzi and Gerschman, 1932), interference with water metabolism, leading to dehydration of the bodies of nerve cells (Barbour, 1931), and disturbance of the acid-base ratio of the blood (Stehle and Bourne, 1924). More than all these, however, certain aspects of the alterations in carbohydrate metabolism have received attention from clinicians and from experimental investigators. Of such changes the most striking and the most widely discussed is the hyperglycaemia fairly constantly produced by some forms of anaesthesia.

Changes in the Blood Sugar

That the administration of ether produces in the dog both hyperglycaemia and glycosuria was shown by Seelig (1905, 1906). Macleod (1913) stated that anaesthesia induced but slight changes in the blood glucose, and two years later Macleod and Pearce (1915) reported that ether actually produces a fall in blood sugar during the first half hour of ether narcosis. Ross and McGuigan (1915), however, measured the hyperglycaemia produced by ether and chloroform and, later, Ross and Davis (1921) attempted to distinguish between the mechanism whereby blood sugar is raised by the two drugs. Since then it seems to have been universally accepted that ether causes hyperglycaemia. Some observers—for example, Mahler (1926), Mackay (1928), Mackay and Dyke (1928), Minnitt (1932), and Hoppers (1933)—have recorded considerable increases in the blood sugar level, sometimes to more than 200 mg. per 100 c.cm.; others, such as Nakamura (1935) and Hasaura (1935), have not detected such large hyperglycaemic responses; whilst Pratt (1938) found that the effect of ether upon the blood sugar level may vary considerably from case to case, generally producing a moderate increase, sometimes not influencing it, and occasionally even producing a fall.

Much less information is available as to the hyperglycaemic potencies of the newer or less common anaesthetic agents. Acetylene (Fuss and Deura, 1932), ethylene (Hoppers, 1933), and nitrous oxide (Minnitt, 1932 ; Hoppers, 1933) all raise the blood sugar level, but not to the same extent as does ether. According to Prasad and Sen (1936) sodium evipan given intraperitoneally in the rabbit raises the blood sugar to a moderate degree, but the barbiturates, generally speaking (Heller and Nathan, 1933 ; Nakamura, 1935 ; Hasaura, 1935 ; Hrubetz and

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Blackberg, 1938), and avertin (Widenhorn, 1931; Nakamura, 1935) are thought to have little or no hyperglycaemic effect. It should be remembered, however, that the level of the blood sugar represents a dynamic equilibrium in which those factors tending to deplete it are balanced against those tending to replenish it, and that therefore the blood sugar level alone is not necessarily a simple or exact index of carbohydrate metabolism.

Action of Adrenaline

A good deal of experimental investigation has been directed towards discovering the mechanism of the production of hyperglycaemia by anaesthetic agents, and so many explanations have been offered that the subject has become confused rather than clarified. Shaffer (1914), for example, concluded that the partial asphyxia commonly produced during attempts to hurry induction was responsible, although King, Moyle, and Haupt (1912) had already shown that this could not be a complete explanation, because ether given intravenously also produces some degree of hyperglycaemia under conditions in which asphyxia is avoided. It is well known that asphyxia does cause hyperglycaemia—for example, Hospers (1933)—but it does not follow that hyperglycaemia must be due to asphyxia.

A more acceptable hypothesis which has gained some currency is that anaesthetic agents bring about the release of adrenaline into the blood stream from the suprarenal glands at an augmented rate, and that this increased concentration of adrenaline in turn accelerates the disintegration of liver glycogen, so mobilizing glucose. This is no doubt partly true (Browne and Evans, 1933; Vidal, 1933; Banerji and Reid, 1933), at any rate during the early stages of anaesthesia when excitation of the autonomic nervous system may be expected to occur. Nevertheless, Mekie (1931) found that in the rabbit the hyperglycaemia due to ether anaesthesia is not prevented by adrenalectomy or by the administration of ergotoxine or atropine. He concluded that the autonomic nervous system cannot be implicated and that the hyperglycaemia cannot be due to the mobilization of adrenaline. The evidence is, perhaps, not altogether conclusive, for atropine and ergotoxine do not entirely abolish all activity of the autonomic nervous system, and adrenaline may be mobilized elsewhere than in the suprarenal glands, but it is sufficient to emphasize the unproven nature of the hypothesis that anaesthetic hyperglycaemia is due in the first instance chiefly or altogether to the liberation of adrenaline.

Mobilization of Glucose from the Liver

The suggestion that anaesthetic agents mobilize glucose by a direct action on the liver has also been investigated experimentally. Linkoz (1926), for example, showed that various narcotics when perfused in moderate concentrations through the isolated frog's liver liberated glucose from that organ, and Fuss (1930) found that in the dog hepatic venous blood contains more glucose than portal venous blood during ether anaesthesia. Here again, however, matters cannot be regarded as settled. Ether and chloroform do not mobilize glucose from the isolated perfused liver of the dog (Ross, 1920) even when its glycogen content is normal. It has been claimed (Hrubetz and Blackberg, 1938) that the glycogenolytic power of the rabbit's liver is actually depressed by chloroform and various barbiturates, so that the hyperglycaemic effect of injected adrenaline is diminished. Mellanby (1919) concluded that since ether does not produce hyperglycaemia or glycosuria in the spinal animal its action

cannot be directly on the liver, but is in fact on the bulb. According to Tuckett (1910) ether produces an acceleration of glycogenolysis not necessarily confined to the liver.

Influence on the Action of Insulin

The question of the influence of anaesthetic drugs upon the action of insulin in the body has also been considered. Ross and Davis (1920) came to the conclusion that in the dog ether produces hyperglycaemia by hampering the action of insulin, but it has been shown (Chambers, Deuel, and Milhorat, 1927) that in the dog under amytal anaesthesia insulin has its usual hypoglycaemic effect, raising the respiratory quotient and increasing carbohydrate utilization as in the unanaesthetized animal. On the other hand, Aubertin and Trinquier (1933) concluded that chloralose actually enhances the effect of insulin in the dog. It may be stated that there is no indisputable evidence that anaesthetic agents interfere with the activity of insulin in the organism. The question as to whether anaesthetic drugs directly depress the pancreas and so diminish its output of insulin has not been adequately studied.

Depressant Action of Anaesthetic Agents

It is fairly well established that most anaesthetic agents diminish the uptake of glucose by the tissues, although whether this of itself could be responsible for the observed hyperglycaemia is very doubtful. This depressant action has been demonstrated by measuring the uptake of glucose from the surrounding solution by the unicellular organism *paramoecium* in the presence and absence of ether or chloroform (Estes and Burge, 1928). A similar effect may be shown indirectly for mammalian tissue. Amytal does not raise the blood sugar, but the glycosuria and hyperglycaemia produced by continuous intravenous transfusion of glucose in the dog are greater when amytal is given than in the unanaesthetized animal (Hines, Boyd, and Leese, 1926; Wierzychowski and Gadomska, 1927). This is good evidence that the ability of the tissues to utilize glucose is depressed even by amytal, although Lambie (1926), using the cat, concluded that ether and chloroform anaesthesia does not alter the rate of glucose uptake if the liver is excluded from the circulation. Hines, Leese, and Barer (1928) further showed that the increase of muscle glycogen produced by continuous intravenous transfusion of glucose is not affected by amytal, but that the increase in liver glycogen under these circumstances is halved by amytal anaesthesia. Fuss (1930) has also supplied evidence bearing on the relation of tissue glucose utilization to the hyperglycaemia of anaesthesia. He showed that in the phloridzinized dog ether does not raise the blood sugar, and deduced that the hyperglycaemia of ether anaesthesia is due to mobilization of glucose from the liver (rendered impossible, in phloridzin poisoning, by depleting the liver of glycogen) and not to any diminished utilization of glucose by the other tissues. Sansum and Woodyatt (1915) recorded a fall of blood sugar in phloridzinized dogs, brought about by ether and chloroform anaesthesia. Moreover, it has been shown that ether may not produce its customary rise of blood sugar in patients with hepatic disease (Canterow and Gehret, 1931).

Breakdown of Carbohydrate

The careful work of Uchida (1926), using the rat, demonstrated that various anaesthetics, including ether and chloroform, diminish the free carbohydrate in the brain to some extent and the total glycogen of the brain

to a much larger extent. Liver glycogen is certainly diminished during anaesthesia. The actual depletion has been measured in nitrous oxide anaesthesia (Browne and Evans, 1933), in amytal narcosis (Evans, Tsai, and Young, 1931), and in ether anaesthesia (Macleod and Pearce, 1910). Ether also diminishes the glycogen of the muscles (Major and Bollman, 1932).

There is thus good evidence that ether and at least some other anaesthetic agents accelerate the breakdown of glycogen in the brain, the liver, the muscles, and, no doubt, in all the tissues of the body. The mechanism whereby this universal glycogenolysis is set in motion is imperfectly understood, but it is probably safe to assert that the central nervous system is involved, and that any direct toxic peripheral action of the anaesthetic drug is prominent only in overdosage and is in any case a late effect. It has been suggested (Pratt, 1938) that the partial breakdown of carbohydrate metabolism may be due to some extent to interference not so much with glycogen itself as with some phosphorylated derivative such as hexose phosphate. This is supported by the observation of Stehle and Bourne (1924) that the acidosis of ether anaesthesia is due to the discharge of phosphoric acid from the tissues, where normally it is concerned with carbohydrate metabolism, into the blood stream. It may be that the hyperglycaemia of some forms of anaesthesia is a compensatory mechanism designed to minimize the effects of anoxia upon nervous tissue. It is known that the sensitivity of the central nervous system to anoxia is greatly increased by hypoglycaemia (Gellhorn, 1938), and that hypoglycaemia as well as anoxia depresses the rate of oxidation in the central nervous system. It is interesting to note that the intravenous injection of glucose in the dog may shorten the period of barbital (veronal) anaesthesia by as much as 50 per cent. (Johnson, Luckhardt, and Lighthill, 1930). Although this effect was ascribed to diuresis, with an increased rate of elimination of the drug, some more specific action may be involved.

Effect on Metabolism

According to Inami (1931) the degree of metabolic disturbance in anaesthesia is proportional to the depth of anaesthesia. This has been confirmed (Pratt, 1938) as far as the hyperglycaemia of ether anaesthesia is concerned.

Anaesthetic agents have an even more intimate and probably much more important influence upon carbohydrate metabolism than any yet touched upon. It is generally agreed that the only oxidative metabolism carried on by nervous tissue is carbohydrate oxidation (Himwich and Nahum, 1932), and this peculiarity clearly renders nervous tissue specially susceptible to any agent which interferes with intermediate carbohydrate metabolism. Indeed, the opinion is steadily gaining ground that anaesthetic drugs may exert their specific effect by inhibiting some phase of the series of reactions involved in the oxidation of carbohydrate in nerve cells. Jowett (1938), using brain slices, has shown that various anaesthetics reversibly inhibit these reactions, and he has proposed to explain narcosis on that basis.

Conclusion

It may be permissible, in conclusion, in a paper that records so much of doubt and so little of certainty, to indulge in one further speculation. According to Mann, Tennenbaum and Quastel (1938), a precursor of acetylcholine exists in brain tissue. This "acetylcholine precursor" is synthesized when carbohydrate oxidation is

occurring, but is not formed under anaerobic conditions. Similarly, MacIntosh (1938) has recently shown that the production of acetylcholine and the transmission of impulses by the superior cervical ganglion is dependent, at least in part, upon the presence of glucose. It is an attractive hypothesis that anaesthetic drugs produce anaesthesia by diminishing the amount of available acetylcholine as a result of cessation or diminution of carbohydrate oxidation, and so preventing the transmission of impulses at synapses in the central nervous system. If this or some such mechanism should prove to be the case it would mean that at last we should have arrived at a theory of anaesthesia capable of being stated in current physiological terminology.

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