THE BLOOD SUGAR IN ANAESTHESIA.

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Interest in the effects of anaesthetics on metabolism has been continual since their universal employment. This study was suggested by the accidental discovery of glycosuria, following the injection of 30 ccs of 2% novocaine into a fractured tibia. The investigation was extended to include general and spinal anaesthesia. The patients selected - apart from those suffering from injury - were those who required an anaesthesia of about half an hour or less. They were chiefly herniae in otherwise healthy people. I propose to discuss the question under four headings viz. (1) Historical survey, (2) Discussion of the literature on this and closely related subjects. (3) The results of my own enquiry. (4) Summary.

Historical Survey: Reynoso (190) first observed in 1853 that glycosuria followed ether anaesthesia. Later in the same century Claude Bernard (19) showed that, of the anaesthetics then in use, chloralose had the least effect on the blood sugar. In 1905 Seelig (268) demonstrated that ether anaesthesia is accompanied by a rise in blood sugar. King (122) and his collaborators published, in 1911, experiments proving that section of the nerves in the hepatic pedicle had no effect on the hyperglycaemia of ether anaesthesia. During the same year Pavy and Godden (179) showed that the intravenous injection of 3% sodium carbonate caused an appreciable diminution in the rise in blood sugar, which accompanies ether anaesthesia. The following year King (121) and his colleagues published the

results of experiments on anaesthesia by means of the intravenous injection of ether. They found there was increased hepatic glycogenolysis. They also stated that, if the portal circulation was excluded from the liver by means of an Eck fistula, no rise in blood sugar occurred. In the same year Elliott (70) wrote that his investigations showed that ether anaesthesia caused an exhaustion of the adrenals. In 1914 Bloor (249) showed that ether anaesthesia is accompanied by a rise in blood fat. Next year Ross and McGuigan demonstrated that the hyperglycaemia of ether anaesthesia was not due to asphyxia of the piqure centre in the medulla, since it occurred in the absence of asphyxia. In 1917 Morriss (174) observed that ether anaesthesia caused a lowered carbon dioxide combining power of the blood plasma. At this time Stewart and Rogoff(217-225) began to publish papers on the relation of ether hyperglycaemia to the adrenals. They stated that epinephrine was not a factor in ether hyperglycaemia. Keeton and Ross (119), in 1919. made public their work on the mechanism of ether hyperglycaemia. They concluded that it was due to the action of epinephrine. The following year Ross and Davis (194) suggested that it was due to depression of the internal secretion of the pancreas. Fujii (84) showed, in 1921, that ether caused hyperglycaemia after section of both splanchnics. A year later Atkinson and Ets (5) published their work. They demonstrated that, under ether anaesthesia, there was a rise in blood sugar, a rise in H. ion concentration and a lowered carbon ~~mon~~di oxide combing power of the blood. They suggested that

the former might be caused by either of the two latter. The same year Tatum & Atkinson (228) suggested that asphyxia might be the cause of these changes. In 1923 papers appeared by Van Slyke (237), Koehler (127), Leake (131) and others on the acidosis of ether anaesthesia. There was agreement about the acidosis but the cause remained obscure. At this time those, who believed that all anaesthetics cause hyperglycaemia,received a rude shock. Page (178) showed that amytal - a barbiturate - was an anaesthetic without effect on the blood sugar. In 1924 Stehle and Bourne (269) investigated the acidosis of ether anaesthesia and found it was associated with a discharge of phosphoric acid from the muscles. The same year Kodama (126) stated that ether anaesthesia decreases the rate of epinephrine output. The following year Mann (155) discussed the relation of anaesthetics to liver function. He showed that ether depresses liver function as well as chloroform. He thought that the hyperglycaemia of ether anaesthesia might, in part at least, be due to a direct action of the ether on the liver. The same year Josephs (116) demonstrated that a hypoglycaemia often follows anaesthesia. The year 1926 was one in which considerable additions to our knowledge of the metabolic effects of ether were made. Mahler (152) showed that there was a rise in blood cholesterol in ether anaesthesia which closed followed the rise in blood sugar. He agreed with ~~Keeton~~ Ross and ~~Ross~~ Davis (194) (119) concerning the cause. Stander (212-213) discussed the marked similarity between the blood changes in ether anaesthesia and eclampsia. He suggested

a common cause. Tachi, Takai and Fujii showed that protection against fall in body temperature markedly lessened the rise in blood sugar during ether anaesthesia. Bolliger (29) observed that there is a fall in the inorganic phosphates of the blood during uncomplicated ether anaesthesia. This is roughly a mirror image of the blood sugar. In 1928 Osterberg (177) discussed ether anaesthesia from the point of view of the biochemist. He stated that insulin prevented the hyperglycaemia of etherization. He agreed with the view of Ross and Davis (~~119~~ 194). The same year Magee, Anderson and Glennie (151) published their work. They found that ether anaesthesia lowered the blood calcium but increases the blood sugar, inorganic phosphate and H. ion concentration. In 1931 several useful papers were published. Cantarow and Gehret (44) found that the hyperglycaemia of ether anaesthesia was much less in patients with liver disease and practically non-existent in those with jaundice. Evans and his collaborators found that both ether and amytal lessened the glycogen content of the liver - amytal more so than ether (75). Zucker and Newburger (242) showed that ether anaesthesia causes a rise in blood amylase. They found no rise with spinal anaesthesia. The following year Major and Bollman (153) demonstrated that there is a marked decrease in muscle glycogen in prolonged ether anaesthesia. The same year Minnitt (172) discussed the toxic symptoms following ether anaesthesia. He considered they were related to the rise in blood sugar. He agreed with Ross and Davis (194) concerning the cause of the hyperglycaemia. He

recommended the pre-anaesthetic use of insulin. The same year Murphy and Young (164) investigated the hyperglycaemic effects of various anaesthetics and concluded that it was least with chloralose and amytal. In 1933 Banerji and Reid (16) showed that removal of the adrenals decreased the hyperglycaemia of ether anaesthesia without abolishing it. They also demonstrated that amytal inhibited the usual increase in blood sugar. During the same year Campbell and Morgan (40) also proved that amytal prevented ether hyperglycaemia in the experimental animal. For the next three years there was a lull in the published work on this subject. In 1936 Knoefel (273) compared the hyperglycaemia of epinephrine injection with that of ether anaesthesia. He found a striking similarity. He concluded that epinephrine was the cause of ether hyperglycaemia. Pratt (182) reviewed the subject of ether hyperglycaemia without coming to any definite conclusion concerning the cause. He noted the the hyperglycaemic response to ether in human beings was variable. He complained that little work had been done on the subject. I cannot agree with this statement. In the same year - 1938 - Cajori and Vari (45) found that there was a decrease in the serum amylase in chloroform anaesthesia. I can find no reference in the literature to blood sugar studies in spinal and local anaesthesia.

Discussion of the Literature. The problem of ether hyperglycaemia is part of the much greater one of carbohydrate metabolism, and knowledge of the latter is essential for the elucidation of the

former. Macleod (144) states that the blood sugar determination is the most useful single method of estimating the behaviour of carbohydrate metabolism. Cammidge and Howard (58) find that the fasting blood sugar is remarkably constant in normal individuals. It represents the balance between the addition or new production of sugar on the one hand, and its loss on the other. Peters and Van Slyke (267) give the normal as .09 to .1 gm%. There is a rise in the blood sugar following the ingestion of carbohydrate. Van Slyke and Hawkins allow a maximum of 50 mg%. The limit of assimilation of glucose is the amount of glucose which can be taken in one dose without causing glycosuria. This varies in different individuals. Taylor and Hulton (230) state that as much as 400 gms. has been taken without causing glycosuria. This no doubt accounts for the individual variation in the hyperglycaemic response to ether. Woodyatt et al (241) have shown that glucose can be injected intravenously in man and animals at the rate of .85 gm. per kilo per hour, without causing glycosuria. According to them the rate of absorption from the intestine does not exceed 1.8 gm. per kilo per hour. Carbohydrate tolerance is the amount of glucose, from whatever source, which a patient can tolerate without any glucose appearing in the 24 hour specimen of urine, as judged by clinical tests. The usual method of giving 50 gms of glucose with 300 to 400 ccs of water, to a patient who has fasted since the night before, and then removing samples of blood at intervals of ½ hour, 1 hour, 1½ hours and 2 hours after, is criticised by Gilbert et Al. (85). They recommend that 1.75 gms per kilo of body weight should be given in 400 ccs of water. With this

method they find that the maximum rise occurs after 15 to 49 minutes. The rise in blood sugar varies from 136 to 206 mgs. %. The return to normal takes place after 2½ hours. They also state that if the blood is taken at 15 minute intervals a fall is observed to follow the initial rise. Peters and Van Slyke recommend 1 gm. per kilo of body weight. Minnitt (172) considers that the sugar tolerance test is of considerable value in estimating the probable occurrence of post anaesthetic toxic symptoms. This concludes the survey of the problem of exogenous hyperglycaemia.

I intend to discuss endogenous hyperglycaemia from the standpoint of the views which have been advanced to explain the hyperglycaemia of ether anaesthesia. These are briefly that:-

(1) It is of nervous origin.
(2) It is due to the secretion of epinephrine.
(3) It is due to asphyxia.
(4) It is due to increase in the H.ion concentration.
(5) It is due to depression of the function of the pancreas.
(6) It is due to direct action of ether on the liver.

(1) The first evidence that the blood sugar was under the control of the central nervous system was obtained by Claude Bernard (18), during his researches on glycogen. In 1857 he found that puncture of the floor of the 4th., ventricle in well-fed rabbits, produced a marked glycosuria lasting for several hours. It is interesting to digress for a moment to consider why he did this. He had tried to influence the glycogen in the liver by stimulating the vagus nerve. He had been unsuccessful. His master, Magendie, had shown him that puncture of the brain in the region of the fifth nerve nucleus caused a copious flow of tears. Puncture of the floor of

the fourth ventricle was therefore an attempt to mobilize glycogen stimulating the nucleus of the vagus nerve. There has been some discussion concerning whether it destroys the glycogen centre or stimulates neighbouring centres. Donhoffer and Macleod (66) and Brooks (250) found the centre in the floor of the fourth ventricle to be just distal to the brachium pontis. Macleod (144) showed that piqure hyperglycaemia was abolished by sectioning the splanchnic nerves. Since the splanchnic nerves innervate both the liver and the adrenals, he removed the adrenals and left the splanchnic nerves intact. The hyperglycaemia of piqure was abolished. He concluded that the activation of the adrenal medulla is the essential factor in the various neurogenic hyperglycaemias. Stewart and Rogoff(217 -225) disagree with this finding. They found that piqure produced hyperglycaemia in well-fed rabbits, which had long survived bilateral adrenalectomy. They suggest that the method of removal of the adrenals was such as to vitiate the result. Macleod also found that insulin prevented piqure hyperglycaemia. He considers that the increase in sugar is due to diminished utilization of sugar. Canon (41 - 42) discusses the question of emotional glycosuria. He quotes many examples from clinical records - Schultze (216) and Boehm and Hoffman (39). He considers that the rise in blood sugar is due to an increased secretion of epinephrine. Katz and Nice (118) found the blood sugar, non-protein nitrogen, urea, creatinine, uric acid, cholesterol and haemoglobin all increased in emotional excitement. The inorganic phosphorus was decreased. They observed no change in

the amino acids, calcium and chlorides. Splenectomy made no difference. They do not advance any explanation. Macleod (144) states that stimulation of the splanchnic nerve causes hyperglycaemia, and the response is greater if the nerve is not sectioned first. Stimulation of the nerves in the hepatic pedicle he also finds, can cause hyperglycaemia. This, he deduces, is strong evidence for the presence of secretory nerves in the hepatic pedicle. On the other hand King and his collaborators (122) showed that ether hyperglycaemia is not abolished by section of these nerves. Macleod (146) reported that ergotamine causes a hyperglycaemia by action on the piqure centre. Stewart and Rogoff (217-225) find that piqure produces a hyperglycaemia after adrenalectomy as in normal animals. They believe that piqure hyperglycaemia depends on the integrity of the sympathetic pathway to the liver. Macleod has stated (144) that amytal prevents the development of piqure hyperglycaemia. I have included a more extensive survey of this question at the end of this section. Despite all the contradictory evidence it was believed that the hyperglycaemia of ether anaesthesia was due to asphyxia of the piqure centre in the floor of the fourth ventricle. McGuigan (193) denied that asphyxia played any part in its causation since the hyperglycaemia could be produced with ether in the absence of asphyxia.

(2) The nervous control of carbohydrate metabolism is apparently closely related to the function of the adrenal glands. Blum - quoted by Macleod (145) - was the first to observe that injections of epinephrine produced glycosuria. He found a rich deposit of glycogen in the liver favoured this result. Cannon (42) considers that adrenalin causes hyperglycaemia by mobilizing liver glycogen. Pollak(180) found that injection of epinephrine caused glycosuria when all glycogen had disappeared from the liver. Markowitz (170) found that epinephrine caused glycosuria in starving rabbits and glycogen was formed in the liver. Since the adrenals play such a part in the rise of blood sugar following emotional, reflex or direct stimulation of the central nervous system, another approach to the problem was tried. Cori and Cori (59) worked on the mechanism of epinephrine action. Their results showed that there was a decreased deposition of glycogen in tissues other than the liver, a decreased oxidation of sugar by the body and an increased deposition of glycogen in the liver. Cannon (42) criticised their work on the grounds that the amounts of epinephrine they had used were excessive, and that there was no physiological mechanism for mobilizing muscle glycogen. He considered there was no evidence that epinephrine prevented the utilization of glucose. Cori (49) determined the concentrations of glucose and lactic acide in the blood after epinephrine injections. The glycogen in the muscles was broken down into lactic acid, which was built up into sugar in the liver, and returned to the muscles. The deposition of glycogen in the

extra-hepatic tissues and the total oxidation of glucose were decreased, demonstrating that there is inhibition of sugar utilization by the tissues after epinephrine injections. This appears to be a very effective reply to Cannon. Stewart and Rogoff (217 - 225) published several papers on the relation of the adrenals to experimental hyperglycaemia. They found that this was best demonstrated in animals in which one adrenal had been removed - the right and the other denervated. They pointed out that animals after bilateral adrenalectomy are in a dying state. They found hyperglycaemia in asphyxia and ether anaesthesia even when no detectable residual liberation of epinephrine was present. Accordingly they believed that the mobilization of sugar, of which the hyperglycaemia was the expression was not mediated through the epinephrine secretion of the adrenals. They found that removal of the pancreas in adrenalectomized animals caused diabetes just as in pancreatectomy in dogs with the adrenals intact. However, they believe that morphine hyperglycaemia is connected with the adrenals in some way. They do not advance any explanation of ether hyperglycaemia. Eadie and Macleod (67) found that epinephrine hyperglycaemia is inhibited by insulin. Macleod (144) showed that epinephrine only antagonises insulin when there is glycogen in the liver. Cori and Cori (52) studied carbohydrate metabolism in adrenalectomized rats. They found that epinephrine was not involved in the changes which have been ascribed to insulin. The low blood sugar of adrenalectomized rats was due to absence of glycogen.

McKay and Barnes (150) found that ketonuria, produced by feeding the sodium salts of diacetic and hydroxy-butyric acids to fasting rats was markedly reduced by adrenalectomy. Keeton and Ross (119) found a persistent hyperglycaemia occurred in dogs under ether anaesthesia. A transient hyperglycaemia - passing off in two hours - occurred in dogs with the splanchnic nerves cut and then anaesthetised. A persistent hyperglycaemia of lower grade occurred under ether in dogs with one splanchnic cut. Denervation of the hepatic artery did not prevent the rise in blood sugar. Section of the nerves in the hepatic pedicle decreased the hyperglycaemia but did not abolish it. The establishment of an Eck fistula also lowers the hyperglycaemia due to ether but does not abolish it. Ligature of the hepatic artery in dogs with an Eck fistula caused profound hypoglycaemia. Reversed Eck fistula had no effect on ether hyperglycaemia. The adrenalin content in dogs with one splanchnic cut is unequal in the two glands. They concluded that the adrenals played the main part in ether hyperglycaemia. Reid (187) also believes that the adrenals play the principle role in ether hyperglycaemia. He admits that after removal of the adrenal factor there is still some unexplained hyperglycaemia. I consider that the operative objections of Stewart and Rogoff impress me a great deal. The question of the Eck fistula is still debatable. Keeton and Ross (119) say that it does not prevent ether hyperglycaemia whereas Mann (155) states that it does. This is an important point because the blood from the adrenal glands enters the systemic

circulation and therefore can only reach the liver via the hepatic artery. Of course it can be explained on the work of the Coris, which I have quoted, namely that adrenalin mobilizes muscle glycogen to lactic acid and the liver converts it into sugar.

(3) Araki (3 & 4) was the first to show that asphyxia with coal gas causes hyperglycaemia. It is believed that this was also known to Claude Bernard. Asphyxia, however produced causes a marked rise in blood sugar. This is found even if the liver contains only little glycogen - Macleod (144). Stewart and Rogoff (217 - 225) use it as a test. Kellaway showed that the important factor is the anoxaemia (124). The carbon dioxide also plays a part. He found it impossible to dissociate the effects of emotion from those of anoxaemia. He considered that the secretion of adrenalin played a part. The other possibilities were direct stimulation of the liver by impulses through the splanchnics, and direct action of the anoxaemia on the liver cells. Stewart and Rogoff (217-225) disagree with Kellaway. They do not consider that the adrenals have any action in asphyxia. Macleod (145) states that:- (a) asphyxia after vascular exclusion of the liver causes a very slight rise in blood sugar. (b) The injection of curare until paralysis occurs does not affect the blood sugar. He concludes that the hyperglycaemia is not dependent on the depression of oxidative processes in the tissues, and that the glycogen of the muscles cannot serve as a source of increased sugar production. He asks whether the hyperglycaemia of asphyxia

is due to direct action through the blood, or to asphyxial stimulation of nerve control or to both. He points out that asphyxia is a more potent cause of hyperglycaemia when the nervous control of the liver is intact. When the asphyxia is intense there is probably direct action on the liver cells due to increased hydrogen ion concentration of the blood. The action of diastase is greatly accelerated by an increase in acidity. He concludes that the asphyxial factor should be borne in mind in considering the hyperglycaemia of anaesthesia. Tatum and Atkinson (228) conducted an investigation to determine if asphyxia was the cause of certain drug hyperglycaemias. They report the views of several workers who support this hypothesis. They used the method of Stewart and Rogoff (217-225) to eliminate the adrenal factor. They showed that ether hyperglycaemia is not essentially central but predominantly a peripheral action. Failure to respond to quinine and picrotoxin showed that the operations were successful in eliminating central stimulation of the glycogenolytic centre, since both these drugs cause hyperglycaemia by central stimulation. A normal response to ephedrine showed that the liver was not deficient in glycogen. Since acidosis has been commonly considered the cause of ether hyperglycaemia, a pre-existing acidosis should increase its effect. They found no significant synergism. They found a slight diminution in the hyperglycaemia of etherization on the administration of alkali. They explained this by an increase in tissue oxidation. They point out that

measuring the alkali reserve of the blood might not give a true picture of what is happening in the liver. They came to the conclusion that ether hyperglycaemia cannot be entirely due to asphyxia and acidosis. They found no synergism between ether and epinephrine and they concluded that the mechanism of the production of hyperglycaemia differs in each case.

(4) In 1911 Pavy and Godden (179) showed that the injection of 3 % sod. barb. caused an appreciable diminution in the hyperglycaemia following the administration of ether. Some six years later Morriss (174) demonstrated that ether anaesthesia causes a lowered carbon dioxide combining power of the blood. Van Slyke and others (237) investigated the effects of ether anaesthesia on the acid / base balance of the blood. They found that the H. ion concentration rose at once or soon after anaesthesia began. They concluded that the changes do not occur as a compensatory mechanism to balance an acapnia. There was a true acidosis with increase in H. ion concentration and a fall in alkali reserve. It was due either to the introduction of acid or the withdrawal of base. Cullen et Al. (55), in 1923, investigated the initial acidosis of anaesthesia. They agreed with Van Slyke that it was a true acidosis. They indicated the importance of exertion and anoxaemia as contributory factors. Leake et Al. (131) investigated the problem of the acidosis of ether anaesthesia in the dog. The conclusion they came to was that this acidosis could be explained neither by a compensatory action due to an

acapnia, nor by the entrance of acid into the blood, but by the withdrawal of base from it. Koehler (127) discussed the question of operative acidosis. He found a marked increase in H. ion concentration of the blood in the first few minutes of the anaesthesia. This was followed by a more gradual increase. He considered that this increase in H. ion concentration the cause of the initial hyperpnoena. He believed that the acidosis was the summation effect of carbon dioxide excess and alkali deficit. The excess of carbon dioxide was due to inefficient respiration from decreased sensitiveness of the respiratory centre. The discussion of acidosis would be incomplete without some mention of the views of Henderson and his collaborators.(91 & 98 -103). He showed that a marked acidosis occurs in asphyxia. He injected sod. bicarb. intravenously in a man suffering from carbon monoxide poisoning with an almost fatal result. He suggested the substitution of acarbia for acidosis. Extreme asphyxia - such as soon to cause death - produces a marked increase in the lactic acid in the blood. It was assumed that lesser degrees of asphyxia produced lesser amounts of lactic acid. Lundsgaard (262) showed that muscles treated with mono-iodo-acetic acid did not produce lactic acid but contracted normally. Henderson and Greenberg (99) subjected two groups of dogs to asphyxia. The first group were normal dogs. The second group had been treated with mono-iodo-acetic acid. The first group survived a slightly lower oxygen pressure than the second. They consider that

Lundsgaard's discovery has destroyed the theory of oxygen debt. Henderson and Haggard (91) wrote a paper on the fallacy of asphyxial acidosis. Their view was that the injection of lactic acid into the blood caused overbreathing and alkalosis. They believe that carbon dioxide in the air inspired raises the carbon dioxide content of the blood and increases the alkali reserve. This is due to the compensatory passage of alkali from the tissues to the blood. Henderson and Greenberg (99) have shown that the bicarbonate content of the blood - alkali reserve - is only a small part of the total blood alkali. It is the part used for the transport of carbon dioxide.

Of course there are many who disagree with Henderson's views. Nevertheless it is fairly well proven that breathing has a profound influence on the H.ion concentration and the alkali reserve of the blood. It is obviously a factor which much be considered in a discussion of the effects of inhalation anaesthesia.

Shock and Hastings (204) made studies of the acid / base balance of the blood during the respiratory cycle and in clinical and experimental acidosis. They found that the existing conditions could be expressed in terms of three variables :- (a) the carbon dioxide tension, (b) the bicarbonate concentration, and (c) the H, ion concentration. The simultaneous determination of any two determines the third.

Stehle and Bourne (269) investigated the mechanism of the acidosis in ether anaesthesia. They found a marked increase

in the excretion of sodium and potassium bases in the urine. This was parallelled by an increase in phosphoric acid in the blood. They concluded that the cause of ether acidosis was the liberation of phosphoric acid from the muscles. Potter (181) criticises these views and suggests that the excretion of phosphate may be a compensatory mechanism on the part of the kidney.

Cammidge (58) believed that the diastatic ferment was of the greatest importance in carbohydrate metabolism. Its potency is greatly increased by an increase in the H. ion concentration of the blood. He considered that this factor explained many of the vagaries of the blood sugar under different conditions. In support of this there is the work of Zucker and Newburger (242) who found that the blood amylase was increased to three or four times its normal value under ether anaesthesia. Against it are the findings of Cajori and Vari (45) who found that the serum amylase was decreased in chloroform anaesthesia.

Atkinson and Ets (5) investigated the changes in the blood under ether anaesthesia. They confirmed the rise in blood sugar, the lowered carbon dioxide combining power of the plasma, and the increase in the H. ion concentration. They concluded that the hyperglycaemia was related to the increase in H. ion concentration and to the lowered carbon dioxide combing power of the plasma.

(5) The discovery by Von Mehring and Minkowski (239) in 1889 of the production of diabetes in dogs by removal of the pancreas, focussed attention on the pancreas as a powerful factor in

the regulation of carbohydrate metabolism. It was therefore only a matter of time until its importance in the hyperglycaemia of anaesthesia, came to be investigated. The first to do this were Ross and Davis (194) in 1919. They concluded from their experiments that the hyperglycaemia of ether is due to depression of the internal secretion of the pancreas. They explained the findings of Keeton and Ross(119) by stating that, since epinephrine and the pancreatic internal secretion were antagonistic, section of the splanchnics depressed the adrenals more that the ether depressed the function of the pancreas. They stated that there were three mechanisms for mobilizing glycogen :- (a) adrenaline, (b) stimulation of the sympathetic nerve endings, and (c) pancreatic internal secretion. In their experiments they used two groups of dogs. The first group had all the pancreas removed except the tail. From the point of view of pancreatic internal secretion they were normal. The second group had the whole pancreas removed. The average increase in the first group under ether was .0395 gm % whereas in the second group it was .0413 gm %. In the depancreatized dogs there was a diminished output of dextrose in the urine under anaesthesia. The difference in the rise in blood sugar between the two groups of dogs is almost negligable. If the depression of the internal secretion of the pancreas were really the cause of ether hyperglycaemia one would expect a more marked difference.

Minnitt (172) discussed this question. He was impressed

by the apparent resemblance between ether hyperglycaemia and diabetes. He showed that the pre-anaesthetic injection of insulin prevents the rise in blood sugar. He found acetone in the urine of 67% of patients after anaesthesia. The occurrence of shock caused a marked increase in the blood sugar during anaesthesia. He discovered that the blood pressure was in inverse proportion to the blood sugar. He tended to agree with the views of Ross and Davis(194).

Mahler(152) found that the blood cholesterol was raised in ether anaesthesia. He showed that the rise was parallel to that of the blood sugar. The similarity to diabetes again was apparent. He agreed with the theory of Ross and Davis (194). Osterberg (177) also found himself in agreement with Ross and Davis.

(6) Although there is disagreement about the mechanism of ether hyperglycaemia, there is general agreement that its source is in the liver. Mann and Magath (158-160) showed that removal of the liver in dogs causes :- (a) profound hypoglycaemia, (b) increase in the uric acid of the blood, and (c) the formation of urea ceases. They also showed that removal of the liver in pancreatectomized dogs abolished the hyperglycaemia. The liver was necessary for the hyperglycaemia. The muscles may have contributed indirectly by the breakdown of their glycogen into lactic acid and its resynthesis into sugar in the liver.

King and his collaborators (121) investigated the problem of the hyperglycaemia of ether anaesthesia. They found

that section of the nerves passing from the coeliac plexus to the liver did not prevent ether hyperglycaemia. The presence of an Eck fistula prevented the occurrence of hyperglycaemia under ether. They concluded that the hyperglycaemia was due to the direct action of the ether on the liver cells. In a second paper King et Al. (121) produced anaesthesia by the intravenous injection of ether. This was done in order to eliminate the asphyxial factor, which is a very potent hyperglycaemic agent. They succeeded in this. They found that glycosuria does not occur in dogs until the condition of anaesthesia is produced. They considered that the rise in blood sugar was roughly proportional to the amount of ether introduced.

Mann(155) investigated the relation of anaesthesia to hepatic function. He found that ether depressed the function of the liver to a lesser extent than chloroform. It depressed the secretion of bile. He verified the fact that exclusion of the portal circulation from the liver practically abolishes the hyperglycaemia of ether. It therefore depends on an intact portal circulation. When the liver is removed there was no hyperglycaemia with ether. He stated that the actual cause was unknown but he made the following suggestions :- (a) ether hyperglycaemia is due to the direct action of the ether on the liver cells, (b) it is due to indirect action on the liver associated with the general stimulation of the stage of excitement, (c) it is due to the asphyxia which accompanies etherization.

These effects of anaesthesia on liver function were

confirmed by Rosenthal and Bourne (188). In a more extensive clinical study Cantarow and Gehret (44) showed that the hyperglycaemic response to ether is lessened by disease of the liver. In cases of jaundice it was almost entirely absent. They considered that the cause of ether hyperglycaemia was due to a direct action of the ether on the liver, causing increased glycogenolysis. They suggested that the ether might also act through the increase in H. ion concentration. They placed great stress on the work of Bolliger (29). He found that there was a considerable drop in the serum phosphate in ether anaesthesia. Cantarow and Gehret considered this evidence against hypo-insulination. Haldane et Al. (92) showed that variations in the serum phosphate might be due to muscular exercise and asphyxia, and not to alteration in the carbohydrate metabolism.

I have included various references in the bibliography which confirm the blood changes already described, following liver damage by various poisons - (212),(213), (252) & (264).

Page recorded in 1923 that amytal was an anaesthetic without effect on the blood sugar. Macleod (146) stated that amytal prevents piqure hyperglycaemia. Evans (75) showed that amytal lowers the glycogen content of the liver appreciably and to a greater extent than ether. Campbell and Morgan (40) examined the hyperglycaemic reactions of certain drugs. They showed that apomorhine produces hyperglycaemia by central action on the piqure centre. They found that amytal prevented this hyperglycaemia.

On the other hand they found that amytal failed to prevent the hyperglycaemia following the injection of epinephrine. They concluded that amytal prevents those hyperglycaemias of central origin. They induced anaesthesia in rabbits by giving 2 ccs of ether by stomach tube. They found that the previous administration of amytal prevented hyperglycaemia occurring. They thus put forward the view that ether produces hyperglycaemia by an action on the piqure centre. They advocated the hypothesis that ether stimulates this centre, and this results in the production of some chemical substance which continues to act after the stimulus for its production has been removed.

In concluding the survey of the literature I would like to include certain papers on the effect of trauma on the blood sugar. In operations on human beings trauma and anaesthesia are combined. Epstein and his collaborators (73,74 & 257). They discovered that loss of blood caused a rise in blood sugar. The explanation they suggested was that the liver poured an amount of sugar into the blood equivalent to that lost in the haemorrhage. In discussing the effect of anaesthesia and operative procedures on the blood they set forward the factors involved as follows :- (a) nature and duration of the anaesthetic, (b) nature and location of the operation, and (c) degree of shock incidental to the operation. They concluded that there was no difference between intra- and extra-peritoneal operations in their effect on the blood sugar. Anaesthesia played the important part in the hyperglycaemia observed. More marked increases in blood sugar appeared when the

operation lasted over an hour. Nephrectomy seemed to cause the most marked rise in blood sugar. Aub and Wu (6) studied the chemical changes in the blood in shock. They found a marked rise in blood sugar. They put forward three possible explanations :- (1) The hyperglycaemia is associated with activity of the sympathetic nervous system. (2) Reduced total metabolism might explain the accumulation of sugar in the blood. However, the respiratory quotient in traumatic shock suggests that a normal amount of carbohydrate is being metabolised. (3) May look to the liver for an explanation. Davidson and Allen (64) investigated the blood sugar curve in head injuries. They found that such injuries cause a profound but temporary disturbance of carbohydrate metabolism. The fasting blood sugar in cases of concussion is within normal limits. The response to the ingestion of glucose is much greater and more prolonged. Weddel and Gale (240) found that preoperative anxiety as measured by the blood sugar must be very ~~sli~~ slight. The duration of the anaesthesia does not determine the height of the rise. This depends more on the nature of the operation. They determined the blood sugar by microchemical methods. The highest reading was 124 mgms %.

Results of my Investigations.

Panton and Marrack state that the best method for determining the blood sugar, if you are not an expert chemist, is the method of Folin and Wu (80). At least two ccs of blood are required. This is placed in a test tube with some potassium oxalate or fluoride.

The procedure consists in measuring 2 ccs of the oxalate blood as soon after withdrawal as possible, into a 50 cc. bottle. Add 14 cc. of distilled water and then 2 cc. of 10% sod. tungstate solution, shaking gently after each. Add 2 cc. of 2/3 N. sulphuric acid shaking gently during the addition. Now stopper the bottle and shake violently. The fluid should not froth. Stand the bottle for 15 minutes, during which time the fluid should go brown. Filter through sugar free filter paper and cover the filter funnel with a petri dish. The filtrate should be clear and colourless. Measure 2 cc. of the filtrate into a blood sugar tube marked X. Into two other tubes marked 1 and 2 measure 2 cc. of standard 1 and 2 sugar solution respectively. To all three tubes add 2 cc. of the alkaline copper solution. Place in a boiling water bath for six minutes. Cool the tubes in water for one minute, and add to each 2 cc. of the phospho-molybdic acid solution. This causes the blue colour to reappear. When the bubbles cease to rise dilute each to 25 cc. Invert several times to mix thoroughly. Pour fluid from the tube X into one cup of the colorimeter, and into the other cup pour an equal amount of standard one or two - which ever matches the colour more completely. Set the standard at 20 mm. The calculation is as follows :-

20/10x gms per 100ccs if standard 1.

40/10x gms per 100ccs if standard 2.

This method has been criticised by Somogyi (205) but it has proved an excellent method in our hands. The comparatively large quantity of blood lessens the experimental error.

The cases selected for the investigation were in the first instance healthy adult males, suffering from hernia or hydrocele. This meant that the period under anaesthesia was of roughly equal length, the amount of anaesthetic used was similar, and the operative trauma was comparable. All received a hypodermic injection of atropine sulphate 1/100 gr. half an hour before operation.

The first group of cases were induced with a mixture of one part of chloroform and two parts of ether. Two and a half ounces of this mixture was used. After induction the anaesthetic used was ether and the average amount was six ounces. The time of the operation was twenty minutes in each case. The blood sugar was taken immediately before commencing the anaesthetic (1), immediately after the operation was finished(2), and three hours later (3).

Age	Sex	Condition	Operation	Blood Sugar. 1.	2.	3.
31	M.	Hernia	Radical cure	.083%	.154%	.12%.
14	M.	Hernia	" "	.11%	.182%	.13%
42	M.	Hernia	" "	.083%	.143%	.105%
20	M.	Hernia	" "	.1%	.174%	.143%.
16	M.	Hydrocele	" "	.095%	.154%	.133%.
28	M.	Hernia	" "	.095%	.166%	.143%.
27	M.	Hernia	" "	.105%	.182%	.143%.
30	M.	Hernia	" "	.095%	.154%	.133%.
44	M.	Hernia	" "	.083%	.143%	.125%
33	M.	Hernia	" "	.105%	.16%	.16%.

From these results it is obvious that the correspondence

between the fasting blood sugars is much closer than the hyperglycaemic response to the anaesthetic.

The second group is a similar one to the first. The only difference is that the induction was carried out by Nitrous Oxide instead of Ether and Chloroform mixture.

				Blood Sugar.		
Age	Sex	Condition	Operation	1.	2.	3.
19	M.	Hernia	radical cure	.087%	.142%	.1%.
47.	M.	Hernia	radical cure	.095%	.166%	.133%
44	F.	Hernia	" "	.105%	.154%	.133%.
30	M.	Hernia	" "	.1%	.166%	.125%.
37	M.	Hernia	" "	.1%	.154%	.133%.
45	M.	Hernia	" "	.09%	.166%	.143%.
22	M.	Hernia	" "	.09%	.166%	.133%.
47	F.	Hernia	" "	.09%	.154%	.143%.
35	M.	Hernia	" "	.1%	.18%	.143%.
28	M.	Hernia	" "	.12%	.2%	.133%.

There is no striking difference in the hyperglycaemic response of this group from its predecessor.

A third similar group in which the induction was carried out by means of ethyl chloride. This was the only difference.

				Blood Sugar.		
Age	Sex	Condition	Operation	1.	2.	3.
47	M.	Hernia	Radical Cure	.1%	.18%	.143%.
23	M.	Varicocele	" "	.105%	.18%	.143%.

Induction by ethyl chloride group contd.

Age	Sex	Condition	Operation	Blood Sugar. 1.	2.	3.
62	F.	Hernia	radical cure	.085%	.154%	.125%
25	M.	Hernia	" "	.1%	.182%	.14%.
17	M.	Hernia	" "	.087%	.144%	.12%.
23	M.	Hernia	" "	.11%	.166%	.125%
47	F.	Hernia	" "	.1%	.154%	.11%.
65	F.	Lipoma	excision	.105%	.166%	.125%.
71	M.	Hernia	radical cure	.083%	.154%	.118%.
41	F.	Hernia	" "	.1%	.166%	.143%.

There is no significant variation observed in this group.
The average rise in blood sugar for the first group is .0657%.
" " " " " " " " 2nd. " " .0675%.
" " " " " " " " 3rd. " " .0672%.
The conclusion is that the method or rather the drug used for induction, does not influence the rise in blood sugar.
Where the preanaesthetic blood sugar is high a higher hyperglycae glycaemic response is obtained.

The next group of cases is composed of patients who had their appendix removed. In none of them was the appendix acutely inflamed - they were interval appendicectomies.

Age	Sex	Anaesthetic	Blood Sugar 1.	2.	3.
27	M.	E.C. and Ether	.11%	.182%	.13%.

Appendicectomy group cont.

Age	Sex	Anaesthetic	Blood Sugar 1.	2.	3.
40	F.	E.C. and Ether	.095%	.166%	.133%.
29	F.	" " "	.09%	.154%	.12%.
23	M.	" " "	.095%	.174%	.148%.
28	F.	" " "	.083%	.143%	.12%.

Operations for torn internal semilunar cartilage.

Age	Sex	Anaesthetic	Blood Sugar 1.	2.	3.
20	M.	E.C. and Ether.	.105%	.2%	.166%
29	M.	" " "	.087%	.166%	.133%
65	M.	" " "	.095%	.174%	.125%
26	M.	" " "	.1%	.2%	.133%
21	M.	" " "	.095%	.174%	.133%

Operations on bones. In this group anaesthesia was induced with the ether and chloroform mixture and continued with pure ether.

Age	Sex	Condition	Operation	Blood Sugar. 1.	2.	3.
57	F.	Hallux Valgus	Mayo	.087%	.143%	.1%.
22	F.	" "	"	.09%	.154%	.125%
22	F.	" "	"	.1%	.154%	.133%
24	F.	Hallux Rigidus	"	.095%	.143%	.125%
38	M.	Arthritis	Arthrodesis	.09%	.18%	.133%
27	M.	Genu Valgum	Osteotomy	.11%	.166%	.143%
35	M.	Fracture	Plating	.093%	.143%	.13%
31	M.	Fracture	Drilling	.1%	.166%	.133%

The operations in the appendicectomy, cartilage and bone groups lasted twenty minutes in each case. Approximately the same amount of anaesthetic was used as in group 1.

This group consisted of patients who had undergone the operation of cholecystectomy. The operation time was thirty minutes. They were all females. None had any clinical signs of liver injury.

		Blood Sugar.		
Age	Anaesthetic	1.	2.	3.
45	E.C. and Ether	.1%	.166%	.143%
36	E.C. and Ether	.085%	.143%	.133%
60	E.C. and Ether	.09%	.174%	.133%

Blood sugars were collected in a group of four patients who had a laparotomy performed and nothing else. They were all males. The operation lasted half an hour in each case. The amount of anaesthetic used was approximately the same as in the cholecystectomy group. The anaesthetic was E.C & Ether in each case.

		Blood Sugar.		
Age	Condition	1.	2.	3.
52	Cancer of colon	.09%	.143%	.133%
31	Sarcoma	.09%	.166%	.133%
51	Cancer of stomach	.095%	.143%	.125%
50	Cancer of stomach	.095%	.166%	.133%

A review of the results so far obtained shows that the type of operation has liitle effect on the hyperglycaemic

response to ether anaesthesia. The rise in blood sugar in females is slightly less than in males.

The next point I attempted to establish was the point at which the rise in blood sugar occurred. The cases were all males. The operation was the radical cure of hernia in each case. The anaesthetic was the same - E.C. & Ether. The amount of the anaesthetic was roughly the same . The operation lasted half an hour in all cases. The blood sugar was determined immediately before the anaesthetic was begun, immediately after induction, at ten minute intervals during the operation, and again three hours after the termination of the operation. The results were as follows :-

	Blood Sugar.					
Age	1.	2.	3.	4.	5.	6.
20	.09%	.125%	.148%	.148%	.125%	.09%
24	.1%	.133%	.154%	.154%	.166%	.133%
41	.09%	.143%	.16%	.166%	.154%	.125%
53	.11%	.148%	.2%	.2%	.18%	.125%
46	.118%	.22%	.22%	.22%	.22%	.154%
46	.095%	.154%	.174%	.174%	.174%	.133%
43	.095%	.142%	.166%	.166%	.148%	.125%
28	.105%	.2%	.2%	.2%	.18%	.143%
27	.1%	.166%	.18%	.18%	.174%	.143%
31	.09%	.143%	.143%	.143%	.133%	.118%

Here again the individual variation is marked. In most cases

the blood sugar has not attained its maximum by the end of the induction of the anaesthesia. It reaches a plateau and by the end of the operation it has begun to decline. This may be due to the fact that the administration of the anaesthetic usually ceases some time before the end of the operation.

In view of the suggestion that the acidosis which accompanies ether anaesthesia, may have some influence on the hyperglycaemia, I tried to influence this by the method suggested by Henderson. His views have already been discussed so I will not recapitulate them. At the conclusion of the operation the patients inhaled 10% carbon dioxide in oxygen. The cases were all males undergoing the radical cure of hernia. The amount of anaesthetic, the duration of the operation, and the anaesthetic were the same in each case. The blood sugar was determined before beginning the anaesthetic, at the end of the operation, after inhaling 10% carbon dioxide in oxygen for fifteen minutes, and again three hours after the operation.

Blood Sugar.

Age	1.	2.	3.	4.
30	.08%	.125%	.118%	.1%
31	.09%	.18%	.174%	.133%
33	.095%	.166%	.143%	.1%
17	.09%	.166%	.16%	.11%
24	.09%	.174%	.143%	.11%
18	.09%	.154%	.143%	.09%
18	.105%	.18%	.18%	.133%

Administration of 10% carbon dioxide in oxygen for 15 minutes after anaesthesia contd.

	Blood Sugar			
Age	1.	2.	3.	4.
58	.085%	.166%	.133%	.125%
17	.095%	.19%	.174%	.133%
32	.08%	.133%	.1%	.09%

The volume of the breathing was greatly increased by this method and the skin became rosy pink in colour. If the acidosis is an acarbia as Henderson states then this method made good the deficiency. Its problematical effect on the blood reaction was not measured. However, the clinical fact that the 4 cases recovered more rapidly from the anaesthetic, was recorded. The results in column four compared with the corresponding column in the first group of cases, show a small but appreciable decrease. Was this due to cure of the acarbia or to more rapid elimination of the anaesthetic ?. I believe the latter is the true explanation.

Since one of the theories concerning ether hyperglycaemia is that the ether acts directly on the liver and causes the mobilization of glycogen, I attempted to increase the amount of glycogen in the liver. I know that Claude Bernard believed that glycogen is an internal secretion of the liver cells and is independent of the carbohydrate of the food. Nevertheless, most experimenters when they want to increase the store of glycogen

feed the animals a carbohydrate-rich diet. In this group of cases I administered 50 grams of glucose, as in the glucose tolerance test, four hours before the beginning of the operation. The anaesthetic was the same in each case - E.C. and Ether. The operations were all appendicectomies in males. They were interval cases. The results were ;-

Blood Sugar.

Age	1.	2.	3.
18	.095%	.143%	.118%
30	.105%	.166%	.125%
29	.11%	.18%	.133%
39	.105%	.133%	.11%
59	.085%	.154%	.13%

The blood sugars were determined immediately before the amaesthetic began, immediately after the operation, and again three hours later. From these results feeding glucose before anaesthesia has no effect on the hyperglycaemic response.

The next point which stimulated my curiosity, was the effect of anaesthesia on the diastatic index of the urine. It would have been better to determine this for the blood serum but I am not sufficiently qualified to do this accurately, according to the method of Somogyi. I did the next best thing, I determined it in the urine, before and after anaesthesia. I estimated it in the 24 hour specimen immediately before operation and in the 24 hour specimen immediately after operation. The method I used was that recommended by Panton and Marrack (265).

There were five cases in this group. The conditions for which they required operation were various but we have seen that the hyperglycaemic response to ether anaesthesia is not dependent on the disease. They were all males . The anaesthetic was E.C. and Ether in each case. The operation lasted thirty minutes in each case.

		Blood Sugar.			Diastatic Index	
Age	Operation	1.	2.	3.	Before	After
39	Gastro-enterostomy	.09%	.174%	.143%	16.7	16.7
52	" "	.09%	.176%	.15%	10.0	16.7
28	Herniotomy	.09%	.143	.105%	16.7	10.0
40	Arthrotomy	.09%	.166%	.133%	10.0	16.7
23	Osteosynthesis	.08%	.148%	.11%	10.0.	10.0

The blood sugars were determined in the usual fashion and the blood was removed immediately before anaesthesia began, immediately after the operation ended, and three hours later. The anaesthetic had no influence on the diastatic index of the urine.

Experience with the fasting blood sugar immediately before operation had long freed me from the delusion that there is any rise due to emotion. In many cases in which there was obvious excitement the fasting blood sugar was perfectly normal. However, I wished to see the effect of pre-anaesthetic medication on the hyperglycaemic response to ether anaesthesia. It is fairly well established that morhine causes an increase in blood sugar (191). If the mechanism of ether hyperglycaemia and morphine hyperglycaemia

was the same then the morphine would have a synergistic action on the hyperglycaemic response to ether. A composite group of cases was selected. The operations lasted from ten to thirty minutes, so that the amount of anaesthetic varied accordingly. The anaesthetic was C.E. and Ether in all cases. One hour before operation each patient was given 1/3 gr. omnipon and 1/150 gr. hyoscine. The blood sugar was determined at the usual intervals.

				Blood Sugar.		
Age	Sex.	Operation	Time in Min.	1.	2.	3.
49	M.	Gastroenterostomy	30	.1%	.154%	.11%
56	M.	Manipulation	10	.105%	.18%	.148%
27	M.	Herniotomy	15	.1%	.154%	.086%
52	M.	Herniotomy	20	.095%	.182%	.143%
34	M.	Herniotomy	15	.1%	.166%	.143%
25	M.	Arthrodesis	25	.1%	.154%	.133%
36	F.	Goitre - non-toxic	30	.095%	.154%	.133%
37	F.	Excision of Coccyx	15	.105%	.19%	.154%
43	M.	Osteosynthesis	20	.09%	.166%	.13%
54	F.	Mayo - Hallux Valg.	15	.11%	.182%	.143%
47	M.	Herniotomy	30	.09%	.144%	.11%

The results of this group are similar to those of group one. The conclusion is that omnipon and scopolamine has no effect on the fasting blood sugar and no synergistic action on ether hyperglycaemia.

The barbiturates have been used in preanaesthetic medication. Moreover one of them, amytal, has been shown to have no

effect on the blood sugar - Page(178). Macleod (146) showed that this drug prevented the development of piqure hyperglycaemia. Campbell and Morgan (40) demonstrated that it prevented the hyperglycaemia of ether in the experimental animal. They also found that it had no effect on epinephrine hyperglycaemia. They considered, on good evidence, that it prevented hyperglycaemia of central origin. A composite group of cases was chosen to investigate the action of amytal. They were all males and the operation time varied from fifteen to thirty minutes. The anaesthetic in each case was E.C. and Ether. Three grains of amytal were given to each at 10 p.m. on the night before operation and six grains one hour before operation. The sedative effect was very much less marked than with omnipon and scopolamine. The blood sugars were taken at the usual times.

				Blood Sugar		
Age	Sex	Operation	Time	1.	2.	3.
59	M.	Gastro-enterostomy	30	.087%	.11%	.1%
20	M.	Herniotomy	15	.085%	.118%	.07%
25	M.	Herniotomy	15	.085%	.11%	.07%
34	M.	Herniotomy	15	.09%	.11%	.077%
42	M.	Herniotomy	15	.09%	.1%	.077%
27	M.	Herniotomy	15	.09%	.11%	.07%
17	M.	Herniotomy	15	.09%	.1%	.08%
45	M.	Gastro-enterostomy	30	.08%	.11%	.085%
51	M.	Herniotomy	20	.087%	.1%	.09%
38	F.	Excision of breast	45	.09%	.118%	.083%

These results show that the pre-anaesthetic administration of amytal has a profound effect on ether hyperglycaemia. It almost entirely inhibits it. The average rise in blood sugar in this series was .0234%. The average rise in group one was .0657%. The marked individual variation in hyperglycaemic response, which was noted in the other cases, has now disappeared and the results irrespective of age, operation, and time of anaesthesia up to forty-five minutes closely conform. Since amytal inhibits those hyperglycaemias of central origin, these results are strong evidence in favour of the view that ether has a central action on the piqure centre.

The effect of spinal anaesthesia on the blood sugar was studied. The anaesthetic used was heavy percaine and the dose was 1.8 ccs. Half an hour before the spinal puncture, ½ gr. of ephedrine was injected intramuscularly. The blood sugar was determined at the usual times i.e. immediately before the anaesthetic was given, immediately after the operation ended, and three hours later. The blood pressure was taken immediately before spinal puncture, and then at five minute intervals until the conclusion of the operation. In this group there were four males and one female. The operations lasted for fifteen minutes in each case. The blood pressure readings will be appended after those of the blood sugar.

				Blood Sugar		
Age	Sex	No.	Operation	1.	2.	3.
38	M.	1.	Herniotomy	.09%	.125%	.1%

Effect of spinal anaesthesia on the blood sugar contd.

Age	Sex	No.	Operation	Blood Sugar 1.	2.	3.
33	M.	2.	Herniotomy	.085%	.11%	.095%
19	M.	3.	Herniotomy	.085%	.143%	.12%
19	F.	4.	Herniotomy	.09%	.125%	.105%
19	M.	5.	Appendicectomy	.085%	.143%	.11%

The blood pressure readings were :-

No. 1. Before spinal puncture - 140/85

At five minute intervals after - 140/85, 130/85, 130/85, 135/90.

No 2. Before spinal puncture- 155/80.

At five minute intervals after - 145/85, 130/85, 120/80, 120/80

No. 3. Before spinal puncture - 140/90.

At five minute intervals after - 120/80, 105/65, 90/60, 95/65.

No. 4. Before spinal puncture - 130/90.

At five minute intervals after - 150/100, 120/90, 120/80, 120/80.

No. 5. Before spinal puncture - 175/100.

At five minute intervals after - 140/100, 155/100, 125/90, 100/75.

There is a slight but definite rise in blood sugar with spinal anaesthesia. The average for the series was .0422%. It appears that there is some relationship between the fall in blood pressure and the hyperglycaemia. Of course each case had ½ gr. of

ephedrine and to exclude its action as a hyperglycaemic action I used myself and my colleagues as controls. The blood sugar was determined in each case and with a similar preparation to those who had received spinal anaesthetics. After the blood had been taken ½ gr. of ephedrine was injected into each intramuscularly The blood sugar was determined immediately after the injection, again in half an hour, and again in 1½ hours. The blood sugars are numbered in the following manner ;- 1. before the ephedrine. 2. immediately after. 3. half an hour later. 4. one and a half hours later.

		Blood Sugar.			
Age	Sex	1.	2.	3.	4.
23	M.	.1%	.09%	.09%	.074%
25	M.	.105%	.09%	.09%	.08%
32	M.	.105%	.1%	.1%	.09%

From these results the injection of ½ gr. of ephedrine has no effect on the blood sugar.

The work of Epstein and his collaborators (73) has shown that trauma has some effect on the blood sugar. Of course under general anaesthesia it is very difficult if not impossible to estimate the hyperglycaemic effects of trauma apart from those of the anaesthetic when the factor of shock is absent. It is well known (6) that shock has a marked hyperglycaemic effect. I estimated the blood sugar in fractures and head injuries, where there were no clinical signs of shock. The results are:-

The blood sugar was taken within two hours of the injury - that is as soon after the receipt of the injury as it was reasonably possible, after an interval of three hours from the first blood sugar estimation, and again the following morning. This last estimation was really equivalent to twenty four hours later, since for various reasons, patients admitted in the forenoon were chosen. There were no clinical signs of shock. The blood pressure readings are appended. The cases were all males who had sustained fractures of the tibia and fibula, in the region of the shaft.

		Blood Sugar		
Age	Blood Pressure	1.	2.	3.
41	140/80.	.154%	.125%	.09%
26	120/70.	.125%	.125%	.07%
60	120/75.	.125%	.125%	.085%
21	120/70.	.11%	.133%	.08%
40	125/70.	.143%	.11%	.1%
56	135/80.	.105%	.11%	.09%
34	115/65.	.133%	.133%	.1%
40	120/70.	.133%	.133%	.09%
56	145/80.	.105%	.11%	.1%
21	115/65.	.1%	.125%	.095%

These results show that trauma can cause a rise in lood sugar for none received any food until after the second blood ugar had been taken. The average period between the last meal and he first blood sugar was four and a half hours. Recent work has hown that the blood pressure is not always an accurate measure of

the degree of shock. If this is so then the influence of some degree of shock undetectable clinically may have been responsible.

The nervous control of carbohydrate metabolism was established by Claude Bernard. Although I could not produce piqure hyperglycaemia in the human subject, I examined the blood sugar in a series of head injuries. The blood sugar was taken at the same times as in the group comprising fractures of the tibia and fibula. They were all males. No food was taken between the receipt of the injury and the estimation of the second blood sugar. The blood pressure was estimated and recorded.

		Blood Sugar		
Age	Blood Pressure	1.	2.	3.
45	130/70	.09%	.125%	.09%
52	140/80	.118%	.125%	.1%
19	120/70	.1%	.125%	.085%
24	120/75	.11%	.125%	.08%
23	110/70	.143%	.143%	.1%
28	115/75	.125%	.143%	.09%
30	105/65	.166%	.154%	.09%
20	120/70	.118%	.133%	.085%
24	120/70	.11%	.125%	.1%
40	130/80	.09%	.125%	.09%

These results show that head injury causes an increase in the blood sugar of temporary duration. The average rise in blood sugar is rather higher than in the corresponding group of

fractured tibiae. Davidson and Allen (64) found that there was diminished sugar tolerance for some considerable time after concussion. In the series I have recorded there was a varying period of unconsciousness but it was of short duration - a few minutes - in each case.

Shock has a marked effect on the blood sugar as well as the blood pressure. This has been shown by Aub and Wu (6). When general anaesthesia extends over an hour signs of shock begin to appear and this complicates the hyperglycaemic response and increase unduly(Minnitt - 172). These views are widely accepted so I have only estimated the blood sugar in three cases of shock. The cause was injury in each case and no anaesthetic was given. The blood sugar was estimated two hours after the injury, five hours after the injury and next morning, as in the head injury group.

				Blood Sugar.		
Age	Sex	Injury	Blood Pressure	1.	2.	3.
15	M.	Fractures	80/60	.2%	.17%	.1%
39	M.	Fract. Skull.	90/65	.15%	.2%	.11%
14	M.	Fractures	75/55	.2%	.24%	.12%

In the first and third cases glycosuria was also present. These results confirm the generally accepted view.

The Effect of Local Anaesthetics on the Blood Sugar.

A popular method in recent years for the reduction of fractures in the injection of 2% novocaine solution into the haematoma at the site of the fracture. The amount of the solution

injected varies according to the bone fractured. For fractures of the shaft of one of the long bones of the lower limb thirty ccs of this solution are injected into the haematoma at the site of fracture. In one case, where a fractured tibia had been reduced by this method, sugar was found in the urine on the following day. It was shown to be glucose by the glucosazone test. The patient had his blood sugar investigated on the second day after injection of the novocaine solution. It was found to be normal. The sugar tolerance curve was also normal. The natural conclusion was that the glycosuria was due to the novocaine injection. A series of cases had their blood sugar investigated after the injection of 2% novocaine into the haematoma round a fracture. The blood sugar was estimated before the injection, three hours after the injection, at 11 a.m. the next day, again at 3 p.m., and the following morning at 11 a.m. The urine was examined for sugar. These times were selected as the most opportune after a series of trial estimations. In several cases a prolonged hyperglycaemia with glycosuria resulted. In others there was a prolonged hyperglycaemia of a lesser degree without glycosuria. In others again there was no very significant variation. The group of fractured tibiae which had no anaesthesia of any kind, and which I have already described, served as controls. A rise in blood sugar occurs following a fracture even when no anaesthetic is used. I could find no reference in the literature to a hyperglycaemic response to novocaine. Hirschfelder and Bieter (245) state that novocaine is

destroyed in the liver. The most likely explanation of the rise in blood sugar appeared to be a direct action on the liver cells. The variability of the response could be explained by the rate of absorption of the novocaine. In those cases in which the rise in blood sugar was well marked, the absorption of the novocaine had been rapid. Intravenous novocain is a liver poison and is fatal when administered this way - Mayer (163). Adrenaline was not added to the novocaine solution. The cases were all fractures of the lower limb and similar to the controls. They all received 30 ccs of 2% novocaine into the haematoma round the fracture.

Blood Sugar

Age	Sex	Fracture	1.	2.	3.	4.	5.	Urine
38	M.	Femur	.12%	.12%	.19%	.19%	.15%	Sugar.
53	M.	Tibia	.09%	.2%	.2%	.16%	.14%	Sugar.
23	M.	Tibia	.1%	.15%	.2%	.18%	.14%	Sugar.
22	M.	Tibia	.11%	.14%	.18%	.15%	.09%	Sugar.
38	M.	Femur	.105%	.16%	.18%	.18%	.13%	Nil.
54	F.	Tibia	.125%	.22%	.22%	.22%	.18%	Sugar.
34	M.	Femur	.133%	.133%	.11%	.12%	.1%	Nil.
47	M.	Tibia	.069%	.1%	.12%	.12%	.11%	Nil.
56	M.	Tibia	.105%	.125%	.125%	.11%	.1%	Nil.
24	M.	Tibia	.105%	.133%	.142%	.1%	.09%	Nil.

In these cases there was no clinical evidence of shock. The blood pressure was not recorded.

In a small series of cases, the effect of 2% novocaine

solution used in operative procedures, was investigated. The operations were performed for herniae and cysts. Very little effect was observed in the blood sugar. This might be due to a slow rate of absorption, and to loss of a certain amount of anaesthetic through the skin incision. There were five cases. The blood sugar was determined before operation (1), at the end of the operation (2), five hours later (3) and next morning (4). The amount of novocaine used was 30 ccs of 2%.

			Blood sugar			
Age	Sex	Operation	1.	2.	3.	4.
58	M.	Cyst of Neck.	.105%	.1%	.12%	.09%
35	F.	Cyst of breast.	.118%	.1%	.09%	.09%
40	M.	Hernia.	.105%	.087%	.118%	.08%
56	M.	Hernia.	.105%	.11%	.118%	.125%
60	M.	Hernia.	.1%	.09%	.12%	.1%

The use of novocaine did not produce a hyperglycaemia. It prevented the occurrence of the hyperglycaemia which is usually associated with trauma.

Summary and Conclusions.

1. I have given a full historical survey of the problem of the rise in blood sugar associated with anaesthesia.
2. I have examined the literature on the subject and the related problems in carbohydrate metabolism, in considerable detail.
3. I have reviewed the various theories of the mechanism of ether hyperglycaemia.

4. There is a well marked hyperglycaemia associated with ether anaesthesia.
5. There is marked individual variation.
6. The type of operation has no effect.
7. The length of the operation has no effect - short of the production of shock which has a marked hyperglycaemic effect.
8. The amount of anaesthetic used has no effect.
9. Induction of the anaesthesia by ether and chloroform mixture, nitrous oxide or ethyl chloride makes no difference.
10. The pre-anaesthetic administration of omnipon and scopolamine has no influence on the hyperglycaemia.
11. The pre-anaesthetic administration of glucose has no effect on the hyperglycaemic response to ether.
12. The post-anaesthetic administration of 10% carbon dioxide in oxygen hastened the recovery from the anaesthetic. It also accelerated slightly the return to normal of the blood sugar.
13. The rise in blood sugar is present at the end of the period of induction. It then continues as a plateau and has usually begun to fall again by the end of the operation. The impression gained was that it began to fall when the administration of the anaesthetic stopped.
14. Ether anaesthesia has no effect on the diastatic index of the urine.
15. The pre-anaesthetic administration of amytal almost entirely prevents the hyperglycaemia of ether anaesthesia. This is in agreement with the work of Campbell and Morgan (40).

16. The number of females in the series is small but the impression gained was that the hyperglycaemic response to ether, was slightly less in females.

17. I believe that the mechanism of ether hyperglycaemia is mainly due to the depressant action of the ether on the piqure centre in the medulla. Alteration in the hydrogen ion concentration - increase - has a slight effect. This is probably caused by some respiratory mechanism. The grounds on which I base this view are :-

(a) Amytal prevents the occurrence of hyperglycaemias of central origin. It prevents ether hyperglycaemia.

(b) Amytal has no effect on the hyperglycaemia due to epinephrine.

(c) The amount of anaesthetic - short of the production of shock - has no effect on the hyperglycaemic response. This rules out the direct effect of ether on the liver cells as a cause.

(c) The blood sugar has begun to fall while the acidosis is still marked. This appears to exclude acidosis as the main factor.

(d) The continuous administration of oxygen during the anaesthetic has no effect on the hyperglycaemic response. I gathered this from my own observations and the literature.

(e) The experiments of Ross and Davis on anaesthesia in dogs without the pancreas and dogs with part of the

(e) contd.

pancreas remaining are inconclusive. The difference in the hyperglycaemic response in the two groups is too small to be of any importance. I consider that depression of the internal secretion of the pancreas is not part of the mechanism of hyperglycaemia of ether anaesthesia.

18. The blood sugar has been estimated in 105 cases under general anaesthesia and I consider this a sufficient number to draw conclusions from.

19. There is a rise in blood sugar under spinal anaesthesia.

20. It is much less marked than ether hyperglycaemia.

21. It appeared to have some relation to the fall in blood pressure.

22. It was not caused by the ephedrine injected before the spinal anaesthetic was given, since the injection of ephedrine in a control group caused no rise in blood pressure.

23. Trauma causes a rise in blood sugar even when there is no clinical evidence of shock.

24. This was compared in a group of fractured tibiae and a group of head injuries. The average rise was slightly greater in the head injury group.

25. A rise in blood sugar was obtained on injecting 30 ccs of 2% novocaine into the haematoma round a fracture.

26. The response of the blood sugar was variable and sometimes

26. contd.

did not occur at all. When it did occur it was prolonged - lasting about 48 hours and often associated with glycosuria.

27. The explanation suggested is that the novocaine was absorbed rapidly and poisoned the liver cells, in those cases associated with marked hyperglycaemia.

28. Small operations performed under 2% novocaine were not associated with hyperglycaemia.

29. The explanation advanced is that the absorption of the novocain was slow.

30. I can find no references in the literature concerning the blood sugar in spinal and local anaesthesia.

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