KETOSIS OF ANAESTHESIA*

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ETHER glycosuria has been known since 1853 (1) and the upset of the blood sugar concentration associated with anaesthesia has been studied in great detail by numerous workers. The ketosis of anaesthesia has however received very little attention indeed from research workers It was first recognized in 1893 by Becker (2) and was investigated extensively by Caldwell and Cleveland (3) twenty years later. These workers were unable to correlate the severity of postoperative ketonuria with duration of operation, with upset of blood carbon dioxide combining power, nor yet with the development of postoperative vomiting. The preoperative administration of sodium bicarbonate did not prevent ketonuria nor was glucose given before operation any more effective. Schulze (4) in 1924 showed that a ketosis could occur after spinal and local anaesthesia equally as severe as that in cases who had received inhalation anaesthetics, and there the matter has rested, though there have been more recent studies (5) which, with one exception, have added very little to our knowledge of the subject

Minnitt in 1932 (6) suggested that anaesthetic ketosis was evidence that the patient had been temporarily converted into a diabetic, and he thought that the adrenalin discharged from the adrenal glands completley antagonized the action of the normal anti-diabetic hormone insulin. It has, however, since become apparent that the antagonism between adrenalin and insulin is by no means as complete as was then believed. Also, the preoperative administration of insulin has proved disappointing as a means of preventing both ketosis and postoperative vomiting. Indeed, the results obtained from this measure when I first began to use it in 1940 were so uniformly unsatisfactory that I felt it desirable to re-investigate the whole matter.

METHODS

Since the basic problem under investigation was a disturbance of uncertain duration which proved to have no regularly recurring peak of severity, the determination of the blood concentration of ketone at some arbitrary time did not seem likely to be of value. Instead the 24-hour output of acetone in the urine was measured. This was estimated in 150 cases. The methods of analysis used were as follows. The acetone and aceto-acetic acid in the urine were removed in one portion by distillation and estimated by combination with alkaline hypoiodite as iodoform (7). In 100 cases the resulting figure was used as a measure of the ketosis. In 25 of these cases, the β-hydroxybutyric acid was converted to acetone by refluxing with potassium dichromate. This estimation was, however, exceedingly tedious to perform and after it had been shown that there was a reasonably close correlation between the hydroxybutyric acid output

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and that of acetone and aceto-acetic acid taken together, only the latter was estimated. In the remaining 50 cases, a quantitative estimate of the aceto-acetic acid content of the urine was made by means of the Rothera nitroprusside reaction.

Blood sugars were estimated by the copper-iodate method of Shaffer, Hartmann, and Somogyi (8) and in most instances the results were checked by a simultaneous Folin Wu estimation with a Lovibond colorimeter.

When Quick's (9) test of liver function was performed the excreted hippuric acid was estimated gravimetrically after precipitation with hydrochloric acid. A correction was made for the amount of hippuric acid still retained in solution. It is freely admitted that this is a somewhat inaccurate test (10) but in the circumstances then prevailing no other method of testing liver function was available which did not presuppose a normal carbohydrate metabolism. Further, the thymol turbidity and caphalin flocculation tests, dependent as they are on a normal blood albumin/globulin ratio, could not be used as they would be liable to be upset by the changes in plasma protein content which are part of the regenerative process which occurs after blood loss at operation.

Urinary acid was determined by titration with N/10 NaOH using phenolphthalein as an indicator and the urinary ammonia by formol titration with the same indicator. When the ammonia/urea ratio was required the latter substance was estimated by the hypobromite method with a Doremus ureometer.

Results

The Anaesthetic

The ketone output for the first 24-hour period was investigated in a group of patients subjected to various types of anaesthesia. The results are shown in Table I It will be apparent that the most severe ketosis appeared in those to whom ether or chloroform were given in quantity When truly minimal ether was used as a supplement to nitrous oxide and oxygen and after the administration of cyclopropane, the severity of the ketosis was much less. When

TABLE I

Anaesthetic	No of cases	24-Hour postoperative acetone output	
		Mean (mg)	Standard deviation (mg)
Ether	124	54	59
Chloroform	6	81	42
Cyclopropane	15	13	10
N_2O and O_2 with minimal ether	19	11	7
N_2O and O_2 with thiopentone	19	19	22
Spinal (alone)	15	49	60
Supplemented spinal	3	73	(range 51–107)
Local for nasal operation	9	23	24

thiopentone was used either alone or as a supplement to N_2O, ketosis was not so severe. With spinal anaesthesia and with topical cocaine and adrenalin for submucus resection of the nasal septum, the output of acetone was very variable. In some patients, it was negligible. In others it was almost as considerable as in those to whom ether or chloroform had been given.

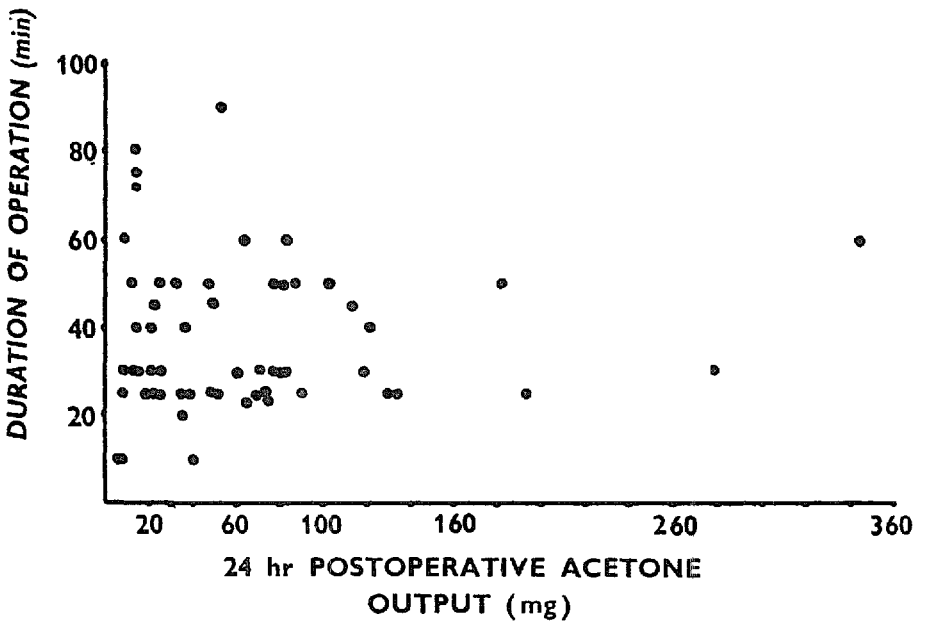

FIGURE 1

Time Factors

The duration of the anaesthetic obviously was of little importance in governing the severity of the ketosis (Fig. 1). Indeed, the correlation coefficient between duration of operation and acetone output was 0.049. Further, when the hourly output of acetone after operation was measured it became apparent that the disturbance was not one which was at its maximum immediately at the end of the anaesthesia and thereafter underwent progressive amelioration. Indeed, the ketone output generally increased for some hours after operation. It recovered a little about 12-16 hours later and then developed a second peak, probably because of the development in some patients of postoperative vomiting. (Fig. 2.)

RELATION TO OTHER METABOLIC UPSETS OF ANAESTHESIA

Acidosis

While it was recognized that the estimation of the plasma CO_2 content and combining power was the most satisfactory method of assessing acidosis at any given moment, it was felt in these cases more appropriate to measure the 24-hour urinary output of acid in order to have some factor to which to relate the acetone output for the same period. To this end, the titrateable acidity of the urine, the ammonia output, and the ammonia/urea ratio were determined in 36 cases where ether anaesthesia had been employed. These results were then examined to see

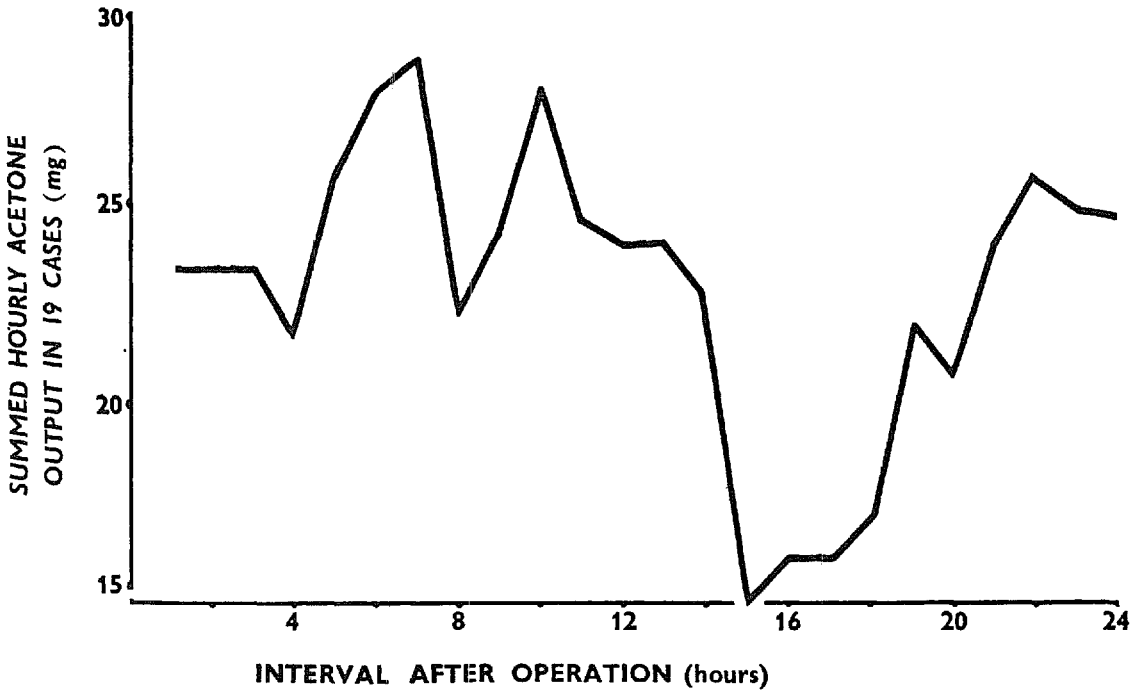

FIGURE 2

whether there was any real association between them and using the correlation coefficient as a measure, no evidence of a parallelism between total acid output, ammonia output, and the ammonia/urea ratio on the one hand, and the degree of ketonuria on the other, could be demonstrated.

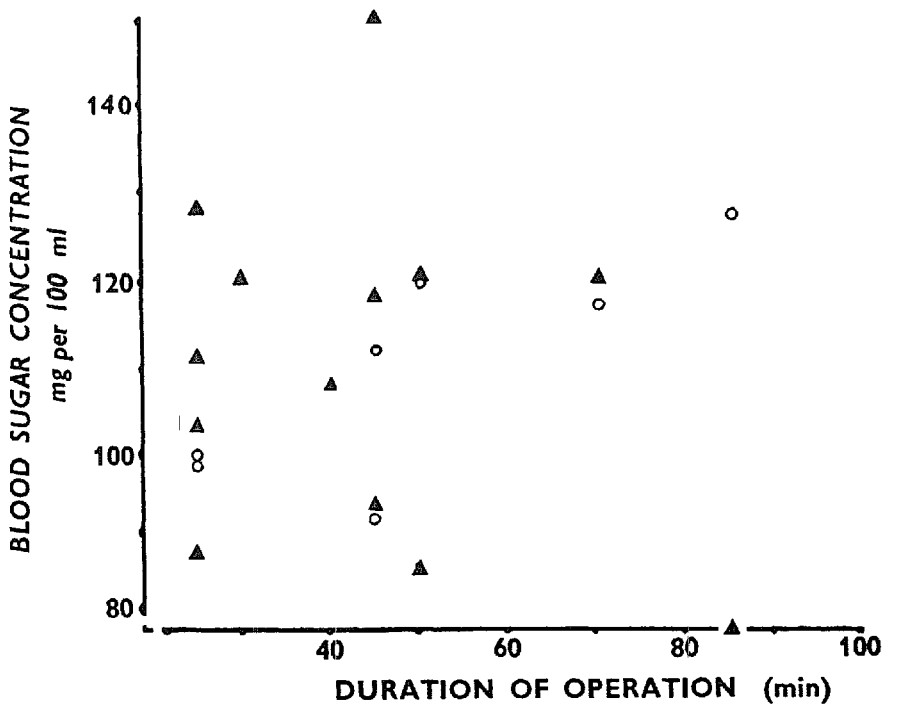

FIGURE 3. O, insulin; △, no insulin

Anaesthetic Hyperglycaemia

In 30 cases the blood sugar level at the end of the anaesthetic was determined (Fig. 3). (Unfortunately it was not practicable to determine the preoperative level but the graph of duration of anaesthesia against blood sugar concentration was nearly a straight line. In fact, if the line obtained was extrapolated to zero time it gave a value corresponding to the normal fasting blood sugar.)

There was no relationship between the blood sugar concentration at the end of the anaesthetic and the severity of the ensuing ketosis in these cases, the correlation coefficient being only 0.11. (Fig. 4.)

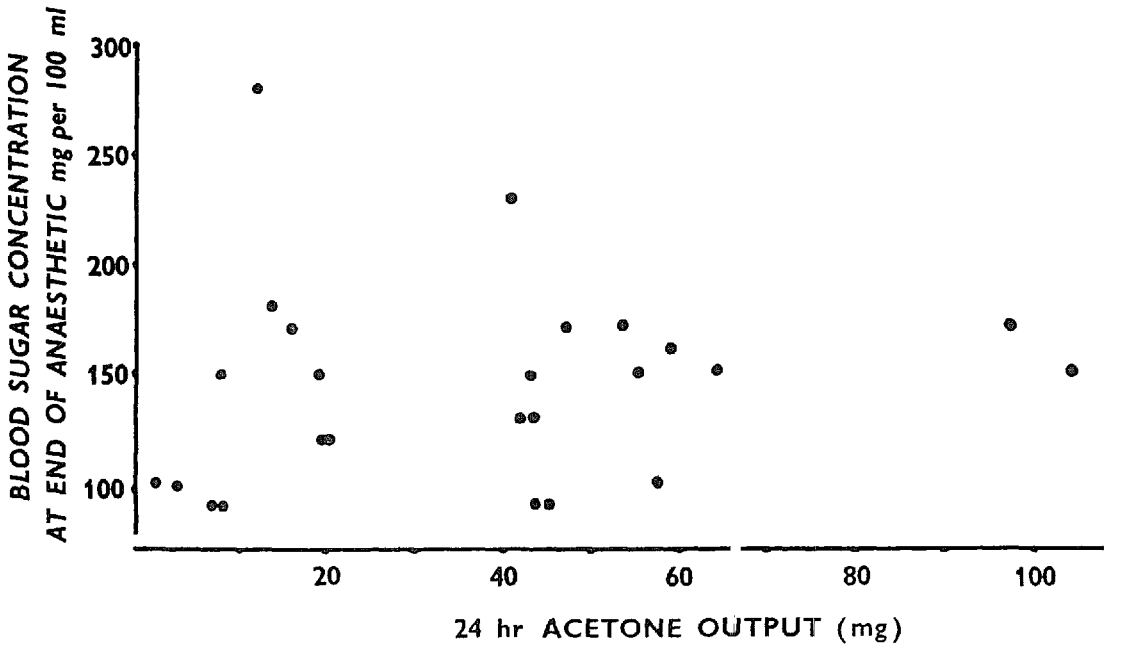

FIGURE 4

Relation to Liver Function

The only feasible measure of liver function available to me in these cases was Quick's test of the ability of this organ to form hippuric acid from sodium benzoate. This was carried out in 6 patients in whom the urinary ketone was estimated. In Table II will be found the amount of hippuric acid excreted by them, expressed as a percentage of the maximum possible. It will be seen that there was no very convincing correlation between the liver function and the amount of ketone produced in the first 24 hours after operation.

Effectiveness of Therapeutic Measures

The first measure used in an attempt to control postoperative ketosis was the administration of insulin in doses varying from 5 to 10 units half an hour before operation. This failed completely in 11 cases (Table III).

On the other hand the administration of glucose in 4 hourly doses of 6 oz. of 10 per cent. solution per rectum during the first 12 hours after operation produced a striking and significant reduction in the severitv of the ketosis following anaesthesia (Table IV).

TABLE II

Anaesthetic	Liver function % of maximum	24-Hour urinary acetone output (mg.)
N_2O and O_2 with minimal ether	83	3
Ethyl chloride and ether	81	24
N_2O and O_2 and minimal ether	68	10
N_2O and O_2 and thiopentone	67	4
N_2O and O_2 and chloroform	64	19
Ethyl chloride and ether	58	44

TABLE III

Special treatment	No of cases	24-Hour postoperative acetone output: Mean (mg.)	24-Hour postoperative acetone output: Standard deviation (mg.)
Nil	124	54	59
Insulin before operation	13	50	36

TABLE IV

Special treatment	No of cases	24-Hour postoperative acetone output: Mean (mg.)	24-Hour postoperative acetone output: Standard deviation (mg.)
Nil	124	54	59
Rectal glucose after operation	6	15	11

Relation to Postoperative Vomiting

In the patients who were anaesthetized with ether the ketosis was undoubtedly more severe in those who vomited after operation (Table V), but in those anaesthetized with cyclopropane or nitrous oxide oxygen and minimal ether this difference was by no means so striking.

In general, then, postoperative ketosis appeared from this study to be a disturbance whose severity was governed mainly by the type of anaesthetic employed. Its severity was unrelated to the duration of the operation, in sharp contrast to the rise in blood sugar produced by ether anaesthesia which continues progressively at least for the first two hours of the administration. There was no convincing relationship between acidosis and ketosis nor between this latter

TABLE V

	No of cases	24-Hour postoperative acetone output: Mean (mg)	24-Hour postoperative acetone output: Standard deviation (mg.)
Patients not sick after operation	33	44	32
Patients sick after operation	24	69	35

upset and the depression of liver function produced by the anaesthetic. Preoperative insulin did not control the ketosis but the rectal administration of glucose after operation largely prevented the upset.

Discussion

For the interpretation of these findings it is necessary to consider the basic physiology of the metabolic processes of the body (11). It has been accepted for many years that ketonuria indicates some upset of carbohydrate metabolism but it was not until recently that it was realized that the essential basis of this phenomenon lies just as much in the processes of fat metabolism. It is now known, partly as a result of studies with radioactive isotopes (12), and partly from other work (13, 14), that ketones are not an endogenous toxin They are not even the inert products of a disordered metabolism. Aceto-acetic acid is in fact a necessary intermediary in the mobilization of fat when this substance provides energy for the tissues of the body.

Fat consists of glycerol and a fatty acid. The first stage in its destruction is the separation of these. The glycerol is at once swept into one of the enzyme cycles where it is metabolized without difficulty by the tissues. The fatty acid is conveyed to the liver where it is broken down by oxidation, probably at each alternate carbon atom until groups of 2 carbon atom fragments are obtained. These may at once unite with the recently discovered substance coenzyme A and then be directly oxidized to carbon dioxide and water in the liver. Alternatively, again, with the aid of coenzyme A two such 2 carbon atom fragments may unite to form aceto-acetic acid. This latter substance then leaves the liver and is carried in the blood stream to the tissues where it is oxidized once more with the aid of coenzyme A to carbon dioxide and water with the release of the energy (Fig. 5).

The liver is the body's metabolic storehouse. It doles out the materials for tissue metabolism from the glycogen and fat in its cells. It is not, however, selective and it provides only the total amount of material necessary to meet the body's energy requirement. The division of this material between fat, which is discharged into the circulation as aceto-acetic acid, and glycogen, which is broken down to glucose for distribution, is determined only by the availability of these substances in the liver cells. If there is a lot of glycogen there, mainly

glucose will be supplied. If there is virtually no glycogen in the liver, all the body's needs will be met by supplying aceto-acetic acid from fat. Ketonaemia therefore signifies essentially a reduction in the liver glycogen content with an accompanying increase in its fat content. Ketonuria simply means that the level of blood ketones has risen above the renal threshold for these substances which lies like that of glucose only a little above the normal resting blood level.

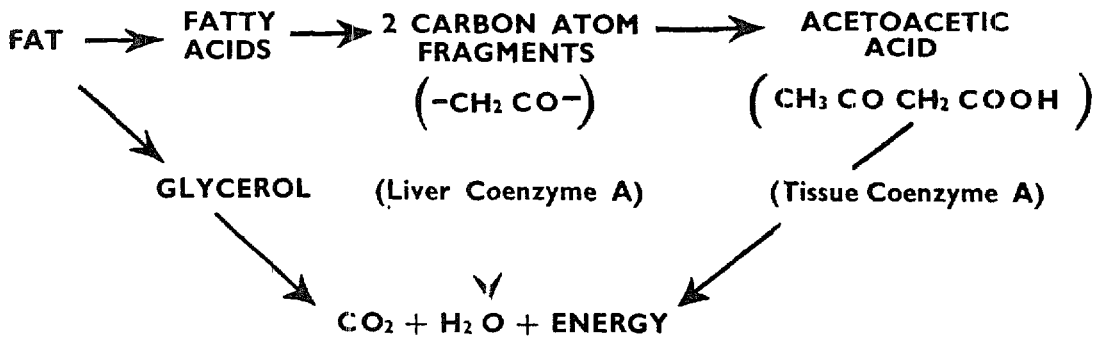

FIGURE 5

The ketosis of anaesthesia thus signifies relative increase in liver fat or relative decrease in liver glycogen. It is therefore necessary to consider what factors go with anaesthesia and operation to tend to bring about such changes. It is conceivable that direct liver poisoning might be responsible but the upset noted had none of the characteristics of a toxaemia induced by the anaesthetic drug. It is true that it was definitely more marked with the "toxic" agents ether and chloroform, but the severity of the upset bore no relation to the length of the anaesthesia. Further, the acme of the disturbance did not appear until after the anaesthetic agent had been withdrawn. This compares sharply with the hyperglycaemia of anaesthesia which becomes progressively worse as the administration of the drug proceeds until all the glycogen in the liver has been mobilized or until the anaesthetic is stopped and then recovers steadily. Also there was no correlation between ketosis and acidosis and this latter change is generally accepted as a true measure of the toxicity of an anaesthetic agent. Lastly, a direct test of liver function failed to indicate any association between ketosis and poisoning of this organ.

The deprivation of food to which the patients were subjected must undoubtedly have played some part in reducing the liver glycogen content. Starvation alone will not, however, account for the conspicious differences in severity of the ketosis produced by different drugs. Further, the ketosis induced by comparable periods of deliberate starvation in experimental studies has not been of the severity noted here (15). Finally, the relative unimportance of starvation is emphasized by the fact that ketosis was almost as severe, when a non-toxic anaesthetic was given, in those who vomited and those who did not.

Another factor which must have been operative in some cases was the hyperadrenalinaemia of fear. Fear, however, was equally likely to mobilize liver glycogen with all types of anaesthesia. It, too, therefore fails to account for the

differences in the severity of the ketosis after the administration of different agents.

The mobilization of liver glycogen to produce hyperglycaemia during the anaesthetic must undoubtedly have played a part in the etiology of the ketosis. But it is difficult to understand the mechanism involved. For there is no apparent reason why some at least of the mobilized glucose should not have returned to the liver whence it was withdrawn. The ketolytic power of the rectal glucose given in the postoperative period indicates that the liver could still synthesize glycogen. Perhaps the mobilized glucose was lost in the urine; for ether glycosuria is a well-known clinical entity which was recognized before blood sugar levels could be estimated (1). There is another possibility. It was shown by Joseph who used the respiratory quotient as an indicator, that during anaesthesia the body burns only carbohydrate to provide energy (16). It may be that some of the mobilized glucose was lost in this way, but final proof of this awaits extended studies of the metabolic rate and respiratory quotient under anaesthesia.

Lastly, there is a completely unknown quantity. It has long been recognized that the lipoid soluble anaesthetics can cause a lipaemia and a transfer of fat from the periphery to the liver, in experimental animals (17, 18). No positive evidence on this matter was provided by the present study, but it is, I think, justifiable to surmise that this factor is the main one in the etiology of anaesthetic ketosis. For it alone will provide an explanation of the differences in severity of ketosis after various types of anaesthesia.

This work was done in the days when ether and chloroform were the mainstays of anaesthesia. I also estimated the acetone output after one modern method and found that the ketosis produced by anaesthesia with ether and chloroform is virtually the same as that which develops when trichlorethylene is used as a supplement to nitrous oxide and oxygen (Table VI).

TABLE VI

		24-Hour postoperative acetone output	
	No of cases	Mean (mg)	Standard deviation (mg)
Ethyl chloride-ether	124	54	59
N_2O and O_2 and trichlorethylene	7	62	67
Chloroform	6	81	42

Clinical Aspects

Before insulin was available it was all too common for a diabetic to go into a coma after an operation. It was, too, generally recognized that this accident was less likely if nitrous oxide and oxygen were used instead of the more toxic agents ether and chloroform. The belief therefore grew up that these agents tended to

aggravate the essential lesion of diabetes—which is a failure of the tissues to burn carbohydrate. This thesis seemed to be supported by Minnitt's (6) investigations. The present study has, however, shown that anaesthetic ketosis merely signifies that the liver's store of glycogen has been depleted without any more serious metabolic upset than a mild inbalance between carbohydrate and fat metabolism. The fact that the administration of a particular agent may give rise to ketosis does not preclude its use in a diabetic as in fact many anaesthetists already know well from practical observation. Indeed, all that is really necessary in the case of the diabetic during the operative period is to ensure that he receives at least his normal amount of insulin, so that his tissue carbohydrate metabolism can continue as usual, together with enough glucose given by a safe and certain route to be sure that his insulin does not cause hypoglycaemia. The period for which such a regimen is maintained must obviously be dictated by the time during which he cannot ingest his normal diet by mouth.

Summary

In summary it was found in a study of the urines of patients after operation that ketosis did not have the features of a toxic phenomenon produced by the anaesthetic. A review of the various physiological factors concerned, however, suggested that this disturbance must indicate a depletion of the liver's stores of glycogen. The factors which might be responsible seemed to be starvation, hyperadrenalinaemia caused by fear, hyperglycaemia due to the anaesthetic itself. This work has, however, tended to indicate that none of these factors will wholly explain the changes observed. It therefore seems probable that the explanation must lie in the increase in the fat content of the liver to which the so-called toxic anaesthetic gives rise. It has been quite clearly shown that the ketosis of anaesthesia is an entity apart from the ketosis of diabetes. An alteration in our outlook on choice of anaesthetic in the diabetic is therefore required.

Résumé

On a découvert en étudiant les urines des opérés que l'acétonémie n'avait pas les caractères d'un phénomène toxique produit par l'anesthésique. Cependant si l'on passe en revue les différents facteurs physiologiques concernés, il semble que ce trouble doit indiquer une déplétion des réserves glycogéniques du foie.

Les facteurs qui pourraient en être responsable semblent être l'inanition, l'augmentation dans le sang des facteurs surrénaux produite par la crainte, l'hyperglycémie causée par l'anesthésique lui-même. Ce travail, cependant, tend à indiquer qu'aucun de ces facteurs explique complètement les changements observés. C'est pourquoi il semble probable que l'explication de ce phénomène doit rester dans l'augmentation des corps gras dans le foie produite par l'anesthésique appelé toxique.

On a demontré définitivement que l'acétonémie de l'anesthésie est une entité différente de celle du diabète. Il faut donc changer notre façon de penser dans le choix d'un agent anesthésique chez le diabétique.

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