BLOOD SUGAR CHANGES IN HAEMORRHAGIC SHOCK OF PREGNANCY AND ASSOCIATED STATES.

by

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PREFACE.

This study was undertaken principally in the wards and Research Department of the Glasgow Royal Maternity and Women's Hospital, and also in the gynaecological department of Glasgow Royal Infirmary and in the Royal Samaritan Hospital.

One paper entitled "Hyperglycaemia and haemorrhagic shock in pregnancy - preliminary study" has been published in the Journal of Obstetrics and Gynaecology of the British Empire, 1953, 60, 785.

Due to the co-operation of Professor R.A. Lennie, Professor D.F. Anderson and Dr. J. Hewitt, it was possible to study all cases of shock occurring in the Glasgow Royal Maternity Hospital. The gynaecological cases were made available by Dr. Hugh Stirling and Dr. D. McIntyre, and the cardiac cases by Mr. K. Fraser and Dr. J.H. Wright. To all these gentlemen and to the various anaesthetists and resident staff who co-operated, I wish to express my thanks. I also wish to express to Dr. A.D.T. Govan, Director of Research at the Glasgow Royal Maternity Hospital, my indebtedness for his constant encouragement and helpful criticism throughout the course of this work.

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Although haemorrhagic collapse is one of the commonest emergencies with which the obstetrician has to deal, it is remarkable that no attempt has been made to study the metabolic responses of this condition with particular reference to the effect on the blood sugar level. Under certain circumstances it has been shown that carbohydrate and nitrogen metabolism may be greatly altered during pregnancy and the mechanism controlling these activities rendered unstable (Mukherjee and Govan, 1950; Govan, Mukherjee, Hewitt & Harper, 1951). In addition many pregnant patients appear to be peculiarly liable to become shocked even after apparently minor degrees of trauma. It would seem, therefore, that one might reasonably expect some variation from the average in the underlying metabolic processes during the shock phase in these patients.

For some considerable time efforts have been made to define these changes since it has been felt that in them the key to many of the problems associated with shock might be found. Since shock is so commonly associated with trauma and tissue destruction it is reasonable to expect some change in nitrogen and carbohydrate metabolism. The first study in relation

to the former appears to have been made by Cuthbertson (1929). This writer found that there was a definite degree of nitrogen catabolism following injury and that the output of nitrogenous material increased for several days subsequently. It soon became apparent however, that this catabolic phenomenon was not simply due to breakdown of tissue but was of more vital nature. In a further study on rats this author and co-workers (1939) concluded that the catabolic nitrogen was derived, not from the area of destruction but from tissue stores of protein. The idea of some fundamental change in general metabolism following injury has been suggested by Selye (1936) who has shown the existence of a common pattern in the response of the animal organism to various forms of injury and has related these changes to adrenal activity. This has received support from the work of Browne (1942) who found an increased output of steroids running almost parallel with the catabolism of nitrogen. Following further work, Cuthbertson (1943) considered that the increased nitrogen loss after injury might result in the breakdown of protein molecules in an attempt to supply some component amino acid of the protein molecules necessary for the repair process. If the remaining portion of

the protein molecule were metabolised, the nitrogenous portion would be transformed into urea, leaving the carbon chains to be stored as glycogen or utilised for energy production.

With regard to carbohydrate metabolism, probably the first study of one particular phase of this namely the changes in the blood sugar, was made by Claude Bernard (1877). He found that hyperglycaemia occurred following haemorrhage in experimental animals. This was subsequently confirmed by a number of workers Robertson (1935), Moon et al (1941), Mylon et al (1944). In the human subject Beecher (1949) and Wiggers (1950) have reported the occurrence of hyperglycaemia after haemorrhage and shock. All of these studies indicate the profound nature of the metabolic change following injury.

Working from another aspect Green and Bullough (1950) have shown that, after the injection of adenosine triphosphate (A.T.P.) into mice, a state of shock was produced similar to that following hind-limb ischaemia. Hyperglycaemia was a constant finding and therefore further support was given to the hypothesis of Green and his colleagues that the state of shock is fundamentally a profound interference with

carbohydrate utilisation.

Coincidental with all this investigation of shock-like conditions has been the discovery of A.C.T.H. and cortisone and their effects on tissue repair and the metabolism of protein, carbohydrate and electrolytes. The complexities associated with these substances are many but the correlation with the stress or shock syndrome has been brought more clearly into perspective and its relationship to the adrenals and anterior pituitary amplified. It was Loeb (1884) who first noted that patients with pituitary tumours frequently had a glycosuria. The work of Houssay and Magenta (1924) showed that the pituitary gland was intimately bound up with carbohydrate metabolism. They found that the removal of the pituitary gland caused an excessive sensitivity to the toxic action of insulin. It was thought up to that timethat the posterior lobe was the important part but Houssay and Potick (1929) showed conclusively by their experiments on toads that it was the anterior lobe which was responsible. Further work on animals by Pencharz, Cori and Russell (1936) confirmed this finding; also it had been demonstrated by Evans et al (1932) and Baumann and Marine (1932) that anterior pituitary extracts possessed a the diabetogenic

action.

It has been shown in experimental animals that A.C.T.H. and cortisone readily induce hyperglycaemia and glycosuria, but in man, the evidence of impaired sugar tolerance is usually slight since the doses are small in relation to body weight. However overdosage often causes an impairment of carbohydrate tolerance with a resulting rise in fasting blood sugar and a glycosuria. This is corroborated by the work of Elkington et al (1949) who noted that in 13 patients treated with A.C.T.H. some developed a slight glycosuria, and a small rise in the fasting blood sugar occurred in a few instances. Hench et al (1950) on the other hand did not find any impairment of carbohydrate tolerance in 23 patients given A.C.T.H. or cortisone.

Selye (1950) suggests that A.C.T.H. (cortico-trophin) is the one hormone of the anterior pituitary necessary for life and that in stress it is produced in increased quantity. This causes the adrenal cortex to increase its output of gluco-corticoids (including cortisone) which in turn act on the blood, lymphatic tissue, reticulo-endothelial system and protein metabolism. On the last named it causes an increased transformation of protein into sugar, although Engel

(1949) is of the opinion that the magnitude of the stress and the availability of new carbohydrate from precursors other than tissue protein might largely determine the magnitude of the protein catabolic response - since there is evidence of increased protein catabolism in all types of stress. According to Engel it may be that an increased need for carbohydrate is the first effect of stress in general.

All of this work related to non-pregnant subjects and so far as is known no communication has been made by any other worker on the nature of the changes particularly relating to blood sugar, which may occur during shock in the pregnant subject. The position is complicated by the fact that there is an increased production of steroids during normal pregnancy and the anterior pituitary is said to be inactive although it is known to hypertrophy during pregnancy. In view of this altered endocrine pattern during pregnancy it is conceivable that the metabolic response of the patient to stress may be grossly different from that found in the non-pregnant subject.

Most cases of shock in pregnancy occur near term in association with or following labour and this in itself may well alter circumstances considerably. It

was decided to investigate changes during and subsequent to shock in the pregnant subject with special reference to carbohydrate metabolism. Initially the changes in blood sugar values in patients suffering from haemorrhagic shock were studied but as the investigation proceeded it soon became evident that other aspects of the problem would require to be taken into consideration. For example the effect of anaesthetics on the patient who was in or had been in the shocked state and the effect of the lack of oxygen associated with shock. For this reason the work has been arranged in the following order:

Section A.

1. Blood sugar changes in haemorrhagic shock in the pregnant subject.
2. Blood sugar changes in operative gynaecology
   (a) without haemorrhage,
   (b) with haemorrhage.
3. Blood sugar changes after haemorrhage in experimental animals.

Section B.

Effect of various anaesthetics on the blood sugar in pregnant and non-pregnant patients.

Section C.

Study of the source of the blood sugar, the rate of mobilisation and the influence of respiration in

(a) experimental animals,

(b) human subjects.

The initial investigation related to the blood sugar level in patients suffering from haemorrhagic collapse in the third stage of labour. It was considered that, if taken just before blood or other transfusion was commenced, the sample would give a blood sugar reading approximately at the height of the collapse. The first few patients from whom blood was taken had been admitted suffering from post-partum haemorrhage and the blood sugar readings varied from 204 to 272 mgms.per cent. These levels were surprisingly high and this raised the query whether this phenomenon was one peculiarly associated with the post-partum patient. For this reason the investigation was extended to include patients suffering from haemorrhagic collapse due to other causes such as abortion, intra-peritoneal bleeding (e.g. from rupture of the uterus) and antepartum haemorrhage. At a later date the investigation also included patients suffering from haemorrhagic collapse in their own homes who were given blood transfusion by the flying squad before being admitted to hospital. It soon became apparent that if an attempt was to be made to determine the mechanism and significance of this hyperglycaemic episode, then a more elaborate scheme would have to be devised. One of the first problems

to be attacked was the timing of the reaction - the time of onset, the duration and the influence of treatment thereon. For the timing of the initial response, a large number of cases was required and it was necessary to obtain samples of blood as soon after the occurrence of haemorrhage and/or shock as possible. As soon as the patient was seen, a sample of blood was withdrawn for cross-matching and half of this sample was put into a fluoride tube and thoroughly mixed to prevent clotting. For the majority of the first specimens I was naturally dependent on the House Surgeons who were usually the first to see the patients, and without such co-operation it would not have been possible to collect so many cases. Altogether 47 cases have been investigated.

Collapse is a clinical term and the degree a matter of arbitrary opinion. In pregnancy the position is made more difficult since the patient may suffer from repeated haemorrhages. For this reason it was decided to date the onset of collapse from the time the pulse rate began to increase or other clinical data. In some patients suffering from the effects of a massive haemorrhage this would be almost immediate: in others where the blood loss was not so great or occurred over

a period of time the onset of collapse might be delayed. It was possible to obtain blood samples from a large series of cases in whom the time of onset of collapse could be assessed reasonably accurately. These time intervals covered a wide range and from this the time of onset of the hyperglycaemic action became obvious.

Subsequently a sample of blood was withdrawn when the patient showed signs of recovery such as rise in blood pressure and improvement in general clinical appearance. In several of the patients fasting samples were also withdrawn during the first few days of the puerperium.

Technique

All samples collected during the night were put in the refrigerator until the following day since blood sugar readings may vary if the containers remain at ordinary room temperature for 12 hours or more. If possible several samples taken at different times from the same patient were estimated together.

The blood sugar was estimated by the Herbert and Bourne (1930) colorimetric method, a modification of Folin & Wu, and was recorded in mgm.per cent.

0.1 ml. of the blood from the fluoride bottle was added to 3.5 ml. 3 per cent. sod.sulphate to which was

added 0.2 ml. sodium tungstate (10 per cent.) and 0.2 ml. 2/3 N Sulphuric acid.

This was mixed rapidly and put into the centrifuge and spun for 5 mins. 2 ml. of the supernatant fluid were added to 2 ml. copper sulphate solution in a Folin Wu tube and then boiled for 6 mins. It was then cooled for 1 minute (in each case using a stop watch). 2 ml. phosphomolybdic acid were added to the solution followed by water sufficient to make a total of 12.5 ml. Each solution was thoroughly mixed before pouring it into a tube (capacity 10 ml.). This was now read in the EEL photo-electric colorimeter using a red filter and was calculated against a known standard into mgm.per cent. by the following formula

$$\frac{U}{S} \times \frac{100}{1} = \text{mgms.per cent.}$$

The 47 cases were divided into five groups according to the cause of haemorrhage. Group 1 consisted of 26 cases of post-partum haemorrhage: group 2 contained 9 cases of accidental haemorrhage: in group 3 there were 8 cases of abortion occurring before the 22nd week, in group 4 there were 3 cases, suffering from intra-abdominal haemorrhage, and in group 5 was one case of placenta praevia. No attempt was made to group the patients according to the degree of shock nor to

assess the amount of blood loss especially as in the majority the haemorrhage had occurred prior to admission to hospital.

Blood Sugar Changes

The average blood sugar value in these 47 cases, irrespective of cause or duration of shock was 219 mg. per cent. with a range from 110 mg.per cent. to 364 mg. per cent. Preliminary analysis of these figures revealed one important point. Shock of short duration produced little change in the blood sugar level and it was only after the shock phase had lasted for approximately 30 minutes that an appreciable rise in blood sugar levels was noted.

In five of these cases blood transfusion was given within 10-15 minutes of the development of the shocked state and a satisfactory response was rapidly produced. The cause of haemorrhage was abortion in 2 cases, retained placenta in 2 cases and accidental haemorrhage in 1 case. The highest blood sugar value in this small group was 172 mgms.per cent. and the lowest was 110 mgms. per cent. The direct relationship between the duration of shock and the level of the blood sugar is clearly demonstrated in Fig.1.

A further analysis was made to determine whether

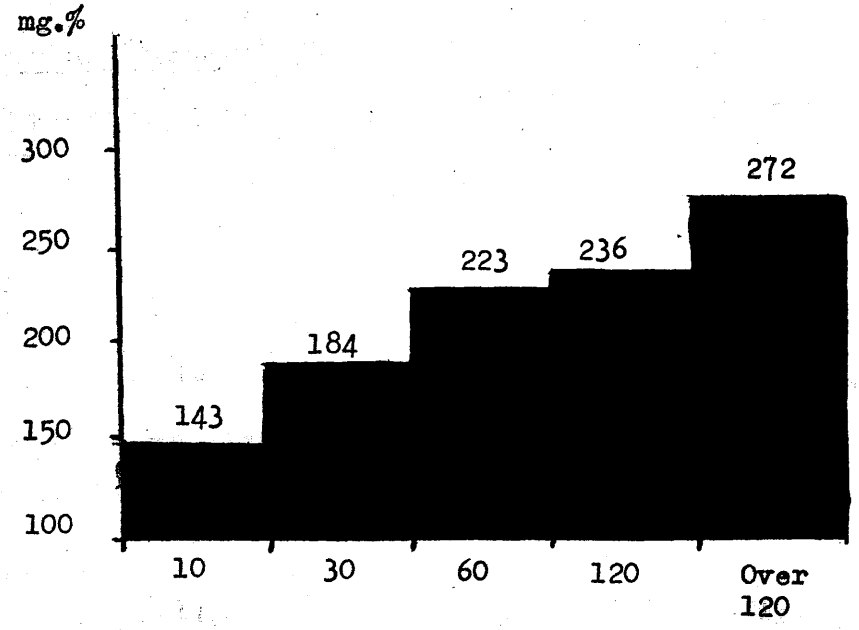

mg.%
300
250
200
150
100
143
184
223
236
272
10
30
60
120
Over 120
Time of shock in minutes.

Figure 1.

the blood sugar level was related to or modified by the cause of haemorrhage. Accordingly the cases were arranged in their five groups, namely, post-partum haemorrhage, accidental haemorrhage, abortion haemorrhage, intra-peritoneal haemorrhage and placenta praevia.

Post-Partum Haemorrhage

This group consisted of 26 cases all of whom suffered from haemorrhage during or immediately after the third stage of labour. The degree of shock was severe in most cases. The highest systolic blood pressure was 90 mm.Hg. and the highest diastolic reading 60 mm.Hg., but the average reading was 70 mm.Hg. systolic and 43 mm. Hg. diastolic. There were, however, 3 cases in whom neither reading was obtainable. No direct relationship could be found between level of blood sugar and either reading nor was there any apparent relationship between pulse pressure and blood sugar. A time relationship was the only positive finding, the blood sugar rising with the duration of shock in a manner similar to that for whole series (Fig.2). Details of the individual results are shown in Table 1. This group differed in one particular respect from the other groups. All of these patients had completed their labour and by virtue of this it is possible that some relationship

Average Readings

Group 1 - Post-partum Haemorrhage - 26 cases.

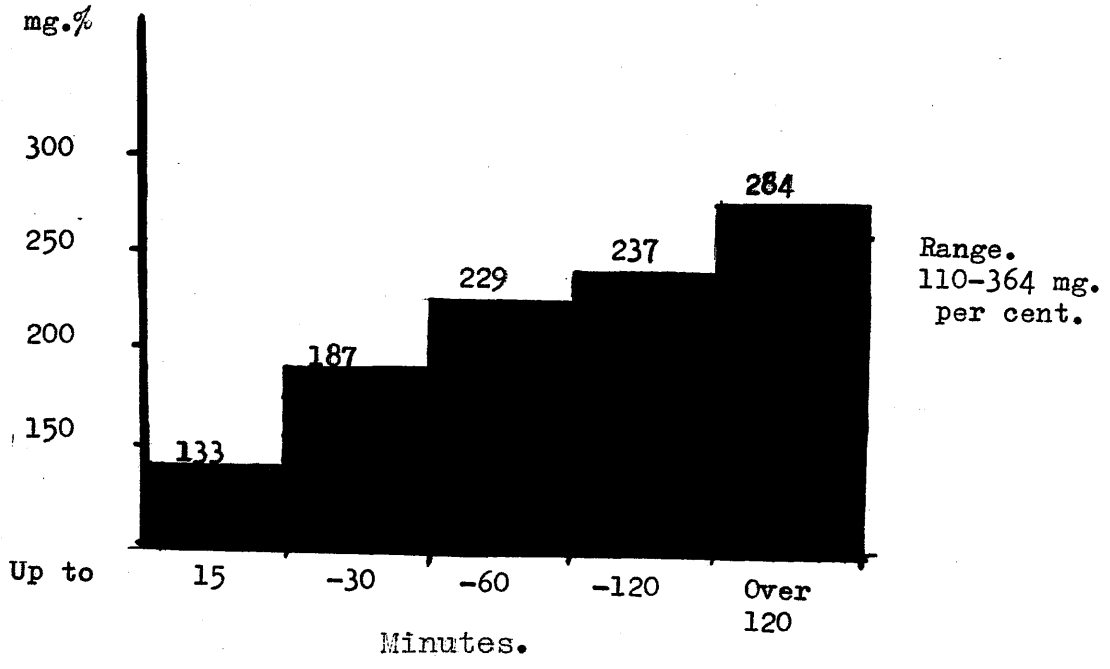


Figure 2.

Table 1.

Post-partum Haemorrhage Group - 26 Cases.
Each column indicates time of shock.

Up to 15mins.		30 mins.		60 mins.		120 mins.		Over 120 mins.	
Case	Blood Sugar Value	Case	Blood Sugar Value	Case	Blood Sugar Value	Case	Blood Sugar Value	Case	Blood Sugar Value
1	157	3	194	9	209	18	204	22	284
2	110	4	189	10	272	19	208	23	219
		5	170	11	197	20	236	24	238
		6	184	12	240	21	298	25	314
		7	171	13	211			26	364
		8	196	14	218				
				15	219				
				16	272				
				17	230				

might exist between the length of labour and the degree of shock, and the change in blood sugar values be thereby affected.

The length of labour in each case was estimated where possible. This varied from 2 hours to 50 hours with an average of 19 hours but no relationship was to be found between the blood sugar reading and the duration of labour, e.g. the patient who was in the shocked state for only 5 mins. with a blood sugar of 157 mgms.per cent. had had a labour lasting 30½ hours and one in the 2 hour shock group with a blood sugar of 236 mgms.per cent. had a short labour of 2 hours. Despite the fact that there was apparently no connection between blood sugar level and labour, it was decided to select some normal cases and follow them through labour, taking samples of blood at different stages. In order to prevent any apparently false readings and impressions, none of these patients was given glucose in any form during labour.

Nine normal cases selected at random, 4 primigravidae and 5 multiparae, were admitted to the labour ward with pains established and with the cervical os from 1-3 fingers dilated. In some cases as many as three samples were taken in the 1st stage, one

preferably at its completion, another at crowning of the head or immediately after delivery, another after the 3rd stage was completed and a fasting specimen on the following morning. In three of the cases a sample was taken 2 hours after completion of the 3rd stage. In all cases labour was normal and delivery spontaneous. Fig.3 has been compiled by taking the average of all readings at the different stages. It will be seen that there was a gradual rise in the blood sugar level from 125 mgms. per cent. in the 1st stage to 145 mgms.per cent. just after the 3rd stage.

Analysis of individual cases showed that the increase in blood sugar in most cases commenced in the 2nd stage and continued throughout the 3rd stage of labour. In two cases, however, the rise was delayed until the 3rd stage. It can be seen from Fig.3 that, although there is a moderate increase in the blood sugar during labour, the levels reached are not comparable with those recorded where shock has been present for 30 minutes and more.

Accidental Haemorrhage

This group consisted of 9 cases, 7 of which were of the mixed accidental type, 1 of the concealed type and one of the revealed type. Shock was particularly

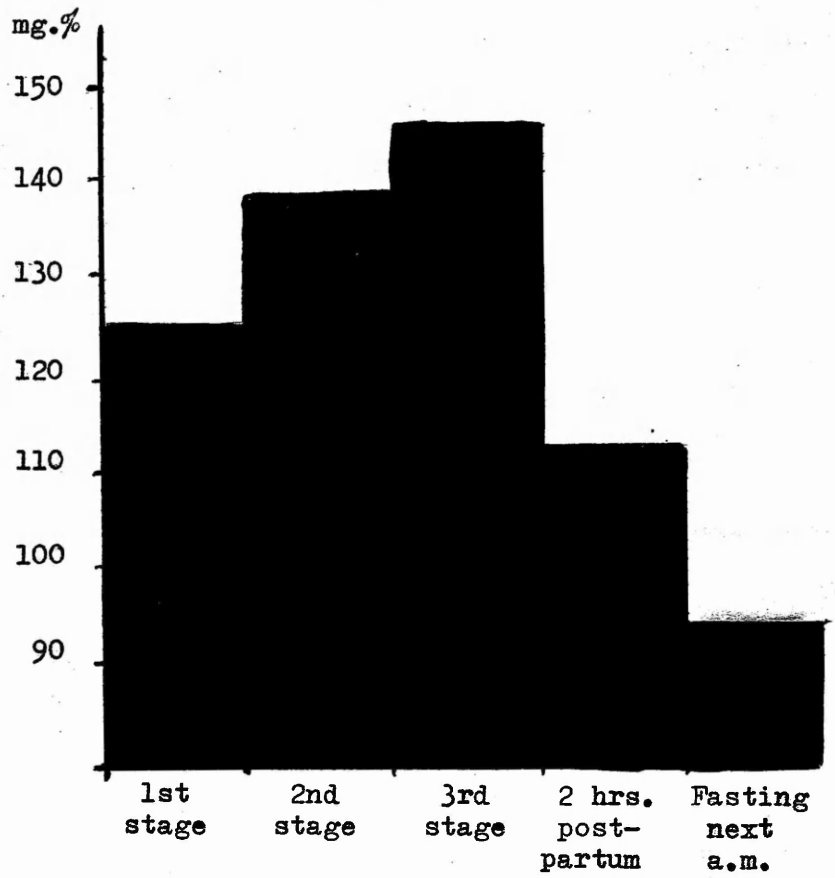

mg.%
150
140
130
120
110
100
90
1st stage
2nd stage
3rd stage
2 hrs. post-partum
Fasting next a.m.

Figure 3.

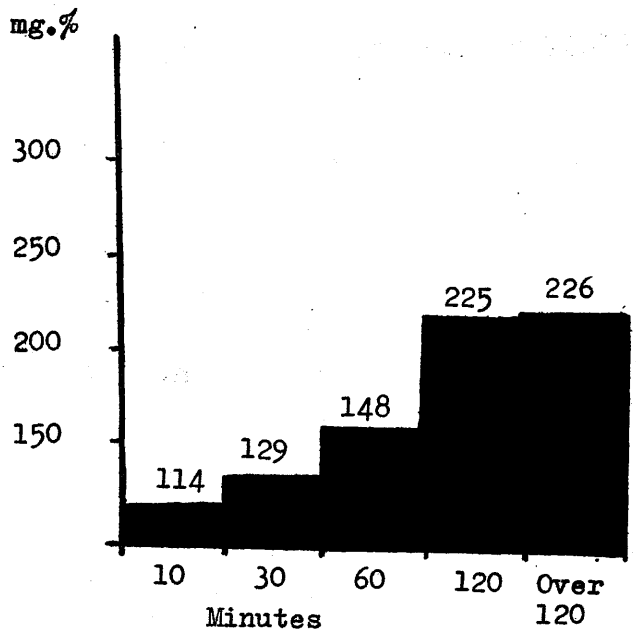
severe in three cases who were unconscious on admission. The highest systolic blood pressure was 130 mm.Hg. and the highest diastolic reading was 85 mm.Hg., the lowest systolic reading was 85 mm.Hg. and the lowest diastolic reading was 40 mm.Hg., the average systolic reading being 105 mm.Hg. and the average diastolic 65 mm.Hg. The highest pulse pressure recorded was 50 mm. and the lowest 27 mm. The only feature noted was that the highest blood sugar reading occurred in one of the cases who was unconscious and had the lowest pulse pressure (Table 2). The weight of retroplacental clot varied from 8 oz. to 1 lb. 12 oz. but no relationship between blood sugar reading and weight of clot or type of haemorrhage (concealed or mixed) was evident. Six of the cases received a blood transfusion, but the other three recovered with shock treatment other than intravenous infusion. Labour was induced in all cases following recovery from shock, so, since all the blood sugar readings were taken at the height of shock, the length of labour is not significant. The time shock relationship was again a positive finding, and the blood sugar reading increased as the duration of shock increased but at lower levels than the P.P.H. group. (See Fig.4). This will be considered in the discussion.

Table 2.

Accidental Haemorrhage - 9 cases.

Up to 15mins.		30 mins.		60 mins.		120 mins.		Over 120 mins.	
Case	Blood Sugar Value	Case	Blood Sugar Value	Case	Blood Sugar Value	Case	Blood Sugar Value	Case	Blood Sugar Value
1	114	2	129	3	148	4	222	8	209
						5	204	9	244
						6	204		
						7	271		

Group 2 - Accidental Haemorrhage - 9 cases.



Range.
114-271 mg.
per cent.

Figure 4.

Abortion

This group consisted of 8 cases in whom the duration of pregnancy varied from 6 weeks to 22 weeks. Haemorrhage was severe in 4 cases, three of whom had been shocked up to 2 hours. The highest systolic blood pressure was 115 mm.Hg. and the highest diastolic reading 80 mm.Hg., the average systolic being 100 mm.Hg. and the average diastolic 66 mm.Hg. In one case the blood pressure was not recordable. On the basis of the classification of shock according to blood pressure readings suggested by Wiggers, these cases would not appear to be so collapsed as those in the post-partum or intra-peritoneal group. The blood sugar level increased from 167 mgms.per cent. in the 10 minutes shock group to 240 mgms.per cent. in the 1 hour and 2 hour group (Table 3). This was the only type of haemorrhage where the average did not rise when the time of shock exceeded one hour. No connection was evident between the duration of the pregnancy and the blood sugar reading.

In 2 of the cases the patient was in shock for less than 10 minutes before treatment was commenced and these gave the lowest blood sugar readings.

Intra-peritoneal bleeding

Table 3.

Abortion - 8 cases.

Up to 15mins.		30 mins.		60 mins.		120 mins.		Over 120 mins.
Case	Blood Sugar Value	Case	Blood Sugar Value	Case	Blood Sugar Value	Case	Blood Sugar Value	
1	172	3	198	5	240	6	224	
2	162	4	204			7	258	
						8	238	

Group 3 - Miscarriages up to 22 weeks - 8 cases.

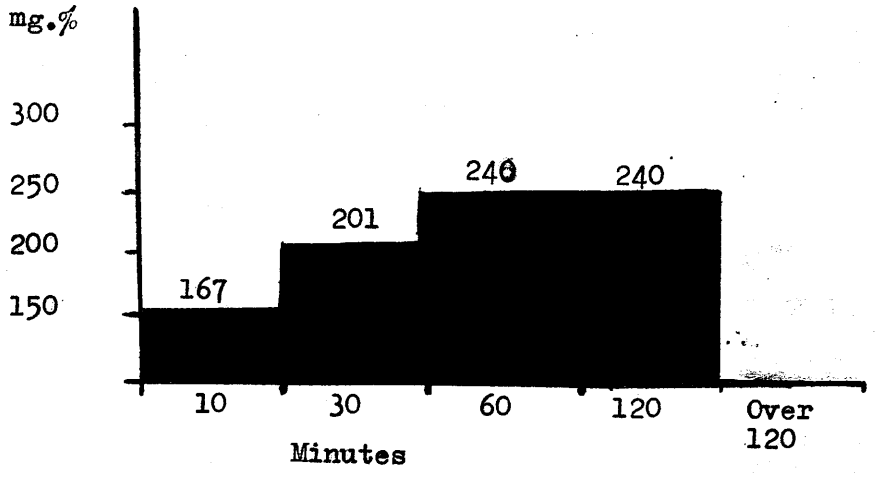


Figure 5.

Intra-peritoneal bleeding

There were 3 cases in this group, two being cases of ruptured uterus (previous Caesarean Section) and one a rupture of a rudimentary horn. All three were in the shocked state for long periods, one for nearly two hours, and the remaining two cases for 3 and 5 hours respectively. The blood glucose levels ranged from 233 mgms.per cent. to 340 mgms.per cent., the average being 281 mgms.per cent. In the case with the highest reading of 340 mgms.per cent. shock had been present for 5 hours and there was a very considerable quantity of blood in the peritoneal cavity (Table 4). After the patient had recovered from shock and the operation of hysterectomy, the blood glucose level had fallen to 210 mgms.per cent. The fasting blood glucose on the 3rd day of the puerperium was 175 mgms.per cent. and on the 5th day 146 mgms.per cent. Further reference will be made to this later in the thesis.

In the above mentioned cases the highest systolic blood pressure reading was 90 mm.Hg. and the highest diastolic 60 mm.Hg., the average reading being 78 mm.Hg. systolic and 55 mm.Hg. diastolic. These readings approximated to those found in the post-partum haemorrhage group.

Again the only positive finding was that the blood

Table 4.

Intra-peritoneal haemorrhage - 3 cases.

Up to 15 mins.	30 mins.	60 mins.	120 mins.		Over 120 mins.	
			Case	Blood Sugar Value	Case	Blood Sugar Value
Nil.	Nil.	Nil.	1	270	2	233
					3	340

Table 5.

Placenta praevia - 1 case.

30 minutes in shock. Blood sugar 207 mgms.per cent.

sugar levels increased with the duration of the shock.

There also appeared to be a direct relationship between the blood sugar levels and the amount of blood lost but the series is too small to allow a statistical evaluation.

Placenta Praevia

Only one case of this nature was studied. In the average case of placenta praevia the patient suffers from repeated haemorrhage, she seldom suffers from shock. This patient, however, suffered from a single brisk haemorrhage and there was no difficulty in timing the reaction. She had been in a state of collapse for 30 minutes when the first specimen of blood was withdrawn. Again the blood sugar had risen (Table 5).

Influence of Blood Transfusion Therapy

In 18 of the cases (10 suffering from post-partum haemorrhage, 5 from accidental haemorrhage, 2 from abortion, and 1 from ruptured uterus) the effects of treatment were noted with regard to the blood sugar readings (Table 6). These were taken at the completion of the transfusion and/or when there was recovery from shock. In 10 of the cases, fasting specimens were taken on one or more days of the puerperium. The times which elapsed between the initial blood sugar and the

Table 6.

Case	Type	Time of Shock (hours)	Blood Sugar mg.% 1	2	% Fall	Recovery time (hours)	Subsequent Fasting Blood Sugar		Notes
1	P.P.H.	2 +	238	131	45	8¾	-	-	Intermediate reading 183 mg.per cent. After transfusion.
2	P.P.H.	1	272	152	44	5	126		
3	P.P.H.	2	298	170	43	3½	1st day 168	2nd day 158	-
4	Ruptured uterus	2	340	210	38	.4	3rd day 175	5th day 146	-
5.	Accid. haem.	1	148	98	34	½	1st day 84	2nd day 76	-
6	Abortion	2	238	162	32	6	-	-	-
7	P.P.H.	2	284	204	28	-	-	2nd day 120	-
8	Abortion	1	240	183	23.7	15	1st day 152		-
9	Accid. haem.	2	204	165	19	2	-	-	Pulse rate 120/mm. for 3 days.
	2nd Shock		204	183	10	4½	-	-	
10	P.P.H.	½	170	120	29	3½	-	-	-
11	P.P.H.	2	219	204	6.8	3½	4th day	7th day	Pulse rate 120/mm.
	2nd Shock		230	?			184	128	for 3 days.
12	Accid. haem.	1/6	114	-	-	-	1st day 96	2nd day 78	-
13	P.P.H.	½	184	140	24		112(2 hrs.after recovery)		
14	Accid. haem.	1+	271				5th day 81	6th day 73	7th day 87
15	P.P.H.	½	171	144	15		107(2 hrs.after recovery)		
16	Accid. haem.	½	129	115	10				
17	P.P.H.	1	230	206	10	1			
18	P.P.H.	1	197	-	-	1	1st day		2nd collapse 2 hrs. after stopping transfusion.
	2nd Shock		230	208	9	5	178		

N.B. Blood sugar 1 - Level at height of shock.
Blood sugar 2 - Level at time of recovery.

recovery or improvement level are shown in column 6 of the table. In two cases, 13 and 15, specimens of blood were withdrawn two hours following recovery and it is obvious from this that, in the average case, there is a steady fall in the blood sugar during this phase. By contrast, the findings in cases 9, 11 and 18 are extremely interesting. All of these patients suffered a second period of collapse. In case 9 the blood sugar rose to the same height as in her first collapse phase, but at the time of apparent recovery it was still high. The blood sugar became higher during the second phase of collapse in case 11 and was still above the physiological level 4 days after recovery. In both of these cases the pulse rate remained rapid, 120 per minute, for several days after collapse. Case 18 was similar to case 11. The blood sugar was higher during the second period of shock. Five hours later, when to all appearances she had recovered, the blood sugar was 208 mg.per cent., and the following day it still registered 178 mg.per cent. We shall return to this question of the effect of repeated stresses at a later part of the thesis. The relationship of pulse-rate to the recovery from shock and the fall in blood-sugar is best illustrated by contrasting cases 1 and 11.

Case 1 was admitted suffering from post-partum haemorrhage and had been in a shocked state for over 3 hours. The blood sugar before treatment was 238 mg. per cent. and after receiving 3 pints of blood it had fallen to 183 mg.per cent.; $8\frac{3}{4}$ hours after the initial sample was taken the value was 131 mg.per cent. The pulse rate at these readings was 120, 102 and 80 per minute respectively. In Case 11, following a second shock phase, the blood sugar remained high for several days and even at the 4th day it was still 184 mg.per cent. Similarly the pulse rate remained high. The return of the blood sugar to normal levels may obviously be affected by a second collapse, despite treatment, or by the degree of shock, taking the initial blood sugar reading as an indication.

Summary

It is clear from the foregoing data that:

(1) Haemorrhagic shock occurring in various phases of pregnancy produces a hyperglycaemia, and

(2) that there is a definite relationship between the level of the blood sugar and the length of time which has elapsed between the onset of the shock and the taking of the sample. During the first 15 minutes little change occurs in the blood sugar but thereafter

a rapid increase takes place and the longer the shock remains untreated the higher is the blood sugar reading.

(3) In shock due to accidental haemorrhage the rate of response is slower, and the evidence suggests that this is due to an alteration in carbohydrate metabolism in toxaemia.

(4) The hyperglycaemia diminishes as the patient recovers from shock particularly with the aid of blood transfusion.

(5) There appears to be a direct relationship between the degree of hyperglycaemia and the amount of blood lost.

(6) If the patient suffers a second collapse, hyperglycaemia is repeated and the blood sugar returns to normal more slowly.

From the foregoing it is apparent that several points require further investigation. Most reports in the literature dealing with hyperglycaemia in shock relate to males, and there are no comparable figures for non-pregnant females. The most obvious first step therefore, was to determine the sequence of events following haemorrhage in the non-pregnant female and to gauge whether pregnancy altered these events in time or degree. At the same time there are other questions

in this study which require to be resolved or at least more accurately defined. Timing of the response to haemorrhage is not easy in the human subject, and the occurrence and depth of shock is purely a matter of opinion on the part of the observer. This is the type of problem best solved by the use of the experimental animal. A further point which cannot be solved by observations on the human subject is the question of how long the increase in blood sugar is maintained. An attempt has been made to answer these questions in a subsequent part of the thesis dealing with planned experiments.

Gynaecological Operations - without & with Haemorrhage.

It has been shown that haemorrhagic shock in the pregnant patient, if present for over 15 minutes, will produce a hyperglycaemia. There was however some variation in the degree of response according, apparently, to the maternal condition in the ante-natal period (e.g. toxaemia). As previously stated there is some evidence that carbohydrate metabolism is upset in certain types of abnormal pregnancy (Govan, Mukherjee, Hewitt and Harper, 1951; Mukherjee and Govan, 1950). It was considered necessary to check the results by a study of the non-pregnant subject suffering from the effects of haemorrhage, in order to determine whether the mechanism was altered in time or degree by pregnancy per se.

Patients undergoing gynaecological operations seemed most suitable for comparison, but it was obvious at once that it had to be ascertained whether the operative interference, apart altogether from blood loss, would initiate the hyperglycaemic episode. At the same time the question of anaesthesia and its effect on the blood sugar had to be considered. This has been discussed in detail in a later section and so care was taken to include in the present section only

those cases receiving an anaesthetic which did not affect the blood sugar level.

In order to determine the influence of operative trauma 13 cases were studied in whom blood loss was negligible - these consisted of a variety of gynaecological complaints and were subjected to various types of operative procedure, some under Pentothal, Nitrous oxide, oxygen and the remainder under a spinal anaesthetic. The time of operation was also noted as it was considered that a lengthy operation might by itself be a cause of a rise in the blood sugar level. The procedure adopted in each case was to take a specimen of blood from an arm vein just before the anaesthetic was administered, a second about mid-way through the operation and a third at its conclusion. In the longer operations samples were taken at 20-30 minute intervals.

It will be seen that, in the absence of anoxia or blood loss, there was little variation in the blood sugar readings in each particular case so that the type of operation and the time of operation had little effect. In some the blood sugar reading was actually lower at the end of operationthan at the commencement.

The operations have been grouped according to

whether the peritoneum was opened or not and also in the former case, according to the operation performed. Many observers consider that trauma to the peritoneum is itself a cause of collapse and others associate trauma to particular organs with a similar sequence of events.

The extra-peritoneal group were all patients suffering from uterine prolapse who were undergoing plastic operations for repair of the pelvic floor. Six cases are reported, five of whom were anaesthetised with pentothal and one with nupercaine given intra-spinally. The duration of the operation varied from 35 to 55 minutes.

In the extra-peritoneal group Table 6 (A), a study was made of 5 patients on whom pelvic floor repair was carried out; 4 of these were given Pentothal, nitrous oxide and oxygen and 1 received a spinal anaesthetic. The duration varied from 40-55 minutes.

Samples of blood were taken from an arm vein before anaesthesia, about midway through operation and at its conclusion. The average blood sugar reading for the 1st specimen was 131 mgms.per cent. and for the 3rd specimen 128 mgms.per cent. indicating that in so far as the blood sugar level can be taken as an

Table 6 (A).

Extra Peritoneal Group

Type of Operation	Time	Anaesthetic	Blood Sugar Readings No.1	No.2	No.3
Pelvic floor repair	40 mins.	Pentothal, N_2O, O_2.	172	170	170
" " "	40 "	do.	123	118	120
" " "	45 "	do.	132	140	121
" " "	50 "	Spinal	90		97
" " "	55 "	Pentothal, N_2O, O_2.	136	129	133
		Aver. 1st spec.	131	Aver. last spec.	128

indicator, there had been no stress. This was also emphasised by the intermediate or 2nd readimgs in individual cases. It will be seen that the blood sugar remained static or even tended to fall. The response of the patient with regard to blood sugar did not appear to vary with either type of anaesthetic. Although plastic repair of the pelvic floor is wholly extra-peritoneal it cannot be regarded as a minor surgical procedure. The trauma may be quite considerable but it is apparent that surgical interference per se does not disturb carbohydrate metabolism significantly.

In the intraperitoneal group (Table 6 (B)), eight cases were studied. These consisted of a variety of abdominal operations on the pelvic organs, varying in time from 35-80 minutes. The average blood sugar just prior to operation was 115 mgms.per cent. and at the end of operation was only 116 mgms.per cent. The response was similar in all cases to average valuesfor the whole group (A + B). Seven of the cases received spinal anaesthesia and to the remaining one Pentothal, cyclopropane and tubarine were administered. Neither of these anaesthetics appear to alter the blood sugar levels. One further point may be made. It is obvious from the average results that opening the peritoneal

Table 6 (B).

Intra-peritoneal Group

Type of Operation	Time	Anaesthetic	Blood Sugar Readings			
Ovarian Cystectomy	35 mins.	Pentothal, Cyclopropane, Tubarine.	149	149		149
OOphorectomy left ovarian resection right.	45 "	Spinal	94	94		98
Salpingo-oophor-ectomy. Appendicectomy	45 "	Spinal	92	96		
Total hysterectomy	60 "	Spinal	102	112		112
Pan hysterectomy	65 "	Spinal	98	116		100
Vaginal hysterectomy	60 "	Spinal	138	144		115
Wertheims hyster-ectomy	80 "	Spinal	173	188	178	167
Wertheims hyster-ectomy	80 "	Spinal	77	73	89	91
			Average.1st spec. 115		Aver.last spec.	116

cavity per se does not affect the blood sugar level and indeed it will be noted that the average values for this group are lower than those of the extra peritoneal group. It is apparent that surgical interference with the proper anaesthesia (and no haemorrhage) is not associated with any significant degree of stress.

As the large majority of routine gynaecological operations do not occasion sufficient loss of blood to have any effect on the blood sugar, it was thought that the only operation which could be described as routine and during which there may be considerable haemorrhage was the Wertheims hysterectomy.

In the unit to which I am attached in the Glasgow Royal Infirmary, the majority of patients with carcinoma of the cervix (Stage 1 or 11) have been treated by this method during the past three years. The anaesthetic used was a spinal (light nupercaine 14 cc.) supplemented if necessary by light nitrous oxide-oxygen analgesia. Six patients undergoing the Wertheims operation were followed through. In two the bleeding was negligible and these are shown in Table 6(B.) In the other four the bleeding was heavy in two cases, moderate in one case and mild in one case. The details of these four patients are shown in

Table 7.

Case	Blood Loss	Time of Operation	Blood Sugar Readings mgms. per cent.					Highest % rise	Blood Transfusion Given
1	Heavy	2½hrs.	157	204	224*	288	314	100	At 224 when bleeding was most severe.
2	Heavy	1½ "	110*		131		217	98	10 mins. after operation begun.
3	Mod. Severe	2-1/3"	98	114	135*		170	73	At reading 135.
4	Mild	1¾ "	139	139	179	183	176	31	Not required.

* Blood transfusion begun.

table 7.

In the three most severe cases blood transfusion was given, but started at different stages of the operation as indicated above. In cases 1 and 3 this was begun on account of the amount of bleeding, whereas in case 2 transfusion was started just at the commencement of the operation as some operative difficulty was envisaged.

From the results in these 4 cases, it is fairly evident that the loss of blood, over a period of time varying from $1\frac{1}{2}$ - $2\frac{1}{2}$ hours, will cause a rise in the blood sugar level and if blood transfusion isgiven it would appear that this quantity must almost equal the total amount lost otherwise the blood sugar will still rise.

The steady loss of blood during an operation (without replacement) brings about a position similar to that seen in say, post-partum haemorrhage, where it is found that a point is reached where shock occurs. This is not so easy to notice where the patient is anaesthetised but is indicated by a fall in blood pressure or rise in pulse rate.

The two cases of severe haemorrhage during operation are comparable with the patients suffering

from post-partum haemorrhage. In both instances there was a heavy loss of blood. Further analysis of the times of bleeding in these two non-pregnant cases reveals some interesting facts. In case 1 the basic reading of 157 mg. was obtained at the time the spinal anaesthetic was administered. Twenty five minutes later the blood sugar had risen to 204 mg. There is usually a delay of approximately 10 minutes between administration of the anaesthetic and opening the abdomen. Bleeding occurred very shortly after this. In effect this means that the blood sugar was over 200 mg. within 15 minutes. Case 2 is slightly more complicated. Transfusion began as the abdomen was opened since difficulty was expected. Many adhesions were present and there was a moderate amount of bleeding, the blood sugar rising from 110 to 131 during the first hour of the operation. At the end of this time haemorrhage was brisk and within the next 30 minutes the reading had risen steeply to 217 mg. In both of these cases the blood sugar rose from relatively normal limits to over 200 mg. within 30 minutes. Haemorrhage in pregnant patients resulted in a hyperglycaemic reaction within 30 minutes but in no case did the value reach 200 mg. in that time. The results would suggest

that the hyperglycaemic response following haemorrhage is much more rapid in the non-pregnant patient.

Summary

An investigation was made of a series of gynaecological operations using different types of anaesthesia to ascertain whether there was any alteration in the blood sugar as a result.

Thirteen (13) cases were studied. These have been divided into two groups.

Group A - where the peritoneum was not opened - consisted of 5 pelvic floor repairs 4 of them receiving an anaesthetic of pentothal, nitrous oxide, oxygen and one a spinal anaesthetic. It was found that these operations caused no disturbance of sugar metabolism: in fact the average of the 1st specimen reading, taken before the start of the operation, was slightly higher than the reading of the last specimen at the end of operation. The time of operation varied from 40-55 minutes and it would appear from the results that this does not cause any disturbance either. In none of these cases was there bleeding of any consequence.

Group B - consisted of 8 cases of major abdominal operations, where bleeding was never more than slight. These included ovarian cystectomy, oophorectomy,

salpingo oophorectomy and appendicectomy, total hysterectomy, vaginal hysterectomy and Wertheims hysterectomy. 7 cases received a spinal anaesthetic and one a general anaesthetic of Pentothal, Cyclopropane and tubarine. The time of operation varied from 35-80 minutes. The blood sugar readings varied only slightly from the start of the operation until its completion, the average 1st specimen being 115 mgms.per cent. and the average 3rd specimen 116 mgms.per cent. It is evident from the readings in these cases that (a) the type of operation (b) length of time of operation and (c) the opening of the peritoneal cavity do not have any significant effect on the carbohydrate metabolism. 4 patients were investigated during the operation of Wertheims hysterectomy for carcinoma of the cervix. In two of these blood loss was heavy, in one moderately severe and in the fourth mild. Blood transfusion was given in 3 of the cases, in two on account of heavy bleeding during the operation and in the third from the commencement. In all but case No.4 there was a marked rise in the blood sugar by 98 per cent. and 100 per cent. in the cases where the bleeding was heavy. In case 1 the blood sugar had risen considerably at the time of starting the transfusion and continued rising till the

end of operation. In case 2 one pint of blood was given throughout but the sugar level continued to rise. It would appear that there is a disturbance of carbohydrate metabolism when the blood replaced does not equal the amount lost. Comparison of the results with those obtained in pregnant patients suffering from haemorrhage suggests that the response is more rapid in the non-pregnant individual. The blood-sugar rises steeply in the non-pregnant patient and within 15 minutes may exceed 200 mg. per cent., whereas in the pregnant patient a state of shock following haemorrhage was usually present for at least 15 minutes before any rise in the blood sugar occurred.

3. ANIMAL EXPERIMENTS .

In so far as is possible it has been established that the blood sugar does not start to rise until at least 15 mins. after the occurrence of haemorrhage. The increase in blood sugar appeared to be proportional to the amount of blood lost and the raised level was maintained as long as the patient remained in the shock state. It is difficult however to be absolutely sure of these points in the human subject since so many other factors such as treatment, continuing blood loss, etc., are involved. It was decided therefore to study the phenomena in an experimental animal. The rabbit was chosen as a suitable subject for the following reasons.

1. The heart and large blood vessels of the upper abdomen had to be of such a size that blood samples could be easily and quickly obtained without producing shock in so doing.

2. The bleeding had to be done under a controlled anaesthesia which did not have any effect on the blood sugar. This was a problem which required considerable investigation in itself and it has been reported in detail in another part of the thesis. Suffice to say that Pentothal proved to be satisfactory for the

experiment at present under consideration. It was found that it could be injected easily into one of the ear veins, the quantity varying with the weight of the animal which ranged from 1500 - 2100 gms. The average dose required for the necessary depth of anaesthesia was 20 minims in a strength of 5 per cent. This produced an immediate response with momentary depression of respiration, and accompanying cardiac acceleration. Provided no anoxia occurred in this phase the blood sugar was unaltered until haemorrhage took place. When necessary Pentothal in doses of 5 minims was given to maintain the animal at the required level of anaesthesia. According to Johnson (1949), the rabbit normally has a blood sugar content of 100-130 mg.per cent., and all the values of samples taken from the animals before and after induction of anaesthesia were within this range.

In animal experiments such as this, one of the problems is to obtain repeated samples of blood for biochemical investigation. It is usually simple to obtain a first specimen from an ear vein but frequently the vessels subsequently go into spasm or become thrombosed and further experimentation is rendered fruitless. According to Johnson (1949) repeated heart puncture, even in non-nacrotised rabbits, does not alter

the blood sugar, provided, of course, that the volume of blood withdrawn is small. As a preliminary to the main investigation it was decided to investigate the usefulness of this procedure in the anaesthetised animal. First of all the thorax of a dead rabbit was opened and by rough measurement it was possible to determine the point at which a needle should be inserted through the chest wall in order to enter the left ventricle. In the living animal, after the administration of Pentothal, the region over the sternum and to 2" below the xiphisternum was shaved. A No.IV needle was inserted just to the left of and 1" above the xiphisternum. As an additional guide it was found that the pulsations of the left ventricle could be easily felt through the chest wall at this point.

Johnson's observation was confirmed and in the following short experiment the results are characteristic of the findings. Blood withdrawn from the ear vein prior to anaesthesia gave a sugar reading of 110 mg.per cent. Following pentothal anaesthesia the left heart was punctured and a small quantity of blood withdrawn. The blood sugar reading was 117 mg.per cent. The difference between this value and the initial reading is to be expected since the central blood sugar reading

is always slightly higher than that of the peripheral venous blood. Eighteen minutes later a further sample was withdrawn and the reading in this case was 119 mg. per cent. In other words samples sufficient for estimation of blood sugar could be withdrawn from the heart without materially altering the blood sugar level. Having determined the safety of this procedure from an experimental point of view the main experiment was devised.

Volume of Blood Lost & Hyperglycaemia

In order to standardise conditions it was necessary to determine the amount of haemorrhage required to produce a rise in the blood sugar. For this purpose a series of animals were subjected to heart puncture, quantities varying from 7 ml. to 20 ml. being withdrawn. In the average adult rabbit withdrawal of quantities of blood less than 5-6 ml. produced no significant change in the blood sugar. It was apparent then that at least 7 ml. of blood had to be withdrawn before a satisfactory response could be obtained. The next problem was to determine whether any direct relationship existed between the quantity of blood withdrawn and the increase in blood sugar.

An initial sample was withdrawn by ear puncture

and following pentothal, the determined volume of blood was obtained by heart puncture. Thereafter small samples were withdrawn at ten minute intervals. It was found that the rate of mobilisation of sugar varied but that a pronounced rise was constantly obtained 10 minutes after withdrawal of the blood. This time was chosen as a point of comparison for the various animals. The results are shown in Table 10. It will be seen that the increase in blood sugar at this time did not vary directly with the amount of blood lost except within wide limits. The minimum rise occurred after loss of 12 ml. and the maximum after 20 ml. Similarly there was a variation in the percentage increase following withdrawal of the same quantity of blood from different animals. This initial hyperglycaemic phenomenon seems to be of automatic total nature and the amount of sugar released may depend more on the liver glycogen available for immediate mobilisation than on the degree of collapse. It is apparent however, that the reaction of animals to haemorrhage is similar to that found in the human subject. Glycogen is mobilised and the sugar level of the systemic circulation shows a distinct rise in 10 minutes. In human subjects there was no rise before 15 minutes. As already stated, however, it is

Table 10.

Animal No.	Initial Blood Sugar	Amount withdrawn by heart puncture	2nd blood sugar 10 mins. later	Rise	per cent. rise
1	113	20 ml.	233	120	106
2	118	15 ml.	208	90	76
3	135	12 ml.	175	40	30
4	104	10 ml.	178	74	71
5	124	10 ml.	177	53	42
6	136	8 ml.	200	64	48
7	132	7 ml.	171	39	29

difficult to time these reactions accurately in the human subject. It was shown in the human subject that the maximum value of the blood sugar seemed to vary according to the length of time during which the patient was shocked. Again this is a debatable point since treatment is naturally given as soon as the patient is seen and a very large number of cases would have to be studied before any reliable estimate of the relationship between the duration of shock and the increase of blood sugar could be established.

Hyperglycaemia & Duration of Collapse

In this experiment animals were anaesthetised with Pentothal, after withdrawing an initial small sample of blood from the ear vein in each case in order to establish the basic level of the blood sugar. Previous experiments had shown that a withdrawal of at least 7 ml. of blood was required to induce some degree of collapse in a rabbit. Thereafter quantities of blood varying from 7-13 ml. were withdrawn from the animals by heart puncture in order to induce varying degrees of collapse. Further small samples $\frac{1}{2}$-1 ml. were withdrawn at 10 minute intervals until the animal recovered from the collapse phase or was killed. The results are shown in Table 11. It was found that the

Table 11.

Animal No.	Initial blood sugar mgms. per cent.	Quantity withdrawn 1st heart puncture	Blood sugar readings at subsequent punctures with time intervals in minutes.
8	110	13 ml.	146 (15) 177 (10) 200 (10) 206 (15) 177 ($3\frac{1}{2}$ hr.) 136 (18hrs.)
9	126	7 ml.	132 (12) 171 (10) 204 (12) 192 (5) 184 (5) 177 (10) 131 (2hr.)
10	135	12 ml.	175 (10) 224 (25) 155 (60) 137 (110)
11	129	10 ml.	188 (15) 208 (7) 196 (6) 165 (5)
12	104	10 ml.	178 (10) 262 (23) 211 (12)

maximum height of the blood sugar obtained and the duration of the rise varied with the amount of blood withdrawn and with the degree of collapse. The blood sugar continued to rise until the animal showed signs of recovery. The results can best be illustrated by comparison of the values and times observed in animals from whom the minimum and maximum quantities were withdrawn.

In animal No.9 7 ml. of blood were withdrawn. The maximum blood sugar recorded was 204 mgm. after 34 minutes had elapsed. Five minutes later the value had fallen to 192 mgm. and at 54 minutes it recorded 177 mg. Withdrawal of 13 ml. on the other hand, as in animal 8, resulted in a maximum value of 206 mg. after 50 minutes but 3½ hours later the level was still 177 mgms. It is obvious that the greater the haemorrhage, the longer is the duration of the hyperglycaemic response. There is however some degree of individual variation. Animal 11 showed a rapid rise after withdrawal of 10 ml. of blood but there was an equally rapid fall. This was the only animal to exhibit this anomalous change.

Hyperglycaemia and continued haemorrhage

Many cases of collapse due to haemorrhage in the human subject are associated with repeated or continuous

bleeding. There appeared to be a connection between this and a continued rise in the blood sugar levels. It was decided to try to duplicate this sequence of events in the experimental animal in order to determine whether this hyperglycaemic mechanism continued in operation or was subject to a phase of exhaustion.

Description of Experiment

The rabbit was selected again as the most suitable animal and was anaesthetised with Pentothal 5 per cent. After the same preparation of the chest wall as indicated previously the left heart was punctured with a No.4 needle and amounts varying from 6-13 ml. were withdrawn. Three rabbits were used in this experiment. Further volumes of blood were withdrawn by heart puncture at 10-25 minute intervals up to periods varying from 30-70 minutes. The results are shown in Table 12. From the values found in these animals it is obvious that no phase of exhaustion has been induced. Each fresh haemorrhage is followed by a further rise in the blood sugar. Animal 15 is particularly interesting. After the initial loss of blood the sugar content increased by 62 mg. in 15 minutes. Thereafter the rate of increase diminished. Even more important is the fact that following withdrawal of a further 9 ml. of blood

Table 12.

Animal No.	Initial blood sugar readings mgms. per cent.	Subsequent blood sugar readings from heart puncture with time intervals.
13	104	13 ml. (20 mins.) 173 — 6 ml. (15 mins.) 237
14	136	8 ml. (20 mins.) 297 — 6 ml. (24 mins.) 414 — 6 ml. (25 mins.) 616 (Died)
15	110	10 ml. (5 mins.) 126 — (10 mins.) 172 — (15 mins.) 204 — 9 ml. (10 mins.) 204 — (10 mins.) 235 — (2 hrs.) 135

the sugar content showed no alteration after 10 minutes. After 20 minutes the blood sugar had only increased by 31 mg.

Summary

1. Cardiac puncture per se does not produce shock in the anaesthetised animal.
2. In the average rabbit, weighing approximately 2 Kilos at least 7 ml. of blood must be withdrawn to produce shock as evidenced by a significant rise in blood sugar.
3. The initial rise in blood sugar occurs 10 minutes after withdrawal of blood.
4. At this time the height of the blood sugar is not directly related to the amount of blood withdrawn.
5. The maximum increase in blood sugar occurs between 35 minutes and 50 minutes after the haemorrhage. There may be some variation in individual cases.
6. The duration of the hyperglycaemia is related to the volume of blood withdrawn.
7. The hyperglycaemic mechanism appears to be in continuous operation and within the limits of the experiments does not appear to be exhausted by repeated loss of blood.

Discussion

Claude Bernard (1877) was probably the first person to record the occurrence of hyperglycaemia following haemorrhage in the experimental animal. This observation has been confirmed repeatedly by many authors including Robertson (1935), Mylon et al. (1944), but surprisingly few reports have appeared relating to changes in the human subject. This may have been due to the lack of suitable clinical material. In 1949, however, Beecher published his observations made on wounded soldiers during the late World War, and confirmed the presence of hyperglycaemia in individuals suffering from shock. Haemorrhage during or following pregnancy and during operative interference in the non-pregnant female causes a similar hyperglycaemic reaction.

The degree of hyperglycaemia is very considerable in these cases and the blood sugar in the female patient following severe haemorrhage rises well above physiological limits and may approach values seen in the diabetic patient. Values over 200 mg. were a commonplace. The levels reported by Beecher were occasionally around 200 mg. but they rarely reached the high values found in many of the patients in the present series.

According to Taylor et al (1944) the blood sugar shows a steady rise following the onset of shock, but Wiggers (1950) states that after a short period of increase a plateau level is reached. This plateau effect was not noted in the series reported in this thesis. The blood sugar appeared to rise as long as shock was present. In one fatal case of post-partum haemorrhage, where bleeding was intermittent and heavy and transfusion could not keep place with the blood lost, the blood sugar mounted to a peak of 364 mg. shortly before death. The findings in this case would also seem to contradict Wiggers (1950) who states that there is a final phase of hypoglycaemia in critical shock.

In the obstetric cases an accurate assessment of the volume of blood lost was in most instances quite impossible as the majority of the patients had suffered from post-partum haemorrhage in their own homes and were admitted in a state of shock. In those who had a haemorrhage while in hospital, the quantity of blood lost was not always collected. In many cases however the pregnant patient seemed to become shocked following the loss of a relatively small quantity of blood. This was particularly noticeable in cases with a pre-existing toxaemia. Profound shock was observed

in cases of accidental haemorrhage where the blood loss was relatively small. This is interesting in view of the differences noted when comparing pregnant with non-pregnant patients. High blood sugar levels were found in non-pregnant patients quite soon after bleeding commenced. This may represent a more active response to stress in the non-pregnant patient. In the toxaemic pregnant patient however the blood sugar rose more slowly and did not reach such high levels. The differences between the pregnant and the non-pregnant patient are most clearly seen when the results are compared on a time basis. In the experimental animals it was found that the blood sugar rose above normal within 10 minutes of withdrawal of blood, the values recorded being comparable with those observed in human subjects. In the latter however the reaction time was longer. A significant rise was noted in non-pregnant patients in 15 minutes but in the pregnant individual this interval was prolonged to 30 minutes. It is interesting to note that the initial rise in blood sugar in animals bears no relation to the quantity of blood lost but the duration and maximal degree of hyperglycaemia were directly related to the amount of blood withdrawn. This is of considerable importance

when comparing the curves of blood sugar values in the various types of patient. Our findings agree with Beecher (1949) in so far as he states that the hyperglycaemia is roughly proportional to the amount of blood lost. I have been unable however, to find any report dealing with the lack of relationship between the degree of haemorrhage and the initial hyperglycaemic reaction. This is clearly shown in the animal experiments. The blood sugar levels ten minutes after withdrawal of quantities of blood, from 7 to 20 ml., varied very much. Animals from which the same quantity of blood was withdrawn gave widely varying responses. The results suggest that the initial hyperglycaemia depends more on the amount of carbohydrate available for immediate mobilisation than on the degree of trauma. They also indicate that the initial hyperglycaemic reaction and the ultimate peak are probably the result of two different mechanisms.

It seems reasonable to suppose that the initial reaction is due to glycogenolysis in the liver following upon release of adrenalin from the adrenal gland. According to Selye (1947) the hyperglycaemia of shock is abolished if the adrenals are destroyed, a statement which seems to confirm the

above hypothesis. Other observers however (Nishi, 1909; Slocum and Lightbody, 1931; Clark and Rossiter, 1944) have found that the increase in blood sugar is not completely prevented by adrenalectomy. It is difficult to resolve the difference between these two statements but the key to the problem may lie in the word "completely". It is again obvious that we are dealing with two mechanisms, in one of which the adrenal medulla is of paramount importance.

A similar inference may be read into the work of Mylon et al (1944, ~~1945~~) who state that the hyperglycaemia due to haemorrhage differs from that produced by epinephrine, particularly in relation to its duration. However, it was felt that a partial answer to this problem might be obtained by observing the time relationship of hyperglycaemia following injection of adrenalin in patients.

Three patients were selected, two being in the antenatal period and one on the first day post-partum. 4 minims of Adrenalin (1,1000) were given intravenously in one case and 5 minims subcutaneously in the other 2 cases. Samples of blood were taken at intervals varying from 10 to 15 minutes later and again at 30 and 45 minutes later. In all cases it was found that a sharp rise occurred after 10 and 15 minutes and

this continued until the 30 minute specimen, although the rise in the second 15 minutes was slower.

The main feature of this experiment is the maximum response at the 30 minute interval, the time at which a significant rise in blood sugar was found in pregnant women suffering from shock. After 30 minutes the blood sugar declines presumably due to a counter-secretion of insulin. One may therefore assume that the initial hyperglycaemic reaction of haemorrhagic shock in pregnant patients is due to adrenalin and that its maximum effect cannot persist for more than 30 minutes. The details are shown in Table 13 .

In haemorrhagic shock affecting pregnant patients two features may be remarked upon. The blood sugar does not diminish at the end of 30 minutes but continues to rise. It remains to be seen whether these two features have a common cause or are the result of independent mechanisms. The normal response to adrenalin hyperglycaemia is a production of insulin which will cause a return to normal levels. Several hypothesis may be advanced to explain the absence of this reaction in shocked subjects: a) there may be a lack or decreased secretion of insulin or b) insulin antagonists may be present. We have no evidence to indicate a lack

Table 13.

Injection of Adrenalin.

Case No.	Method of injection	Blood sugar readings & intervals in minutes.
1	Subcutaneous	108 10 mins. 120 20 mins. 122
2	Subcutaneous	110 10 mins. 124 20 mins. 131
3	Intravenous	152 15 mins. 178 15 mins. 188 15 mins. 168 15 mins. 162

of insulin in these patients, and without estimations of blood insulin, which would be difficult both from clinical and technical points of view, no satisfactory answer can be given to this question. Similarly we have no direct answer to the second hypothesis. Naturally occurring insulin antagonists belong to the pituitary-adrenal group of hormones (Houssay, 1936; Young, 1939), and disturbances of carbohydrate metabolism are found in both acromegaly and Cushing's disease. The antagonistic action of certain anterior pituitary hormones to insulin has been demonstrated by many workers (Houssay and Potick, 1929; Cope and Marks, 1934; Russell and Bennett, 1936; Young, 1936, 1938). Adrenocorticotrophic hormone is one of a number capable of this type of action, and it was decided to test its influence in the experimental animal suffering from haemorrhagic shock. It was argued that, if an active secretion of insulin took place in these animals in response to the hyperglycaemia, and it its action was hindered by antagonists then a further supply of antagonist might intensify the hyperglycaemia. A rabbit was anaesthetised and shock produced by withdrawing 15 ml. of blood by heart puncture. Ten minutes later 25 mg. A.C.T.H. were injected intramuscularly. The blood sugar results are

shown in the following table. For comparison the results from a rabbit from which 16 ml. of blood was withdrawn are shown.

	Initial	10 min.	30 min.	50 min.
1.	118	208 (A.C.T.H. given)	333	370
2.	104	152	173	237

It would appear from this short experiment that A.C.T.H. does augment the hyperglycaemic reaction to haemorrhage. The idea that insulin antagonism due to activity of the pituitary-adrenal system is present in these cases would fit in with the work of Fraser, Albright and Smith (1941) in relation to carbohydrate metabolism. Whether insulin antagonists are present or not one must explain the continuing rise in the blood sugar of these patients. It is obvious that the liver glycogen will be quickly exhausted unless further supplies are made available. This is easily demonstrated by observing the effects of repeated haemorrhage in animals. The experiments carried out on rabbits demonstrated clearly that there is no exhaustion of the hyperglycaemic reaction. Repeated withdrawal of blood resulted in a continued rise in blood sugar. More important, however, was the observation that the rate of increase in the blood sugar

was slower following subsequent withdrawals of blood than that observed after the initial bleeding. This is a further indication that the mechanism responsible for maintaining and increasing the hyperglycaemia differs in nature from that which causes the initial rapid increase in blood sugar.

The immediate source of the blood sugar is almost certainly the liver (Robertson, 1935; Engel et al, 1943, 1944). During haemorrhagic collapse there must be continuous glycogenesis and glycogenolysis. From the time relationship the initial phase would appear to be due to mobilisation of liver stores by adrenalin but thereafter the reaction is slowed and adrenalin probably plays little part. The only other factors at present known to affect the formation and mobilisation of glycogen in the liver are those belonging to the pituitary adrenal system of hormones. That this is more than a possibility in the present instance is suggested by reports in the literature relating to increased nitrogen catabolism during shock (Cuthbertson, 1929, 1939, 1943; Selye, 1950). It is apparent therefore that both insulin antagonism and the continuously increasing hyperglycaemia during shock may both be explained by a dual mechanism, namely the

action of pituitary and adrenal hormones. This would agree with the opinion of Long (1947) who suggests that a double mechanism underlies the secretion of A.C.T.H. following stress: 1) a quick autonomic mechanism depending on reflex secretion of adrenalin which activates the anterior pituitary: and 2) a slower metabolis mechanism which is not dependent on adrenaline secretion and which is therefore not abolished by adrenal demedullation or denervation. According to Nishi (1909), Slocum and Lightbody (1931), and Clark and Rossiter (1944), however, the adrenals are not necessary for the hyperglycaemic reaction following shock, and therefore it is possible that the pituitary is solely responsible for the phenomena observed.

While hyperglycaemia during shock is an observed fact, the reason for its occurrence is not clear. One must assume that there is a demand for energy. Taylor, Levenson and Adams (1944) found a slightly increased metabolic rate in a few of their cases. From the clinical condition of the patient in shock, however, it is difficult to believe that there is an increased production of energy. The extra sugar produced is certainly not being utilised to any great extent.

Equally it is not being stores in the usual sites of glycogen formation. Haist (1946) and Nastuk (1947) have both shown that muscle glycogen is depleted early in the course of shock, and liver glycogen is similarly reduced. Several authors have reported an increase of lactic and pyruvic acids in the blood of shocked animals (Engel, Winton and Long, 1943), a finding which would tend to suggest incomplete combustion of carbohydrate. It has been shown by De Witt Stetten (1949) that the energy produced in the initial phase of glucose breakdown to lactic and pyruvic acids is much less than that resulting from the oxidation of these substances to carbon dioxide. An interference with this latter part of the cycle would thus in itself be sufficient to explain the diminished production of energy and the continuing demand for it which can only be answered by further mobilisation of glucose. It may be significant that Le Page (1946) found a marked increase in the stores of glycogen in the brain during shock. It is known that glucose is essential for cerebral metabolism (Scheinberg and Jayne, 1952). In addition the brain is unable to metabolise glucose by anaerobic methods and therefore a constant supply of oxygen is necessary. From this, a reasonable

hypothesis may be elaborated. It is obvious from the presence of abundant glycogen in the brain during the shock phase (Le Page 1946) that metabolism of carbohydrate in that organ is hindered. This naturally follows from the fact that lack of oxygen is bound to result from severe haemorrhage. In such circumstances the reduced oxidation of glucose will stimulate a demand for energy-producing material and mobilisation of additional carbohydrate will occur.

Much of what has been discussed above is of hypothetical nature, and although it is obviously impossible to cover the whole field in the scope of this thesis an attempt has been made to confirm a few of the hypotheses. Although the liver would appear to be the main source of the blood sugar, the depletion of muscle glycogen early in shock suggests the possibility of other sources and this is one point which must obviously be investigated. Secondly, if the theory of the relationship of brain metabolism to hyperglycaemia is true, one would expect that any interference with oxidation would result in an increase of blood sugar. This is an important factor in obstetric practice. Hypoxia, both maternal and foetal, is an inevitable accompaniment of delivery and if this

results in a degree of stress indicated by hyperglycaemia, in any way comparable with that observed in the cases of haemorrhagic shock, then it is of serious import. The influence of anoxia on the stress mechanism has been made the subject of a separate study later in this thesis. Before attempting to investigate these various factors in haemorrhagic shock, however, it was necessary to determine the influence of anaesthetics on the blood sugar level. Anaesthetics and analgesics are widely used in obstetric practice and their influence on the metabolism of both mother and foetus has received little attention. Some of these anaesthetics, such as chloroform and ether are hepato-toxic, while others, such as nitrous oxide exert their influence by interfering with oxygenation. In both instances an alteration in carbohydrate metabolism may ensue. In addition to these, new anaesthetics and relaxants have recently been introduced. These substances in many cases act upon the sympathetic-parasympathetic mechanism and may interfere with some of the normal reactions found in surgical practice. The following section of the thesis deals with an investigation of many types of anaesthetic under various conditions in gynaecological and obstetric practice.

SECTION B

ANAESTHESIA

As it had been ascertained that hyperglycaemia occurred following haemorrhagic shock in the pregnant patient, it became obvious that, as these patients frequently require an anaesthetic for some operative procedure before recovery from shock had taken place, a separate investigation into the metabolic changes associated with the common anaesthetics was required.

Also this information was of particular interest with reference to the patient in labour when operative delivery was necessary. It has been shown in Section A that a patient in labour, when given no glucose by mouth, has an average blood sugar of 135 mgs.per cent. at the time of the 2nd stage, and 145 mgms.per cent. at the time of the 3rd stage. It is at these stages that anaesthesia is usually required, there being a much higher basic blood sugar level than in non-pregnant patients who averaged 116 mgms.per cent.

In obstetric operations for delivery of the child, the question of the effect of hyperglycaemia on the child has to be considered. This hyperglycaemia is probably to be interpreted as a form of stress and it

becomes necessary to know if any of the anaesthetics commonly used in obstetrics are of this nature and which is the most suitable.

Hyperglycaemia resulting from anaesthesia has been the subject of many workers for more than 40 years. The studies have been made on experimental animals and on the human subject. Particular reference to the hyperglycaemic effect of ether is found in the studies of Keeton and Ross (1917), Stewart and Rogoff (1920), Cantarow and Gehret (1931), Phillips and Freeman (1933), Banerji and Reid (1933), Adriani (1946) and Johnson (1949).

Several other anaesthetics are known to cause a hyperglycaemia and a summary of these is given by Adriani (1947). It was decided to study in general the effects of the various anaesthetics but in view of the altered metabolism associated with pregnancy it was essential to compare the non-pregnant with the pregnant subject, therefore the investigation was divided primarily into two parts. Another reason for this investigation was that frequently in obstetric practice emergencies occur which necessitate anaesthesia, and it becomes difficult to carry out detailed studies such as may be possible in the non-pregnant subject undergoing planned surgical treatment.

In the first instance groups of patients undergoing gynaecological operations were studied in relation to the anaesthetic involved. It has already been shown that operative interference per se, provided it is not accompanied by haemorrhage, does not alter the blood sugar level. The cases chosen were those in whom bleeding was minimal, although all cases investigated are quoted in the table.

The anaesthetics employed ranged over 12 different types or combinations.

1. Spinal anaesthetic - with ephedrine.
2. Spinal anaesthetic - without ephedrine.
3. Pentothal, nitrous oxide, oxygen.
4. Pentothal, nitrous oxide, oxygen, trilene.
5. Pentothal, nitrous oxide, oxygen, cyclopropane.
6. Pentothal, cyclopropane, oxygen, tubarine.
7. Pentothal, cyclopropane, oxygen, tubarine, ether.
8. Nitrous oxide - oxygen.
9. Nitrous oxide, oxygen, ether.
10. Nitrous oxide, oxygen, neothyl (N-methyl propyl ether).
11. Ether.
12. Nitrous oxide, oxygen, trilene.

Spinal anaesthesia frequently causes a fall in blood pressure and to prevent this, ephedrine (gr.1) is

usually given with it. It was felt that it might be interesting to compare the effects of spinal anaesthesia with and without ephedrine in order to find out whether this fall in blood pressure could induce a state of stress with consequent rise in blood sugar levels.

The results of all spinal anaesthetics are shown in Table J - Subsection A, with ephedrine; Subsection B, without ephedrine. For abdominal operations, 12 cc.of 1/1500 light nupercaine were given, following premedication with ¾ gr.morphia and 1/100 gr.Hyoscine 1½ hours before operation and a further 1/200 gr.Hyoscine 1 hour later. For extra-peritoneal operations such as plastic repairs, 2 cc.of 1/200 nupercaine were given, following the same premedication.

If the patient was over 60 years of age, the second injection of Hyoscine was omitted.

It will be observed that of the 17 cases in J(A) Nos.11-15 were complicated by hypoxia or haemorrhage leaving 12 cases with no complications. Of these 12, only one (No.10) showed a rise of more than 24 per cent.on the initial blood sugar, five patients showed a rise of 8 per cent.or less and in the remaining six, the rise varied from 10-24 per cent.

The blood sugar did not appear to be particularly affected by the type of operation, whether intra-abdominal or extra-peritoneal, nor did it bear any

Table J (A).

Spinal Anaesthesia with Ephedrine

Operation	Case No.	Blood Sugar Range				Max. %rise	Time
Total hysterectomy	1	102	112	112		10	1 hr.
	2	121	140	144		19	1 "
	3	98	116	100		18	1 "
	4	128	144	150		17	1 "
Vaginal hysterectomy	5	138	144	115		4	1¼ "
Pelvic floor repair	6	106	132	132		24	¾ "
	7	90		97		8	50/60
Salpingo-oophorectomy, appendicectomy, etc.	8	94	94	98		4	35/60
	9	92	-	96		4	35/60
	10	85		109		28	½ hr.
	11	158	198	187		25	50/60
		Hypoxic episodes throughout					
Wertheims hysterectomy	12	98	114	114	135 170	73	1¾ hr.
	13	110	131	217		98	1½ "
	14	139	139	179	183 176	31	1¾ "
	15	157	204	224	288 314	100	2¼ "
	16	173	188	178	167	8	1½ "
	17	77	73	89	91	14	1-1/3"

Average rise between 1st and 2nd sample (excl.11-15) = 11.75.

Table J (B).

Spinal Anaesthesia without Ephedrine

Operation	Case No.	Blood Sugar Range	Max. %rise	Time
Total hysterectomy	18	102 (45mins.) 127 110	24	1-1/3hr.
Salpingo-oophorectomy	19	86 (30mins.) 118 108	37	¾ hr.
Broad left cyst and ovarian cyst	20	130 (20mins.) 143 (35 mins.) 152 156 B.P. 170/80 130/65 125/60	20	1½ "
Pelvic floor repair	21	137 (20 mins.) 166 (20 mins.) 177 (20 mins.) 158 B.P. 130/84 90/55 90/60 95/60	29	55/60

Average rise between 1st and 2nd samples = 24.75.

relationship to the time of operation. In 2 of the cases, the blood sugar level was found to be lower at the end of operation than at the beginning and in 3 of the cases the 2nd and 3rd reading were the same.

In all but 2 cases (14 and 17) the 2nd specimen of blood taken midway through the operation was higher than the initial sample. It is known that spinal anaesthesia causes a fall in blood pressure and so ephedrine is given to counteract this. However, from these findings it may well be that in the majority there is a drop which is the factor influencing the metabolism and causing a rise in the blood sugar.

In order to note the effect of spinal anaesthesia without ephedrine, 4 cases were chosen (Table J B). In all of these the rise of blood sugar ranged from 20–37 per cent. and it was noticeable that the average difference between 1st and 2nd samples was greater than in the ephedrine group, being 24.75 as against 11.75.

In only two of the cases (Nos. 20 and 21) was the blood pressure taken throughout. It shows a big drop from the pre-spinal level of 170/80 to 130/65 in one case and from 130/84 to 90/55 in the other. The intervals were 20 minutes in each case. The blood pressure fell slightly lower in case 20 but rose slowly in case 21. As in Table J(A) neither the type of operation nor the length of time of

operation seemed to have any effect. Presumably with a drop in blood pressure there is a release of adrenaline which in turn causes a rise in the blood sugar as an emergency reaction.

Pentothal, Nitrous oxide, Oxygen. (Table K).

In the group given this anaesthetic, there were 5 cases, all being operated upon for uterine prolapse. One case, No.3 was complicated in that three hypoxic episodes occurred during operation, causing a rise in the blood sugar. Apart from this there was no material change. In 3 cases the blood sugar was slightly lower at the end of operation but the difference is within the range of experimental error so no particular importance can be attached to these findings. In all these cases the blood loss was minimal and it might be of importance in regard to this to state that the table was tilted slightly before commencing operation so that the head was a little lower than the pelvis. The anaesthetist concerned with these 5 cases now adopts this position with the majority of patients in order to lessen bleeding.

Pentothal, Nitrous oxide, Oxygen Trilene. (Table L).

In this group there were 8 cases, 4 undergoing a pelvic floor repair, one a vaginal hysterectomy, and

Table K.

Operation	Case No.	Blood Sugar Readings			% change	Time mins.
Pelvic floor repair	1	172	170	170	-	40
do.	2	132	140	121	+6	40
do.	3	142	157	176	+24	35
		hypoxic episodes				
do.	4	136	129	133	-5	55
do.	5	123	118	120	-4	40

Table L.

Operation	Case No.	Blood Sugar Readings				% change	Time of opern. mins.
Pelvic floor repair	1	126	149	151	149	+20	45
do.	2	124	124	131		+5	55
Colpo-perine-oophaphy(diabetic)	3	194	185	171		-11	25
Colpo-perine-orrhaphy	4	109	109	139		+27	25
Vaginal hyster-ectomy	5	124	145	150		+20	60
Nitrous oxide, oxygen, trilene.							
Dilatation & curettage	6	125	10	135	5 136	+8	15
Biopsy of cervix, dilatation and curettage(hypoxia at induction)	7	117	15	160	168	+43	25
Dilatation and curettage	8	133	5	170	15 170	+28	20

three a dilatation and curettage (Pentothal omitted). One patient (No.3) was a mild diabetic. The blood sugar levels in all cases except the diabetic showed a rise between first and third specimens varying from 5 per cent. to 27 per cent. In two cases the first and second specimens gave the same reading with a rise in the third while in the other five the rise occurred between first and second specimens with the third sample remaining about the same level as the second. In the diabetic case the blood sugar level fell by 11 per cent. from 1st to 3rd specimen. There did not appear to be any difference between the intra-peritoneal case (No.5) and the pelvic floor repairs or minor procedures. The length of time of the anaesthetic varied from 15-60 mins. but this did not appear to affect the results.

In all cases induction was straightforward except No.7 where there were hypoxic episodes. In view of the quick rise of 43 per cent. it might be assumed that this, and not the trilene, was mostly responsible.

Pentothal, Cyclopropane, Oxygen, Tubarine. (Table M).

There were 4 cases in this group, all undergoing different gynaecological abdominal operations. The time of anaesthetic ranged from 35-50 mins. In one case

Table M.

Operation	Case No.	Blood Sugar Readings			% change	Time mins.
Ovarian cystectomy	1	149	149	149	Nil.	35
Right salpingo-oophorectomy	2	106	119	108	+12	50
Salpingo-oophorectomy appendicectomy	3	128	156	152	+21	45
Hysterectomy	4	149	178	165	+19	50

all three readings were the same but in the other 3, the rise varied from 12-21 per cent. occurring between the 1st and 2nd specimens. There seemed to be no relationship between the blood sugar readings and the duration of anaesthesia or the operative procedure.

Pentothal, Nitrous oxide, Oxygen, Cyclopropane. (Table N).

Only one case, a pelvic floor repair, received this anaesthetic. There was a rise of 6 per cent. between 1st and 3rd specimens and the operation lasted for 55 mins.

Pentothal, Cyclopropane, Oxygen. (Table O).

One patient was given this anaesthetic to find out whether any change in blood sugar occurred in the absence of operative procedure. A pelvic examination was made, and the total time under anaesthesia was 15 minutes. There was a fall of only 5 mgms. but again this is within the experimental error range.

Pentothal, Cyclopropane, Tubarine and Ether. (Table P).

Two patients undergoing major abdominal operations were given ether in addition, commencing it just after the stage of induction. It was noted that a rise in blood sugar occurred in both cases. In Case 1, the ether was continued throughout the operation and the blood sugar levels rose steadily. This operation

Table N.

Operation	Case No.	Blood Sugar Readings			% change	Time Mins.
Pelvic floor repair	(1)	107	111	114	+6	55

Table O.

Operation	Case No.	Blood Sugar Readings		% change	Time mins.
Pelvic examination	(1)	144	139	-3	15

Table P.

Operation	Case No.	Blood Sugar Readings			% change	Time mins.
Panhysterectomy	1	157	188	233	+48	60
Ovarian cystectomy	2	137	180/	172	+31	30

/Ether stopped.

lasted for 60 minutes. In Case 2 the ether was stopped when the 2nd specimen was withdrawn and here it was found that the level fell slightly between 2nd and 3rd specimens. Fifteen minutes elapsed between 1st and 2nd and between 2nd and 3rd specimens.

Nitrous Oxide, Oxygen and Ether. (Table Q).

Three cases undergoing dilatation and curettage were given this anaesthetic and all showed a rise varying from 17-31 per cent. It will be noted that the duration of anaesthesia was short in all cases, 11 to 21 minutes, and the amount of ether was small and was administered intermittently. Despite this the blood sugar rose significantly within 6 to 10 minutes.

Nitrous oxide, oxygen, N-propyl methyl ether. (Table R).

The two cases in this group showed a greater rise which occurred in 10 to 12 minutes with a slower rise between specimen 2 and 3 in case 1, and a slight fall in case 2, but in the latter case the anaesthetic was stopped just after specimen 2 was taken.

Open Ether. (Table S).

Ether alone through an ether mask. Two patients were anaesthetised for 24 and 13 minutes and had dilatation and curettage performed. In the first case Specimen 2 was taken 11 minutes after the beginning of the anaesthetic and specimen 3,

Table Q.

Operation	Case No.	Blood Sugar Readings	% change
Dilatation and curettage	1	165 (15) 192	+17
Dilatation and curettage	2	95 (6) 116 (5) 125	+31
Dilatation and curettage	3	110 (10) 128 (6) 134 (5) 121	+22

Table R.

Operation	Case No.	Blood Sugar Readings	% change
Dilatation and curettage	1	116 (10) 175 (7) 183	+57
Dilatation and curettage	2	81 (12) 121/ 119	+49

Table S.

Operation	Case No.	Blood Sugar Readings	% change
Dilatation ad curettage	1	96 (11) 127 (13) 190	+97
Dilatation and curettage	2	81 (10) 106 (3) / (10) 154 (15) 135	+90

/anaesthetic stopped.

13 minutes later. The rise was more particularly marked after the patient was in the correct plane of anaesthesia, i.e. between 2nd and 3rd specimens, and gave a total rise of 97 per cent. This is more in keeping with statements made by Adriani, etc., that the blood sugar will rise to 100 per cent. or over with Ether anaesthesia.

Ether Anaesthesia in Animals.

From the above observations made on the human subject it would appear that ether causes a rapid rise in blood sugar. It is however difficult to eliminate other factors in clinical practice and for this reason the effects of etherwere studied in normal animals. Four rabbits were given ether by open mask for varying lengths of time. Repeated samples of blood were withdrawn for sugar estimation and the results are shown in the following table. It was found that during the first five minutes there was a distinct rise but the percentage increase varied from 19 to 41. After 10 to 12 minutes however the curve became more steep and the percentage increase varied from 49 to 108. This agrees with findings in human subjects. (See Table S).

Experiments with Ether Anaesthesia.

Animal No.									% Rise
1	120	5 mins.	149						24
2	98	10 mins.	173						76
3	119	5 mins.	142	5	177	5	204		19,49,71
4	94	5	133	7	196.				41,108

It was noted during the course of this study that where hypoxic episodes occurred, the blood sugar rose, although in other cases having the same anaesthetic (without hypoxia) no alteration in the blood sugar occurred.

This hypoxia, occurring during the administration of a so called innocuous anaesthetic, is a very important point in relation to obstetrics, when the mother may suffer from a degree of hypoxia due to moderate haemorrhage, previous anaemia or some condition interfering with respiration such as cardiac disease, hypertension or a pulmonary lesion. The foetus normally suffers from a considerable degree of hypoxia even during normal delivery and asphyxia neonatorum remains one of the most important causes of stillbirth.

Eastman (1936) was the first to show the close correlation between the occurrence of hypoxia and the condition of the foetus. McGregor (1946) has stated that 37.2 per cent. of foetal deaths are due to asphyxia. These figures substantiate the findings of Dunham (1932) and according to Tandy (1933) asphyxia is the dominating cause of stillbirth after the 35th week. The same conclusion was arrived at by Litchfield and Beilly (1938) who pointed out that long and difficult labour and the use of various analgesic and anaesthetic drugs employed to alleviate labour pains, are predetermining factors which influence the degree of nacrosis in the newborn.

Within recent years the work of Guilhem et al (1952) and Walker (1954) have proved that the oxygen carrying capacity of the umbilical blood lessens with post-maturity and that there is an unmistakable correlation between the infants condition at birth and the oxygen saturation of its blood. These authors have also shown that any process which interferes with oxygenation greatly diminishes the chance of foetal survival.

It was therefore decided to study cases where short periods of anoxia could be produced during the

induction phase of anaesthesia without danger to the patient.

There were 9 patients in this group (Table T). All required an anaesthetic for the minor gynaecological procedures of dilatation and curettage, avulsion of polyp, biopsy of cervix or cauterisation of cervix, and were considered by the anaesthetist to be suitable to receive the maximum amount of nitrous oxide in induction.

The following procedure was adopted in eight of the nine cases. All had been premedicated with 3 grs. Nembutal and 1/60 gr. Atrophine $\frac{3}{4}$ hour before. Just prior to starting the anaesthetic 1 ml. of blood was withdrawn from an arm vein. Pure nitrous oxide was given until there was deep cyanosis and jactitations commenced. This period varied from $1\frac{3}{4}$ - $2\frac{1}{4}$ minutes, when oxygen 4 per cent. was added. When the oxygen was turned on a 2nd sample was withdrawn from an arm vein. A 3rd sample

was taken in the same way 5 to 7 minutes later when the oxygen was increased to 8 per cent. and in cases 5-9 further samples were withdrawn at intervals of 5 to 60 minutes as indicated in Table T. As some were taken after the anaesthetic had been stopped, a dotted line indicates the cessation of anaesthesia.

The time of anaesthetic varied from 8½ minutes to 25 minutes, and 5 were anaesthetised for 10 minutes or less. The time factor did not appear to have any influence on the individual rise or the percentage rise in blood sugar.

One interesting point which emerged in studying the results was the initial drop which occurred in 3 cases (3, 4 and 6) followed by a very marked rise 5 minutes later. Cases 2 and 8 are not included in this observation as the readings are so close that they fall within the experimental error range.

In all cases the blood sugar level was higher at the end of the operation than at the beginning. In five cases blood was withdrawn at intervals after cessation of anaesthesia but in only one (No.5) did the blood sugar continue to rise.

The percentage rise - from lowest to highest readings - varied from 22 to 91, occurring in 5 minutes

Table T.

Operation	Case No.	Blood Sugar Readings	% Rise
Dilatation and curettage	1	102 —(25)— 140	37
do.	2	110 — 109 —(5)— 140	28
do.	3	124 — 94 —(5)— 163	73
do.	4	113 — 104 —($6\frac{1}{2}$)— 144	38
do.	5	102 — 110 —(6)— 154 / —(13)— 195 —(10-)— 181	91
do.	6	106 — 91 —($5\frac{1}{2}$)— 173 / —(13)— 171 —(9)— 162	90
do.	7	86 — 88 —($4\frac{1}{2}$)— 105 —(5)— 100 —(11)— 101 /	22
do.	8	124 — 122 —(5)— 195 —(6)— 195 —(5)— 180 / 126 (60)	58
do.	9	88 —(6)— 165 —(7)— 154 / —(12)— 146	87

/ = anaesthetic stopped.

in the eight cases considered. Of all the investigations this anoxia has caused the most rapid rise of blood sugar.

ANAESTHESIA IN OBSTETRIC CASES.

In many instances in obstetric practice an anaesthetic has to be given at the time of delivery. The patients may have been in labour for varying times and it is necessary therefore to ascertain whether the effect of the anaesthetic is modified or altered by the effect of the labour. In addition an anaesthetic is often necessary where delivery is complicated by haemorrhage and/or shock.

Our material has therefore been arranged in three primary groups.

The 1st group consisted of patients requiring delivery by Caesarean Section.

The 2nd group consisted of patients who had been in labour for varying times and who required delivery by operative means or curettage.

The 3rd group consisted of these patients who had suffered or were suffering from haemorrhage and collapse.

Table 1 shows the results in the 1st group and consists of 6 cases who were delivered by Caesarean Section, three by Classical section on account of placenta praevia or transverse lie and three by lower uterine section

Table 1.

Abdominal Deliveries.

Cases who had not been shocked

Type of Operation	Case	Anaesthetic	Time mins.	Blood Sugar Readings			% change
L.U.S. Caesarean Section	1	Spinal (+ephedrine)	50	98	104	102	+4
Classical Caesarean Section (Plac.Praev. III)	2	Pentothal N_2O, O_2.	20	92	98	100	+8
Classical Caesarean Section (Transverse lie - early labour)	3	Kemithal, C_{10}, N_2O, O_2, Pethidine.	30	84 Fasting	87 84 next a.m.	95	+13
L.U.S. Caesarean Section (Foetal distress - membranes ruptured - not in labour)	4	N_2O, O_2, Ether.	40	65		117	+80
Classical Caesarean Section (Plac.praevia) (Moderate blood loss) (at operation).	5	Kemithal, C_{10}, N_2O, O_2,	30	102	111	134	+31
L.U.S. Caesarean Section (Not in labour)	6	Kemithal, C_{10}, N_2O, O_2, Pethidine.	30	94	100	105	+10

on account of disporportion or foetal distress.

A wide variety of anaesthetics was used -

In 1 case - spinal anaesthetic (Planocaine 2 ccs.)

In 3 cases - Kemithal, C_{10}, N_2O, oxygen, pethidine.

In 1 case - Pentothal N_2O, oxygen.

In 1 case - N_2O, oxygen, ether.

Loss of blood was not a significant feature in this group apart from Case 5, where, owing to placenta praevia some unavoidable haemorrhage occurred during the operation. It will be noted from the table that a significant rise in blood sugar occurred only in 2 cases, numbers 4 and 5. The increase in case 5, which has already been mentioned, was moderate, namely 31 per cent. Case 4 showed a more pronounced rise, approximately 80 per cent. of the original value. This was the only case to receive ether. Apart from these two cases the increase in blood sugar during Caesarean section, whether classical or by lower uterine segment, was negligible.

Table 2 contains 9 cases requiring operative interference during or following delivery. All had been in labour, although in the case of the two patients with incomplete abortions this was naturally of short duration. Six of the patients required

Table 2.

Vaginal Deliveries

Cases who had not been shocked

Type of Operation	Case	Anaesthetic	Time mins.	Blood Sugar Readings			% change
Low forceps. Labour 16 hours.	1	N_2O, O_2, Trilene.	35	103	117	113	13
Mid forceps. Labour 23½ hours.	2	N_2O, O_2, Trilene.	40	121	129 2¼hrs.	108	6
Mid forceps. Labour 7 hours.	3	N_2O, O_2, Trilene.	45	133	153 105 (1 hr.later)		15
Mid forceps. Labour 3 hrs.50 mins.	4	N_2O, O_2, Trilene.	45	136	162(1½hrs. Later)		19
Expression of Placenta	5	N_2O, O_2, Trilene.	30	102	124		21
Dilatation & Curettage (Incomplete abortion)	6	N_2O, O_2, Trilene.	15	129	148		15
Dilatation & Curettage (Incomplete abortion)	7	N_2O, O_2, Ether.	20	107	122	122	24
Mid forceps. Labour 31 hours.	8	N_2O, O_2, Trilene, Ether.	30	100	156 Fasting 136	156	56
Low forceps. Labour 27½ hours.	9	N_2O, O_2, Trilene, Ether.	35	129	129	136	5

anaesthesia for delivery by forceps - either mid or low pelvis, two cases required dilatation and curettage on account of an incomplete abortion and in one the placenta was retained and had to be expressed.

Eight of the nine cases received an anaesthetic of nitrous oxide, oxygen and Trilene and in two of these ether was added. The ninth case received N_2O, oxygen and ether.

The duration of anaesthesia varied from 15 mins. to 45 mins.

In the six patients receiving N_2O, oxygen and Trilene the blood sugar levels were higher at the end of the operation, the increase varying from 6 to 21 per cent. The 1st specimen averaged 120 mgms. per cent. and the 3rd or final one averaged 138 mgm. Neither the length of labour nor the duration of the anaesthetic appeared to have any effect on the blood sugar as will be seen in cases 1, 2, 3 and 4. In the three cases where ether was also given the blood sugar levels were higher at the end of the operation, the increase varying from 5 to 56 per cent. The 1st specimen averaged 112 mgms. per cent. and the final specimen at the end of the anaesthesia averaged 138 mgms. per cent.

Table 3 gives details of 6 cases who required an

Table 3.

Obstetric Cases given Anaesthetics.

Cases who had suffered or were suffering from haemorrhagic shock

Type of Operation	Case No.	Time of Anaes-thesia	Anaes-thetic	Condition	Blood Sugar Readings	Time in Shock
Manual removal of placenta (P.P.H.)	1	20mins.	N_2O,O_2, Trilene, Ether.	Shock present.	250 272 After B.Trans. 152 Fasting 126	¾ hr.
Manual removal of placenta (P.P.H.)	2	15 "	N_2O,O_2, Ether.	Recovered	220 (1 hr. after anaesthesia)	1½ hr.
Manual removal of placenta (P.P.H.)	3	20 "	N_2O,O_2, Trilene, Ether.	Recovered	221 (1½hrs. after anaesthesia) 157 (1¾hrs. later-after blood transfusion)	20 mins.
Manual removal of placenta (P.P.H.)	4	15 "	N_2O,O_2, Trilene, Ether.	Shock present.	219 before trans. for shock. 214 anaesthetic begun 204 3½ hrs. later 230 2½ hrs. later.	2 hr.+
Manual removal of placenta (P.P.H.)	5	15 "	N_2O,O_2, Trilene.	Recovered	133 164	?Given 4pts. at home. Not shocked on admission.
Placenta expressed	6	15 "	N_2O,O_2, Ether.	Recovered	Collapsed just after anaes. finished - 236.	

anaesthetic when suffering from or having recovered from haemorrhagic shock. All patients required removal of placenta with the complication of post-partum haemorrhage. The anaesthetics employed were N_2O, oxygen and ether in 2 cases, N_2O, oxygen and trilene in 1 case and N_2O, oxygen, trilene, ether in 3 cases.

It will be noted that where the patient had not completely recovered from shock and where the blood sugar had not returned to normal, there was a further rise following anaesthesia with N_2O, O_2, trilene, ether. Where the patient had recovered (Nos.2, 3, 5 and 6) the blood sugar was high either just after the anaesthetic was finished or 1-1½ hours later. The level at end of operation in Case 5 is not so high but ether was not used and the recovery had been more complete due to blood transfusion at her home. There was no sign of shock on admission to hospital. It would appear that when given during or after the shock phase, ether produces a more marked rise in blood sugar levels.

Summary

It would appear from these studies that surgical interference in the average case is not a major factor in the development of shock, provided that a careful, choice of anaesthetic is made. Major alterations in

the blood sugar level only occur in three sets of circumstances; (1) loss of blood; (2) Ether anaesthesia; (3) anoxia or hypoxia. The influence of anaesthesia can best be demonstrated by the following table which shows the percentage increase in blood sugar following administration of different types of anaesthetic.

Anaesthetic	Percentage increase in Blood Sugar.
Ether	93
Neothyl	53
Intermittend ether with other anaesthetics	31
Spinal anaesthetic (no ephedrine)	22
Pentothal, nitrous oxide, trilene	14
Spinal anaesthetic with ephedrine	13
Pentothal, nitrous oxide, oxygen, cyclopropane	1
Pentothal oxygen, cyclopropane	1
Pentothal, nitrous oxide oxygen	No change.

Prolonged Anaesthesia.

Our thesis with regard to the absence of stress following major surgical interference and administration of anaesthetics of a non-ethereal type hinges largely upon our cases of Wertheim's hysterectomy. It will be remembered that we came to the conclusion that haemorrhage in these cases was the factor inducing a rise in the blood sugar, but all of these cases had undergone major surgical interference with very prolonged anaesthesia and these factors have to be taken into consideration. In addition, although in several of these cases blood transfusion was given, the blood sugar continued to rise. It was felt that this was due to inadequate replacement of blood both in quantity and time, but this is still a hypothesis. We were fortunate enough to be able to study the results in 5 cases undergoing the operation of mitral valvotomy. These cases were undergoing a very major surgical procedure involving prolonged anaesthesia but although some blood loss was inevitable, the replacement transfusion was instituted from the commencement of the operation. In addition since the blood lost is collected and accurately measured it is possible in most cases to maintain the circulatory volume near its original level.

Technique

A routine procedure was adopted with patients undergoing the operation of mitral valvotomy in the theatre which I attended. Blood transfusion was commenced and given slowly into an arm vein before anaesthesia was started. In all cases this consisted of induction with Pentothal followed by nitrous oxide, oxygen, curare, and pethidine at intervals. CO_2 absorption was used in all cases.

The 1st sample of blood was withdrawn from an arm vein just before the Pentothal was administered. The 2nd sample was taken from an arm vein at the same moment as the left auricular appendage was opened and the blood which escaped was collected by the surgeon in a receiver and handed over to me. The 3rd specimen was taken from an arm vein at the conclusion of the operation. All samples were at once transferred to a heparinised container and then to a tube containing fluoride. Blood pressure readings and the pulse rate were recorded frequently throughout the operation. The details are shown in Table 4.

The average interval between 1st and 2nd specimens was 42 minutes and between 2nd and 3rd specimens one hour. Until the heart was opened, bleeding was negligible,

Table 4.

Case No.	Age	1st blood sample (pre-anaesthetic) B.P.	Pulse Rate	2nd blood sample (on opening heart) B.P.	Pulse Rate	3rd blood sample (post-anaesthetic) B.P.	Pulse Rate
1	28	120/60	84	110/60	88	100/60	92
2	43	120/80	96	120/80	92	115/70	98
3	34	120/70	74	120/70	90	120/70	88
4	26	100/60	140	90/50	120	85/50	108
5	16	135/80	84	115/65	100	120/70	88

but thereafter there was a variable amount of haemorrhage, heavy in some, moderate in others. The results are shown in Table 5 .

It is interesting to note that there was little change in the blood sugar values between specimens 1 and 2 despite the fact that the patient had been anaesthetised for over 40 minutes and was subjected to considerable trauma during the process of opening the chest wall. However, changes in the blood sugar did occur in the period between withdrawing samples 2 and 3. In all but one there was an increase in the blood sugar level. The exception occurred in a young woman of 26 (Case 4). Considerable difficulty was experienced by the resident surgeon in setting up the transfusion, and one hour had elapsed before the needle was satisfactorily placed in the vein. The patient was markedly upset, and her pulse rate had mounted to 140 per minute when the Pentothal was due to be administered. The surgeon seriously considered postponing the operation in view of her excitement. However following administration of the anaesthetic her pulse rate began to fall. This fall continued throughout the operation which continued without any further complications. At the end of the operation the patient was in much better

Table 5.

Case No.	Blood Sugar Readings: Pre-anaesthetic Vein 1	Interval in minutes	On opening heart Vein 2	On opening heart Heart	Post-anaesthetic Vein 3
1	86	35	78	89	107
2	105	50	111	119	165
3	78	45	81	94	109
4	200	35	158	162	113
5	91	45	90	95	110

condition than before and her pulse rate had fallen to 108/minute. Blood loss was minimal in this case and it was comparatively simple to keep pace with the amount lost by means of the intravenous transfusion. It is interesting to note that the blood sugar in this case before commencing operation was 200 mgm.per cent. and that it showed a steady fall throughout, reaching 113 mgms. per cent. at the finish.

Table 5 also includes the blood sugar level of the heart blood collected at the same time as the venous specimen 2.

Summary

The first stage of the operation in these patients confirms my impression that surgical interference, provided the patient is properly anaesthetised, is not a cause of stress. No change in the blood sugar of any significance occurred during this phase of the operation. It also provides a further indication that prolonged anaesthesia by this method has no influence on the blood sugar level. During the second stage of the operation changes in blood sugar level did occur. Although this phase is also associated with major surgical interference in a vital organ it should be kept in mind that all of the patients underwent the same

operation by the same surgeon and that the duration of this part of the operation was almost exactly the same in all cases. Despite this there was a considerable variation in the blood sugar increase during this stage. The only factor which can be correlated with the change in blood sugar at this stage is the loss of blood. The increase in blood sugar varied from 18 mg. to 54 mg. In the latter instance a rapid loss of blood occurred at one point in the operation whereas in the other cases the loss was only moderate. The exceptional case in whom blood loss was moderate and easily replaced and which actually showed a fall in the blood sugar would also support the argument that a rise in blood sugar in the other cases is related to loss of blood.

Although one case did show a considerable increase in blood sugar it is to be noted that in none of them, did the value exceed the physiological limit and it was in no way comparable with the values found in our Wertheim's cases who suffered from severe haemorrhage. This is remarkable in view of the fact that the volume of blood lost in the two series of cases was comparable. The only difference to be noted is that blood transfusion is instituted before the operation is begun in the cardiac cases. Obviously early transfusion will

prevent stress in cases where haemorrhage is bound to occur. An interesting point is to be seen in the sugar values for heart blood specimens taken at the same time as specimen 2 was withdrawn from the vein. The blood sugar content of the heart specimen is always higher than that of the venous blood. This is in agreement with other writers on this subject, and will be considered in more detail in Part 3 of this thesis.

Discussion

As a result of the investigations made on the foregoing patients using different types of anaesthetic, we may conclude that hyperglycaemia occurs in varying degree with ether, methyl-n-propyl ether, trilene (trichloroethylene) and spinal anaesthesia in the absence of ephedrine. It is known also to occur with chloroform, but this anaesthetic has not been considered in this investigation as it is seldom used in hospital practice. In addition hyperglycaemia was found with other inhalation anaesthetics when anoxia or hypoxic episodes were present, as evidenced in the series of patients who were given pure nitrous oxide for induction. These findings agree in general with Adriani (1946), Hunter (1950) and many other writers on the biochemical changes occurring during anaesthesia.

It has also been shown that Pentothal or similar barbiturate when used for induction does not have any effect on the blood sugar, although it is stated by Adriani (1947) that it is raised slightly but the data are controversial. However prolonged use of Pentothal does cause material changes in the blood sugar level as shown by Booker (1946) in his experiments on dogs.

In considering ether first of all, it was observed

that when it was administered in light concentration with nitrous oxide and oxygen, either to obstetric or gynaecological cases the total rise in blood sugar averaged 23 per cent. over an average time of 17 minutes. In heavy concentration or given alone through an ether mask, the rise was much more marked, increasing by 80 to 97 per cent.

Even when hyperglycaemia has been induced by severe loss of blood ether anaesthesia causes the blood sugar to mount even higher. Occasionally too, the blood sugar, which tends to fall after completion of the operation shows a second rise some hours later. Quite apart from this phenomenon for which no explanation can be offered, it is apparent from the results that ether anaesthesia in these haemorrhage cases delays the return of the blood sugar to normal. This delay in return to normal is rather similar to the changes noted in some pregnant patients who suffered from repeated haemorrhage. In these patients too there was a marked delay in the fall of the blood sugar to normal. It would seem reasonable to assume that in cases of haemorrhage the administration of ether has acted as an additional stressor.

It was observed in the gynaecological cases that the

rise in blood sugar averaged 23 per cent. in the first 6-11 minutes but increased quickly thereafter depending on the amount of ether administered. With methyl-n-propyl ether on the other hand the rise was more marked in the first 10-12 minutes.

Trilene also produced a rise in the blood sugar level but to a much lesser degree unless combined with ether.

The general consensus of opinion is that ether and its allies produce a rise in blood sugar as a result of sympathetic stimulation, and presumably trilene acts in the same way but to a lesser degree.

The explanation may be as Johnson (1949) suggests, that ether stimulates the adrenal glands by way of the sympathetic system and as a result the adrenalin liberated causes hepatic glycogenolysis.

A lesser degree of hyperglycaemia occurred following the administration of spinal anaesthetics but omitting the injection of ephedrine. Presumably in such cases the hyperglycaemia resulted from a different mechanism and may be related to the fall in blood pressure. It is therefore akin to that which occurs in haemorrhagic shock or which follows myocardial infarction (Boulin, Uhry and Kaufman, 1954).

The pathway may be through the carotid sinus. It is known that with a fall in blood pressure, the carotid sinus effects a release of adrenalin which causes cardiac acceleration, and also a vasoconstriction to adjust the vascular tone and so maintain the blood pressure (Heymans, 1938).

It was noted (Section A) that the blood sugar did not begin to rise until at least 15 minutes after the production of shock and at 30 minutes after the average level was just under 200 mgms.per cent. With ether the rise in the blood sugar began within 6-10 minutes after commencing anaesthesia but became more marked in the following 5-10 minutes. This was confirmed in the animal experiments. In spinal anaesthesia where ephedrine was omitted a definite rise occurred after 20 minutes with an accompanying drop in blood pressure. It continued to rise for a further 10 to 40 minutes, varying in individual cases.

However where anoxia was produced by giving pure nitrous oxide for an average time of two minutes, the rise in blood sugar was much more dramatic and reached greater heights in an average time of 5 minutes. This was the most striking feature in the investigation of the effects of anaesthetics.

In all cases of stress causing hyperglycaemia whether due to haemorrhage, ether anaesthesia or anoxia the mechanism is almost certainly mediated through the nervous system in the first instance. Nevertheless there appears to be considerable difference in the rate of reaction according to the type of stimulus. It is difficult to believe that, if the reaction is of nervous origin, the rate of travel of the impulse will vary with the stimulus. One must assume therefore that some other factor is responsible for the rapid increase in the sugar level of the peripheral blood in cases suffering from anoxaemia. This apparent variation in the rate of mobilisation of liver glycogen has been made the subject of further study in the third section of this thesis.

SECTION C.

Source of Blood Sugar & Rate of Mobilisation.

Certain anomalies were noted in the results of our previous studies particularly in relation to the rate of mobilisation of sugar. Following haemorrhage there was an interval of some 15 minutes before any appreciable change in the blood sugar occurred, with ether this interval was reduced to 6 to 10 minutes but in those patients in whom anoxia was produced by induction with pure nitrous oxide, the blood sugar showed a marked increase in less than 5 minutes. It is understood of course that given with an adequate supply of oxygen nitrous oxide has no glycolytic effect such as is possessed by ether. It was therefore decided to study more closely the release of sugar from the liver. This also served to confirm the source of the sugar, although, of course, it was already apparent from reports in the literature that the liver was the main source of glucose. (Robertson, 1935; Engel et al 1943; 1944; Mylon et al, 1944).

Mobilisation of liver glycogen in the experimental animal.

In order to make this study it was necessary to obtain samples of blood simultaneously from the hepatic vein and the left side of heart. A dead rabbit was dissected, and it was found that by making an incision 2" long in the mid-line of abdomen, commencing at the

xiphisternum, it was possible to expose the hepatic vein and inferior vena cava by inserting a finger below the diaphragm and depressing the liver.

In the first experiment a rabbit was anaesthetised with 5 per cent. Pentothal after taking a sample of blood from the ear vein. The abdomen was then opened and by depressing the liver as previously described 3 ml. of blood were withdrawn from the hepatic vein. At the same time an assistant punctured the left ventricle and another 3 ml. were withdrawn, making 6 ml. in all. This volume was chosen deliberately since it has been shown that more than 6 ml. of blood had to be withdrawn from a rabbit to produce a mild degree of collapse, and it was hoped that this volume would initiate the process and thus allow a study to be made of the early phases of liver glycogenolysis. Eighteen minutes later further samples of blood were withdrawn from the hepatic vein and left ventricle. The results are shown in Table 1. It will be apparent that the initial values for hepatic vein, left ventricle and ear vein form a gradient with the highest value in the blood just as it leaves the liver. Eighteen minutes later when the effect of loss of blood might be expected, the sugar level of the left ventricle blood shows little change

Table I.

Blood Sample from	Blood Sugar Values
Ear	110 mgms. per cent.
Anaesthetic given - abdomen opened - 6 ml. blood withdrawn.	
Left heart	117 mgms. per cent.
Hepatic vein	129 " " "
18 minutes later.	
Left heart	119 " " "
Hepatic vein	167 " " "

although the hepatic blood value is considerably increased. A distinct difference exists between the values for left heart and hepatic vein under normal conditions but it cannot compare with the difference between the values at the end of the experiment. Initially the difference amounted to 10 per cent. of the left heart reading, but terminally the gap had increased to 40 per cent. While the mixing of the hepatic blood with the systemic blood could account for a certain reduction in the concentration of glucose, it is difficult to conceive that it could result in a fall in value of such magnitude. The results suggest that there is a loss of glucose from the blood during circulation from the right side of heart to left. The problem was pursued further in a more prolonged experiment.

After anaesthetising with Pentothal as before, 13 ml. of blood were withdrawn from a rabbit. Within a short time the blood sugar of both hepatic vein and left ventricle showed a moderate increase. Twenty minutes after withdrawal of the blood the hepatic vein value had risen well above normal limits, but the level on the left side of the heart was just approaching the upper limit of normal. A further 6 ml. of blood were withdrawn and fifteen minutes later the values for both

hepatic vein and left side of heart were above 200 mg. per cent. This experiment indicates that glycogenolysis occurs with great rapidity in the liver but the blood sugar level on the arterial side of the circulation increases relatively slowly. As the duration and depth of shock increases the values for left heart and hepatic vein tend to approximate. (See Table 2).

In another similar experiment repeated withdrawals of blood were made until the animal died (Table 3). Initially 8 ml. of blood were withdrawn and when shock was established the values for both left heart and hepatic vein were well above normal. Twenty minutes later the blood sugar was still rising and a further 6 ml. blood were withdrawn. After a further twenty-five minutes the values were within the range found in cases of diabetic coma. Another 6 ml. of blood were withdrawn. Fifteen minutes after this as blood was being withdrawn the animal died. From the table it can be seen that repeated haemorrhage causes a continuous rise in the sugar content of the blood and at no time is there any evidence of exhaustion of the hyperglycaemic mechanism. In addition the experiment demonstrates the constant difference in value between the sugar value of the blood from hepatic vein and left heart, but with increasing

Table 2.

Blood Sample from	Blood Sugar Values
Ear	104 mgms. per cent.
Anaesthetic given and abdomen opened. 13 ml. blood withdrawn.	
Left heart	152 mgms. per cent.
Hepatic vein	165 " " "
Twenty minutes later	
Left heart	173 " " "
Hepatic vein	208 " " "
6 ml. blood withdrawn	
15 minutes later	
Left heart	229 " " "
Hepatic vein	237 " " "

Table 3.

Blood Sample from	Blood Sugar Values
Ear	136 mgms.per cent.
Rabbit anaesthetised, abdomen opened and 8 ml. blood withdrawn - shock produced.	
Left heart	200 mgms.per cent.
Hepatic vein	225 " " "
20 minutes later, 6 ml.blood withdrawn.	
Left heart	297 mgms.per cent.
Hepatic vein	309 " " "
25 minutes later, 6 ml.blood withdrawn.	
Left heart	414 mgms.per cent.
Hepatic vein	470 " " "
25 minutes later, 6 ml.blood withdrawn.	
Left heart	616 mgms.per cent.
Hepatic vein	666 " " "

Animal died.

Total time of shock = 70 minutes.

shock this tends to diminish.

The continuing hyperglycaemia is contrary to the finding of some authorities (Wiggers, 1950) who have reported hypoglycaemia in the terminal phases of shock. It would appear from the above experiments that there is a consumption of glucose during circulation of the blood through the lungs but that this diminishes with increasing loss of blood. These changes may possibly be related to alteration in respiratory activity as the condition of the patient deteriorates. In the initial phase of haemorrhagic collapse respiration is stimulated and becomes both deeper and more rapid. This, no doubt, is a matter of attempted accommodation to the loss of oxygen-carrying power of the blood. As the shock increases respirations become shallower and slower. It is tempting to assume that the disparity between the glucose levels of the hepatic vein and the left ventricle, in the early phase of shock, is related to the increased respiratory effort. Contrariwise, in the later phase of shock the decrease in the difference between the two levels may follow on the deficient respiratory activity. This is a point which has been pursued further in later experiments.

Ether and Hepatic Glycogenolysis

The experiments in this section were similar to those detailed above with the exception that ether was used as the anaesthetic and only small quantities of blood, sufficient for analysis, were withdrawn. The procedure was as follows. A small quantity of blood was withdrawn from an ear vein. The animal was then anaesthetised with ether and the abdomen opened. At varying intervals thereafter small specimens were withdrawn from the hepatic vein and left heart. The results are shown in Table 4.

In animal 1 it will be noted that after only 5 minutes of ether anaesthesia the sugar value of blood withdrawn from the ear vein has begun to increase. After a further five minutes specimens taken from left heart and hepatic vein show a marked increase. Once more there is a discrepancy between these two values amounting to 49 per cent. of the left heart sugar level. This experiment was more or less repeated in animal 2. Again, after 10 minutes of ether anaesthesia the blood sugar shows a marked increase and there is the same difference between the hepatic and left heart bloods, amounting to 43 per cent. in this case. Ten minutes later the blood from the hepatic vein showed a

Table 4.

Anaesthesia with Ether.

Blood Sugar readings in mgms.per cent.

Animal	Ear	Heart	Hepatic Vein	Duration in Minutes
1	111	-	-	-
	120	-	-	5
	-	149	222	5
2	98	-	-	-
	-	173	250	10
	-	-	354	10
3	94	-	-	-
	-	133	162	5
	-	196	300	5
4	119	-	-	-
	-	142	177	5
	-	204	219	5

further increase. Both of these experiments serve to demonstrate the marked sugar mobilisation effect of ether and the loss of sugar from the blood in its passage through the lungs.

The third animal was anaesthetised in the same way and the hepatic vein laid bare. Specimens were withdrawn from the vein and the left heart 5 minutes after the commencement of ether anaesthesia and again 5 minutes later. Within five minutes the sugar value in both has increased but the difference between themamounts to 21 per cent. of the left heart value. Five minutes later the blood sugar is greatly augmented and the difference between the two readings has increased to 53 per cent. of the left heart value. A fourth animal was treated in the same way. In this instance the same rapid mobilisation of sugar has occurred, but the difference between the left heart and hepatic veins, while still large, is not so striking as in the other animals. The details of the experimental findings are shown in Table 4 .

These experiments confirm our findings in human subjects. Ether induces an extremely rapid mobilisation of sugar from the liver. The time taken for an appreciable increase in blood sugar to be produced is

less than half that by means of haemorrhage. Once more the findings suggest that the fall in glucose level between the hepatic vein and left heart is related to respiratory activity.

Commentary

In 1935 Robertson noted that following haemorrhage in animals the sugar level of the hepatic vein rose quickly. He also found that blood taken from the left side of the heart at the same time did not show the same rapid increase in sugar content. He made no further comment on this finding and was only concerned with the hyperglycaemic reaction following haemorrhage.

The experiments detailed above confirm the existence of this phenomenon. Even under normal circumstances there appears to be a significant difference between the sugar levels of the right and left sides of the heart. Under stress with hyperglycaemia, whether due to haemorrhage or ether anaesthesia, this disparity is considerably augmented. The findings indicate that sugar is lost in the passage of blood through the lungs. It is possible that this may offer an explanation for some of the other phenomena noted in the experiments.

The experiments have shown that sugar is rapidly

liberated from the liver in all forms of stress, but the increase in blood sugar of the left heart appears at varying intervals according to the nature of the stimulus. In the case of haemorrhage it has been found that the blood sugar of the left heart showed a significant increase only after the elapse of approximately 15 minutes. With ether anaesthesia a comparable increase was obtained in 10 minutes, but in hypoxia due to nitrous oxide the rate of increase was speeded up and the time thereby reduced to five minutes. It is possible, of course, that ether may act by virtue of its toxic nature, thereby interfering with metabolism and allowing a more rapid liberation of glucose. In view of the results with nitrous oxide, however, it seems more likely that interference with respiration is the key to the situation. In animals suffering from the effects of haemorrhage there is initially no interference with the function of the lungs and indeed respiration is usually stimulated. On the other hand both ether and nitrous oxide will interfere with pulmonary function. Nitrous oxide prevents oxygenation completely and gaseous exchange cannot take place. Ether probably also does this but in addition it may interfere with the activity of respiratory enzymes

in the lung. Such an hypothesis would serve to explain the varying rates at which increase in the glucose content of the left heart blood occurs with these different stimuli. Where there is no interference with oxygenation and therefore normal metabolism of glucose in the lung the sugar content of the left heart blood will increase relatively slowly. With slight upset in gaseous exchange as in ether anaesthesia, the sugar mobilised from the liver will appear on the left side of heart in a shorter period of time. Where gaseous exchange is abolished the sugar increase will occur in the left side of heart almost at the same time as in the hepatic vein.

In the previous sections of this thesis the findings in animals are similar to those in the human subject and it remains to be seen whether the sequence of events noted in the above experiment can in some measure be duplicated in the human subject.

Glucose Levels and Pulmonary Function in the Human Subject.

The only evidence obtained so far from the observations on human subjects, which might suggest a similar conclusion, was to be found in those patients in whom anaesthesia was induced by pure nitrous oxide. It was noted in these cases that the rise in the blood sugar occurred more rapidly than in the other conditions causing hyperglycaemia, and so it would appear that the sugar content of the blood from the left side of the heart would be virtually the same as the right side since no oxygen was present while the blood was passing through the lungs. Oxygen would seem to be a necessity in the conversion of some of the glucose to carbon dioxide and water. An occurrence which is somewhat similar takes place in the late stages of shock when it is usually observed that respirations are shallow and less frequent with therefore less oxygen available.

It may be postulated that when stress occurs, whether it be due to hypoxia or haemorrhagic shock, the increase in the blood sugar means that sugar is urgently required for energy by many parts of the body. The lungs may require it in order to produce a greater quantity of CO_2 as one of the end products, thereby

causing a greater ventilation with a consequent increase in oxygen consumption.

Although it is not at the moment possible to make observations in the human subject similar to those observed in animal experiments and so confirm these views, it was considered that some corroborative information might be obtained during operations on the heart (mitral valvotomy) and in cardiac catheterisation.

Accordingly the opportunity was taken to attend a series of operations for mitral valvotomy performed by Mr. Kenneth Fraser at the Western Infirmary, Glasgow, and a series of cardiac catheterisation carried out by Dr. Ralph Thomson at the Eastern District Hospital, Glasgow.

In the valvotomy series quoted on page 109 it was noted that neither the anaesthetic nor the operation concerned with opening the chest had any appreciable affect on the blood sugar. Therefore it was thought that if a sample of blood from the left auricular appendage was obtained at exactly the same moment as blood from an arm vein it would give an idea of the difference between venous and true arterial blood with regard to the sugar content. The results are shown in Table X , where it will be seen that in all cases

Table X.

Case No.	Blood Sugar Readings: Pre-anaesthetic Vein 1	Interval in minutes	On opening heart: Vein 2	On opening heart: Heart	Post-anaesthetic Vein 3
1	86	35	78	89	107
2	105	50	111	119	165
3	78	45	81	94	109
4	200	35	158	162	113
5	91	45	90	95	110

the blood sugar reading in arterial blood is higher than that in peripheral venous blood. This has been noted by many authors including Mylon et al (1944) and Mosenthal and Barry (1945).

Even with this knowledge, we still required the information concerning the blood from the inferior vena cava (above and/or below the hepatic vein), from the right side of the heart and from the peripheral venous blood. It was possible to obtain some of this information when cardiac catheterisation was in progress. Samples were withdrawn from the inferior vena cava (below and above hepatic vein), from the right side of the heart and from the brachial or innominate vein. These readings are shown in Table Y .

It will be seen that the blood sugar levels in the innominate or brachial veins in all cases were lower than those obtained from the right side of the heart.

From these experiments two facts are established. The sugar level of the blood in the right side of the heart is higher than that of blood in the innominate vein, and similarly the level in the blood from left heart is higher than that of the peripheral blood. This agrees with the findings in experimental animals, and it seems justifiable to transfer findings and

Table V.

Blood Sugar Readings mgms.per cent.

Case No.	Peripheral Vein	Right Heart	Inferior Vena Cava near hepatic vein
1	101	109	107
2	75	84.7	83
3	86	91.5	
4	88	92	94

conclusions from these animals to the human subject. There remains however, one finding in the animals which so far has not been duplicated in the human subject. It has been shown in animals that as the blood passes through the lungs the sugar content is diminished provided aeration in the lungs is unimpeded. This phenomenon was naturally most marked in cases of hyperglycaemia with hyperventilation, but even under normal circumstances a significant difference between the sugar levels of the right and left sides of the heart was found. Fortunately, it was possible, through the kind co-operation of Mr. Kenneth Fraser, to obtain suitable samples of blood during thoracic operations. It has already been demonstrated that both in experimental animals and in the human subject, opening of the chest wall does not cause any recognisable degree of stress, provided suitable anaesthesia is employed. In the present instance the anaesthetic mixture consisted of pentothal, curare, pethidine, nitrous oxide and oxygen. This was the same method and combination of anaesthetics which were used in the mitral valvotomy operation (Table X , on page 133), and it was shown that these had no influence on the blood sugar levels. Respiration was maintained by means of a Pulmoflator using a carbon

dioxide absorption apparatus and so prevented any periods of apnoea which might lead to asphyxia. Immediately the chest was opened and the organs displayed, samples of blood were withdrawn simultaneously from the pulmonary artery, the aorta and a peripheral vein. Specimens have been obtained from four patients under these circumstances. The results are shown in Table Z.

From this table it is obvious that the findings in the human subject are similar to those in animals. The highest blood sugar readings are found in the blood withdrawn from the pulmonary artery which contains a mixture of blood from portal and systemic circulations. Samples were taken from the aorta rather than the left side of the heart as it was surgically more safe and quicker and would give the same blood sugar reading. The difference in the sugar levels of the blood from pulmonary artery and the aorta shows that, during its circulation through the lungs, the blood has lost a certain amount of sugar. A further loss usually occurs in its passage from arterial to venous side of the circulation but this loss is not so great as that which occurs in the pulmonary circulation. The sugar level in the right side of the heart is

Table Z.

Blood Sugar Readings mgms.per cent.

Case No.	Pulmonary Artery	Aorta	Peripheral Vein
1	144	129	131
2	162	141	122
3	149	140	135
4	192	183	179.

thereafter built up again by the blood from the liver.

From these studies it would appear that in the anaesthetised patient the metabolism of glucose in the lungs is considerable. Approximately 7-14 per cent. of the glucose is utilised in the lungs. This may appear to be a relatively small amount compared with the 70 per cent. said to be abstracted from the blood by the brain (Scheinberg and Jayne, 1952) but one must take into consideration that in each complete circulation the whole of the blood passes through the lungs, whereas only part reaches the brain. This must necessarily be associated purely with pulmonary function and one is therefore forced to the conclusion that the metabolism of glucose in the lungs is intimately concerned with gaseous exchange. In the normal state and with certain anaesthetics where an adequate supply of oxygen is available this will continue but anything which interferes with respiration and the normal gaseous exchange in the lungs will result in an upset of the normal release of glucose from the liver. It seems likely from the results that a considerable amount of energy is required for respiratory function. If the energy required by the lungs and made available by the

metabolism of glucose is hindered by lack of oxygen, the body responds by increasing the amount of circulating glucose. This is yet another aspect of the stress syndrome which results from lack of oxygen whether it be due to haemorrhagic shock or anoxia with anaesthesia and may explain in part the hyperglycaemic reactions reported in this thesis.

This phenomenon of glucose metabolism in the lungs has apparently not been studied hitherto and a search of the literature has failed to produce any reference to the subject.

Final Summary and Discussion.

The work for this thesis was embarked upon when I noted the occurrence of a marked degree of hyperglycaemia in several patients who were admitted to the Glasgow Royal Maternity and Women's Hospital in a state of shock. They had all been confined in their own homes and had been sent to hospital on account of severe post-partum haemorrhage which had caused the collapse. In the first few patients investigated the blood sugar ranged from 204 to 272 mgms.per cent. It followed naturally that haemorrhagic collapse due to other causes such as abortion, ruptured uterus and ante-partum haemorrhage might also produce changes in the blood sugar, so specimens of blood were collected from as many of these types as possible. The investigation extended over a period of three years and in all 47 cases were examined.

The main object of this thesis has been to study the metabolic response of the subject to haemorrhage under the very varying conditions associated with pregnancy and delivery. For this purpose it was necessary to accumulate data not only in the pregnant but also in the non-pregnant subject. Similarly the influence of anaesthetics and the effect of operative

interference had to be observed. In these different circumstances the response may well differ both in quality and time and if any practical significance is to be read into the results timing of the response is essential. Only thus can a reasonably logical approach to treatment be made. An attempt was made to provide these data. Experimental animals were necessary for investigating the variation in rate of response. From these experiments I was able to relate the variation in the rate of the hyperglycaemic reaction under differing conditions to the respiratory function.

Since in the majority of the 47 patients the haemorrhage causing the shock occurred post-partum, it appeared that the first investigation which seemed necessary was the effect of normal labour on the blood sugar. De Lee (1943) states that this drops markedly during labour, especially if the latter is hard and long, and is usually restored by the 10th day post-partum. This does not agree with the finding in a series of nine patients whom I investigated during normal labour. None of these patients was given glucose in any form throughout the labour as false readingsmight have been thus obtained. The results showed on the average that there was a

gradual rise in the blood sugar level from 125 mgms. per cent. in the 1st stage to 145 mgms.per cent. just after the completion of the 3rd stage. It was evident therefore that although a rise in the blood sugar level did occur during labour, it was within the physiological range and not comparable with the readings obtained from those patients suffering from haemorrhagic shock. It was also clear that the length of labour per se did not have any particular bearing on the blood sugar level of the collapse cases following 3rd stage haemorrhage (p.18) and this received further proof in the results obtained from those patients who collapsed prior to labour, e.g. with accidental haemorrhage, or in cases of abortion.

In each case investigated, the duration of the shock was assessed as accurately as possible from the data available and it became noticeable that the highest blood sugar readings were found in those who had been in the shocked stage for the longest time, the maximum being 6 hours. It was also observed that shock of short duration produced little alteration in the blood sugar level and that it was only in cases where the shock phase had lasted for approximately 30 minutes that an appreciable rise occurred. In the case of

accidental haemorrhage however the rate of response appeared to be slower (Fig.4) which suggests that this may be due to an alteration in carbohydrate metabolism in toxaemia.

It has been known for many years that severe haemorrhage causes a hyperglycaemia (Bernard, 1877; Robertson, 1935; Moon et al, 1941; Mylon et al, 1944) following work on experimental animals, and confirmed by Beecher (1949) and Wiggers (1950) following observations on the human. Beecher's work was done on wounded soldiers but the blood sugar levels found were seldom above 200 mgms.per cent. The levels observed in my series are very much higher, and rather similar to those recorded by Taylor et al (1944) in patients suffering from burns.

The cause of the hyperglycaemia may be due (1) to the stress mechanism of Selye involving the pituitary-adrenal axis: (2) circulatory failure either of central (Boulin et al, 1954) or peripheral type (Davidson et al, 1946) or (3) a severe reduction in the number of red cells sufficient to cause anoxia of the liver (Frank, Seligman and Fine, 1946). The nervous system no doubt also participates through the hepatic branches of the sympathetic division, Selye

(1950). From my investigations it would appear that there are two phases in the hyperglycaemic reaction, the initial phase associated with hepatic glycolysis due to adrenalin release and the subsequent and slower phase probably related to a more complex gluconeogenesis - glycolysis mechanism.

Whatevery may be the cause or group of causes, it is interesting to note the effect of blood transfusion on the blood sugar in 18 of the 47 cases. As the amount of blood replaced became sufficient to cause an improvement or recovery in the general condition judged by rise in blood pressure, skin warmth and slowing of the pulse rate, the level of the blood sugar fell. In several cases this seemed proportional to the initial shock level, but if a second shock occurred following further haemorrhage or operative procedure the blood sugar showed a second rise and subsequently took a much longer time to return to normal.

As all these results were obtained in pregnant women, it was considered necessary to examine the blood from non-pregnant patients undergoing operations where haemorrhage might occur. This information was obtained from 4 patients undergoing Wertheims hysterectomy and 5 patients on whom mitral valvotomy was performed. It was noted that where

bleeding was heavy in the Wertheim cases, the blood sugar occurred after 15 minutes, but if the blood lost was adequately replaced by transfusion little alteration took place

In order to utilise these facts accurately an investigation had to be made first of all on the effect of operative interference on the blood sugar. Thirteen cases were studied in the gynaecological theatre - 5 having the operation of pelvic floor repair and 8 having one of the major abdominal operations. The results showed that (a) the type of operation, (b) the length of time of operation and (c) the opening of the peritoneal cavity did not have any effect on the blood sugar provided the bleeding was only slight.

The effect of haemorrhage on the blood sugar was extended to controlled experiments on rabbits in order to find confirmation if possible of the results obtained in the human subject. Among the various findings, it was observed (a) that the initial rise in the blood sugar occurred 10 minutes after blood loss, (b) that the duration of the hyperglycaemia was related to the volume of blood withdrawn and (c) that the hyperglycaemic mechanism did not appear to be exhausted by continued loss of blood. Related to these results is the work of Mylon et al (1944) who showed in dogs that the more

quickly blood is withdrawn, so the clinical picture of shock tended to become increasingly evident and the blood sugar rose proportionately. However the last finding is contrary to the suggestion of Wiggers that there is a terminal hypopglycaemia. In the one fatal case in my series of 47 the blood sugar rose continuously and reached a final level of 364 mgms.per cent.

The initial reaction, whatever may be the method of stimulation, is probably due to glycogenolysis in the liver following the release of adrenalin, although Slocum and Lightbody (1931) and Clark and Rossiter (1944) have found that the increase in blood sugar is not completely prevented by adrenalectomy. However it was considered that some light might be thrown in this problem by injecting adrenalin into patients in the Maternity Wards and observing the time relationship of the hyperglycaemia which followed. In these a sharp rise occurred within 10 to 15 minutes and continued more slowly up to 30 minutes at which time was the maximum response. It was after this interval in the patients suffering from the haemorrhagic shock during pregnancy that the blood sugar showed an appreciable rise. The immediate source of this blood sugar is most probably

the liver (Robertson, 1935; Engel et al, 1943, and the animal experiments in Section 3) but the subsequent rise in cases of shock may be attributable to the pituitary adrenal system and the increased liberation of A.C.T.H. This would agree with Long (1947) who suggests a double mechanism underlying the secretion of A.C.T.H. following stress - 1) a quick release of adrenalin activating the anterior pituitary and 2) a slower metabolic mechanism not dependent on adrenalin secretion. The assumption is that in any stress there is a demand for energy and that glucose is produced in greater quantities as the stress increases. The organ of the body which must have an adequate supply of glucose is the brain and to utilise it an adequate supply of oxygen is essential. (Scheinberg and Jayne, 1952). When the blood pressure falls in haemorrhagic shock with a consequent decrease in the number of circulating red cells an anoxia of the brain results.

During the investigation of obstetric and gynaecological cases, anaesthetics of various types had to be used and as some of these are known to have a hyperglycaemic effect it had to be ascertained how these might complicate the results obtained. This investigation formed part 2 of the thesis. In this section twelve

different anaesthetics or combinations of anaesthetics were employed during gynaecological operations. It was found that ether caused the greatest percentage rise in blood sugar whereas at the opposite end of the scale no change occurred with Pentothal nitrous oxide and oxygen.

The percentage changes are as follows:-

Ether	93
Neothyl	53
Intermittend Ether with N_2O O_2, etc.	31
Spinal anaesthesia (no ephedrine)	22
Pentothal, N_2O O_2, Trilene	14
Spinal anaesthetic (with Ephedrine)	13 - excluding haemorrhage, hypoxia.
Pentothal N_2O, O_2, Cyclopropane	1
Pentothal O_2, Cyclopropane	1
Pentothal, N_2O_2 O_2. No change (excluding hypoxia).	

It had been found during the investigation of these anaesthetics that when an hypoxic episode occurred, there was a corresponding increase in the blood sugar. Although it is well known that asphyxia or hypoxia cause hyperglycaemia, it was decided to investigate a series of cases taking particular note of the interval which elapsed before the blood sugar began to rise. Nine patients were given pure nitrous oxide for an average of 2 minutes to the stage of jactitation - oxygen was added thereafter in 4-8 per cent. and specimens of blood taken at pre-determined intervals. The interesting finding which emerged was the very rapid rise of the

blood sugar within 5 minutes of the induction with pure nitrous oxide, a quicker response than that elicited from ether. It would appear that the importance of this finding may be applied most cogently to anaesthetics in obstetrics where it becomes so necessary to prevent any hypoxic episodes during induction or prior to delivery as the foetus may already be suffering from a considerable degree of hypoxia due to various causes.

Having ascertained the effect of the various anaesthetics and their glycogenolytic properties it was possible to correlate the results with those obtained in the obstetric series. These patients were divided into 3 groups - abdominal deliveries, vaginal deliveries and those who were in a state of or had recovered from shock. Once again as expected ether produced the greatest rise in the blood sugar and in the shocked cases a further rise resulted from ether anaesthesia. The inference to be taken from this finding is that ether - or any anaesthetic which causes a hyperglycaemic response - is inadvisable when a patient is suffering from or has recently suffered from haemorrhagic shock. According to Cantarow and Gehert (1931) if ether is administered to patients whose livers are damaged and poor in glycogen the subsequent convalescence is usually stormy and a

fatal result may ensue. In this respect it is interesting to note that Govan and MacGillivray (1950) demonstrated that haemorrhagic shock in pregnancy results in varying degrees of hepatic damage.

Another aspect of anaesthesia which had still to be considered was the effect on the blood sugar of a long operation. It has been shown that Pentothal Gas Oxygen did not cause a hyperglycaemia provided no anoxic episodes occurred so when these were used in conjunction with curare and pethidine in lengthy operations, they gave a fair indication of the effect of prolonged anaesthetics was used for the five operations of mitral valvotomy, which I attended. The results would appear to prove that the addition of Pethidine and curare had no effect, and that prolonged anaesthesia had no influence unless complicated by haemorrhage. This was confirmed also in prolonged spinal anaesthetics in those cases undergoing Wertheims hysterectomy where bleeding was minimal.

As a result of the investigations in cases of haemorrhagic shock, in the administration of ether and spinal anaesthetics, omitting ephedrine, and on the anoxia produced in nitrous oxide induction one very interesting point emerges. This related to the varying

times taken for the blood sugar to rise following the stimulus. The slowest response followed the administration of a spinal anaesthetic and omitting ephedrine - this averaged 20 minutes. In the shock following haemorrhage in the pregnant patient, the blood sugar did not begin to rise until after 15 minutes had elapsed and only passed the upper physiological limit after 30 minutes. With ether anaesthesia there was a marked rise in the blood sugar from 6 to 10 minutes after commencing the anaesthetic but where anoxia was present for 2 minutes during nitrous oxide induction there was a rapid rise in 5 minutes. This apparent variation in the rate of mobilisation of liver glycogen was made the subject of study in part 3 of the thesis.

This problem was attacked first of all by means of the experimental animal. In the first group of animals samples of blood were taken from the hepatic vein and left side of heart totalling 6 ml. and repeated 18 minuted later. There was marked increase in the 2nd hepatic vein reading but little change in the heart reading. This suggested a loss of sugar from the blood in its circulation through the lungs. In the second experiment, animals were shocked by haemorrhage and it was found that the blood sugar in the hepatic vein

increased more quickly but was always maintained at a higher level than in the left heart. It was also shown that with repeated haemorrhages, and consequently increasing degree of shock, the blood sugar continued to rise to diabetic levels. This showed that the hyperglycaemic mechanism is not exhausted, contrary to the suggestion of Wiggers (1950). The experiments of Mylon et al (1944) would appear to agree with my findings. In addition the table on page 122 shows that there is a constant difference between the sugar value of the hepatic vein and left heart but with increasing shock this tends to diminish. In such cases there is a decrease in the oxygen consumption by the lungs on account of shallower and slower breathing and so a smaller quantity of glucose will be degraded presumably to carbon dioxide and water.

A third animal experiment was pursued with ether as the anaesthetic. This confirmed the findings in human subjects that ether causes a rapid glycogenolysis from the liver and that the time taken to do so was less than half that by means of haemorrhage. The results continued to show a constant difference between the blood sugar level of the hepatic vein and left side of heart, related apparently to respiratory activity.

This difference in the sugar levels of the blood between hepatic vein and left side of heart and the effect of severe haemorrhage thereon was demonstrated by Robertson (1935) but the loss of sugar during respiration was not commented upon. It would appear from the experiments on animals and from the findings in the 9 patients in whom anoxia was produced (Section 2) that the degree of interference with gaseous exchange determines the rapidity with which the increased amount of sugar released from the liver appears in the left side of heart and systemic circulation.

In the human subject at rest the blood sugar levels in the brachial vein, right heart and inf. vena cava were measured by obtaining samples during cardiac catheterisation. These showed that the highest level was on the right side of the heart or in the inferior vena cava near the entrance of the hepatic vein. The lowest levels were in the brachial vein which is representative of the peripheral circulation.

The investigation was further extended through the assistance of a thoracic surgeon who obtained the samples I required during the operation of mitral valvotomy. The results in the 5 cases investigated show that the blood sugar level is always higher in the

left heart blood (by an average of 8 mg.per cent.). This finding, that the arterial blood has a slightly higher sugar content than peripheral venous blood has been shown by previous workers (Mylon et al, 1944) and Mosenthal and Barry (1946). It remained to be proved that the right heart blood had a higher sugar level than the left and this information was obtained, again by the same thoracic surgeon, who took off for me a sample from the pulmonary artery (equivalent to right heart) the aorta (equivalent to left heart) and an arm vein. In the 4 patients examined the blood sugar was lower in the aorta than in the pulmonary artery. All these patients received a combination of anaesthetics which have proved to have no influence on the blood sugar (viz. Pentothal, Nitrous Oxide, Oxygen, Pethidine and Curare). The conclusion one may be permitted to reach is that there is a fall in the sugar level of the blood in passing through the lungs and that this phenomenon is dependent on the presence of oxygen.

This latter point once more emphasises the importance of hypoxia in conditions of shock. The release of glucose from the liver is undoubtedly due to a demand for energy, and the rising blood sugar together with the clinical condition of the shocked

patient are an indication of the failure to convert this glucose to energy. The hyperglycaemia per se is obviously a natural response and in itself must be beneficial. It has been shown by Mylon et al (1944) that if the hyperglycaemia following haemorrhage is prevented from occurring, the outcome is more frequently fatal. In a similar fashion Sadove, Wyant and Gittelson (1953) have demonstrated the benefit of administering glucose and oxygen to patients suffering from acute hypoxia.

Nevertheless, hyperglycaemia must be considered as an indication of severe stress, and my results emphasise the importance of the fact, already well known, that early transfusion is beneficial. In this instance, however, we have been able to set a time limit. Following haemorrhage, in the average case, transfusion within the first half hour will probably prevent the onset of serious shock.

All of the points touched upon in relation to the maternal condition apply equally to the foetus. The foetus depends upon the maternal circulation for its oxygen supply. This was first clearly demonstrated by Eastman (1936) and he also reported on the influence of anaesthesia on the foetus. His work has been confirmed in more recent years by Guilheim et al (1952) and Walker (1954). Eastman (1936) clearly showed that gas-air

analgesia even in 50:50 concentration is not entirely devoid of risk to the foetus. When used as an anaesthetic for Caesarean Section, nitrous oxide may be equally dangerous, and Bourne and Williams (1948) state that this explains the unsatisfactory post-natal condition of some children delivered in this way.

The fatal hypoxia inevitable upon maternal haemorrhage and the administration of certain anaesthetics is obviously important from the work of Windle and Becker (1943), but it is also possible that the upset in maternal carbohydrate metabolism itself may influence the well being of the foetus. This may come into play, not only following haemorrhage but also during unskilled induction of anaesthesia or with the misuse of analgesia.

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