A STUDY OF THE BLOOD SUGAR IN HEALTH AND DISEASE

with special reference to

Infancy and Childhood

By

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A STUDY OF THE BLOOD SUGAR IN HEALTH AND DISEASE.

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Introduction.

The study of carbohydrate metabolism, such as may be done in the case of protein and fat, cannot be carried out owing to the nature of the end-products, CO_2, lactic acid and water; i.e. carbohydrate ingested cannot be balanced against carbohydrate or its end products excreted. An investigation of carbohydrate metabolism is therefore performed either by giving the individual a definite amount of glucose by mouth and noting the presence or absence of sugar in the urine, or by estimating the percentage of sugar in the blood before and at regular intervals after the ingestion of glucose. The former method leads to serious error owing to variations in the kidney threshold for sugar but an estimation of the percentage of sugar in the blood eliminates this factor and gives some idea of the glycogenic function of the organism.

Within recent years simple and accurate methods of blood sugar analysis have been devised and much work has been done on this subject but the results obtained are still very contradictory, owing probably to the complex nature of carbohydrate metabolism.

The following investigation was undertaken primarily/

primarily to determine if by estimating the fasting blood sugar content and the sugar content of the blood after the ingestion of glucose in a series of normal and undernourished children some light might be thrown on the much discussed problem of the cause of "marasmus" in infancy. Within recent years the tendency has been to attribute this condition to intolerance of the organism to one or other of the proximate principles of the food. In some quarters it has been suggested that inability to digest or absorb protein or fat might be the underlying factor, and much work has been done to find support for such a contention; but the recent work of Hutchison (1) and Fleming (2 and 3) is distinctly against this explanation. The ability of the marantic infant to digest and absorb carbohydrate is much more difficult to decide; part of the ingested carbohydrate is certainly fermented in the gastro-intestinal tract and thus lost, but there is no evidence that in the marantic infants without diarrhoea there is an excessive fermentation of carbohydrate. Certainly marasmic infants frequently develop gastro-intestinal disturbances but in this paper those cases designated "marasmus" showed no evidence of any gastro-intestinal upset.

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While performing this investigation a number of older children suffering from other diseases in which some disturbance of carbohydrate metabolism might be suspected were also examined.

It has been found that the different forms of carbohydrate do not all cause the same sequence of changes in the sugar content of the peripheral blood and the effect of the ingestion of laevulose on the blood sugar was also tested in a number of normal and abnormal conditions of childhood and the results obtained will be discussed.

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METHOD OF INVESTIGATION.

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Throughout the following experiments Maclean's[4] method was used. This method has the advantage of requiring only a very small quantity of blood (0.2 c.c.), an amount which after practice can easily be obtained even in the smallest infants from the capillaries of the thumb. After withdrawal of the blood the estimations were carried out at once. Tolstoi[5] has shown that glycolysis is very active subsequent to the withdrawal of the blood. He obtained 20 c.cs. of blood from 8 normal subjects and at once discharged it into sterile flasks containing 40 mgms. potassium oxalate. He then estimated the sugar content immediately and 1½, 3, 5, and 24 hours later and found that if the blood was kept at room temperature there was very slight loss during the first hour and a half, but after 24 hours as much as 90 mgms. might be lost. This was confirmed later by Lemann and Liles,[6] who found that even if kept in a refrigerator as much as 90% might be lost after 24 hours. They found, however, that the glycolysis proceeded more slowly if the level of the blood sugar was raised.

I have found that after a sample of blood has stood for 2 hours at room temperature its sugar content is markedly reduced.

In the cases cited in Table I two samples of blood were/

were taken synchronously from the one patient; in the one sample the sugar was estimated immediately after withdrawal, while the other was allowed to stand at room temperature for at least two hours before the determination of the sugar content. If, however, the protein is removed from the blood, the filtrate may be left for some considerable time without glycolysis occurring.

Table I.

Case I.	Blood Sugar.	12 p.m. 2.30 p.m.	.100% .087%
Case II.	Blood Sugar.	2 p.m. 4 p.m.	.098% .068%
Case III.	Blood Sugar.	2 p.m. 4 p.m.	.081% .062%

It was shown by Jacobsen (7) in 1913 that the most important factor influencing the sugar content of the blood at any particular time, was the ingestion of food. It is therefore essential for the obtaining of comparable results that the blood be withdrawn after a fast of sufficient duration to eliminate this factor. In my experience with children a fast of 5-6 hours is sufficient for this purpose. The dose of glucose required to provoke a rise in the blood sugar was given immediately after the withdrawal of the first sample of blood, and an amount equal to 1 grm. of glucose per kilo of expected weight was always found sufficient. The glucose was dissolved in the requisite amount of water to make up a feed of sufficient quantity/

quantity for the age of the child; in the case of the older children 150 c.cs. of water was used. The subsequent estimations were carried out at half-hourly intervals until the blood sugar had returned to the normal, or nearly normal, fasting level. In some of the smaller infants 30 minutes and longer were required for the child to take the feed and the figures in these cases have been discarded as practically no rise in the blood sugar was obtained.

As Hale White and Payne,(8) also Levine et al(9) have shown that variations in the blood sugar may occur due to exercise, all the children were kept at rest in bed both for some time before the experiment began and also during the experiment.

Capillary blood was always used as variations may occur due to the source of the blood. G.L.Foster(10) found that at the normal fasting level there was no difference between the venous and capillary blood, but that after the ingestion of glucose the percentage of sugar in the finger blood rose to a much higher level than in the venous blood, but tended to fall again nearer the venous level as the normal fasting level was again approached. Hagedorn,(11) on the other hand, found that even at the fasting level the percentage of sugar in the capillary blood was higher than that of the venous blood.

In order to determine the experimental error involved in the use of the method 10 consecutive estimations on the same sample/

sample of blood were carried out. In each case 0.2 c.cs of blood was taken and after precipitating out the protein 20 c.cs. of the filtrate was used for the ultimate titration. The results are given in Table II.

Table II.

No.	Estimated percentage of sugar in the blood.
1	.100
2	.098
3	.100
4	.096
5	.106
6	.094
7	.100
8	.094
9	.100
10	.100
Average:	.099 + .007 - .005

From this series of figures the average result is calculated as 0.099 while the error is plus or minus .006 or roughly 5%. This is therefore taken as the margin of experimental error.

The Distribution of the Sugar in the Blood.

Graham (12) and Falta, (13) among others, have raised the question of the distribution of the sugar in the blood and have maintained that an accurate estimation of the sugar content can not be made without correcting for the variations between the volume of the cells and the volume of plasma.

The following observations were made on the relationship between the volume of cells as determined by the haematocrit and the percentage of sugar in the blood. It will be seen, however, from Table III, that the percentage of blood sugar is not dependent upon the relative volumes of cells and plasma. Accordingly the determination of the cell volume is of no significance in estimating the blood sugar.

Table III.

Blood Sugar Content in Relation to Volume of Cells. (by Haematocrit).

Name.	Percentage of Cell.	Percentage of Blood Sugar.
J.H.	45	0.100
E.F.	45	0.085
A.J.	44	0.081
H.M'C.	43	0.080
G.A.	40	0.100
J.R.	40	0.092
J.M'G.	40	0.093
J.M'V.	40	0.085
C.M.	40	0.087
F.D.	40	0.081
S.M'L.	38	0.100
C.R.	38	0.087
M.C.	38	0.100
D.M'K.	37	0.100
R.H.	37	0.068
E.C.	37	0.087
C.B.	37	0.065
N.M'K.	37	0.100
M.C.	35	0.081
O.C.	31	0.075

THE PERCENTAGE OF SUGAR IN THE BLOOD.

A. In Normal Children.

While examining the results for the normal fasting blood sugar content in children, which were obtained by previous workers, it was found that there was a wide variation according to the method employed and these results have been summarised in Table IV.

As such wide variations are found it is necessary to establish for oneself a normal figure for comparison with the results obtained in pathological conditions. To obtain this normal figure a study of the blood sugar content was made in sixty-five children whose ages ranged from a few hours to 12 years and the results obtained are shown in Table V. These subjects so far as is known were not suffering from any disease which was likely to affect their carbohydrate metabolism; they were children suffering from epilepsy or recuperating from broncho-pneumonia, lobar pneumonia or rheumatic fever.

It will be seen from these results that the percentage of sugar in the blood of a normal child using MacLean's[4] method varies between .072% and .116%, giving an average of .099%; which figures compare favourably with those obtained by Spence[26] who used the same method.

Table IV.

Fasting Blood-Sugar Content obtained by different Workers in Normal Children.

Author.	Date.	Age of Children.	Method Employed.	Blood Sugar Content. %	Mean Blood Sugar Content. %
Schirokauer (15)	1914	8-14 days.	Moeckel Frank	.080-.130	.106
Cobliner (16)	1911	9-21 days.	"	.076-.098	.085
Cobliner (16)	"	1-12 mths.	"	.09-.15	.119
Cobliner (16)	"	over 1 yr.	"	-	.105
Gotzky (17)	1913	Infants.	Bang.	-	.077
Gotzky (17)	"	2-14 yrs.	"	-	.105
Mogwitz (18)	1914	4-13 mths.	"	.07-.11	-
Mogwitz (18)	"	7 hrs-3 wks	"	.07-.103	-
Mogwitz (18)	"	3 years.	"	-	.099
Mogwitz (18)	"	12 "	"	-	.107
Bergmark (19)	"	Children.	"	.08-.09	-
Bass (20)	1915	2-14 years.	Lewis-Benedict	.072-.113	.091
Nieman(21)	1916	Under 1 yr.	Bang.	.07-.085	.079
Cannata (22)	1917	First 24 hrs	Lewis-Benedict	.074-.10	-
Chapin & Myers(23)	1919	Children.		Slightly lower than in adults, which is .09-.13.	-
Sedgwick & Ziegler (24)	1920	3-43 days.	Folin & Wu.	.07-.11	-
Lucas et alia(25)	1921	Few hrs.to 14 days.	"	.052-.093	-
Spence (26)	1921	Under 3 yrs	Maclean.	-	.098
Spence (26)	"	2-7 yrs.	"	.094-.111	.103
Guy (27)	"	Under 1 yr	Lewis-Benedict	.06-.09	.068
Nysten (28)	"	" 1 mth	Bang.	-	.101
Nysten (28)	"	1-12 mths.	"	-	.123
Tisdall, Drake & Brown (29)	1924	Infants.	Modif. of Shaffer-Hartman.	.081-.100	.090
Rumpf (30)	"	Infants.	Bang.	.071-.089	.076
Muggia (31)	"	1st year.	Foster & Thivollés.	.105-.155	.126

Table V.

The Fasting Blood Sugar Content obtained in Normal Children.

Case No.	Age.	% of sugar in blood.	Case No.	Age.	% of sugar in blood.
1	12 hours.	.091	33	11 months	.100
2	1 day	.075	34	8 weeks	.116
3	2 days	.072	35	7 weeks	.095
4	3 days	.075	36	20 weeks	.112
5	3 days	.088	37	7 months	.100
6	4 days	.085	38	29 weeks	.118
7	5 days	.088	39	6 weeks	.098
8	6 days	.082	40	39 weeks	.112
9	8 days	.082	41	1 year	.112
10	10 days	.098	42	13 months	.100
11	11 days	.091	43	1 year	.110
12	12 days	.095	44	1 year	.100
13	6 weeks	.095	45	2 years	.084
14	8 weeks	.098	46	6 years	.112
15	8 weeks	.100	47	8 years	.086
16	9 weeks	.088	48	7 years	.100
17	10 weeks	.100	49	12 years	.106
18	10 weeks	.108	50	7 years	.098
19	11 weeks	.116	51	7 years	.106
20	3 months	.112	52	5 years	.086
21	3½ months	.100	53	8 years	.106
22	4 months	.108	54	9 years	.108
23	5 months	.112	55	10 years	.090
24	5 months	.112	56	11 years	.094
25	4½ months	.112	57	12 years	.090
26	6 months	.100	58	4 years	.084
27	7 months	.100	59	5 years	.100
28	8 months	.100	60	12 years	.110
29	7½ months	.118	61	6 years	.108
30	9 months	.108	62	7 years	.098
31	10 months	.112	63	3 years	.094
32	10 months	.118	64	4 years	.106
			65	5 years	.084

Average = .099%.

Variation with age.

It is evident from the above series of estimations that the most striking feature is the influence of age. The results are graphically represented in Charts I and II, which show all the blood sugar values according to the age of the child.

A careful examination of Chart I shows that the younger the child the lower the blood sugar percentage. In the children under 2 weeks of age the fasting blood sugar level ranged from .072% to .097%, with an average of .087%, while in the children between 6 weeks and one year the sugar content varied from .086% to .116%, the average being .106%. In the older children from one to twelve years, the blood sugar varied between .084% and .112%, with an average of .099%. Unfortunately, I had not the opportunity of examining normal children between the ages of two weeks and six weeks, so that I cannot say at what age the higher level was reached and whether it was a sudden or a gradual transition. From the trend of the distribution of the findings in the children under two weeks of age it would seem as if the transition was a gradual one.

Previous workers have already noted a variation in the sugar content with the age of the child. Cobliner (16) in 1911 found that except during the first month of life the normal infant has a slightly higher blood-sugar content than the adult. He obtained a mean figure of .085% in children under one month as/

as compared with .119% in children from one to twelve months of age. This low blood-sugar in the very young was confirmed two years later by Gotzky (17) and still later by Nysten. (28) Lucas et Alii (25) in their investigations on the blood sugar content of the new-born found a steady increase as age advanced from a few hours to fourteen days after birth. Sedgwick and Ziegler (24) also investigated a series of children varying in age between three and forty-three days and found that the blood sugar rose from .07% to .11%. Guy (27) and Nieman, (21) on the contrary, state that there is no variation with age, but on reviewing their results I find that in the former no estimations were made in children under one month and in only one of the latter's cases was an estimation made in a child under that age. This child gave a fasting blood sugar value of .085%, which figure is higher than his average for children under one year. From these results I think it can be concluded that after the first 2-3 months of life, age per se has no effect on the blood sugar content, but that in children under 3 months the factor of age is of significance.

Chart 1

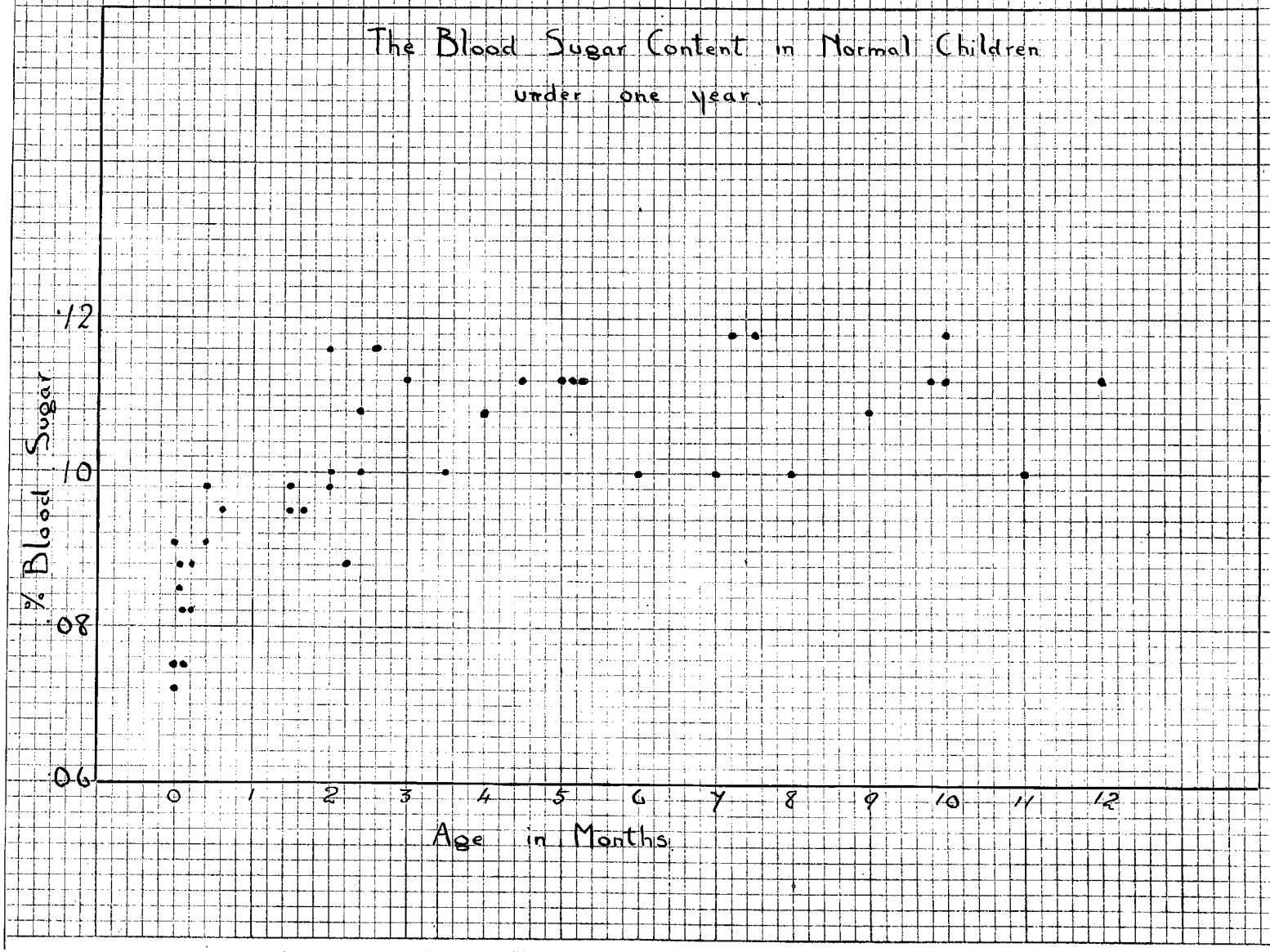
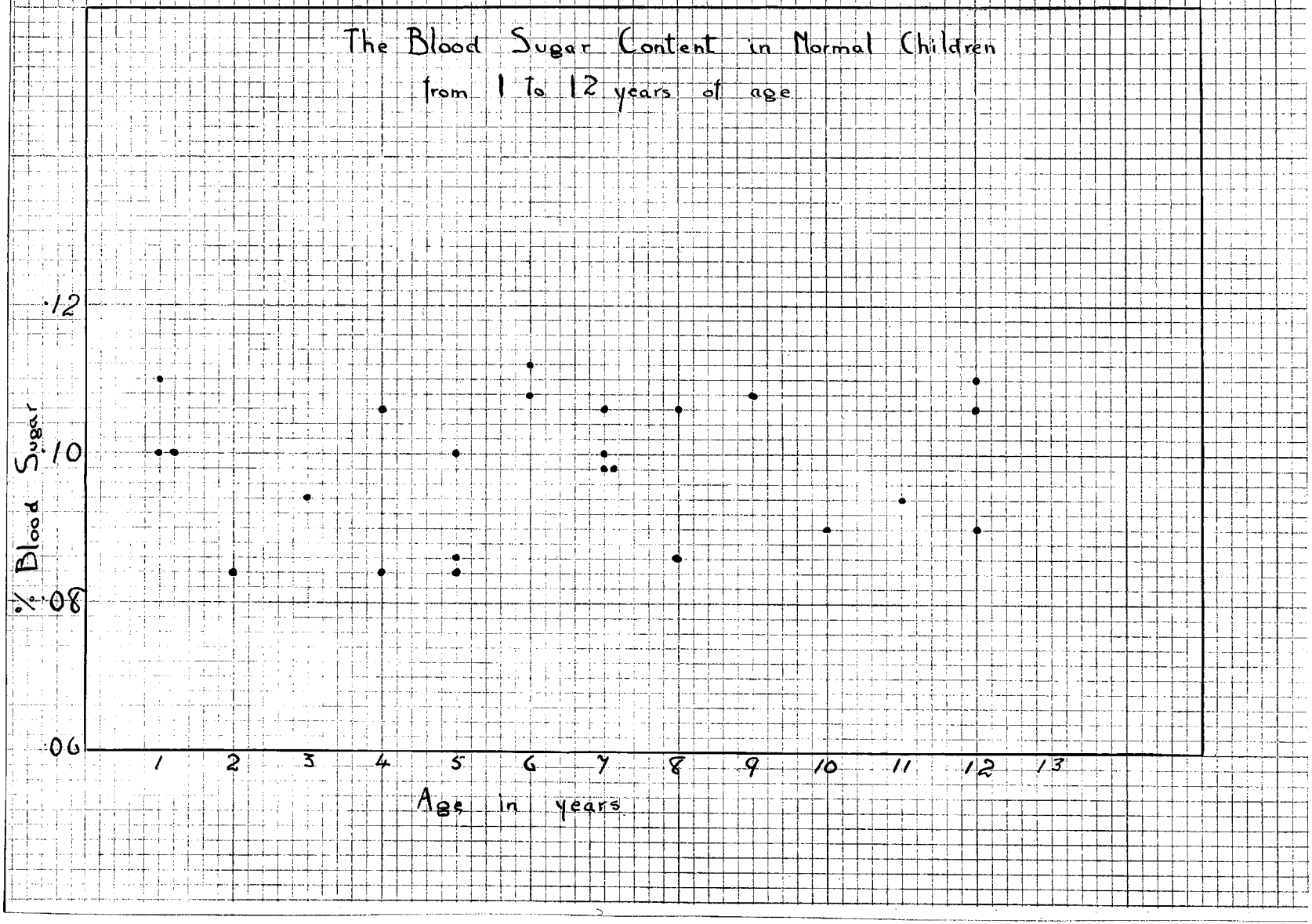

The Blood Sugar Content in Normal Children
under one year.
% Blood Sugar
.12
.10
.08
.06
0
1
2
3
4
5
6
7
8
9
10
11
12
Age in Months

Chart II


The Blood Sugar Content in Normal Children
from 1 to 12 years of age
% Blood Sugar
·12
·10
·08
·06
1
2
3
4
5
6
7
8
9
10
11
12
13
Age in years

Discussion of the low Blood Sugar obtained in young infants.

This low figure in the young infant may be accounted for in one of three possibilities, namely,

(1) Difference in diet.

(2) Starvation.

(3) Lessened requirements of mobilised sugar due to diminished amount of active metabolic tissue.

(1) Variation according to previous diet.

The next physiological problem which presents itself for consideration is the question as to whether in the normal child the amount of carbohydrate in the diet has any influence on the sugar content of the blood. In this connection it must be remembered that the blood was always taken at least four hours after the last intake of food.

The children used for the present series of experiments were fed on varied diets. Those under six weeks of age were breast-fed, while the majority of those between two months and one year of age were on ordinary cow's milk with in addition a small quantity of sugar; a few, however, were receiving only breast-milk and on comparing their results with the former no appreciable change in the percentage of sugar in the blood could be obtained. Furthermore no significant difference appeared to exist between the sugar content of the blood of milk-fed children and those on a general mixed diet.

While investigating "Ketonaemia and Ketonuria in Childhood"

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along with Dr Grace Graham (14) I had the opportunity of examining the percentage of sugar in the blood after a period of low carbohydrate intake. The children who were the subjects of investigation were for the most part epileptics of between 6 and 12 years of age. After the child had been for a few days on general diet, the blood sugar content was determined along with the alkaline reserve, the blood acetone and the urine acetone. The patient was then given a ketogenic diet consisting of fat bacon, butter, cream and diabetic rolls. During the experiment all the patients were kept at rest in bed and the diet supplied contained on an average 600 to 700 calories more than the calculated basal requirements. Despite the abundant caloric supply all the children except two lost weight slightly. The blood sugar content was examined at intervals during this period and the results are shown in Table VI and Chart III. It will be seen from these that no appreciable fall in the blood sugar was obtained. The most marked fall was in Case No.5, where the fasting blood sugar when the patient was on ordinary diet was .106% and 0.085% after eight days on the carbohydrate free diet, and still remained at the same low level four days later. Ross and Josephs, (32) doing a similar experiment on two children, found a slight fall in the blood sugar following an increase in the fat-carbohydrate ratio of the diet. In the first case the fasting blood sugar was .096% when the child was on ordinary diet, while after the child had been 10 days on a ketogenic diet it/

it had fallen to .084%. In the second case it fell from .112% to .091% under similar experimental conditions.

From these experiments it is concluded that the amount of carbohydrate in the previous diet causes only a very slight fall in the blood sugar level. The store of carbohydrate in the body is probably kept at a fairly constant level by the formation of carbohydrate from the catabolism of exogenous and endogenous proteins, and perhaps also from the fats, though so far no conclusive proof has been brought forth that fats can form carbohydrate.

The total intake of fluid in the diet was not estimated, but it has been shown by Strouse (33) that increasing or diminishing the water intake and excretion has no effect on the percentage of sugar in the blood.

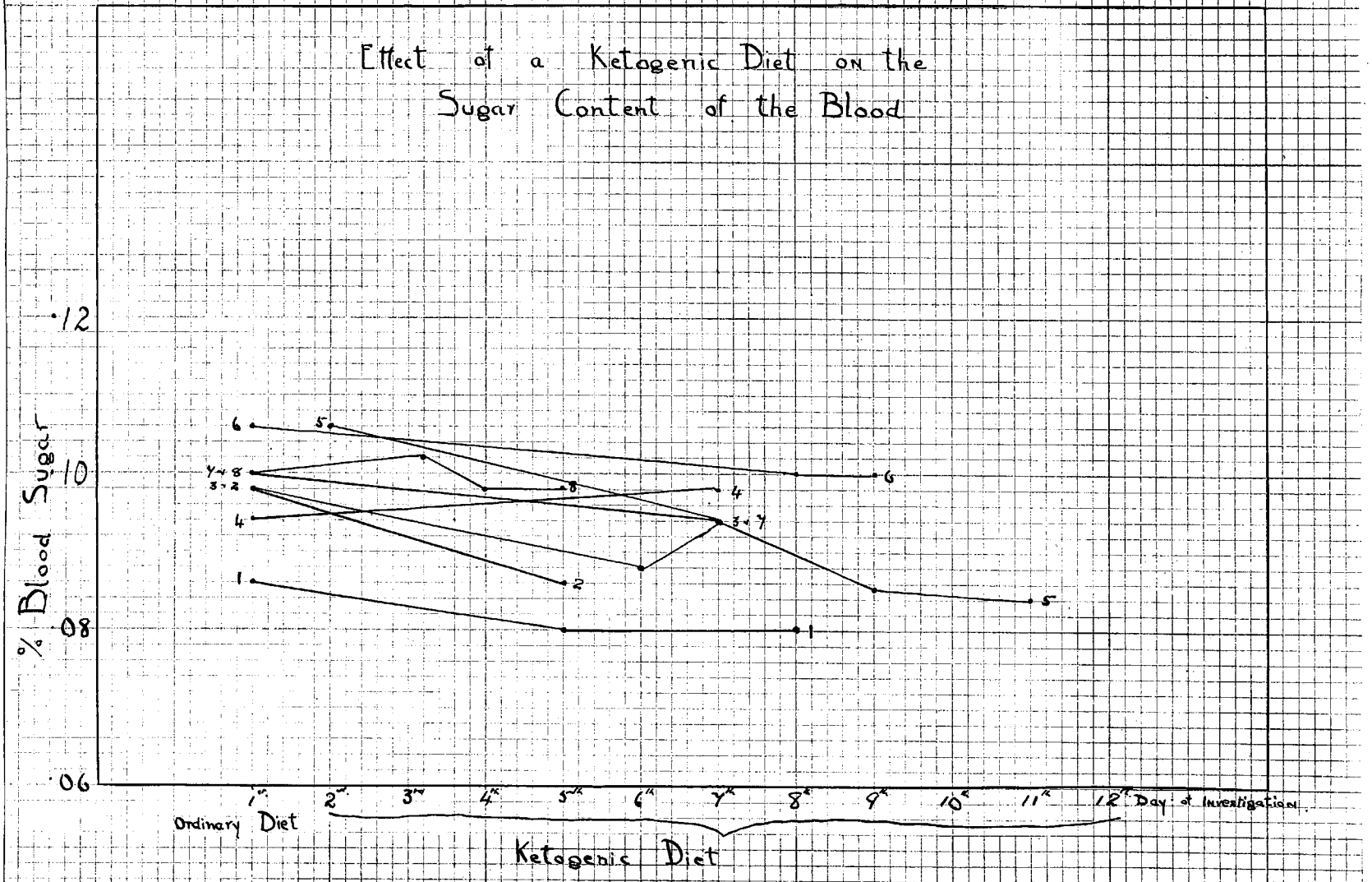
The new-born child seldom, if ever, gets a sufficiency of nourishment; not only does it take some time for lactation to be thoroughly established, but in addition the first milk (colostrum) is very poor in carbohydrate. Lowenfeld et al (34) have found that the amount of sugar in human milk, which is at its lowest in the early days of lactation rises irregularly to the normal level by the end of the second week.

Table VI.

Effect of Low Carbohydrate Diet on the Blood Sugar Content.

Case No.	Days of Investigation.	Diet.	Percentage of Blood Sugar.
1	1	Ordinary Diet.	.086
	5	Ketogenic Diet.	.080
	8	" "	.080
2	1	Ordinary Diet.	.098
	5	Ketogenic Diet.	.086
3	1	Ordinary Diet.	.098
	6	Ketogenic Diet.	.088
	7	" "	.094
4	1	Ordinary Diet.	.094
	7	Ketogenic Diet.	.098
5	1	Ordinary Diet.	
	2	Ketogenic Diet.	.106
	7	" "	.094
	9	" "	.085
	11	" "	.084
6	1	Ordinary Diet.	.106
	8	Ketogenic Diet.	.100
	9	Ketogenic Diet + 100 c.cs. 5% Glucose. 5+	.100
7	1	Ordinary Diet	.100
	7	Ketogenic Diet	.094
8	1	Ordinary Diet	.100
	3	Ketogenic Diet	.102
	4	" "	.098
	5	" "	.098

Chart III


Effect of a Ketogenic Diet on the Sugar Content of the Blood
·12
·10
·08
·06
% Blood Sugar
6
5
7+8
3+2
4
1
8
2
4
3+7
6
5
1
1st
2nd
3rd
4th
5th
6th
7th
8th
9th
10th
11th
12th Day of Investigation
Ordinary Diet
Ketogenic Diet

II. Effect of Starvation.

It has usually been held that prolonged starvation, both in man and in animals, does not lead to a lowering of the blood sugar. Allen (35) states definitely that "no fall in the blood sugar occurs even after prolonged starvation" and Cammidge (36) also says that "the length of the fast does not appear to exert any material influence on the proportion of sugar in the peripheral blood." During the past few years, however, this has been contradicted, especially by the American workers, who have found a very definite fall in the blood sugar of fasting children. It might be expected that in fasting, where the carbohydrate insufficiency is extreme, a low blood sugar would inevitably follow depletion of the glycogen reserve of the liver, but for a considerable time the glycogen supply may be maintained by the glucose derived from the body proteins.

On reviewing the literature I have been unable to find any reference to a low blood sugar content in the adult after fasting. In children, however, there may be a more rapid utilization of the mobilised glucose. Mogwitz (18) in 1914 reported a lowering of the blood sugar in five fasting children. In one infant, after a fast of 72 hours, he found that the blood sugar which was .09% 3 hours after the last feed, had fallen to .047%. Rumpf (30) states that the average blood sugar percentage of .076 fell after a fast of 28 hours to .062%. Talbot, Shaw and Moriarty (37) in 8 cases in which they produced a ketosis by fasting, found a marked/

marked fall in the blood sugar in all, recording in some instances figures of .045% and .038%. Ross and Josephs (32) found only a very slight fall in the blood sugar on the 4th to the 5th day of starvation. Schlossmann (38) found that the blood sugar remained normal till 72 hours after food and then fell sharply. Hoeffel and Moriarty (39) fasted two epileptic children 8 and 9 days respectively and got a marked fall in the blood sugar in both. In the former a fall from .075% to .059% was obtained, while in the latter the fall was more marked, from .100% before the fast to .052% after 9 days of fasting. Shaw and Moriarty (40) kept 5 epileptic children on a fixed diet for 3-4 days, after which they were fasted for 10-14 days, only water being given during this period; a fall in the blood sugar level took place, but rose again towards the end of the fast. Sawyer, (41) who gave diets of very low caloric value to several children, got very variable results; in some cases a slight rise in the blood sugar was obtained, while in one case a very marked fall to .020% was got, a figure which seems hardly compatible with life.

One child aged 8 years was starved for 5 days and it was found that the fasting blood sugar which was .090% 3 hours after a meal, fell to .086% after 2 days of fasting and after 5 days was again .094%. These figures which are not outside the limit of experimental error indicate that in the one case investigated starvation did not cause a lowering of the blood sugar.

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III. It is possible then that this lowered blood sugar, found in the very young children, is due to the smaller demand for mobilised sugar because of the diminished amount of active metabolic tissue. With increased metabolism as in fever and hyperthyroidism a hyperglycaemia results, and it would seem not improbable that in diminished metabolism the reverse would be obtained.

B. In Pathological Conditions.

The interpretation of a fasting blood sugar level which is near the normal is always a matter of difficulty and it is always necessary to amplify one's results by estimation of the blood sugar curves after the ingestion of glucose.

It has been generally agreed, however, that there is a decrease in the blood-sugar in all cases of atrophy or decomposition and in dyspepsia, and an increase as a rule in enteritis. The results obtained by different workers have been summarised in Table VII.

Table VII.

Fasting Blood Sugar Content obtained in Certain Pathological Conditions by Various Authors.

Author.	Disease.	No change in blood sugar.	Inc.	Dec.	Blood Sugar Content.
Tisdall, Drake & Brown (29)	Marasmus	-	-	+	.077
Cobliner (16)	Atrophy	-	-	+	.04-.07
Guy (27)	Atrophy	-	-	+	.06
Nysten (28)	Atrophy	-	-	+	.114-.115
Cobliner (16)	Decomposition	-	-	+	.04-.135
Chapin & Myers (23)	Malnutrition with Acidosis	-	-	+	.08-.09
Nysten (28)	Dyspepsia	-	-	+	.114-.158
Guy (27)	Vomiting	-	-	+	.037-.059
Cobliner (16)	Dyspepsia	+	-	-	.094-.13
Gotzky (17)	Enteritis	-	+	-	-
Mogwitz (18)	Enteritis	-	+	-	-
Nysten (28)	Intoxication	-	+	-	.137-.198
Cobliner (16)	Intoxication	+	-	-	.11-.123
Chapin & Myers (23)	Intoxication	+	-	-	.08-.11
Niemann (21)	Diarrhoea	-	+	-	.103
Tisdall, Drake & Brown (42)	Diarrhoea	-	-	+	.077
Tisdall, Drake & Brown (42)	Acute Intestinal Intoxication.	-	+	-	.102

In the following series of experiments the fasting blood sugar content obtained in children between one month and one year of age suffering from various nutritional conditions will be discussed. For want of a better classification they have been divided into the following three groups:-

1. Malnutrition.
2. Vomiting.
3. Diarrhoea.

As seen from Table V the average fasting blood sugar obtained in twenty-seven normal children whose ages ranged from 6 weeks to one year was found to be .106%, the highest figure obtained being .118% and the lowest .095%.

(1) Malnutrition.

Under this heading I have taken all children who were less than 90 per cent. of their expected weight irrespective of the cause of the emaciation, except that no case in which there was diarrhoea or vomiting has been included. There is no doubt, of course, that both vomiting and diarrhoea will bring about malnutrition, but as this is apparently due in great part to simple loss of food-stuffs these cases have been classified apart.

Thirty-five undernourished children, all over one month old, were examined and the results are given in Table VIII. From Chart IV in which the fasting blood sugar has been plotted according to the percentage of expected weight, and thus to their relative state/

state of nutrition, it is seen that not only is there a lower fasting blood-sugar level in malnutrition, but that the level rises steadily as the child approaches the normal state of nutrition for its age. It would thus seem that the blood sugar level bears a definite relationship to the degree of wasting. In the child of less than 50 per cent of its expected weight the fasting blood sugar varied between .072% and .081%. with an average reading of .077%, in the child of 50 to 80% of its expected weight the blood sugar varied between .081 and .116%, with an average of .091%, whereas in the child of 80% or more of its expected weight the average blood sugar was .106% with a maximum of .118% and a minimum of ,095%.

In view of these results it seemed to me that it would be of interest to study the behaviour of the blood sugar in marasmic infants during the period of recovery, and in consequence I selected four children, two of whom were treated in hospital and two as outdoor patients. To all, sufficient food was given, and all the children were gaining steadily in weight, and, as shown in Table IX there occurred in each instance a steady rise in the blood sugar as the state of nutrition improved.

Cobliner[16] states that as the condition of the atrophic infant improves, the percentage of blood sugar increases, a fact confirmed later by Mogwitz.[18] Guy[27] in the few cases which she examined found no constant relation between the percentage of expected weight and the low blood sugar.

(2) Vomiting.

Seventeen children in whom vomiting was the predominant symptom were examined. The results are represented on Chart IV in red. All reveal, quite irrespective of the state of nutrition, a very low blood-fasting level. That vomiting has a definite effect on the blood-sugar has been shown by other workers, Guy[27] and Nysten[28] both finding abnormally low fasting levels in the presence of vomiting.

(3) Diarrhoea.

As seen in Table VII previous workers, e.g., Gotzky[17] and Mogwitz[18] found an increase of the fasting blood sugar level in diarrhoea, while others again, e.g., Cobliner[16] and Chapin[23] obtained normal readings. In my cases as seen from Chart IV where the cases in which there was diarrhoea are marked in green the blood sugar level would appear to depend simply on the state of nutrition of the child.

TABLE VIII.

The Fasting Blood Sugar Content in Children suffering from Malnutrition.

Case No.	% Expected Weight.	No Blood Sugar.	Case No.	% Expected Weight.	% Blood Sugar.
1	40	.083	20	62	.082
2	44	.075	21	63	.106
3	48	.072	22	65	.082
4	48	.075	23	65	.095
5	50	.075	24	66	.088
6	54	.082	25	66	.100
7	54	.084	26	68	.094
8	54	.088	27	68	.096
9	55	.088	28	69	.095
10	55	.088	29	70	.106
11	55	.082	30	70	.088
12	55	.084	31	75	.100
13	55	.084	32	75	.094
14	55	.094	33	76	.112
15	55	.098	34	78	.118
16	58	.082	35	80	.090
17	58	.098			
18	60	.088			
19	62	.096			

Chart IV

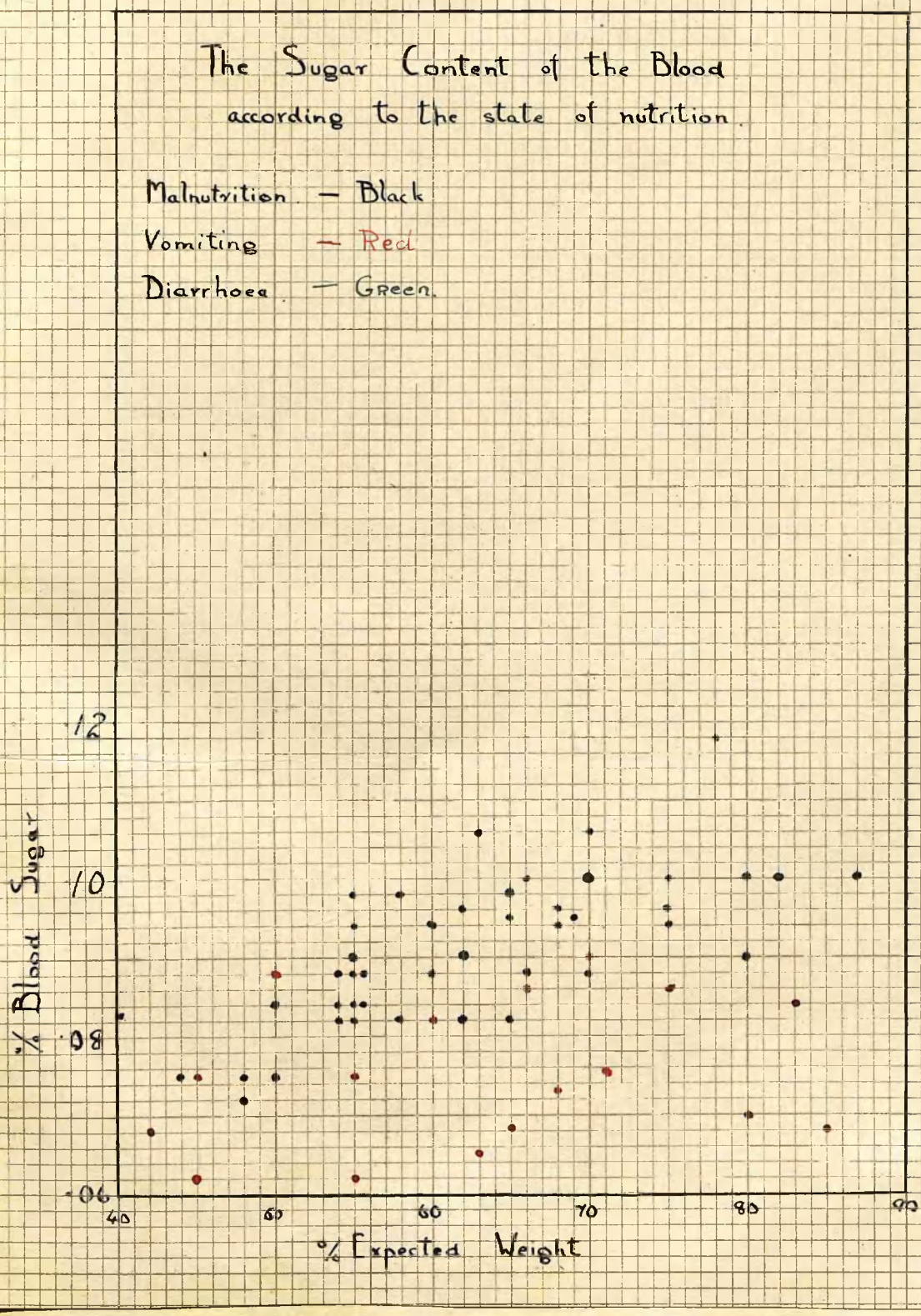

The Sugar Content of the Blood
according to the state of nutrition.
Malnutrition — Black
Vomiting — Red
Diarrhoea — Green.
% Blood Sugar
·12
·10
·08
·06
40
50
60
70
80
90
% Expected Weight

Table IX.

Increase of Blood Sugar as State of Nutrition improves.

Case.	Age.	Date.	% Exp.Wt.	% Blood Sugar.
1	8 months.	5.7.23. 13.9.23 5.10.23 10.12.23	59 59 65 75	.062 .068 .075 .098
2	6 months.	29.7.23 15.8.23 9.11.23	64 69 76	.068 .075 .095
3	8 months.	19.11.23 24.12.23 5.2.24	47 54 61	.075 .081 .094
4	7 months.	19.11.23 20.12.23 5.2.24	48 52 60	.075 .075 .095

Discussion of Results.

The first problem which naturally arises from an analysis of the above findings is the cause of the hypoglycaemia met with in the severely undernourished child. The closely similar figures which have been obtained in the young infants under 6 weeks of age would seem to indicate that they are both due to the same cause and similar theories as to their causation come up for consideration.

An estimate of the rate of utilization of carbohydrate may be obtained by studying the respiratory quotient, and Fleming (3) has found that the respiratory quotient of marantic infants is the same as that of normal infants, which would indicate that there is no marked derangement in the combustion of carbohydrates or fats. It is to be remembered, however, that a slight or even moderate derangement of carbohydrate metabolism might not cause any change in the respiratory quotient. It may therefore be assumed that if carbohydrates are properly absorbed they can be utilized by the marantic infant as well as by the normal child.

Is the hypoglycaemia then due to an insufficient supply of carbohydrate consequent on defective intake or defective absorption? As will be seen later as far as an examination of the blood after the ingestion of glucose can be taken as an index of absorption there is no evidence of defective absorption of carbohydrate in these cases. But this aspect of the problem is very difficult to investigate as it would require only a few grammes of carbohydrate to be added to the blood to raise its

sugar/

sugar content considerably. If carbohydrate remains in the bowel unabsorbed it undergoes fermentation.

As previously shown I was unable to obtain a low fasting blood sugar in children on a low carbohydrate intake but the very low blood sugar found in the cases with vomiting where it is apparent that the child is not getting sufficient food lends support to the hypothesis of starvation. Nevertheless, it seems difficult to explain in this way the steady increase in the blood sugar proportionate to the improvement in the state of nutrition. One would have thought that in the presence of ample food the blood sugar would quickly reach the normal level. It is quite possible, and in fact, not unlikely, that the children had been starved before the onset of the atrophy, and also before coming under observation, but at the time of the blood examination they had all been, for some days at least, on an ample diet. To some of the children, too, e.g., those observed during recovery and recorded in Table IX an ample supply of carbohydrate had been given; in one child this had been the case for as long as four months, and yet the blood sugar had not returned to normal. During this time the children were all gaining steadily in weight, showing that they had been absorbing a sufficiency for their needs.

Tisdall, Drake and Brown (42) have shown that after the intravenous ingestion of glucose the marasmic infant is able to remove the glucose from the blood as quickly as the normal infant and they bring forward the theory that the hypoglycaemia found in these marasmic cases is due to an inadequate reserve of glycogen. If possible it would be of interest to starve these children for some considerable time and to find if the blood sugar could be considerably lowered below the normal fasting level.

Might this lowered sugar be due to the diminished amount of both active and inactive tissue from wasting of muscle, etc? Fleming (3) has shown that until 35% of the expected weight has been lost the heat output remains fairly constant but below 65% of expected weight the heat output per kilo of expected weight gradually diminishes with the degree of atrophy. This diminution in metabolism would therefore call for a decreased need of sugar transportation from one set of tissues to the other.

The question of blood volume in various states of nutrition should also be borne in mind, and is a point on which more research work might be performed. Marriott and Perkins (43) found the blood volume in marasmus lower than in normal infants, but if there is as Bakwin and Rivkin (44) state, a relative increase of blood volume in marasmus, then the whole variation in the sugar-content may be explained by simple dilution.

The Blood Sugar Curve after the Ingestion of Glucose.

Sugar tolerance work began by feeding sugar by mouth and watching for its appearance in the urine. If an individual could take 100 gms. of glucose and show no sugar in the urine his tolerance was said to be normal. If he was able to take more than 100 gms. his tolerance was increased and if he showed glycosuria his tolerance was decreased. Lately it has increasingly been recognised that the testing of the presence of glycosuria after the oral administration of glucose is unsatisfactory as the three following factors are involved:-

(a) rate of absorption of the sugar:

(b) the action of the glycogenic-glycogenetic powers of the organism upon the absorbed sugar: and

(c) the excretion of sugar by the kidneys.

Dextrose, after absorption, is carried by the portal circulation to the liver where part is laid down as glycogen and part passes into the systemic circulation to the other tissues, where it is either oxidised or stored. The percentage of sugar in the blood serves only as an index of the balance between the rate of supply and utilization.

It has been found by many workers that the rate of absorption is not likely to be an important source of fallacy; a far more serious error lies in the variations of the kidney threshold for sugar. When a certain threshold is reached active excretion results; in normal individuals this threshold may/

may be placed at a blood sugar level of .17%. If the blood sugar rises above this level, glycosuria, which is recognised by the ordinary methods of examination, results. This sugar threshold or "leak point" is a variable factor and in certain cases may occur when the blood sugar lies at a level of .10-.12%.

With the increase in care and accuracy with which the blood sugar can be estimated "sugar tolerance curves" have come into use as an aid to diagnosis in many diseases in which errors of metabolism are suspected. Even after simpler methods had been found too infrequent estimations were undertaken and very inconsistent results were obtained.

Baudouin (45) in 1911 was the first to show that there occurs a slight increase in the blood sugar one hour after a meal and this was confirmed by Frank (46) in the same year. Jacobsen (7) in 1913 pointed out that the rise in the blood sugar occurred much earlier than one hour and might be present 5 minutes after ingestion of the glucose, that it usually reached its maximum in 15-30 minutes and returned to the normal fasting level in 60 minutes, though in some cases longer time was required for it to fall to its previous low level. Sakagueli estimated the blood sugar at 10 minute intervals and got similar results to Jacobsen. In the normal case the highest point was reached within 50-90 minutes and then there was a rapid fall to the normal fasting level, this rapid fall being due to the efficiency/

efficiency of the carbohydrate storing mechanism. Since then much confirmatory work has been done.

The method which was employed for the sugar tolerance test has previously been described and the results obtained in 30 normal children whose ages ranged from a few weeks to twelve years of age are given in Table X. It will be seen from this table and from composite curves represented in Chart V where the average curve obtained is plotted beside the maximum and minimum curves that there is a wide range of variation. In the majority of cases, however, the blood sugar has risen to its height in half an hour and within two hours has returned to the normal fasting level. In only a few of the cases - Nos. 34, 39, 63 and 69 - was a hypoglycaemia consequent on the rise obtained, such as has been observed by many other workers, e.g., Maclean,(4) Spence,(26) Folin and Berglund(47) and Goetzky.(48)

Reference to Table X and also to Chart VI where the average blood sugar curves at different age periods are plotted will show that age is an important factor on the height of the curve obtained after the ingestion of glucose - a flatter curve being obtained in the children under 2 years. This can be better exemplified by calculating the percentage increase in the blood sugar and it will be seen that in children under 2 years this increase varies from 15 to 56%, while in children from 2-5 years it varies from 45 to 106% and in children from 5-12 years the average is 62%, with a maximum of 102% and a minimum of 34%.

Table X.

Blood Sugar Curve after the Ingestion of Glucose in Normal Children.

No.	Age.	% of sugar in blood.					
		Fasting.	½ hr. after gluc.	1 hr. after gluc.	1½ hrs. after gluc.	2 hrs. after gluc.	% increase in blood sugar.
72	8 weeks.	.116	.134	.120	.114	.114	15
93	7 weeks.	.095	.142	.123	.095	-	47
92	20 weeks.	.112	.150	.136	.112	.110	25
66	7 months.	.100	.145	.125	.100	-	45
54	39 weeks.	.112	.156	.125	.112	.120	21
74	29 weeks.	.118	.141	.125	.118	-	19
14	6 months.	.098	.106	.120	.106	.098	22
21	9 months.	.087	.130	.112	.108	.088	49
56	1 year.	.112	.150	.132	.112	-	33
37	1 year.	.100	.156	.137	.112	.100	56
46	1½ years.	.094	.136	.142	.100	.098	51
64	1½ years.	.086	.112	.100	.100	.094	30
69	2 years.	.100	.145	.112	.094	.098	45
22	2 yrs.4 mths.	.098	.156	.112	.100	.100	58
34	3 years.	.110	.165	.143	.104	.110	49
70	3 yrs.7 mths.	.100	.156	.112	.100	.102	56
65	4 years.	.090	.134	.164	.100	.100	82
61	4 yrs.2 mths.	.090	.165	.112	.112	.094	75
58	4 yrs.8 mths.	.100	.170	.156	.134	.100	70
48	5 yrs.2 mths.	.084	.156	.170	.112	.086	102
43	5½ years.	.086	.112	.156	.084	.084	81
39	6¼ years.	.112	.170	.134	.094	.100	51
32	7 years.	.100	.164	.134	.100	.100	64
55	8 years.	.098	.156	.144	.112	.094	57
35	9 years.	.110	.134	.165	.118	.112	50
50	10 years.	.100	.154	.094	.112	.100	54
67	10 years.	.094	.164	.134	.112	.100	69
63	11 years.	.112	.164	.125	.098	.094	46
79	11 years.	.100	.134	.112	.100	.100	34
86	12 years.	.094	.164	.134	.100	.098	74
	Maximum rise	.080	.156	.170	.112	.086	106
	Minimum rise	.116	.134	.120	.114	.114	15
	Average rise	.099	.147	.130	.105	.096	47

Chart V

The Sugar Tolerance Curve in Normal Children

Average Curve - Black.
Maximum Curve - Red
Minimum Curve - Green.

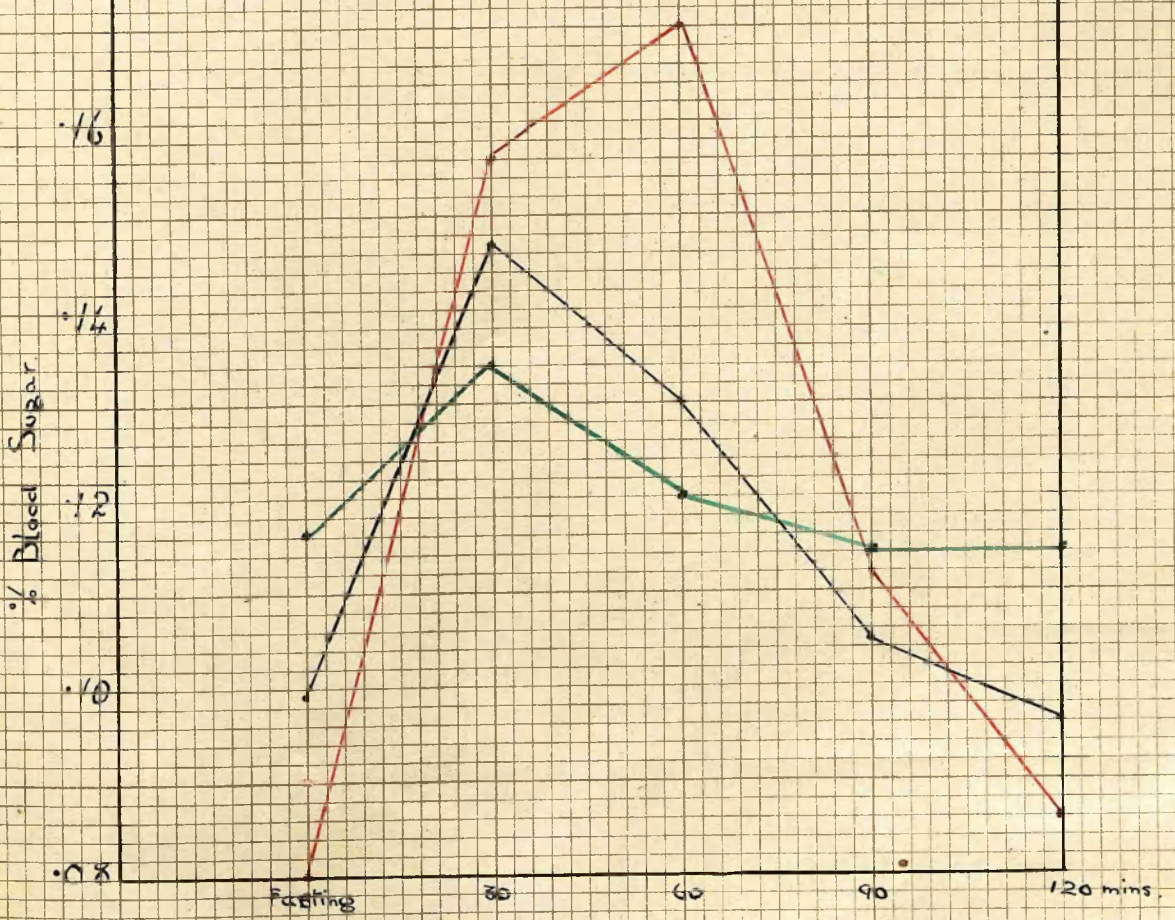


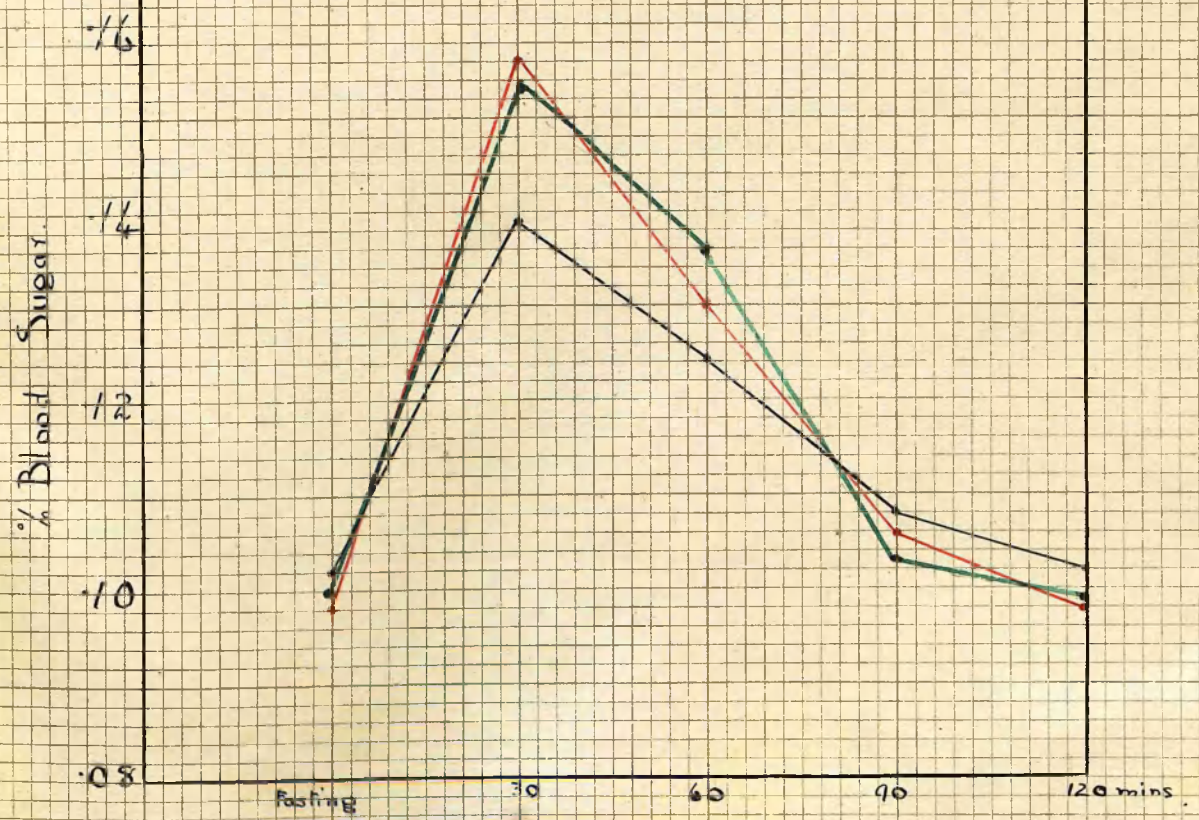
Chart VI

The Average Sugar Tolerance Curve in Normal Children According to Age.

Under 2 years – Black

2 to 5 years – Red

5 to 12 years – Green.



It must be obvious from these findings that the young infant is able to tolerate more glucose than the older child. This increased tolerance for sugar has also been shown by Mogwitz,(18) Bergmark(19) and Spence,(26) the latter finding that by the age of 3 years the normal adult curve was obtained, and that as old age advances the tolerance for glucose becomes decreased. Tisdall, Drake and Brown(42) obtained variable results in different infants with the administration of the same sugar.

On the other hand the observed facts find a ready explanation on the assumption that in the young infant absorption takes place so slowly that the liver is able immediately to deal with all the sugar and so none passes into the general systemic circulation. Tisdall, Drake and Brown(42) administered glucose subcutaneously and so excluded the question of absorption and they found that after the injection of a 5 per cent. solution of glucose - the amount of solution given in each instance being 10 cc. per pound of body weight, - a very low curve was obtained, showing that the injected glucose disappears very rapidly from the blood stream. This amount is practically equivalent to the amount given in my cases, i.e., 1 gm. per kilo of expected weight, the actual weight and the expected weight being in the normal infant almost the same.

The Sugar Tolerance Test in Certain Pathological Conditions.

It has been shown in the earlier part of the paper that variations in the fasting blood sugar content do occur in certain pathological conditions of infancy, and it was thought that light might be thrown on the question of absorption and metabolism of carbohydrate in certain of these cases by studying the blood sugar curves after the ingestion of glucose.

Eight cases of marasmus were chosen whose percentage of expected weight varied from 43 to 69 and in whom there was neither diarrhoea nor vomiting and as far as is known no constitutional or organic disease.

The results of this investigation are given in Table XI and graphically represented in Chart VII, where also the average curve obtained in normal infants of the same age is plotted. On comparing these curves it will be seen that, although, as already shown, the blood sugar level in marasmus is lower than in health, the rate and extent of rise and also the duration of the rise in the blood sugar after ingestion of glucose are absolutely parallel. Case No.84 showed practically no rise in the blood sugar, probably due to the length of time the child required to take the feed.

Eleven cases of acute gastro-enteritis accompanied by fever and severe diarrhoea with vomiting were also investigated and the results are tabulated in Table XI. From this table and Chart VIII, where the average curve is plotted, it will be seen that/

that here also a normal curve was obtained. One might have expected a delayed fall due to defective storage as a large number of cases of acute gastro-enteritis show pathologically some lesion of the liver. This was observed by Tisdall, Drake and Brown (42) who found that infants suffering from acute intestinal intoxication were unable to remove injected glucose from the blood stream at the normal rate.

Three cases of definite pyloric stenosis were also examined; they had all been vomiting for some considerable length of time before the test was carried out, but for a few days immediately preceding the test there had been very little vomiting and none of the glucose given was vomited.

The results obtained from these cases are given in Table XI and Chart IX and it will be observed that there is a prolonged rise in the blood sugar curve, the highest point not being reached in two of the cases until one and a half hours after the ingestion of the glucose, and in the other case until one hour after. In only one case - No.9 - had the blood sugar returned to the normal fasting level within two hours. This delayed absorption in pyloric stenosis with its much impaired gastric motility is not to be wondered at, as practically no sugar is absorbed from the stomach.

It does not seem, therefore, that in marasmus or gastro-enteritis there is any gross defect in the absorption of metabolism of carbohydrates although we know that excess of carbohydrate in the diet will set up gastro-intestinal symptoms.

Table XI.

Blood Sugar Curve after ingestion of glucose in Marasmus, Gastro-Enteritis and Pyloric Stenosis.

No.	Age.	% Expected Weight.	% of sugar in blood. Fasting.	½ hr. after gluc.	1 hr. after gluc.	1½ hrs. after gluc.	2 hrs. after gluc.	Disease.
45	6 months.	63	.064	.100	.131	.064	-	Marasmus.
25	9 weeks.	69	.074	.094	.131	.106	.078	"
15	4 months.	59	.098	.150	.143	.108	.095	"
84	9 months.	54	.097	.115	.104	.098	-	"
44	7 weeks.	53	.083	.131	.100	.083	-	"
17	9 weeks.	53	.081	.140	.156	.131	.081	"
85	10 weeks.	53	.087	.114	.094	.079	.086	"
28	15 weeks.	43	.075	.100	.098	.068	.073	"
Average:		-	.082	.118	.119	.092	.083	
29	9 weeks.	85	.087	.150	.112	.108	.081	Gastro-enteritis
36	1 year.	88	.119	.156	.137	.119	-	"
78	11 weeks.	77	.112	.187	.129	.125	.112	"
33	5 weeks.	75	.100	.140	.131	.100	.098	"
41	45 weeks.	67	.096	.156	.131	.096	-	"
19	38 weeks.	54	.088	.131	.156	.112	.094	"
57	15 weeks.	71	.106	.137	.144	.118	.106	"
38	19 weeks.	70	.068	.100	.110	.100	.068	"
88	2 weeks.	65	.107	.182	.114	.118	.112	"
82	3 months.	64	.099	.132	.139	.099	-	"
23	42 weeks.	56	.062	.112	.131	.062	.068	"
Average:		-	.098	.143	.128	.104	.092	
9	4 weeks.	84	.068	.094	.130	.116	.094	Pyloric Stenosis.
27	10 weeks.	80	.081	.093	.108	.118	.081	"
87	5 months.	51	.089	.107	.113	.132	.104	"
Average:		-	.079	.098	.117	.122	.096	

Chart VII

The Average Blood Sugar Curve in Marasmus

Compared with

the average normal curve in infancy

Normal Curve - Black

Marasmic Curve — Red

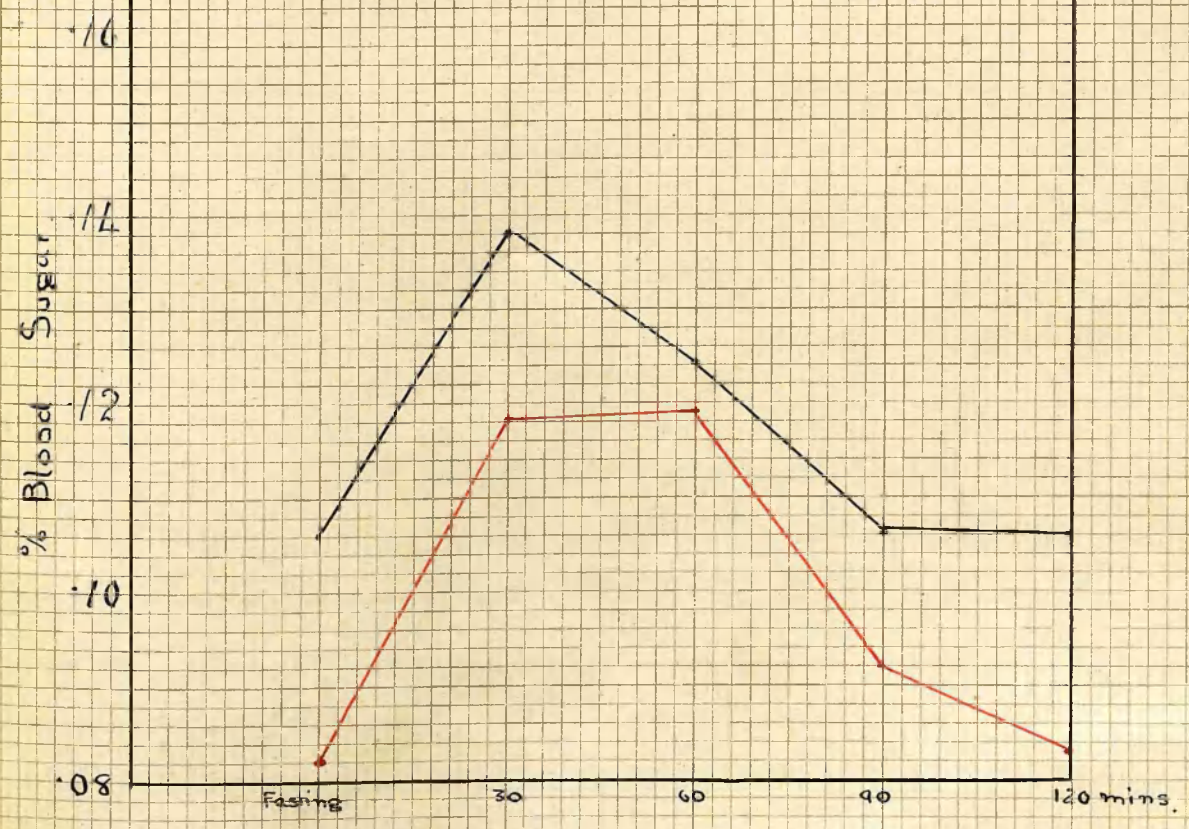


Chart VIII

The Average Blood Sugar Curve in Gastro-Enteritis
compared with
the average normal curve in infancy

Normal curve – Black
Gastro-Enteritis Curve — Red

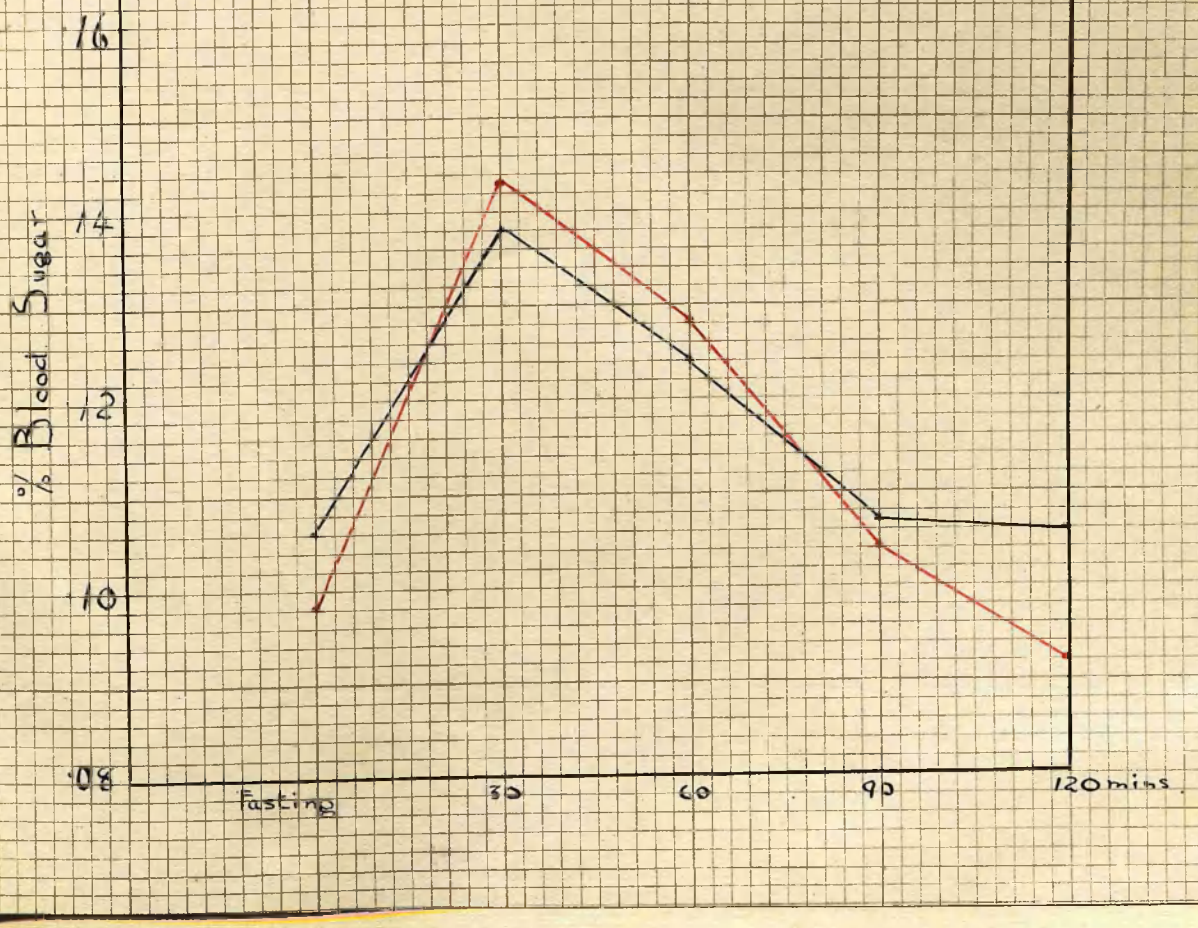


Chart IX

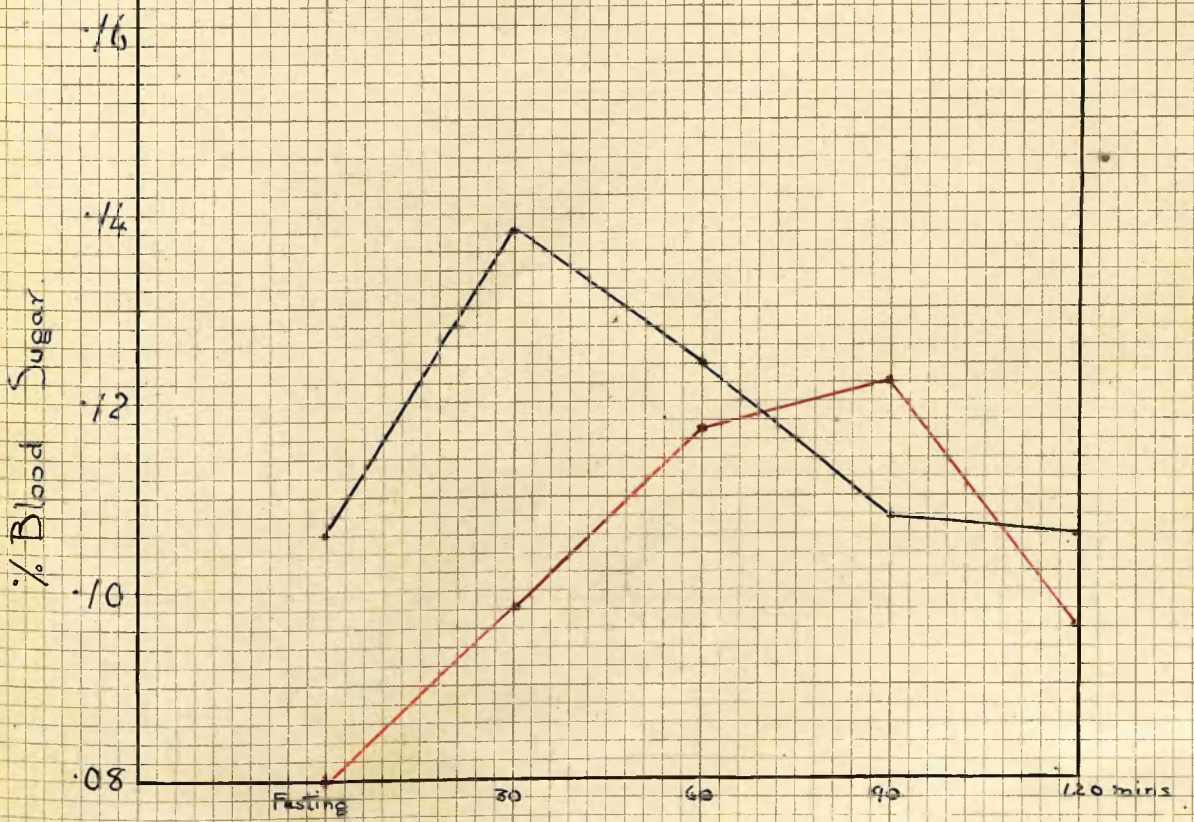
The Average Blood Sugar Curve in Pyloric Stenosis

compared with

the average normal curve in Infancy

Normal curve — Black.

Pyloric Stenosis Curve — Red



THE SUGAR TOLERANCE TEST IN DISEASES OF THE DUCTLESS GLANDS.

It is evident from experiments on animals and from clinical observation that the so-called ductless glands - the thyroid, parathyroid, pituitary and suprarenal - do influence in some way the carbohydrate metabolism and thus the sugar content of the blood and urine. The only means we have at our disposal of studying the influence of these glands on carbohydrate metabolism is by examining the sugar content of the blood and urine in animals after extirpation of the gland or after the administration of extracts of the gland. These means are very unsatisfactory as the physiological action of an organ is not necessarily identical with the pathological processes which go on within the body and it is known that one gland may exert an influence either inhibitory or stimulating on another gland.

THE EFFECT OF THE THYROID GLAND ON CARBOHYDRATE METABOLISM.

It is known that the thyroid gland exerts a profound influence on growth and development, and it is now generally conceded that this gland also exerts an influence on carbohydrate metabolism. Riddle, Honeywell and Spannuth (49) from experiments on/

on pigeons have shown that both the thyroid and the suprarenal are connected in the establishment of a normal concentration of sugar in the blood, a high blood sugar being obtained where there are small thyroids and small suprarenals and a low blood sugar where there are large thyroids and large suprarenals. Cammidge (36) reported an increase in the blood sugar with consequent glycosuria after the subcutaneous injection of thyroid, and Cramer and Krause (50) demonstrated that the feeding of small amounts of thyroid causes the liver glycogen to disappear and decreases the glycogenic function of the liver. Bodansky (51) found that in dogs after thyroidectomy there was an increase in the tolerance for sugar, while after the administration of thyroid-gland extract a decrease was obtained. Lund and Richardson, (52) on the contrary, found that after extirpation of the thyroid a normal blood sugar curve was obtained; while Holman (53) obtained a marked hyperglycaemia immediately following thyroidectomy and later a hypoglycaemia.

A similar controversy has occurred as the result of recent work done on diseases of the thyroid gland in man. Gray, (54) on reviewing the literature and quoting the average findings of numerous workers, found that there was very little difference in the sugar tolerance curves in hyperthyroidism as compared with hypothyroidism, the blood sugar rising to a height of .16 per cent in half an hour with a slightly prolonged fall, the normal fasting level not being reached till at least 3 hours after the/

the ingestion of the glucose. Janney and Isaacson[55] in 1915 found a hypoglycaemia with a prolonged curve in all cases of cretinism and in myxoedematous patients, while a hyperglycaemia was obtained in exophthalmic goitre. In 1920 Janney,[56] working along with Henderson, found that the results in such cases were not always consistent, though in the majority a prolonged curve was obtained. Similar observations were made by Major,[57] Hamman and Hirschmann,[58] who examined 6 cases of thyroid disease, found a lowered sugar tolerance with a high prolonged curve in hyperthyroidism. Katayama,[59] giving 1.75 gm. glucose per kilogram of body weight, confirmed this in 8 out of 9 cases of exophthalmic goitre examined by him. Langdon Brown[61] has shown that in exophthalmic goitre even though no glycosuria may be produced by giving glucose the hyperglycaemia is more pronounced than in the normal person and that there is a delay in returning to the normal fasting level - in other words he states that in exophthalmic goitre there is usually a high renal threshold.

Gardiner Hill, Brett and Forest Smith[61] examined 4 cases of severe exophthalmic goitre and found that after the ingestion of 50 gms. of glucose the blood sugar rose to .200% and the curve showed definite prolongation, glycosuria was always present at the end of the test in each case. In 15 cases of myxoedema examined by them a normal fasting blood sugar was obtained in 12, one showed a definite hypoglycaemia

and/

and two showed hyperlgycaemia. The curves obtained after 50 gms. of glucose were higher and the fall more delayed than in the normal but in only two of the cases was there any glycosuria. From their results they state that, as against the ordinary conception given in text books, that myxoedematous patients have an increased carbohydrate tolerance, in the majority of cases there is a decreased carbohydrate tolerance with a raised renal threshold. The administration of thyroid extract did not raise the fasting blood sugar level but lowered the high blood sugar curve which was previously obtained and decreased the prolongation of the curve. They are of the opinion, however, that improvement in the clinical condition is a very much safer guide in treatment than any results of a carbohydrate tolerance test.

Geyelin (62) found a low fasting blood sugar level in myxoedematous patients.

Olmsted and Gay (63) found that in hyperthyroidism one may get a marked hyperglycaemia with a sustained fall and in some cases of hypothyroidism examined by them a hypoglycaemia was obtained, the blood sugar falling still lower even after the ingestion of glucose.

These results have practically all been obtained in adults and as far as I can find from the literature very little work on the sugar tolerance curve in disease of the thyroid in children has been performed.

In children one finds all degrees of deficiency of

the/

the thyroid from the slight cretins which show little beyond stunted growth and some mental dulness, to the severe cretins with extreme stunted growth, thick dry skin, and subnormal temperature, forming a clinical picture which is not likely to be mistaken for anything else. Increased activity of the thyroid gland such as one sees in the adult is very rare.

I have had the opportunity of performing the sugar tolerance test in 17 children suffering from some disease of the thyroid gland as shown by clinical examination and in 14 of these the blood sugar content was examined after the ingestion of glucose, while in the other three the tolerance for sugar was tested by giving glucose by mouth and noting its presence or absence in the urine. These cases have been described under the following headings:-

1. Cases No.I to V - which show severe signs of cretinism and have undergone no previous treatment.
2. Cases VI and VII - which are typical cretins, but before admission to hospital had been on thyroid extract for some time.
3. Cases VIII to X - which show a milder degree of thyroid deficiency such as dwarfism with mental backwardness and delayed ossification.
4. Cases XI to XIV - which show only enlargement of the thyroid gland but no symptoms of hyperthyroidism.
5. Cases XV to XVII - where there is some sign of hyperthyroidism as evidenced by tremor, exophthalmos or tachycardia.

The results obtained in these cases are shown in Table XII, and a short resumé of the cases is given.

Table XII.

The Sugar Tolerance Test in Children suffering from some disturbance of the Thyroid Gland.

Case No.	Fasting Blood Sugar %	Amt. of glucose given.	Amt. of gluc. per Kilo body weight.	½ hr. after gluc.	1 hr. after gluc.	1½ hrs. after gluc.	2 hrs. after gluc.	2½ hrs. after gluc.	3 hrs. after gluc.	Remarks.
I.	.084	30 gms	2.5 gms.	.112	.100	.100	.098			No sugar in urine 3 hrs. after glucose.
II.	.075	10 gms	3 gms.	.086	.092	.094	.094			
III.	.082	6 gms.	1.5 gms.	.104	.100	.100	.100			
IV.		50 gms 100 gms	4 gms. 8 gms.							No definite reduction of Fehlings 2 hrs after. Sugar + in urine 2 and 4 hrs. after.
V.		60 gms.	5.5 gms.							No sugar in urine up to 6 hours after.
VI.	.075	15 gms.	1.25 gms	.075	.100	.125	.148	.155	.125	
VII.	.084	39 gms.	2 gms.	.136	.112	.080				
VIII.	.084	30 gms.	2 gms.	.100	.136	.125	.112			No sugar in urine.
IX.	.086	30 gms. 56 gms.	1.5 gms. 3 gms.	.118	.131	.118	.112			No sugar in urine. Urine 4 hrs. after showed a trace of sugar. No sugar 4-6 hrs. later.
X.		50 gms. 75 gms. 100 gms.	3 gms. 4.5 gms. 6 gms.							No sugar in urine. No sugar in urine. Sugar + 2 hrs. after. None in other specs.

Table XII. (Contd).

Case No.	Fasting Blood Sugar %.	Amt. of glucose given.	Amt. of gluc. per Kilo body weight.	½ hr. after gluc.	1 hr. after gluc.	1½ hrs. after gluc.	2 hrs. after gluc.	2½ hrs. after gluc.	3 hrs. after gluc.	Remarks.
XI.	.108	25 gms.	1.25 gms.	.156	.198	.175	.156	.125	.112	Sugar + in urine 1½ 2, and 2½ hrs. after
XII.	.106	30 gms.	1.5 gms.	.132	.156	.100	.112			
XIII.	.112	35 gms.	1 gm.	.150	.200	.187	.150			Slight reduction of Fehlings 1 hr. after, none 2 hrs. after.
XIV.	.085	25 gms.	1 gm.	.120	.160	.145	.125	.090		Fehlings partially reduced 1 hr after. No reduction 1½, 2 or 2½ hrs. after.
XV.	.087	35 gms.	1.5 gms.	.125	.136	.125	.112	.092		
XVI.	.092	10 gms.	.25 gm.	.105	.118	.112	.088	.092		
	.085	15 gms.	.5 gm.	.132	.112	.100	.104	.094	.085	
	.100	20 gms.	.75 gm.	.118	.142	.125	.120	.102	.098	
	.085	25 gms.	1 gm.	.162	.158	.125	.120	.090	.084	No sugar in urine.
		50 gms.								No sugar in urine.
XVII.	.106	25 gms.	1 gm.	.136	.164	.125	.110			
		40 gms.	1.5 gms.							No sugar in urine.
		52 gms.	2 gms.	.168	.137	.118	.100			No sugar in urine.

Case I.

Girl. 7 2/12 yrs. Height 88 cm. (Normal height for age 116 cm.). Weight 13.6 kgs. (Normal weight for age 21.8 kgs.) Mental Ratio 58.
Admitted with history of being very backward. Did not walk or speak till 4 years. At 4 years features noticed to be becoming coarser and skin dry. Has also become very lethargic. Small flabby child. Skin and hair dry. Tongue square but not protruding. Hands square. Pad of "fat" over back. Ossification at wrist same as that of a child of $2\frac{1}{2}$ years.

Case II.

Girl 26/52 yrs. Height 51 cms. Weight 3.8 kgs. (Normal Height 64 cms; normal weight 7.5 kgs).
Brought to hospital on account of swelling of abdomen of 3/12 duration.
Very small child, cretinoid facies. Tongue large and protruding. Abdomen markedly distended, with umbilical hernia.
No centres of ossification seen on X-ray photo of wrists.

Case III.

Girl 11/12 yrs. Height .55 cms. Weight 4.8 Kgs. (Normal Height 72 cms; normal weight 5.4 kgs.)
Admitted to hospital as mother thought child backward. Thick-set infant with typical cretinoid facies. Tongue large and eyes set apart. No ossification centres seen on X-ray of wrists.

Case IV.

Boy, 4 4/12 yrs. Height 81 cms. (Normal for age 96 cms.) Weight 12.9 kgs. (Normal weight 16.5 kgs.).
Walked at 3 3/12 but not making any attempt to talk. Soft flabby child. Hair scanty and dry. Lethargic. Hands short, broad. Cretinoid facies. X-ray of wrist shows ossification of a child of 1 year.

Case V.

Girl 4 8/12 yrs. Height 70 cms. (Normal Height 100 cms.).
Weight 11.3 kgs. (Normal weight 17 kgs).
Brought to hospital as child not developing properly. Typical cretin. Skin, hair and nails dry. Pot-bellied. Tongue square and tendency to/

Case V.(Contd). to protrude. X-ray of wrist shows ossification same as child of 1 year.

Case VI.

Girl 3 9/12 yrs. Height 74 cms. (Normal Height 90 cms.).
Weight 12 kgs. (Normal weight 15 kgs).
Did not walk till 3 years of age and only beginning to talk.
Treated with thyroid extract for six months at age of 1½ years. Typical cretinoid facies. Square protruding tongue. Spade-like hands. Dull countenance. Mental ratio could not be done Ossification at wrists equal to that of a child of 9/12 years.

Case VII.

Girl 10 4/12 yrs. Height 115 cms. (Normal height 136.3 cms.)
Weight 21.36 kgs. (Normal weight 30 kgs.).
Did not walk till 3 years of age. Since 2 years of age has had thyroid regularly but during past 2 years has ceased to grow and become dull and quiet. Small flabby child, dull expression. Skin dry. Tongue square. Slightly delayed ossification as seen by X-rays of wrist.

Case VIII.

Girl 8½ years. Height 93 cms. (Normal height 124 cms.).
Weight 15.7 kgs. (Normal weight 25 kgs).
Walked at 2½ years and talked at 2 years.
At 4 years noticed to be small and backward mentally. Small fat child, somewhat lethargic. Prominent abdomen with slight umbilical hernia. Ossification at wrists that of child of 3½ yrs.

Case IX.

Girl 9 8/12 yrs. Height 93.5 cms. (Normal height 138 cms.).
Weight 14.3 kgs. (Normal weight 28 kgs.).
Walked and talked at 1 year and seemed to grow normally till 3 years, since then growth has ceased. Small flaccid child.
X-ray of wrist that of a child of 3 years.

Case X.

Girl 9 2/12 yrs. Height 98 cms. (Normal height 127 cms.). Weight 16.5 kgs. (Normal weight 27 kgs.). Said to have been healthy till 4 years old, and since then has not grown. Small child. Fat with prominent lips and squat nose. Hair dry and falling out. No fat pads. Intelligence good. Ossification of wrists that of child of 4½ years.

Case XI.

Girl 9 years. Height 121 cms. (Normal height 126 cms.). Weight 20.47 kgs. (Normal weight 26 kgs). Said always to have had slight swelling on neck. There is definite enlargement of the thyroid, both lobes. No exophthalmos, no tremor. Mental ratio = 90.

Case XII.

Girl 6 years. Height 110 cms. (Normal height 112 cms.). Weight 19.2 kgs. (Normal weight 19.8 kgs.). 3/12 ago swelling of neck noticed. There is a soft swelling of the thyroid gland affecting both lobes. No tremor, tachycardia or exophthalmos.

Case XIII.

Girl 11 9/12 yrs. Height 140 cms. (Normal height 140 cms.). Weight 31.72 kgs. (Normal weight 34 kgs.). For past 6/12 has been taking epileptic turns and 3/12 ago swelling of thyroid noticed. Well developed child. Breasts well developed, small amount of pubic and axillary hair. Has not menstruated. Marked enlargement of thyroid gland affecting especially isthmus and right lobe. No tachycardia. No exophthalmos. No tremor. Mental ratio = 77.

Case XIV.

Boy 9 yrs. Height 121.5 cms. (Normal height 127 cms.). Weight 24 kgs. (Normal weight 26.5 kgs.). 6/52 before admission to hospital swelling of neck was noticed. Fair sized well nourished boy. Symmetrical enlargement of thyroid, isthmus not affected. No tremor. No exophthalmos. No tachycardia. Mental ratio = 81.

Case XV.

Girl 12½ years. Height 150.5 cms. (Normal height 149 cms.).
Weight 25 kgs. (Normal weight 37 kgs.).
2 years before admission to hospital said to have goitre and change in child's eyes noticed.
Tall emaciated child with definite exophthalmos. No definite tremor but constant choreiform movements of the arms and very definite enlargement of the thyroid. Slight amount of pubic hair but none in axillae, and mammae poorly developed.

Case XVI.

Boy 9 years. Height 124 cms. (Normal height 127 cms.).
Weight 24.8 kgs. (Normal weight 26.5 kgs.).
History of swelling in neck of 6/12 duration which has gradually increased in size and child has become very nervous.
Well nourished child. Skin clear and soft and warm. Marked enlargement of thyroid - both lobes and isthmus being affected. Definite tremor of hands. No exophthalmos or other ocular symptoms of hyperthyroidism. No tachycardia; pulse rate about 80 per minute.

Case XVII.

Girl 9 years. Height 126 cms. (Normal height 126 cms.).
Weight 24 kgs. (Normal weight 26 kgs.).
6 months ago swelling of neck noticed and child became very breathless on exertion and for past two months has been vomiting.
Fair sized healthy looking child. Thyroid slightly enlarged. Fine tremor of hands. Tachycardia. Pulse 110-130 per minute. Marked pulsation in neck.

THE EFFECT ON THE BLOOD SUGAR CONTENT OF DIMINISHED ACTIVITY OF THE THYROID GLAND.

From a scrutiny of Table XII it is seen that in cases I to X showing evidence of diminished activity of the thyroid secretion the fasting blood sugar varied from .075% to .086% with an average of .081%. This figure is decidedly lower than that of .099% previously obtained in the normal child. Even in the two cases Nos. VI and VII which had undergone previous treatment with thyroid extract for some considerable time the low fasting level was maintained. A general survey of the figures shows that in cases I to III which had undergone no treatment only a very slight rise in the blood sugar was obtained after the ingestion of glucose even although they were given from 1.5 to 3 gm. of glucose per kilo of body weight. For some reason which I am unable to explain the absorption of glucose in Case VI was very much delayed as evidenced by the fact that the hyperglycaemia was most marked 2 hours after the ingestion of glucose. In Case No.VII,which had received thyroid extract for about 8 years, and where on clinical examination the symptoms of hypothyroidism were not marked and there was only slight delay in the ossification, the duration of the hyperglycaemia was the same as the normal curve obtained for that age but the degree of hyperglycaemia was less marked. In other words the sugar tolerance was slightly increased. The curves obtained in the other cases of hypothyroidism are slightly lower and the fall more prolonged than in the healthy individual.

THE EFFECT ON THE BLOOD SUGAR CONTENT OF INCREASED ACTIVITY OF THE THYROID GLAND.

The figures for the fasting blood sugar content which were obtained in the cases of simple goitre and hyperthyroidism fall within the usual normal limits.

Cases XI, XIII and XIV are rather interesting as the only symptoms of thyroid disease was enlargement of that gland; yet on testing their sugar tolerance they all showed marked abnormal carbohydrate metabolism, sugar appearing in the urine after a dose of glucose of only about 1 gm. per kilo of body weight and the blood sugar curve after the glucose tending to be higher and the fall more prolonged than normal; the renal threshold in none of these cases was raised. These cases should be contrasted with the three following cases XV, XVI, and XVII, where there were definite symptoms of increased activity of the thyroid gland. In the two cases XVI and XVII where urinary specimens were obtained no glycosuria was noted and the blood sugar curve in cases XV, XVI and XVII tended more to the normal though the fall in the blood sugar was slightly delayed.

Table XII, therefore, shows that where carbohydrate tolerance is estimated by examination of the blood sugar after the ingestion of glucose in the cases of hypothyroidism there is a definite increased carbohydrate tolerance which still persists after prolonged treatment with thyroid extract. Defective thyroid function/

function as evidenced by enlargement of that gland but no definite clinical symptoms, may only be discovered by performing the sugar tolerance test; and on the other hand there may be definite clinical symptoms with very slight disturbance of the carbohydrate metabolism. It will be seen, also, that the blood sugar curves in certain cases of hyperthyroidism may be indistinguishable from that of a mild diabetic. The essential difference lies in the fact that in the diabetic there is impaired oxidation of carbohydrate, whereas in hyperthyroidism this is if anything excessive. A determination of the respiratory quotient after the ingestion of glucose would help to settle the question.

THE EFFECT OF THE SUPRARENAL GLAND ON CARBOHYDRATE METABOLISM.

The suprarenal glands have been proved by experimental pathology to be necessary for life and the active constituent (adrenalin) of the medullary substance of these glands has long been known to modify metabolism considerably, leading to an increase of sugar in the blood and to its excretion in the urine.

Since Blum and then Zuelzer in 1901 described the glycosuria following the subcutaneous or intravenous injection of suprarenal extract a great deal of work has been done on the effect of suprarenal extract and adrenalin on carbohydrate metabolism. Archard and Desbouis (64) showed that after the injection of adrenalin there is a decrease in the power of the tissues to burn glucose and the former working with Ribot and Binet (65) found that this substance acts by preventing the formation/

formation of the glycolytic ferment from the pancreas and has not a direct action on the glucose itself.

Removal of the suprarenals in animals has been investigated by many observers and has been shown to be followed by the disappearance of glycogen from the liver and muscles and also from the blood. Subcutaneous injection in animals of .5 cc. (1 in 1000) adrenalin causes a rise in the blood sugar reaching its height in one hour and then rapidly falling to practically the normal level within 2 hours. Doubling the dose causes a more marked hyperglycaemia with a prolonged fall.

I have had the opportunity of examining the sugar tolerance curve in one case of possible Addison's disease.

> This was a boy of 8 years admitted with a history of general weakness of 18 months' duration and abdominal pain with slight yellowness of skin of four months' duration. On admission it was noted that he was a fair-sized poorly nourished child. Skin slightly pigmented but no pigmentation of the mucous membranes. On examination a small mass was felt in the right iliac region but otherwise physical examination was negative. The Pirquet was markedly positive both human and bovine. After admission there was slight irregular fever and occasionally sugar was noted in the urine and the sugar tolerance test was performed with the following result:-
>
> Fasting blood sugar = .093%.
> ½ hr. after 25 gms. gluc. blood sugar = .125%.
> 1 hr. " " " " " = .175%.
> 1½ hrs. " " " " " = .150%.
> 2 hrs. " " " " " = .120%.
> 2½ hrs. " " " " " = .100%.
>
> The urine was also examined at half-hourly intervals and there was a slight reduction of Fehling's in the specimen obtained 1 hour after the ingestion of glucose.
>
> The child seemed to improve and was sent to the country branch where he remained 5 months, but while there had a/

a relapse and was readmitted to hospital. At this time child was very ill with marked pyrexia and marked pigmentation of skin but still none of the mucous membranes. Abdomen was doughy with a small amount of free fluid present. The sugar tolerance was again done with the following result:-

Fasting blood sugar	=	.112%.				
½ hr. after	25 gms.	gluc.	blood	sugar	=	.156%.
1 hr.	"	"	"	"	=	.212%.
1½ hrs.	"	"	"	"	=	.198%.
2 hrs.	"	"	"	"	=	.175%.
2½ hrs.	"	"	"	"	=	.164%.

Sugar was present in the urine passed 1, 2 and 3 hours after the glucose, but none was present in the 4-hourly specimen.

The child went rapidly downhill after re-admission and died, but unfortunately no post-mortem was obtained to confirm the diagnosis.

The first curve obtained showed a slightly decreased carbohydrate tolerance which became much more marked as the condition progressed (vide Curve II). One would have expected to have found an increased tolerance due to hypofunction of the gland but probably in this case where there was also tubercular peritonitis there was an extension of the disease to the pancreas. The second curve is typical of that found in mild cases of diabetes but there were no symptoms suggestive of diabetes.

THE EFFECT OF DISTURBANCE OF THE PITUITARY GLAND ON CARBOHYDRATE METABOLISM.

It is quite certain that like the thyroid the pituitary gland is intimately concerned with growth and carbohydrate metabolism but its mode of action is even less understood.

This/

This gland is composed of three parts, the anterior lobe, the pars intermedia and the pars nervosa, the two latter forming the posterior lobe. The anterior lobe controls skeletal and muscular growth while the posterior lobe is associated with sugar metabolism. Partial removal of the anterior lobe in animals leads to lack of development of the skeleton with under-growth, while in man infantilism is produced. Hypersecretion, during the growing period, leads to gigantism, while if full growth has been attained acromegaly follows. Glycosuria may occur in the early stage of acromegaly but whether this is due to a secretion from the anterior lobe or to pressure on the floor of the 4th ventricle is not clear. Destruction of the posterior lobe which arises as a down-growth from the floor of the embryonic brain increases the sugar tolerance and the opposite occurs after feeding with extract of the posterior lobe.

Cammidge (66) injected pituitrin into rabbits and got a marked rise in the blood sugar. Similarly Borchardt (67) found that in rabbits the injection of hypophyseal extract produced glycosuria and may also produce hyperglycaemia. Lawrence and Hewlett, (68) on the contrary, found that the subcutaneous injection of 1 to 2 cms. of pituitrin in normal individuals has no appreciable effect on the blood sugar. Houssay (69) and Sachs and McDonald (70) also found no difference in the carbohydrate metabolism between normal dogs and those that had the pituitary removed. Goetsche, Cushing and Jacobsen (71) demonstrated the occurrence of glycosuria after electrical/

electrical stimulation of the pituitary body and of increased carbohydrate tolerance in animals after hypophysectomy. Gardiner Hill et al (72) investigated the carbohydrate metabolism in 60 cases of pituitary obesity between the ages of 8 and 20 years of age and found that when the onset of obesity was of comparatively recent origin the curve approached to the normal height but the fall was delayed and there was a slightly decreased sugar tolerance. If the obesity was of longer duration the blood sugar curve was very low and in none of the cases did sugar appear in the urine. The giving of thyroid extract and pituitary extract by mouth tended to approximate the curves to normal.

Gordon Holmes (73) in a series of 56 patients suffering from acromegaly and hypopituitarism found that the form of the blood sugar curve after the injection of glucose was similar in both types of cases, the highest point being reached late and the fall to the initial fasting level slow. The fasting blood sugar in acromegaly, however, was high; while in obesity and other signs of hypofunction the fasting blood sugar was small in amount.

Janney and Isaacson (55) obtained a hypoglycaemia with a prolonged curve in hypopituitarism and a hyperglycaemia in cases of acromegaly and this has also been confirmed by Olmsted and Gay. (63) Bailey, (74) on the contrary, reports a case of hypopituitarism with a prolonged hyperglycaemic blood sugar curve. Griffiths (75) reports a case of Frohlich's hypopituitarism where before treatment was commenced the blood sugar was .104% one hour/

hour after 100 gms. glucose, while after treatment for two months with pituitary extract the blood sugar rose to .18% one hour after the same amount of glucose and sugar appeared in the urine. Major[57] in eight cases of obesity with other symptoms of Frohlich's Syndrome got marked variations in the blood sugar curve. Langmead and Calvert[76] state that the beneficial effect of the different extracts of the gland on the sugar tolerance curve can be used as a means of differential diagnosis and appropriate treatment carried out by administering that lobe of the pituitary which produces the best effect on the sugar tolerance.

Only one case of obesity was examined and the question arose was this due to a tumour of the pituitary causing some destruction of the posterior lobe? On X-ray examination of the skull, a shallow pituitary fossa was observed but on clinical examination the constitutional effects of altered glandular activity were not marked.

According to Gordon Holmes[73] and Gardiner Hill et al[72] if the obesity is due to hypofunction of the pituitary one would expect a low fasting blood sugar with a low prolonged fall and the absence of sugar in the urine even after large amounts of glucose. In the case examined a normal fasting blood sugar was obtained and although the blood sugar rose to .168% immediately after the ingestion of 50 gms. of glucose, i.e., 1 gm. per kilo body weight or 1.5 gm. per kilo expected weight, the fall in the blood sugar was definitely delayed, indicating defective storage.

An/

An increased tolerance for glucose was also obtained, no sugar appearing in the urine after 100 gms. of glucose (i.e., 3 gms. per kilo of expected weight).

If the increase in sugar metabolism is accepted as an indication of diminished endocrine activity it is obvious that in this case there is a certain amount of pituitary under-activity, but any case of obesity with lowered metabolism may be able to deal with larger quantities of sugar than the normal.

Girl. Aet. 12 yrs. Weight 57 kgs. (Normal weight 36 kgs.). Height 148 cms. (Normal height 149 cms.). Healthy till 1 year ago except for typhus at 6 years and measles at 11 years. One year ago began to get very fat and complained of slight headaches and tiredness. For the past year she has had regular menstrual periods with much pain and loss of blood. On examination it was noted that she was a large obese child. Skin coarse and rough with growth of hair on anus and legs and abundant axillary and pubic hair. Mammae large. X-ray of skull showed a shallow pituitary fossae - otherwise physical examination negative.

TABLE XIII.

Sugar Tolerance Curve obtained after 50 gms. Glucose in a Case of Obesity.

Fasting blood sugar.	% of Blood Sugar.			
	½ hr. after glucose.	1 hr. after glucose.	1½ hrs. after glucose.	2 hrs. after gluc.
.100	.168	.155	.148	.132

The following three cases of dwarfism in which the carbohydrate tolerance was performed are of interest as they each show a different symptom complex. Cases No. 1 and 2 show definite rudimentary sexual development, while Case No.3 shows mental backwardness. The details of these three cases are given below and the results of their sugar tolerance test aregiven in Table XIV.

Case No.1.

Boy. aet 10 years. Height 102 cms. (Normal height 134 cms.). Weight 17.24 kgs. (Normal weight 30 kgs.). Did not walk or talk till 3 years of age but otherwise healthy till 6 years, since when he has not grown, hands and feet remaining of same size. On examination - marked dwarfism with delayed ossification and hypoplasia of testes, only the left being in the scrotum and this of small size. Milk teeth all present. Quite bright, mental ratio 88. Field of vision normal in each eye and ophthalmoscopic examination negative. Child was then put on 1 cc. antuitrin intramuscularly weekly for 8 weeks, then on thyroid gr. $\frac{1}{2}$ t.i.d. increased to gr.i t.i.d. for 4 months and after this period of 6 months he had only grown 2 cms. in height and weight was I.S.Q.

Case No.2.

Boy. aet 12 years. Height 121 cms. (Normal height 141 cms.). Weight 30.2 kgs. (Normal weight 36 kgs.). Healthy till 2 years ago when began to vomit in the morning and this has persisted off and on since. No definite headache but "funny feeling" in frontal region. No visual disturbance. On examination he was found to be a short obese boy. Skin clear. Much fat in chest and anterior abdominal wall. Breasts prominent but nipples rudimentary. Penis rudimentary but testes of fair size and in scrotum. Physical examination negative except that left pupil smaller than right while right only reacted sluggishly to light. X-ray of head negative. Mental ratio - 91.

Case No.3.

Girl 5 2/12 years. Height 72 cms. (Normal height 105.3 cms.). Weight 9.5 kgs. (Normal weight 18 kgs.). Did not walk or talk till 3 years of age and has never grown in length like other children but is bright and plays with the other children. On examination found to be a very small child with large head and short neck. Extreme lordosis and prominent abdomen, short upper arms but otherwise nothing to suggest achondroplasia.
X-ray of wrist showed delayed ossification and the bones generally are unduly transparent.
Mental Ratio - 61. X-ray of head normal.

Table XIV.

Sugar Tolerance Test in Three Cases of Dwarfism.

Case No.	Amt. of gluc. (gms.)	Blood Sugar %. Fasting blood sugar.	½ hr. after gluc.	1 hr. after gluc.	1½ hrs after gluc.	2 hrs after gluc.	Remarks.
1. Before treatment.	30	.086	.136	.132	.120	.112	No glycosuria.
	70						No glycosuria.
	100	.090	.146	.172	.175	.168	Glycosuria 90 mins. after but none in other specimen.
After treatment with Antuitrin & thyroid.	30	.093	.112	.143	.137	.125	No glycosuria.
	110	.098	.125	.132	.130	.125	No glycosuria.
	120						No glycosuria.
	130						No glycosuria.
2.	36	.100		.150	.106	.100	No sugar in urine.
	75						No sugar in urine.
3.	18	.081	.156	.137	.142	.126	No glycosuria.
	36						Sugar + 1 hr, 1½ hrs. and 2 hrs. after glucose.

From Table XIV it will be seen that these cases show great differences. Case No.2 showed no evidence of any carbohydrate disturbance while the findings in Case No.1 indicate a definite increased tolerance for sugar which one would have thought would have conformed to the normal after prolonged treatment with antuitrin and thyroid. The reverse, however, occurred, a more marked increased tolerance for carbohydrate being obtained. From the clinical examination of Case No.3 it is very difficult to locate the cause of the dwarfism, and although this child showed a markedly decreased tolerance for carbohydrate with defective storage of sugar by the liver, it might probably be due to over-activity of any of the endocrine glands. Unfortunately the sugar tolerance test was not performed after the larger amounts of carbohydrate, so it is impossible to say at what level the renal threshold for sugar lies.

DISCUSSION OF RESULTS OF BLOOD SUGAR STUDIES IN ENDOCRINE DISORDERS.

Such cases as these reported only emphasise the complexity of the problem. In the majority of cases where the clinical condition pointed to assured endocrine disorder there was definite disturbance in the carbohydrate metabolism. In those cases showing deficiency of thyroid secretion an increased tolerance was obtained, but the reverse was not always found in those/

those showing increased activity; in some no diminished tolerance for carbohydrate occurring. Probably this is dependent on the stage of the disease, and further work on the sugar tolerance before and at regular intervals after treatment has been commenced, would be of interest and is, I think, necessary, before definite conclusions can be drawn. For this purpose it would be necessary to keep the child under strict supervision and to correlate the clinical improvement and the improvement in ossification by X-ray examination if necessary with the change in the carbohydrate metabolism. All the cases of thyroid disease, however, showed defective storage of carbohydrate.

Disturbances in the function of the pituitary gland are not clearly grouped either clinically or physiologically into the effects of deficiency and excess. The two parts of the gland are so intimately related that disease of one part may cause compression or increased activity of the other part. This is exemplified in the results of testing the carbohydrate efficiency, in some cases an increased tolerance for carbohydrate being obtained, and in others a diminished tolerance. Generally speaking it would seem that the clinical examination is of more value in the diagnosis of disease of the pituitary than determination of the sugar tolerance.

THE EFFECT OF LAEVULOSE ON THE SUGAR CONTENT OF THE BLOOD.

So far only the effect on the blood sugar of the ingestion of glucose alone has been studied. The effect of laevulose has also been carried out and will now be discussed since it has been shown by various workers that the different forms of carbohydrate, e.g., lactose, maltose, saccharose and laevulose do not all behave in exactly the same manner.

It is at present believed that laevulose after its absorption from the alimentary tract is carried direct to the liver via the portal system and immediately stored there as glycogen; it therefore does not appear normally in the systemic circulation. If the liver is defective, however, the cells are supposed to be unable to convert the laevulose into glycogen fast enough and some of it filters through and produces an increase of sugar in the blood stream. It is upon this theory that the laevulose test for liver inefficiency is based. The test was first brought forward by Strauss (77) in 1901. He regarded the presence of laevulose in the urine as evidence of impaired hepatic efficiency, and found laevulosuria after the ingestion of 100 gms. of laevulose in 90% of cases of liver disease, while its presence was only noted in 10% of normal cases.

With/

With the more accurate methods of blood sugar analysis it was found that the presence of laevulose in the urine could not be taken as an accurate index of liver inefficiency as the renal threshold for laevulose varies very much in different individuals and also lies at a very much lower level than that of glucose. Tallerman (78) estimated the renal threshold for laevulose to lie at the blood sugar level of .115% to .13%.

Shirokauer (79) in 1913 was the first to demonstrate that periodic examination of the percentage of sugar in the blood after the ingestion of laevulose was a much more delicate test of liver inefficiency than the presence of laevulose in the urine. He obtained a more marked rise in the blood sugar after the ingestion of laevulose in liver diseases than in the healthy case. Bergmark (19) in the following year found no appreciable rise in the blood sugar in normal adults after the ingestion of laevulose, and this was confirmed later by Maclean and De Wesselow (4) and also Folin and Berglund. (47) Spence and Brett (80) concluded that this test afforded a valuable means of estimating the actual degree of liver inefficiency, but concluded that a rise in the blood sugar content of 20 mgm. may be obtained in the normal adult after the ingestion of 50 gms. of laevulose. Tallerman (78 & 81) also, found that the normal variations are greater than those usually considered; he presumed a degree of liver inadequacy if the rise in the blood sugar exceeded 30 mgms. Prolongation of the curve is also regarded/

regarded as strong evidence of some disorder of the liver.

The value of this test may be questioned by the work of Graham (12) and Cammidge Forsyth and Howard, (66) who found a definite rise in the blood sugar content after the ingestion of laevulose even in normal cases, the former obtaining in adults a rise in the blood sugar to .150% after 50 gms. laevulose with a delay in returning to the normal fasting level. Frank and Melhorn (82) working with children found that in the normal child after the ingestion of 89 gms. of laevulose in 200 ccs. tea there was a rapid rise in the blood sugar with a slow irregular fall. It is possible that these variations may be due to the purity of the laevulose used, a question which will be discussed later.

The functions of the liver are so numerous and are so little understood that no single test has been evolved which will serve as a true index of the efficiency of this organ. The laevulose test of course is of value only in estimating the glycogenic function of the liver. In testing liver efficiency many other tests should be taken into account such as the Van den Bergh and the Phenoltetrachlorphthalein tests as evidence of the biliary function of the liver, and the glycuronic acid test and Widal's Haemoclasic crises test which are regarded by some workers as of value in estimating the antitoxic function of the liver.

The Method used for performing the Laevulose Test.

The technique employed for the laevulose test is the same as that for the "glucose tolerance test," 1 gm. of laevulose per kilo of expected weight being given to the children under 12 years of age and 50 gms. of laevulose to the adult cases. The percentage of sugar in the blood was estimated at half-hourly intervals after the ingestion of the laevulose.

The laevulose used throughout was Merck's pure laevulose; laevulose obtained from the British Drug House was tried but as seen from Table XV the resultant curves obtained in the few normal cases examined were found to be higher than those obtained with the Merck's Laevulose.

TABLE XV.

The Blood Sugar Content after "Merck's" Laevulose and "B.D.H." Laevulose.

Case No.	Fasting blood sugar.	½ hr. after Laev.	1 hr. after Laev.	1½ hrs. after Laev.	2 hrs. after Laev.	% increase in blood sugar.
1. B.D.H.	.093	.125	.118	.106	.093	34
Mercks.	.090	.112	.106	.093	-	24
Mercks + 3 gm. gluc.	.090	.120	.112	.106	.096	33
2. B.D.H.	.106	.143	.120	.106	-	34
Mercks.	.100	.125	.112	.100	.100	25
Mercks + 3 gm. gluc.	.100	.136	.125	.100	-	36
3. B.D.H.	.106	.134	.125	.100	-	26
Mercks.	.100	.108	.112	.100	-	12
Mercks + 3 gm. gluc.	.100	.125	.112	.100	-	25

Because of this discrepancy in the two results Professor Patterson kindly analysed for me the two samples. He found the specific rotation of the Merck's specimen at a concentration of 10, at a temperature of 22°C. to be -91.63, while the B.D.H. specimen gave a specific rotation for sodium light of -82.49. This indicates an impurity in the B.D.H. laevulose of about 9%.

To find if this impurity was glucose 3 gms. of glucose were added to 30 gms. of the Merck's laevulose in the same three cases and the blood sugar estimated. It will be seen from Table XV that this caused practically the same increase in the blood sugar as when the B.D.H. laevulose alone was used. It can, therefore, be presumed that the greater part of the impurity in the B.D.H. laevulose is glucose or some allied carbohydrate. The purity of the laevulose therefore is a factor which should be taken into consideration in judging the normal rise in the blood sugar after the ingestion of laevulose. It is therefore necessary to obtain for oneself the normal rise according to the laevulose used.

It was found (see Table XVI) that when glucose alone was given to a child 5 gms. were required before any definite increase in the blood sugar occurred. The liver appears to be able to deal normally with 3 gms. of glucose but when this is superimposed on laevulose some of it passes immediately into the blood stream and increases its sugar content.

TABLE XVI.

The Blood Sugar Content after varying amounts of glucose.

Case No.	Amt. of glucose.	Fasting blood sugar.	½ hr. after gluc.	1 hr. after gluc.	1½ hr. after gluc.	2 hrs. after gluc.	% increase in blood sugar
1	3 gms.	.112	.106	.112	.100	-	-
	5 gms.	.106	.118	.131	.118	.100	22
2	3 gms.	.093	.106	.100	.090	-	14
	5 gms.	.100	.118	.131	.112	.100	31

Result of the Laevulose Test in Normal Children.

To obtain some idea of the comparative value of such a test, its scope and limitations, twenty children who were recuperating from various diseases in which there was no apparent evidence of disease of the liver were examined and have been taken as representing the normal curve. The results are tabulated in Table XVII, and the average curve obtained is graphically represented in Chart X.

A study of the figures obtained furnishes evidence that the average rise in the blood sugar content is 10 mgm., the highest being 27 mgms. and the lowest a fall of 10 mgms. If one calculates on the percentage increase the greatest increase was 28% with an average of 15%. In two of the cases examined no rise in the blood sugar was obtained, a fall of 6 mgms. and 10 mgms. respectively being found. This increase is greater than can be allowed for by experimental error. One might have expected a lesser rise in the younger child, as it has previously been shown that after the ingestion of glucose the rise is not so marked, but from the results obtained age does not appear to have any effect; the greatest rise being obtained in a child of 4 months. In all the cases except Nos. 10 and 15 the blood sugar had returned to the normal fasting level within one and a half hours after the ingestion of laevulose. In the two latter cases the blood

sugar/

sugar was tending to fall but unfortunately the result two hours after was not obtained.

For the purpose of comparison with the results obtained in pathological conditions an increase in the blood sugar of more than 30% has been taken as evidence of liver inefficiency; also the presence of a prolonged curve, the blood sugar not having returned to the normal fasting level within two hours.

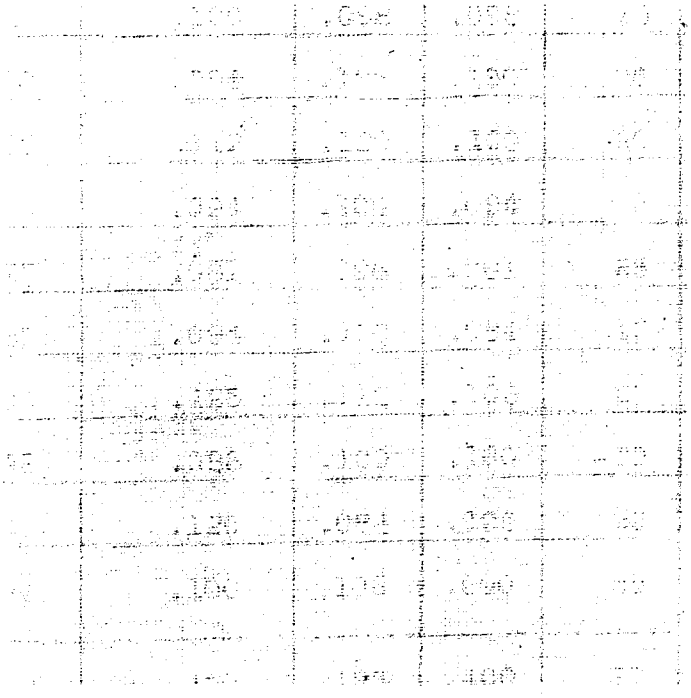


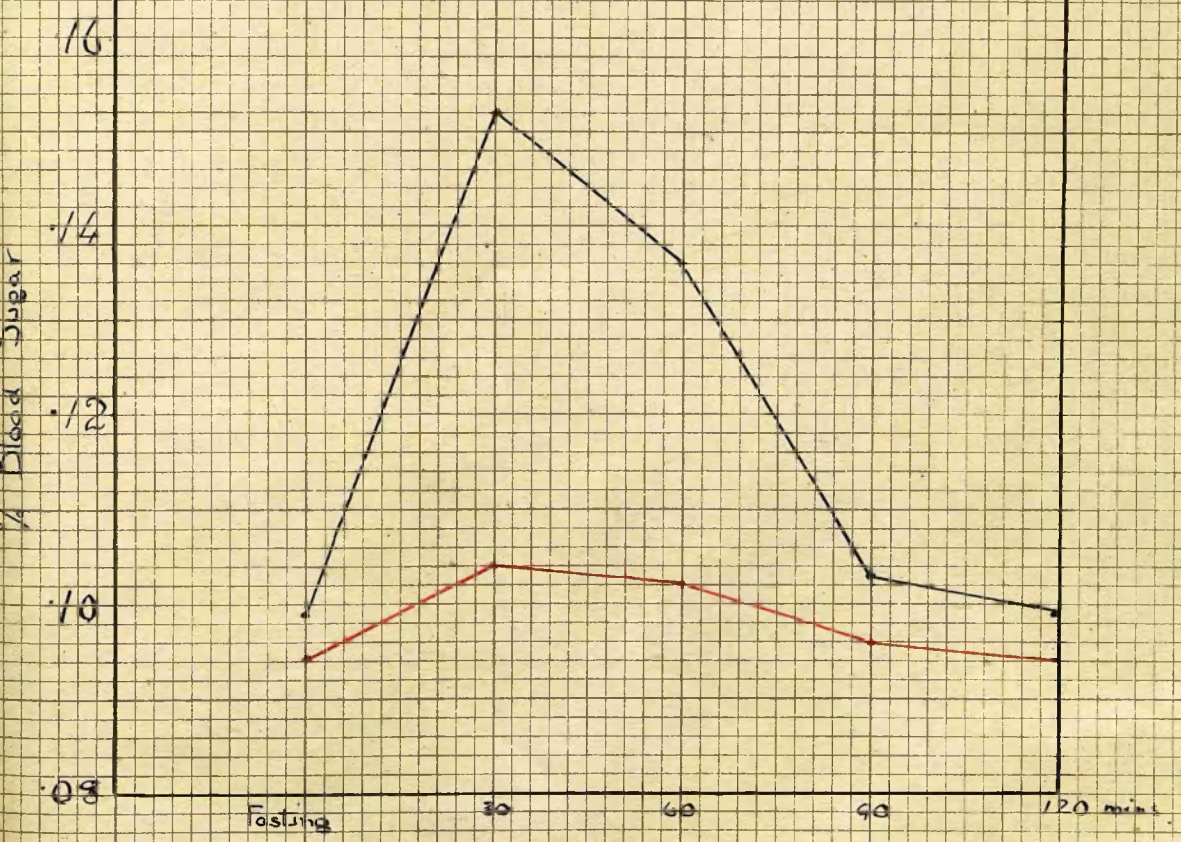
TABLE XVII.

The Sugar Content of the Blood after the ingestion of Laevulose in Normal Children.

Case No.	Age.	Fasting blood sugar.	½ hr. bl. sugar ½ hr. after.	1 hr after.	1½ hr. after.	% inc. in blood sugar.	Disease.
1	7 years.	.098	.112	.096	.106	13	Recuperated. Lobar Pneumonia.
2	7 years.	.106	.098	.112	.100	5	Recuperated. Lobar Pneumonia.
3	5 years.	.086	.098	.106	.084	23	Recuperated. Lobar Pneumonia.
4	8 years.	.106	.112	.094	.100	5	Recuperated. Lobar Pneumonia.
5	9 years.	.108	.112	.098	.100	5	Recuperated. Acute Rheumatism. No heart lesion.
6	8 years.	.086	.100	.098	.098	16	Epilepsy
7	7 years.	.100	.094	.126	.100	26	Epilepsy
8	12 years.	.100	.112	.120	.100	20	Epilepsy
9	5 weeks.	.100	.094	.100	.094	-6	Incorrect Feeding
10	4 months.	.075	.081	.096	.081	28	Incorrect Feeding.
11	3 months.	.088	.094	.100	.084	13	Dyspepsia. Vomiting stopped.
12	1½ yrs.	.100	.125	.112	.106	25	Unresolved Pneumonia.
13	3 years.	.098	.088	.100	.100	-10	Unresolved Pneumonia.
14	2 years.	.100	.120	.084	.106	20	Rickets.
15	5 years.	.084	.100	.106	.090	25	Recuperating. Acute rheumatism. No heart lesion.
16	10 years.	.098	.120	.125	.100	27	Epilepsy.
17	3 months.	.088	.094	.100	.084	14	Normal infant.
18	4 months.	.094	.108	.094	.094	15	Incorrect feeding.
19	11 yrs.	.100	.125	.112	.098	25	Recuperating. Acute rheumatism. No heart lesion.
20	8 mths.	.081	.094	.100	.080	23	Incorrect Feeding
	Average:-	.094	.104	.102	.096	15	

Chart X

The Average Blood Sugar Curve
in Normal Children
after Glucose — Black
after Laevulose — Red



The Laevulose Test in certain Pathological Conditions.

The laevulose test was applied to a series of pathological conditions in childhood and the results will be discussed under the following headings:-

1. Cases where there was definite clinical or pathological evidence of disease of the liver.

   (a) Catarrhal Jaundice. (b) Icterus Neonatorum.
   (b) Banti's Disease. (d) Hanot's Biliary Cirrhosis.
   (e) Multilobular Biliary Cirrhosis. (f) Congenital Syphilis.

2. Cases where there was some possible functional impairment of the liver as evidenced clinically or pathologically by enlargement of the liver.

   (a) Hodgkin's Disease. (b) Hepatomegaly.
   (c) ? Cirrhosis of Liver. (d) Cardiac Failure.

3. Cases where clinically there was no evidence of liver insufficiency but where from the nature of the illness some pathological lesion of the liver might be presumed to co-exist.

   (a) Acholuric Jaundice. (b) Wilson's Disease.
   (c) Gaucher's Disease. (d) Ketosis + Gastro-Enteritis.
   (e) Coeliac Disease.

The results obtained in the various conditions are given in Table XVIII, p.102.

I. Cases of Liver Disease.

(a) Catarrhal Jaundice.

Ten cases showing the clinical symptoms of this disease were examined; six of them being adults (Nos. 5 to 10) and four children (Nos. 1 to 4). If we now study the results obtained it will be seen that the rise in all the cases was much more marked than the normal rise and the fall also definitely delayed. In only two of the cases, Nos. 1 and 10, had the blood sugar returned to the normal fasting level within two hours after the ingestion of the laevulose. In case No.1 the jaundice had been present for two months before the test was performed and at the time of the examination it was fading though bile was still present in the urine. In case No.10 the jaundice was of short duration, was as marked as the other cases, and like them the test was performed during the acute stage of the disease, in fact all the adult cases were examined within a few days of the onset of the illness. On comparing the increase in the blood sugar with the severity of the illness no parallelism could be found. Case No.7 appeared clinically as severe as Case No.6, although the increase in the blood sugar in the former was 59% as compared with 85% in the latter. The test was repeated in cases Nos. 7 and 8, ten days after the first test, during a period when the jaundice was fading although still present to a slight degree and bile still present in the/

the urine. At this time a normal curve was found although previously a definite rise in the blood sugar with a prolonged fall had been obtained.

From these cases it would appear that there is definite impairment of the glycogen storing power of the liver at the height of the disease which passes off as recovery takes place. This confirms the work of Spence (83) who found a severe degree of liver inefficiency as evidenced by the laevulose test during the early stages of catarrhal jaundice, with a rapid recovery of the hepatic efficiency, in some cases even before the jaundice reached its height.

(b) Icterus Neonatorum.

It is now generally agreed that the jaundice in icterus neonatorum is hepatogenous in origin and not haematogenous but the negative curve obtained in the one case, No.11, examined by me does not reveal any evidence of liver damage.

This case, No.11, was a boy of 9 days whose grandfather and two other children of the family had had severe jaundice after birth. This child became jaundiced when 36 hours old and since then the jaundice has become much more severe. The spleen was just palpable at the C. margin. Liver 3 f.b. below c. margin. Urine:- Bile +. No urobilin. Motions slightly greenish in colour. The child ultimately got quite well and all the jaundice disappeared.

(c) Banti's Disease.

In this study I have applied the term "Banti's Disease" (splenic anaemia) to a group of cases in which the characteristic features were a progressive enlargement of the spleen, the occurrence of gastric haemorrhage and the presence of an anaemia of varying degree, of the so-called secondary type, associated with leukopenia. Clinical evidence of hepatic disturbance was noted in all the cases and the results of the functional tests are shown in Table XVIII, p.102.

Case No.12 is interesting as clinically the condition of the patient at the time of the test pointed to the last stage of Banti's Disease with the presence of cirrhosis of the liver and ascites; yet the laevulose test did not in any way reveal any impairment of the hepatic function. Unfortunately although the child died no post-mortem was obtained.

The other two cases both showed clinically impaired liver function and the positive laevulose test only helped to confirm the diagnosis. In case No. 14, although the percentage increase in the first test was not more marked than that obtained in the normal child, the return to the normal fasting level was delayed and this slow fall was also noted two weeks later, with at this time a more marked increase in the blood sugar content.

Case No.12.

Boy - 8 years - well till 3 months before admission when became pale and listless and 1/12 yr. later abdomen noticed to be swollen and complained of dyspnoea on exertion. For one month before admission feet noticed to be swollen.

On examination found to be a poorly nourished child with marked pallor of skin and mucous membrane. Oedema of feet and sacral region.

Heart - enlarged to right and left with loud V.S. murmur at pulmonic and mitral areas and conducted to axilla.

Lungs - nil.

Abdomen - free fluid present. Spleen 4 f.b. below c. margin.

Liver just palpable at c. margin.

W.R. Blood - Negative.

Marked anaemia with a leucopenia.

Fragility of R.B.C.'s normal.

Urine - nil.

Child died - no post-mortem.

Case No.13.

Boy - 8 years - when 9 months had diarrhoea and since then noticed to be pale and to bruise easily. Two days before admission struck on abdomen and after this complained of pain in abdomen with sickness and following day vomited blood.

On examination:- well nourished pale child with faint yellow colour of skin and several small ecchymoses on skin.

Heart - V.S. Murmur at pulmonic area.

Abdomen - small amount of free fluid. Liver $4\frac{1}{2}$ f.b. below c. margin at mid. line. Spleen $6\frac{1}{2}$ f.b. below c. margin.

W.R. - negative. Pirquet test - negative.

Blood - R.B.C.'s diminished. Hb. diminished. W.B.C.'s diminished. Fragility of R.B.C's normal.

Urine - no urobilin or bile.

Splenic puncture showed thickening of the fibrous tissues supporting the sinusoids, some hyperplasia of the endothelial cells lining the sinusoids and a fair number of eosinophils.

Case No.14.

Girl - 6 $^{3}/12$ yrs. Healthy till 6 months before admission when vomited blood and spleen found to be enlarged. After this apparently well till 3 weeks before admission when had diarrhoea and abdomen noticed to be getting larger and free fluid was present in abdomen which was tapped by doctor. Seemed to improve slightly after this. On examination on admission:- Fair sized child with slight icteroid tint of skin and pale mucous membrane. Heart - V.S.murmur heard all over pericardium.

Abdomen/

Abdomen - full but no free fluid detected. Spleen 4 f.b. below c. margin.
Liver not palpable.
Urine - no urobilin.
Blood - marked reduction of R.B.C.'s, W.B.C's and Hb.
W.R. blood negative. Pirquet test negative.
2 weeks after admission free fluid present in abdomen and urobilin at times present in urine. No bile.
Splenic puncture performed and several small pieces of splenic tissue which showedincrease of fibrous tissue in walls of sinuses and some hyperplasia of endothelium lining the sinuses obtained.

(d) Hanot's Monolobular Biliary Cirrhosis.

Two cases of this disease were examined and both were found to give definitely positive laevulose tests. This is what one would expect as pathologically this disease is characterised by an overgrowth of fibrous tissue enclosing small areas of liver tissue, the fibrous tissue sending strands into the lobules (mostly single lobules).

Case No. 15.

Boy - 1 $^{11}/_{12}$ yrs. Three months before admission noticed to be getting thinner and to be pale and listless. On admission he was a fair sized child with a big abdomen and icteroid tint of skin.
Heart - basal V.S. murmurs.
Abdomen. Liver 4½ f.b. below c. margin. Tip of spleen palpable. No free fluid.
Blood. Secondary anaemia.
Urine - Urobilin +, no bile.
W.R.Blood - negative. Pirquet - negative.
Fragility of R.B.C's. - normal.

Case No. 16.

Boy - 9 years. Complained of headache of 4 weeks' duration and abdomen swollen.
On examination:- Fair sized spare child. No evidence of jaundice. Veins of chest protuberant.
Heart - nil.
Abdomen - Liver smooth 3½ f.b. below c.m. Spleen not palpable. Urine - no bile.
W.R. blood - negative.

(e) Multilobular Biliary Cirrhosis.

The next case to come up for consideration is one of multilobular biliary cirrhosis of the liver with a Chronic Bronchiolectasis. The only clinical evidence of liver inefficiency until a few days before death was a much enlarged liver and the laevulose test here at an early stage revealed the presence of definite disease of the liver. The diagnosis in this case was doubtful. At first it was thought to be a tubercular condition of the lung with probably fatty changes in the liver causing the enlargement. The absence of tubercle bacilli in the sputum and the course of the disease questioned the diagnosis and the presence of a positive laevulose test pointed to a cirrhosis of the liver which was confirmed at the post-mortem when a multilobular cirrhosis of the liver was found.

Case No.17.

Boy - 2 3/12 yrs. Six weeks before admission became flushed and fevered and since then got much thinner.
On admission he was a small wasted irritable child.
Heart - nil.
Lungs - harsh R.M. and râle left base.
Abdomen. Liver 4 f.b. below c.m. Spleen not palpable.
X-ray of chest showed mottling ? T.b. lung. Pirquet and Monteau tests negative. Sputum neg. for tubercle bacilli.
W.R. negative.
Urine - nil.
Child seemed to do well and went to country branch for 3 months and on readmission had good colour.
Liver 2½ f.b. below c.m. Spleen not palpable.
X-ray of chest showed pseudo-mottling.
Urine - nil.
It was during this time that the liver tests were performed.

Child/

Child was dismissed improved but was readmitted 3 months later acutely ill with icteroid tinge of skin and cornea.

Abdomen - Liver $5\frac{1}{2}$ f.b. below c.m. Spleen 2 f.b. below c.m. No free fluid.

Urine - Urobilin +. No bile.

Child died a few hours after admission and on post-mortem examination there was found to be a chronic bronchiolectasis with a multilobular cirrhosis of the liver and pancreas.

(f) Congenital Syphilis.

Duzar and Hensch (84) obtained a positive laevulose test in all cases of congenital syphilis but it will be seen from my results that this definite statement cannot be made.

The blood sugar curve after the ingestion of laevulose was performed in two cases of this disease. Case No.18, which clinically showed evidences of congenital syphilis and where the Wassermann reaction of the blood was positive ++, gave a blood sugar curve which differed in no respect from that of the normal child, the actual rise being 18 mgms. or an increase over the fasting level of 28%. Pathologically the liver in this case showed intense venous congestion with a slight increase of fibrous tissue. Case No.19 clinically was diagnosed as one of broncho-pneumonia and congenital syphilis although the Wassermann reaction of the blood was negative. Nevertheless the clinical signs were sufficiently convincing to leave the diagnosis in little doubt, and the mother's Wassermann reaction was definitely positive. The child had undergone treatment before admission to hospital with mercurial inunction and grey powder. The blood sugar curve in this case showed an increase of 72% with a delayed fall/

fall, and the only pathological lesion found in the liver was fatty changes.

These results are difficult to interpret as one would have expected Case No.18 to show marked inefficiency for storing laevulose. Both children were acutely ill at the time of the examination and the question of the rate of absorption of the sugar from the alimentary tract must be taken into account, the laevulose being so slowly absorbed that no rise in the blood sugar would occur. Unfortunately the glucose tolerance test was not performed in these cases as this would have shown in a more marked degree the effect of absorption.

The following is a short resumé of the pathological findings in the two cases.

Case No.18.

Heart and lungs - nothing abnormal.
Liver showed intense venous congestion with slight increase of fibrous tissue.
Spleen - firm and congested.
Intestine - marked inflammation of the large intestine and lower part of the ileum. Scattered areas of enteritis in upper part of small intestine.

Case No.19.

Fatty degeneration of the heart muscles.
Broncho-pneumonia right lung upper lobe and left lung lower lobe.
Liver and kidneys show fatty changes.
Spleen enlarged and firm.

II. Cases of possible functional impairment of the liver as evidenced by enlargement of that organ.

(a) Hodgkin's Disease.

Although this is not a true disease of the liver, Rolleston (85) states that the liver is affected in 50% of all cases of the disease, though usually it is a post-mortem, not a clinical observation.

In the first case (No.20) examined, there was definite clinical evidence of a previous impairment of the liver function as evidenced by an attack of jaundice six months before admission to hospital and at the time of the examination the liver was enlarged with the presence of urobilin in the urine. The second case (no. 21) showed clinically slight yellowness of the skin with urobilin in the urine and pathologically the liver was found to be pale and scattered throughout with firm whitish foci which on histological examination suggested lymphadenoma - the tumour growth replacing the normal tissue.

Both cases showed an increased rise in the blood sugar after laevulose - the former an increase of 50% and the latter an increase of 37%. The blood sugar, however, returned to the normal fasting level within two hours.

Case No.20.

Girl - 10 6/12 years. 1 year before admission enlarged glands in neck noticed and since then child had been pale and listless and breathless on exertion. Six months later had an attack of jaundice with lasted 3 months and since then been very weak with attacks of diarrhoea and abdomen has become distended.

On/

On examination - much emaciated child with extreme pallor. Mass of glands in right side of neck and in left axilla. Gland in neck excised and showed the histological picture of lymphadenoma.

Heart - Lungs - normal.

Abdomen - Liver 3 f.b. below c.m. Spleen 5 f.b. below c.m. W.R.Blood - negative.

Urine:- Urobilin +. No bile.

Child died but no post-mortem was obtained.

Case No.21.

Boy - 5 years. Admitted with history of pallor and breathlessness of 1 year's duration.

On examination very pale child with slight yellowness of skin.

Heart and lungs - negative.

Abdomen - Liver not palpable. Spleen 2 f.b. below c.m.

Urine - Urobilin present.

Child went steadily downhill and developed generalised oedema with ascites.

On post-mortem examination the liver was pale and scattered throughout with firm whitish foci suggesting lymphadenoma.

Spleen much enlarged with similar foci, similar tissue also present in bone-marrow.

(b) Hepatomegaly and ? Cirrhosis of Liver.

In the following two cases the laevulose test was employed to find if the enlargement of the liver was of serious import. Passive congestion of the liver may cause marked enlargement without any damage to the liver cells, the hepatic vessels alone being much engorged. Portal fibrosis also may cause hypertrophy without any destruction of the liver cells, while in tumour growth or cirrhosis of the liver damage to the liver cells is almost certain to occur.

Case No.22 is interesting. Two weeks before admission to hospital there had been definite evidence of impairment of the liver function as evidenced by jaundice. At the time of the/

the examination the liver was slightly enlarged but there was no jaundice nor bile in the urine. This child had probably been having attacks of acute hepatitis and the laevulose test which was negative only confirms the results previously obtained in catarrhal jaundice that the laevulose test returns to the normal before clinically the condition is quite better. Unfortunately the child took no attacks while resident in hospital.

The second case, No. 23, which probably was one of cirrhosis of the liver, gave on the first examination a negative laevulose test and 9 months later when clinically the child appeared in the same condition a very definite positive result was obtained, a prolongation of the curve with an increase in the blood sugar of 35% being found. This is probably due to a gradual increase of damage to the liver cells, and instead of proliferation of the liver cells themselves occurring, they are replaced by connective tissue.

Case No.22.

Boy - 6 years. For past 2 years has been taking attacks of fever and abdominal pain with jaundice though motions normal in colour. Two weeks before admission to hospital had one of these attacks.

On examination:- Well nourished boy, no icteroid tint of skin.

Heart - nil. Lungs - nil.

Abdomen - Liver 3 f.b. below c.m. Spleen not palpable.

Urine - nil. W.R.blood - negative.

He remained well while in hospital and on dismissal liver only palpable at c. margin.

Case No.23.

Boy - 2 5/12 yrs. Admitted with history of delayed development and protuberant abdomen.
On examination - very small child, pale but no icteroid tint of skin.
Heart and lungs - normal.
Abdomen - protuberant and liver extends to iliac crest on right side and 4 f.b. below c.m. in left nipple line.
Spleen 1 f.b. below c.m.
Urine - urobilin. No bile.
W.R.Blood - negative.
Readmitted 9 months later when physical examination I.S.Q. and urobilin but no bile present in urine.

(c) Cardiac failure.

On account of the marked enlargement of the liver in this case it was thought worth while to perform the test, which on two occasions was found to be definitely positive, an increase of 34% and 42% respectively being obtained.

Case No.24.

Girl 3 9/12 yrs. Pallor and loss of weight and protuberant abdomen since 1 year old and 11 days before admission to hospital vomited blood.
Heart - systolic and presystolic murmur at apex, systolic being conducted to axilla and well heard at base.
Abdomen - Liver 5 f.b. below c.margin. Spleen 4 f.b. below c.margin.
Blood - secondary anaemia.
Urine - Alb. +, no bile.
Child died but no post-mortem was obtained.

III. Cases where there was no clinical evidence of Liver Disease.

(a) Acholuric Jaundice.

The characteristic features of this disease have recently been discussed by Tileston (86) and the following two cases which were characterised by chronic enlargement of the spleen with anaemia, increased fragility of the R.B.C's and/

and the presence of urobilin in the urine and bile in the faeces were examined. The jaundice in this disease is of extra-hepatic origin and no special changes have been observed pathologically in the liver or bile passage. One would therefore not expect any marked involvement of the liver.

A negative laevulose test was obtained in case No. 25 while case No.26 gave a positive result; the blood sugar after the ingestion of laevulose increased 36% and had not returned to the normal fasting level 2 hours later.

In both children splenectomy was performed and they were again seen 6 months after the operation when both on clinical examination appeared very well. One would have expected from the result of the laevulose test that the prognosis in case No.26 would be poor but so far this has not been substantiated.

The following is a short resumé of their case history.

Case No.25.

Girl - 10 years. Complained of pallor and listlessness of 2 years' duration accompanied by attacks of vomiting and diarrhoea.
On examination she was seen to be a very pale child.
Physical examination of lungs normal.
Heart dulness increased with the presence of haemic murmur.
Liver - 1 f.b. below c.m.
Spleen - 4 f.b. below c.m.
W.R. Blood - negative.
Increased fragility of R.B.C's.
Blood showed a secondary anaemia with a large number of nucleated red cells and marked anisocytosis.
Urine - negative. Faeces - bile obtained.

Case No.26.

Girl - 4 years. When 7 months old noticed to be pale. At 1 year had attack of severe diarrhoea and 6 months before admission to hospital urine noticed to be red in colour and this has appeared at intervals since;6 days before admission became very pale and listless.

On examination intense pallor of the skin and mucous membrane noted.

Heart - loud V.S. murmur at pulmonic area.
Lungs - nil.
Spleen 1 f.b. below c.m.
Liver 2 f.b. below c.m.
W.R.Blood - negative.

Blood showed a secondary anaemia with a few nucleated red cells.

Increased fragility of R.B.Ccs.
Urine - Urobilin +. Faeces - bile obtained.

Father of this child is definitely jaundiced with icteroid tinge of conjunctiva.

(b) Wilson's Disease.

Two children whose clinical condition pointed to a diagnosis of Wilson's disease were examined. This disease is characterised by a progressive degeneration of the lenticular nuclei with a cirrhosis of the liver. One case (No.27) was found to give a negative laevulose test, while the other (Case No.28) gave a definite increase in the blood sugar after the ingestion of laevulose. One would naturally think that the laevulose test would be positive in these cases if this test is to prove of any value, but Greenfield, Paynton and Walshe,(87) however, state that "the multilobular hepatic cirrhosis is clinically latent, and such function tests as have been performed have not sufficed to render its recognition possible during life of suspected cases."

The/

The following is a resumé of these two cases:-

Case No.27.

Girl - 10 years. Complained of tiredness of 3 months' duration with dragging of left leg for past 7 weeks and want of concentration. Gradual mental and physical slowness for 3 months.

On examination mask-like facies with aimless smile.
Generalised stiffness of legs.
Superficial and deep reflexes normal.
Abdomen - liver not palpable. Spleen 3 f.b. below c.m.
Urine - nil.
W.R.Blood - negative.

Case No.28.

Girl 12 2/12 years. When 5 years old took an illness characterised by nightmares, restlessness and sleeplessness at night and drowsiness during the day. After 9 months appeared perfectly well.

At 8½ years slight tremor of upper limbs noticed and this spread to head, body and legs. Tremor worse on voluntary movement and disappears during sleep. Later, loss of power in legs with difficulty in walking noticed. Speech has gradually become affected and after any length of time complains that words won't come and voice weakens.

On examination - Big girl, very slow in her movements. Apathetic expression with occasionally a slow smile across face. Movements all slow. Tremor of limbs more marked on voluntary movemet. Limbs spastic. Reflexes very active.
Abdominal reflexes present.
Pupils equal and react normally. Fundi normal.
Heart and lungs - normal.
Hepatic dulness 2" in nipple line.
W.R.Blood and C.S.Fluid negative.

(c) Gaucher's Disease.

Splenomegaly of the Gaucher type is of particular interest because it is considered as an example of an over-growth of the reticulo-endothelial cells which show a peculiar infiltration. The liver also participates in the change. Three cases in which on histological examination the spleen showed/

showed the characteristic cells of Gaucher's disease were examined. It will be seen from Table XVIII that the test did not in any way indicate impairment of the liver function. In Case No.30 the laevulose test was repeated one month later and a normal curve was again obtained.

A short resumé of their case histories is given below:-

Case No.29.

Girl - 10 years. Fourteen months before admission had ? pneumonia which was accompanied by jaundice of the skin and conjunctiva with dark coloured urine and pale motions. The pneumonia cleared up but the jaundice persisted. Since then has had two similar attacks.

On examination noted to be a fair-sized child with marked icterus of skin and conjunctivae.

Heart and lungs - normal.

Abdomen distended. Liver 2 f.b. below c.cm. Edge hard and irregular but not tender. Spleen 4 f.b. below c.m. stretching to level of umbilicus.

No free fluid in abdomen.

W.R.Blood - negative.

Urine - no bile. Urobilin ++.

Fragility of R.B.C's normal.

Splenectomy was performed but child died and no post-mortem was obtained.

Histological examination of spleen showed cells typical of Gaucher's Disease.

Case No.30.

Boy 5½ years. Complained of marked constipation and protuberant abdomen of 5 months' duration.

On examination - heart and lungs negative.

Spleen - 2 finger-breadths below the costal margin.

Liver - 2 finger-breadths below c. margin. No ascites.

W.R.Blood - negative. Urine - nil.

Fragility of R.B.C.'s - negative.

Blood count showed a secondary anaemia.

Spleen was punctured and cells typical of Gaucher's Disease found.

Splenectomy was performed and child was seen 6 months later and appeared very well.

Case No.31.

Boy 10 years. (Brother of Case No.30) - complained of pain in left side of abdomen of six months' duration with diarrhoea and shortness of breath.
On examination - child was a good colour, no jaundice.
Heart and lungs - normal.
Spleen - 8 f.b. below c.m.
Liver 4 f.b. below c.m. No ascites.
W.R. - negative. Urine - nil.
Splenectomy was performed and on histological examination spleen showed sinusoids lined with large cells with a reticulated appearance.

(d) Ketosis accompanying Gastro-Enteritis.

The ketone bodies, B-hydroxybutyric acid, aceto-acetic acid and acetone, which are produced by the dissimilation of one part of the fat bodies, are in the normal individual rapidly burned and broken up into H_2O and CO_2 in the presence of sufficient glucose to maintain combustion. It is a well-known fact that in a large majority of cases of toxaemia, ketonuria is found and this is due to partial deprivation of carbohydrate. If the hepatic function becomes deranged as a result of toxaemia the glycogen reserve becomes depleted and there may then be a failure to utilize the carbohydrate with a resultant ketosis. If this is the case one would expect to find some evidence of liver deficiency in all cases of toxaemia accompanied by ketonuria. On the other hand the ketonuria in these cases of toxaemia may be due to the fact that the liver receives the ketone substances in such a state that it is unable even normally to deal with them and they pass into the circulation and are eliminated by the kidneys and the expired air.

Tallerman (81) in twelve cases of ketosis accompanying infection found in the majority a high fasting blood sugar content with a definite rise in the blood sugar after laevulose of more than 30 mgms. This he took as an indication of derangement of the carbohydrate metabolism due to hepatic inadequacy.

These results I was unable to confirm in the four cases (Nos 32, 33, 34, and 35) of acute gastro-enteritis which were examined. They were all accompanied by vomiting, diarrhoea and fever with signs of intoxication and the presence of a considerable quantity of acetone in the urine. The maximum rise obtained in the blood sugar was 25% with a return to the normal fasting blood sugar level in all the cases one and a half hours after the ingestion of the laevulose.

(e) Coeliac Disease.

Although much prominence has been given by certain workers to the disturbed function of the liver in this disease it is evident from the three cases, Nos. 36, 37 and 38, examined that there is no defect in the glycogenic function of the liver.

TABLE XVIII.

The Sugar Content of the Blood after the Ingestion of Laevulose in Various Pathological Conditions.

Case No.	% of sugar in the blood. Fasting.	½ hr. after laev.	1 hr. after laev.	1½ hrs after laev.	2 hrs. after laev.	% inc. in blood sugar.	Disease.
1	.093	.132	.108	.098		41	Catarrhal Jaundice.
2	.100	.112	.154	.134	.125	54	" "
3	.098	.145	.160	.132	.112	63	" "
4	.084	.134	.130	.125	.112	59	" "
5	.100	.165	.150	.134	.112	65	" "
6	.084	.156	.134	.112	.125	85	" "
7	.098	.134	.156	.156	.148	59	" "
epeat 0 days ater.	.100	.125	.125	.118	.100	25	" "
8	.106	.168	.148	.152	.134	58	" "
0 days ater	.100	.112	.084	.092		12	" "
9	.118	.156	.162	.137	.132	37	" "
0	.106	.131	.125	.118	.100	23	" "
1	.130	.150	.125	.100		15	Icterus Neonatorum.
2	.112	.112	.108	.100		-4	Banti's Disease.
3	.134	.178	.162	.154	.150	32	Banti's Disease.
4	.115	.140	.137	.125	.120	21	" "
epeat	.118	.143	.156	.131	.136	32	" "
5	.081	.112	.137	.131		69	Hanot's Disease.
6	.100	.137	.130	.110	.100	37	Hanot's Disease.
7	.100	.131	.118	.116		31	Multilobular Cirrhosis of liver.
8	.064	.082	.075	.064		28	Congenital Syphilis.
9	.081	.112	.150	.132	.112	72	" "

Table continued next page.

TABLE XVIII(Continued).

Case No.	Fasting.	½ hr. after laev.	1 hr. after laev.	1½ hrs. after laev.	2 hrs. after laev.	% inc. in blood sugar.	Disease.
20	.112	.168	.156	.118	.106	50	Hodgkin's Disease.
21	.098	.135	.125	.096	.100	37	" "
22	.100	.108	.106	.100		8	Hepatomegaly.
23	.112	.125	.114	.112	.112	20	"
9/12 yr later.	.112	.152	.134	.125	.134	35	"
24	.112	.150	.125	.118	.112	34	"
1/52 yr later	.100	.142	.120	.100		42	"
25	.098	.126	.106	.096		28	Acholuric Jaundice.
26	.100	.125	.131	.136	.131	36	" "
27	.106	.100	.112	.094		5	Wilson's Disease.
28	.086	.118	.098	.086	.090	35	Wilson's Disease.
29	.112	.112	.136	.106	.112	21	Gaucher's Disease.
30	.100	.108	.100	.084		8	" "
1/12 yr later.	.100	.106	.098	.086		6	" "
31	.088	.076	.094	.106	.080	20	" "
32	.075	.094	.075	.081		25	Ketosis and Gastro-Enteritis.
33	.091	.085	.108	.094		19	Ketosis and Gastro-Enteritis.
34	.112	.126	.124	.106		8	Ketosis and Gastro-Enteritis.
35	.084	.098	.093	.084		16	Ketosis and Gastro-Enteritis.
36	.100	.106	.100	.098		6	Coeliac Disease.
37	.098	.106	.100	.100		8	" "
38	.087	.085	.094	.080		8	" "

DISCUSSION.

In carrying out the laevulose test in the apparently normal child I was impressed with the wide range of variation obtained in the blood sugar content after the ingestion of laevulose - a fall of 10% to an increase of 28% occurring. The blood sugar in all the cases, however, returned to the normal fasting level within two hours after the ingestion of the laevulose. Different factors must be taken into account in considering these variations and the share taken by the other parts of the body, such as the pancreas and the rate of absorption must be borne in mind.

Perhaps the most striking feature of the investigation in the pathological cases is the very marked rise in the blood sugar and the prolongation of the curve which was obtained in catarrhal jaundice. The height of the blood sugar, however, did not appear to bear any relationship to the severity of the illness and was of no value regarding prognosis; a normal blood sugar curve being obtained when clinically jaundice was still present with bile in the urine.

In Table XIX where the clinical findings and the results of the laevulose test are shown, the following points may be exemplified:-

Of 23 cases showing clinical evidence of impairment of the liver function as evidenced by enlargement of the liver with jaundice and the presence of bile or urobilin in the/

the urine, sixteen showed an increase in the blood sugar content of more than 30% and thirteen of these also showed a delay in the return of the blood sugar to the normal fasting level. In only one case, No.15, was a prolonged curve obtained without also showing an increase in the blood sugar content. In this case an increase in the blood sugar was obtained on the second examination.

Of the four cases in which a pathological lesion of the liver was obtained, three gave a definite positive laevulose curve while in the other the rise in the blood sugar was not greater than that obtained in the normal child and the fall was not delayed.

Of the three cases of Banti's disease which clinically gave evidence of hepatic cirrhosis, a positive curve after laevulose was obtaimed in two and a negative in one.

I do not think, therefore, that a negative test can be used to exclude the presence of changes in the liver. The reserve power of the liver is very large. It is possible for an animal to live on 30% of the normal amount of liver tissue. It is probably because of this that a negative result of a functional test in excluding liver disease has only limited value. On the other hand there were cases in which the question of liver dysfunction or actual liver disease was raised and in which a positive result to the ingestion of laevulose seemed to be of value and helped to confirm the diagnosis which was finally/

finally reached. The only clinical evidence of liver disease in cases Nos. 17 and 24, was enlargement of the liver. The laevulose test in both was positive and a repeat test on the latter when the child's general condition was worse gave a more marked rise than the first observation.

Although enlargement of the liver was obtained in the three cases of Gaucher's disease and a slight icteric tint of the skin with urobilinuria was also present in Case No.29, the laevulose tests did not reveal any evidence of liver inefficiency.

From these results I conclude that -

(1) a blood sugar curve similar to that obtained in the normal child may be obtained although clinically there is definite impairment of the liver function.

(2) if a positive curve is obtained, i.e., an increase in the blood sugar of more than 30% with or without a prolonged curve, it indicates definitely derangement of the liver function.

(3) the test has little or no value in unmasking a latent inefficiency.

(4) in the majority of cases the test merely corroborates the clinical evidence and is of no value in deciding the stage of the illness.

TABLE XIX.

: Crisis Test contrasted with the Clinical Findings.

Evidence Liver.	% inc. in blood sugar after laev.	Prolongation of Blood Sugar curve after laev.	Diagnosis	Result on Dismissal from hospital.
	41	-	Catarrhal Jaundice.	well.
	54	+	"	well.
	63	+	"	well.
	59	+	"	well.
	65	+	"	well.
	85	+	"	well.
	59	+	"	well.
	25	-	"	well.
	58	+	"	well.
	12	-	"	well.
	37	+	"	well.
	23	-	"	well.
	15	-	Icterus Neonatorum.	well.
	0	-	Banti's Disease.	died.
	52	+	"	I.S.Q.
	21	+	"	I.S.Q.
	32	+	"	"

XIX.(Continued).

al Evidence of liver.	% inc. in blood sugar after laev.	Prolongation of Blood Sugar curve after laev.	Diagnosis.	Resultion Dismissal from hospital.
	69	+	Hanot's Disease.	I.S.Q.
	37	-	"	Improved.
onchio- ar of	31	-	Multilobular Cirrhosis of liver.	Died.
nous of in- issue.	28	-	Congenital Syphilis.	Died.
ved ges.	72	+	Congenital Syphilis.	Died.
	50	-	Hodgkin's Disease.	Died.
e and t with foci g lym- .	37	-	Hodgkin's Disease.	Died.
	8	-	Hepatomegaly	Well.
	20	-	Hepatomegaly	I.S.Q.
	35			I.S.Q.

BLE XIX (Continued).

Evidence of liver.	% inc. in blood sugar after laev.	Prolongation of Blood Sugar curve after laev.	Diagnosis.	Result on Dis-missal from hospital.
	34	-	Hepatomegaly.	Died.
	42	-	"	"
	28	-	Acholuric Jaundice.	Well.
	36	-	Acholuric Jaundice.	Well.
	5	-	Wilson's Disease.	I.S.Q.
	35	-	Wilson's Disease.	I.S.Q.
	21	-	Gaucher's Disease.	Died.
	8	-	Gaucher's Disease.	Well (after operation.
	6	-	"	"
	20	-	Gaucher's Disease.	Well (after operation.
	25	-	Gastro Enteritis+Ketosis.	Well.
	19	-	"	Well.
	8	-	"	Well.
	16	-	"	Well.
	6	-	Coeliac Disease.	I.S.Q.
	8	-	"	Improved.
	8	-	"	Improved.

SUMMARY AND CONCLUSIONS.

The sugar content of the blood in 65 normal children whose age ranged from a few hours to 12 years was found to vary between .072% and .116%, giving an average of .099%.

A definite diminution in the blood sugar content could be demonstrated in the children under 6 weeks of age, but in the older children age did not appear to have any effect.

The nature of the diet did not appear to be responsible for the variations occurring in the normal child.

A very low carbohydrate diet, such as a ketogenic diet, caused only a very slight fall in the fasting blood sugar level.

No appreciable fall in the blood sugar was obtained in the one case which was starved 5 days.

In 35 cases of varying severity of malnutrition the blood sugar was found to vary between .072% and .116%. This variation was found to be due to the state of nutrition, the blood sugar rising steadily as the percentage of expected weight increased. Definite increase in the blood sugar was obtained in marasmic infants during the period of recovery. Vomiting *per se* causes a marked diminution in the blood sugar but diarrhoea did not appear to influence the blood sugar level.

In 30 normal children in whom the sugar tolerance test was performed, the blood sugar after the ingestion of 1 gm. of glucose/

glucose per kilo expected weight was found to rise to its height in 30 to 60 minutes, falling again to the fasting level within 1½ to 2 hours. The form of the curve appeared to be affected by the patient's age; a flatter curve being obtained the younger the child.

The sugar tolerance curve in marasmus was found to be identical to that obtained in normal infants of the same age although lying at a lower level; the rate and extent of rise and also the duration of the rise being parallel.

In three cases of pyloric stenosis examined a delayed rise in the blood sugar was obtained.

A hypoglycaemia with an increased sugar tolerance and a prolonged curve was obtained in all cases of cretinism and this increased carbohydrate tolerance still persisted after treatment with thyroid extract.

In hyperthyroidism the results of the sugar tolerance test were not consistent; a slightly delayed fall in the blood sugar being the only abnormality found in certain of the cases, while others showed a normal fasting blood sugar content with a diminished tolerance of carbohydrate.

The one case of possible Addison's disease which was examined showed a decreased carbohydrate tolerance which became more marked as the condition improved.

The diagnostic value of determinations of the sugar tolerance in pituitary disease does not appear to be of much value; the curves obtained in the cases of dwarfism being diverse/

diverse in their outline.

The sugar tolerance test was also performed after the ingestion of laevulose. It was found that in 20 normal cases getting 1 gm. per kilo of expected weight of Merck's laevulose, an average rise in the blood sugar content of 10 mgms. was obtained, the highest being 27 mgms., and the lowest a fall of 10 mgms., the blood sugar returning to the normal fasting level within two hours after the ingestion of the laevulose.

An increase in the blood sugar content after the ingestion of laevulose of more than 30% with or without a prolonged curve indicates definite derangement of the liver function. A normal blood sugar curve was obtained when clinically there was definite evidence of impairment of the liver function.

The laevulose test is therefore of assistance where there is marked liver damage but is of little or no value in milder hepatic dysfunction.

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