STUDIES OF CARBOHYDRATE TOLERANCE

IN

DISEASES OF CHILDREN:

THE INTRAVENOUS GLUCOSE TOLERANCE TEST

By

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PREFACE

The investigations upon which this thesis is based were conducted in the Department of Paediatrics, Glasgow University, and in the Wards and Biochemical Laboratory of the Royal Hospital for Sick Children, Glasgow, during the tenure of a Hall Tutorial Fellowship.

Part of the work has already been published in the Archives of Disease in Childhood, 1938, 13, 69, under the title of "A Standard Intravenous Glucose Tolerance Test," and in the Quarterly Journal of Medicine, 1939, N.S. 8, 251, under the title of "The Causation of the Low Blood-Sugar Curve in Coeliac Disease."

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S E C T I O N I

INTRODUCTION: CARBOHYDRATE TOLERANCE TESTS.

Abnormalities of carbohydrate metabolism have for many years been investigated by observing the effects of the administration of glucose; the capacity of the body to deal with this administered glucose has formed the basis of a great variety of so-called glucose tolerance tests. The evolution of these glucose tolerance tests can be traced through the following stages.

1. Tests depending upon the appearance of sugar in the urine following ingestion of glucose.

2. Tests depending upon the appearance of sugar in the urine after parenteral administration of glucose, usually by the intravenous route.

3. Tests in which the fluctuations of the blood-sugar are determined following ingestion of glucose.

4. Tests in which blood-sugar fluctuations are followed after parenteral glucose administration, usually by the intravenous route.

Tests depending on the Production of Glycosuria.

The appearance of sugary substances in the urine in cases of diabetes mellitus has been known since ancient times. It was only following the classical researches of Claude Bernard (1855), however, that clinicians and physiologists came to seek the appearance of glycosuria after the ingestion of sugar, as evidence of abnormal metabolic processes.

Worm-Müller in 1884 demonstrated in two healthy men, following a period on a diet poor in carbohydrate, that recognisable urinary excretion of sugar occurred after administration of 50 grams of glucose or of sucrose, or after 100 grams of lactose.

It is, however, to Hofmeister (1889) that credit must be given for the first detailed quantitative study of glucose tolerance. Working with dogs he found that there was a certain dose of glucose which could be administered and which would just fail to cause glycosuria, but any increase of which would immediately cause the appearance of reducing bodies in the urine. He termed this dose the Assimilation Limit ("Assimilationsgrenze") and showed it to be constant for the individual dog, though varying widely in different dogs.

Hofmeister introduced also the term Tolerance ("Toleranz") though he employed it somewhat differently from the way in which it has come subsequently to be used. Working with mild diabetic patients on a meat diet he found that a certain amount of carbohydrate could be added to the diet without causing glycosuria; greater quantities, however, resulted in sugar appearing in the urine. The amount which just fell short

of producing glycosuria he spoke of as the patient's tolerance for carbohydrate.

Following these workers clinicians came to apply this test for alimentary glycosuria in order to estimate the carbohydrate tolerance of their patients. Glycosuria following moderate dosage of glucose (100 to 200 grams) was regarded as indicating diminished tolerance, whereas failure to produce glycosuria with larger doses was taken as evidence that tolerance was increased. This procedure remained the standard clinical practice for many years.

Taylor and Hulton (1916) point out that "by common consent, rather than by accurate experimentation, the limit of assimilation of glucose on alimentary administration has been set at 200 to 250 grams, on the empty stomach. From this figure downwards the student of diabetes applies the test; from this figure upwards the student of the diseases of the ductless glands applies the test." Working on healthy medical students these investigators found, however, that the majority of individuals showed no limit of assimilation of glucose; glycosuria did not occur following even the largest possible ingestions of pure glucose (500 grams). These results confirmed the earlier findings of Woodyat, Sansum and Wilder (1915).

These were not, however, the first expressions of dissatisfaction with the alimentary glycosuria test of glucose tolerance. Linossier and Roque, in 1895, had proposed as a "coefficient of assimilability" the ratio of sugar excreted to sugar ingested, but the value was found to be inconstant.

Gilbert and Carnot (1898) showed that if doses of 2.5 to 10 grams of glucose per kilogram of body weight were given by intravenous injection, a more constant value for the ratio was obtained; but Doyon and Dufourt (1901) found that the ratio could be altered by varying the rate of injection.

This conception of carbohydrate tolerance as a matter of velocity rather than as an absolute weight of glucose assimilable was more strongly emphasized by Blumenthal in 1905. He declared that assimilability of glucose could only be accurately measured as weight of sugar assimilated per unit weight of tissue in unit time; and he also pointed out that when sugar is given by mouth the rate at which it is brought to the tissues cannot be gauged, as absorption from the bowel is a variable process. Accordingly, he evolved a test, the object of which was to ascertain the quantity of glucose which, injected repeatedly at fifteen-minute intervals, just failed to produce glycosuria. This quantity he termed the Utilisation Limit ("Ausnutzungsgrenze") and he found that for rabbits it lay between 0.6 and 1.2 grams of glucose per kilogram of body weight per hour.

Blumenthal's technique was followed by Comessatti (1906) who demonstrated that the Utilisation Limit was increased during exercise; and by Loeb and Staddler (1914) who repeated Blumenthal's observations, but obtained lower values - 0.36 to 0.64-gram of glucose per kilogram of body weight per hour - for the utilisation limit in resting rabbits. The method was not,

apparently, employed on human subjects; the difficulties in the way of its clinical application are self-evident.

Other procedures depending on the appearance of glycosuria following intravenously injected glucose were devised by different workers. McGuigan and Mathews (1907), using a 0.5 per cent. sugar solution, gave the injection at the rate of 5 c.c. every five minutes; the assimilability of the sugar, or the tolerance of the subject, was gauged by the time required for sugar to appear in the urine. This method again was inapplicable to clinical practice.

Physiologists, as distinct from clinicians, had investigated the effects of injected carbohydrate many years previously. This work is not reviewed in detail here as it has no direct bearing on the evolution of glucose tolerance tests; but one cannot pass over without mention the work of Lehman (1844) and Kersting (1844) who showed that glucose was better utilised than other carbohydrates after injection, and of Voit (1897) who made similar studies following subcutaneous injections of various carbohydrates in human subjects.

Pavy in 1899 published a report of a detailed investigation of the effects of intravenously and subcutaneously injected sugars and glycogen in rabbits. He studied the proportions excreted, and the forms in which the different sugars appeared in the urine; and he foreshadowed later work by making blood-sugar estimations, though this necessitated killing the animals, as his method required 30 c.c. of blood.

The most successful attempt to apply these methods to clinical practice was that of Woodyat, Sansum and Wilder (1915). They devised an apparatus including an accurately controlled electric pump, designed to deliver into the subject's vein 18 per cent. glucose solution at a constant measured rate. Every half-hour the rate of glucose injection was increased 0.1 gram per kilogram of body weight per hour, until glycosuria occurred. The immediately preceding rate was then accepted as the glucose tolerance limit. In the four normal subjects tested (Wilder and Sansum, 1917) the limit in each case was found to be 0.8 gram of glucose per kilogram of body weight per hour. Lower figures were obtained in cases of hyperthyroidism, pancreatic disease and acromegaly.

Though this procedure which Woodyat, Sansum and Wilder introduced, and the results which it yielded, were superior to any other tolerance test which depended on the appearance of glycosuria, it is not surprising that it never came to be widely used. Expensive and complicated apparatus was required, and the test was long and arduous for the patient. In addition, and of more basic importance, the introduction by Bang in 1913 of his method of blood-sugar estimation, had already started a slow but definite revolution in the methods of sugar tolerance assessment: the method of Woodyat, Sansum and Wilder was, in principle, out of date two years before it was introduced.

A few attempts were also made to assess glucose tolerance by the investigation of glycosuria following subcutaneous

injections of sugars (Voit, 1897; Pavy, 1899). Such a procedure had nothing to recommend it; control over absorption rate was not obtained, and a dangerous possibility of infection was introduced.

Tests depending on Blood-Sugar Fluctuations following Oral Glucose Administration.

In 1913 Bang (as mentioned above) introduced his micro-method for estimation of the blood-sugar content. Thereafter the emphasis gradually moved from the study of glycosuria to the study of glycaemia following glucose administration in the guaging of glucose tolerance. Numerous other methods of estimating the blood-sugar have been introduced since Bang's original procedure. Amongst those which have been most widely employed are the titrimetric methods of MacLean (1919) and Hagedorn and Jensen (1923) and the colorimetric method of Folin and Wu (1920).

Jacobsen (1913) was amongst the earliest investigators to adopt the new methods of glucose tolerance assessment. He studied the hyperglycaemia following various foodstuffs and found that after 100 to 150 grams of glucose, the blood-sugar level rose to 150 to 170 mg. per 100 c.c. without glycosuria occurring.

Hopkins (1915) employed a test dose of 100 grams of glucose dissolved in 420 c.c. of water. He observed that the greatest concentration of the blood-sugar was obtained in one-half to two hours in normal subjects, but was delayed until one-

and-a-half to three hours in diabetic patients. Hamman and Hirschman (1917) used a similar technique, but dissolved the 100 grams of glucose in 300 c.c. of water and gave a further 200 c.c. of water one half and one hour later. They noted that glycosuria did not occur unless the blood-sugar level exceeded 170 mg. per 100 c.c., a finding which was confirmed by Bailey (1919).

The penetration of the new methods into clinical practice was slow; as late as 1921 MacLean and de Wesselow wrote of the customary method of testing glucose tolerance being by examination for glycosuria following the oral administration of glucose. MacLean had already, in 1919, introduced his simpler and more reliable method of blood-sugar estimation, using only 0.2 c.c. of blood; and it was largely due to his efforts that blood-sugar studies came into general use in Great Britain in the assessment of glucose tolerance (MacLean, 1922).

MacLean's procedure was as follows: the patient fasted for four hours or longer and was then given 50 grams of glucose in 150 c.c. of water. Capillary blood was removed for sugar estimation before the glucose drink and at half-hourly intervals thereafter for two hours. Specimens of urine were obtained fasting and at one and two hours after the test dose, for examination for sugar.

The method remains essentially unchanged in routine clinical and insurance practice at the present day. It is now customary to employ a somewhat longer fasting-period, the overnight fast of eight to twelve hours being generally used. Many

workers also have modified the dosage of glucose in proportion to the body weight of the subject: thus Hagedorn (1921), Malmros (1928) and Soisalo (1930), working on adult patients, all employed a dose of one gram of glucose per kilogram of body weight, given as a 10 per cent. aequeous solution. This variation of glucose dosage with body weight is the usual method employed in children. Goetzky (1921) gave 2 to 3 grams of glucose per kilogram of body weight; Rumpf (1924) and Herlitz (1928), 1.3 gram; and Brown (1928) and Macrae and Morris (1931), one gram. Brown calculated the dose in terms of the correct weight of the child for its age, rather than from its actual weight.

Svensgaard (1931) employed a dose of 2 grams of glucose per kilogram of body weight in infants under one year of age, but for older children she reduced the dosage to 1.5 gram per kilogram of body weight. She stressed the importance of frequent blood sampling, and took specimens every five minutes for two-and-a-half hours in her investigations.

As already pointed out, these methods based on a study of the hyperglycaemia following the oral administration of glucose, remain the standard technique for the clinical investigation of glucose tolerance. While generally satisfactory for the differentiation of the various types of glycosuria, they are less suitable as a research weapon. Though the variable factor of the renal threshold for glucose is controlled, there is no control over the still more variable factor of rate of absorption of glucose from the bowel; and that this is of real

FIGURE I

Case 1. Two Oral Glucose Tolerance Tests at an interval of one week, under standard conditions. Age, 12 yrs.

Test of 23.10.36.

Test of 30.10.36.

importance has been demonstrated in a variety of ways. Beeler, Bryan, Cathcart and Fitz (1922) measured the glucose residue aspirated from the stomach and duodenum one hour after the administration of 100 grams of glucose. The amount of glucose recovered varied from 22 to 68 grams, indicating great variations in the amount of glucose absorbed during the hour.

Corresponding to this finding, results obtained with the oral glucose tolerance test show both a wide normal range and wide variations from time to time in the same individual even when the tests are performed without alteration in the controllable conditions. This variability has been studied especially by Svensgaard (1931) and her results have been confirmed in the present investigation (Figures I and II and Table I). Adults and older children subjected to the oral glucose tolerance test on two occasions usually gave fairly similar curves; but in a proportion of cases I have found wide variations within normal limits (Figure I). In young children such variations are more frequent, and Svensgaard has shown that in infants they appear to be the rule rather than the exception.

In these children and infants the variations may be very considerable, two curves on the same subject sometimes differing in the three important features of maximum level, time of maximum level and duration of hyperglycaemia (Figure II). In Table I are given the results of two oral glucose tolerance tests performed on each of five subjects of the present series, varying in age from four to thirteen years. In only one of these cases

TABLE I.

The results of two oral glucose tolerance tests on each of 5 cases. Interval between tests: 7-10 days. Dose of glucose: one gm. per kg. body wt.

CASE	1			2			3			4			5		
Age: years			13½			4			7			10			6½
	a	b	c	a	b	c	a	b	c	a	b	c	a	b	c
Fasting	77	68	9	69	73	4	86	72	14	86	80	6	71	74	3
20 Minutes	114	109	5	-	-	-	-	-	-	-	-	-	-	-	-
30 "	-	-	-	87	81	6	188	111	77	131	141	10	110	131	21
40 "	154	140	14	-	-	-	-	-	-	-	-	-	-	-	-
1 Hour	166	123	43	167	138	29	172	145	37	120	123	3	107	148	41
1½ Hours	158	86	72	150	121	29	154	143	11	101	98	3	60	126	66
2 "	67	71	4	78	108	30	108	84	24	96	88	8	54	101	47

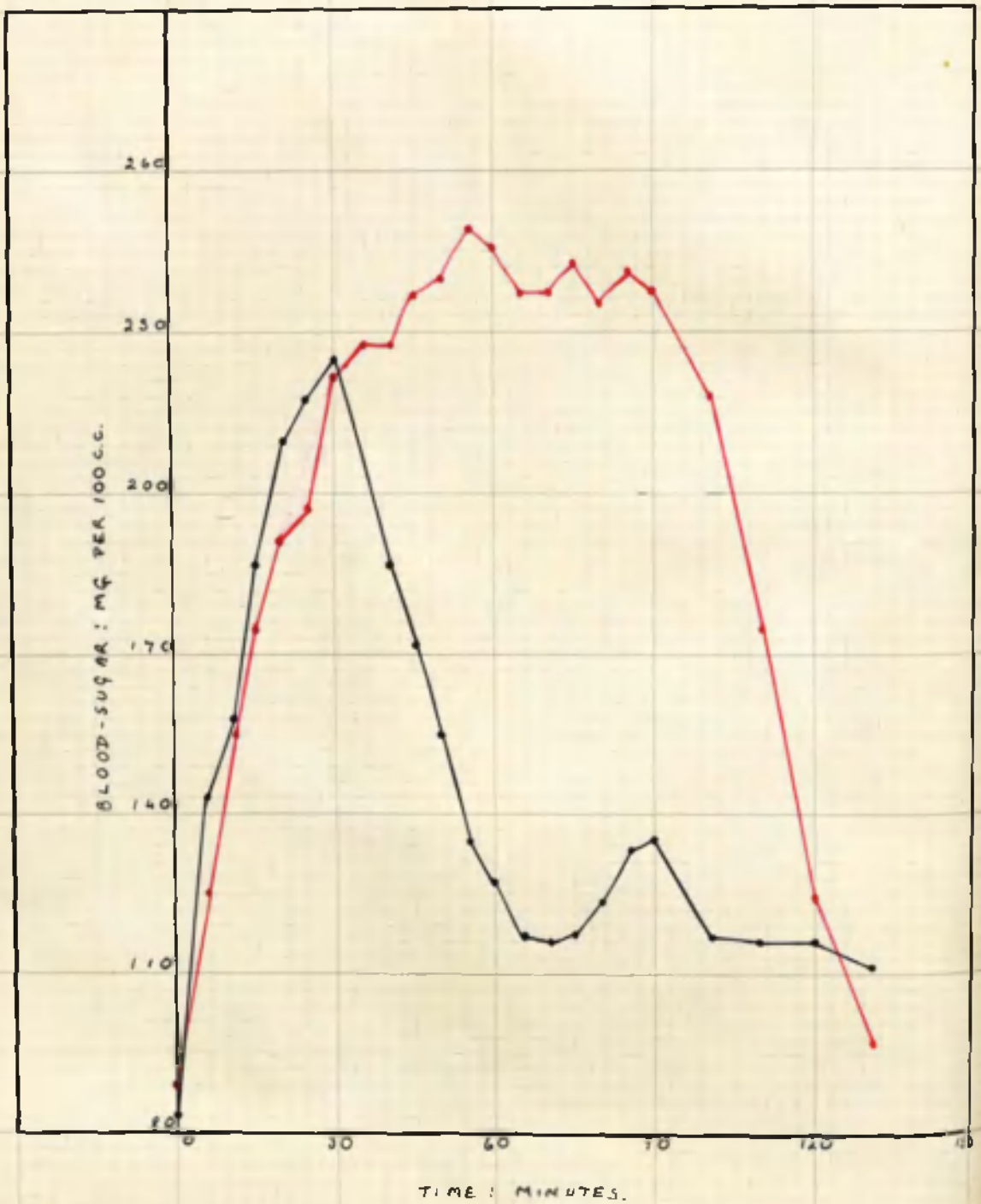
a = First test. Blood-sugar levels in mgm. per 100 c.c.
b = Second test. " " " " " " " "
c = Difference between corresponding readings in mgm. per 100 c.c.

FIGURE III

From Svensgaard(1931). Two Oral Glucose Tolerance Tests on an infant. 2.0 gm. glucose per kg. body wt.

——— Test at age 9 months 22 days.

——— Test at age 9 months 28 days.



(Case 4) were closely similar figures obtained at the two tests.

A typical result of one of Svensgaard's experiments on infants (1931) is shown in Figure III: here the variation between the two curves is enormous.

It would therefore appear that even with standardized external conditions the state of the alimentary canal itself cannot be so regulated as to produce a consistent rate of absorption.

In view of these facts it is evident that any conclusions based on slight variations in the blood-sugar curve following oral glucose administration must be guarded. Also it must be borne in mind that unusual results with this test may be the result of abnormalities of absorption rather than abnormalities of the intermediary metabolism itself. Thus a low blood-sugar curve is generally interpreted as indicating increased carbohydrate tolerance; but it may also occur in conditions of delayed or deficient absorption from the bowel. Similarly, a curve rising to abnormally high levels, though regarded as evidence of defective tolerance, can be produced by unusually rapid emptying of the stomach and absorption from the bowel, as may occur in patients with a gastroenterostomy (Lawrence, 1936).

Tests depending on Blood-Sugar Fluctuations following Parenteral Glucose Administration.

Just as the older workers quoted above had become dissatisfied with tolerance tests depending on the appearance of sugar in the urine after glucose ingestion, and had turned to methods in which the glucose was injected intravenously, so, in more recent times, certain workers have studied the blood-sugar curve following glucose administration by the intravenous route. By this procedure the variable factor of absorption from the gut is excluded, so that the factors tested are the rates of utilisation, storage and excretion.

First use of this method was made by Thannhauser and Pfitzer as long ago as 1913. They gave an injection of 500 c.c. of a 7 per cent. glucose solution over a fifteen-minute period, and noted the time after the conclusion of the injection at which normal fasting blood-sugar levels were regained. In normal subjects this required about fifteen minutes, the time being greatly prolonged in cases of liver disease and in diabetes.

Since then a variety of similar procedures has been employed by several workers for the testing of glucose tolerance. The methods used have varied in dosage of glucose given, concentration of and solvent for the glucose solution, rate of injection, frequency of sampling for the blood-sugar estimations, source of blood used for the estimations (capillary or venous)

TABLE II.

Intravenous Glucose Tolerance Tests.

Author	Year of Publication	Dose of Glucose: Grams	Strength of Solution per cent.	Injection time	Frequency of Blood-sampling: Minute intervals
Thannhauser & Pfitzer	1913	35	7	15 mins.	5
Allen & Wishart	1920	1-1.5 g. per kg. body wt.	10-20	-	20
Nonnenbruch & Szyszka	1920	30-60	15-30	10-55 mins.	10-30
Beumer	1921	0.8-3 g. per kg. body wt.	25-70	50-80 secs.	1-20
Niemeyer	1922	40	20	10 mins.	10-30
Titus & Givens	1922	25	15	30 mins.	5-30
Jörgensen & Plum	1922	20	40	2-3 mins.	2-10
Rigler and Ulrich	1923	0.3-1 g. per kg. body wt.	20	10-30 mins.	5-30
Rosenberg	1923	100	33	10 mins.	30
Tisdall, Drake & Brown	1925	1 g. per kg. body wt.	10	Variable	30
Davidson & Allen	1925	25	25	10 mins.	15-30
Lennox	1927	0.3 g. per kg. body wt.	20	20 c.c. per min.	15-30
Rowe & Rodgers	1927	0.3 g. per kg. body wt.	50	8-10 mins.	10-30
Schwentker & Noel	1930	10-20	-	-	10-60
Torning	1932	Jörgensen's technique (1922)			
Thaysen	1932	" " "			
Rost	1932	8	40	-	5-30
Begg & Harries	1935	20	50	-	10-30
McKean, Myers & Van der Heide	1935	0.2 g. per kg. body wt.	50	1½ mins.	1-5
Fairley	1936	50	-	10 mins.	10
Nussbrecher & Morton	1937	10	5	15	10-30
Mogensen	1937	Jörgensen's technique (1922)			
Fikri & Ghalioungui	1937	0.3 g. per kg. body wt.	-	-	-
Ross	1938	5-20	20	1-3 mins.	2-10
Wilson	1939	Ross's technique (1938)			
Allibone & Tunbridge	1939	25-30	-	3 mins	3-5

and the actual manner of interpreting the results obtained. In Table II there have been summarised the essential features of the procedures employed by some of the workers who have used intravenous glucose tolerance tests.

Typical examples are the methods used by Jörgensen and Plum (1922), McKean, Myers and Van der Heide (1935) and Ross (1936, 1938).

Jörgensen and Plum, using the test for the differentiation of benign and "malignant" glycosurias, employed a constant dosage of 20 grams of glucose in 50 c.c. of sterile water injected in two to three minutes. Capillary blood-sugar estimations were made every two to three minutes for fifteen minutes and subsequently every five to ten minutes for one-and-a-half to three hours. For the interpretation of the results obtained, Jörgensen in 1926 introduced the "Loading Figure" - the sum of the area (in square centimetres) of the curve above the fasting level and the time in minutes for the fasting level to be restored.

The fixed dosage which these workers employed is unsuitable for use in children: an infant weighing 5 kg. and having a blood volume in the region of 400 c.c. can hardly be subjected to the same size of injection as a child of twelve years of age with a blood volume of between three and four litres, if the resulting curves are to be comparable.

The use of distilled water as solvent for the glucose has, in our experience, proved less satisfactory than physiological saline. In comparing the effects of glucose injections using the two media, nausea and vomiting were more common and the blood-sugar level more erratic when pure water was the solvent. Finally, the introduction of such a mixed and

artificial factor as Jörgensen's "Loading Figure" seems undesirable. The technique of Jörgensen and Plum has been followed by Torning (1932), Thaysen (1932) and Mogensen (1937).

McKean, Myers and Van der Heide (1935) introduced a procedure which they termed "The Micro-interval Technique." One-fifth of a gram of glucose per kilogram of body weight was injected as a 50 per cent. solution in water, the period of injection occupying one-and-a-half minutes. A needle was then introduced into a vein of the opposite arm and left in position for the remainder of the test, and blood was aspirated for sugar estimation three, four, five, ten and fifteen minutes after the end of the injection. The diagnostic criteria of the blood-sugar curve obtained with this technique were stated to be: (a) the height of the peak point; 175 mg. per 100 c.c. or less was regarded as normal: (b) the fifteen-minute blood-sugar level - 125 mg. per cent. or less in the normal subjects. This technique has much to recommend it. The rapid introduction of the total dose of glucose into the blood stream cuts out completely the absorptive period, while the ease and rapidity with which the whole test is completed gives it added value for routine and diagnostic purposes. The procedure has not, however, been adopted in the present investigations for the following reasons:

1. The dose of glucose employed is too small. While large enough to unmask the faulty metabolism of the severe diabetic, it is inadequate to tax an intermediary mechanism which is less grossly abnormal.

The authors themselves point out that there is considerable overlapping between normal subjects and mildly diabetic patients. Similarly, the hyperglycaemia produced by this small dose of glucose is too transient in the normal subject to allow of any clear-cut difference when the intermediary mechanism is more active than normal.

2. The injection of a 50 per cent. glucose solution in water has, in our hands, caused frequent reactions (nausea, elevation of temperature, powerful diuresis).
3. The use of venous blood for the sugar estimations introduces a further complication and seems undesirable, for it has been shown by Himsworth (1933) that the arterio-venous blood-sugar difference undergoes wide fluctuations after the injection of glucose.

Ross (1936, 1938), working with children, has used a technique similar to that introduced by Jorgensen and Plum, but with certain modifications. The dosage of glucose which he employed was 5 grams with children of less than 10 kilograms in weight, 10 grams when the weight was between 10 and 20 kilograms and 20 grams for heavier children. He gave the injection as a 20 per cent. solution in normal saline; cutting down over a vein using a local anaesthetic, and inserting a blunt cannula is recommended, the fluid being allowed to gravitate into the vein.

His injection times varied from one to four minutes, an attempt being made to run the fluid in in one minute if possible. Capillary blood specimens were taken fasting and at two, four, six, eight, ten, fifteen, twenty, thirty, forty, fifty and sixty minutes after the injection, though Ross points out that "such frequent sampling is unnecessary when familiarity with the test has been attained." The blood-sugar estimations were made with an ultramicro method described by Rappaport and Pistiner (1934) using a minute amount of blood - 0.02-c.cm. Ross's technique has been followed by Wilson of Vancouver (1939), working on liver diseases. This method of tolerance estimation has been regarded as unsatisfactory for the following reasons:

1. A strict body weight basis for the glucose dosage is not observed. The grounds upon which this objection is based have been mentioned above and are further elaborated in succeeding sections of this thesis.
2. The complicated procedure of exposing a vein and introducing a cannula under local anaesthesia seems unnecessary and perhaps even unjustifiable. In addition, it precludes the possibility of carrying out a considerable number of tests on one subject as the number of accessible veins is limited. It seems likely that such an operation in a nervous patient would cause more upset than the introduction of a sharp, fine-

bore needle directly into a superficial vein (a procedure which Ross condemns).

3. The use of gravity as the injecting force does not permit of precise timing of the injection.
4. The use of such a minute amount of blood (0.02 c.c.) for the sugar estimation introduces an unnecessary risk of inaccuracy; there is never any difficulty in obtaining 0.1 to 0.2 c.c. of blood for the standard micro-methods.

THE PRESENT INVESTIGATIONS

The present investigations were initiated in an endeavour to determine the origin of the abnormal oral blood-sugar tolerance curves known to occur in certain diseases of childhood; in short, to determine whether these abnormal curves were associated with an abnormality of absorption of glucose from the bowel, or were dependent upon alterations of the intermediary metabolism itself. The use of an intravenous glucose tolerance test seemed to offer the most direct approach to the problem; but, as pointed out in the preceding pages, no completely satisfactory test has been found in a perusal of the earlier work on the subject. It was therefore necessary to devise a suitable standard intravenous glucose tolerance test applicable at all ages, and to determine the normal range and constancy of the curves obtained and what constituted a significant variation in any particular case.

These matters form the subject of the succeeding section.

S E C T I O N II

A STANDARD INTRAVENOUS GLUCOSE TOLERANCE TEST

Introduction.

In devising a standard intravenous glucose tolerance test which would be applicable at all ages, a variety of considerations had to be borne in mind and a number of conditions fulfilled.

Firstly, for reasons which have already been mentioned, variation of the glucose dosage with the size of the patient was considered essential. The theoretical ideal would be to vary the dosage in proportion to the amount of the patient's active metabolic tissue, but for practical purposes the body weight was regarded as providing a sufficiently close standard for adjusting the glucose dose. It has been established by Benedict and Talbot (1921) that in young children the basal metabolism varies directly with the body weight. In the interests of the simplicity and general applicability of the test it was thought undesirable to introduce a function of the patient's surface area in the determination of the dose of glucose. Secondly, the glucose dosage must be sufficient to tax the intermediary carbohydrate metabolism and to unmask even mild degrees of impaired tolerance. Too small a dose of glucose produces so

transient a hyperglycaemia in the normal subject that the recognition of increased tolerance is impossible. On the other hand the dosage of glucose should not be so great as to produce a long-drawn-out unwieldy test, at once uncomfortable to the patient and inconvenient to the investigator. Thirdly, the glucose should be injected in the form in which it produces fewest side-effects and the least general disturbance. Too concentrated a solution gives rise to an upset of osmotic relationships in the blood and tissues, while the use of a very dilute solution necessitates a bulky injection, with corresponding disturbances of the blood volume. The use of distilled water for the glucose solution is physiologically unsound, 0.9 per cent. sodium chloride being a more suitable medium. Though the addition of glucose to this leads to a hypertonic solution, the ionic concentration is similar to that of the blood into which it is to be injected. Fourthly, the actual injection should be made in such a way as to occasion a minimum of discomfort to the patient and, at the same time, allow exact control over the rate of the injection. The injection rate should be neither so fast as to risk embarrassment to the right side of the heart, nor so slow as to make the injection wearisome, and to add a considerable "absorptive period" to the test. In short, it is desirable to create a maximum hyperglycaemia in as brief a time as is convenient, the actual time being standardised. Finally, the samples of capillary blood for sugar estimation must be taken sufficiently frequently to allow of

accurate charting of the blood-sugar curve and the detection of minor changes of tolerance. Unnecessarily frequent sampling, adding discomfort to the patient and labour to the test, is to be avoided.

To summarise the desiderata of the ideal intravenous glucose tolerance test it may be said that it should combine simplicity, to allow of routine clinical application, with accuracy sufficient for research purposes; it should yield a maximum of information with a minimum of inconvenience to the patient.

Technique of the Test.

Fasting period: The actual duration of the fasting period prior to the performance of an intravenous glucose tolerance test is probably of little importance provided that a sufficient period has elapsed since the preceding ingestion of food to allow the blood-sugar to regain a fasting level. After an ordinary mixed meal this usually occurs in four to five hours and beyond this period the actual fasting time is quite arbitrary. It should, however, be constant throughout any series of investigations. For the purposes of the present study a fasting period of eight hours was found satisfactory and convenient, and it was strictly adhered to throughout. During the eight-hour fast, though no food whatsoever was allowed, the subject was permitted to drink as much water as desired. When a series of tests is to be made on one subject, or when it is

FIGURE IV.

Case 6, male, age 12 yrs. Blood-sugar curves following intravenous injections of varying doses of glucose.

1.0 Gm. per kg. body wt.

0.5 Gm. per kg. body wt.

0.3 Gm. per kg. body wt.

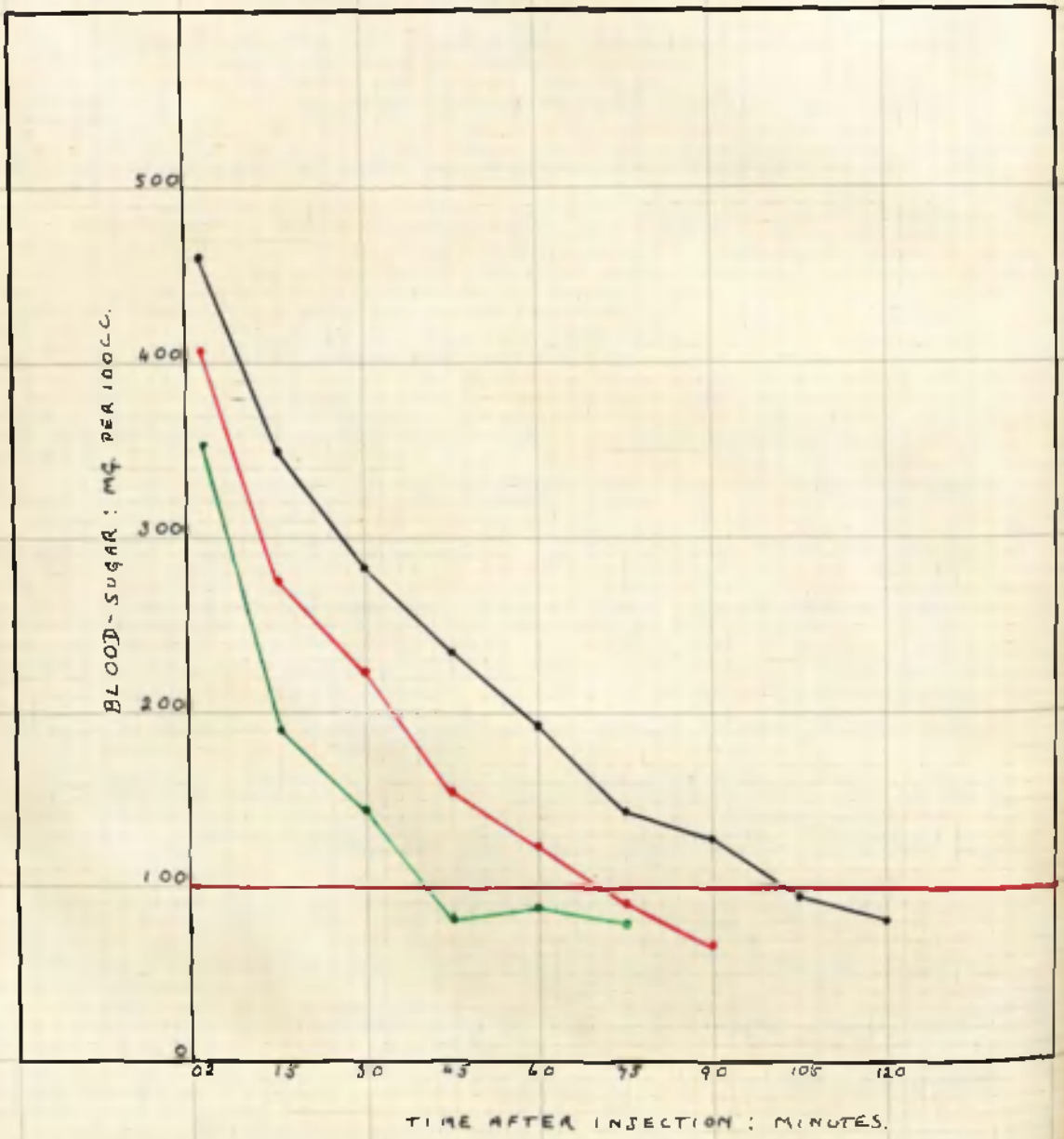
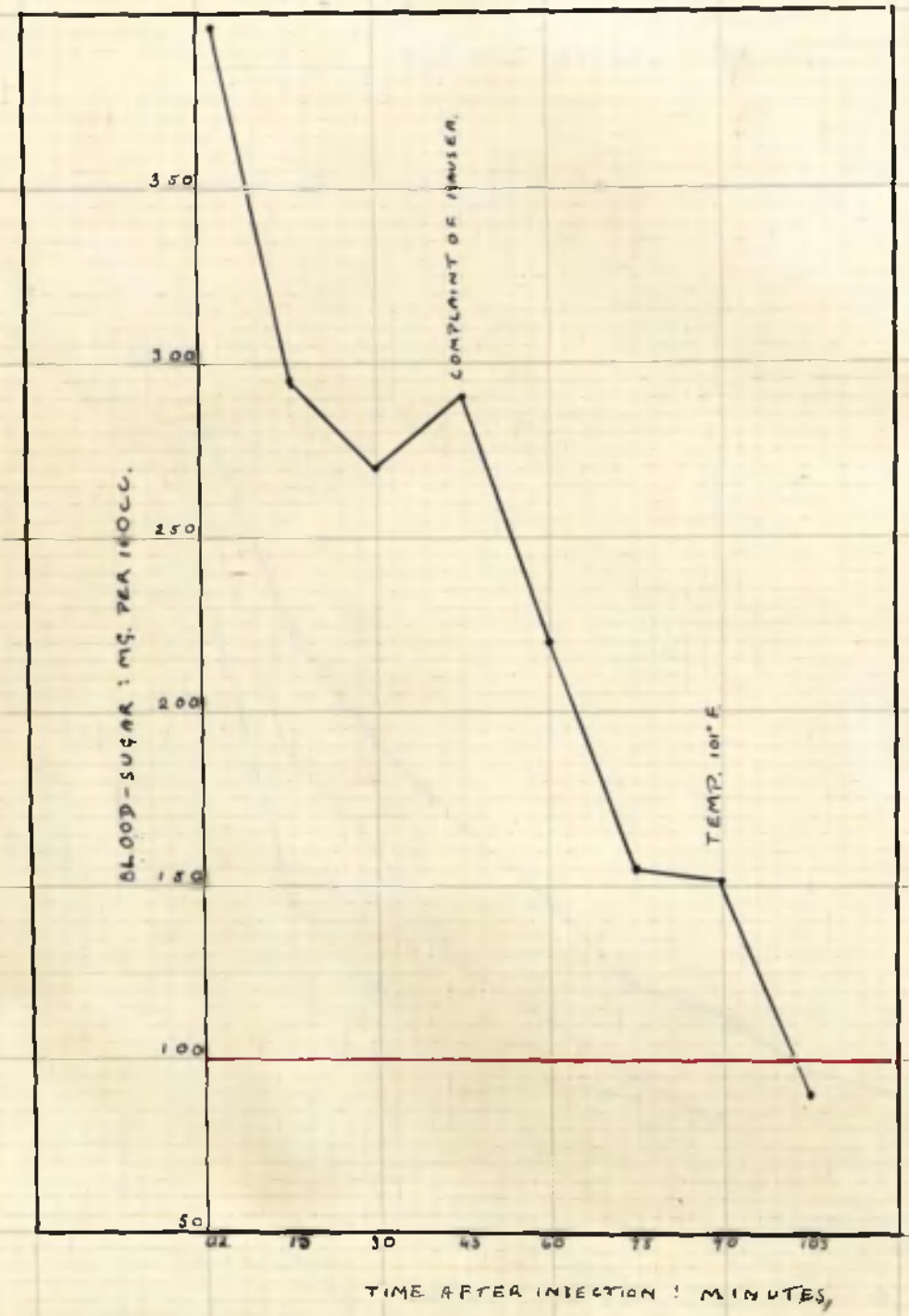


FIGURE V.

Case 7, male, age 14 yrs. Wt. 40 kg. Intravenous injection of 20 gm. glucose in 100 c.c. distilled water.



desirable that tests on different subjects should be strictly comparable, it is advisable that the tests be made always at the same time of day. Except for acute cases, the tests of the present investigations were all commenced at 2.15 p.m., the patient having fasted since breakfast at 6 a.m.

Glucose Dosage: The effects of varying doses of glucose were investigated in an attempt to determine the most satisfactory quantity for routine use. In Figure IV are illustrated the results of injecting 1.0 gram, 0.5-gram, and 0.3-gram of glucose per kilogram of body weight. Using 1.0 gram per kilogram of body weight, the fall of the blood-sugar to fasting levels was delayed until one-and-three-quarter hours after the injection, so that it would be necessary to continue the blood-sampling for two to two-and-a-half hours in order to establish a delayed fall. With 0.5-gram per kilogram of body weight, the fall occurred seventy-five minutes after the injection, and with 0.3-gram it occurred at forty-five minutes. As the use of 0.3-gram of glucose per kilogram of body weight would have involved very small actual dosage in underweight infants, the 0.5-gram dose was selected and was adhered to throughout the investigations.

Injection Medium: Only one injection was made in which the glucose was dissolved in pure distilled water. This injection was associated with some nausea and a mild febrile reaction, and there was some irregularity of the blood-sugar curve (Figure V). While it is unjustifiable to draw conclusions

FIGURE VI.

The Simple Apparatus employed for the Intravenous Injections.

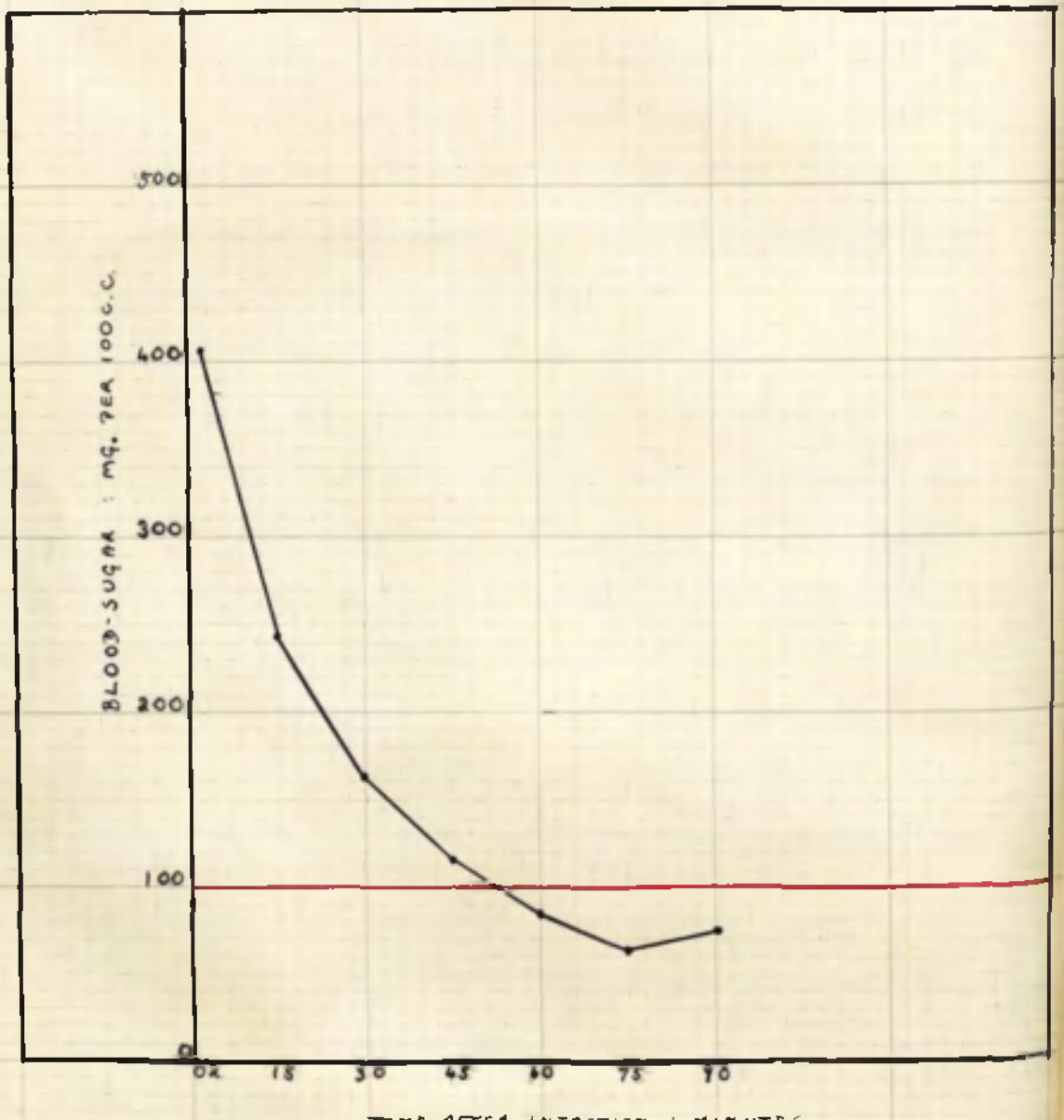
from this single case, the use of physiological saline as the solvent seems sounder, and in only one case (an adult) was any febrile reaction observed when it was employed. On account of the known tissue-dehydrating effect of an intravenous injection of 50 per cent. glucose it was thought inadvisable to employ a solution of this concentration. The use of the usual 10 per cent. solution, however, involved the injection of rather large amounts of fluid (200 c.c. to a child weighing 40 kilograms), so that a 20 per cent. solution was tried and gave satisfactory results. The glucose was thus given as a 20 per cent. solution in 0.9 per cent. sodium chloride throughout these experiments. The solution was sterilised by boiling for twenty minutes.

The Injection: The simplest method of giving an intravenous injection is by direct puncture of a superficial vein through the skin, using a sharp fine-bore needle. It is only on rare occasions that a satisfactory vein cannot be entered by one experienced in the procedure, and this method was employed almost exclusively in these investigations. Twice, in obese subjects, it was necessary to expose a vein at the ankle; and in a few instances in infants the injections were made into the superior longitudinal sinus. A 20 c.c. syringe was employed for the injections and was fitted with a two-way stop-cock, the side-arm of which was connected by means of fine rubber tubing to the glucose reservoir. This simple apparatus, illustrated in Figure VI, allowed accurate timing of the rate of injection. A suitable rate was found to be obtained by allowing forty-five seconds for

FIGURE VII

Case 8. Female, age 7 yrs. Wt. 20 kg.

Normal Intravenous Glucose Tolerance Curve.



glucose.

Summary of technique of test: The patient has no food for eight hours prior to the test, but may be allowed water to drink. A specimen of capillary blood is removed, the bladder is emptied, and then the injection is given by direct puncture of a superficial vein. The dose of glucose used is 0.5-gram per kilogram of body weight and it is given as a 20 per cent. solution in 0.9 per cent. sodium chloride. By using a syringe for the injection the rate is accurately timed, forty-five seconds being allowed for each 20 c.c. Capillary blood specimens are removed two minutes after the conclusion of the injection and at fifteen-minute intervals for an hour-and-a-half. A final specimen of urine is taken at the end of the test.

Characteristics of the Normal Curve.

The features of a typical curve in a subject with normal carbohydrate metabolism are illustrated in Figure VII, and in Table III the results are recorded of intravenous tests on forty-four subjects who were regarded as normal as far as carbohydrate metabolism was concerned. Thirty-eight of the subjects were children many weeks convalescent from various ailments not associated with disturbance of carbohydrate metabolism, for example, enlarged tonsils, rheumatism, enuresis; the remainder were healthy, active subjects. In none of the convalescent cases was the test performed until all signs of active disease had subsided and the erythrocyte sedimentation rate was within

Table III.

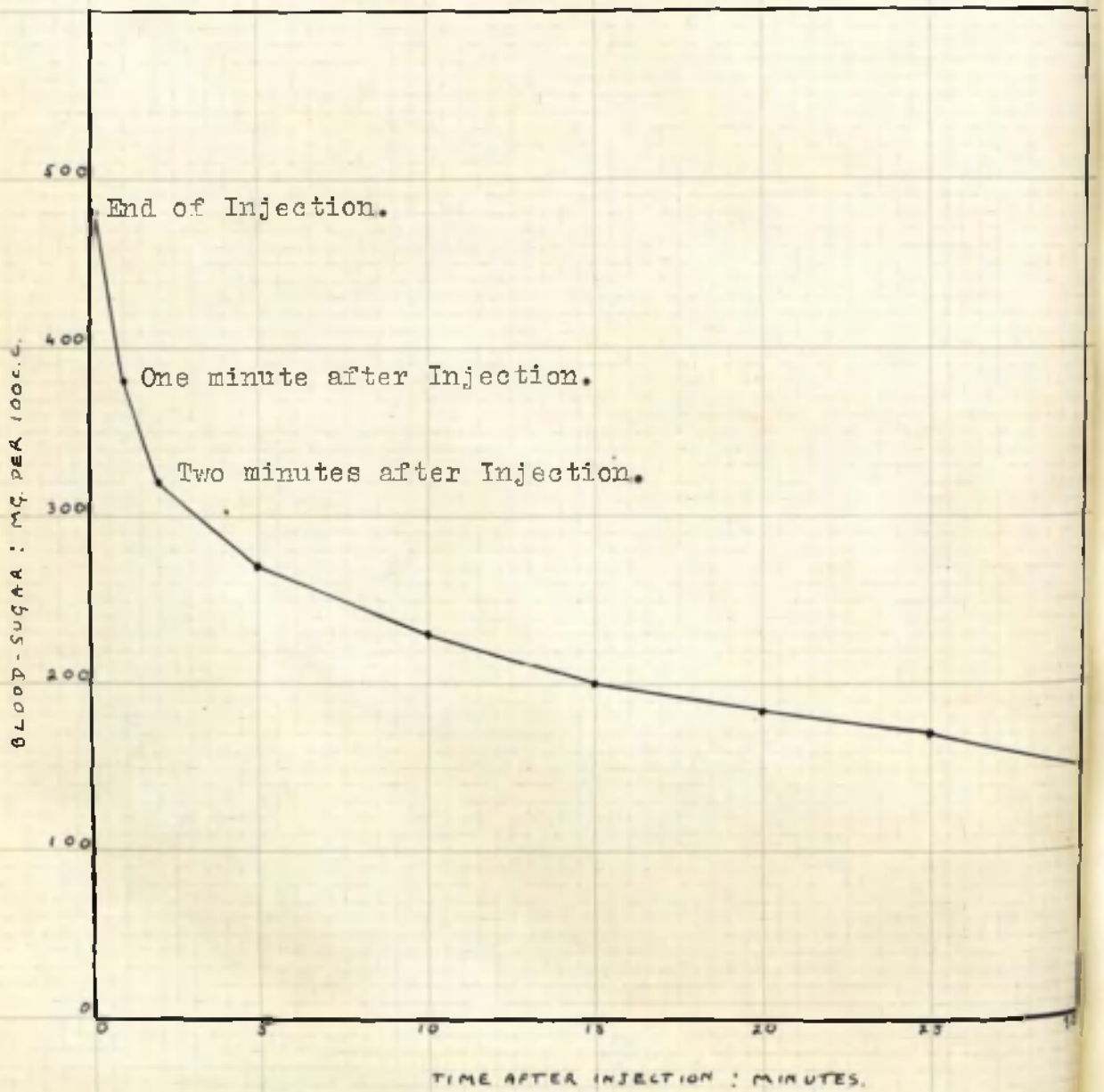
Results of Intravenous Glucose Tolerance Tests on 44 Normal Subjects.

Case	Age in years.	Body Wt. Kg.	BLOOD SUGAR mgm. per 100 c.c.								Urinary Sugar. Per cent. of dose.
			Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	
9	5/12	7.6	68	262	164	90	72	62	74	70	2.8
10	1	8.3	72	280	170	98	80	71	76	73	3.0
11	1 4/12	9.7	78	260	184	127	82	70	74	-	6.0
12	2 7/12	9	90	222	139	115	81	74	-	-	-
13	2 4/12	9	61	228	150	146	86	59	66	74	3.4
14	3½	13	84	308	197	141	97	79	70	65	4.0
15	3½	13	91	335	238	154	83	61	58	61	3.1
16	4	15	90	354	224	182	143	97	83	79	2.8
17	4	14	88	406	245	196	147	97	80	81	10.3
18	4	14	93	390	219	139	95	86	92	81	3.3
19	4½	14	81	267	172	143	95	88	79	72	4.1
20	4½	17	70	306	226	147	86	50	69	76	3.8
21	5	13	97	286	168	111	84	83	63	66	3.3
22	5½	15	86	314	222	161	127	88	79	65	4.2
23	5 10/12	15	88	278	221	117	101	86	94	83	4.6
25	6	16	80	274	193	128	89	65	67	73	-
5	6½	23	62	344	202	133	93	64	77	78	6.0
26	7	24	70	292	208	168	145	110	90	81	4.2
27	7	22	74	323	220	165	102	79	67	77	4.7
3	7	19	70	294	191	146	111	97	60	92	3.6
28	7 3/12	20	71	339	204	123	76	64	55	58	7.2
8	7 3/12	20	91	408	244	165	119	83	66	76	6.3
29	8	18	92	306	202	139	111	77	61	59	7.7
30	8	20	56	312	196	172	128	101	74	63	3.9
31	8	21	65	416	313	230	195	141	85	75	7.1
32	9	26	98	390	251	199	154	115	98	84	4.6
33	9	23	90	335	238	200	166	127	92	74	5.0
34	9	26	77	314	208	173	131	96	81	76	-
35	9½	21	65	371	248	157	110	91	71	63	2.3
36	10	30	76	377	247	204	125	102	83	65	6.3
4	10	30	92	329	230	177	138	90	86	81	5.8
37	10	27	83	336	241	191	146	115	92	72	5.2
38	11	27	95	298	246	178	135	110	90	94	7.4
39	11	28	62	428	274	202	157	109	76	66	5.7
40	12	24	99	324	190	152	122	86	75	68	6.6
6	12⅔	36	77	408	277	222	158	125	90	68	7.0
41	12⅔	40	74	400	263	235	167	111	74	65	13.0
42	23	81	84	412	294	195	110	70	56	52	10.1
43	24	52	72	345	170	139	112	81	73	57	6.3
44	26	76	76	308	294	217	164	114	78	60	8.5
45	27	52	75	339	227	194	143	104	83	77	-
46	30	55	72	362	228	175	125	110	88	75	-
47	35	62	77	376	253	194	116	109	67	60	8.0

FIGURE VIII.

Case 38, male, age 11 yrs. Wt. 27 kg.

Intravenous Glucose Tolerance Curve with frequent Readings during the first half-hour.



from this single case, the use of physiological saline as the solvent seems sounder, and in only one case (an adult) was any febrile reaction observed when it was employed. On account of the known tissue-dehydrating effect of an intravenous injection of 50 per cent. glucose it was thought inadvisable to employ a solution of this concentration. The use of the usual 10 per cent. solution, however, involved the injection of rather large amounts of fluid (200 c.c. to a child weighing 40 kilograms), so that a 20 per cent. solution was tried and gave satisfactory results. The glucose was thus given as a 20 per cent. solution in 0.9 per cent. sodium chloride throughout these experiments. The solution was sterilised by boiling for twenty minutes.

The Injection: The simplest method of giving an intravenous injection is by direct puncture of a superficial vein through the skin, using a sharp fine-bore needle. It is only on rare occasions that a satisfactory vein cannot be entered by one experienced in the procedure, and this method was employed almost exclusively in these investigations. Twice, in obese subjects, it was necessary to expose a vein at the ankle; and in a few instances in infants the injections were made into the superior longitudinal sinus. A 20 c.c. syringe was employed for the injections and was fitted with a two-way stop-cock, the side-arm of which was connected by means of fine rubber tubing to the glucose reservoir. This simple apparatus, illustrated in Figure VI, allowed accurate timing of the rate of injection. A suitable rate was found to be obtained by allowing forty-five seconds for

each syringeful of 20 c.c., including refilling the syringe from the reservoir.

Frequency of blood-sampling: During the preliminary tests made with this technique very frequent blood-sugar estimations were made; but as familiarity with the test was gained, and when the diagnostic criteria were established, it was found that sufficient information was obtained by taking specimens of blood fasting and at two, fifteen, thirty, forty-five, sixty, seventy-five and ninety minutes after the end of the injection. In subjects under five years of age the seventy-five- and ninety-minute specimens could be omitted.

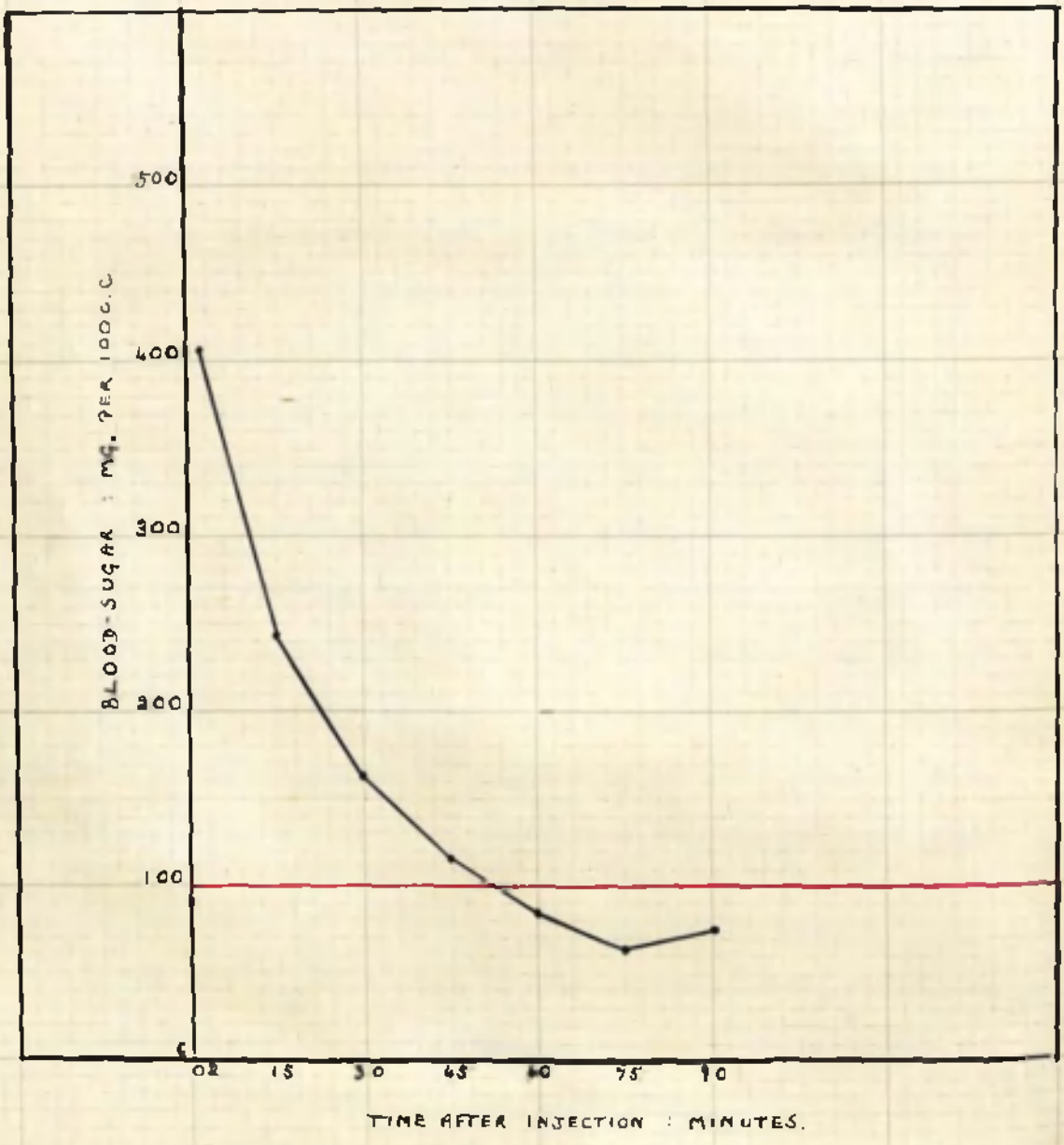
All blood-sugar estimations have been made on capillary blood taken from the lobe of the ear, or from the heel in the case of infants. The blood was received into a small tube containing a few granules of a dry mixture of potassium oxalate and sodium fluoride - the former to prevent coagulation, the latter to prevent the glycolysis which has been shown by Brown (1925) to occur after taking the specimen, and prior to the sugar estimation being made. The estimations were made by a modification of the Hagedorn-Jensen method (see Appendix).

Urine examinations: In order to estimate the proportion of the injected sugar lost in the urine it was found sufficient if the bladder was emptied before the injection and again when the final blood-sugar specimen had been taken. Except in grossly abnormal cases the latter specimen contained all the excreted

FIGURE VII

Case 8. Female, age 7 yrs. Wt. 20 kg.

Normal Intravenous Glucose Tolerance Curve.



glucose.

Summary of technique of test: The patient has no food for eight hours prior to the test, but may be allowed water to drink. A specimen of capillary blood is removed, the bladder is emptied, and then the injection is given by direct puncture of a superficial vein. The dose of glucose used is 0.5-gram per kilogram of body weight and it is given as a 20 per cent. solution in 0.9 per cent. sodium chloride. By using a syringe for the injection the rate is accurately timed, forty-five seconds being allowed for each 20 c.c. Capillary blood specimens are removed two minutes after the conclusion of the injection and at fifteen-minute intervals for an hour-and-a-half. A final specimen of urine is taken at the end of the test.

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The features of a typical curve in a subject with normal carbohydrate metabolism are illustrated in Figure VII, and in Table III the results are recorded of intravenous tests on forty-four subjects who were regarded as normal as far as carbohydrate metabolism was concerned. Thirty-eight of the subjects were children many weeks convalescent from various ailments not associated with disturbance of carbohydrate metabolism, for example, enlarged tonsils, rheumatism, enuresis; the remainder were healthy, active subjects. In none of the convalescent cases was the test performed until all signs of active disease had subsided and the erythrocyte sedimentation rate was within

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11	1 4/12	9.7	78	260	184	127	82	70	74	-	6.0
12	2 1/12	9	90	222	139	115	81	74	-	-	-
13	2 4/12	9	61	228	150	146	86	59	66	74	3.4
14	3½	13	84	308	197	141	97	79	70	65	4.0
15	3½	13	91	335	238	154	83	61	58	61	3.1
16	4	15	90	354	224	182	143	97	83	79	2.8
17	4	14	88	406	245	196	147	97	80	81	10.3
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19	4½	14	81	267	172	143	95	88	79	72	4.1
20	4½	17	70	306	226	147	86	50	69	76	3.8
21	5	13	97	286	168	111	84	83	63	66	3.3
22	5½	15	86	314	222	161	127	88	79	65	4.2
23	5 10/12	15	88	278	221	117	101	86	94	83	4.6
25	6	16	80	274	193	128	89	65	67	73	-
5	6½	23	62	344	202	133	93	64	77	78	6.0
26	7	24	70	292	208	168	145	110	90	81	4.2
27	7	22	74	323	220	165	102	79	67	77	4.7
3	7	19	70	294	191	146	111	97	60	92	3.6
28	7 3/12	20	71	339	204	123	76	64	55	58	7.2
8	7 3/12	20	91	408	244	165	119	83	66	76	6.3
29	8	18	92	306	202	139	111	77	61	59	7.7
30	8	20	56	312	196	172	128	101	74	63	3.9
31	8	21	65	416	313	230	195	141	85	75	7.1
32	9	26	98	390	251	199	154	115	98	84	4.6
33	9	23	90	335	238	200	166	127	92	74	5.0
34	9	26	77	314	208	173	131	96	81	76	-
35	9½	21	65	371	248	157	110	91	71	63	2.3
36	10	30	76	377	247	204	125	102	83	65	6.3
4	10	30	92	329	230	177	138	90	86	81	5.8
37	10	27	83	336	241	191	146	115	92	72	5.2
38	11	27	95	298	246	178	135	110	90	94	7.4
39	11	28	62	428	274	202	157	109	76	66	5.7
40	12	24	99	324	190	152	122	86	75	68	6.6
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41	12½	40	74	400	263	235	167	111	74	65	13.0
42	23	81	84	412	294	195	110	70	56	52	10.1
43	24	52	72	345	170	139	112	81	73	57	6.3
44	26	76	76	308	294	217	164	114	78	60	8.5
45	27	52	75	339	227	194	143	104	83	77	-
46	30	55	72	362	228	175	125	110	88	75	-
47	35	62	77	376	253	194	116	109	67	60	8.0

normal limits. This latter test was employed to confirm the clinical evidence that no active disease was present. As the curves from "convalescent" and "healthy" subjects were in every way similar, the assumption seems justified that the series, as a whole, can be regarded as normal. Details of the individual cases are included in Appendix B.

The blood-sugar level attains its maximum value at the end of the injection and immediately thereafter it begins to fall rapidly. Even when frequent samples of blood have been examined during the first thirty minutes after the injection (Figure VIII) no interruption of the descent of the curve during this period has been found. Ross (1936 a,b,c), on the other hand, reports several double-peaked curves with minor rises during this period, but he does not advance any explanation for what is a rather unexpected finding.

Normal fasting levels are regained in from forty-five to seventy-five minutes and the later specimens frequently show subnormal blood-sugar values (below 70 mg. per 100 c.c.). Examination of the results suggests that it is possible to divide the curves into three phases: (a) a phase lasting for two to five minutes after the injection, during which the blood-sugar level falls very rapidly. This phase merges into (b) the second phase, during which the curve declines more gradually to normal fasting levels, and (c) an inconstant third phase, during which subnormal values may be recorded. Though the precise cause of these phases is uncertain, the following explanation

seems not unreasonable.

The very rapid fall of the curve during the first five minutes is in all probability due to simple diffusion of glucose from the blood into the extra-vascular fluids of the body. The fact that this phase is seen even in severely diabetic subjects (see Section X) is evidence in support of this purely physical basis. The phase of gradual decline to fasting levels represents the activity of the intermediary processes and is due to the combined effects of utilisation, storage and excretion. The period of mild hypoglycaemia, when it occurs, probably indicates a delay in the return to activity of the normal glycogenolytic processes which have been inhibited by the presence of an excess of glucose in the circulation; or it may result from over secretion of insulin in response to the injected glucose. It appears to be of scant significance.

The Constancy of the Curve in the Individual.

In order to determine the constancy of the curve for the individual the test was performed on two occasions at an interval of five to ten days on each of ten subjects. The results of these tests are recorded in Table IV in which column (a) represents the findings on the first occasion and column (b) those on the second occasion. Column (c) gives the difference between corresponding readings in the two experiments.

The concentration of the blood-sugar in the two-minute sample is of little importance. At this stage the blood-sugar

TABLE IV.

The results of two intravenous tests on each of ten cases.

Case	8			18			29			32			33			38			39			48			49			50		
Age in years	7 3/12			4			8			9			9			11			11			10 4/12			4 8/12			8 10/12		
	a	b	c	a	b	c	a	b	c	a	b	c	a	b	c	a	b	c	a	b	c	a	b	c	a	b	c	a	b	c
Fasting	91	81	10	93	95	2	92	92	0	98	82	16	90	88	2	86	86	0	62	61	1	90	89	1	81	77	4	87	89	2
2 mins.	408	460	52	390	388	2	306	340	34	390	364	26	335	321	14	298	282	16	428	500	72	368	394	26	296	308	12	408	400	8
15 "	244	255	11	219	221	2	202	216	14	251	238	13	238	231	7	232	228	4	274	282	8	253	245	8	206	212	6	282	277	5
30 "	165	169	4	139	146	7	139	148	9	199	190	9	200	192	8	168	163	5	202	205	3	188	182	6	175	173	2	194	202	8
45 "	119	126	7	95	94	1	111	119	8	154	149	5	166	160	6	125	122	3	158	167	9	154	150	4	122	126	4	114	123	9
60 "	83	90	7	86	89	3	77	81	4	115	111	4	127	124	3	101	102	1	109	110	1	104	106	2	95	97	2	97	99	2
75 "	66	79	13	92	87	5	61	76	15	98	97	1	92	90	2	88	79	9	78	81	3	91	88	3	92	94	2	75	90	15
90 "	76	69	7	81	83	2	59	72	13	84	87	3	74	79	5	88	83	5	66	70	4	77	71	6	81	84	3	68	83	15

a = First test. Blood-sugar levels in mg. per 100 c.c.
b = Second test. " " " " " " " "
c = Difference between corresponding readings in mg. per 100 c.c.

is falling very rapidly, so that quite slight variations in rate of injection, time of collection of the blood sample and rate of flow of blood from the skin puncture may produce wide variations

in this reading. In five of the pairs of tests recorded in Table IV the difference between the two-minute readings at the two tests was more than 20 mg. per 100 c.c.; but usually by the fifteen-minute reading, and always at thirty minutes, the curves were within 10 mg. per 100 c.c. of one another - a much closer proximation of the curves than is found after successive oral glucose tolerance tests. Occasionally, when subnormal values occurred, the curves became more widely separated again at the end of the tests (Cases 29 and 30, Table IV).

The Interpretation of Results.

The following points are those which have been used most frequently by different workers for the interpretation of intravenous glucose tolerance tests.

1. The maximum blood-sugar level attained.
2. The time taken for the restoration of the fasting level.
3. The area enclosed by that part of the curve which lies above the fasting level.
4. Jörgensen's "Loading Figure" - the arithmetic sum of the area of the curve, in milligram-minutes, plus the time required to restore the fasting blood-sugar level, in minutes.

Throughout the present investigations interpretation of the intravenous tolerance tests has been based largely on the consideration of two factors:

(a) The time after the injection at which a blood-sample first showed a concentration of 100 mg. per 100 c.c. or less.

The choice of this point - the time of restoration of the blood-sugar to 100 mg. per 100 c.c. or less - requires some explanation, the usual point taken by other workers being the time at which the original fasting value has been regained. In children, however, the fasting value fluctuates from time to time to a greater extent than in adults, and after eight hours of fasting it tends in many subjects to be about the lower limit of normal (Table III, Cases 5, 9, 13, 20, 30, 31, 35, 39). In these circumstances it seems fairer to judge the intermediary mechanism by its ability to restore a normal fasting blood-sugar level rather than the actual level present when the test commenced. The upper limit of normal fasting blood-sugar levels with the technique employed in these investigations was 100 mg. per 100 c.c.

This time of restoration of normal fasting levels, taken in conjunction with the age of the subject (vide infra), has been found to yield the most definite evidence of the normality or abnormality of any particular curve. Alteration of this time when the curve was repeated in an individual provided definite evidence of a change in carbohydrate tolerance - a diminution of tolerance if the time had increased, a gain of tolerance if the time had diminished. When the test was repeated in a subject, without change of conditions, the time of fall to 100 mg. per 100 c.c. or less was constant (Table IV).

(b) The actual shape of the charted curves.

This provides additional information in special circumstances and

Figure IX.

Relationship between Age and Time of Fall of Intravenous Tolerance Curve to Normal Fasting Levels.

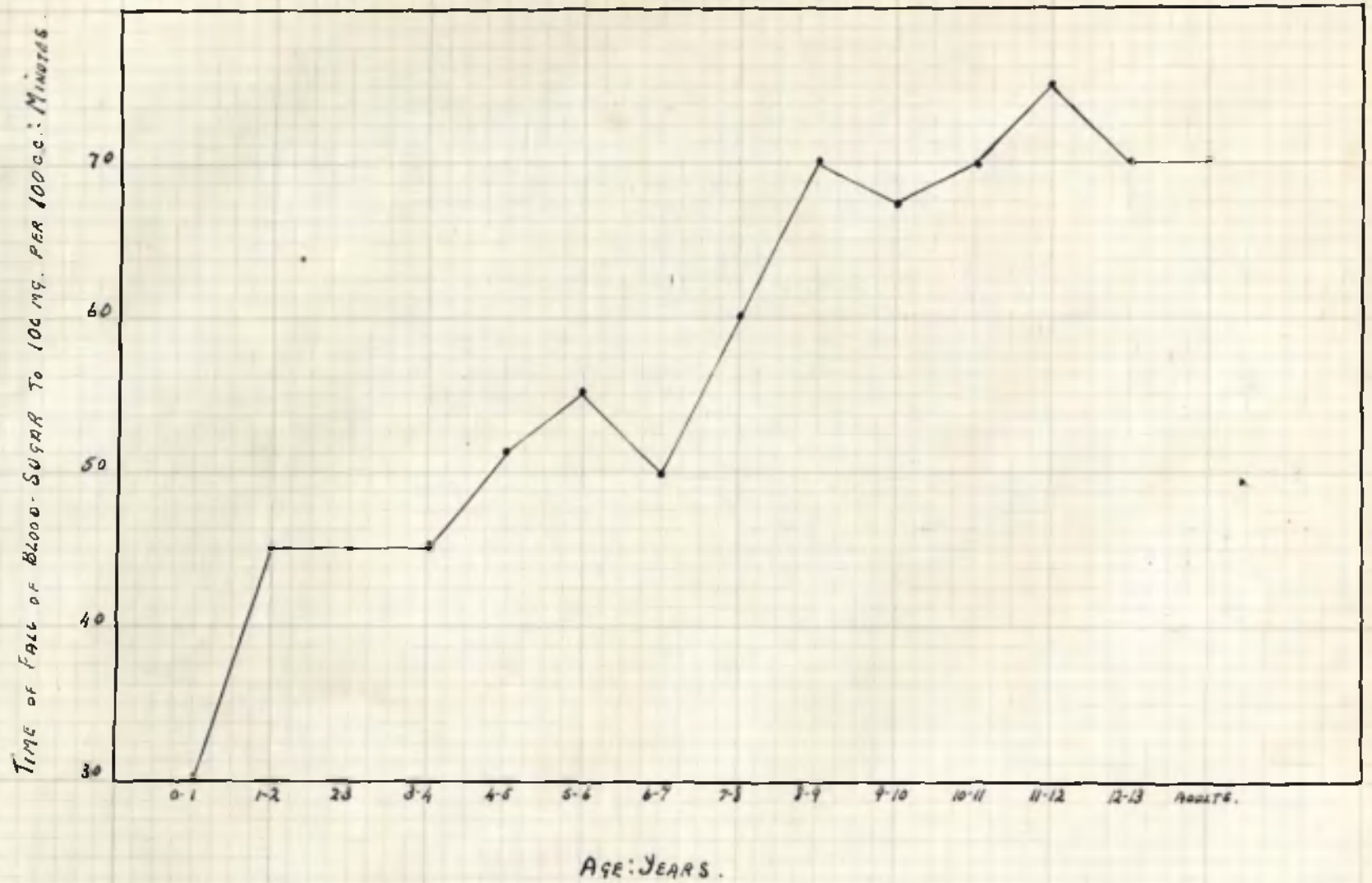


FIGURE IX.

gives evidence of minor changes of tolerance insufficient to affect the time of fall to normal fasting levels. A study of the areas enclosed by the curves and of the Loading Figures was found to yield no further information.

The Normal Range: Variation with Age.

A considerable degree of constancy of the intravenous glucose tolerance curve for the individual having been demonstrated, it remains to consider the amount of variation between normal subjects. Inspection of Table III (page 29) reveals that the times of fall of the blood-sugar concentration to normal fasting levels vary widely, from thirty to seventy-five minutes. When, however, the cases are subdivided into age-groups it is clear that the limits of normality at any particular age are sharply defined. This is illustrated in Tables III and V and in Figure IX. In Table III the cases are arranged in order of increasing age from above down and the red line has been drawn at the time intervals during which the fall to normal fasting levels occurred. It will be seen that the line moves gradually, though somewhat irregularly, from left to right as the age of the subjects increases. Table V summarises the times at which normal fasting values were regained in each age-group and in Figure IX the age of the subjects has been plotted against the average time taken. Although the numbers of cases in the lower age-groups are small, these figures show that the capacity of the infant, relative to body weight, to utilise and store carbohydrate is high; and that this so-called

high carbohydrate tolerance falls off progressively during childhood until the adult level is reached in the ten-to-thirteen-year age-group.

TABLE V.

Summary of times at which the first blood-sugar value at or below 100 mg. per 100 c.c. was obtained.

Age-group	0-3 years	3-6 years	6-10 years	10-13 years	Adults
No. of cases	5	10	15	8	6
Fall in 15 mins.	-	-	-	-	-
" " 30 "	40%	-	-	-	-
" " 45 "	60%	60%	20%	-	-
" " 60 "	-	40%	46.6%	25%	33.3%
" " 75 "	-	-	33.3%	75%	66.6%
" " 90 "	-	-	-	-	-
Mean glucose excretion in urine. Per cent. of dose injected.	3.8	4.4	5.1	7.1	8.5

From these findings it can be stated that if the fall of the blood-sugar concentration to 100 mg. per 100 c.c. occurs in less than forty-five minutes in children between three and ten years of age, or in less than sixty minutes in subjects over ten years of age, then increased tolerance is present. If, on the other hand, the fall to 100 mg. per 100 c.c. is delayed beyond sixty minutes in children under six years of age, or beyond seventy-five minutes in older subjects, then there is some degree of impairment of the carbohydrate tolerance.

Side-Effects of the Glucose Injection.

Glycosuria: renal threshold for glucose. When glucose has been administered intravenously with the technique described above, glycosuria has always been found when its presence has been sought. The amounts of glucose excreted, expressed as percentages of the glucose injected, are included in Tables III and V. It will be seen that the amount excreted varies from 2.8 to 13.0 per cent., the lower values occurring in the younger subjects more frequently and the average amount increasing with age. The precise quantity of sugar excreted during the test in non-diabetic subjects has proved of little importance, and in the later tests its estimation was frequently omitted.

The conditions of these experiments have allowed in some cases a rough estimate to be made of the renal threshold for glucose. It was Claude Bernard who, in 1877, introduced the conception of the renal threshold for glucose as that level of the blood-sugar at which glycosuria appeared. More recently, however, physiologists have tended to discard this view (McLeod, 1921), but clinically the concept of a precise renal threshold for glucose has proved of definite value. It may be defined as the blood-sugar level at which a sufficient degree of glycosuria becomes established to cause the urine to react to the ordinary clinical tests for sugar.

Following oral administration of glucose Jacobsen (1913) placed the threshold value at 170 mg. per 100 c.c., while Hamman and Hirschman (1917), Bailey (1919) and Williams and Humphreys

(1919) accepted 170 to 180 mg. per 100 c.c. as the normal value. Himsworth in 1931 introduced a new method for the determination of the threshold, depending upon the relationship between sugar concentrations in the blood and the urine, above the threshold value. Working with diabetic subjects he showed that a considerable difference might exist between the threshold determined when the blood-sugar was rising and when it was falling. He introduced the terms "threshold of appearance" and "threshold of disappearance" and showed that the former was usually higher than the latter. The values he found varied from 128 to 304 mg. per 100 c.c., but it is to be remembered that he was not working with normal subjects.

During the intravenous glucose tolerance tests performed in these investigations changes in the blood-sugar concentration were occurring too rapidly about the level of the threshold value for its position to be determined with any exactness. In a number of cases, however, examination of several specimens of urine did allow some limits to be drawn within which the critical value must lie. Such information as has been obtained is included in Table VI. It will be seen that, while most of the limits are too wide to permit of any precise placing of the threshold value, it is clear that in many of the experiments the critical blood-sugar level was considerably above 200 mg. per cent.

Several possible causes suggest themselves for the high values of the renal threshold found here, compared with the

TABLE VI.

Placing of the renal threshold for glucose.

Case	Age: years	Possible limits of renal threshold mg. per 100 c.c.
39	11	160 - 202
25	6	130 - 195
27	7	210 - 314
8	7 3/12	165 - 230
59	5	180 - 243
36	10	Below 204
54	4 9/12	Above 215
58	11 8/12	213 - 285
50	9	(1) Above 194 (2) Above 202
52	3	156 - 212
62	1 6/12	111 - 250
60	11	116 - 217
51	5	Below 224
35	9½	Above 220
57	7	Above 226
55	1 6/12	140 - 270
56	8	Below 266
31	8	229 - 286
41	12½	Below 200
53	8 4/12	Above 200

results of other workers. These tests were made on children whereas the investigators quoted above worked solely on adults. It is of interest to note that Gilchrist (1932) quotes blood-sugar curves in children rising to 201, 231, 234, 204, 221 and 218 mg. per 100 c.c. during which glycosuria did not occur; and Svensgaard (1931) also had curves rising above 200 mg. per 100 c.c. in which glycosuria was not noted. It appears probable that the threshold value for glucose is normally higher in children than in adults. In addition, the glucose was administered intravenously in the present tests and the threshold of disappearance of glycosuria was determined. Previous workers determined the threshold of appearance of glycosuria after oral glucose administration.

Diuresis. The diuretic effect of intravenously injected glucose is well-known and is frequently employed for therapeutic purposes. When the glucose is given with this end in view higher concentrations are employed - up to 50 per cent. - than have been used in the present investigations.

The cases in which detailed measurements of the quantity of urine secreted have been made are recorded in Table VII. It will be seen that the total urinary excretion during the period of the test was generally of the same order of magnitude as the actual volume of fluid injected. In nineteen of the twenty-five examples the urine volume during the one-and-a-half hours of the test was between 60 and 140 per cent. of the volume of fluid injected. Inspection of the figures from the cases in which two or more specimens of urine were obtained during the test shows that

TABLE VII.

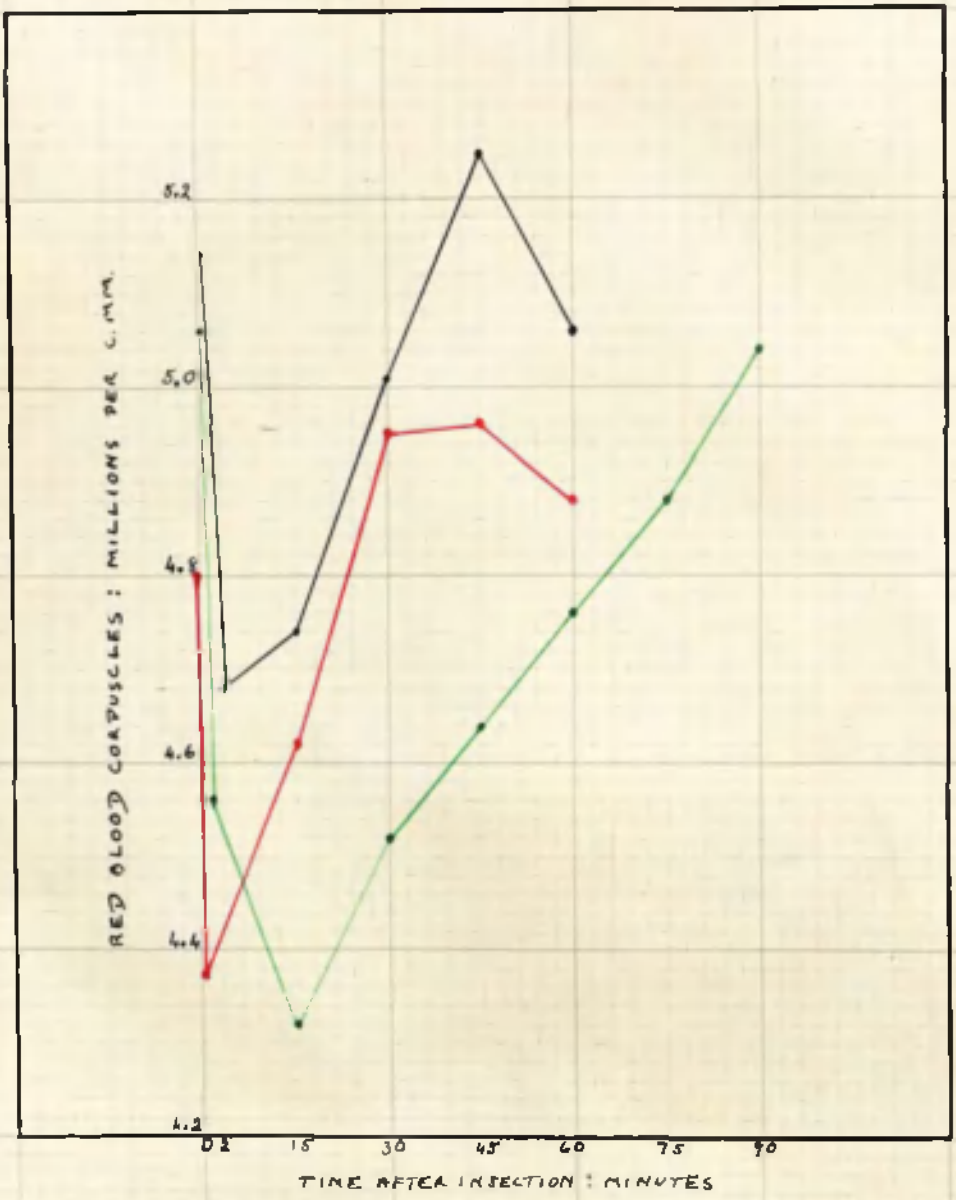
Volume of urine excreted during intravenous glucose tolerance tests.

Case	Age: years	Injection c.c.	Urine vol. in c.c.				
			¼-hr.	½-hr.	1½ hrs.	Total	Per cent. of injected fluid
6	12½	90 90	- -	78 48	5 21	83 70	92 77
8	7½	50	-	40	30	70	140
15	3½	37.5	-	20	25	45	118
25	6	40	-	14	11	25	63
27	7	55	-	16	26	42	76
31	8	70 70	- -	82 72	25 34	107 106	152 152
39	11	70	-	25	16	41	59
41	12½	100 100	- -	85 59	15 30	100 89	100 89
35	9½	70	53	-	24	77	110
44	26	190	180	-	22	202	106
47	35	155	-	-	-	130	84
50	9	65 65	- -	45 38	32 10	77 48	118 74
52	3	32.5	15	-	8	23	72
54	5	45	-	35	20	55	122
59	5	65	-	15	20	35	54
61	9½	70	-	25	15	40	56
62	1½	50	-	-	50	50	100
63	11	70	-	33	12	45	64
64	8	90	-	32	22	55	61
	8½	95	-	-	90	90	94
	9	120	-	-	55	55	46

FIGURE X.

Changes in Red Blood Cell Count during an Intravenous Glucose Tolerance Test.

Case 6. Case 31. Case 35.



there was a rapid diuresis following the injection and that urine secretion throughout the remainder of the test proceeded at a slow pace. For example, in Case 44, 180 c.c. of urine were secreted during the fifteen minutes after the injection, while only 22 c.c. of urine were secreted during the succeeding seventy-five minutes.

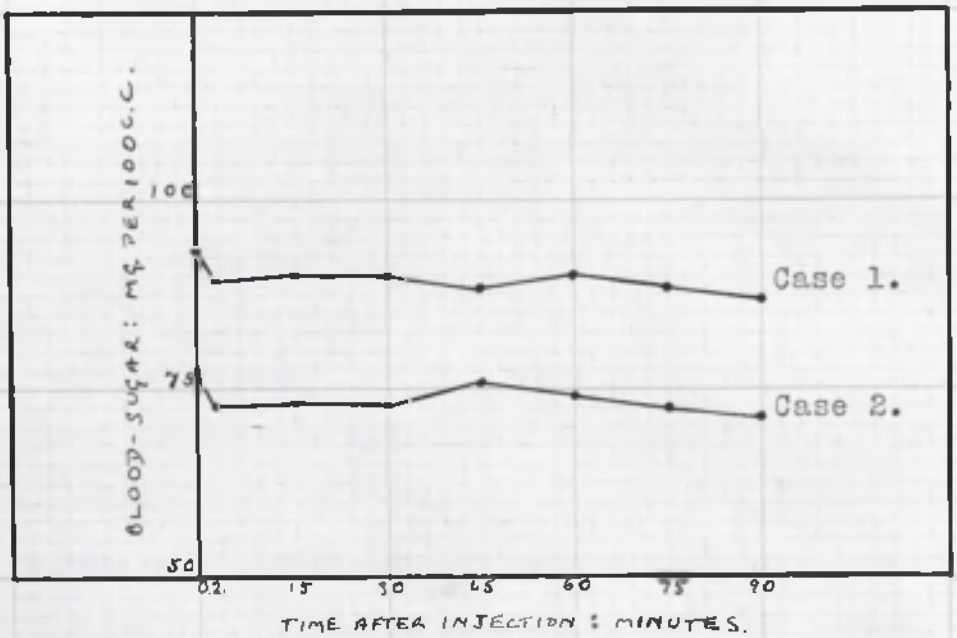
It may thus be concluded that, while the injection of glucose employed here as a glucose tolerance test causes a brief diuresis immediately following the injection, the amount of fluid lost never exceeds the volume of the injected fluid to an extent sufficient to bring about serious side-effects.

Changes in blood-concentration. In an attempt to ascertain the course of changes in the concentration of the blood during the test, repeated red-blood-cell counts were made in three cases. The same haemocytometer pipette and counting slide were employed for all the counts on each case in an attempt to minimise the known experimental error of the procedure. The utmost care was exercised with each count. The results of these counts are charted in Figure X. From this graph it can be seen that the injection is followed by a sharp fall in the red-cell count. In each case, however, the count is commencing to rise after fifteen minutes and the pre-injection level has been regained by the end of the test.

Assuming that, over the brief period of the test, the concentration of the blood is directly proportional to the red-blood-cell count, it can be stated that a rapid, though slight,

FIGURE XI.

Cases 1 and 2: Blood-Sugar Curves after the injection of 0.9 per cent. sodium chloride solution.



dilution of the blood follows the injection. The amount of the dilution varied from 8.9 per cent. (Case 31) to 14.6 per cent. (Case 35) of the original value. The dilution is followed by a more gradual increase of blood-concentration until the pre-injection value is regained.

Other effects. In two subjects the whole procedure of the test was followed, but a simple 0.9 per cent. saline solution was substituted for the glucose-saline solution. The blood-sugar curves obtained are recorded in Figure XI: no significant changes in blood-sugar concentrations occurred. It can be concluded that the manipulations involved in the carrying out of the intravenous glucose tolerance test are in themselves not such as to cause significant fluctuations in the blood-sugar level. In another child blood chloride estimations were made during the test, while in a further case the erythrocyte sedimentation rate was measured at intervals. In neither case was any significant alteration found to follow the injection.

Summary.

An intravenous glucose tolerance test has been described, applicable to children at all ages as well as to adults. Carbohydrate tolerance is gauged by the time taken after the injection for a normal fasting blood-sugar level to be regained. The test shows a high degree of constancy for the individual and the limits of normality are well-defined. The blood-sugar curve descends

more rapidly in young children than in adults. Glycosuria is an invariable accompaniment of the test, the amount of glucose excreted varying from 2.8 to 13.0 per cent. of the glucose injected. The injection is followed by a brief diuresis and there is a transient dilution of the blood after the injection, the pre-injection concentration being resumed by the end of the test.

S E C T I O N III

CARBOHYDRATE TOLERANCE IN HYPERTROPHIC PYLORIC STENOSIS OF INFANCY.

Introduction.

Hypertrophic pyloric stenosis of infancy has been selected for early discussion in this thesis because its study provided an excellent example of the way in which the intravenous glucose tolerance test may be made use of for the elucidation of abnormal oral glucose blood-sugar curves.

Three cases of pyloric stenosis have been studied. In each the diagnosis was based on a typical history combined with the characteristic clinical findings. A pyloric tumour was palpated in each case. Two of the cases (65 and 66) were treated by surgical operation, while the third received medical treatment with a preparation of atropine methyl nitrate ("Eumydrin"). All three ultimately recovered and throve.

Oral Glucose Tolerance.

Oral glucose tolerance tests were carried out on each of the three patients and in Case 65 the test was repeated two weeks after the operation, when the infant was apparently healthy. A dosage of 2 grams of glucose per kilogram of body weight, as a 10 per cent. solution, was employed. It was introduced through

FIGURE XII.

Oral Glucose Tolerance Curves in three cases of Pyloric Stenosis, and in a normal infant aged 6 weeks.

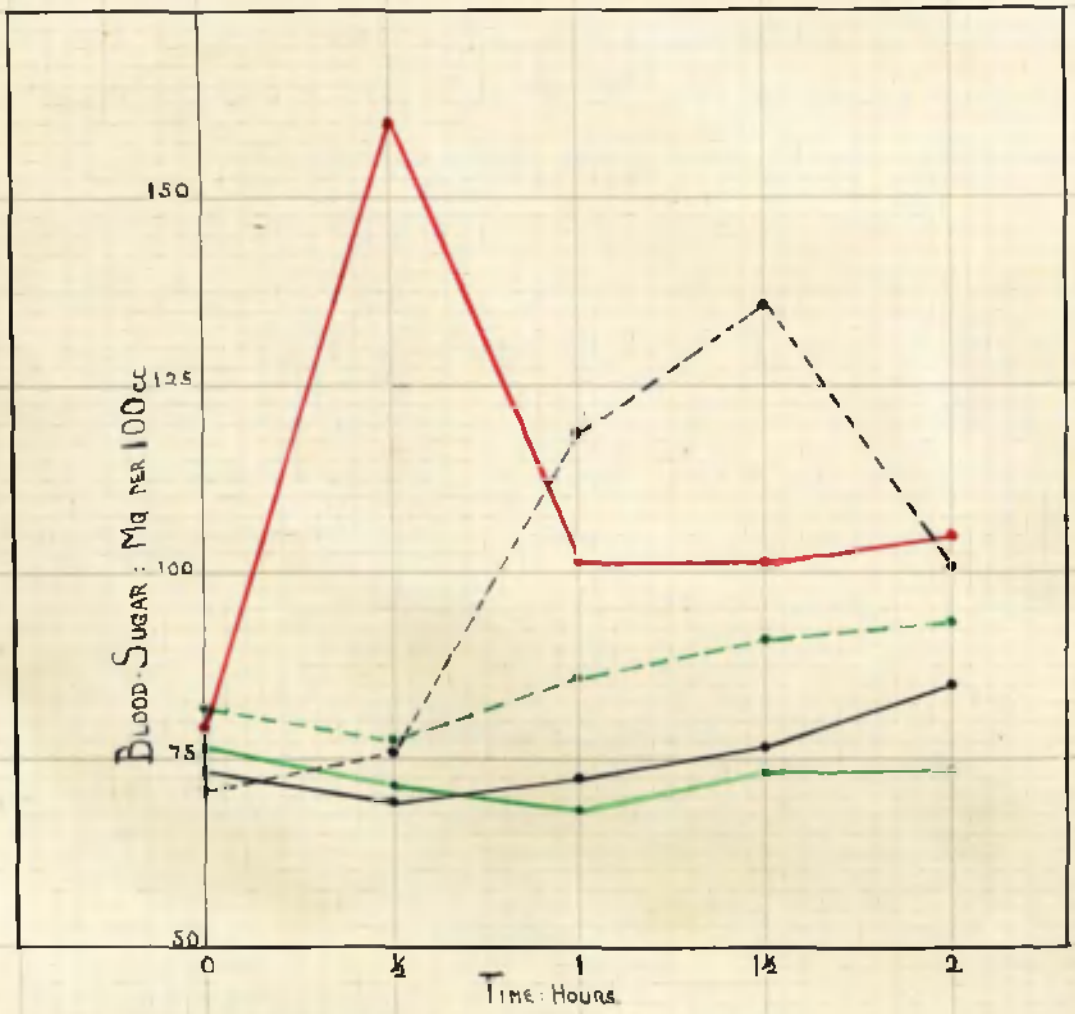
——— Case 65 before operation.

– – – – – Case 65 after operation.

——— Case 66.

– – – – – Case 67.

——— Normal infant, aged 6 weeks.



a stomach-tube after the stomach had been washed out and emptied. Blood-sugar estimations were made fasting and at half-hourly intervals for two hours after the glucose administration. The results of these tests are recorded in Table VIII and Figure XII, in which a typical curve from a normal infant aged six weeks has been included for comparison.

TABLE VIII.

Results of oral glucose tolerance tests in three cases of pyloric stenosis.

Case	Age: wks.	Wt. kg.	Blood-sugar in mg. per 100cc					Remarks
			Fasting	½-hr.	1 hr.	1½ hr.	2 hr.	
65	9	3.1	74	69	73	77	86	Before operation
	11	3.3	71	76	119	136	101	2 Weeks after operation
66	4	2.5	77	72	68	74	74	Before operation
67	7	3.5	82	76	87	91	93	Before treatment
Normal (Svensgaard 1931)	6	3.8	80	160	101	100	106	

It will be seen that in each case of pyloric stenosis a remarkably small rise of the blood-sugar concentration occurred; indeed, in one case (Case 66) there was no increase whatsoever above the fasting blood-sugar level during the two hours of the test. The second curve on Case 65, after operative cure of the pyloric obstruction, approaches normal form. In none of the tests did glycosuria occur.

FIGURE XIII.

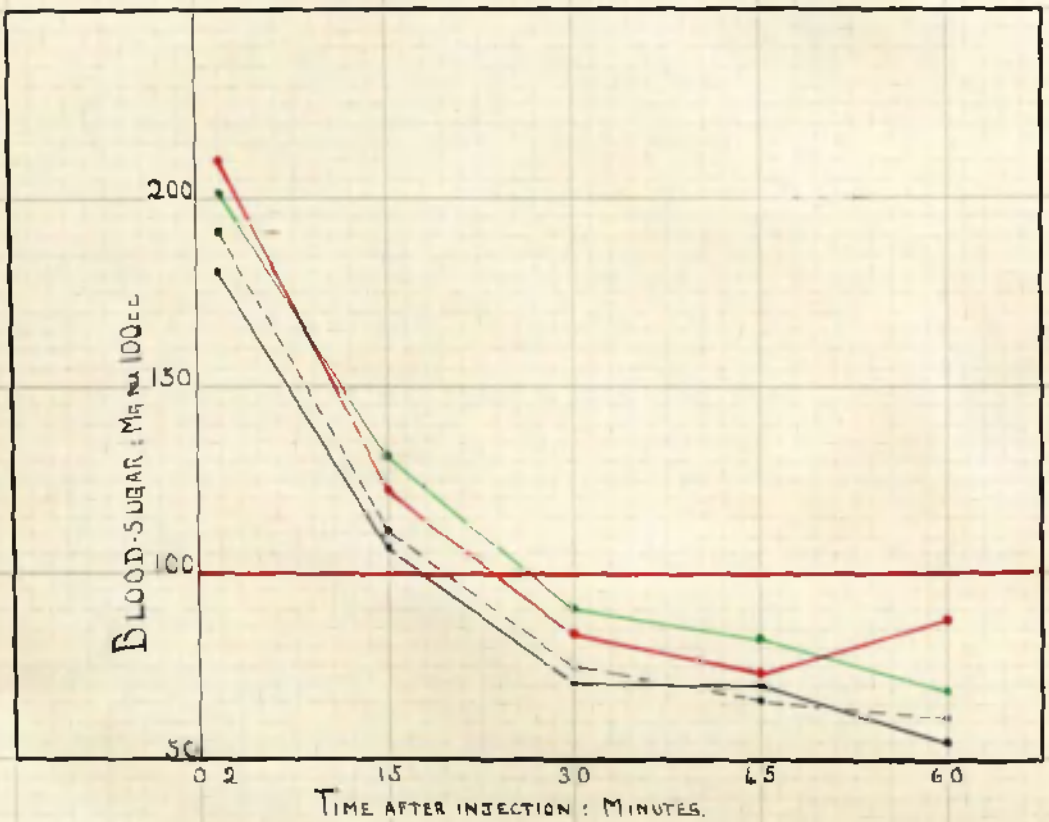
Intravenous Glucose Tolerance Curves in three cases of Pyloric Stenosis.

——— Case 65, before operation.

– – – – – Case 65, after operation.

——— Case 66.

——— Case 67.



Intravenous Glucose Tolerance.

Using the technique described in the preceding chapter, intravenous glucose tolerance tests were made on the three cases of pyloric stenosis already mentioned, and in Case 65 the test was repeated two weeks after operation. The results of these tests are detailed in Table IX and shown graphically in Figure XIII. In each case the fall of the blood-sugar level below 100 mg. per 100 c.c. occurred with the thirty-minute specimen. In Case 65 the curves before and after operation were practically identical.

TABLE IX.

Results of intravenous glucose tolerance tests in three cases of pyloric stenosis.

Case	Blood CO_2 Vol.%	Blood-sugar in mg. per 100 c.c.						Remarks
		Fasting	2 min.	15 min.	30 min.	45 min.	60 min.	
65	86	77	180	112	72	70	54	Before operation
	67	72	191	117	73	69	62	2 Weeks after operation
66	94	73	201	133	90	82	69	Before operation
67	74	82	210	123	84	72	87	Before treatment

Discussion.

In the absence of glycosuria, the diminished or absent hyperglycaemia which these cases of pyloric stenosis showed after oral administration of glucose might theoretically be produced by either abnormally active intermediary carbohydrate metabolism or by failure or delay of absorption of glucose from the alimentary canal. Consideration of the functional pathology of pyloric stenosis, the essential feature of which is the failure of the stomach (partial or complete) to pass its contents through the narrowed pyloric canal into the bowel, strongly suggests that the latter explanation is the correct one. It seems probable that the low oral blood-sugar curves result from the ingested glucose remaining in the stomach during the two hours of the test, or being absorbed so slowly that only a trivial rise of the blood-sugar occurs. It is clear, also, that if any absorption of glucose occurs through the gastric mucosa, its extent must be quite trivial.

These cases, however, all showed a well-marked non-gaseous alkalosis, evidenced by a diminished respiratory rate, absence of urinary chlorides and elevation of the blood carbon-dioxide content (Table IX), and it seemed not impossible that some change in intermediary metabolism might co-exist with the alimentary abnormality. The normality of the intravenous tests, however, puts this possibility aside and in this connection it is of special significance that no change of tolerance to intravenous glucose occurred after operation in Case 65, although the

alkalosis was relieved.

These findings show that in pyloric stenosis there is no abnormality of intermediary metabolism of carbohydrates; and it is clear that the flat oral glucose blood-sugar curves which have been found in the present series of cases are produced directly by the alimentary abnormality. The presence of alkalosis has apparently no effect on the tolerance to intravenous glucose.

Summary.

Pyloric stenosis in infants is associated with abnormally flat oral glucose tolerance curves, but intravenous glucose tolerance curves are normal. After operation the oral curve approaches normal and the intravenous curve remains unchanged. The abnormality of carbohydrate metabolism is purely one of absorption; intermediary metabolism of carbohydrate is normal.

S E C T I O N IV

CARBOHYDRATE TOLERANCE ON DIFFERENT DIETS AND IN VARIOUS CONDITIONS ASSOCIATED WITH ACIDOSIS AND KETOSIS.

A. THE EFFECT OF DIET.

Introduction.

Kaguera in 1922 (a and b) first demonstrated that dogs maintained for several days on a high-fat diet subsequently showed an abnormally great hyperglycaemia after a glucose meal. Since then the observation has been frequently repeated and extended. Southwood (1923) found the same changes of carbohydrate tolerance in men, and Gilchrist (1932a and b) observed the changes in children. Du Vigneaud and Karr (1925) made similar observations in rabbits.

Sweeney (1927) investigated in healthy men the effects upon oral glucose tolerance of high-fat diets, high-carbohydrate diets and starvation. He found invariably a high blood-sugar curve after oral administration of glucose to a subject previously starved or on a high-fat diet; while a high-carbohydrate diet was accompanied by a low curve. The most complete investigation of the influence of diet on oral glucose tolerance is that of Himsworth (1933). His findings agree with those of previously quoted workers. Seeking the explanation of the changes of

tolerance which he found on different diets, he showed (1934a) that the tolerance was proportional to the absolute amount of carbohydrate in the diet and was independent of any condition of acidosis or alkalosis or of the absolute caloric value of the diet.

At first (1934 a and b) he explained the changes by postulating an insulin activator - "Insulin-kinase." The concentration of this activator he regarded as being proportional to the amount of carbohydrate in the preceding diet.

More recently Himsworth has modified his views as the result of a study of rabbit preparations after exclusion of the liver (Himsworth, 1938) and after hypophysectomy (Himsworth and Scott, 1938 a, b and c). These workers find that in rabbits after hypophysectomy the changes in carbohydrate tolerance with change of diet do not occur, tolerance remaining high on all diets. The changes can be reproduced, however, by the administration of Young's (1936, 1937, 1938 a,b,c) Glycotropic Factor of the anterior pituitary gland. Himsworth and Scott suggest, therefore, that changes in oral glucose tolerance with change of diet are produced by varying activity of the anterior pituitary gland. On a high-carbohydrate diet the secretion of the glycotropic (contra-insular) factor is depressed; on a low-carbohydrate diet it is increased.

In all this work the guage of carbohydrate tolerance has been the oral glucose test. The unreliability of this test in children has already been pointed out and because of this unreliability, an investigation of changes in both oral and

intravenous glucose tolerance with change of diet has been made on some of the children from the normal group in the present series.

Method.

Six of the "Normal" subjects were employed for the investigation - Cases 3, 4, 26, 34, 38 and 40. Oral and intravenous glucose tolerance tests were carried out during periods on a balanced diet, a high-carbohydrate diet and a low-carbohydrate diet. (The high-carbohydrate diet was not employed in Case 26). In Case 34 the effect of a further diminution of carbohydrate allowance below that of the standard "low-carbohydrate" diet was observed, while in Case 38 the effect of additional carbohydrate above the "high-carbohydrate" diet was tried. (See Table X). For the oral test 1.0 gram of glucose per kilogram of body weight was given as a 10 per cent. solution in water. Blood-sugar estimations were made fasting and at half-hourly intervals for two hours. Intravenous tests were made with the technique described in Section II. At each test the urine was examined both for sugar and for ketone bodies. A period of at least forty-eight hours was allowed between tests, and the order in which the tests were performed was varied from case to case - the oral tests first in Cases 3, 38 and 40, the intravenous tests first in Cases 4, 26 and 34. Estimations of the blood carbon dioxide content were also made, as an index of the state of the acid-base balance. Normal values with the technique employed were 45 to 60 volumes per cent. The composition of the diets used, together with their ketogenic

TABLE X.

Composition of experimental diets.

Diet	Grams per day			Ketogenic millimols	Anti-Ketogenic millimols	Ketogenic ratio	Calory value
	Carbohydrate	Protein	Fat				
Balanced	90	112.5	112.5	426	748	0.57	1860
High-carbohydrate	350	50	10	160	2120	0.08	1690
Extra high-carbohydrate	400	30	6	96	2327	0.04	1800
Low-carbohydrate	15	50	160	475	330	1.44	1700
Extra low-carbohydrate	8	45	170	693	280	2.47	1740

factors (Shaffer, 1921 a,b,c) are given in Table X.

Results.

Fasting blood-sugar levels were found to vary somewhat with the carbohydrate content of the diet. Abnormally low levels were frequently obtained during the periods on low-carbohydrate diet, thirteen of the seventeen estimations of the fasting level made on this régime being below 70 mg. per 100 c.c. On the high-carbohydrate diet fasting levels tended to be high, while intermediate values were obtained on balanced diet, though considerable overlapping occurred. The average figures for the fasting blood-sugar levels are 89 mg. per 100 c.c. for twelve estimations on high-carbohydrate diet, 81 mg. per 100 c.c. for fourteen estimations on balanced diet and 62 mg. per 100 c.c. on low-carbohydrate diet. These figures, together with the standard deviations, are given in Table XI and the results are shown diagramatically in Figure XIV. The difference between the fasting values on low-

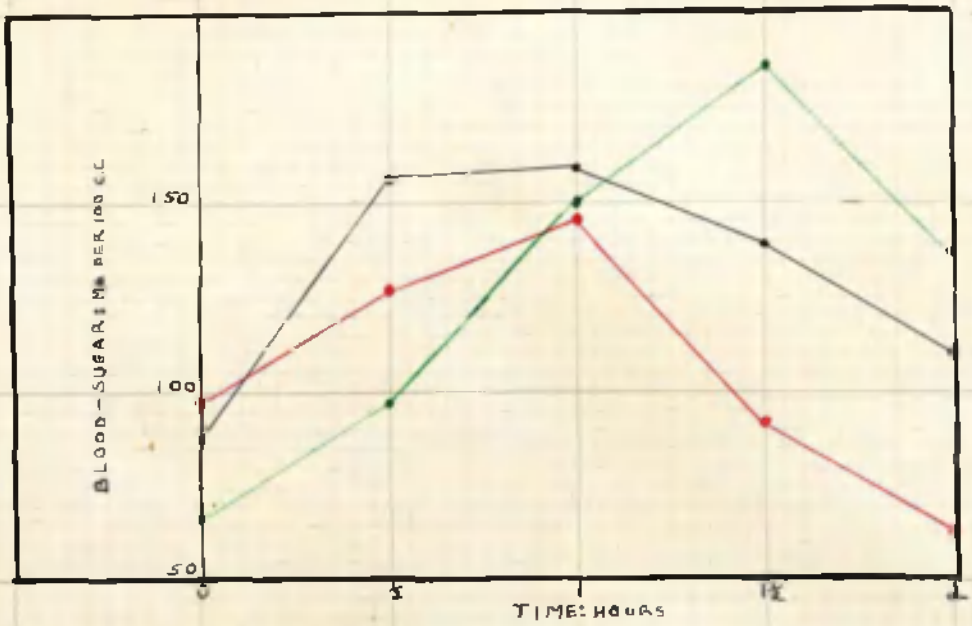
TABLE XI.

Fasting blood-sugar levels (in mg. per 100 c.c.) on balanced, and low- and high-carbohydrate diets.

Diet	No. of Estimations	Range	Mean	Standard Deviation
Balanced	14	70-98	81	9.7
High-carbohydrate	12	72-99	89	7.2
Low-carbohydrate	17	43-79	62	11.5

FIGURE XV.

Case 40. Oral Glucose Tolerance Curves showing typical response to change of diet.



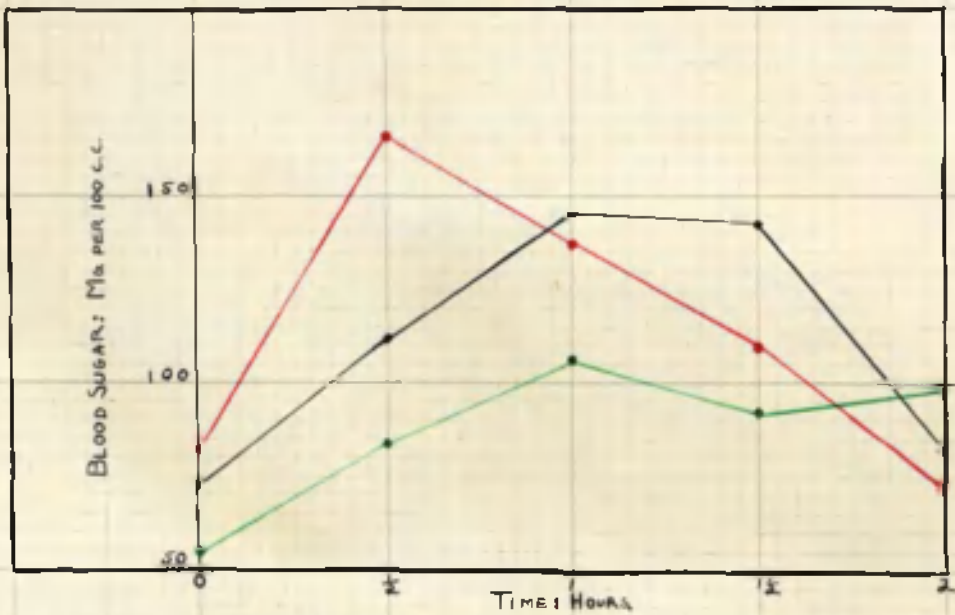
Balanced Diet

High-Carbohydrate Diet.

Low-Carbohydrate Diet.

FIGURE XVI.

Case 3. Oral Glucose Tolerance Curves showing atypical response to change of diet.



Balanced Diet.

High-Carbohydrate Diet.

Low-Carbohydrate Diet.

carbohydrate diets and those obtained on the other diets appears to be of real statistical significance.

Results of the oral glucose tolerance tests are shown in Table XII. It will be seen that in every case except Case 3 the high-carbohydrate diet was accompanied by some increase in oral glucose tolerance and the low-carbohydrate diet by some diminution of oral glucose tolerance. The changes are not, however, of a very striking degree. In each case a heavy ketonuria accompanied the low-carbohydrate diet, and in Case 40 slight glycosuria occurred on this diet. In Case 3 an abnormally low fasting blood-sugar concentration (54 mg. per 100 c.c.) was obtained on the low-carbohydrate diet. The greatest concentration attained by the blood-sugar during the oral tests on this subject was much lower on the low-carbohydrate diet than on the high-carbohydrate or balanced diets; but on the low-carbohydrate diet the concentration was rising at the end of two hours and was much in excess of the low fasting level. The greatest hyperglycaemia occurred in the half-hour specimen during the high-carbohydrate régime, but the curve subsequently fell steeply. In Figures XV and XVI the oral tolerance tests from Cases 40 and 3 are charted as examples of the typical and atypical responses of oral glucose tolerance to change of diet.

From these results it appears that alterations in oral glucose tolerance as a sequel to changes of diet may occur less constantly and be of smaller range in children than has been generally accepted.

TABLE XII.

Oral glucose tolerance tests on normal subjects during periods on balanced diet, low-carbohydrate diet and high-carbohydrate diet.

Case	Age: years	Blood-sugar in mg. per 100 c.c.					Max. level	Max. rise	Blood CO_2 vols. %	Diet and Duration
		Fasting	½-hr.	1 hr.	1½ hrs.	2 hrs.				
3	7	72	111	145	143	84	145	73	55	Balanced
		84	167	138	110	72	167	83	56	High CHO. 14 days
		54	84	106	93	99	106	52	45	Low CHO. 8 "
4	10	81	131	120	101	96	131	45	-	Balanced
		96	128	119	99	84	128	32	-	High CHO. 1 week
		54	129	150	131	129	150	96	30	Low CHO. 5 days
26	7	70	96	150	142	131	150	80	-	Balanced
		60	102	181	174	140	181	121	35	Low CHO. 1 week
34	9	75	131	120	90	84	131	56	48	Balanced
		44	118	131	136	152	152	108	45	Low CHO. 3 weeks
		86	114	125	84	78	125	39	50	High CHO. 1 week
38	11	98	161	157	113	95	161	63	52	Balanced
		83	138	163	104	79	163	80	55	High CHO. 12 days
		88	148	108	108	96	148	60	58	" " 3 weeks
		79	139	177	136	117	177	98	40	Low CHO. 10 days
40	12	88	155	159	139	108	159	71	51	Balanced
		96	128	141	92	64	141	45	50	High CHO. 1 week
		66	97	146	186	138	186	120	40	*Low CHO. 1 week

*Slight glycosuria.

CHO = carbohydrates.

TABLE XIII.

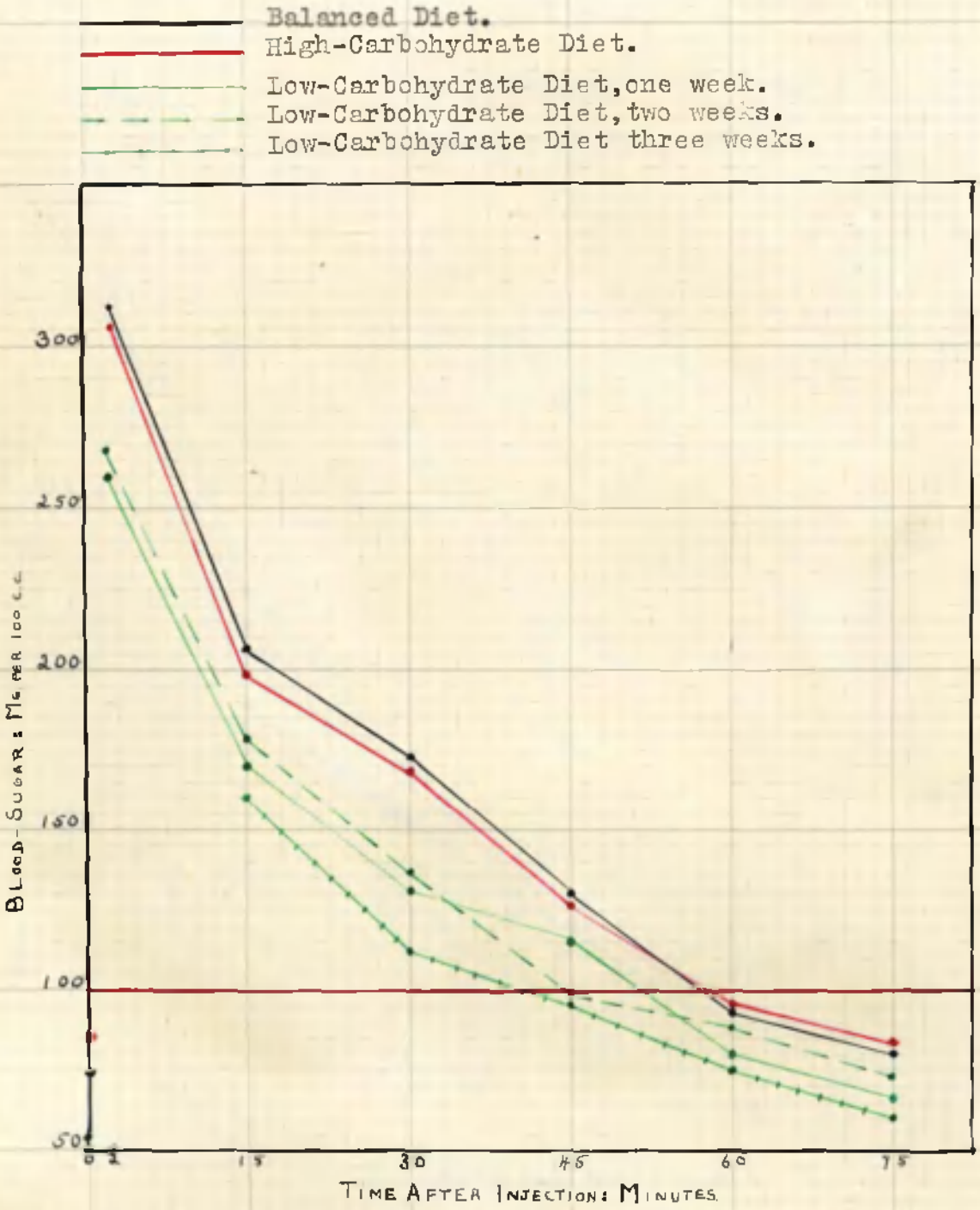
Intravenous glucose tolerance tests on normal subjects during periods on balanced diet, low-carbohydrate diet and high-carbohydrate diet.

Case	Age: yrs.	Blood-Sugar: mg. per 100 c.c.								Blood CO_2 vols. %	Diet	Remarks
		Fasting	2 mins	15 mins	30 mins	45 mins	60 mins	75 mins	90 mins			
3	7	70	294	191	146	111	97	90	92	55	Balanced.	Normal curve
		72	276	209	138	110	93	81	84	56	High CHO. 12 days	No significant change
		68	288	195	136	102	74	61	88	40	Low CHO. 2 days	" " "
		68	305	188	141	106	92	72	75	45	" " 8 days	" " "
4	10	92	329	230	177	138	90	86	81	48	Balanced.	Normal curve
		95	334	228	175	140	88	80	78	50	High CHO. 7 days	No significant change
		73	262	190	134	102	74	68	59	28	Low CHO. 3 days	Increased tolerance
26	7	70	292	208	168	145	110	90	81	53	Balanced.	Normal curve
		51	304	225	171	141	119	94	83	31	Low CHO. 4 days	No significant change
34	9	71	314	208	173	131	94	81	77	50	Balanced.	Normal curve
		52	260	171	132	120	80	66	57	32	Low CHO. 7 days	Slightly increased tolerance
		48	268	182	136	99	88	74	68	38	Extra low. 14 days	More marked increase of tolerance
		43	264	161	125	99	75	61	68	45	" " 21 days	Further increase of tolerance
		86	308	199	171	128	96	83	80	50	High CHO. 7 days	Tolerance as on balanced diet
38	11	95	298	246	178	135	110	90	94	-	Balanced.	Normal curve
		86	298	232	168	125	101	88	88	52	"	No change
		86	282	228	163	122	102	79	83	55	High CHO. 7 days	" "
		92	296	234	168	120	101	88	86	58	Extra high. 21 days	" "
		84	301	215	168	127	104	93	77	53	Balanced.	" "
		70	305	199	152	120	77	66	70	38	Low CHO. 6 days	Increased tolerance
		79	272	209	157	113	93	74	75	40	" " 10 days	" "
		74	282	215	161	119	97	74	72	43	" " 14 days	" "
40	12	88	329	190	152	122	86	75	68	51	Balanced.	Normal curve
		99	306	215	166	124	95	83	61	50	High CHO. 9 days	No significant change
		68	336	224	168	113	92	79	77	40	Low CHO. 6 days	" " "

The results of the intravenous glucose tolerance tests are recorded in Table XIII and they reveal quite different changes. In no case did the change from a balanced diet to a

FIGURE XVIII.

Intravenous Glucose Tolerance Curves in Case 34, showing progressive increase of tolerance on low-carbohydrate diet, but no change of tolerance on high-carbohydrate diet.



high-carbohydrate diet cause any significant alteration in the tolerance to intravenously injected glucose, though the high-carbohydrate diet was persisted in for three weeks in Case 38, with additional carbohydrate during the second and third weeks. The diet was never employed for a shorter period than one week.

On the low-carbohydrate diets the speed with which ketosis and acidosis developed, as judged by the ketonuria and the blood carbon dioxide content respectively, varied greatly from case to case. Thus the duration of the diet varied from three days in Case 4, who quickly developed a severe acidosis, to three weeks in Case 34, in whom acidosis was never severe. During the period on low-carbohydrate diets Cases 3, 26 and 40 showed no significant change of intravenous glucose tolerance compared with the results obtained during the period on balanced diets. Case 34, on the other hand, showed definite increase of tolerance on the low-carbohydrate diet, and a further increase of tolerance occurred when carbohydrate was further restricted at the end of the first week. Cases 4 and 38 showed a similar, though slighter change. In Figures XVII and XVIII the curves from Cases 40 and 34 are charted as examples of (1) no change in tolerance to intravenous glucose on high- and low-carbohydrate diet (Figure XVII) and (2) no change of intravenous glucose tolerance on high-carbohydrate diet, but progressive increase of tolerance on low-carbohydrate diet (Figure XVIII).

It is important to note that in these normal subjects any change in intravenous glucose tolerance while on a low-carbohydrate diet was in the direction of <u>increased</u> tolerance;

and that this change occurred simultaneously with diminished tolerance to oral glucose. Similarly, while on a high-carbohydrate diet, tolerance to oral glucose increased in four out of five cases, though tolerance to intravenous glucose showed no significant change in any of the cases.

Discussion.

Gilchrist (1932 a and b) also obtained lower fasting blood-sugar levels on a low-carbohydrate diet than on a balanced diet in children. In Himsworth's adult cases (1934) the difference was not more than a few mg. per 100 c.c.; and in the present series it is noteworthy that the lowest fasting levels on low-carbohydrate diet were obtained among the younger subjects. The findings suggest that in young children the hepatic mechanism for the formation of glucose from non-carbohydrate sources is less active than in older subjects. Thus, when the glycogen stores become depleted as the result of carbohydrate deprivation, the blood-sugar concentration becomes stabilised at a lower level. Even with blood-sugar values as low as 43 mg. per 100 c.c. no hypoglycaemic manifestations have been observed from this cause. It would seem that the entire organism adapts itself to a lower "head of pressure" of glucose in the circulating fluid.

The interpretation of the apparently conflicting results of the oral and intravenous glucose tolerance tests must remain a matter of conjecture. It is possible that the changes in oral glucose tolerance reflect merely some local change in the bowel

or in hepatic function whereas the intravenous tests give a more general index of "systemic" tolerance.

Himsworth (1934a) showed that changes of oral glucose tolerance on low-carbohydrate diet were not due to ketosis or acidosis; and it is clear from the results in Case 34 that the opposite change of intravenous glucose tolerance is also independent of these factors. In this subject tolerance increased progressively during three weeks on low-carbohydrate diet, though (as is usual) acidosis and ketosis gradually diminished after the seventh day. In Case 38 also, tolerance remained at a high level, while acidosis and ketosis diminished.

While the explanation of the findings remains in doubt it is clear that caution must be exercised in interpreting the changes of oral glucose tolerance with change of diet. In particular a great deal of theorising concerning insulin and pituitary action (Himsworth, 1933, 1934 a and b; Himsworth and Scott, 1938 a and b), the etiology of diabetes mellitus (Himsworth, 1935 a and b; Himsworth and Marshall, 1935) and the pathogenesis of sprue (Fairley, 1936), coeliac disease (Ross, 1936a) and anorexia nervosa (Ross, 1938b) must be questioned on the strength of the present findings.

Summary.

In six normal subjects the effects of high- and low-carbohydrate diet on oral and intravenous glucose tolerance were investigated.

All but one showed the typical impairment of oral glucose tolerance on low-carbohydrate diet and increase of oral tolerance on high-carbohydrate diet. Intravenous glucose tolerance remained unaltered on high-carbohydrate diet but, in three cases, the intravenous tolerance became definitely increased during the period of low-carbohydrate intake.

The explanation of this apparently paradoxical finding remains obscure, but one fact seems clear - carbohydrate starvation does not interfere with the ability of the tissues to metabolise glucose introduced directly into the systemic circulation.

B. THE EFFECT OF STARVATION.

The phenomenon of "hunger diabetes" has been known for many years; Bernard (1877) encountered it in dogs, and Hofmeister (1889) found it in human subjects. Many observers have since confirmed its occurrence. It may be defined as the occurrence of glycosuria, following ingestion of carbohydrate in moderate amount, in a subject previously starved or on a defective diet for a considerable period.

It has been repeatedly shown that oral glucose tolerance undergoes a similar deterioration during starvation to that which occurs on low-carbohydrate diet (Bang, 1913; Boe, 1913; Barrenscheen, 1913; Bergmark, 1915; Staub, 1922; Severinghaus, 1925). Du Vigneaud and Karr (1925) showed that the longer the preceding starvation period in rabbits the higher and later did the apex of the oral blood-sugar curve become, and the slower was the fall. They stated, however, that this deterioration of oral tolerance could be prevented by the administration of sodium bicarbonate - a finding which later experimenters have failed to confirm. Respiratory metabolic studies (Hines, Boyd and Leese, 1929; Dann and Chambers, 1930) have shown that there may be almost complete suppression of the ability to oxidise ingested glucose after a prolonged fast, the ability being gradually and progressively restored with successive doses of glucose.

A detailed investigation of the effects of starvation is obviously impossible in a clinical study. During the course of the present researches, however, two patients were encountered on whom a seventy-two-hour fast was imposed as a therapeutic measure for the treatment of tapeworms, shorter fast-periods having failed. The opportunity was taken of performing intravenous glucose tolerance tests at the beginning and end of the fast. During the seventy-two hours between the tests nothing but water was taken by the mouth. A heavy ketonuria developed in both cases, but blood carbon dioxide estimations were not made.

The results of the intravenous glucose tolerance tests are recorded in Table XIV, in which test I refers to the tolerance test at the beginning, and test II to that at the end, of the seventy-two-hour fast in each case. It is clear that in Case 21

TABLE XIV.

The effect of starvation on intravenous glucose tolerance.

Case	Age in years	Test	Blood-sugar: mg. per 100 c.c.								Remarks
			Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	
21	5	I	97	286	168	111	84	83	63	66	Normal
		II	85	307	171	119	90	87	79	68	No change
68	$3^{10}/_{12}$	I	84	291	186	140	111	88	84	86	Normal
		II	72	267	166	127	95	81	77	74	Increase of tolerance

the starvation period was without effect on intravenous glucose tolerance, while in Case 68 a slight increase of tolerance occurred.

This finding is in agreement with the findings on low-carbohydrate diet: any change of intravenous glucose tolerance which occurs during a period of carbohydrate deprivation is in the direction of increased tolerance.

C. THE EFFECT OF ACID-SALT ADMINISTRATION.

Haldane, Wigglesworth and Woodrow (1924) demonstrated that transient sudden changes in the reaction of the blood, either to the acid or the alkaline side, were associated with impairment of sugar tolerance. Field and Newburgh (1927), studying the effect of direct injections of acid and alkali on blood-sugar levels, concluded that the addition of acid to the blood exerted a depressing influence on sugar metabolism. Gilchrist (1932a) investigated the action of ammonium chloride administration on the oral glucose tolerance of nine healthy children. The results were somewhat conflicting; two of the children showed definitely impaired oral tolerance, two showed slight increase of tolerance, while the remainder showed little change. The author concluded that the acidosis produced by ammonium chloride administration caused no notable disturbance

of carbohydrate metabolism. Himsworth (1934a) showed that the impaired oral glucose tolerance produced by low-carbohydrate diet could not be brought back to normal by sodium bicarbonate administration; and similarly, that the improvement of oral tolerance on high-carbohydrate diet could not be prevented by ammonium chloride administration.

In the present investigation the effect of ammonium chloride administration on the intravenous glucose tolerance of three of the children from the normal series has been studied. A dosage of 10 grams of ammonium chloride a day was employed and was continued until the reaction of the urine reached a pH of 4 and a moderate reduction of the blood carbon dioxide content had occurred. This required from five to nine days. Intravenous glucose tolerance tests were carried out before commencing administration of the salt and were repeated when the full effect had been produced. A standard balanced diet was given throughout.

The results of the tests are detailed in Table XV. It will be seen that in two of the cases (27 and 29) no alteration in tolerance to intravenous glucose occurred, while in the third (Case 33) slight impairment of tolerance resulted. This child showed some gastric upset as a result of the drug and this may have been responsible for the prolongation of the curve.

TABLE XV.

Intravenous glucose tolerance tests before and during ammonium chloride administration

Case	Age in yrs.	Test	Blood-sugar: mg. per 100 c.c.								Blood CO_2 vols.%	Remarks
			Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.		
27	7	A	74	323	220	165	101	79	67	77	-	Normal tolerance
		B	78	340	218	160	103	84	78	81	-	No change
29	8	A	92	306	202	139	111	77	61	59	48	Normal tolerance
		B	81	290	206	144	110	83	73	70	40	No change
33	9	A	90	335	238	200	166	127	92	74	52	Normal tolerance
		B	84	341	242	210	174	140	112	88	41	Slight diminution of tolerance

Test A - prior to ammonium chloride administration.
" B - during " " "

D. ACIDOSIS AND KETOSIS ACCOMPANYING ACUTE INFECTIONS.

I. Alimentary Infection.

Acidosis and ketosis are almost constant accompaniments of the more severe infections of the alimentary tract in childhood. They are regarded as resulting from the starvation which the child suffers due to inability of his stomach to retain food or of his bowel to absorb it. In addition, there is increased loss of fixed base in the stools (Holt, Courtney and

Fales, 1915; Hoag and Marples, 1931). The severity of the ketosis and acidosis bears an approximate relationship to the severity of the alimentary infection.

In the present investigation three cases of alimentary infection have been studied - one case of moderate severity, one severe case which recovered, and one case in which the infection proved rapidly fatal. Intravenous glucose tolerance tests were carried out on each patient at the height of the infection, and, in the two children who recovered, the test was repeated when convalescence was well-established. The results of the intravenous tolerance tests are recorded in Table XVI, and brief notes of the three cases are here appended.

Intravenous

Case	Age in years	Blood-suga:			
		Fasting	2 mins.	15 mins.	
69	15/12	64	272	180	:
		81	280	174	1
70	11/12	66	241	186	1
		77	272	188	1
71	3½	143	385	272	2

Case 69. J.J., a male child, aged 15 months, was admitted to hospital with a history of diarrhoea and vomiting for fourteen days. There was a moderate degree of dehydration and the urine contained abundant ketone bodies. The blood carbon-dioxide content at this time was 40 volumes per 100 c.c. and the intravenous glucose tolerance test showed a slight delay in return of the blood-sugar to normal fasting levels (sixty minutes, compared with the normal limits, for the child's age, of thirty to forty-five minutes). Response to dietetic treatment was rapid, and following recovery, the intravenous test was repeated and yielded a normal result.

Case 70. J.W., a male infant, aged 11 months, had had severe vomiting and diarrhoea for one week prior to admission to hospital. On admission he was severely dehydrated and acidotic breathing was marked. The blood carbon-dioxide content had fallen to 25 volumes per 100 c.c. and the intravenous glucose tolerance test showed definite delay in the fall to fasting values. Repetition of the test during convalescence gave a normal result. (Table XVI).

Case 71. B.A., a female child, aged 3½ years, was brought to hospital with a history of vomiting and diarrhoea for one week. Prior to this she had been in perfect health, and no history of polydipsia or polyuria could be obtained. On admission she was semi-comatose, dehydrated and severely acidotic. The urine contained abundant ketones, but no sugar. The blood carbon-dioxide content was only 21 volumes per 100 c.c. and the intravenous test (Table XVI) indicated an almost complete failure of the tissues to deal with intravenously injected glucose. There was no response to treatment and the child died thirty-six hours after admission.

Post-mortem examination (performed by Dr. K.J. Guthrie) revealed an intense inflammatory lesion of the ileum and colon. In the liver areas of focal necrosis were present, in addition to diffuse fatty change.

The possibility, suggested by the result of the glucose tolerance test, that this child had a very acute form of diabetes mellitus, was discarded in view of the history and the post-mortem findings.

We thus find that alimentary tract infection is associated with impairment of tolerance to intravenous glucose, and that the extent of the impairment is approximately proportional to the severity of the infection and the degree of ketosis

TABLE XVI.

Intravenous glucose tolerance tests in 3 cases of acute alimentary infection.

Case	Age in years	Blood-sugar: mg. per 100 c.c.								Blood CO_2 vols.%	Clinical condition	Remarks
		Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.			
69	15/12	64	272	180	121	104	82	80	-	40	Moderately severe gastro-enteritis	Slightly impaired tolerance
		81	280	174	116	95	78	80	-	48	Convalescent	Normal tolerance
70	11/12	66	241	186	131	111	90	93	93	25	Severe gastro-enteritis	Impaired tolerance
		77	272	188	132	90	83	75	81	43	Convalescent	Normal tolerance
71	3½	143	385	272	249	241	239	236	234	21	Fulminating fatal ileo-colitis	Grossly impaired tolerance

Fales, 1915; Hoag and Marples, 1931). The severity of the ketosis and acidosis bears an approximate relationship to the severity of the alimentary infection.

In the present investigation three cases of alimentary infection have been studied - one case of moderate severity, one severe case which recovered, and one case in which the infection proved rapidly fatal. Intravenous glucose tolerance tests were carried out on each patient at the height of the infection, and, in the two children who recovered, the test was repeated when convalescence was well-established. The results of the intravenous tolerance tests are recorded in Table XVI, and brief notes of the three cases are here appended.

Case 69. J.J., a male child, aged 15 months, was admitted to hospital with a history of diarrhoea and vomiting for fourteen days. There was a moderate degree of dehydration and the urine contained abundant ketone bodies. The blood carbon-dioxide content at this time was 40 volumes per 100 c.c. and the intravenous glucose tolerance test showed a slight delay in return of the blood-sugar to normal fasting levels (sixty minutes, compared with the normal limits, for the child's age, of thirty to forty-five minutes). Response to dietetic treatment was rapid, and following recovery, the intravenous test was repeated and yielded a normal result.

Case 70. J.W., a male infant, aged 11 months, had had severe vomiting and diarrhoea for one week prior to admission to hospital. On admission he was severely dehydrated and acidotic breathing was marked. The blood carbon-dioxide content had fallen to 25 volumes per 100 c.c. and the intravenous glucose tolerance test showed definite delay in the fall to fasting values. Repetition of the test during convalescence gave a normal result. (Table XVI).

Case 71. B.A., a female child, aged 3½ years, was brought to hospital with a history of vomiting and diarrhoea for one week. Prior to this she had been in perfect health, and no history of polydipsia or polyuria could be obtained. On admission she was semi-comatose, dehydrated and severely acidotic. The urine contained abundant ketones, but no sugar. The blood carbon-dioxide content was only 21 volumes per 100 c.c. and the intravenous test (Table XVI) indicated an almost complete failure of the tissues to deal with intravenously injected glucose. There was no response to treatment and the child died thirty-six hours after admission.

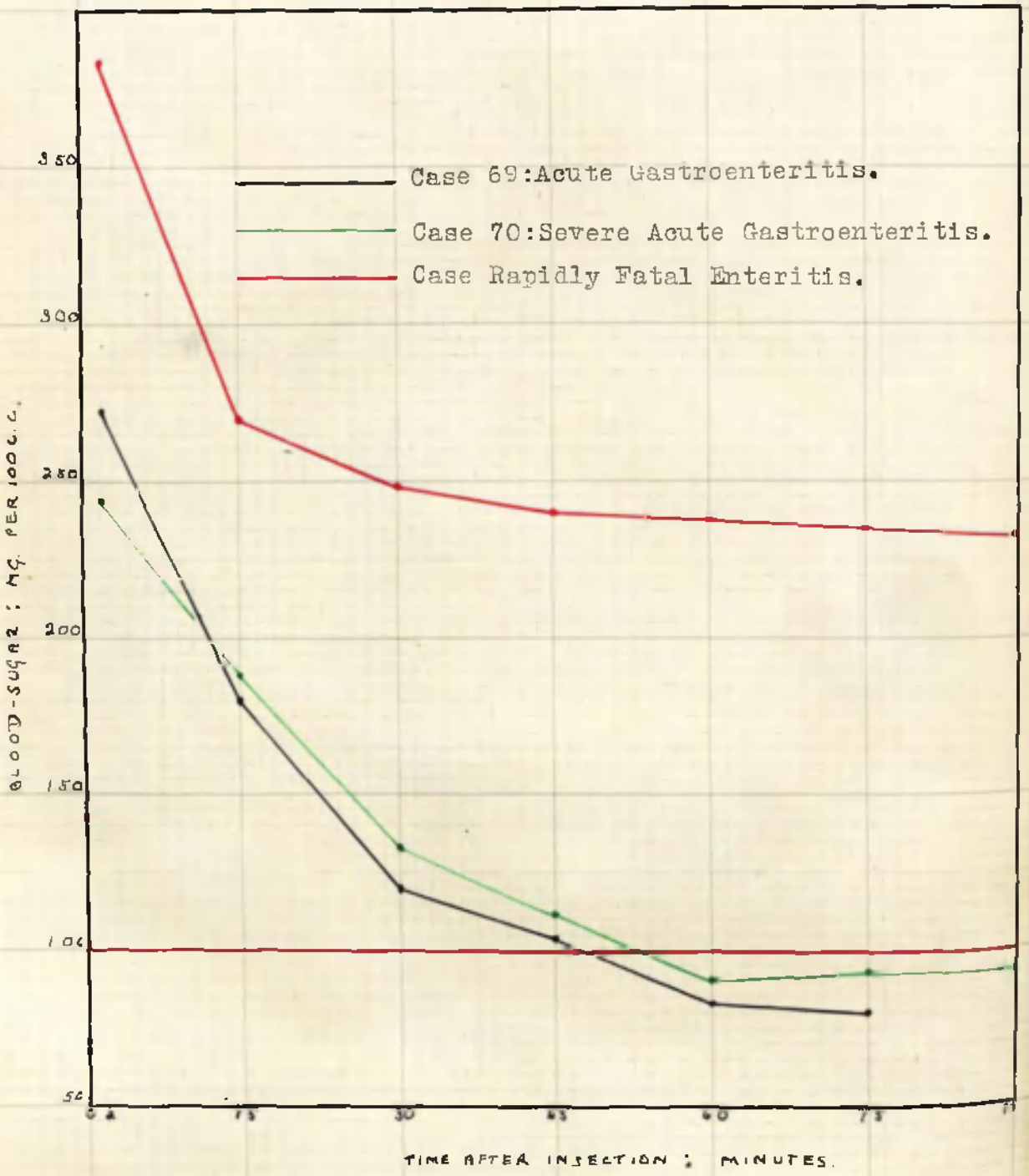
Post-mortem examination (performed by Dr. K.J. Guthrie) revealed an intense inflammatory lesion of the ileum and colon. In the liver areas of focal necrosis were present, in addition to diffuse fatty change.

The possibility, suggested by the result of the glucose tolerance test, that this child had a very acute form of diabetes mellitus, was discarded in view of the history and the post-mortem findings.

We thus find that alimentary tract infection is associated with impairment of tolerance to intravenous glucose, and that the extent of the impairment is approximately proportional to the severity of the infection and the degree of ketosis

FIGURE XIX.

Intravenous Glucose Tolerance Curves in Cases of Acute Alimentary Infection.



and acidosis produced. This is further illustrated in Figure XIX where the intravenous tolerance tests from the three cases during the height of the infection are charted together. In Cases 69 and 70 a moderately severe alimentary infection was associated with a moderate impairment of intravenous glucose tolerance; in Case 71 an overwhelming infection was responsible for an almost complete failure of the intermediary carbohydrate mechanism.

2. Respiratory Infection.

Infections of the respiratory tract are not usually accompanied by any considerable acidosis or ketosis, but from time to time, amongst children, cases are encountered in which such an infection is associated with these changes. Four such cases have been investigated in the present study - two children with pneumonia and two with relatively mild upper respiratory infections. Intravenous glucose tolerance tests were carried out during the acidotic period and again after recovery in each case and the results of these tests are recorded in Table XVII. In each case there was impairment of tolerance to intravenous glucose during the acute phase, with normal tolerance after recovery. In Case 51 an additional test was made the day after the pyrexia had subsided by crisis. The result of this test was intermediate in character between the grossly impaired tolerance found at the height of the infection and the normal tolerance found when convalescence was well-established.

FIGURE XX.

Intravenous Glucose Tolerance Curves in Cases of Respiratory Infection with Ketosis.

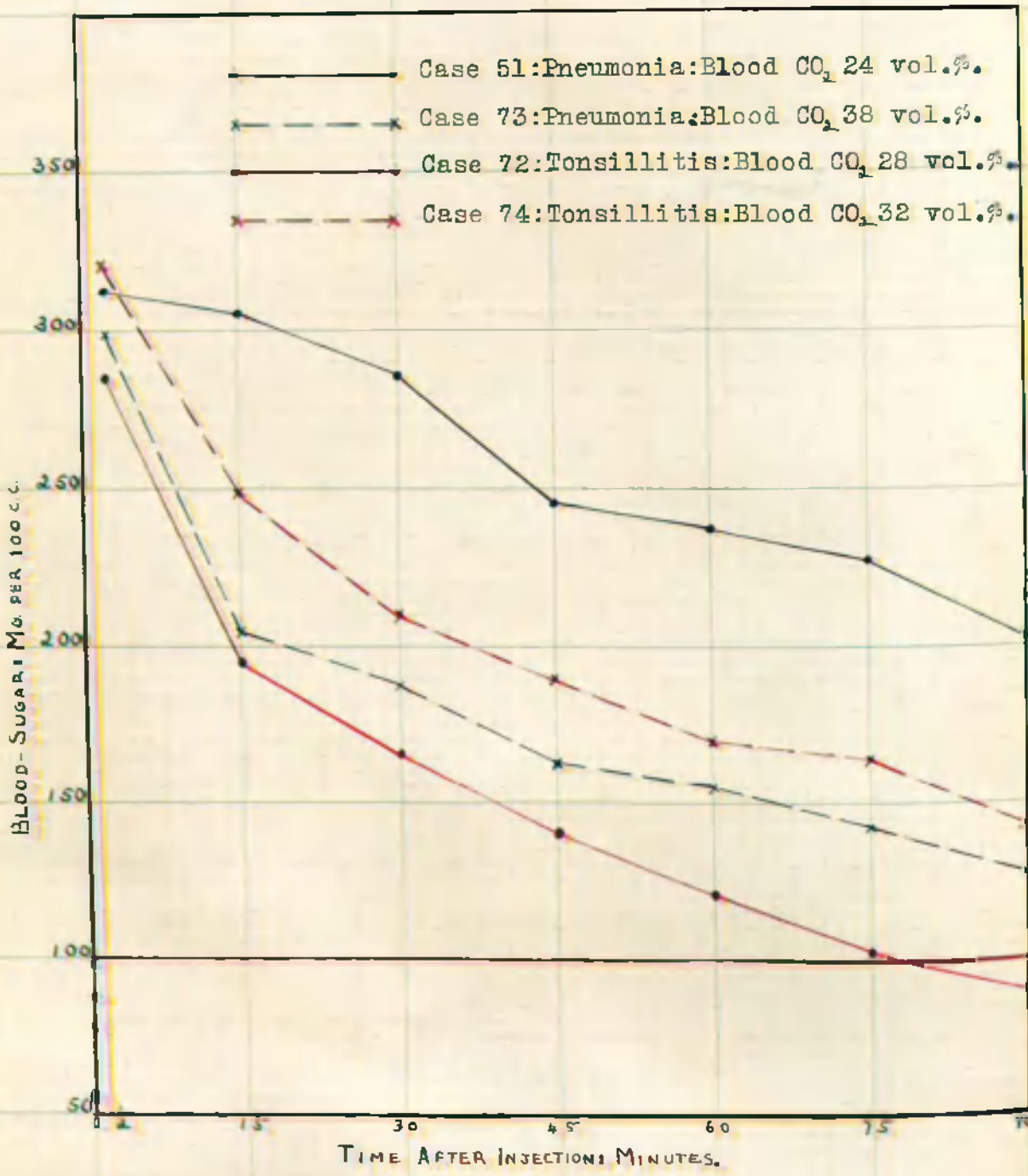


TABLE XVII.

Intravenous glucose tolerance tests in respiratory infections associated with acute ketosis.

Case	Age in years	Blood-sugar: mg. per 100 c.c.								Blood CO_2 vols.%	Clinical condition	Remarks
		Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.			
51	5	87	312	308	285	248	238	227	202	24	Pneumonia. Ketonuria. Fever.	Grossly impaired tolerance
		81	313	300	250	202	124	120	88	48	Day following crisis.	Impaired tolerance
		84	302	292	224	158	92	86	87	-	Convalescent.	Normal tolerance
72	7	54	286	195	168	139	122	102	81	28	Upper respiratory infection. Ketonuria. Fever.	Impaired tolerance
		83	312	197	168	127	93	84	81	49	Convalescent.	Normal tolerance
73	8½	99	298	204	188	164	154	142	127	38	Pneumonia. Ketonuria. Fever.	Severely impaired tolerance
		70	348	234	145	113	105	79	65	52	Convalescent	Normal tolerance
74	10½	77	321	249	209	188	170	166	143	32	Upper respiratory infection. Ketonuria. Fever.	Grossly impaired tolerance
		84	385	245	179	152	108	79	70	50	Convalescent.	Normal tolerance

In Figure XX the results of the intravenous glucose tolerance tests during the acute periods in the four cases are charted together. There appears to be no relationship between the degree of impairment of tolerance to intravenous glucose and the severity of the infection as judged by clinical standards. Case 73 was the most gravely ill of the patients, but showed only a moderate impairment of tolerance, whereas Case 51, though never gravely ill, showed a grossly impaired tolerance.

These four children all had some elevation of temperature at the time of the initial tolerance tests, and the possibility that this may have been the disturbing factor in glucose tolerance was considered. Accordingly, the test was applied to three cases of respiratory infection (one case of pneumonia and two cases of upper respiratory infection) with a comparable degree of fever, but in whom ketosis was absent or minimal in amount (Rothera's test in the urine was weakly positive, the ferric chloride test negative). The results of these tests are given in Table XVIII.

TABLE XVIII.

Intravenous glucose tolerance tests on three cases of respiratory infection with pyrexia, but no gross ketosis.

Case	Age	Blood-sugar: mg. per 100 c.c.								Clinical condition	Remarks
		Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.		
75	5	73	281	202	164	118	90	71	74	Acute tonsillitis Pyrexia	Normal curve
76	9	68	312	214	176	141	111	84	72	Acute tonsillitis Pyrexia	Normal curve
77	9	84	338	206	168	121	104	90	81	Lobar pneumonia Pyrexia	Normal curve

The times at which normal fasting blood-sugar levels were regained are normal in each case. It seems apparent, therefore, that the impaired tolerance present during the acute infection period in the cases in Table XVII was not the result of the pyrexia.

FIGURE XXI.

Case 73: Intravenous Glucose Tolerance Curves showing the effect of Low-carbohydrate diet.

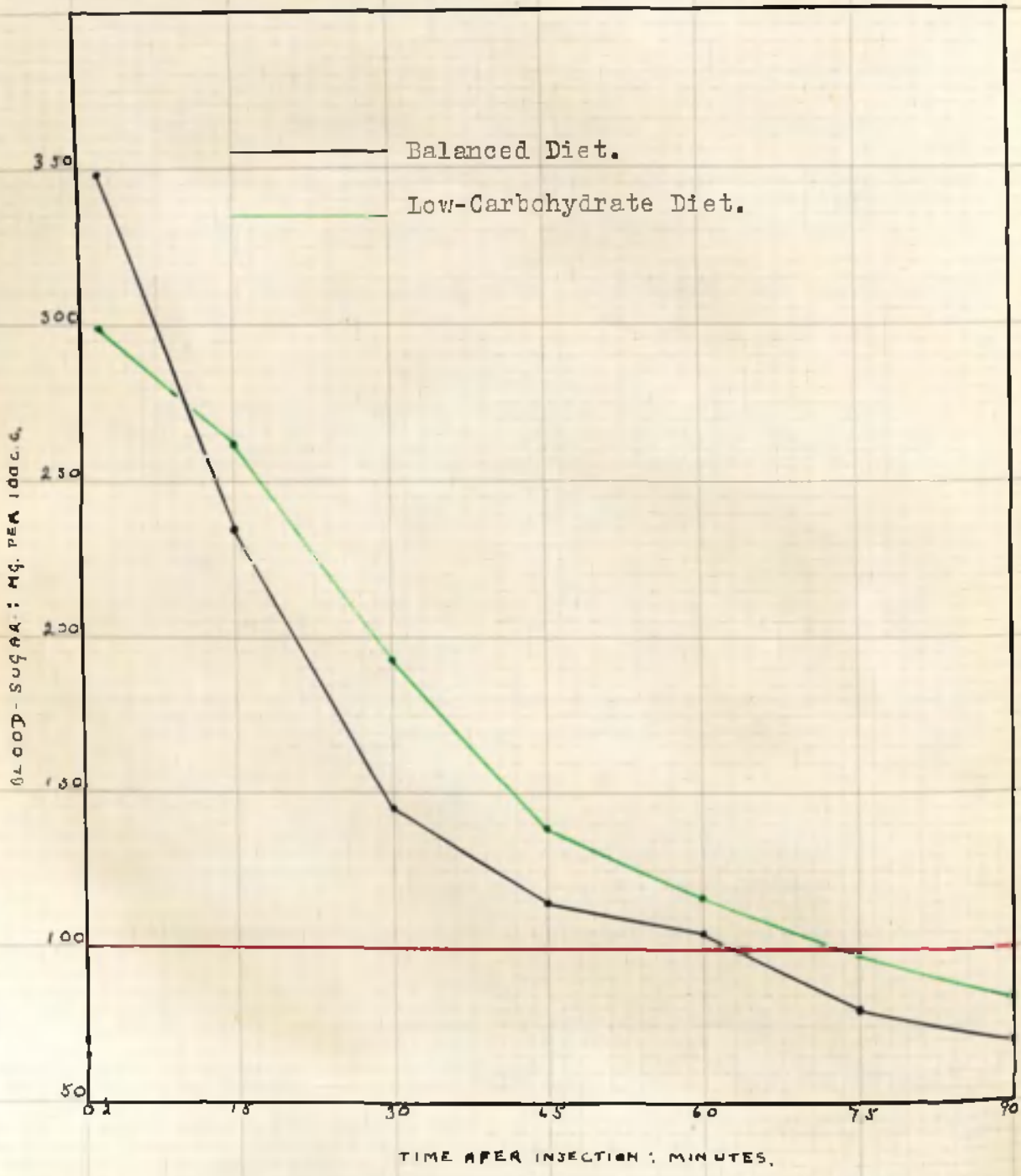
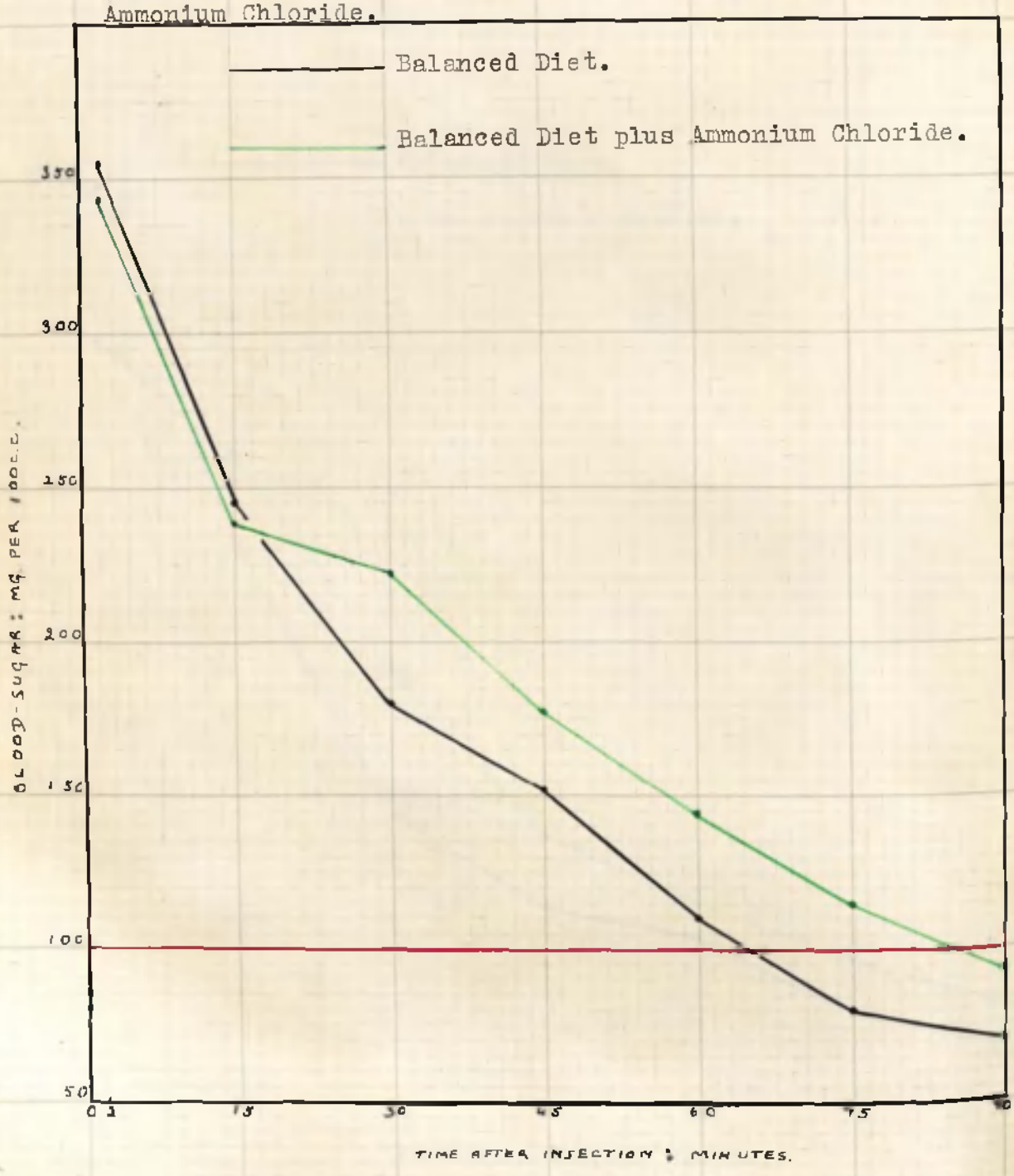


FIGURE XXII.

Case 74: Intravenous Glucose Tolerance Curves showing the effect of the administration of Ammonium Chloride.



As impairment of intravenous glucose tolerance thus appears to be a rather exceptional result of respiratory infection, an attempt was made to determine whether those patients showing the impairment gave evidence of undue instability of the intermediary carbohydrate metabolism under other conditions. To this end the effect of low-carbohydrate diet was studied in Case 73 and the effect of ammonium chloride administration in Case 74. The conditions were identical with those of the investigations on normal subjects reported above.

The results of the intravenous glucose tolerance tests before and during the administration of low-carbohydrate diet (Case 73) or ammonium chloride (Case 74) are recorded in Table XIX. In Case 73 a slight diminution of tolerance occurred during the period on low-carbohydrate diet (Figure XXI). Though the change is slight it is in marked contrast to the findings in the normal subjects in whom any change of tolerance to intravenous glucose on a low-carbohydrate diet was in the direction of an increased tolerance. (See Table XIII). Case 74, during the period of ammonium chloride administration showed a definite impairment of intravenous glucose tolerance (Figure XXII) in contrast to the findings in normal subjects (Table XV).

These results suggest that in those subjects in whom respiratory infection is associated with unusually marked ketosis there may be an underlying instability of the intermediary carbohydrate metabolism which is more readily disturbed by the products of infection than is the carbohydrate metabolism of the

TABLE XIX.

Intravenous glucose tolerance tests during periods on (a) Low-carbohydrate diet and (b) Ammonium chloride, in subjects previously showing impaired tolerance with respiratory infection.

Case	Age in years	Diet	Blood-Sugar: Mg. per 100 c.c.								Blood CO_2 vols.%	Remarks
			Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.		
73	8½	Balanced	70	348	234	145	113	105	79	65	52	Normal tolerance
		Low CHO: $\frac{2}{52}$	68	296	264	191	138	116	97	81	40	Slight diminution of tolerance
		" " $\frac{3}{52}$	95	286	195	163	139	118	95	83	-	" " " "
74	10	Balanced	84	355	245	179	152	108	79	70	50	Normal tolerance
		" + NH_4Cl	79	343	241	222	179	146	115	93	40	Impaired tolerance

individual in whom this response to infection is not seen. The impaired tolerance would lead to increased ketosis which would possibly augment the disturbance produced by the infective process and thus establish a vicious circle.

E. CARBOHYDRATE TOLERANCE IN SPONTANEOUS KETOSIS (CYCLICAL VOMITING).

Introduction.

Few paediatric subjects can have aroused such wide and at the same time unfruitful discussion as "cyclical vomiting." Among its many designations cyclical vomiting, recurrent acidosis or ketosis, or simply "acidosis" are those most frequently employed; I have preferred the term Spontaneous Ketosis as it stresses an essential feature of the condition, neglect of which has led to much of the existing confusion. Cases in which there is any discoverable cause for the ketosis should be rigidly excluded from this diagnosis. I have already in the preceding parts of this section dealt with the subject of ketosis accompanying infections, but many investigators including Ross and Josephs (1924) and Salomonsen (1930) have not made this distinction.

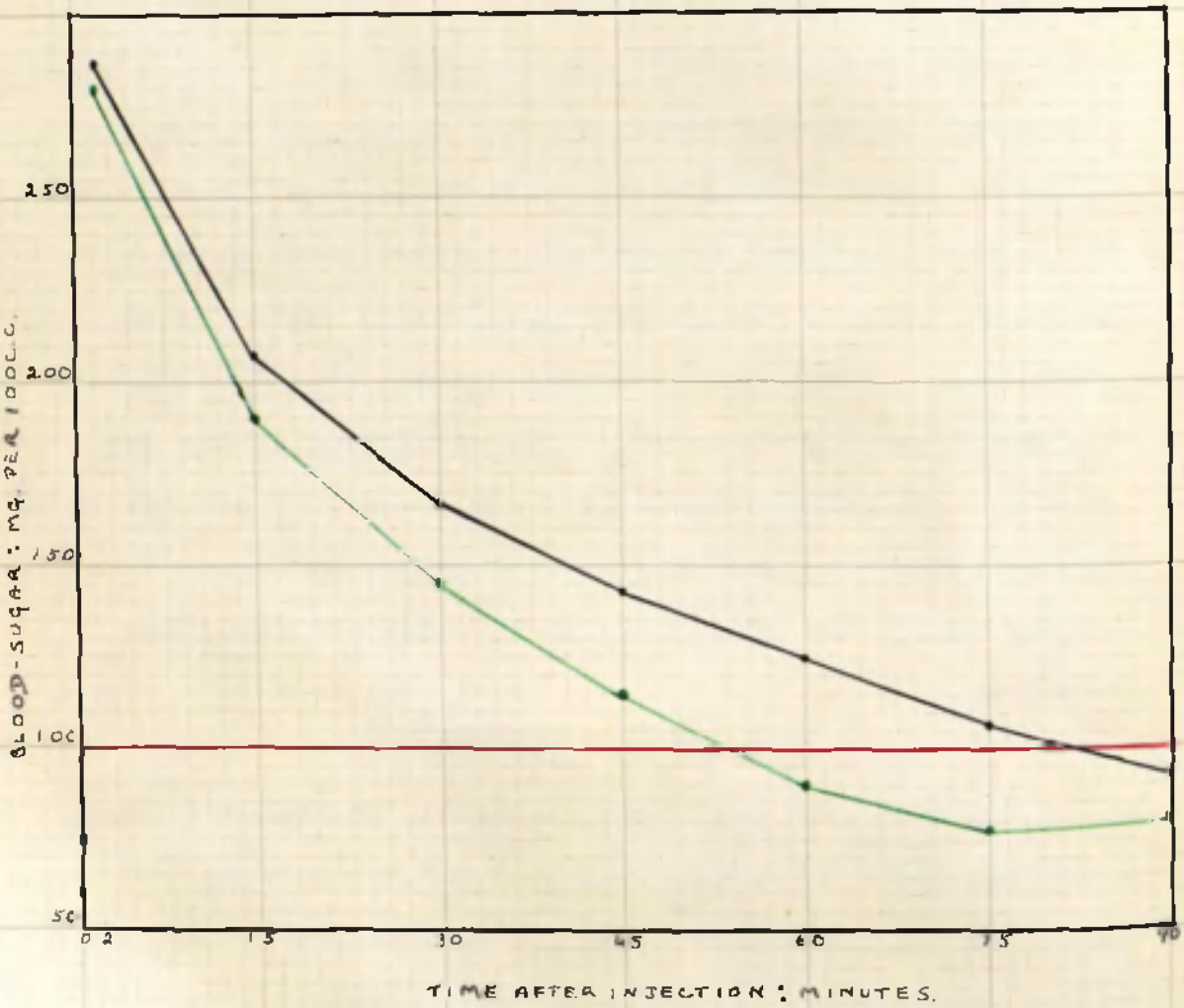
Investigations of carbohydrate tolerance during attacks of spontaneous ketosis have been singularly incomplete. Most observers agree in finding somewhat lowered fasting blood-sugar levels during the course of an attack (Hilliger, 1914; Knoepfelmacher, 1921; Ross and Josephs, 1924; Josephs, 1926; Salomonsen, 1930) and some (Ross and Josephs) have regarded this hypoglycaemia as being the essential feature of the disease. Graham and Morris (1933) however, point out that the hypoglycaemia is of only

FIGURE XXIII.

Intravenous Glucose Tolerance Curves in Spontaneous Ketosis: mean Curves during Attack and after Recovery.

Between Attacks.

During Attacks.



moderate degree, and in a case which they studied the blood-sugar level actually continued to fall slowly during the period of recovery. They noted also a positive laevulose test during the attack - evidence of impaired hepatic function.

Owing to difficulties dependent upon the vomiting, oral glucose tolerance tests have not been investigated during attacks of spontaneous ketosis. In these circumstances the intravenous test is especially useful.

Present Investigation.

Five children have been investigated in whom recurrent attacks of ketosis and vomiting (cyclical vomiting) remained unexplained by any underlying infection or other recognised pathological process. In each case intravenous glucose tolerance tests were carried out during an acute attack and again after recovery from the attack when all ketones had disappeared from the urine and the child appeared healthy. The results of these tests are detailed in Table XX and depicted in Figure XXIII, and it will readily be observed that in every case considerable impairment of tolerance to intravenous glucose was present during the attack and was replaced by normal tolerance after the attack had subsided. In each case the fasting blood-sugar levels were lower during the attack than after recovery. During attacks the values varied from 52 to 72 mg. per 100 c.c. (mean value 60.2), while after recovery the figures were 70 to 92 mg. per 100 c.c., with a mean value of 76.4

TABLE XX.

Intravenous glucose tolerance tests in cases of spontaneous ketosis (cyclical vomiting).

Case	Age in years	Blood-sugar: mg. per 100 c.c.								Blood CO_2 vols.%	Conditions of test	Remarks
		Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.			
78	7½	52	299	215	181	150	136	124	101	-	Acute attack	Markedly impaired tolerance
		92	331	208	166	132	94	81	88	-	Well	Normal tolerance
79	5	72	302	208	164	148	134	110	99	35	Acute attack	Impaired tolerance
		74	302	197	160	125	99	77	79	51	Well	Normal tolerance
80	6	61	284	204	170	146	124	102	86	32	Acute attack	Impaired tolerance
		70	234	177	131	115	92	88	77	48	Well	Normal tolerance
		72	266	181	134	111	90	82	86	38	After 8 days on NH_4Cl	No change
81	5½	60	286	222	179	148	128	106	94	-	Acute attack	Impaired tolerance
		70	292	190	128	96	80	72	76	-	Well	Normal tolerance
		64	298	186	132	94	82	68	70	36	After 6 days on low CHO diet	No change
82	5	56	259	191	141	120	106	95	87	37	Acute attack	Impaired tolerance
		76	268	184	138	106	83	71	82	-	Well	Normal tolerance

The effects of low-carbohydrate diet in Case 81, and of ammonium chloride administration in Case 80 were investigated, and the results of intravenous glucose tolerance tests performed before and during the period on diet or drug have been included in Table XX. In neither case did any disturbance of intravenous glucose tolerance occur, nor were the features of an acute "acidotic" attack precipitated. The responses were, in fact, identical with those obtained in normal children under similar conditions (Tables XIII and XV).

Discussion.

These findings are in agreement with Findlay's assertion (1930) that the metabolism in children subject to cyclical vomiting is not abnormal between the attacks. During attacks, however, the intravenous test has shown invariably moderate impairment of glucose tolerance as compared with the tolerance found between attacks. This supports the suggestion made by Graham and Morris (1933) that the cause of cyclical vomiting is a recurring temporary impairment of hepatic function.

As comparisons are frequently drawn between diabetes mellitus and cyclical vomiting it may be of interest to state, on the above hypothesis, the relationship between the ketoses in the two instances.

(1) In diabetes mellitus there is, from whatever cause, failure in the peripheral utilisation of glucose. In an attempt to

stimulate this peripheral utilisation by raising the "head of pressure" of glucose in the blood (Himsworth, 1939) hepatic formation of glucose from fat and protein runs riot. The waste products of this conversion accumulate and the result is ketosis with an elevated blood-sugar level.

(2) In spontaneous ketosis a sudden diminution of hepatic efficiency, the cause of which is unknown, affects especially the hepatic formation of sugar from non-carbohydrate sources. Peripheral utilisation of sugar is not seriously impaired, but as soon as the direct carbohydrate stores are exhausted no further supplies are available and fat combustion predominates over other catabolic processes. The waste products accumulate and the result is ketosis with a depressed blood-sugar level.

The lowering of the blood-sugar level during the acute attacks was somewhat greater than occurred with fasting in normal subjects (Table XIV) but of approximately the same degree as occurred in normal subjects during administration of a low-carbohydrate diet (Table XI). It seems clear that the hypoglycaemia is itself due to the hepatic disturbance (though possibly accentuated by the enforced fast after vomiting has commenced) and that it bears no causal relationship to the disturbance.

There has been much difference of opinion as to the possibility of reproducing the features of an attack of cyclical vomiting by the artificial induction of ketosis or acidosis in a child subject to attacks of spontaneous ketosis. Thus Hilliger

(1914), Knoepfelmacher (1921) and Ross and Josephs (1924) claimed that this could be accomplished, whereas Findlay (1930) and Ellis (1931) found no difference between normal children and cyclical vomiters in their response to artificially induced ketosis. Findlay actually showed that the deliberate administration of a ketogenic diet at the commencement of a mild attack of spontaneous ketosis did not prevent a rapid recovery. Salomonsen (1930) adopts an intermediate position; he found the administration of a ketogenic diet to the subjects of cyclical vomiting to reproduce the nervous agitation and restlessness of the spontaneous attack without the characteristic vomiting. In the present investigations none of the subjective symptoms of the spontaneous attack was reproduced either by ketogenic diet or by ammonium chloride administration. The children felt well and behaved normally.

Summary.

During an attack of spontaneous ketosis the following effects on carbohydrate metabolism are noted:

1. A fall of the fasting blood-sugar level, comparable in degree to that occurring in normal children during administration of a low-carbohydrate diet, but somewhat greater than occurs in normal children during a period of starvation.

2. Definite (but not extreme) impairment of intravenous glucose tolerance.

3. A strongly positive laevulose test, indicative of impaired

hepatic function (Graham and Morris, 1933).

Between attacks the subjects show a normal carbohydrate tolerance, and the response to induced ketosis and acidosis is normal.

The features of the spontaneous attack cannot be produced artificially.

SECTION V

CARBOHYDRATE TOLERANCE IN COELIAC DISEASE: THE CAUSATION OF THE LOW BLOOD-SUGAR CURVE.

Introduction.

Convincing evidence has been brought forward by Thaysen (1929b, 1932, 1935) that tropical and non-tropical sprue in adults and coeliac disease in children are essentially identical conditions, and he has grouped the three together as subdivisions of "Idiopathic Steatorrhoea," a syndrome which has also been referred to as "Gee-Thaysen disease." In 1926 Thaysen first drew attention to the abnormally small rise in the blood-sugar content following the ingestion of glucose in cases of non-tropical sprue. In subsequent papers (Thaysen, 1929a, 1932, 1935; Thaysen and Norgaard, 1929) he extended this observation and defined the low blood-sugar curve as one showing a rise of 40 mg. per 100 c.c. or less during two hours following the ingestion of 60 grams of glucose in adults. He showed such a curve to occur as an inconstant phenomenon in 5 per cent. of normal subjects, while in non-tropical sprue it occurred fairly constantly in 50 per cent. of the cases. Thaysen's findings in non-tropical sprue have been confirmed by many later observers (Holst, 1927; Engel, 1931;

Bennett, Hunter and Vaughan, 1932; Thorfinn, 1933; Anderson and Lyall, 1933; Moore, O'Farrell, Geraghty, Hayden and Moriarty, 1936; Mogensen, 1937; Nussbrecher and Morton, 1937).

A similar low blood-sugar curve in children suffering from coeliac disease was demonstrated independently by Fanconi (1928), Svensgaard (1929) and MacLean and Sullivan (1929), and their findings have been frequently confirmed (Thaysen, 1929b; MacRae and Morris, 1931; Badenoch and Morris, 1936). The low curve appears to be a more constant feature of coeliac disease than of sprue.

In the present investigation the occurrence of the low blood-sugar curve in coeliac disease has been confirmed, and an attempt has been made to determine its causation. Accepting Thaysen's contention that sprue and coeliac disease are essentially the same condition, deductions from biochemical changes found in one should be applicable to the other. The origin of the low blood-sugar curve in these conditions has been the subject of considerable experiment and discussion. The possible causes of such a curve are:

1. Lowered renal threshold to glucose.
2. Diminished or delayed absorption of sugar from the bowel.
3. Increased rate of utilisation or storage of glucose in the tissues following absorption.

MacLean and Sullivan (1929) investigated the possibility of a lowered renal threshold to glucose and showed that glycosuria was not a feature of the patients showing the low blood-sugar curve; its occurrence in one of their fourteen cases must be regarded as

a coincidence. Their observations have been abundantly verified by subsequent observers (Svensgaard, 1931; MacRae and Morris, 1931; Badenoch and Morris, 1936). The low curve must, therefore, be caused either by faulty absorption or by an abnormality of the intermediary carbohydrate metabolism. In view of the generally accepted fact that there is defective fat absorption in idiopathic steatorrhoea, a similar abnormality of carbohydrate absorption seems the likely explanation of the low blood-sugar curve, and this view has been supported by the observations of MacRae and Morris (1931), Badenoch and Morris (1936), Fairley (1936), Ross (1936) and Nussbrecher and Morton (1937). The opposing view, however, was put forward by Thaysen (1929a, 1932, 1935) and has received support from Mogensen (1937).

As abnormalities in the blood-sugar curve after oral administration of glucose may be caused either by defective absorption from the bowel or by disturbance of intermediary metabolism, the most direct evidence of the latter should be afforded by a study of the response to intravenously injected glucose; for, as has already been stressed, by this procedure variations caused by alterations in the rate of absorption of glucose from the bowel are excluded.

Present Investigation.

Twelve well-established cases of coeliac disease have been investigated, the diagnosis being based on a history of recurrent attacks of diarrhoea in conjunction with a majority of the following clinical and biochemical findings:

1. Bulky, pale, pultaceous, frothy or loose, foul-smelling stools containing an increased fat-content on normal or on low-fat diet. Thirty per cent. of the dry weight has been regarded as the upper limit for the normal faecal fat content, the majority being in the form of soaps and free fatty acids.
2. Emaciation and dwarfing, varying in degree with the duration of the symptoms.
3. Muscular wasting and flabbiness, especially flattening of the buttocks.
4. Abdominal distension, without ascites or palpable glandular masses.
5. Rickets, clinical or radiological, especially if associated with a lowered calcium content of the blood-serum.
6. The presence of a low blood-sugar curve following oral administration of 2 grams of glucose per kilogram of body weight.
7. Anaemia.

As only undoubted cases of coeliac disease in whom the clinical features were particularly well-marked have been included, the proportion of these features occurring in each case, and the proportion of the cases in which any one feature occurs, are naturally higher than they would be if mild or doubtful cases had been included.

Fasting Blood-Sugar Levels.

Numerous estimations of the fasting blood-sugar levels of the twelve cases were made during the course of this work and the results of these are shown in Table XXI. They have been divided into two sets according to the clinical condition of the patient at the time, termed "active" when frequent stools of coeliac type were being passed and "quiescent" when not more than one stool of relatively normal character was passed each day. In five cases (88, 89, 90, 93 and 94) no satisfactory quiescent period was observed.

It will be seen from Table XXI that during the quiescent periods all the fasting levels were within the normal range found in these studies of 70 to 100 mg. per 100 c.c. The mean value during the quiescent phases was 86.0 mg. per 100 c.c. During the active phases the fasting levels varied considerably even for an individual case. Many subnormal values (44 to 70 mg. per 100 c.c.) were, however, recorded and the mean value for the fasting estimations made during the active phases was 70.7 mg. per 100 c.c.

TABLE XXI.

Fasting blood-sugar levels in coeliac disease.

Case	Blood-sugar: mg. per 100 c.c.	
	Active	Quiescent
83	61,74,72,79	88,79
84	61,52,57,68	84,66
85	66,68,66,59, 68,69,98,70	77,81
86	77,88,86,95, 74,72,75	93,90,95,81, 90,98
87	74,70	81,86
88	65,66,44	-
89	66,74,90	-
90	75,65,66	-
91	77,75	83
92	56,83	92
93	75,70	-
94	52,79,66	-
Mean	70.7	86.0

Oral Glucose Tolerance.

Oral glucose tolerance tests were carried out in these cases using a glucose dosage of 2 grams per kilogram of body weight. With the more customary dosage of one gram per kilogram of body weight a considerable proportion of normal children, and particularly of undernourished children, show a somewhat limited rise in the blood-sugar level; with a dosage of 2 grams per kilogram of body weight this proportion is greatly diminished. Blood-sugar estimations were made fasting and at fifteen- to thirty-minute intervals for two hours after the test dose. The results of the tests are detailed in Table XXII. All the cases except one (Case 92) showed a maximum rise in the blood-sugar concentration of less than 40 mg. per 100 c.c. during an active phase of the disease. In the remaining case (Case 92) the rise was 50 mg. per 100 c.c., but the curve commenced from the abnormally low fasting value of 56 mg. per 100 c.c. This corresponds to the alternative "low-level" curve described by Thaysen (1929a, 1932). Thus in all these severe cases of coeliac disease an abnormal oral glucose tolerance curve was found during the active phases. In no case did glycosuria occur.

In six of the cases the oral tests were repeated during quiescent phases of the disease and the results of these tests are also recorded in Table XXII. In each instance the rise of the blood-sugar level after oral glucose was greater during the quiescent than during the active phase and in those cases in which

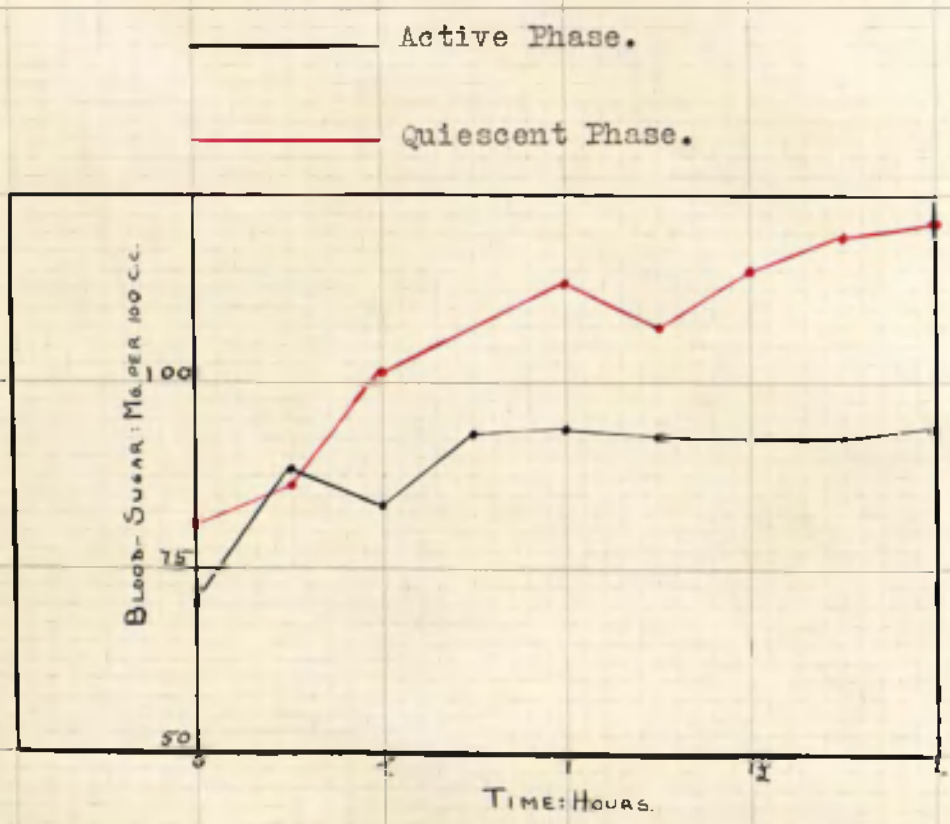
TABLE XXII.

Oral glucose tolerance tests in coeliac disease.

Case	Age in years	Blood-sugar: mg. per 100 c.c.									Maximum rise	Clinical condition	Remarks
		Fasting	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	105 mins.	120 mins.			
83	2 3/12	79 79	110 -	100 76	111 75	110 93	97 97	110 95	- 122	107 150	32 71	Active Quiescent	Low curve Late rise
84	1 2/12	57 66	- -	93 120	- -	70 115	- -	79 132	- -	77 138	36 72	Active Quiescent	Low curve Late rise
85	3	70 81	68 -	75 81	78 83	90 88	91 83	86 95	93 117	101 109	31 36	Active Quiescent	Low curve Low curve: sl. improvement
86	7½	88 81	108 92	106 97	111 86	113 122	- 141	115 108	- -	111 94	27 60	Active Quiescent	Low curve Normal curve
87	2 4/12	70 86	68 84	75 91	72 94	77 104	- -	74 128	- -	77 144	7 58	Active Quiescent	Low curve Late rise
88	1 4/12	44	-	47	-	59	-	77	-	74	33	Active	Low curve
89	1 7/12	66	-	81	-	88	-	84	-	79	22	Active	Low curve
90	1 4/12	65	-	60	-	83	-	74	-	68	18	Active	Low curve
91	5	77	-	95	-	101	-	104	-	88	27	Active	Low curve
92	3 7/12	56 92	- -	59 141	- -	106 162	- -	92 130	- -	95 88	50 70	Active Quiescent	"Low-level" curve Normal curve
93	8	70	-	81	-	88	-	86	-	88	18	Active	Low curve
94	1 4/12	79	-	112	-	90	-	95	-	75	33	Active	Low curve

FIGURE XXIV.

Coeliac Disease: Mean Oral Glucose Tolerance Curves during Active and Quiescent Phases.



the remissions were most complete (Cases 86 and 92) the curves were normal. Three of the cases (83, 84 and 87) showed a well-marked late rise of the curve during the quiescent phase, the highest value in each case being in the two-hour specimen. Of the six cases investigated during both active and quiescent phases Case 85 alone showed a low curve within Thaysen's definition on the two occasions. In Figure XXIV mean curves are drawn from the tests performed during active, and quiescent, periods. The increased hyperglycaemia and the tendency to high values at the end of the test during the quiescent phase are evident. This late rise suggests that even in the quiescent phase absorption is slow, compared with normal subjects.

Intravenous Glucose Tolerance.

Using the technique described in Section II, intravenous glucose tolerance tests were carried out during an active period of the disease in all twelve cases; in five cases the test was repeated during a quiescent phase. The results of these tests are detailed in Table XXIII. In every instance, during both active and quiescent phases, the time of fall of the blood-sugar to normal fasting levels was within the normal limits defined in Section II (Table V). Sugar excretion in the urine was also within normal limits in each of the seven cases in which it was estimated.

In Table XXIV and in Figures XXV, XXVI and XXVII the cases are subdivided into age-groups and compared with the average findings from normal subjects of the same age, the average age of

TABLE XXIII

Intravenous glucose tolerance tests in 12 cases of coeliac disease.

Case	Age in years	Wt. in kg.	Blood-sugar: mg. per 100 c.c.								Sugar in urine following injection; per cent. of injected glucose.	Clinical condition
			Fasting	2 mins	15 mins	30 mins	45 mins	60 mins	75 mins	90 mins		
83	2 3/12	10.0	88 74	284 308	181 213	115 125	74 75	68 68	57 64	51 77	- -	Quiescent Active
	1 2/12	5.25	61	260	146	97	57	56	63	70	-	Active
84	1 6/12	5.4	84 52	314 202	168 132	134 113	95 95	75 73	- -	- -	- 3.3	Quiescent Active
85	3	11.7	66 77	270 296	177 181	129 121	93 96	79 86	79 75	72 -	5.3 6.1	Active Quiescent
86	9	15.2	77 93	278 282	177 211	117 110	84 77	83 77	81 -	83 -	5.2 -	Active Quiescent
87	2 4/12	11.5	74 81	355 340	163 157	134 130	106 104	70 79	- 76	- 80	- 5.4	Active Quiescent
88	1 4/12	7.0	66	230	166	122	95	93	83	75	-	Active
89	1 7/12	7.1	74	274	182	145	95	92	-	-	-	Active
90	1 8/12	7.3	75	230	139	110	83	72	-	-	-	Active
91	5	13.6	75	296	190	104	75	83	86	79	4.3	Active
92	5	10.4	83	240	172	111	81	77	74	86	4.7	Active
93	8	15.2	75	304	209	166	112	86	72	-	3.8	Active
94	1 4/12	7.0	66	281	188	139	84	70	62	-	-	Active

TABLE XXIV

Mean figures from intravenous glucose tolerance tests in coeliac disease and normal children, divided in age-groups.

Time of specimen	0 to 2 years.		2 to 4 years.		4 to 9 years.	
	5 Coeliacs mg. per 100 c.c.	6 Normals mg. per 100 c.c.	3 Coeliacs mg. per 100 c.c.	10 Normals mg. per 100 c.c.	4 Coeliacs mg. per 100 c.c.	10 Normals mg. per 100 c.c.
Fasting	66	71	71	81	77	86
2 mins.	243	238	311	315	280	315
15 "	161	158	184	198	187	204
30 "	125	116	129	138	125	143
45 "	90	88	91	93	89	97
60 "	80	77	72	76	82	81

FIGURE XXV.

Intravenous Glucose Tolerance Tests in Normal Subjects and in Cases of Coeliac Disease, aged 0 - 2 years.

———— Normal Subjects, aged 0 - 2 years.

———— Cases of Coeliac Disease, aged 0 - 2 Years.

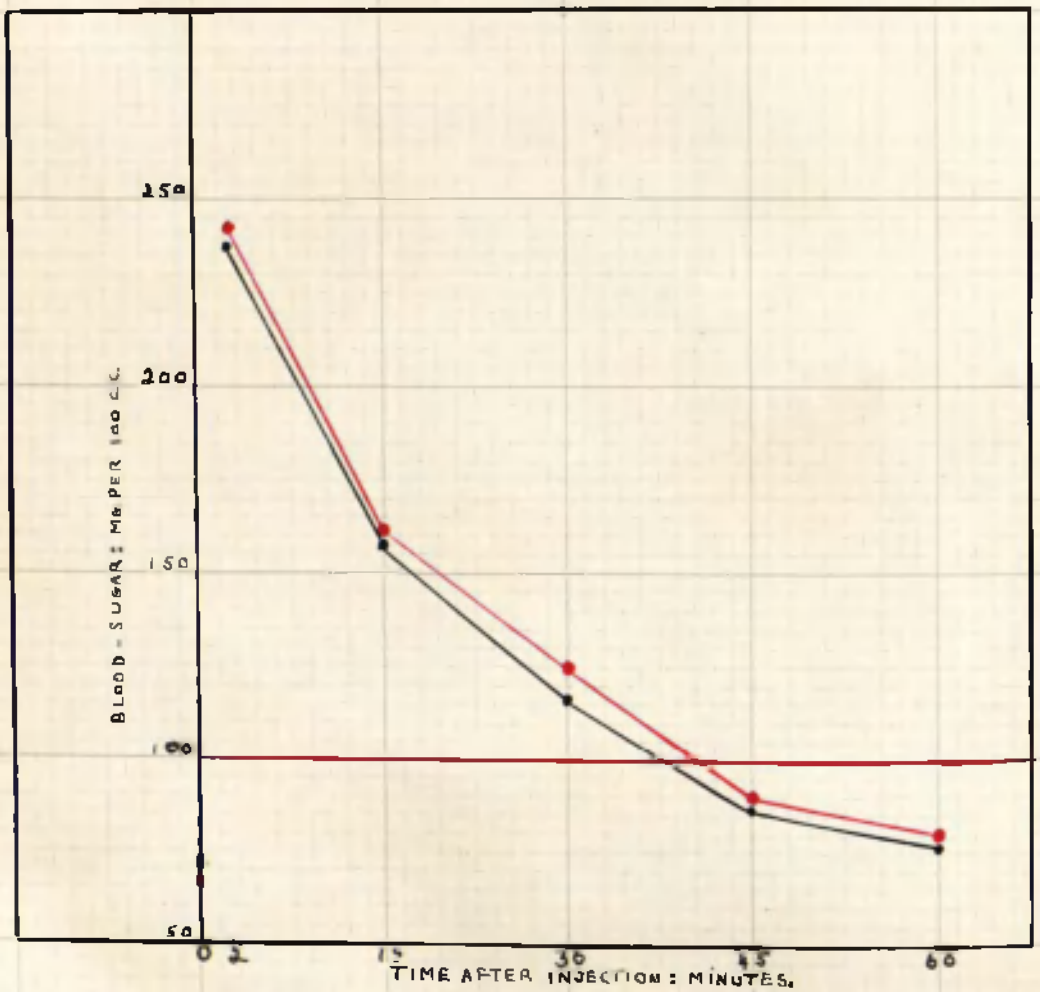


FIGURE XXVI.

Intravenous Glucose Tolerance Tests in Normal Subjects and in Cases of Coeliac Disease, age 2 - 4 years.

Normal Subjects, aged 2 - 4 years.

Cases of Coeliac Disease, aged 2 - 4 years.

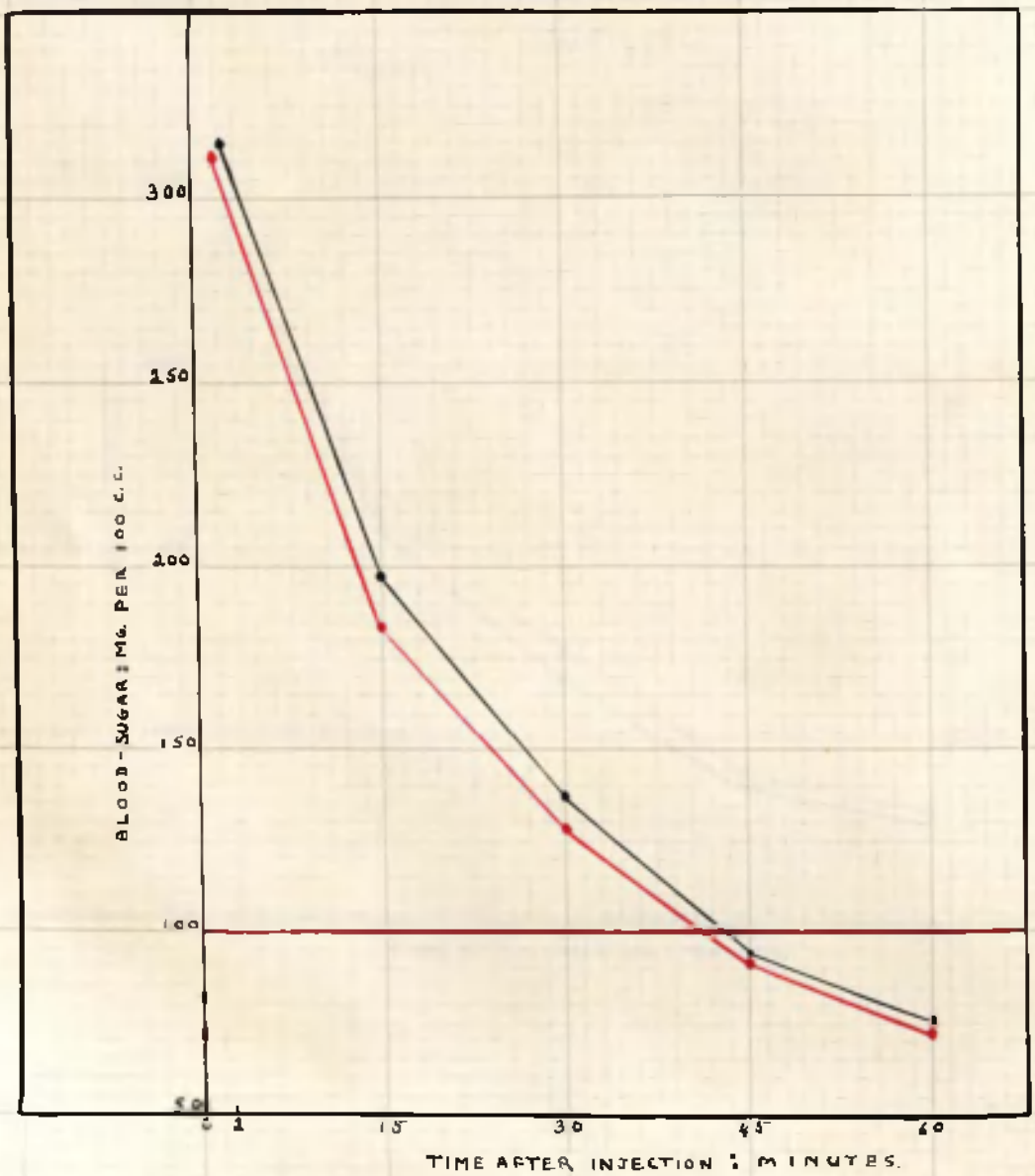


FIGURE XXVII.

Intravenous Glucose Tolerance Curves in Normal Subjects and in Cases of Coeliac Disease, aged 4 - 9 years.

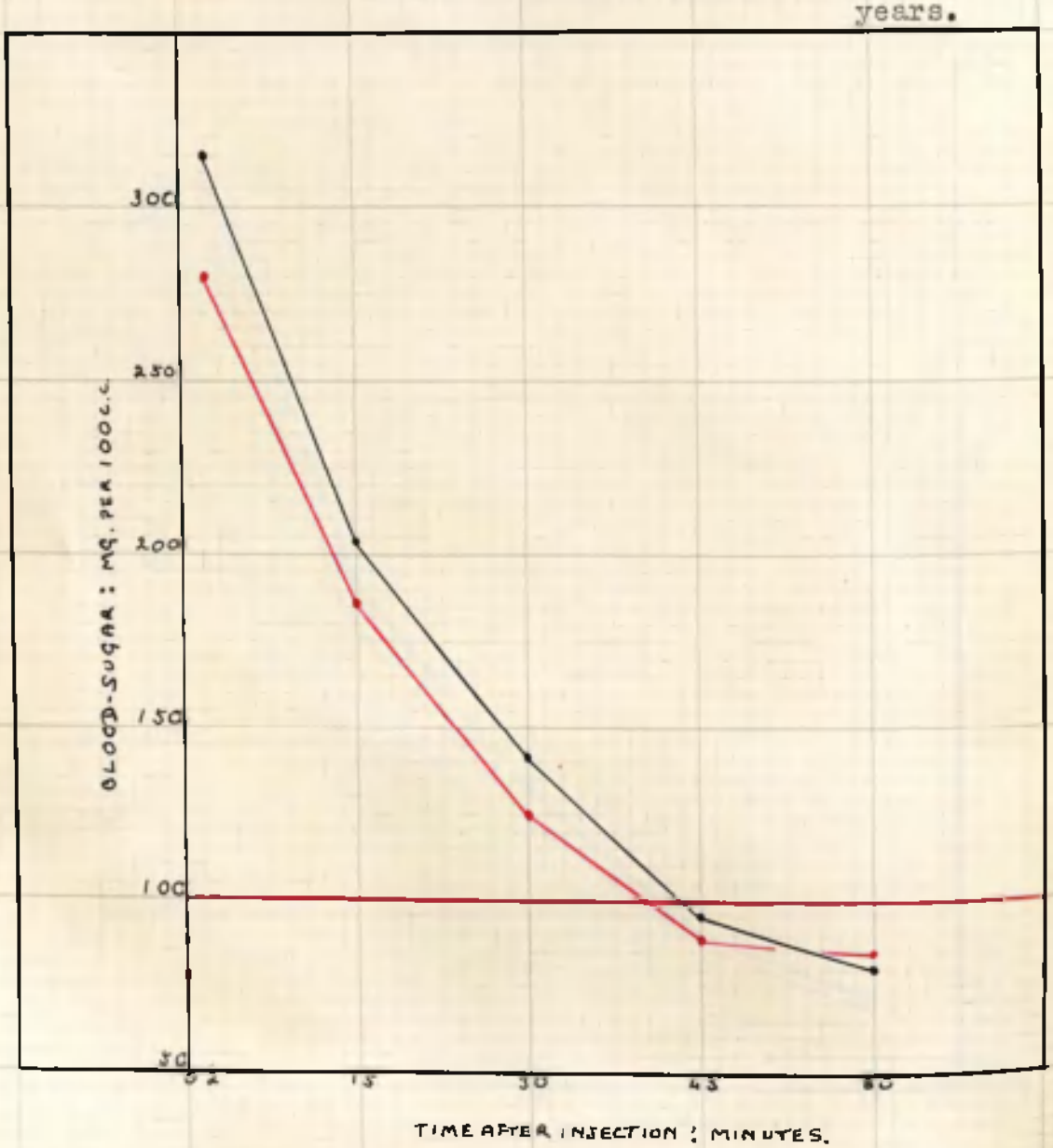
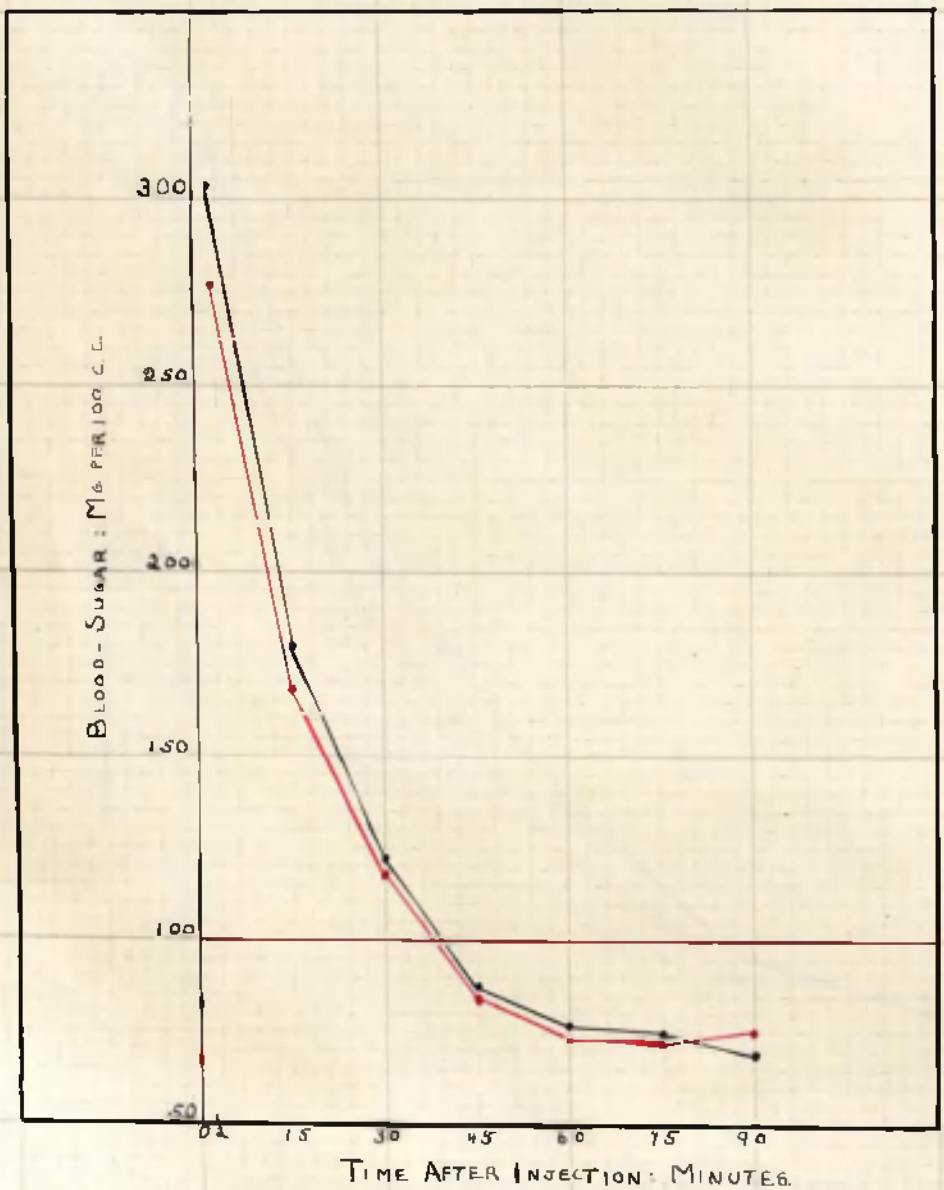


FIGURE XXVIII.

Mean Curves from Intravenous Glucose Tolerance Tests during Active and Quiescent Phases, in Five Cases of Coeliac Disease.

——— Active Phase.

——— Quiescent Phase.



coeliac patients and normal subjects in each age-group being the same. It will be seen that the times at which normal fasting levels are regained are the same in patients and controls, and the slight differences found between the average curves from the coeliac patients and the corresponding figures from the normal subjects cannot be regarded as significant; the tendency to lower levels in the coeliac curves no doubt reflects the low fasting blood-sugar values found in many of these cases. Figure XXVIII shows composite curves constructed from the results of tests carried out during active and quiescent phases of the disease in Cases 83 to 87. Here again there is no significant difference.

Discussion.

From these results it does not appear that there is any abnormality in the intermediary metabolism of carbohydrate in coeliac disease. In view of this, and as all the evidence points to there being no abnormality in the renal threshold, the remaining hypothesis, namely, defective absorption from the bowel, seems to be the most likely explanation of the low blood-sugar curve.

Ross (1936) has reached a similar conclusion based upon very different experimental findings. Using a different technique from that employed in the present investigation, he found a high, slowly falling curve after the intravenous injection of glucose in cases of coeliac disease. He argued that this impairment of carbohydrate tolerance was the result of carbohydrate starvation, a condition which is generally recognised to produce an impairment

of tolerance as guaged by the oral test. Thus, in spite of the presence of carbohydrate in the diet, the patients showed a curve characteristic of carbohydrate starvation, and from this Ross concluded that carbohydrate was not being absorbed. It seems probable, however, that carbohydrate deprivation in coeliac disease is rarely severe, for ketonuria is seldom seen; none of the cases in the present series gave even a positive Rothera's test at the time when the low oral blood-sugar curve was obtained. It is known that if carbohydrate deprivation is persisted in over a long period the ketonuria diminishes, but it does not disappear completely unless the deprivation is of quite a mild degree. In the preceding section it has been shown that even severe carbohydrate starvation does not interfere with the tolerance for injected glucose.

Thaysen (1929a, 1932) demonstrated in patients with idiopathic steatorrhoea, that the respiratory quotient, following ingestion of carbohydrate, rose to levels which indicated that considerable quantities of sugar were being metabolised, and he also showed that these patients yielded a higher respiratory quotient when given a high-carbohydrate diet than when on ordinary diet. Thaysen regarded these results as indicating that there was no interference with carbohydrate absorption, but, as MacRae and Morris (1931) have pointed out, they merely show that there was not an absolute failure of carbohydrate absorption; they do not exclude the possibility of delayed or inefficient absorption. Indeed the striking point which Thaysen's experiments show is that

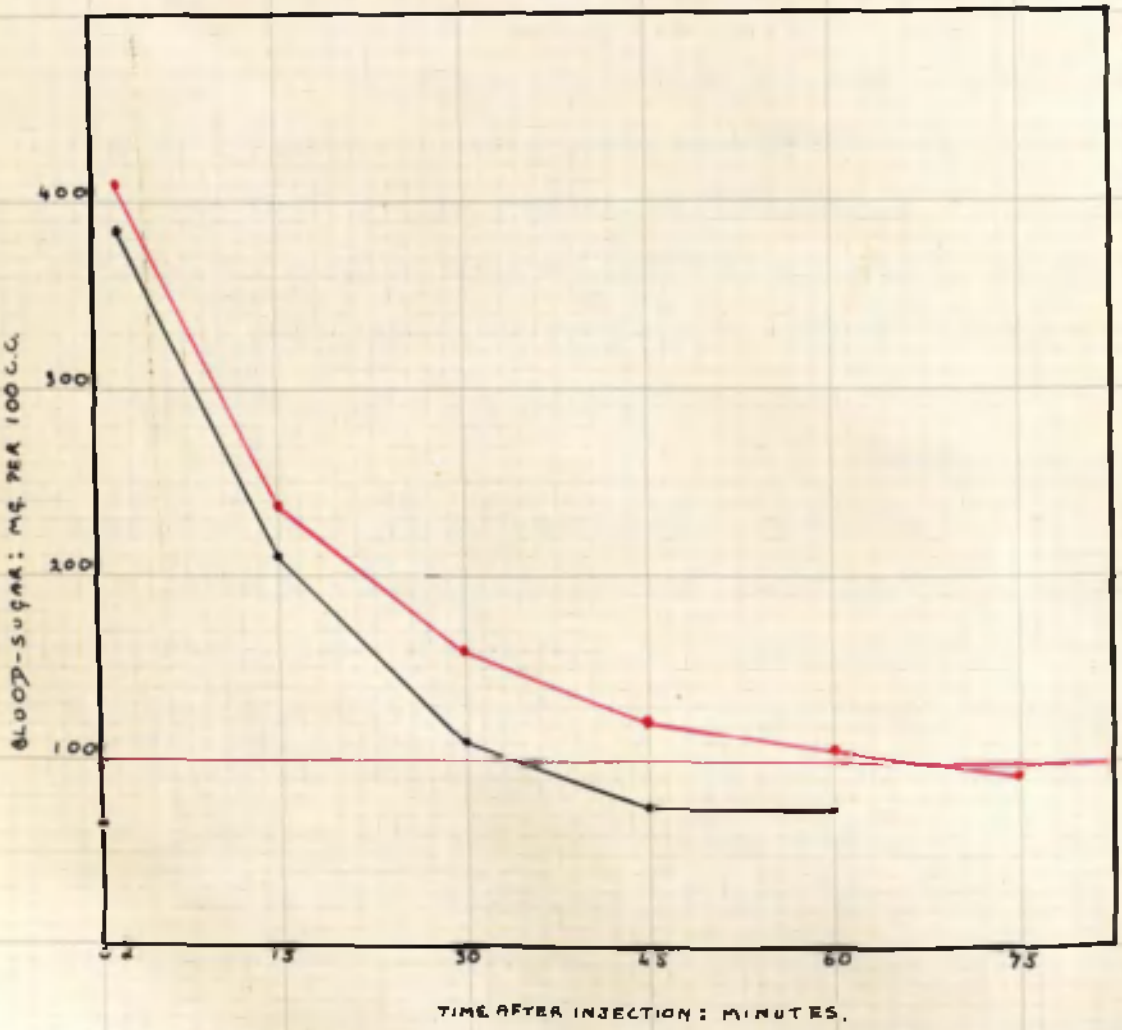
FIGURE XXIX.

Case 86, age 9 years, wt. 15.2 kg.: Coeliac Disease.

Effect of Increased Dosage of Glucose on the Intravenous Glucose Tolerance Curve.

———— 0.5 gm. glucose per kg. actual body wt.

———— 0.5 gm. glucose per kg. body wt. of a healthy child aged 9 years.



there is no failure on the part of the tissues in coeliac disease to oxidise carbohydrate. This, taken in conjunction with the fact that ketosis is not a feature of coeliac disease, and with the experimental findings on high-fat low-carbohydrate diets recorded in Section IV, suggests that it is improbable that there is sufficient deprivation of carbohydrate in coeliac disease to cause any metabolic upset.

There can be little doubt that the discrepancies between the results of Ross and those arrived at in the present investigation depend on differences in the technique employed in carrying out the intravenous glucose tolerance tests. The essential difference lies in the dosage of glucose. In the present series a dose of 0.5-gram of glucose per kilogram of body weight has been used, whereas Ross employed a standard dosage of 10 grams of glucose both for normal and coeliac cases, irrespective of body weight. He does not report the weights of his coeliac patients, but as these children are usually from 30 to 50 per cent. below the weight of healthy children of the same age, it is evident that his patients received, relative to body weight, a much larger dose of glucose than did his normal subjects. The results of the administration of such increased dosage of glucose to a child with coeliac disease are shown in Figure XXIX. In this case, when a dose appropriate to a normal child of the same age was given, the time of fall to a normal fasting blood-sugar level was increased. This curve closely resembles many of those given by Ross (1936). It seems evident that the "impaired tolerance" which Ross reports

in his coeliac patients is, in fact, the result of the relatively greater dosage of glucose which they received as compared with the control normal subjects. The same explanation is applicable to similar findings reported by Fairley (1936) in cases of tropical sprue.

Thaysen (1929a, 1932), in contrast to Ross, observed an increased tolerance to intravenous glucose in three out of six cases of idiopathic steatorrhoea which he investigated, using the technique devised by Jörgensen and Plum (1922). The remaining cases gave normal results. The reason for the difference between Thaysen's results and those of the present investigation are not evident; it is noteworthy, however, that Thaysen examined no normal series of his own, but compared his results with the normal series reported by Jörgensen (1926). While differences of technique prevent direct comparison with the normal curves in this study, Jörgensen's normal curves appear to be within narrower limits than experience here has indicated.

The Response to Insulin in Coeliac Disease.

The reaction of the blood-sugar level to insulin injections has been used as a test of the normality of the carbohydrate metabolism of patients with coeliac disease. Badenoch and Morris (1936), using a subcutaneous injection of 4 units, obtained a fall in the blood-sugar level greater than they found in normal subjects of the same age, and they suggest that in coeliac disease there is a deficiency of some contra-insular hormone.

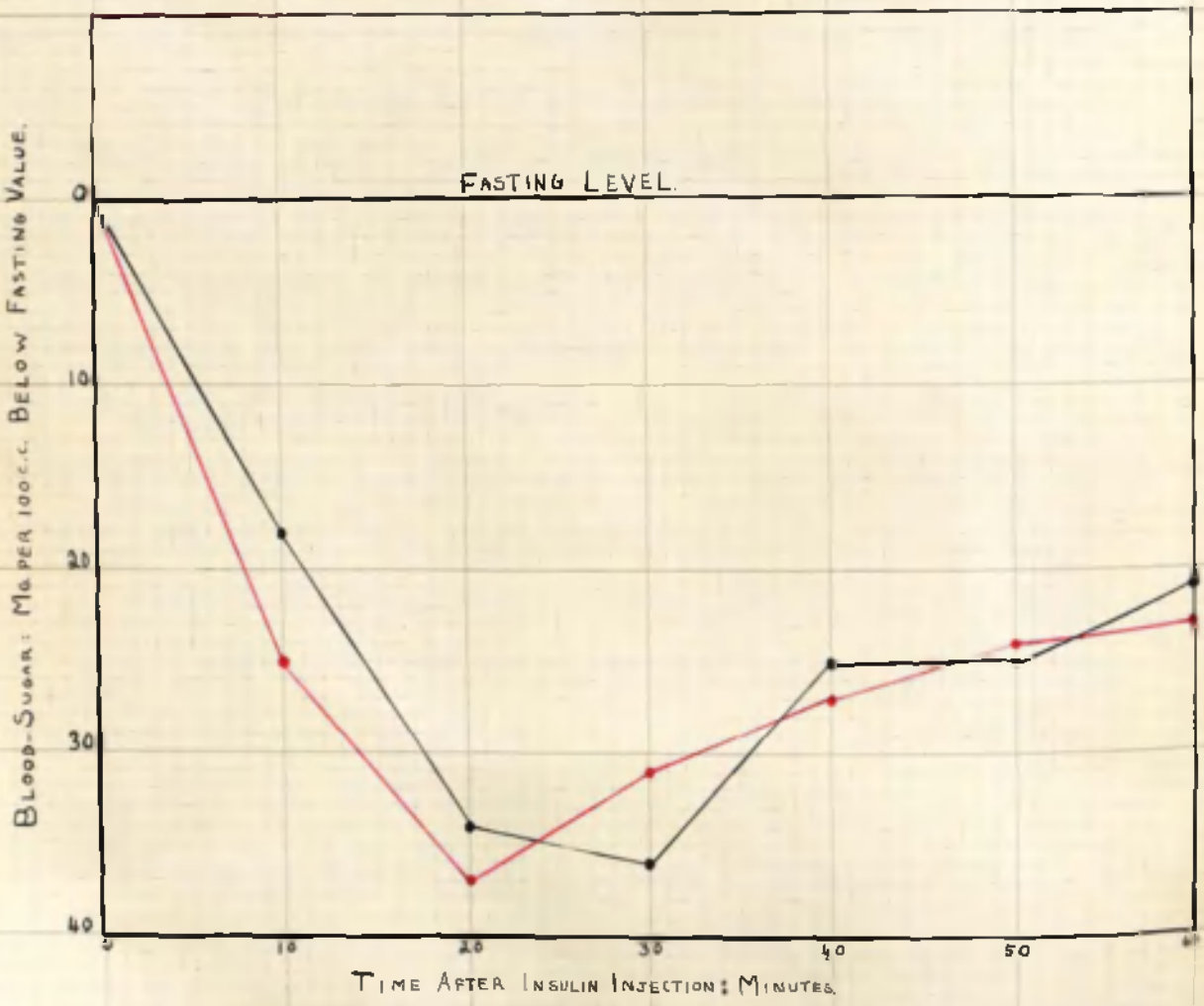
FIGURE XXX.

Mean Insulin Depression Curves from Six Normal Subjects and Six Cases of Coeliac Disease.

(1/3 Unit Insulin per kg. body weight, Intravenously.)

_____ Normal Subjects.

_____ Cases of Coeliac Disease.



On the other hand, Ross (1936), using an intravenous injection of 4 units of crystalline insulin, found a smaller depression of the blood-sugar level in coeliac than in normal children. A similar curve to that found in coeliac disease was obtained from normal children when the test was performed after a period on low-carbohydrate diet. Ross interpreted his findings as indicating again that the patient with coeliac disease was, in respect of carbohydrate, in the same position as a normal subject starved of carbohydrate; though the coeliac patient might receive carbohydrate in his diet, it was not adequately absorbed.

The effect of intravenously injected crystalline insulin on the blood-sugar level has been studied in six of the cases of coeliac disease in the present series, and has been compared with the results from six cases of the "normal" series (Cases 38, 40, 58, 95, 96 and 97). A dosage of one-third-of-a-unit of insulin per kilogram of body weight was employed, and the blood-sugar was estimated before the injection and at ten-minute intervals thereafter for one hour.

The results of these insulin sensitivity tests are detailed in Table XXV and in Figure XXX the mean depression curves for the two sets of cases are drawn. These results show that the time and extent of the maximum response to insulin vary considerably amongst the normal subjects, and that a similar variability occurs amongst the coeliac cases. From these figures it seems clear that there is no significant difference between the two groups in their response to insulin. This normality of the

TABLE XXV.

Insulin sensitivity tests in normal subjects and in cases of coeliac disease.
(1/3-unit insulin per kg. body weight intravenously).

Case	Blood-sugar mg. per 100 c.c.													
	Normal subjects							Cases of coeliac disease						
	38	40	58	95	96	97	Mean	83	84	85	86	89	90	Mean
Time:														
Fasting	79	76	93	90	70	96	84	72	68	98	95	90	66	81
10 minutes	66	68	88	55	52	66	66	61	50	48	61	77	43	56
20 "	48	59	75	56	24	38	50	57	32	45	41	61	31	44
30 "	50	50	57	54	39	40	48	61	41	45	67	56	32	50
40 "	57	54	68	65	45	64	59	47	47	50	70	54	56	54
50 "	70	45	54	67	65	52	59	47	52	52	68	54	72	57
60 "	68	54	66	69	63	57	63	48	52	57	70	48	72	58

insulin sensitivity tests in the present series of cases of coeliac disease provides further corroborative evidence that in coeliac disease there is no abnormality of the intermediary carbohydrate metabolism and therefore that the low oral blood-sugar curve is produced by defective absorption of glucose from the bowel.

Summary.

Twelve well-established cases of coeliac disease have been investigated, with special reference to the causation of the abnormal oral glucose tolerance curves. The following points have been made out with regard to carbohydrate metabolism in this disease:

1. Subnormal fasting blood-sugar levels are of frequent occurrence during the active phase of the disease, though normal levels may be found. During quiescent phases fasting blood-sugar levels are normal.

2. Abnormal oral blood-sugar curves are common during the active periods, having been found in all twelve of the present cases. The usual abnormality is the "low curve" (flat curve) in which the maximum increase of blood-sugar concentration during two hours after the administration of 2 grams of glucose per kilogram of body weightis 40 mg. per 100 c.c. or less. Occasionally the curve is of the "low-level" type in which the fasting level is below 65 mg. per 100 c.c. and the greatest hyperglycaemia attained is below 120 mg. per 100 c.c. The possible causes of this abnormal oral glucose tolerance are lowered renal threshold for glucose, abnormally active intermediary processes (storage and utilisation), or defective absorption of sugar from the bowel. Glycosuria has not been found.

3. During quiescent periods of the disease the oral glucose tolerance moves towards normal. The occurrence of a late rise in the oral tolerance curve is common.

4. Intravenous glucose tolerance is normal during both active and quiescent periods.

5. The response of the blood-sugar to intravenously injected insulin is the same in coeliac disease as in normal children.

6. From these findings it is concluded that there is no abnormality of the intermediary carbohydrate metabolism in patients

with coeliac disease; and, by exclusion, it seems certain that the low blood-sugar curve of coeliac disease must be due to delayed or defective absorption of carbohydrate from the bowel. This conclusion is presumably applicable to other forms of idiopathic steatorrhoea as well as to coeliac disease.

S E C T I O N VI

CARBOHYDRATE TOLERANCE IN DISTURBANCES OF THYROID GLAND SECRETION.

Introduction.

Current views upon the changes of carbohydrate tolerance which occur when thyroid secretion is disturbed may be summarised by quotations from two standard British textbooks of medicine. Leyton (1937), in Price's Textbook, writes that in hypothyroidism there is "considerable increase in the tolerance for dextrose," while Beaumont (1938) states that in hyperthyroidism "sugar tolerance is often diminished" and in hypothyroidism "sugar tolerance is increased." Similar statements can be read in almost any textbook of medicine.

Reports of experimental work, however, reveal less unanimity of opinion. Janney and Isaacson (1918) and von Noorden and Isaac (1927) observed that in hypothyroidism the blood-sugar curve after oral glucose was of flatter type than in normal subjects and the former workers showed also that the curve became normal under thyroid gland therapy. Gardiner-Hill, Brett and Smith (1925), on the other hand, obtained precisely opposite results. In fifteen myxoedematous adults they found the blood-sugar curve to be both higher and more prolonged than in normal

subjects, while administration of thyroid gland lowered and shortened the curve. Diminished oral glucose tolerance in hypothyroidism was found also by Flesch (1913) and Gray (1923).

In hyperthyroidism there is more general agreement. Denis, Aub and Minot (1917), Janney and Isaacson (1918), Gardiner-Hill, Brett and Smith (1924), von Noorden and Isaac (1927), Torday (1927) and Joslin (1928) all observed a protracted hyperglycaemia, frequently associated with glycosuria, after oral administration of glucose to the subjects of toxic goitre. Attempting to explain this loss of tolerance to oral glucose Cramer and Krause (1912) and Coggeshall and Greene (1933) have demonstrated that animals receiving excess thyroid gland fail to store glycogen in the liver and muscles. Griffiths (1939), using a combined "insulin-glucose test" claims to have demonstrated that in toxic and non-toxic goitre there is marked peripheral resistance to insulin and a slighter degree of central resistance.

Investigations on children have been scanty. Svensgaard (1931) investigated the oral glucose tolerance of four untreated cretins and in two of the cases she repeated the tests after thyroid treatment had been established. She found somewhat lowered fasting blood-sugar levels in the untreated cases, but the tests performed during treatment gave normal values. The blood-sugar curves after oral glucose (2 grams per kilogram of body weight) were somewhat low, the maximum elevation above the fasting level varying from 43 to 82 mg. per 100 c.c. In passing it may be stated that, in my experience, such curves are not uncommon in

healthy children. In the two cases in whom the tests were repeated after thyroid treatment was well-established, the second curves showed rises of 133 and 170 mg. per 100 c.c., with maximum hyperglycaemic levels of 204 and 254 mg. per cent.

I have been unable to find any reports of investigations of carbohydrate tolerance in cases of juvenile myxoedema or in children with hyperthyroidism.

Cretinism.

Six cases of cretinism (congenital hypothyroidism or athyroidism) have been investigated as regards their tolerance to oral glucose before and after commencement of treatment with thyroid gland preparations. In five of these cases, and in two older cretins who had been under treatment for several years, intravenous tolerance tests were also carried out. Subjects are recorded as "untreated" prior to the commencement of thyroid gland administration and as "treated" when they had been receiving adequate amounts of thyroid gland for two weeks or longer and showed definite evidence of clinical improvement. During the course of the investigations *fasting blood-sugar levels* were estimated on fifteen occasions on untreated subjects and on nineteen occasions after treatment was established. The values prior to treatment ranged from 45 to 88 mg. per 100 c.c., with a mean value of 60.8 mg. Four were below 50, and a further four below 60 mg. per 100 c.c. In treated subjects the fasting blood-sugar levels ranged from 50 to 99 mg. per 100 c.c., with a mean value of 71.0 mg.

In none of the treated cases was a level below 50 recorded, but in six of them the fasting value was below 60 mg. per 100 c.c. Thus, while a marked tendency to low fasting blood-sugar levels was found in untreated cretins, with more normal values occurring after treatment, great irregularity was observed - some normal values occurred in untreated, and some subnormal values in treated cases.

The results of Oral Glucose Tolerance Tests are recorded in Table XXVI. The test dose of glucose employed was 2 grams per kilogram of body weight. The irregularity of the response of young children to the oral administration of glucose, and the consequent difficulties in the interpretation of the results of oral glucose tolerance tests have been emphasised previously (Section I) and they are well-exemplified in the present series of tests. In evaluating these tests the following arbitrary standards have been used for descriptive purposes:

1. Low curve = maximum increase in blood-sugar concentration of 30 mg. per 100 c.c. or less.
2. Low-normal curve = maximum rise of 30 to 50 mg.
3. Normal curve = maximum rise of 50 to 70 mg.
4. High-normal curve = maximum rise of 70 to 100 mg.
5. High curve = maximum rise of 100 mg. or more.

Three of the cases (62, 98 and 100) showed, before treatment, a well-marked low curve, while a fourth case (101) gave a low-normal curve. Case 99 showed a high curve, and Case 102 a high curve

TABLE XXVI.

Oral glucose tolerance tests in 6 cretins before and after treatment.

Case	Age in years	Blood-sugar: mg. per 100 c.c.						Clinical condition	Type of curve
		Fasting	½-hour	1 hour	1½ hours	2 hours	Maximum rise.		
98	4/12	48	56	69	71	63	23	Untreated.	Low
		56	69	96	80	69	40	Treated 3 weeks.	Low-normal
		50	125	135	121	91	85	" 7 "	High-normal
62	16/12	45	52	52	45	43	7	Untreated.	Low
		51	56	64	57	52	13	Untreated.	Low
		81	125	86	75	57	44	Treated 2 weeks.	Low-normal
		63	65	77	61	53	14	Treatment stopped 1 wk.	Low
		59	53	56	49	63	4	" " 3 wks.	Low
99	27/12	56	104	166	188	143	132	Untreated.	High
		65	90	110	99	101	45	Treated 2 weeks.	Low-normal
		75	92	113	134	99	59	Treated 4 weeks.	Normal
100	1	67	64	81	65	67	14	Untreated.	Low
		60	86	78	77	62	26	Treated 3 weeks.	Low
101	47/12	72	99	102	101	106	34	Untreated.	Low-normal
		79	97	138	204	184	125	Treated 4 weeks.	*High
102	1 - 1½	66	175	204	200	209	143	Untreated.	*High
		75	129	122	74	65	54	Untreated.	Normal
		63	152	206	179	164	143	Untreated.	*High
		99	226	190	122	86	127	Treated 3 weeks.	*High
		90	158	163	119	101	73	Treated 3 months.	High-normal
		70	181	110	83	81	111	Treated 4 months.	High
61	96/12	50	83	111	72	60	61	Treated 9 years.	Normal

*Glycosuria

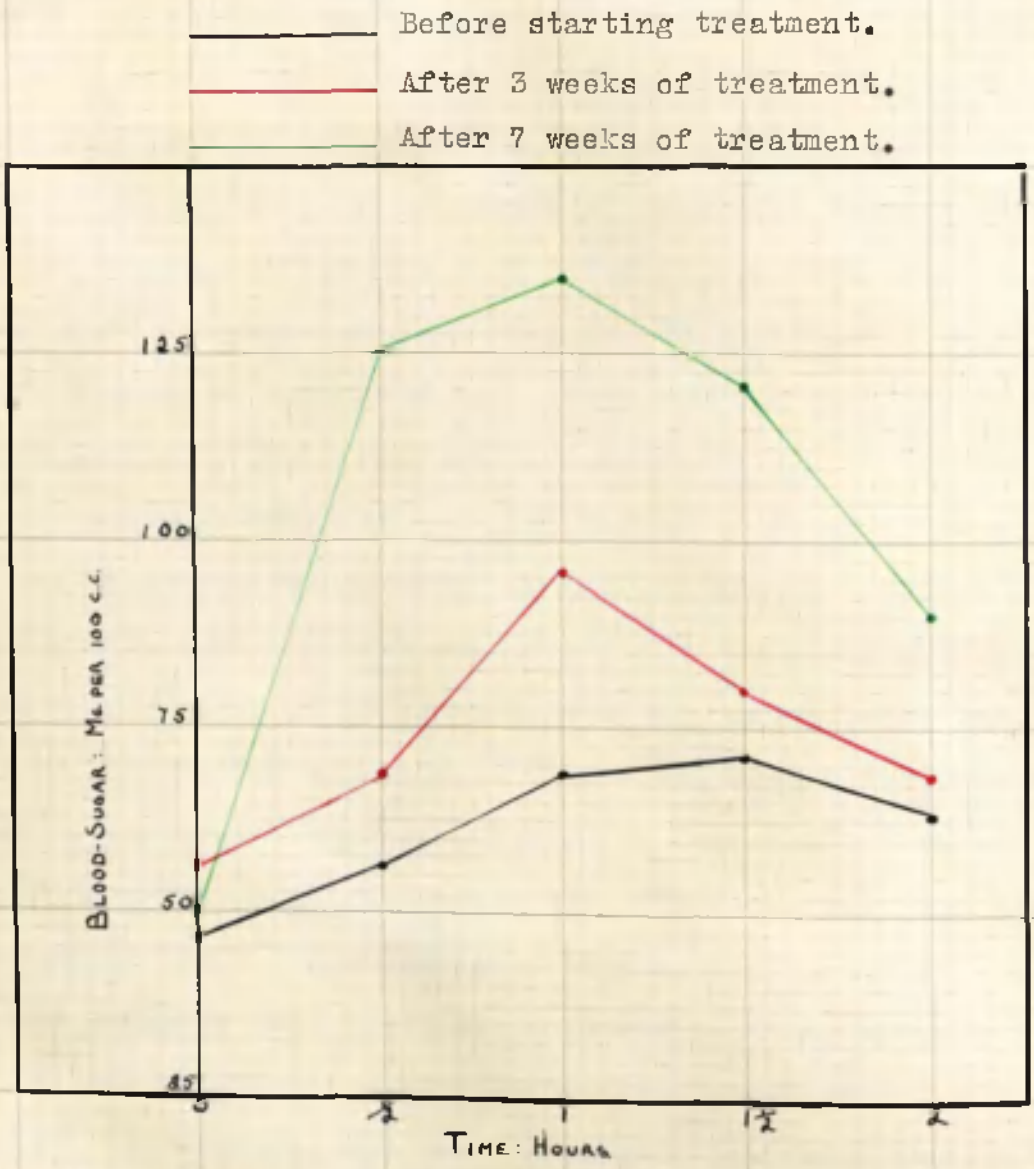
twice and a normal curve once. It is thus clear that the response to oral glucose in cretinous children is very variable; while the blood-sugar curve tends most frequently to be depressed, normal and high curves may occur and there may be great variation from time to time in the same subject.

The effect of thyroid gland therapy on oral tolerance also varied greatly from case to case. In Case 62 the low curve present before treatment was elevated to a low-normal curve after two weeks of treatment, but the low curve was restored when treatment was withheld at a later date. The low curve in Case 98 rose to a low-normal after three weeks of treatment and to a high-normal after seven weeks. In Case 100 the low curve remained low after four weeks of treatment, though the rise had increased from 14 to 26 mg. per 100 c.c. The low-normal curve present before treatment in Case 101 changed, after four weeks of treatment, to a high curve and glycosuria occurred. Some tachycardia was present at the time of the second test and it is possible that the dosage of thyroid gland was then excessive. In Case 99 the high curve of the period before treatment was changed to a low-normal curve after two weeks of treatment and to a normal curve after four weeks; while in Case 102 the findings were as irregular on treatment as they had been before treatment was commenced - two high curves and a high-normal curve were obtained, though there were no signs of thyroid over-dosage. Case 61, an older cretin treated regularly for nine years, gave a normal curve.

From these results it would seem that the general effect

FIGURE XXXI.

Case 98:Cretinism: Oral Glucose Tolerance Curves.



of thyroid treatment on the abnormal oral tolerance curves of cretinism is to cause a movement in the direction of normality. Low curves before treatment were constantly raised by treatment; but in cases not showing the low curve the effect was irregular. The curves from Case 98, representing what may be regarded as the typical findings in cretinism, are charted in Figure XXXI.

Intravenous Glucose Tolerance Tests were performed in five of the cases before and after commencing treatment and also in two older cretins who had received continuous thyroid treatment for six and nine years, respectively. The results of these tests are detailed in Table XXVII. Prior to the commencement of treatment every case showed a delay in the fall of the blood-sugar level to normal fasting values. The extent of the delay varied from case to case. Cases 100 and 101 showed only slight delay, the fall occurring in sixty minutes in the former (normal for age, thirty to forty-five minutes) and in seventy-five minutes in the latter (normal, forty-five to sixty minutes). In Cases 98 and 102 the delay was of greater degree, while in Case 99 there was gross impairment of tolerance to intravenous glucose.

Treatment with thyroid gland preparations caused a change to a normal curve in three of the five cases (Cases 98, 99 and 102), and normal curves were also found in the two older, treated cretins (Cases 61 and 103). In Cases 100 and 101 no improvement of intravenous tolerance occurred, the descent of the blood-sugar curve remaining slow after the commencement of treatment, though in Case 101 this may have been due to excessive dosage of thyroid, as

TABLE XXVII.

Intravenous glucose tolerance tests in 5 cases of cretinism, before and after commencement of treatment, and in 2 older, treated cretins.

Case	Age in years	Blood-sugar: mg. per 100 c.c.								Clinical condition	Type of Curve
		Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.		
98	4/12	55	372	266	188	140	101	84	66	Untreated.	Markedly delayed fall
		53	347	206	140	98	87	59	61	Treated 4 weeks.	Normal curve
99	27/12	57	262	200	168	155	141	136	124	Untreated.	Grossly delayed fall
		102	336	217	161	131	111	83	83	Treated 4 weeks - dose excessive.	Delayed fall
		72	251	186	83	50	43	52	61	Treated 8 weeks - dose adjusted.	Rapid-normal
100	1	48	376	278	170	102	55	-	-	Untreated.	Delayed fall
		55	401	313	197	133	66	-	-	Treated 3 weeks.	Delayed fall
101	47/12	76	300	199	145	122	104	79	75	Untreated.	Delayed fall
		81	343	243	193	164	119	97	83	Treated 4 weeks - ? dose excessive.	Delayed fall
102	1	88	310	188	141	124	104	86	84	Untreated.	Markedly delayed fall
		93	257	148	104	90	81	68	-	Treated 3 weeks.	Normal curve
		90	284	163	124	104	85	74	77	Treated 4 weeks - dose excessive.	Delayed fall
61	96/12	46	357	210	135	88	62	51	44	Treated 9 years.	Normal curve
103	610/12	68	333	217	154	103	70	60	-	Treated 6 years.	Normal curve

Doses mentioned refer to treatment with thyroid gland.

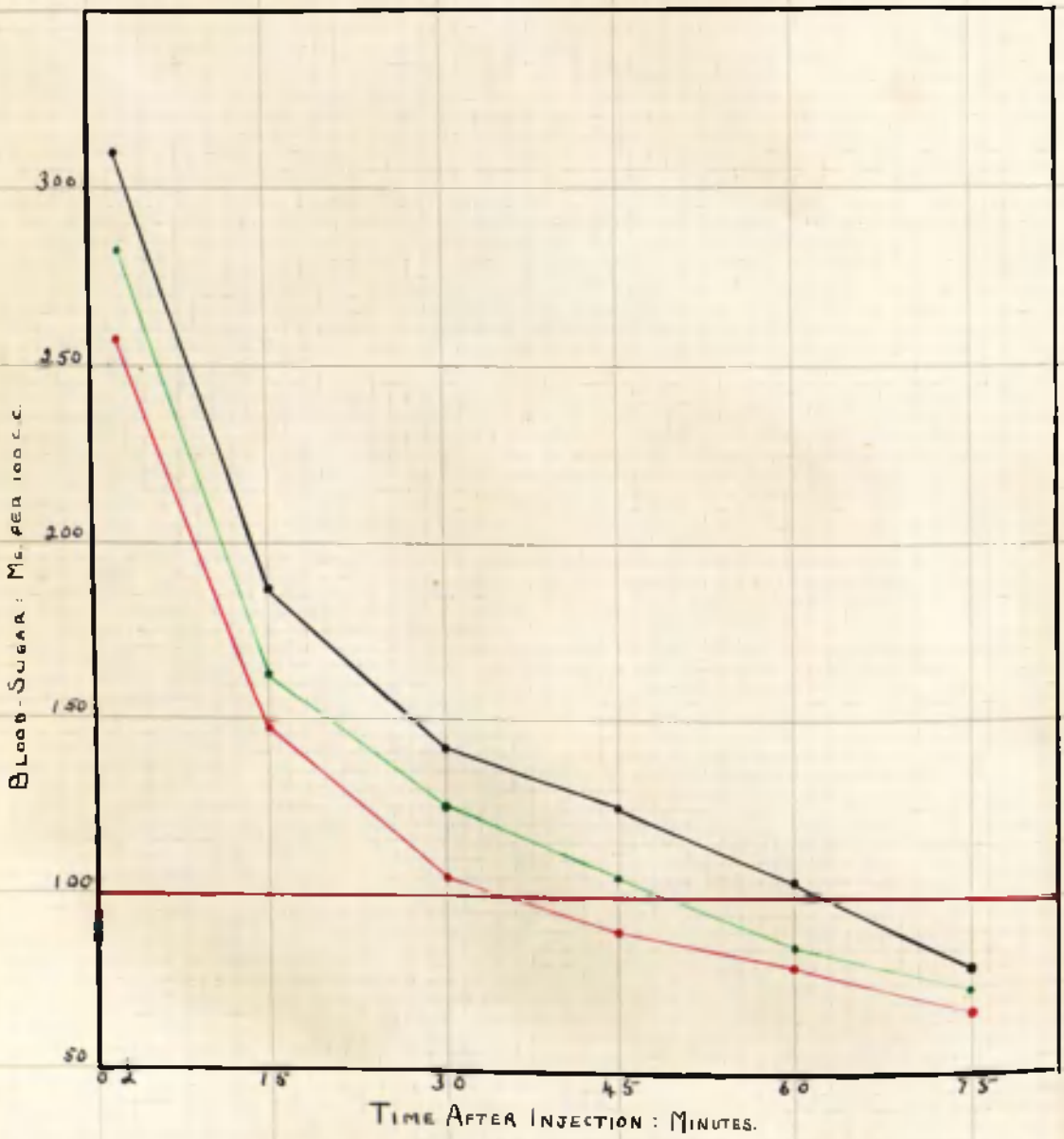
FIGURE XXXII.

Case 102 : Cretinism : Intravenous Glucose Tolerance Curves.

Before starting treatment.

On Thyroid Gland Treatment.

Excessive dosage of Thyroid.



pointed out above in connection with the oral curves in this case.

In two cases (99 and 102) intravenous glucose tolerance tests were performed at a time when definite clinical evidence of overdosage with thyroid was present. In each instance the fall of the blood-sugar level was delayed, but a normal curve was obtained by appropriate adjustment of the thyroid dosage.

From these results it appears that in cretinism the tolerance for intravenous glucose is diminished, but that normal tolerance can be restored by treatment with the correct dosage of thyroid gland. If too much thyroid is given impairment of tolerance reappears. As examples of these typical findings the curves from Case 102 are shown in Figure XXXII.

Juvenile Myxoedema.

Two children have been encountered in whom symptoms and signs related to diminution of thyroid function appeared during childhood, after a normal infancy. Unfortunately, the investigations were interrupted in both cases and oral and intravenous glucose tolerance tests were obtained only prior to the commencement of treatment. The results of these tests are recorded in Tables XXVIII and XXIX. The oral tests are normal, but the more delicate intravenous tests reveal slight but definite impairment of tolerance to intravenous glucose.

TABLE XXVIII.

Oral glucose tolerance tests in 2 cases of Juvenile Myxoedema.

Case	Age in years	Blood-sugar: mg. per 100 c.c.						Clinical condition	Type of curve
		Fasting	½-hour	1 hour	1½ hours	2 hours	Maximum rise		
104	5 5/12	70	167	111	88	85	97	Untreated	High-normal
105	6 2/12	71	133	128	95	91	62	Untreated	Normal

TABLE XXIX.

Intravenous glucose tolerance tests in 2 cases of Juvenile Myxoedema.

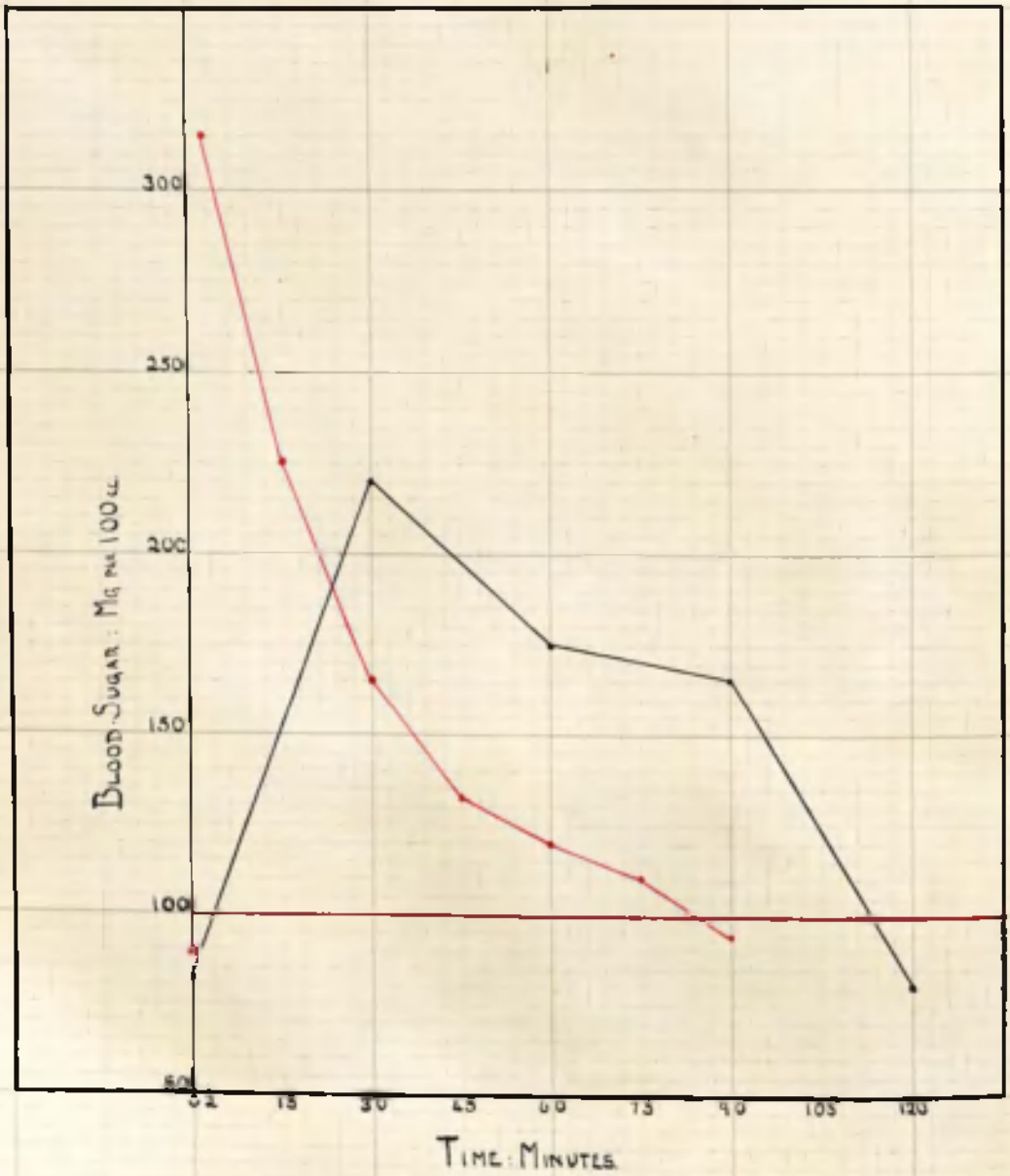
Case	Age in years	Blood-sugar: mg. per 100 c.c.								Clinical condition	Type of curve
		Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.		
104	5 5/12	83	300	241	163	141	112	81	76	Untreated	Delayed fall
105	6 2/12	86	290	236	182	150	110	104	90	Untreated	Delayed fall

FIGURE XXXIII.

Blood-Sugar Curves after Oral and Intravenous Glucose in a Case of Exophthalmic Goitre.(Case 107).

——— Oral Glucose Tolerance Curve.

——— Intravenous Glucose Tolerance Curve.



Hyperthyroidism.

Hyperthyroidism is not a common condition in children. During the course of this study two cases only were encountered. In the first (Case 106), a boy aged six-and-a-half years, enlargement of the thyroid gland was occasioning some discomfort, and on investigation mild signs of hyperthyroidism were found. Unfortunately, the child died of diphtheria two months after he was first seen. The second case (Case 107) was one of severe exophthalmic goitre in a girl aged ten years and four months. No abatement of the condition occurred during the period of observation.

I have thus been able to observe the tolerance to oral and intravenous glucose in two cases of active hyperthyroidism, one mild and one severe. The results of the tests are recorded in Tables XXX and XXXI, and in Figure XXXIII the curves from the severe case are shown. After oral administration of glucose Case 106 yielded a normal blood-sugar curve, but in Case 107 the curve was high and glycosuria occurred. After intravenous glucose the fall of the blood-sugar concentration to normal fasting limits was delayed in both cases, indicating impairment of tolerance.

TABLE XXX.

Oral glucose tolerance tests (1 gm. glucose per kg. body weight) in 2 cases of hyperthyroidism.

Case	Age in years	Blood-sugar: mg. per 100 c.c.						Clinical condition	Type of curve
		Fasting	½-hour	1 hour	1½ hours	2 hours	Maximum rise		
106	6½	81	105	140	106	83	59	Mild hyper-thyroidism	Normal
107	10 4/12	83	222	174	167	77	139	Severe exophthalmic goitre	High. Glycosuria +

TABLE XXXI.

Intravenous glucose tolerance tests in 2 cases of hyperthyroidism.

Case	Age in years	Blood-sugar: mg. per 100 c.c.								Clinical condition	Type of curve
		Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.		
106	6½	97	336	219	193	154	129	108	99	Mild hyper-thyroidism	Delayed fall
107	10 4/12	88	316	226	163	132	120	108	92	Severe exophthalmic goitre	Delayed fall

Summary of Results.

In cretinism the following features of the carbohydrate metabolism have been observed.

1. The fasting blood-sugar level is frequently subnormal, tending to rise under treatment.

2. Results of oral glucose tolerance tests are irregular. Low curves are of frequent occurrence, but normal and high curves also occur.

3. Intravenous glucose tolerance tests show, constantly, impairment of glucose tolerance; this contrasts strongly with the usual assertion that tolerance to carbohydrate is increased in hypothyroidism.

4. Under treatment all the curves tend to approach normal; but if excessive dosage of thyroid is given impairment of tolerance reappears in the form of high oral and delayed intravenous curves.

In two cases of Juvenile Myxoedema oral glucose tolerance tests were within normal limits, but intravenous tolerance tests revealed impairment of tolerance. Two cases of Hyperthyroidism exhibited impaired tolerance to intravenous glucose. One case showed a high oral curve, with glycosuria; in the other the oral curve was within normal limits.

Discussion.

The results recorded above leave three rather paradoxical findings to be explained:-

1. The occurrence of both low and high oral glucose tolerance curves in untreated cretins.
2. In untreated conditions of diminished thyroid activity the constantly occurring impaired tolerance to intravenous glucose has frequently been found associated with a low oral curve - the so-called "increased tolerance to glucose" of the textbooks.
3. The diametrically opposed conditions of cretinism and myxoedema on the one hand and hyperthyroidism on the other are both associated with impairment of intravenous glucose tolerance.

Concerning the first two of these questions, the constancy of the impaired tolerance to intravenous glucose contrasted with the irregularity of the response to oral glucose, suggests that it is the intravenous test which reflects the true state of the carbohydrate tolerance in hypothyroidism. Impaired carbohydrate tolerance seems a more logical result of the slowing of all metabolic processes which is known to occur in conditions of thyroid deficiency, than the increased tolerance which some of the oral tests suggest. If this explanation is correct then the inconstant low oral glucose curves must be due to faulty or slow

absorption of carbohydrate from the bowel. That such a fault exists seems not unlikely for constipation and abdominal distension are almost constant features of cretinism. I have frequently observed, during the oral tests on these children, that the stomach was as full and prominent at the end of the test as it had been immediately after the dose of glucose. It is probable that the low oral curves frequently encountered in cretinism result from slow absorption of glucose from the gut, itself dependent upon sluggishness of the movements of the alimentary canal comparable to the sluggish movements of limbs, face and body which are so characteristic of the disease. Myxoedema of the wall of the bowel, and torpidity of the portal circulation may also play some part.

The occasional occurrence of high oral curves in hypothyroidism, as recorded by Flesch (1913), Gray (1923) and Gardiner-Hill, Brett and Smith (1925), and as observed in Cases 99 and 102 of the present series, is explicable by the assumption of more rapid absorption of glucose occurring in these cases and thus unmasking the impaired carbohydrate tolerance which the intravenous test has shown to be present. That the rate of intestinal absorption is, in children, both variable and uncontrollable has already been pointed out. In addition, it may be that variations in the amount of myxoedematous tissue from case to case lead to considerable differences in the proportion of glucose dosage to metabolic activity, when body weight is used as the basis for dosage.

As regards the occurrence of impaired tolerance to glucose as demonstrated by the intravenous test in conditions of both hypo- and hyperthyroidism, an explanation is readily available. In hypothyroidism there is a general slowing of the rate of all the constituent factors of carbohydrate metabolism which affect the fall of the curve. In hyperthyroidism utilisation of glucose is increased, but the effect of this on the total tolerance is overshadowed by impairment of the power of storing glucose as glycogen. This interference with glycogen formation in conditions of hyperthyroidism has been demonstrated in animal experiments by Cramer and Krause (1912), Coggeshall and Greene (1933) and Johnston (1934), and is itself probably caused by excess of adrenalin secretion. The thyroid gland is well-known to exert a stimulating secretory action on the adrenal medulla, and many of the other features of hyperthyroidism owe their origin to this.

As was to be expected, the predominant effect of thyroid treatment on the abnormal glucose tolerance curves in hypothyroidism was a move towards normal values; but if too great a dosage of thyroid substance were employed (Cases 99 and 102) impairment of glucose tolerance recurred. The case was, in fact, converted by this excessive dosage to one of hyperthyroidism.

It might be possible to employ the intravenous glucose tolerance test as a gauge for the correct dosage of thyroid extract for any case. The correct dose would be that amount, any increase over which caused prolongation of the intravenous curve. It would be necessary to carry out the test after a period on each

dose (the dose being gradually increased). The time of fall to fasting levels would diminish until the ideal dose was reached, but any increase in dosage above this level would lead to prolonging of the time. It is perhaps of interest to note that in Mongolian idiocy, a condition frequently confused with cretinism, the intravenous glucose tolerance is normal. Results of the test in four typical cases are given in Table XXXII.

TABLE XXXII.

Intravenous glucose tolerance tests in 4 cases of Mongolian idiocy.

Case	Age in years	Blood-sugar: mg. per 100 c.c.								Remarks
		Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	
108	4/12	64	261	140	96	71	73	-	-	Normal tolerance
109	6/12	74	281	166	98	64	76	-	-	Normal tolerance
110	5	61	351	217	122	83	77	54	63	Normal tolerance
111	24/12	75	296	186	134	95	93	-	-	Normal tolerance

Conclusions.

In cretinism and juvenile myxoedema carbohydrate tolerance is impaired. This impairment is due to slowing of the processes of catabolism and storage of carbohydrate. The low oral glucose blood-sugar curve which occurs frequently, and which accounts for the textbook statements that carbohydrate tolerance is increased in hypothyroidism, is due to slow absorption of carbohydrate from the gut.

In hyperthyroidism also there is impairment of carbohydrate tolerance, the fault being traceable to defective glycogen formation. This probably results from increased secretion of adrenalin from the suprarenal medulla, under the stimulating influence of the excess thyroxin. This would tend to mobilise any hepatic glycogen as quickly as it was formed.

S E C T I O N VII

CARBOHYDRATE TOLERANCE IN CONVULSIONS AND IN OTHER CEREBRAL DISTURBANCES.

Convulsions : Introduction.

The observations recorded in this section are based upon the important work of Dr. Margaret MacLean (1936) on the changes of blood-sugar concentration which occur in association with convulsive seizures. Following up suggestions contained in the publications of Fleming, Herring and Morris (1935) and Darrow (1936) she demonstrated that convulsions are frequently succeeded by characteristic blood-sugar changes - first a hyperglycaemic phase during which glycosuria may occur, and second a hypoglycaemic phase, blood-sugar levels below 30 mg. per 100 c.c. being not uncommon. She brought evidence to show that the hyperglycaemic phase was associated with an outpouring of adrenalin into the blood as a direct result of cerebral irritation, and that the hypoglycaemic phase resulted from a subsequent adrenal exhaustion. The importance of these observations is evident, in correcting many wrong diagnoses and in displacing many false theories of the etiology of convulsive states.

In the present study an attempt has been made to follow the glucose tolerance through these changing phases. It was

clearly impossible to perform a tolerance test during both phases in each patient as the second test would have been vitiated by the glucose administration of the first test (the "Staub-Trangott" phenomenon). However, the intravenous glucose tolerance test was carried out during the hyperglycaemic phase in one case and during hypoglycaemic phases in three other cases. The test was repeated in all four cases after recovery was complete. These four patients were all children without any organic brain lesion in whom convulsions occurred as an isolated phenomenon, associated with infection.

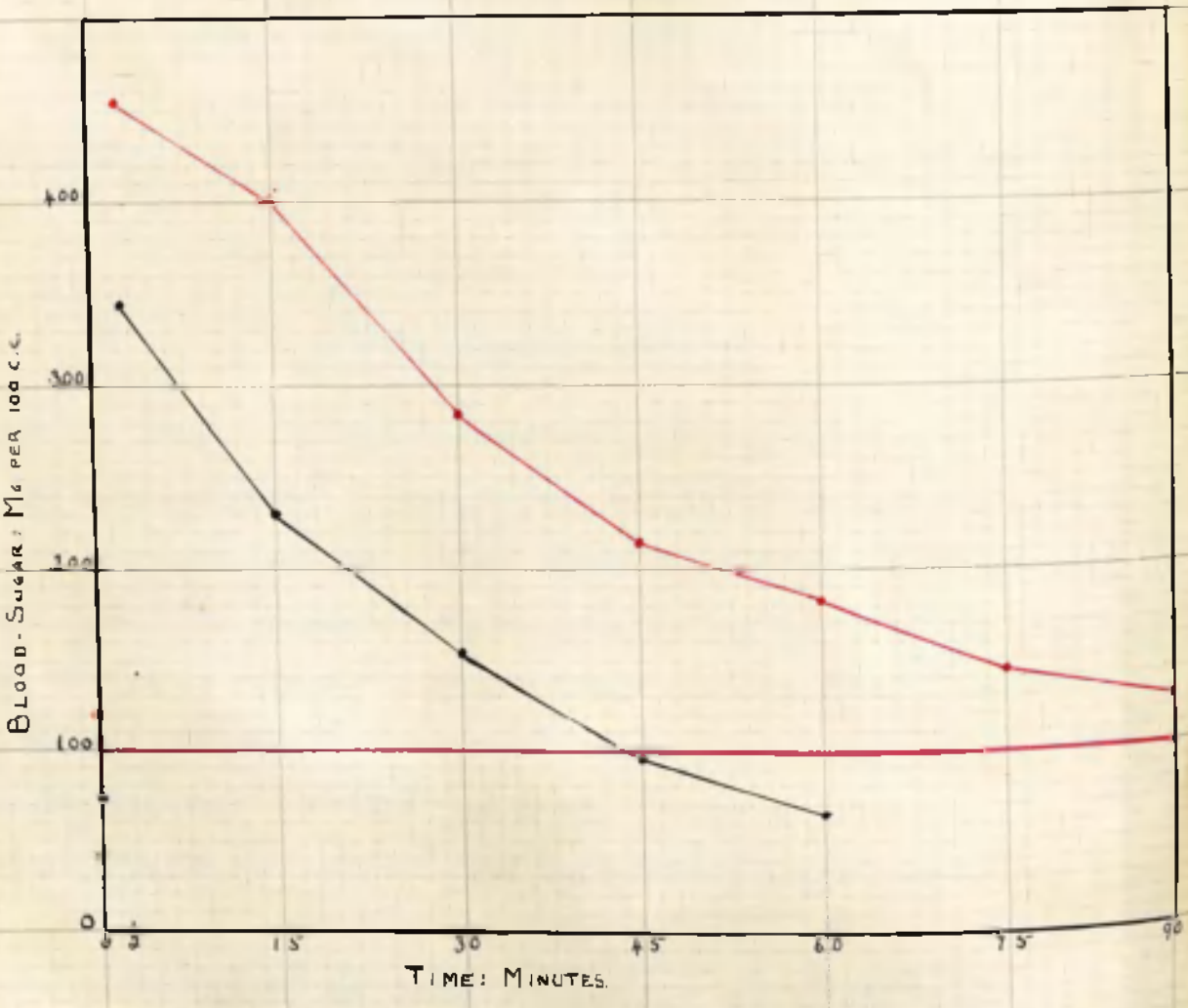
The Hyperglycaemic Phase.

In only one case was it found possible to carry out the intravenous glucose tolerance test during a hyperglycaemic phase. This patient (Case 112), a female child aged two years and five months, was admitted to hospital on 13th January, 1937, at 4.30 p.m. Convulsive movements which were said to have commenced at 1.45 p.m. were still present at the time of admission, but ceased about twenty minutes later. The urine contained abundant sugar and the blood-sugar concentration was found to be 313 mg. per 100 c.c.

As attempts had been made to feed the child, though she had swallowed little, a period of four hours was allowed to elapse before the intravenous glucose tolerance test was commenced at 8.45 p.m. By this time the hyperglycaemia was only moderate and the test was commenced from a fasting blood-sugar level of 121 mg.

FIGURE XXXIV.

Case 112: Convulsions. Intravenous Glucose Tolerance Curves during Hyperglycaemic Phase and after Recovery.



per 100 c.c. The child had no further convulsions and recovered rapidly from the mild respiratory infection which was presumably responsible for the disturbance. A week later the intravenous glucose tolerance test was repeated. The results of both tests are recorded in Table XXXIII and shown graphically in Figure XXXIV. It will be seen that during the post-convulsive hyper-

TABLE XXXIII.

Case 112: age 2 5/12 years. Intravenous glucose tolerance tests during the hyperglycaemic phase following a convulsion, and one week later, after recovery.

Date	Blood-sugar: mg. per 100 c.c.								Clinical condition	Type of curve
	Fasting	2 min.	15 min.	30 min.	45 min.	60 min.	75 min.	90 min.		
13/1/37	121	455	400	286	213	182	148	127	4 hours after convulsion	Grossly impaired tolerance
20/1/37	72	344	233	157	97	66	-	-	Well 1 wk. later	Normal tolerance

glycaemic phase there was gross impairment of tolerance to intravenous glucose; but that one week later, when recovery was complete, tolerance was normal.

The Hypoglycaemic Phase.

Intravenous glucose tolerance tests were made during a post-convulsive hypoglycaemic phase in three children, and were repeated at a later date after recovery was complete.

In Case 54 a convulsion, associated with the onset of acute tonsillitis, occurred at 10 p.m. on 30th January, 1937. Next morning the urine contained sugar, but the blood-sugar level was only 52 mg. per 100 c.c. By mid-day it had fallen to 37 mg. per 100 c.c. It was clear that a hyperglycaemic phase, with glycosuria, had occurred during the night and had been succeeded by a hypoglycaemic phase. When the intravenous test was commenced at 2 p.m. the blood-sugar concentration had risen slightly to 47 mg. per 100 c.c.

In Case 113 a convulsive attack lasted from 11 p.m. on the 6th to 2 a.m. on the 7th April, 1937. At the end of the convulsion the blood-sugar level was 233 mg. per 100 c.c., and the urine contained sugar. At 10.30 a.m. next forenoon the value had fallen to 40 mg. per 100 c.c. and the intravenous glucose tolerance test was commenced from this level.

In the third child (Case 114) convulsions occurred during the night of 18th November, 1937, and the test was carried out the following afternoon. At the commencement of the test the blood-sugar level was 55 mg. per 100 c.c. and the presence of sugar in the urine indicated a preceding hyperglycaemic phase.

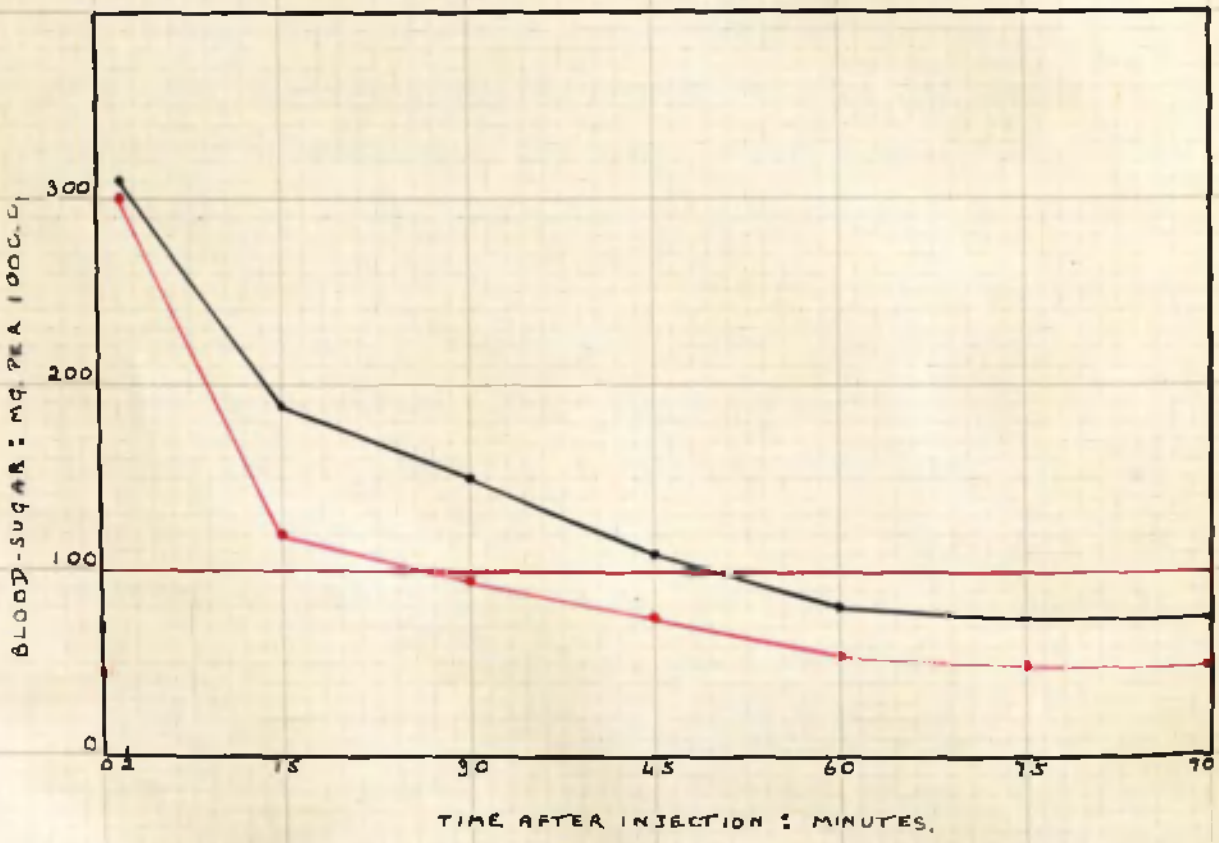
The results of the tests are detailed in Table XXXIV,

FIGURE XXXV.

Cases 54,113 and 114: Convulsions. Intravenous Glucose Tolerance Curves during Hypoglycaemic Phase and after Recovery.

——— Mean Curve during Hypoglycaemic Phase.

——— Mean Curve after Recovery.



while in Figure XXXV mean curves are drawn from the three cases during the hypoglycaemic phase and after recovery.

TABLE XXXIV.

Intravenous glucose tolerance tests during the hypoglycaemic phase following convulsions, and after recovery.

Case	Age in years	Blood-sugar: mg. per 100 c.c.								Clinical condition	Type of curve
		Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.		
54	4 9/12	47	333	132	111	74	83	77	78	Hypoglycaemic phase after convulsion	Rapid-normal
		71	330	266	216	135	84	74	71	Well	Normal
113	2	40	364	139	88	61	33	30	26	Hypoglycaemic phase	Rapid-normal
		72	343	162	114	87	67	75	74	Well	Normal
114	1 4/12	55	209	106	95	84	81	66	-	Hypoglycaemic phase	Normal
		66	255	134	111	104	90	73	-	Well	Slight delay

Accepting in each instance the curve obtained after recovery as the normal for that individual, it is seen that increased tolerance to glucose was present during the hypoglycaemic phase in all three cases.

Discussion.

From these results it can be stated that, following convulsions, the glucose tolerance passes through a well-defined series of changes - impaired tolerance during the hyperglycaemic phase, increased tolerance during the hypoglycaemic phase and normal tolerance after recovery. These findings are in accord with the contention of MacLean (1936) that the hyperglycaemic phase is due to flooding of the system with adrenalin and the subsequent hypoglycaemia to a resultant adrenal exhaustion. The presence of an excess of circulating adrenalin during the hyperglycaemic phase would interfere with glycogen deposition and thus lead to the delayed fall of the intravenous glucose blood-sugar curve; while subnormal adrenalin concentrations during the hypoglycaemic phase would leave insulin action unantagonised and allow rapid storage of the injected glucose.

Ketonuria is a constant finding during the hypoglycaemic phase, and it sometimes reaches a severe degree. It is due, no doubt, to the absence of adrenalin, which is apparently essential for the mobilisation of hepatic glycogen. In the absence of available carbohydrate, fat catabolism predominates and ketone bodies are formed in excess. Sugar-containing drinks should, therefore, be administered frequently during this phase in an attempt to produce some degree of alimentary hyperglycaemia; and in the more severe cases intravenous administration of glucose may be found to be of value.

The danger of giving insulin injections on the result of urinary examination alone in children who have had convulsions is also to be emphasised; for it is not uncommon to find both sugar and ketone bodies in the urine though the patient is actually in the hypoglycaemic phase. If insulin is given under these circumstances a severe hypoglycaemia will be produced, and it may occur without the usual warning symptoms; for many of these symptoms are due to a secondary outpouring of adrenalin in response to a lowered blood-sugar level, a response which cannot occur in post-convulsive hypoglycaemia, because of the adrenal exhaustion state which exists.

Other Cerebral Disturbances.

Since Claude Bernard's classical "Piqure" experiments (1855) it has become widely recognised that a variety of cerebral lesions may be associated with disturbances of carbohydrate tolerance. A detailed study of these conditions has not formed part of the present investigations, but as a number of intravenous glucose tolerance tests have been carried out on the subjects of cerebral disease, it has been thought worth while to include the results here.

The test was made in three cases of intracranial tumour, three of tuberculous meningitis and six of cerebral diplegia. The results are given in Table XXXV.

Of the three cases of Intracranial Tumour, one (Case 116) showed gross impairment of tolerance to intravenous glucose, while in the remaining two cases tolerance was just within normal limits,

TABLE XXXV.

Intravenous glucose tolerance tests in cases of Intracranial Tumour, Tuberculous Meningitis and Cerebral Diplegia.

Case	Age in years	Blood-sugar: mg. per 100 c.c.								Type of curve	Clinical condition
		Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.		
115	6½	77	357	244	191	143	137	89	71	Slow-normal	Hypothalamic glioma. Very slow growth.
116	10 8/12	96	515	404	345	282	171	167	149	Grossly delayed	Pontine tumour. Very rapid growth.
117	6	74	312	249	206	157	124	90	77	Slow-normal	Brain-stem tumour. Slow growth.
118	2 9/12	86	372	286	204	172	131	112	96	Delayed fall	Tuberculous meningitis.
119	3½	91	381	298	260	204	174	141	112	Grossly delayed	Tuberculous meningitis.
120	6	92	386	331	296	270	206	166	136	Grossly delayed	Tuberculous meningitis.
52	2 10/12	53	308	289	206	156	154	122	110	Grossly delayed	Cerebral diplegia. Mentally defective. Frequent screaming fits.
58	11 8/12	62	388	328	253	213	179	154	143	Grossly delayed	Cerebral diplegia. Very emotional. Occasional convulsions.
121	5 10/12	90	316	220	140	83	52	53	56	Normal	Cerebral diplegia. No fits.
122	3	73	385	211	161	99	86	79	73	Normal	Cerebral diplegia. No fits.
123	4/12	86	264	199	155	115	77	-	-	Delayed	Cerebral diplegia. Very frequent minor convulsions.
124	4 5/12	79	292	193	120	88	81	75	-	Normal	Cerebral diplegia. No fits.

the blood-sugar concentration descending to fasting levels in seventy-five minutes - the slower limit of normal.

The three cases of Tuberculous Meningitis all exhibited impairment of intravenous glucose tolerance. In two the impairment was gross, in the third (Case 118), of moderate degree.

In the six cases of Cerebral Diplegia variable results were obtained. Three cases (121, 122, 124) displayed normal intravenous glucose tolerance, and it is notable that these children were free from fits and gave no evidence of active or progressive cerebral disease. In the remaining three cases there was impairment of glucose tolerance. Two of these children were subject to frequent minor fits, while the third (Case 58) was a very emotional, unstable girl showing advanced mental defect, with occasional major convulsions.

Interpretation of these results must be largely speculative, and it would be unprofitable to discuss them at great length. It would appear, however, that those cerebral lesions of a more acute and irritant character are fairly constantly associated with some degree of impairment of carbohydrate tolerance, while quiescent or very slowly progressing lesions leave the tolerance unimpaired.

Thus the fall of the intravenous curve was delayed in the three cases of tuberculous meningitis, in a child with a rapidly growing pontine tumour, and in three cases of cerebral diplegia subject to fits. On the other hand, three cases of cerebral diplegia in which the clinical condition was stationary and fits did not occur showed normal tolerance. It may be that the

presence of increased intracranial pressure is of importance in causing impairment of glucose tolerance.

SECTION VIII

CARBOHYDRATE TOLERANCE IN GLYCOGEN DISEASE (VON GIERKE'S DISEASE)

Introduction.

The earliest report of glycogen disease came from Snapper and van Creveld (1928) under the title of "Chronic hepatogenic hypoglycaemia in Childhood." Von Gierke in 1929 published full details of autopsies on two similar cases and called the condition "hepato-nephromegalia glycogenica." Since then some forty cases of the condition have been described from all parts of the world except the Orient. A variety of names has been employed, the ones now in most frequent use being "von Gierke's disease" and "Glycogen disease" or "Glycogen storage disease" ("Glykogen-speicherkrankheit").

The essential feature of the condition is the accumulation of excessive quantities of glycogen in the liver, kidneys, or heart muscle. Most often, to clinical criteria, the liver is affected alone, but cases have been described in which only the heart was involved ("Cardiomegalia glycogenica" - Bischoff, 1932; Putschar, 1932; Pompe, 1933). In other cases the liver and kidneys were involved together.

Clinically, the disease usually manifests itself between the ages of one and four years by arrest of growth and abdominal enlargement. Though the metabolic error probably exists from birth medical advice is frequently not sought for some years, by which time dwarfing and abdominal enlargement are usually severe. On examination a greatly enlarged liver and perhaps palpable kidneys are found. The child is usually pale and flabby, and muscular development is poor. General development is also backward, but, apart from the effects of interference with education, the mentality is in most cases normal. Cardiomegalia glycogenica presents a different clinical picture from the other forms of glycogen disease; it has usually been discovered at autopsy on an infant who has died suddenly of cardiac collapse.

Glycogen disease is to be suspected from the discovery of hepatic enlargement without splenic enlargement in a young child of less than normal height and weight. A presumptive diagnosis can be made from the results of careful biochemical investigations of the carbohydrate metabolism; but the disease can be diagnosed with certainty only after histological or biochemical examination of a portion of the liver, obtained either at autopsy or biopsy.

No treatment has been found to influence the course of the disease. Management of a case consists of careful protection from intercurrent infection and the treatment of such infection if it arises. There is evidence to suggest that if puberty is reached the metabolic disorder, whatever its nature may be, passes off and is succeeded by a period of active growth which may leave the

subject little the worse for his childhood disease. Many of the cases reported have, however, died from intercurrent infection, usually respiratory, during the active period of the disease before puberty is reached.

Case Histories.

In the present investigation three cases of glycogen disease have been studied. Owing to the rarity of the disease the case histories are given here in some detail.

Case 125. W.R., male, age 12 years at the time of these investigations. He was a healthy baby and throve for six months, but at that age he began to have frequent attacks of vomiting. At age 1½ years his parents noticed that his abdomen was becoming swollen, and he was first taken to hospital in January, 1928 at the age of 3 years. He was then found to be considerably below normal height and weight and the liver extended to the umbilicus. The spleen was not palpable. Physical development remained backward, and at the age of 12 years the investigations reported below were carried out. At that time his height was 117 cms. and his weight 22.8 kgs., compared with normal values for his age of 142 cms. and 36.2 kgs. respectively - he corresponded in height and weight to a boy of 7 years. His liver, the surface of which was smooth and firm, extended four-and-a-half inches below the costal margin and the spleen was not palpable. His general health was fair apart from the smallness of stature and abdominal distension.

The family history is of interest in this case. A brother of the patient, five years younger, was also observed in hospital. Similar hepatic enlargement was present and, as a result of biochemical investigations, a presumptive diagnosis of glycogen disease was made. Unfortunately, this child died of measles shortly after he was first seen. An elder sister of the patient was stated to have been "like the boys" in early childhood. Examined at the age of 15 2/12 years, she was only slightly below normal height and weight. Her liver, however, was slightly enlarged and it is possible that she was a recovered case of glycogen disease. A maternal uncle of the patient was also stated to have been like the two boys in childhood, but to have "grown out of it."

Case 126. J.J., female. This child appeared normal at birth and throve during the first year. At 18/12 year, however, abdominal swelling was noticed and she began having frequent attacks of diarrhoea and vomiting. Medical advice was not sought until the age of 8 years, when she was first seen in hospital. Her height was then 106 cms. and her weight 17.8 kgs., compared with normal values of 122 cms. and 24 kgs. The liver extended down below the umbilicus and the spleen was not palpable. She was seen again at the age of 12 11/12 years when the present investigations were made. At this age her height was 120 cms. (normal 145 cms.) and her weight 20.6 kgs. (normal 36.9 kgs.). The liver still extended to the umbilicus and intravenous pyelography revealed considerable enlargement of the parenchyma of both kidneys.

When last seen, at the age of 13½ years, her general health was fair and some growth was occurring, but she still suffered frequently from vomiting. She was an only child and no history of a similar condition in her relatives could be traced.

Case 127. W.G., male, age 1 11/12 year. This patient is the only child of an unmarried woman who disclaimed knowledge of the child's father. Nothing relevant could be discovered in the mother's family history, but, of course, the father's family is not known about. The boy was born at full-time after a normal pregnancy. He was breast-fed for eight months and appeared to thrive at first. At the age of 8/12 year he had one tooth and could sit up alone. Little further progress was made, however, and at the age of 1 11/12 year, when first seen, he could not stand or walk and speech was barely commencing. For four months prior to admission progressive abdominal enlargement was observed and he suffered from frequent vomiting attacks.

On admission to hospital he was found to be a fairly well-nourished, rather pale, flabby child. His weight was 9.5 kgs. and his height 74 cms., compared with the normal values for his age of 12 kgs. and 83 cms. respectively. Gross abdominal distension was present and the swelling was found to consist of a greatly enlarged, smooth, firm liver extending down to the iliac crests. The spleen was not palpable, but the lower pole of the left kidney could be felt. The size of the liver caused some respiratory embarrassment and during his stay in hospital the child had several mild bronchitic attacks. On 9th November, 1938, a laparotomy was performed by Mr. White. The surface of the greatly enlarged liver appeared normal, and a piece was removed for examination. It contained 7.69 per cent. of glycogen. Histologically, a strong glycogen reaction was obtained and the amount of fat in the liver appeared extremely small (Dr. G.L. Montgomery).

When dismissed from hospital the child's condition was unchanged; he has since reported as an out-patient and, when last

seen at the age of 24/12 years, the condition of the liver showed no change, but he was walking and talking fairly well.

The results of the investigations on these cases are described under the following headings: Ketosis, Fasting Blood-Sugar Levels, Oral Glucose Tolerance, The Effect of Adrenalin, Blood-Glycogen Content, Plasma and Urinary Diastase, and Intravenous Glucose Tolerance.

Ketosis.

Ketone bodies were present in fasting specimens of urine in all three subjects, though in Case 127 the finding was inconstant, fasting specimens being occasionally found to be ketone-free. In no case was the concentration of ketones sufficient to yield a positive result with the ferric chloride test; the usual finding was a weak or moderately brisk response to Rothera's test. The concentration of ketones in the urine was observed to increase following injections of adrenalin, an observation noted also by van Creveld (1939). Anderson and Anderson (1927) however, have shown that such an occurrence is physiological in rats.

Fasting Blood-Sugar Levels.

In each case the blood-sugar level was estimated under fasting conditions on several occasions. The results are shown in Table XXXVI. It will be seen that the predominating values are low, but that in each case one value at the lower limit of normal was obtained.

FIGURE XXXVI.

Cases 125, 126 and 127: Glycogen Disease.

Oral Glucose Tolerance Curves.

Case 125.

Case 126.

Case 127.

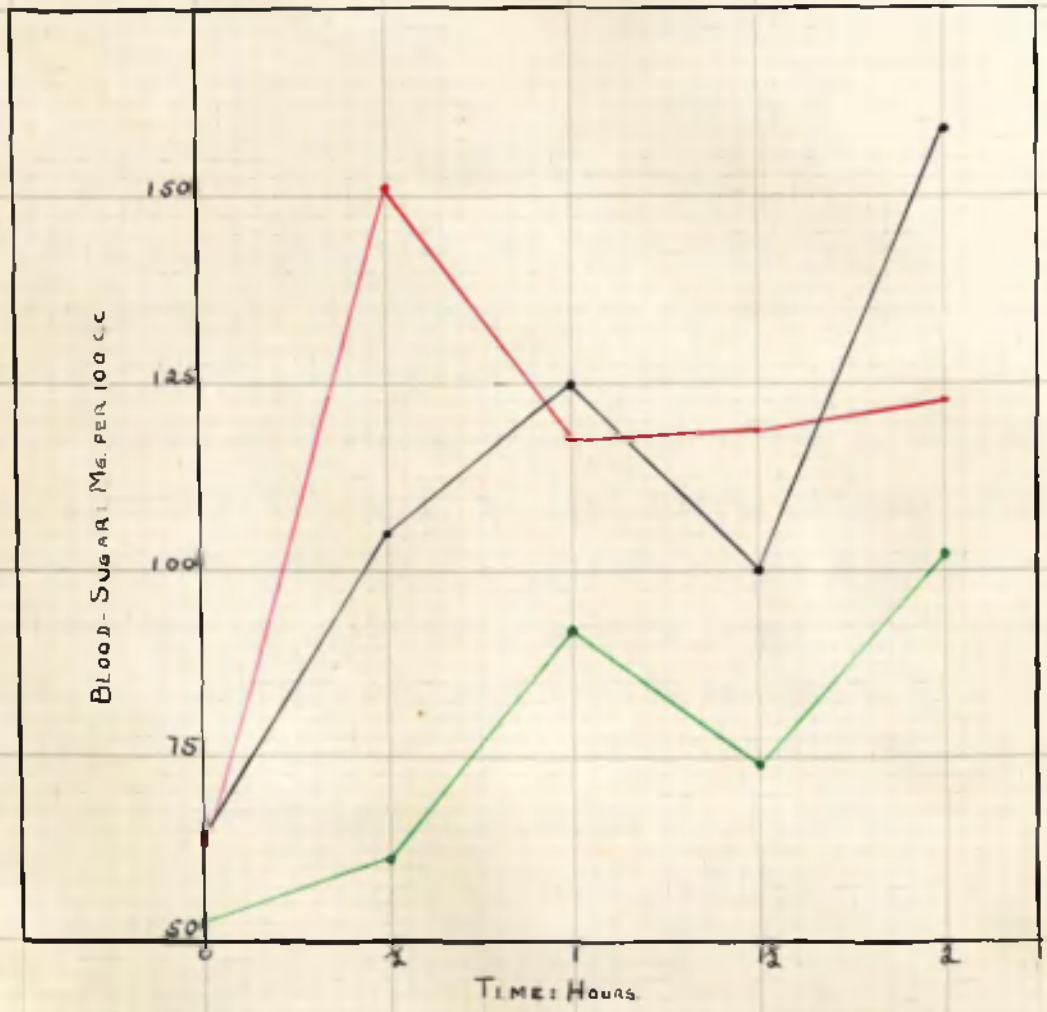


TABLE XXXVI.

Fasting blood-sugar levels in Glycogen Disease.

Case	Fasting blood-sugar levels: mg. per 100 c.c.
125	49, 70, 64
126	64, 63, 61, 70
127	52, 47, 72, 54

Oral Glucose Tolerance.

Oral glucose tolerance tests were performed in each case, using a test dose of 2 grams of glucose per kilogram of body weight in the young child (Case 127) and of one gram per kilogram of body weight in the two older children. The results of the tests are given in Table XXXVII and shown graphically in Figure XXXVI. The three curves show a marked similarity to one another

TABLE XXXVII.

Oral glucose tolerance tests in Glycogen Disease.

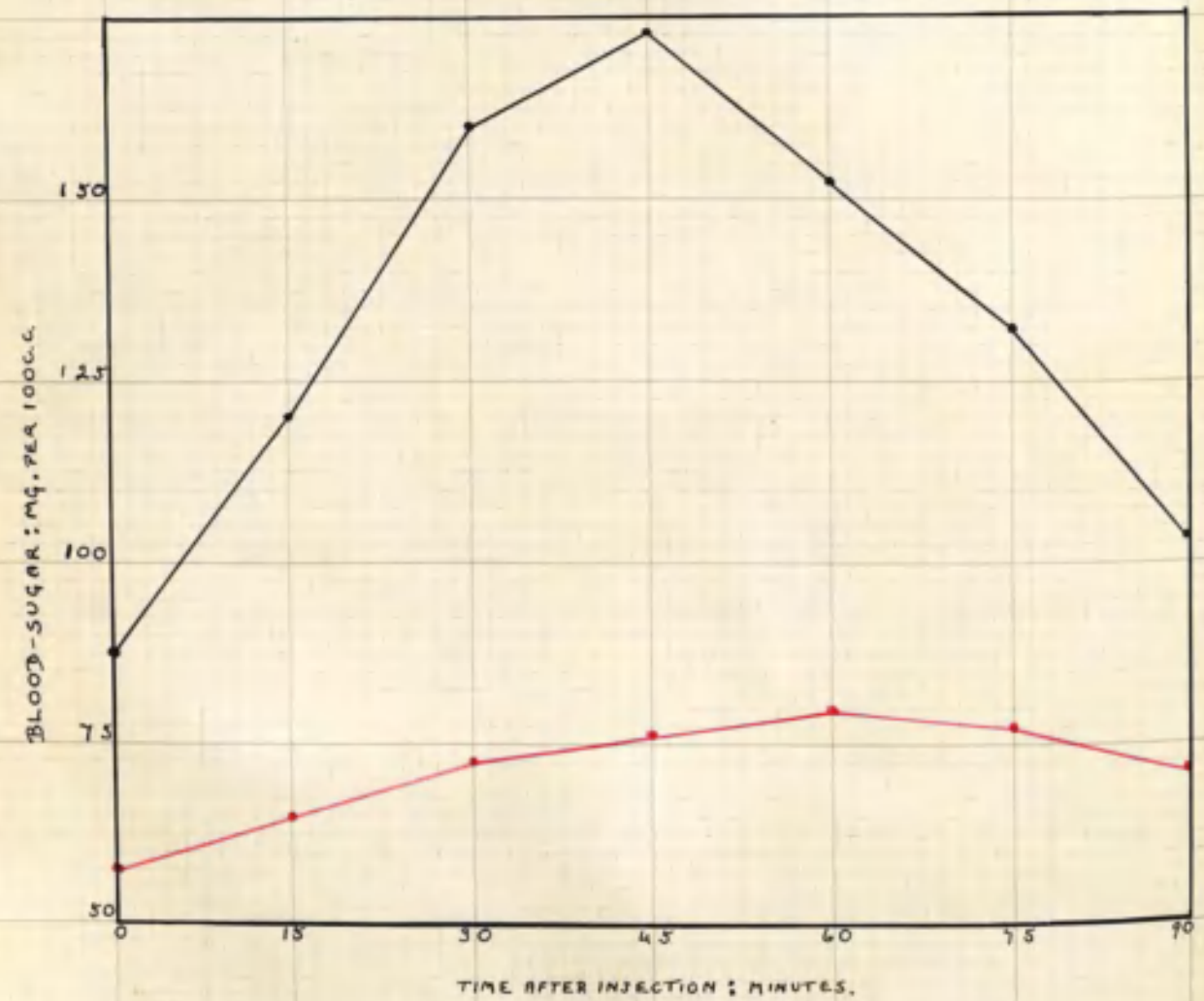
Case	Age in years	Blood-sugar: mg. per 100 c.c.						Type of curve
		Fasting	½-hour	1 hour	1½ hours	2 hours	Maximum rise	
125	12	64	111	125	101	167	103	High. Double-peaked
126	12 11/12	64	152	117	119	122	88	Normal. Double-peaked
127	1 11/12	52	61	92	74	102	50	Normal. Double-peaked

FIGURE XXXVII.

Mean Blood-Sugar Curves after Adrenalin Injection in Three Cases of Glycogen Disease and in Four Normal Subjects.

——— Mean Curve from four Normal Subjects.

——— Mean Curve from Three Cases of Glycogen Disease.



In each curve a peak value is attained in the half- or one-hour specimen, a fall occurs in the subsequent specimen and a secondary rise follows at two hours. The expression "biphasic" has been used to describe such curves, but "double-peaked" seems both more accurate and less ambiguous.

In none of the cases did glycosuria occur, and ketonuria was present at both the beginning and the end of the test in each.

The Hyperglycaemic Effect of Adrenalin.

The effect upon the blood-sugar of a subcutaneous injection of adrenalin hydrochloride was tested in each of the patients and in a series of four children in whom the question of glycogen disease did not arise. A test dose of 0.5-c.c. of a 1:1000 solution of adrenalin hydrochloride (natural, not synthetic) from a freshly opened bottle, was used in all cases except Case 126 who received 0.75-c.c. In making this test in suspected cases of glycogen disease it is of prime importance to test the adrenalin solution used on a normal subject to make certain that it is active. A solution which shows any discolouration is useless. The results of the tests are shown in Table XXXVIII, and in Figure XXXVII mean curves are drawn from the patients and from the normal controls. In the patients with glycogen disease the increases noted in the blood-sugar level after adrenalin administration are trivial compared with those obtained in the control cases. In the former the rise varied from 21 to 37 mg. per 100 c.c., while in the latter the smallest

rise noted was 84 mg. per 100 c.c.

TABLE XXXVIII.

Adrenalin Hyperglycaemia in Glycogen Disease and Control Subjects.

Case	Age in years	Blood-sugar: mg. per 100 c.c.								Maximum rise	Clinical Condition
		Fasting	¼-hour	½-hour	¾-hour	1 hour	1¼ hours	1½ hours	2 hours		
125	12	70	83	82	91	88	69	-	-	21	Glycogen Disease
126	12 11/12	61	63	72	70	75	83	58	-	22	
127	1 11/12	47	52	61	66	77	79	84	65	37	
18	4	94	131	160	178	164	118	88	-	84	Controls
29	8	96	118	143	166	178	181	130	-	85	
32	9	80	101	166	190	114	94	90	-	110	
58	11 8/12	77	128	167	163	-	133	-	106	86	

Blood-Glycogen Content.

An estimation of the glycogen content of the blood was made in each case, and also in a number of children with a variety of other diseases. The object of this was to observe whether the high values found in Cases 126 and 127 were characteristic of glycogen disease or could occur in other conditions. The results are given in Table XXXIX where they are graded in descending order. It will be seen that in two of the cases of glycogen disease the blood-glycogen concentration was

far in excess of that found in other conditions. In the other case (125) the concentration seems to be about the upper limit of "normal." In only one other case, a child aged six years with acute myeloblastic leukaemia, was the blood-glycogen concentration above the apparently normal levels.

TABLE XXXIX.

Whole-blood glycogen content in glycogen disease and various other conditions.

Case	Age in years	Whole-blood Glycogen mg. per 100 c.c.	Clinical condition.
127	1 11/12	26.6	Glycogen disease
126	12 11/12	23.0	Glycogen disease
24	6	13.1	Leukaemia
30	8	7.2	Oesophageal stricture
125	12	6.8	Glycogen disease
131	10 10/12	6.6	Diabetes mellitus
130	5 7/12	6.1	Bronchiectasis
128	6 11/12	5.0	Tonsillitis
103	6 10/12	5.0	Cretin (treated)
52	2 10/12	5.0	Cerebral diplegia
27	7	5.0	Rheumatism
36	10	4.5	Tonsillitis
129	7 3/12	4.3	Rheumatism
132	10½	3.8	Diabetes mellitus
58	11 8/12	2.0	Cerebral diplegia

Plasma and Urinary Diastase.

Estimations of the diastatic activity of the blood and urine were made in two of the patients with glycogen disease (Cases 125 and 126), and in a number of control subjects. The results are detailed in Table XL.

TABLE XL.

Diastatic activity of blood and urine in glycogen disease patients and in control subjects.

Case	Age in years	Date	URINE			Blood-Plasma Diastase. Units per c.c.	Clinical condition
			Vol. c.c.	Diastase units			
				Per c.c.	Total		
125	12	4/2/37	550	26.5	14,575	-	Glycogen Disease
		5/2/37	495	18.5	9,158	7.0	
		6/2/37	720	19.5	14,040	-	
126	$12^{11}/12$	15/12/37	780	21.0	16,380	-	
		16/12/37	660	20.0	13,200	8.2	
		17/12/37	645	19.5	12,577	-	
128	$6^{11}/12$	1/2/37	485	25.0	12,125	-	Tonsillitis - recovered
		2/2/37	500	21.0	10,500	6.6	
		3/2/37	350	19.5	6,825	-	
129	$7^{3}/12$	11/2/37	620	21.0	13,020	-	Chorea - recovered
		12/2/37	708	19.5	13,806	14.0	
		13/2/37	680	20.0	13,600	-	
58	$11^{8}/12$	8/2/37	-	-		8.5	Cerebral Diplegia
133	$5^{2}/12$	10/2/37	-	-		8.3	

It is clear that the values for the glycogen disease patients fall within the apparently wide normal limits.

Intravenous Glucose Tolerance.

The results of intravenous glucose tolerance tests on the three cases of glycogen disease are shown in Table XLI.

TABLE XLI.

Intravenous glucose tolerance tests in 3 cases of Glycogen Disease.

Case	Age in years	Blood-sugar: mg. per 100 c.c.								Type of curve.
		Fasting	2 min.	15 min.	30 min.	45 min.	60 min.	75 min.	90 min.	
125	12	49	294	270	198	165	125	103	81	Slightly delayed fall
126	12 11/12	63	232	193	157	131	111	84	95	Normal
127	1 11/12	72	239	168	152	134	110	92	-	Delayed fall
	2	54	264	174	136	111	88	83	-	Slightly delayed fall

In Case 126 the result just falls within normal limits, but in each of the other cases moderate or slight increase is found in the time taken for the restoration of normal fasting levels. There is thus some degree of impairment of intravenous glucose tolerance in these cases.

Summary of Results.

The following are the features of the carbohydrate metabolism which have been observed in three cases of glycogen disease.

1. In two cases Rothera's test for ketone bodies was constantly positive in the fasting morning urine. In the third case it was occasionally negative.

2. Subnormal fasting blood-sugar levels were the rule, though isolated normal values were found.

3. Oral glucose tolerance tests gave a constant double-peaked curve. The primary peak occurred at the half- or one hour, and, after an intervening fall, a secondary rise at two hours.

4. The hyperglycaemia after adrenalin injection was of very limited extent compared with the effect in normal children.

5. The blood-glycogen content was greatly increased in two cases, but normal in the third.

6. Plasma and urinary diastase were normal.

7. Intravenous glucose tolerance showed slight impairment.

These results are given in tabular form in Table XLII.

TABLE XLII.

Summary of results of investigations in Glycogen Disease.

Test	Result of Test		
	Case 125	Case 126	Case 127
Ketonuria (Rothera)	Constant	Constant	Inconstant
Fasting blood-sugar	Subnormal	Subnormal	Subnormal
Oral glucose tolerance	Double-peaked curve	Double-peaked curve	Double-peaked curve
Hyperglycaemic action of adrenalin	Diminished	Diminished	Diminished
Blood-glycogen	Normal	Greatly increased	Greatly increased
Urinary and plasma diastase	Normal	Normal	Normal
Intravenous glucose tolerance	Impaired	Slow-normal	Impaired

Discussion.

Ketonuria and hypoglycaemia have been found in the great majority of undoubted cases of glycogen disease recorded, though in several cases, as in Case 125, these have been inconstant. Lindsay, Ross and Wigglesworth (1935) report a case, confirmed by hepatic biopsy, in which ketonuria was not found. The occurrence of ketonuria and hypoglycaemia are clearly the direct result of failure of the body to utilise its stores of carbohydrate. In these circumstances catabolism of fat outbalances other oxidative processes and ketone bodies are formed in excess.

The double-peaked blood-sugar curve found after oral administration of glucose in all the present cases has been reported also by van Creveld (1934). All forms of curve have, however, been reported by other workers. Thus, in the case of Lindsay, Ross and Wigglesworth (1935) the curve was low, while one patient of Schall (1932) exhibited a high prolonged curve. The explanation of these irregular findings is uncertain: they are probably related to irregularities in the rate of absorption and to variations in the glycogen saturation of the liver at the time of the test.

The finding of a greatly increased amount of glycogen in the blood of two of the present cases agrees with results obtained by van Creveld (1934), Schönheimer (1929), Beumer and Loeschke (1932), Hertz (1933a) and Sundal (1936). On the other hand, Schall (1932) and Rauh and Zelson (1934) found diminished

amounts and in Anderson's case (1935) the value was normal. These latter cases, with Case 125 of the present series, are to be regarded as exceptions to the more usual finding. The finding of a raised blood-glycogen is important evidence in favour of the existence of glycogen disease; but a normal or low glycogen level does not exclude the possibility of glycogen disease. Apparently the only other condition to cause considerable elevation of the blood-glycogen level is the existence of a high leucocytosis.

Diminution of the hyperglycaemia produced by adrenalin is perhaps the most constant and characteristic feature of glycogen disease. Many cases reported have shown no rise whatsoever of the blood-sugar after injections of adrenalin. There are three possible explanations of such a diminished hyperglycaemic action of adrenalin in an intact subject:

1. Hyperinsulinism (Wilder, Allan, Power and Robertson, 1927), causing increased glycogen formation.
2. Absence of a glycogen store in the liver, such as may occur in extreme fatty degeneration, e.g., congenital hypertrophic steatosis of the liver (Bjørum, 1927).
3. Defective glycogenolysis.

In glycogen disease the second of these possibilities can be immediately discarded, leaving the two groups of alternatives: (a) abnormally vigorous glycogen formation as occurs in hyperinsulinism and (b) a failure of glycogenolysis. Results of intravenous glucose tolerance tests in the present cases show clearly that there is no abnormally active storage of glucose proceeding; the process is, in fact, somewhat tardy, for the fall

of the intravenous curve is definitely delayed in two of the cases, while in the third case the full seventy-five minutes are required - the longer limit of normal. This finding excludes the possibility of hyperinsulinism or of any other form of rapid glycogenogenesis being the fundamental cause of the accumulations of glycogen in glycogen disease. There remain the two possible causes of failure of glycogenolysis - abnormal glycogen, or a failure of action of the hepatic glycogenolytic ferment.

While two of the present cases showed normal diastatic activity of the plasma and urine other investigators (Loeschke, 1932; Hertz, 1933b; Rauh and Zelson, 1934; Harnapp, 1936) claim to have found the activity of the blood to be low and that of the urine high. The significance of these findings is doubtful as it is uncertain that the diastatic enzyme appearing in the blood and urine has any connection with the normal glycogenolytic ferment of the liver.

The final solution to the problems of glycogen disease would seem to depend upon investigation of the chemistry of glycogen and the nature and action of the hepatic glycogenolytic ferment.

S E C T I O N IX

INTRAVENOUS GLUCOSE TOLERANCE IN DISEASES OF THE LIVER

Introduction.

Numerous tests have been devised by various workers with the object of giving to clinicians a single test which could be applied as a measure of hepatic function, and which would yield immediate information as to the presence or absence of liver damage and as to its extent, if present. It must be stated at once that no claims are made here that the intravenous glucose tolerance test fills this want. Indeed it is unlikely, considering the complex nature of hepatic function, that any single test could supply information of this kind; for, while a certain disease process may seriously impair one hepatic function (for example, the formation of bile), it may leave others (for example, the deaminating and detoxicating functions) quite adequate for the needs of the body.

An important factor - perhaps the most important - in determining the form and rate of fall of the intravenous glucose tolerance curve is the rate at which the injected glucose is stored as glycogen. Since the liver cells are probably the most important site of such storage it is to be anticipated that if a

large proportion of liver cells is destroyed, or if the glycogen-forming properties of these cells are interfered with in any other way, prolongation of the intravenous tolerance curve will result.

Results.

The intravenous glucose tolerance test has been carried out with the customary technique in three cases of catarrhal jaundice, two cases of obstructive jaundice (one due to congenital atresia of the bile-ducts, the other to a malignant tumour in the portal fissure), two cases of Banti's syndrome, and two cases of cirrhosis of the liver, one of which was of the Hanot type. The results are detailed in Table XLIII.

Of the three cases of catarrhal jaundice delay of the fall of the curve was found in all. In two the delay was moderate, in the third severe.

Slight delay was found in the infant with congenital atresia of the bile-ducts, while in the child in whom obstructive jaundice was the result of a liver tumour the curve was normal.

The two cases of Banti's syndrome showed a similar moderate impairment of intravenous glucose tolerance.

The child with cirrhosis of the Hanot type showed severely impaired tolerance, but in the boy with ordinary multilobular cirrhosis tolerance was normal.

TABLE XLIII.

Intravenous glucose tolerance in Liver Diseases.

Case	Age in years	Blood-sugar: mg. per 100 c.c.								Diagnosis	Type of Curve
		Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.		
134	3½	63	286	201	136	116	101	92	-	Catarrhal jaundice	Delayed fall
135	4½	75	300	177	161	154	136	115	93	Catarrhal jaundice	Delayed fall
136	10	57	262	204	179	161	145	139	131	Catarrhal jaundice	Grossly delayed fall
137	7/52	63	246	164	150	138	113	90	78	Atresia of bile-ducts	Delayed fall
138	3½	83	286	177	150	115	94	83	85	Liver tumour: obstructive jaundice	Normal
139	12	84	361	270	191	164	136	128	96	Banti's disease	Delayed fall
140	10½	86	380	264	177	158	141	113	95	Banti's disease	Delayed fall
141	7	61	245	200	170	141	134	115	113	Hanot's cirrhosis	Markedly delayed fall
142	6	86	282	175	122	92	75	70	-	Cirrhosis of liver	Normal

Discussion.

From these results it is clear that a variety of different types of liver damage can interfere with the glycogen-storage function of the liver and lead to impaired intravenous glucose tolerance. As already recorded in a single observation by Wilson (1939), the toxic disturbance of the liver in catarrhal jaundice produced a moderate or severe impairment of intravenous tolerance. On the other hand, the more severe jaundice produced by obstructive lesions caused little or no delay in the fall of the curve. This observation is in accordance with the accepted pathological findings that in catarrhal jaundice there is invariably an acute diffuse hepatitis, whereas in obstructive lesions damage to liver cells is late and of slight degree.

In the conditions associated with fibrosis in the liver it is noteworthy that impairment of tolerance was seen in those where the lesion was of a diffuse nature (Banti's syndrome and Hanot type of monolobular cirrhosis), whereas in the case of multilobular cirrhosis with an irregular nodular liver, tolerance was normal.

Clearly the intravenous glucose tolerance test is of no diagnostic value in these cases. It does not even give positive information of the presence of liver disease, for it has been repeatedly shown in previous sections of this thesis that other conditions may cause similar changes in the form of the intravenous tolerance curve; and glycogen formation in a healthy liver

may itself be interfered with by extra-hepatic disease, for example, by hyperthyroidism. On the other hand, in known hepatic disease, the test does afford information as to the presence and extent of impairment of the glycogenic function.

SECTION X

THE INTRAVENOUS GLUCOSE TOLERANCE TEST IN THE INVESTIGATION OF GLYCOSURIA

Introduction.

The investigation of cases of glycosuria provides the bulk of instances in which glucose tolerance tests are employed in routine clinical practice. For this purpose the oral glucose tolerance test has proved fairly satisfactory. This is especially the case in children, for the diabetic child usually has the disease in a severe form so that an oral test rarely leaves any doubt as to the diagnosis. In elderly subjects, on the other hand, "borderline" results are disconcertingly frequent with the oral test, and there is no reason to suppose that they would be less frequent with the intravenous test. There is one form of glycosuria, however, in which the intravenous curve may be expected to provide some assistance, that is, in the glycosuria with a so-called "Lag-storage curve." The lag-storage curve was first described by McLean (1922) as an oral tolerance curve in which the blood-sugar level ascended steeply, reaching a value above the normal renal threshold at one-half- or one hour, but falling rapidly to fasting levels in one-and-one-half to two

hours. He attributed this form of curve to delay of the storage mechanism in coming into action. Lawrence (1936) however, brought strong evidence to show that such curves were produced merely by abnormally rapid emptying of the stomach, with consequent abnormally rapid absorption of the test dose of glucose. Indeed McLean himself mentioned such a likelihood, though he coined the misleading name of "Lag curve." This type of curve is not of frequent occurrence in children and unfortunately no opportunity has arisen to observe whether or not it is associated with the normal curve which one would anticipate after intravenous administration of glucose.

Present Investigation: Results.

Tolerance tests have been carried out in five cases of undoubted diabetes mellitus, two cases of renal glycosuria, and one patient of the "borderline" diabetic type. As the diabetic children were in need of prompt treatment it was usually impossible to make more than one tolerance test in each case before insulin was given. The results of the oral tests on one diabetic and the other cases are shown in Table XLIV. The intravenous test was carried out in all the cases and the results of these are given in Table XLV. The tests on the diabetic children were all made before the commencement of treatment except in Case 143. This boy had received 42 units of Protamine-Insulin at 7 a.m. and the test was commenced at 2.30 p.m. In Case 132 the second intra-

venous test was made after insulin and dietetic treatment had been instituted and the ketosis present at the time of the first test had been overcome. He had received 10 units of soluble insulin six hours before the test, so it is unlikely that he was under the influence of insulin during the test.

TABLE XLIV.

Oral glucose tolerance tests in cases of Glycosuria.

Case	Age in years	Blood-sugar: mg. per 100 c.c.					Urine-sugar			Diagnosis
		Fasting	½-hour	1 hour	1½ hours	2 hours	Fasting	1 hour	2 hours	
145	11	86	154	215	240	195	Trace	++	++	Diabetes mellitus
146	5	90	188	159	163	129	Nil	+	Trace	"Borderline"
147	10	77	157	136	119	92	Nil	+	+	Renal glycosuria
148	6	68	93	143	138	116	Nil	Nil	+	Renal glycosuria

In Case 146 - the "borderline" case - the oral test showed a rapid rise of the blood-sugar concentration to 188 mg. per 100 c.c. and at two hours fasting levels had not been restored. In the intravenous test the fall of the blood-sugar to normal fasting levels was delayed until the ninety-minute specimen. Thus both tests gave a "borderline" result.

The cases of renal glycosuria gave results within normal limits for both oral and intravenous tests, but in the latter

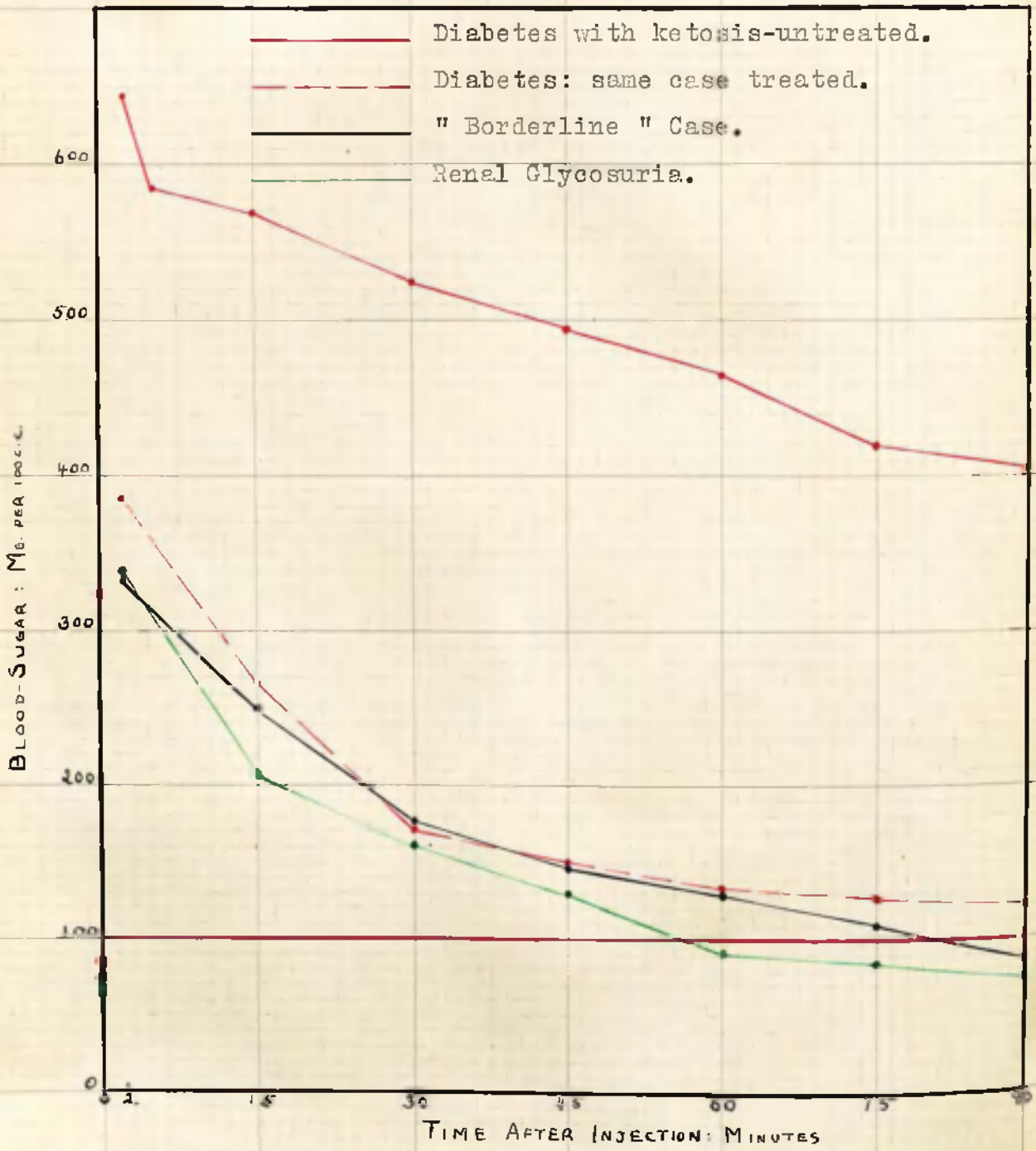
TABLE XLV.

Intravenous glucose tolerance tests in cases of Glycosuria.

Case	Age in years	Blood-sugar: mg. per 100 c.c.										Sugar in Urine: % of dose.	Diagnosis
		Fasting	2 mins.	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	105 mins.	120 mins.		
131	10 10/12	155	417	323	290	282	233	225	215	211	220	14.4	Diabetes mellitus (untreated)
132	10½	323	645	571	526	494	465	421	404	396	377	21.0	Diabetes mellitus (untreated)
		84	385	263	175	154	132	127	123	104	89	8.6	Diabetes mellitus (treated)
143	8	101	332	268	240	191	188	169	163	-	-	8.5	Diabetes mellitus (treated)
144	7½	148	571	364	320	333	342	325	329	-	-	17.4	Diabetes mellitus (untreated)
145	11	80	375	273	231	214	167	160	174	148	164	13.4	Diabetes mellitus (untreated)
146	5	77	338	251	188	150	134	111	84	-	-	8.0	"Borderline" case
147	10	88	331	228	191	179	132	93	95	-	-	16.5	Renal glycosuria
148	6	72	340	208	166	130	94	86	74	-	-	14.3	Renal glycosuria

FIGURE XXXVIII.

Intravenous Glucose Tolerance Curves in Cases of Diabetes Mellitus and Renal Glycosuria, and in a "Borderline"Case.



excess loss of sugar in the urine occurred.

In Figure XXXVIII the results of the intravenous tests in Cases 132, 146 and 148 are charted as examples of diabetes with and without ketosis, a "borderline" case, and renal glycosuria, respectively.

Discussion.

The gross impairment of intravenous glucose tolerance found in the diabetic children was to be expected and is in agreement with the findings of Jörgensen and Plum (1922) and Torning (1932). It is of interest to find, however, that the phase of rapid fall of the blood-sugar, noted in connection with the test in normal subjects (Section II) and occurring for two to five minutes after the end of the injection, is preserved in the diabetic curves. This finding gives support to the suggestion that the primary rapid fall of the curve is due to simple diffusion of the injected sugar out of the blood into the extra-vascular tissue fluids. The fall is of short duration and the curve flattens out more quickly than in normal subjects.

The normal intravenous curves found in the two children with renal glycosuria lend support to the now widely held view that this condition is without deleterious effect on carbohydrate tolerance. Case 146, who has been designated as a "borderline" case from the results of both oral and intravenous tests, presents some points of interest. The patient is a boy of five years of

age, the son of a severely diabetic father. His father thought the boy looked unwell one day and, testing his urine, found it to contain sugar. The question arises as to whether the tolerance tests, showing a rather high and slowly falling oral curve, and a slight prolongation beyond the normal time of fall of the intravenous curve, indicate an early diabetic condition. The family history is strongly suggestive that this is the case; but the boy has now been under observation for a year and no deterioration has occurred.

In conclusion it may be said that the intravenous glucose tolerance test is unnecessary for the investigation of glycosuria. The oral test is more suitable for the detection of renal glycosuria, and doubtful cases of diabetes mellitus give "borderline" results with both tests.

S E C T I O N XI

THE VALUE AND SCOPE OF THE INTRAVENOUS GLUCOSE TOLERANCE TEST

In considering results obtained with an intravenous glucose tolerance test the essential point must never be lost sight of that the test measures the net result of the various processes constituting what is conveniently termed the intermediary carbohydrate metabolism; absorption of glucose from the bowel plays no part.

Confusion in the interpretation of results may arise from the fact that different abnormalities of the intermediary mechanism can produce the same alteration of the blood-sugar curve obtained with the intravenous test. Thus increased glycogenogenesis and increased oxidation of glucose both lead to a rapidly falling curve. Similarly, increased glycogenolysis, diminished glycogenogenesis, and diminished carbohydrate oxidation all lead to a slowly falling curve. In these circumstances it becomes necessary on many occasions to consider the results of the intravenous glucose tolerance tests in conjunction with collateral evidence from other sources.

In general it may be said that the employment of the test is most straightforward in those cases in which it is applied to

the elucidation of abnormally low oral curves. Among such conditions which have been studied the position is clearest in pyloric stenosis of infancy. Here low or flat blood-sugar curves are found with the oral glucose tolerance test, while with the intravenous test the results are normal. We know beyond a doubt, from consideration of the clinical findings and of the morbid anatomy, that the abnormal oral curves in these cases arise as the direct result of impaired absorption of glucose from the bowel. It is thus established that the association of a normal intravenous curve with a low oral curve occurs when the latter is due to interference with the absorption of glucose from the bowel.

In coeliac disease precisely similar curves are obtained to those found in pyloric stenosis - low curves with the oral test, normal curves with the intravenous test. By analogy with the conditions known to exist in pyloric stenosis this provides strong evidence that the low oral curve of coeliac disease results from defective absorption of glucose from the bowel, a conclusion which is supported by evidence from other sources.

Consideration of cretinism brings us up against a more complex situation, for here the inconstantly occurring low oral tolerance curve is constantly associated with impairment of tolerance to intravenous glucose. Tolerance becomes normal on thyroid treatment, but if too much thyroid is administered the abnormality is reproduced. Clearly the abnormality must have a different origin in the overtreated cretin (or in the case of hyperthyroidism) from what it has in the untreated cretin, though

the intravenous test gives no evidence of this. From primary considerations it has been suggested that in untreated cretinism the delayed fall of the curve results chiefly from diminished oxidation of glucose, whereas in overtreated cretinism and in spontaneous hyperthyroidism the same abnormality of the curve results from increased glycogenolysis due to the associated excessive adrenalin secretion. The irregular and often low oral curves found in cretinism result from irregularities of intestinal absorption.

Convulsive attacks have been shown to be associated with an outpouring of secretion from the suprarenal medulla, with a subsequent period of adrenalin exhaustion. The initial period is accompanied by a hyperglycaemic phase during which the intravenous glucose tolerance curve is found to be prolonged. The prolongation of the curve in this instance is clearly associated with excessive hepatic glycogenolysis. During the period of adrenalin exhaustion a hypoglycaemic phase occurs and at this time the intravenous tolerance curve is found to fall abnormally rapidly. Here the abnormality is produced by active glycogen formation, insulin acting without the opposition of adrenalin.

In Glycogen Disease slight impairment of tolerance to intravenously injected glucose is found, comparable in degree to that occurring in other liver diseases. This provides strong evidence that the abnormal accumulation of glycogen in the liver results not from increased glycogenogenesis, but from a failure of glycogenolysis; for, if glycogenogenesis were overactive, the

curve would descend more quickly than normal. That the fall is actually slowed results, no doubt, from the fact that the liver cells, already stuffed to capacity with glycogen, react sluggishly to the stimulus for further glycogen formation. The impaired tolerance for intravenous glucose found in other forms of liver disease is again traceable to diminished glycogen-forming powers of the liver cells under a variety of pathological influences.

Though the intravenous glucose tolerance test is of little value in the routine investigation of cases of glycosuria, its use has provided corroborative evidence of the normality of carbohydrate metabolism in cases of renal glycosuria.

A further sphere of usefulness of the intravenous glucose tolerance test is in the estimation of the tolerance in cases where vomiting is a prominent feature, and in subjects in whom oral administration of glucose causes gastro-intestinal disturbance. Thus it was possible to carry out estimations of intravenous glucose tolerance during acute attacks of cyclical vomiting and during acute ketosis and acidosis associated with infections, in circumstances where the oral test could not be applied.

Finally it may be said that the intravenous glucose tolerance test, used with a due consideration of its limitations and of the varying interpretations possible for any particular curve, provides a valuable method of investigation in many cases. Its use has thrown light on the nature and pathogenesis of the disturbance in coeliac disease, cyclical vomiting, dysfunction of the thyroid gland, convulsions, glycogen disease and other liver

diseases; and with its aid interesting observations have been made on carbohydrate tolerance in acute infections and of the effects of variations in diet.

S E C T I O N XII

GENERAL SUMMARY

As individual summaries have been appended to the principal sections of this thesis only the briefest account of the contents of the work is included here.

In the introductory section the evolution of glucose tolerance tests is sketched. The disadvantages of the oral glucose tolerance test in current use, and its inconstancy in children are stressed. The theoretical advantages to be gained from intravenous administration of the glucose are discussed.

Section II deals with the elaboration of an intravenous glucose tolerance test for use in children or adults. The resulting curve has a high degree of constancy for the individual and the normal limits are sharply defined in each age-group. Intravenous carbohydrate tolerance is relatively high in infants, but falls off progressively during childhood until the adult level is reached in the ten- to thirteen-year age-group. Some side-effects, produced by the glucose injection, are also studied.

In the succeeding sections a number of conditions are considered in which the intravenous glucose tolerance test, taken in conjunction with other investigations, throws some light upon

the nature of the metabolic disorders present. Thus in pyloric stenosis of infancy flat oral tolerance curves are found in association with normal intravenous tolerance curves, the abnormality being clearly one of absorption; and similar results are obtained in coeliac disease.

Variations in the carbohydrate and fat contents of the diet are found to produce rather paradoxical results: while oral glucose tolerance increases on a high-carbohydrate diet and diminishes on a low-carbohydrate diet, intravenous glucose tolerance remains constant on the former, but in some cases actually increases on the latter. Ketosis occurring in acute infections is associated with definite impairment of intravenous glucose tolerance. In alimentary infections the degree of impairment is directly related to the severity of the infection; but in respiratory infections no such relationship exists. There is some evidence that those children who develop impaired glucose tolerance and ketosis during respiratory infections are inherently more readily upset by abnormal conditions than are those in whom similar infections produce no such upset. They have, apparently, some special susceptibility to the products of infection.

The subjects of cyclical vomiting show, during an attack, impairment of intravenous glucose tolerance, but between attacks no evidence of abnormality can be found.

The somewhat low oral glucose tolerance curves found in cretinism are associated with slowly falling intravenous glucose tolerance curves. It is clear that the true state of the

carbohydrate tolerance in this condition is one of impairment due to diminished rate of oxidation and possibly of storage also. When the cretin is treated with the correct dose of thyroid gland substance the curve moves towards normality; but in the over-treated cretin, and in cases of hyperthyroidism, impairment of tolerance is again found. Here it is thought to be due to the associated hyperfunction of the suprarenal medulla causing increased glycogenolysis.

Following convulsions, impaired tolerance to intravenous glucose is found during the hyperglycaemic phase and increased tolerance during the hypoglycaemic phase. These findings provide corroborative evidence that the hyperglycaemic phase is due to flooding of the system with adrenalin during and following the convulsion; and that the hypoglycaemic phase is associated with a resultant adrenal exhaustion. Some other active cerebral disturbances cause impairment of glucose tolerance.

The biochemical findings are studied in three cases of glycogen disease (von Gierke's disease). The finding of a somewhat slowly falling intravenous glucose tolerance curve excludes the possibility that the glycogen accumulations result from over-active glycogenogenesis. They are due apparently to an abnormally stable form of glycogen being laid down, or to a defect of the hepatic glycogenolytic ferment.

In liver diseases there may or may not be impairment of tolerance to intravenous glucose depending upon the presence and extent of any interference with the glycogen-forming properties

of the liver cells. This impairment of tolerance is most marked in lesions of a diffuse nature - it may be severe in catarrhal jaundice, but absent in cases of liver tumour.

The intravenous glucose tolerance test is not important in the investigation of cases of glycosuria, the oral test being more suitable for this purpose. The intravenous test may be of use, however, to confirm the normality of the carbohydrate tolerance in cases of renal glycosuria.

Finally, theoretical considerations on the interpretation of the intravenous glucose tolerance test, and on its value and scope, are discussed.

APPENDIX

A. BIOCHEMICAL METHODS

1. Estimation of the Blood-Sugar Concentration. The procedure employed for estimations of the blood-sugar was a modification of the method of Hagedorn and Jensen (1923). The blood was collected in a small dry glass tube containing a few grains of a mixture of potassium oxalate and sodium fluoride. The estimation was proceeded with as soon as convenient, but the small amount of fluoride present in the blood prevented deterioration for several hours. 0.2-c.c. of the blood was measured into a centrifuge tube containing 3.6 c.c. of a 3 per cent. solution of sodium sulphate. To this was added 0.1-c.c. of 10 per cent. sodium tungstate and 0.1-c.c. of 2/3 N sulphuric acid. After being allowed to stand for two minutes or longer the contents of the tube were mixed and the tube centrifuged. Two c.c. of the clear supernatant protein-free filtrate, representing 0.1-c.c. of the original blood, was then used for the usual Hagedorn-Jensen technique. Blank determinations were made on appropriate quantities of all the reagents employed.

2. Urinary-Sugar Concentrations were estimated by the method of Benedict (1911).

3. The Diastatic Action of the Urine and Blood-plasma was estimated by the technique of Cohen and Dodds (1924).

4. Blood-Glycogen estimations were made by the method of van Creveld (1934).

5. The Carbon dioxide Content of the Blood was estimated by the gasometric method of van Slyke and Sendroy (1927).

B. CASE NOTES

In this appendix no attempt is made to give a detailed account of the subjects who have been studied; only the salient features are included. The results of tolerance tests and other investigations, and the details of diets, having been included in the text, are not repeated here.

Case 1. M.R., female, age 12½ years, weight 37 kg. Admitted to hospital 14/9/36 with chorea and rheumatic carditis. The chorea gradually subsided and she was dismissed home apparently well, but with signs of mitral incompetence on 4/12/36.

Case 2. W.B., male, age 4 years, weight 15 kg. Admitted to hospital 28/8/36 with complaint of joint pains. These rapidly subsided, but the tuberculin skin tests were strongly positive and radiological examination revealed evidence of hilum tuberculosis. He was transferred to the convalescent home at Strathblane on 27/11/36.

Case 3. M.L., female, age 7 years, weight 19 kg. Admitted to hospital on 11/11/37 with rheumatic arthritis which rapidly subsided, the sedimentation rate being normal by 22/11/37. There was no evidence of permanent damage to the heart and she was dismissed home well on 8/2/38.

Case 4. J.C., male, age 10 years, weight 30 kg. Admitted to hospital 8/12/37 with rheumatic arthritis and carditis. The erythrocyte sedimentation rate, which had been elevated at first, had fallen to 3 per cent. in one hour by 8/2/38. He was dismissed home apparently well on 9/4/38.

Case 5. A.G., male, age 6⅓ years, weight 22 kg. Admitted to hospital 18/9/36 with tonsillitis. The tonsils were removed and after a period in the country, he was sent home well on 19/12/36.

Case 6. R.B., male, age 12½ years, weight 31.5 kg. Admitted to hospital 2/1/37 for the treatment of nocturnal enuresis. The condition responded to simple drug treatment and investigation of the renal tracts revealed no abnormality. He was dismissed home well on 18/1/37.

Case 7. W.J., male, age 14 years, weight 40 kg. This boy was in the surgical wards of the hospital (under Mr. Matthew White's care) for a prolonged period (1936 to 1937) undergoing treatment for congenital deformities of the lower limbs.

Case 8. H.S., female, aged 7 3/12 years, weight 20 kg. Admitted to hospital 2/3/37 for the removal of enlarged tonsils. Dismissed home well 16/3/37.

Case 9. D.E., male, age 5/12 year, weight 7.6 kg. Admitted to hospital 17/8/37 with a complaint of "stiff turns." No abnormality was found and he was dismissed home well on 25/8/37.

Case 10. J.W., female, age 1 year, weight 8.3 kg. Admitted on 24/3/37 because of difficulty in walking. Two days later the child was transferred to the surgical wards for the treatment of deformities of the feet.

Case 11. W.T., male, age 14/12 year, weight 9.7 kg. Admitted to hospital on 17/10/36 following on injury to the leg. No abnormality was found and he was sent home, well, two days later.

Case 12. M.McC., female, age 2 years, weight 9.4 kg. Admitted on 4/3/38 for the treatment of rickets. She was kept in hospital for three months and the rickets was well-healed on dismissal.

Case 13. B.S., female, age 24/12 years, weight 8.3 kg. Admitted on 26/10/37 with a complaint of vomiting. A chronic empyema was found and responded well to conservative treatment.

Case 14. D.W., male, age 3½ years, weight 13 kg. Admitted to hospital 31/5/37 with a complaint of asthmatic attacks. He had no attacks in hospital and was sent for a spell in the country two weeks later.

Case 15. F.T., male, age 3½ years, weight 13 kg. Admitted on 4/12/36 because of frequent colds. The tuberculin skin test was strongly positive, but the sedimentation rate not increased. X-Ray examination gave evidence of mediastinal tuberculosis and he was sent to a country home six weeks after admission.

Case 16. M.B., male, age 4 years, weight 15 kg. Admitted on 16/6/37 following a bilious attack. There was a trace of jaundice on admission, but this rapidly cleared and he was dismissed home well on 25/6/37.

Case 17. M.C., female, age 4 years, weight 14 kg. An attack of acute tonsillitis subsided rapidly. She was sent home well on 10/4/38, three weeks after admission.

Case 18. C.S., female, age 4 years, weight 14 kg. This child was admitted to hospital on 8/4/37 with rheumatic arthritis and she later showed signs of cardiac involvement. The sedimentation rate, increased at first, was normal by 5/5/37 and the child was dismissed home apparently well, but with a valvular heart lesion, on 27/6/37.

Case 19. J.S., female, age 4½ years, weight 14 kg. Admitted to hospital 14/1/37 for the treatment of enuresis. Radiological investigation showed some dilatation of the renal tracts, but renal function was normal.

Case 20. F.McK., female, age 4½ years, weight 16.5 kg. Admitted to hospital on 14/11/36 for the removal of carious teeth.

Case 21. P.M., male, age 5 years, weight 13 kg. Admitted to hospital on 29/11/38 for the treatment of tapeworm.

Case 22. H.D., female, age 5½ years, weight 15 kg. Following one week's illness at home, the child was admitted to hospital on 19/4/37. Clinical and radiological signs, which rapidly cleared up, suggested a resolving pneumonia and she was dismissed home well on 7/5/37.

Case 23. W.McV., male, age 5½ years, weight 14.8 kg. Admitted to hospital on 13/10/38 with a trace of jaundice, which rapidly disappeared. Dismissed home well on 28/10/38.

Case 24. A.McK., female, age 6 years, weight 19.6 kg. Admitted on 12/3/37 with joint pains. She turned out to have leukaemia and was taken away by her parents ten days later.

Case 25. J.D., female, age 6 years, weight 16 kg. The child was admitted on 19/2/37 with an ataxic gait. She turned out to be a case of juvenile tabes dorsalis, and went home, improved, on 15/3/37.

Case 26. D.S., male, age 7 years, weight 24 kg. This child was in hospital for a long period (1937) with the results of rheumatic carditis. The sedimentation rate was normal at the time the tolerance tests were carried out. He was ultimately removed to Stobhill Hospital.

Case 27. A.R., male, age 7 years, weight 22 kg. Admitted to hospital on 27/2/37 with rheumatic arthritis. The sedimentation rate was 28 per cent. in one hour on admission, but had fallen to 4 per cent. by 15/3/37. He was dismissed home well on 21/5/37.

Case 28. T.B., male, age 7 years, weight 20 kg. Admitted to hospital with a pleural effusion on the left side (23/4/37). This soon absorbed and after a spell in the country, he went home well.

Case 29. D.H., female, age 8 years, weight 18 kg. Admitted on 23/4/37 with a left-sided pleural effusion. The effusion subsided rapidly and after six weeks in hospital, she was sent to a country home.

Case 30. C.D., male, age 8 years, weight 18 kg. This boy, a case of oesophageal stenosis treated for many years, was readmitted for the passage of a bougie.

Case 31. S.F., female, age 8 years, weight 21 kg. Admitted to hospital 14/12/36 with a large, left-sided, pleural effusion. The Mantoux test was strongly positive. The effusion rapidly absorbed, and after a spell in the country, she was sent home, well, in March, 1937.

Case 32. F.H., male, age 9 years, weight 26 kg. Admitted with erythema nodosum in May, 1937. The Mantoux test was strongly positive, but the eruption soon subsided and, after a spell in the country, he was dismissed home, well, in June, 1937.

Case 33. F.G., male, age 9 years, weight 23 kg. Admitted to hospital on 7/6/37, turned out to have enlarged mediastinal glands and a positive Mantoux test. After a period at the Country Branch, he was dismissed home, well, on 16/7/37.

Case 34. J.C., male, age 9 years, weight 260 kg. He was sent into hospital because of "choreiform movements," but none was observed after admission. Though the sedimentation rate was normal throughout it was thought advisable to keep him at rest for three months, and the opportunity was taken for the dietetic experiments described in the text.

Case 35. W.M., male, age 9½ years, weight 21.0 kg. Admitted to hospital 22/12/36 with a right-sided pleural effusion. This rapidly subsided and after a spell in the country, he went home, well, on 12/2/37.

Case 36. A.W., female, age 10 years, weight 30 kg. Admitted to hospital in February, 1937 for the removal of enlarged tonsils.

Case 37. C.W., male, age 10½ years, weight 27 kg. Admitted to hospital 2/9/37 with a mild attack of jaundice, which rapidly cleared up. Dismissed home, well, 19/9/37.

Case 38. A.T., male, age 11 years, weight 27 kg. Admitted to hospital 28/5/37 with acute rheumatic arthritis. The joint pain and fever soon subsided, but there was evidence of cardiac damage. The sedimentation rate, increased at first, was normal by June 12th. He was dismissed home on 2/10/37, well except for signs of mitral regurgitation.

Case 39. M.W., female, age 11 years, weight 28 kg. Sent to hospital in March, 1937 with chorea. The sedimentation rate was never raised and the chorea cleared up in two weeks.

Case 40. H.McL., male, age 12 years, weight 24 kg. Admitted on 22/6/38 with mild chorea. There was no cardiac involvement and the sedimentation rate was not increased. He was well on dismissal on 16/9/38.

Case 41. A.F., female, age 12 years, weight 27 kg. Admitted on 6/12/36 because of headaches. Evidence of mediastinal tuberculosis was found, but she was well on dismissal, after a spell in the country.

Case 42. H.McL., healthy male, age 23 years, weight 81 kg.

Case 43. A.B.P., healthy female, age 24 years, weight 52 kg.

Case 44. T.C., healthy male, age 26 years, weight 76 kg.

Case 45. M.McL., healthy female, age 27 years, weight 52 kg.

Case 46. O.D.P., healthy female, age 30 years, weight 55 kg.

Case 47. F.J.F., healthy male, age 35 years, weight 62 kg.

Case 48. I.I., male, age $10^{4}/12$ years, weight 30 kg. A well-developed case of pseudo-hypertrophic muscular dystrophy. At the time of examination (November, 1936) many of the muscles were reaching the atrophic stage and contractures were developing.

Case 49. R.C., male, age $4^{10}/12$ years, weight 17 kg. Admitted to hospital 11/4/37 with a complaint of abdominal pain. No abnormality was found and he was dismissed home well.

Case 50. A.W., male, age $8^{10}/12$ years, weight 21 kg. A typical case of pseudo-hypertrophic muscular dystrophy, the symptoms being of six years' duration

Case 51. G.S., male, age 5 years, weight 19 kg. Admitted to hospital 19/11/36 with a right-sided lobar pneumonia of three days' duration, accompanied by a severe ketosis. The pyrexia subsided after five days in hospital, and after a week in the country, he was dismissed home well (19/12/36).

Case 52. E.McL., female, age 3 years.
A mentally defective child, brought to hospital because of failure to walk and frequent screaming fits.

Case 53. J.D., male, age 8 years, weight 24 kg. Admitted to hospital with rheumatic arthritis 13/6/36. A severe rheumatic carditis developed, leaving the heart badly damaged. He was transferred to a home for physically defective children, 7/11/36.

Case 54. J.K., male, age 4 9/12 years, weight 18 kg. Admitted to hospital 31/1/37 in a generalised convulsion, which turned out to be the herald of an acute tonsillitis. The acute infection subsided in four days and he was dismissed home, well, a week later.

Case 55. A.McG., female, age 1 5/12 year, weight 7.0 kg. Admitted to hospital 13/10/36 with a complaint of indigestion, loss of weight and irritability. She was probably a case of coeliac disease, but her parents removed her from hospital before investigations were complete.

Case 56. M.McN., female, age 8 years, weight 14 kg. A case of coeliac disease, admitted to hospital in a relapse. She improved considerably on a low-fat diet and was sent for a period in the country.

Case 57. M.McL., female, age 6 9/12 years, weight 18 kg. A case of coeliac disease, admitted during a relapse for the adjustment of her diet.

Case 58. E.W., female, age 11 8/12 years, weight 27 kg. Admitted to hospital 11/1/37 because of difficulty in walking and epileptic fits from time to time. She turned out to be a case of cerebral diplegia, possibly the result of birth injury. While in hospital she had no fits. The intelligence quotient was 63 per cent.

Case 59. M.M., female, age 5 years, weight 25 kg. Admitted to hospital 21/1/37 with rheumatic arthritis. The rheumatic signs cleared quickly and she was dismissed home, well, on 16/4/37. There was some degree of sexual precocity, but no evidence of pituitary or adrenal tumour could be detected.

Case 60. H.McK., female, age 10 11/12 years, weight 28 kg. Admitted for investigation and treatment of enuresis.

Case 61. A.G., female, age 9 6/12 years, weight 26 kg. A case of cretinism who had been on thyroid treatment since the age of four months. She appeared normal and showed no signs of cretinism.

Case 62. M.McM., female, age 1 6/12 year, weight 8.5 kg. Admitted to hospital on 6/10/26 with the complaint of failure to grow since age six months. The child presented the characteristic appearances of cretinism and responded well to thyroid administration.

Case 63. J.D., male, age 11 years, weight 29 kg. A case of catarrhal jaundice. The van den Bergh reaction on admission was biphasic, 22 units. Jaundice disappeared within a week and he was dismissed home well two weeks after admission.

Case 64. J.H., male, age 7 years, weight 40 kg. A case of obesity associated with hypopituitarism.

Cases of Pyloric Stenosis.

Case 65. R.L., male, age 9/52 year, weight 3.1 kg. Admitted to hospital 31/5/37 because of persistent vomiting and constipation. Gastric peristalsis could be seen and a typical hypertrophic pyloric tumour palpated. Rammstedt's pylorus-splitting operation was performed on 3/6/37 and thereafter vomiting ceased and the child began to gain weight. He was dismissed home well on 18/6/37.

Case 66. W.G., male, age 4/52 year, weight 2.5 kg. Admitted to hospital 6/8/37 with a complaint of persistent expulsive vomiting. Gastric peristalsis was seen, and a pyloric tumour was palpated. Rammstedt's operation on 8/8/37 completely relieved the obstruction and he was dismissed home well on 24/8/37.

Case 67. E.M., female, age 7/52 year, weight 3.8 kg. Admitted 8/10/38 with a history of vomiting and constipation for two weeks. She was treated with Eumydrin (a preparation of atropine methyl-nitrate) and improved rapidly.

The Effect of Diet. Cases 3, 4, 26, 34, 38 and 40.

The Effect of Starvation. Cases 21 and

Case 68. M.McK., female, age 3 10/12 years, weight 15.6 kg. She had been passing segments of tapeworm in the stools for six months and was admitted to hospital 23/8/37 for treatment, home treatment having failed.

The Effect of Acid-Salt administration. Cases 27, 29 and 33.

Cases of Acute Infection.

Case 51 and

Case 69

Case 70

Case 71

Notes on these cases are included in the text (pages 67 and 68).

Case 72. E.D., female, age 7 2/12 years, weight 20 kg. Admitted to hospital 15/3/38 with fever and vomiting, accompanied by severe ketosis. An acute upper respiratory infection was present, but subsided rapidly in hospital. She seemed well after a week and later her tonsils were removed.

Case 73. J.C., male, age 8½ years, weight 20 kg. Admitted to hospital 27/10/38 acutely ill with pneumonia, accompanied by severe ketosis. He remained gravely ill for three days, but thereafter his temperature subsided and convalescence was uneventful.

Case 74. H.C., male, age 10½ years, weight 34 kg. Admitted to hospital 5/2/39 with erythema nodosum, acute tonsillitis and pharyngitis, accompanied by a severe ketosis. The respiratory infection rapidly subsided and he made a good recovery. He was sent to the country for a period.

Cases of Respiratory Infection without Ketosis.

Case 75. C.F., male, age 5 years, weight 14.6 kg. Admitted to hospital with fever of a few hours' duration. This was due to acute tonsillitis from which he made a rapid recovery.

Case 76. A.G., male, age 9 years, weight 30.0 kg. Fever lasting four days was associated with acutely inflamed tonsils.

Case 77. J.B., male, age 9 years, weight 26.0 kg. A case of left-sided lobar pneumonia. The temperature fell by crisis on the seventh day of illness.

Cases of Spontaneous Ketosis.

Case 78. E.McD., male, age 7½ years, weight 24 kg. This child had been subject to attacks of vomiting, associated with severe headaches, and ketosis, at regular monthly intervals for fifteen months. No cause could be determined.

Case 79. N.R., female, age 5 years, weight 14.5 kg. For two years the child had been subject to recurring vomiting attacks unexplained by any infection or other apparent cause. The attacks occurred at somewhat irregular intervals averaging eight to twelve weeks. The attacks, two of which were seen in hospital, were characterised by vomiting, constipation, heavy ketonuria and collapse. Recovery was complete within three days.

Case 80. P.E., female, age 5½ years, weight 16.2 kg. Since measles, eight months previously, the child had been subject to monthly attacks of severe vomiting, each lasting two to three days. No explanation could be found.

Case 81. D.McC., male, age 5 years, weight 17.8 kg. Since the age of three years he had had typical recurrent ketosis arising spontaneously, and accompanied by vomiting, at very regular monthly intervals.

Case 82. M.P., female, age 5 years, weight 16.4 kg. This child was apparently seen in her initial attack of spontaneous ketosis. In this attack the vomiting persisted for eleven days and ketosis was severe. Frequent attacks followed at somewhat irregular intervals.

Cases of Coeliac Disease.

Case 83. C.C., male, age 2 3/12 years, weight 8.7 kg., height 80 cm. Admitted to hospital with a history of recurrent attacks of diarrhoea since the age of nine months. The stools were frequent, loose and foul-smelling, the fat content being 33 per cent. on a skimmed-milk diet. There was marked muscle wasting, with flattening of the buttocks. Rickets was evident both clinically and radiographically. There was no gross anaemia. Attacks of diarrhoea, interspersed with remissions, continued in spite of treatment.

Case 84. L.S., female, age 14/12 year, weight 6.2 kg., height 68 cm. First seen at the age of one year and two months, with a history of loss of weight and attacks of diarrhoea for three

FIGURE XXXIX.

Case 85: Coeliac Disease, showing typical Clinical Features.

months. There was marked muscle atrophy and some rickets and the stools, which were loose and foul-smelling, contained 39 per cent. of fat. She improved with treatment, but continued to have alternating relapses and remissions.

Case 85. M.S., male. First seen at the age of three years when he was brought to hospital with a history of loose stools for three months. His appearance was typical of severe coeliac disease (Fig. XXXIX), weight 11 kg., height 90 cm. Muscle atrophy marked. Slight rickets. Severe anaemia (Hb. 54 per cent.). Faecal fat 43 per cent.

Case 86. B.S., female, age 7½ years, weight 14 kg. Typical features of coeliac disease had existed since the age of two years. Height 101 cm. Faecal fat 64.75 per cent. Moderate rickets and anaemia. Severe relapses frequent. Growth stationary.

Case 87. E.McD., female, age 2 4/12 years, weight 11.0 kg., height 90 cm. Hb. 74 per cent. Loss of weight, with attacks of diarrhoea for three months, was the primary complaint. The general appearance was characteristic of coeliac disease and there was considerable improvement with treatment. Faecal fat 54.95 per cent.

Case 88. W.McD., male, age 1 4/12 year, weight 6.6 kg., height 69 cm. Hb. 72 per cent. Admitted with a history of large, milky, offensive stools for three months, with enlargement of the abdomen and wasting of the rest of the body. Faecal fat content 23 per cent. on a fat-free diet, during a period of temporary improvement. Later he relapsed, went rapidly downhill and died.

Case 89. W.R., male, age 1 7/12 year, weight 6.5 kg. Loss of weight, with frequent pale, foul stools had been noted since age one year. Muscle atrophy, abdominal distension and flattening of the buttocks were very marked. Hb. 52 per cent. Slight rickets. Faecal fat 46.73 per cent. There was some improvement with treatment, but no satisfactory remission was obtained.

Case 90. J.C., male, age 1 4/12 year, weight 7 kg. Complaint of attacks of diarrhoea for five months. Muscle atrophy and rickets were marked and the stools were large, pale and foul-smelling. Faecal fat 53.45 per cent. Hb. 80 per cent.

Case 91. J.S., male, age 5 years, weight 13.6 kg., height 103 cm. He had had only occasional attacks of diarrhoea previously, but when seen, had been passing pale, foul-smelling motions three to four times a day for four weeks. Faecal fat 40.48 per cent. Hb. 82 per cent. Abdomen prominent. Muscles atrophied. No rickets. He improved on low-fat diet and has had only mild attacks during the succeeding year.

Case 92. H.S., female, age 37/12 years, weight 10 kg., height 95 cm. She was said to have had large, pale, foul-smelling stools all her life. Emaciation and muscle atrophy were marked. No rickets. Hb. 70 per cent. Faecal fat 34 per cent.

Case 93. J.McK., female, age 8 years, weight 15 kg., height 106 cm. She was admitted to hospital with a history of "diarrhoea since infancy," the stools having a porridge-like consistence. Faecal fat 32.46 per cent. Hb. 70 per cent. No rickets. She rapidly improved with treatment, but has had frequent relapses.

Case 94. J.R., male, age 14/12 year, weight 7 kg. Complaint of vomiting and attacks of diarrhoea since age ten months. Some abdominal prominence and muscle atrophy. Stools formed, but pale; fat content 46 per cent. Hb. 58 per cent. Considerable improvement followed dietetic treatment, but subsequently sight of the case was lost.

Normal Controls for Insulin Sensitivity Tests. Cases 38, 40, 58 and

Case 95. C.R., female, age 11 years, weight 23 kg. Admitted to hospital for the treatment of bronchitis.

Case 96. T.B., male, age 59/12 years, weight 17 kg. Admitted to hospital for the investigation of hoarseness which proved to be of functional origin.

Case 97. J.G., male, age 9 years, weight 22.5 kg. He was taken into hospital for the investigation of persistent nocturnal enuresis, which was apparently of nervous origin.

Cases of Cretinism.

Cases 61, 62 and

Case 98. M.C., female, age 4/12 year on admission, weight then 4.9 kg. She was brought to hospital with the complaint of difficulty in feeding and "mental dulness." The appearance was typical of cretinism and she responded well to treatment. Two years later she appeared normal on tab. thyroid, gr. IV, daily.

Case 99. A.McM., female, age 27/12 years, weight 90 kg. She was brought to hospital because of slowness in development. Her general appearance was typical of cretinism. She responded well to thyroid treatment and at age four years appeared normal on 4 grains daily.

FIGURE XL.

Case 100: Cretinism, showing typical Clinical Features.

Case 100. H.W., female, age 1 year, weight 7.45 kg. The mother complained that the child was mentally backward and, on examination, she showed the characteristic clinical features of cretinism (Fig. XL). She improved rapidly on thyroid treatment and at the age of three years, though small, she was unrecognisable as a cretin. (Receiving 4 grains of thyroid daily).

Case 101. M.W., female, age 4 7/12 years, weight 13.7 kg. Since the age of nine months the child had "gone back" both mentally and physically. The appearance was diagnostic of cretinism and rapid improvement occurred on thyroid treatment. As she came from a remote Hebridean island, her later progress is unknown.

Case 102. S.M., male, age 1 year, weight 5.9 kg. His mother complained that he was making no progress. His appearance was typical of cretinism and he responded well to thyroid therapy, but his mother failed to carry out the treatment at home and at the age of one year and ten months he was seen again, and had relapsed to his original state. He again improved rapidly on thyroid, gr. I, daily.

Case 103. S.C., female, age 6 10/12 years, weight 17 kg. Cretinism was diagnosed in infancy and the child had been on treatment for six years. On 4 grains of thyroid daily she appeared bright and normal, both mentally and physically.

Cases of Juvenile Myxoedema.

Case 104. M.L., female, age 5 5/12 years, weight 15.6 kg. The child was healthy at birth and remained well for two years, but subsequently growth ceased. The bowels became irregular and the abdomen prominent. There was a mild anaemia, and radiography revealed marked delay in carpal ossification. Hypothyroidism was diagnosed and some improvement occurred with thyroid medication.

Case 105. N.McL., male, age 6 2/12 years, weight 14 kg. The child was normal at birth and developed normally until the age of two years. After that age growth was slow and he was brought to hospital for this reason and because of nightmares. He was considerably under height and weight for his age. His hair was thin and his skin dry and thick. Hypothyroidism was diagnosed and he improved on thyroid treatment, but failed to report back after dismissal from hospital.

Cases of Hyperthyroidism.

Case 106. P.M., male, age 7 years, weight 23.6 kg. The boy was brought to hospital complaining of a swelling in the neck which was causing some discomfort and breathlessness. The swelling consisted of the thyroid gland which was uniformly enlarged and soft. Slight tachycardia and exophthalmos were noted and there was a definite fine tremor of the hands. Two months later he contracted diphtheria and died.

Case 107. E.C., female, age $10^{4}/12$ years, weight 24.2 kg. She was admitted with a complaint of marked nervousness for one month. The thyroid gland was soft and uniformly enlarged. Exophthalmos, tachycardia, tremor, sweating and emotionalism were severe. Three estimations of the basal metabolic rate gave results of 78, 73 and 80 per cent. No abatement of the condition occurred during six months under observation.

Cases of Mongolian Idiocy.

Case 108. J.C., male, age $^{4}/12$ year, weight 3.9 kg. The infant was admitted to hospital with an upper respiratory infection from which he gradually recovered. He had a marked Mongoloid facies. His thin, pointed tongue was constantly protruded from the small mouth.

Case 109. W.S., male, age $^{6}/12$ year, weight 5 kg. His mother came for advice as the child was not holding his head up or showing any signs of mental development. He was a typical Mongolian idiot.

Case 110. J.McR., male, age 5 years, weight 12 kg. He was brought to hospital because, at the age of five years, he was still unable to say more than a few words. His appearance was typical of Mongolian idiocy.

Case 111. E.G., female, age $2^{4}/12$ years, weight 10.6 kg. The mother came for advice as the child was not beginning to talk. She was a typical Mongol and had also bilateral cataract.

Cases of Convulsions.

Case 54 and

Case 112. M.B., female, age 2 5/12 years, weight 14 kg. Admitted on 13/1/37 at 4.30 p.m. with generalised convulsions of three hours' duration. These ceased soon after admission and the child made an uninterrupted recovery. The convulsion was apparently associated with a mild respiratory infection.

Case 113. J.D., male, age 2 years, weight 13 kg. Admitted to hospital with a generalised convulsion which lasted three hours. No further convulsions occurred and he recovered rapidly from an acute tonsillitis which was at the root of the trouble.

Case 114. M.R., female, age 14/12 year, weight 9 kg. She was admitted to hospital at 10 a.m. on the 18/11/37, following a series of convulsions during the preceding night. She made a rapid recovery from a mild respiratory infection.

Cases of Intracranial Tumour.

Case 115. J.McP., male, age 6½ years, weight 18 kg. He was born with an occipital meningocele which was removed at the age of one year and one month. He had become increasingly listless and drowsy for a year before admission to hospital, and he complained of frequent headaches. There was severe optic neuritis. At operation a gliomatous condition of the hypothalamic region was found. He died without regaining consciousness after the operation.

Case 116. A.S., female, age 10 8/12 years, weight 30 kg. The child was well until ten weeks prior to admission when she developed a squint. Later fits and vomiting came on. There was no papilloedema, but paralysis of the 3rd, 6th, 7th and 9th nerves followed rapidly. She went downhill and died eight weeks after she was first seen. At autopsy a pontine glioma was exposed.

Case 117. J.B., female, aged 6 years, weight 20 kg. Symptoms of weakness of the legs with involuntary movements of the arm came on gradually over the preceding year. Neurological signs indicated a very slowly growing neoplasm of the brain-stem.

Cases of Tuberculous Meningitis.

Case 118. E.W., female, age 2 9/12 years. Three months previously she had whooping-cough, and since then her health had been poor. She was brought to hospital after a vomiting attack and presented signs of miliary tuberculosis. She died eight days after admission.

Case 119. M.I., female, age 3½ years. Screaming attacks came on three days before the child was admitted to hospital with typical signs of meningitis. Tubercle bacilli were found in the cerebro-spinal fluid. Death occurred eleven days after admission.

Case 120. C.B., female, age 6 years, weight 20 kg. Two weeks before admission the child complained of headache, and she became drowsy and listless. On admission the appearance was typical of meningitis. Tubercle bacilli were found in the cerebro-spinal fluid. The child died two weeks after admission.

Cases of Cerebral Diplegia.

Cases 52, 58 and

Case 121. O.P., male, age 5 10/12 years, weight 20 kg. He was brought to hospital because of difficulty in walking since infancy. There was a "scissors gait" and some weakness of the left arm. He was mentally backward.

Case 122. D.McR., male, age 3 years, weight 13 kg. At the age of three years he was unable to walk or talk or to feed himself. There was some spasticity of the limbs and a definite degree of microcephaly.

Case 123. R.D., male, age 4/12 year, weight 4.5 kg. The infant had frequent minor fits since soon after birth. There was marked spasticity of the limbs and a degree of microcephaly.

Case 124. M.W., female, age 4 5/12 years, weight 14 kg. She had never been able to sit up alone or to walk. Adductor spasm was present. She was mentally backward, but had never had fits.

Cases of Glycogen Disease.

Cases 125, 126 and 127. Described in text (pages 131 and 132).

Control Cases for Adrenalin Test. Cases 18, 29, 32 and 58.

Control Cases for Blood-Glycogen Test. Cases 24, 27, 30, 36, 52, 58, 103, 131, 132 and

Case 128. T.McH., male, age $6^{11}/12$ years, weight 22 kg. Admitted to hospital in January, 1937 with tonsillitis from which he made a rapid recovery.

Case 129. A.B., female, age $7^{3}/12$ years, weight 26 kg. The child was convalescent from rheumatic chorea at the time the tests were made.

Case 130. W.A., male, age $5^{7}/12$ years, weight 19 kg. Admitted because of a troublesome cough, this boy was found to have bronchiectasis of the whole left lung. His general health was good.

Control Cases for Diastase Tests. Cases 58, 128, 129 and

Case 133. I.S., female, age $5^{2}/12$ years, weight 20 kg. Admitted to hospital for the treatment of enuresis. She appeared quite healthy in hospital, apart from the enuresis which was resistant to treatment.

Cases of Diseases of the Liver.

Case 134. L.B., female, age $3\frac{1}{2}$ years, weight 10 kg. A gastro-intestinal upset six days before admission to hospital was followed by slight jaundice. The stools remained pigmented, but bile-pigment appeared in the urine. After a week in hospital the child was quite well and jaundice had disappeared.

Case 135. W.S., male, age 4 years, weight 16 kg. Vomiting and fever had been present for a week before admission, when jaundice was found to be fairly deep. Some enlargement of the liver was present. The urine contained bile-pigment and the faeces remained pigmented. Van den Bergh reaction biphasic. He made a rapid recovery.

Case 136. C.S., female, age 10 years, weight 23 kg. She complained of abdominal pain and vomiting for five days and jaundice for three days before admission to hospital. The urine contained abundant bile-pigment and the stools were pale at first. The van den Bergh reaction was biphasic, the indirect reaction being 8 units. Recovery was rapid.

Case 137. E.B., age 7/52 year, weight 3.8 kg. Jaundice was first observed four days after birth and it deepened steadily. The stools were persistently white and the urine contained bile-pigment. The liver became increasingly large and firm, but the spleen was not palpable. The blood contained no erythroblasts. She ultimately died at home.

Case 138. A.L., male, age 35/12 years, weight 14 kg. Progressively deepening jaundice with unpigmented stools and bile-pigment in the urine were the symptoms. On examination the liver was found to be greatly enlarged and the distended gall-bladder was readily palpable. Laparotomy was performed by Mr. Fleming who found a tumour of the liver invading and obstructing the bile-ducts. The obstruction could not be relieved, and the child died five weeks later.

Case 139. E.P., female, age 12 years, weight 34 kg. Three years previously, because of anaemia associated with splenomegaly, splenectomy had been performed. She now reported with jaundice and an enlarged, firm liver. Epistaxis was frequent, but never severe. The blood-haemoglobin was 50 per cent., the van den Bergh reaction biphasic, indirect 5 units. The urine contained a trace of bile-pigment and occasionally urobilinogen was present in excess. No change was observed in her condition.

Case 140. S.P., female, age 10½ years, weight 28 kg. This child was admitted to hospital following a copious haematemesis. She was severely anaemic (haemoglobin 32 per cent.) and the spleen was greatly enlarged. The liver was not enlarged, but splenectomy was performed by Mr. MacFarlane who noticed that the liver was cirrhotic. Further gastric haemorrhages have occurred.

Case 141. M.S., female, age 7 years, weight 28 kg. Jaundice had been present for four months before admission to hospital and was unchanged a year later. The liver was uniformly enlarged and of firm consistence, but the spleen was not palpable. The van den Bergh reaction was biphasic, indirect 4 units. Marked anaemia was present (haemoglobin 53 per cent.) but red cell fragility was normal. The urine contained excess urobilin and occasionally traces of bile-pigment. When last seen the liver was increasing in size (3 fingers breadth below the costal margin), the spleen still could not be palpated and the jaundice and anaemia were unchanged.

Case 142. W.McN., male, age 6 years, weight 17 kg. This boy was well until the age of two years when, following a series of acute infections, his abdomen became gradually distended and he suffered from attacks of diarrhoea. When seen in hospital the liver was hard and nodular and extended 2 fingers breadth below the costal margin. The Mantoux, van den Bergh and Wassermann tests were negative. Ascites diminished while he was in bed, but returned when he was allowed up. During the succeeding year his general condition has remained unchanged.

Cases of Diabetes Mellitus.

Case 131. J.McN., male, age 10 years, weight 22 kg. He was brought to hospital with the complaints of increasing thirst and polyuria, with loss of weight, for six weeks. On admission the urine contained abundant sugar and ketone bodies and the diagnosis of diabetes was clinched by finding a blood-sugar concentration of 645 mg. per 100 c.c. The boy did well on insulin and dietetic treatment and he has remained in good health under observation. When last seen he was receiving 20 units protamine zinc insulin daily.

Case 132. J.H., male, age 10½ years, weight 26 kg. This boy was quite well until one week before being brought to hospital. He then developed great thirst and polyuria and lost weight very rapidly. Sugar and acetone were found in abundance in the urine and the fasting blood-sugar level was 317 mg. per cent. He has remained well for two years on insulin and diet treatment; (20 units protamine zinc insulin daily).

Case 143. A.McL., male, age 8 years, weight 28.8 kg. Increasing thirst, with loss of weight, had been noticed for three weeks before admission. The urine contained abundant sugar and acetone and the blood-sugar on admission was 471 mg. per cent. He had remained in good health for four years on insulin and diet treatment. When last seen he was receiving 48 units daily of protamine zinc insulin.

Case 144. A.McK., male, age 7½ years, weight 21 kg. Excessive eating and drinking had been observed for about two months before admission. An older sister had died of diabetes and the boy's mother suspected the same disease. Her suspicions were well-founded, for the urine contained abundant sugar and acetone, and the fasting blood-sugar was 342 mg. per cent. He responded well to insulin and diet treatment and was finally sent to a children's home as the home conditions were unsatisfactory. He was receiving 12 units daily of protamine zinc insulin.

Case 145. A.B., male, age 11 years, weight 27 kg. Enuresis and loss of weight were complained of for three months before admission. Sugar and acetone were abundant in the urine. He was finally stabilised on an adequate diet and 10 units daily of protamine zinc insulin.

Case 146. N.C., male, age 5 years, weight 19 kg. This boy's father is a severe diabetic. Finding his son out-of-sorts and losing weight, he tested the urine and found it to contain sugar. In hospital sugar was found in the urine on only two occasions in ten days. He has since remained well, under observation, for one year.

Cases of Renal Glycosuria.

Case 147. E.H., female, age 10 years, weight 34 kg. This child was sent into hospital for investigation of glycosuria, found, incidentally, at a dispensary for skin diseases where she was being treated for furunculosis. She has remained well for a year under observation.

Case 148. J.W., male, age 6 years, weight 20 kg. He was admitted to the surgical wards under Mr. White on suspicion of appendicitis. The symptoms proved to be due to intestinal colic, but sugar was found in the urine.

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