CARBOHYDRATE TOLERANCE IN HYPOTHYROIDISM AND HYPERTHYROIDISM

BY

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Since the beginning of the present century it has been recognized that disturbances of thyroid secretion are associated with characteristic alterations of the carbohydrate tolerance (Knöpfelmacher, 1904; von Noorden, 1910), and current views upon the nature of the changes remain substantially unaltered.

Thus Leyton (1937), in Price's textbook, writes that in hypothyroidism there is considerable increase in the tolerance for dextrose, whilst Beaumont (1937) states that in hypothyroidism sugar tolerance is increased, but that in hyperthyroidism sugar tolerance is often diminished. Similar statements may be found in almost any general 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. Knöpfelmacher (1904) had previously demonstrated an increased assimilation limit for glucose in cases of myxoedema. 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, whilst administration of thyroid gland substance lowered and shortened the curve. Diminished oral glucose tolerance in hypothyroidism was found also by Flesch (1913) and Gray (1923).

Concerning hyperthyroidism there is more general agreement. Denis, Aub and Minot (1917), Janney and Isaacson (1918), Gardiner-Hill, Brett and Smith (1925), 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 action and a slighter degree of central resistance.

Investigations of these problems in children have been scanty; Svensgaard (1931) studied the oral glucose tolerance of four untreated cretins, and in two of the cases she repeated the test after thyroid treatment had been established.

The blood-sugar curves after oral glucose (2 grammes per kgm. of body weight) were low in the untreated cretins, the maximum elevation above the fasting level varying from 43 to 82 mgm. per 100 c.c. In the two patients in whom the test was repeated after thyroid treatment was well established, rises of 133 and 170 mgm. per 100 c.c. were obtained, with maximum hyperglycaemic levels of 204 and 254 mgm. per 100 c.c. Perusal of the literature has not disclosed any reports of investigations of carbohydrate metabolism in children with hyperthyroidism.

The present investigation has been conducted in an attempt to determine the nature of the changes of carbohydrate tolerance brought about by conditions of hypo- and hyperthyroidism in children, and to explain, as far as possible, the manner in which these changes are produced. Children are particularly suitable subjects for this study, for in them the lesions usually occur in a pure form, so that the metabolic disturbances noted can be assumed to depend upon the altered state of the thyroid secretion. In adult myxoedematous subjects, on the other hand, conflicting factors, such as arteriosclerosis and post-menopausal polyglandular disturbances, are frequently present and tend to distort the results of metabolic tests and to render their interpretation more difficult.

Methods of investigation

As gauges of glucose tolerance, two tests have been employed:

1. The oral glucose tolerance test. For this procedure a test dose of 2.0 grammes glucose per kgm. body weight was employed for children under three years of age, and a dose of 1.0 gramme glucose per kgm. body weight for older children. The sugar was given as a 10 per cent. solution in water, the child having fasted from the previous night—a period of twelve to fifteen hours. The capillary blood sugar content was estimated on samples taken fasting and at fifteen-minute intervals for two hours after the glucose administration, and the urine was examined for sugar one and two hours after the test dose, or, in the younger subjects, whenever a specimen could be obtained. In estimating the results of these tests (tables 2 and 4) the following arbitrary standards have been used for descriptive purposes:

- A. Low curve: maximum increase in blood-sugar concentration of 30 mgm. per 100 c.c. or less.
- B. Low-normal curve: maximum rise of 30 to 50 mgm. per 100 c.c.
- C. Normal curve: maximum rise of 50 to 85 mgm. per 100 c.c.
- D. High-normal curve: maximum rise of 85 to 100 mgm. per 100 c.c.
- E. High curve: a rise of more than 100 mgm. per 100 c.c.

2. The intravenous glucose tolerance test. The value of the intravenous test and its advantages over the oral test have been frequently emphasized (Crawford, 1938, 1939; Ross, 1938; Tunbridge and Allibone, 1940), and it is now coming into general use as a method of investigation of carbohydrate tolerance. Owing to the wide variations between the results of previous workers, variations probably due to differences in technique, the present investigations were preceded by a detailed examination of the response of healthy children and adults to the intravenous injections of glucose. This work has already been published (Crawford, 1938) and the following is a brief description of the standard test used in this and in the previous investigations, and of the findings in normal subjects.

A test dose of 0.5 gramme of glucose per kgm. body weight, dissolved in

normal saline to form a 20 per cent. solution, is injected intravenously following an eight-hour fast. Capillary blood is removed for sugar estimation prior to the injection, two minutes after its completion and at fifteen-minute intervals until ninety minutes after the injection. Tolerance is gauged by noting the time after the injection at which the blood sugar concentration returns to a value of 100 mgm. per 100 c.c. or less—the upper limit of normal fasting blood-sugar values with the technique employed. The time at which this occurs was shown to be constant for the individual under standard conditions and to vary within definite limits among normal subjects. It was shown that in health the blood-sugar reached a level of 100 mgm. per 100 c.c. at thirty, forty-five, sixty, or seventy-five minutes after the injection according to the age of the subject (table 1). The amount of sugar excreted in the urine varied from 3 to 9 per cent of the injected glucose.

TABLE 1
INTRAVENOUS GLUCOSE TOLERANCE TESTS IN NORMAL SUBJECTS

AGE GROUP				TIME OF FALL OF BLOOD-SUGAR TO 100 MGm. PER 100 C.C.
0-2 years	..	..	..	30-45 minutes
2-4 years	..	..	..	45-60 minutes
4-10 years	..	..	..	45-75 minutes
Over 10 years	..	..	..	60-75 minutes

Blood-sugar estimations were made by a modification of the method of Hagedorn and Jensen (1923), urinary estimations by the method of Benedict (1911).

Cretinism

Six cases of cretinism (congenital hypothyroidism or athyroidism) have been investigated as regards their tolerance to oral glucose before and after the start 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 designated as 'untreated' prior to the start 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.

THE FASTING BLOOD-SUGAR LEVEL was 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 mgm. per 100 c.c., with a mean value of 60·8 mgm. Four were below 50, and a further four below 60 mgm. per 100 c.c. In treated subjects the fasting blood-sugar levels ranged from 50 to 99 mgm. per 100 c.c. with a mean value of 71·0 mgm. In none of the treated cases was a level below 50 recorded, but in six of them the fasting value was below 60 mgm. 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 ORAL GLUCOSE TOLERANCE TESTS. The results of these tests are recorded in table 2. The irregularity of the response of young children to the oral administration of glucose, and the consequent difficulties in the interpreta-

tion of the results of oral glucose tolerance tests, have been frequently emphasized (Svensgaard, 1931; Crawford, 1938; Ross, 1938), and they are well exemplified in the present series of tests. Three of the cases (1, 2 and 4) showed, before treatment, a well-marked low curve, while a fourth (case 5) gave a low-normal curve. Case 3 showed a high curve, and case 6 a high curve twice and a normal curve once. It is thus clear that the response to oral glucose in cretinous children is variable; whilst 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 glucose tolerance also varied greatly from case to case. In case 1 the low curve present before treatment was elevated to a low-normal curve after two weeks of treatment, and the low curve was restored when treatment was withheld at a later date. The low curve in case 2 rose to a low-normal curve after three weeks of treatment and to a normal curve after seven weeks. In case 4 the low curve remained low after four weeks of treatment, though the blood-sugar rise had increased from 14 to 26 mgm. per 100 c.c. The low-normal curve present before treatment in case 5 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 3 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; whilst in case 6 the findings were as irregular on treatment as they had been before treatment was commenced; two high curves and a normal curve were obtained, though there were no signs of thyroid over-dosage. Case 7, an older cretin treated regularly for nine years, gave a normal curve.

From these results it would seem that the general effect of thyroid treatment on the abnormal oral glucose 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 2, representing what may be regarded as the typical findings in cretinism, are charted in fig. 1.

INTRAVENOUS GLUCOSE TOLERANCE TESTS were performed in five of the cases before and after starting treatment and also in two older cretins who had received continuous thyroid treatment for three and nine years respectively. The results of these tests are detailed in table 3. Prior to the start 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 4 and 5 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 2 and 6 the delay was of greater degree (fall in seventy-five minutes, normal in thirty to forty-five minutes), whilst in case 3 there was gross impairment of tolerance to intravenous glucose, a normal fasting level not having been reached in the ninety-minute specimen.

Treatment with thyroid gland preparations caused a change to a normal

TABLE 2
RESULTS OF ORAL GLUCOSE TOLERANCE TESTS IN CASES OF CRETINISM

CASE	AGE		BLOOD-SUGAR : MGM. PER 100 C.C.						CLINICAL CONDITION	TYPE OF CURVE
	YEARS	MONTHS	FASTING	$\frac{1}{2}$ HR.	1 HR.	1 $\frac{1}{2}$ HRS.	2 HRS.	MAXIMUM RISE		
1	1	6	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 week	Low
2			59	53	56	49	63	4	Treatment stopped 3 weeks	Low
			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	Treated 7 weeks	Normal
3	2	7	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
4	1		67	64	81	65	67	14	Untreated	Low
			60	86	78	77	62	26	Treated 3 weeks	Low
5	4	7	72	99	102	101	106	34	Untreated	Low-normal
			79	97	138	204	184	125	Treated 4 weeks, ? dose excessive	High*
6	1	0	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	Normal
			70	181	110	83	81	111	Treated 4 months	High
7	9	6	50	83	111	72	60	61	Treated 9 years	Normal

* Glycosuria.

TABLE 3
RESULTS OF INTRAVENOUS GLUCOSE TOLERANCE TESTS IN CASES OF CRETINISM

CASE	AGE		BLOOD-SUGAR : MGM. PER 100 C.C.									CLINICAL CONDITION	TYPE OF CURVE
	YEARS	MONTHS	FASTING	2 MINS.	15 MINS.	30 MINS.	45 MINS.	60 MINS.	75 MINS.	90 MINS.			
2		4	55	372	266	188	140	101	84	66	Untreated	Markedly de- layed fall	
			53	347	206	140	98	87	59	61	Treated 4 weeks	Normal curve	
3	2	7	57	262	200	168	155	141	136	124	Untreated	Grossly delayed fall	
			102	336	217	161	131	111	83	83	Treated 4 weeks ; dose exces- sive	Delayed fall	
			72	251	186	83	50	43	52	61	Treated 8 weeks ; dose ad- justed	Rapid-normal fall	
	1		48	376	278	170	102	55	—	—	Untreated	Delayed fall	
4			55	401	313	197	133	66	—	—	Treated 3 weeks	Delayed fall	
	4	7	76	300	199	145	122	104	79	75	Untreated	Delayed fall	
5			81	343	243	193	164	119	97	83	Treated 4 weeks ; ? dose exces- sive	Delayed fall	
	1		88	310	188	141	124	104	86	84	Untreated	Markedly de- layed fall	
6			93	257	148	104	90	81	68	—	Treated 3 weeks	Normal curve	
			90	284	163	124	104	85	74	77	Treated 4 weeks ; dose exces- sive	Delayed fall	
7	9	6	46	357	210	135	88	62	51	44	Treated 9 years	Normal curve	
8	6	10	68	333	217	154	103	70	60	—	Treated 3 years	Normal curve	

intravenous glucose tolerance curve in three of the five cases (cases 2, 3 and 6), and normal curves were also found in the two older treated cretins (cases 7 and 8). In cases 4 and 5 no improvement of intravenous tolerance occurred, the descent of the blood-sugar curve remaining slow after the start of treatment, though in case 5 this may have been due to excessive dosage of thyroid, as pointed out above in connexion with the oral curves in this case. In two cases (cases 3 and 6) intravenous glucose tolerance curves were obtained at a time when definite clinical evidence of overdosage with thyroid gland was present.

FIG. 1.—Case 2. Cretin: Oral glucose tolerance curves before and after commencing treatment.

In each instance the fall of the blood-sugar curve 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 6 are shown in fig. 2.

Hyperthyroidism

Hyperthyroidism is not a common condition in childhood, but the opportunity has arisen of investigating two cases. In the first (case 9), a boy aged six-and-a-half years, enlargement of the thyroid gland was occasioning some discomfort and on investigation signs of mild hyperthyroidism were found.

Unfortunately the child died of diphtheria a few months after he was first seen. The second case (case 10) 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. It has thus been possible 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 4 and 5, and in fig. 3 the curves from the severe case are shown. After oral administration of glucose case 9 yielded a normal blood-sugar curve, but in case 10 the curve was high and glycosuria occurred. After intravenous glucose the return of the

FIG. 2.—Case 6. Cretinism: Intravenous glucose tolerance curves before and after commencing treatment.

blood-sugar concentration to within normal limits was delayed in each case, indicating impairment of tolerance.

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 with thyroid preparations.
2. Results of oral glucose 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

TABLE 4

RESULTS OF ORAL GLUCOSE TOLERANCE TESTS IN HYPERTHYROIDISM

CASE	AGE		BLOOD-SUGAR : MGM. PER 100 C.C.							CLINICAL CONDITION	TYPE OF CURVE
	YEARS	MONTHS	FASTING	½ HR.	1 HR.	1½ HRS.	2 HRS.	MAXIMUM RISE			
9	6	6	81	105	140	106	83	59	Mild hyperthyroidism	Normal	
10	10	4	83	222	174	167	77	139	Severe hyperthyroidism	High : glycosuria	

TABLE 5

RESULTS OF INTRAVENOUS GLUCOSE TOLERANCE TESTS IN HYPERTHYROIDISM

CASE	AGE		BLOOD-SUGAR : MGM. PER 100 C.C.									CLINICAL CONDITION	TYPE OR CURVE
	YEARS	MONTHS	FASTING	2 MINS.	15 MINS.	30 MINS.	45 MINS.	60 MINS.	75 MINS.	90 MINS.			
9	6	6	97	336	219	193	154	129	108	99	Mild hyperthyroidism	Delayed fall	
10	10	4	88	316	226	163	132	120	108	92	Severe hyperthyroidism	Delayed fall	

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 gland is given impairment of tolerance reappears in the form of high oral and delayed intravenous curves.

5. Two cases of hyperthyroidism were studied. One case showed a high oral

FIG. 3.—Case 10. Blood-sugar curves after oral and intravenous glucose in a case of exophthalmic goitre.

curve, with glycosuria; in the other the oral curve was within normal limits. Both exhibited impaired tolerance to intravenous glucose.

Discussion

The results recorded above present three rather paradoxical findings: first, the occurrence of both high and low oral glucose tolerance curves in untreated cretins; second, the fact that in untreated cretins 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; and third, the observation that such diametrically opposed conditions as cretinism on the one hand, and hyperthyroidism on the other, both are associated with impairment of intravenous glucose tolerance.

Consideration of the factors which determine the nature of the curves obtained after oral and intravenous administration of glucose offers an explana-

tion of these apparently contradictory findings. Following oral glucose, the height and form of the blood-sugar curve depend upon:

1. The rate of absorption of the glucose from the alimentary canal.
2. The rate at which glucose oxidation is proceeding.
3. The rate at which the absorbed glucose is laid down as glycogen in the liver and muscles.

With intravenous administration of the glucose the absorption factor is eliminated and the duration of the hyperglycaemia depends upon the rates of oxidation and storage only.

Confusion in the interpretation of the results of intravenous glucose tolerance tests may arise from the fact that different abnormalities of the intermediary carbohydrate metabolism can produce the same alteration of the blood-sugar curve obtained. Thus increased formation of glycogen and increased oxidation of glucose both lead to a rapidly falling curve; whilst increased breakdown of glycogen, diminished formation of glycogen and diminished oxidation of glucose all result in abnormally prolonged curves.

The irregular response of cretins to the oral administration of glucose and the constantly high intravenous glucose tolerance curves suggest that it is the latter which reflects the true state of the carbohydrate tolerance of these children. Impairment of tolerance seems the more logical result of the slowing of the metabolic processes in general, which is known to occur in conditions of thyroid deficiency, than does the increased tolerance which some of the oral curves suggest. If this is correct then it is probable that the low oral glucose curves result from slow or faulty absorption of glucose from the bowel, being analogous to the low oral curves of idiopathic steatorrhoea (Thaysen, 1932; Crawford, 1939). That some such faulty or delayed absorption exists seems not unlikely, for constipation and abdominal distension are almost constant features of cretinism. It was frequently observed that the stomach was as full and prominent at the end of the oral tolerance test as it had been immediately after administration of the dose of glucose. Sluggishness of the movements of the alimentary canal, myxoedema of the bowel wall, and torpidity of the portal circulation may all play some part in the delayed absorption.

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 3 and 6 of the present series, is explicable by the assumption that in these cases unusually rapid absorption of glucose from the bowel has occurred and has thus unmasked 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 (Crawford, 1938). 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 metabolically active tissue, 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 the delayed fall of the

curve reflects the effect on carbohydrate metabolism of the general slowing of the metabolic processes of the body: there is certainly a diminution in the rate of glucose oxidation, and it is probable that the rate at which the injected glucose is stored as glycogen is also slowed. Carbohydrate metabolism in conditions of hyperthyroidism, both clinical and experimental, has been extensively investigated.

Many workers (Cramer and Krause, 1912; Cramer, 1916; Cramer and McCall, 1916; Kuriyama, 1917; Coggeshall and Greene, 1933) have shown that hyperthyroidism produced in animals by thyroid feeding leads to a rapid discharge of the liver glycogen. Cramer and Krause (1912) found glycogen absent from the liver of thyroid-fed animals, even when they were maintained on a high carbohydrate diet and the liver was examined shortly after a meal. Muscle glycogen was also found to be diminished in amount. Seeking the cause of this inhibition of glycogen storage in thyroid-fed animals, and basing their work on the original demonstration by Eppinger, Falta and Rudinger (1908) of the close relationship existing between thyroid and suprarenal activity, Hoskins (1910), Herring (1916, 1917) and Cramer (1918) have found evidence of hypertrophy and increased activity of the suprarenal medulla. Broking and Trendelenburg (1911) actually demonstrated an increase of the adrenaline content of the blood of patients suffering from exophthalmic goitre, and Cannon, Binger and Fitz (1915) succeeded in producing the syndrome of hyperthyroidism in cats by the operation of unilateral phrenico-sympathetic anastomosis. From his own observations as well as those of other workers Cramer (1918) concluded that hyperthyroidism is in effect a slight but definite hyperadrenalism, though Asher and Flack (1910, a and b) and Levy (1916) recorded observations from which they concluded that excessive thyroid secretion rendered the tissues hypersensitive to the action of adrenaline, even in normal amounts. More recently Himsworth (1939) has put forward the hypothesis that the anterior-pituitary hormones are concerned in the production of the defective hepatic glycogen storage which occurs in hyperthyroidism. In his view the raised metabolic rate causes an increased demand by the tissues for sugar; this stimulates the anterior-pituitary gland to secrete in excess the factor concerned in carbohydrate metabolism, and this in turn leads to increased breakdown of hepatic glycogen.

Whichever of these views is regarded as correct, it is clear that the impaired carbohydrate tolerance, both oral and intravenous, in conditions of hyperthyroidism results from interference with the normal storage of the ingested or injected glucose as glycogen. Though the rate of oxidation of glucose may be actually increased (Cramer and McCall, 1917), the effect of this on the total tolerance is overshadowed by the failure of glycogen storage.

As was to be expected, the predominant effect of thyroid gland therapy on the abnormal tolerance curves of hypothyroidism was a move towards normal values; but if too great a dose of thyroid substance were employed (cases 3 and 6) impairment of tolerance recurred. The case was in fact converted by this excessive dosage to one of hyperthyroidism. These findings suggest the possibility of employing the intravenous glucose tolerance test as a gauge for the correct dosage of thyroid substance for any given case. The optimum dose would be the greatest amount compatible with a normal intravenous curve.

Conclusions

In conditions of hypothyroidism carbohydrate tolerance is impaired. This impairment is due to a general slowing of the processes of katabolism, and possibly also to a diminution in the rate of storage of carbohydrate. The low oral blood-sugar curve which occurs frequently, and which accounts for the text-book statements that carbohydrate tolerance is increased in hypothyroidism, is due to slow absorption of the carbohydrate from the bowel.

In hyperthyroidism also there is impairment of carbohydrate tolerance, the fault being traceable to defective glycogen formation. This probably results from the excessive secretion of thyroxin causing an increased liberation of adrenaline, which in its turn mobilizes hepatic glycogen and inhibits its reformation.

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Case summaries

Case 1. M. McM. Female, aged one year six months. Complaint: failure to grow since the age of six months. History: appeared normal at birth; throve until the age of six months, since when growth has been defective; sleeps excessively; is not walking or talking; has not cut any teeth; constipated. Examination: weight 8.5 kgm. (normal for age 10.0 kgm.); height 68 cm. (normal 77 cm.); appears dull mentally; skin dry and coarse, with thickened subcutaneous tissues; tongue large and frequently protruded; small umbilical hernia. Blood: red blood cells, 3,750,000 per c.mm.; haemoglobin 68 per cent. Carpal ossification: no centres (normal for age, three centres).

Case 2. M. C. Female, aged four months. Complaint: difficulty in feeding; mental backwardness. History: infant appeared healthy until the age of three months, when progress ceased and she became listless, constipated and disinclined for her feeds. Examination: weight 4.8 kgm. (normal 5.6 kgm.); skin dry; features coarse and cretinoid; hoarse cry; some nasal obstruction; supraclavicular pads of fat. Blood: red blood cells 2,400,000 per c.mm.; haemoglobin 50 per cent. Carpal ossification: no centres.

Case 3. A. McM. Female, aged two years seven months. Complaint: failure to walk and talk. History: throve normally until the age of nine months; subsequent development slow; sleeps excessively and makes no attempt to talk or walk; constipated. Examination: weight 9 kgm. (normal 13 kgm.); height 70 cm. (normal 86 cm.); protruding tongue; skin dry and myxoedematous; hoarse cry. Blood: red blood cells 2,950,000 per c.mm.; haemoglobin 63 per cent. Carpal ossification: one centre (normal three to four centres).

Case 4. H. W. Female, aged one year. Complaint: slow development. History: appeared normal at birth, but progress was very slow; talking and walking have not commenced; constipated. Examination: weight 7.45 kgm. (normal 9.8 kgm.); skin dry; broad cretinoid facies, with large protruded tongue; umbilical hernia. Blood: red blood cells 3,170,000 per c.mm.; haemoglobin 60 per cent. Carpal ossification: no centres (normal two centres).

Case 5. M. W. Female, aged four years seven months. Complaint: failure to grow. History: following a normal birth child grew very slowly; first tooth at one year three months; walking began at two years; speech still

very defective. Examination: weight 13.7 kgm. (normal 16.8 kgm.); height 82 cm. (normal 93 cm.); skin dry and myxoedematous; facies typically cretinoid; primary dentition fully erupted, but carious. Blood: red blood cells 4,100,000 per c.mm.; haemoglobin 84 per cent. Carpal ossification: four centres (normal seven centres).

Case 6. S. M. Male, aged one year. Complaint: failure to thrive since the age of two months. History: birth normal; child seemed well up to age of two months, after which made little progress; cannot sit up and has cut no teeth. Examination: weight 5.8 kgm. (normal 9.3 kgm.); height 61 cm. (normal 74 cm.); dry skin; thick, protruding tongue, coarse features; hoarse low-pitched cry; supraclavicular pads of fat; umbilical hernia. Blood: red blood cells 4,460,000 per c.mm.; haemoglobin 68 per cent. Carpal ossification: no centres (normal two centres).

Case 7. A. G. Female, aged nine and a half years. Attended hospital for the supply of thyroid tablets, which she had received from various clinics since the age of six months, when cretinism was diagnosed at a maternity hospital infant clinic. On thyroid treatment made slow progress: first tooth appeared, and talking began, at age of one year; walked alone at age of two years. She is rather backward at school. Examination: weight 26 kgm. (normal 28 kgm.); height 120 cm. (normal 129 cm.); appears healthy—not obviously a cretin; intelligence quotient 58 per cent.; umbilical herniotomy scar present. Carpal ossification normal.

Case 8. S. C. Female, aged six years ten months. Diagnosed as a cretin in hospital at the age of four years—then not talking or walking, and appearance described as typically cretinoid. Since then on regular thyroid treatment, and has made good progress. Examination: weight 16.8 kgm. (normal 21 kgm.); height 102 cm. (normal 116 cm.); mental condition good (intelligence quotient 80 per cent.); no anaemia. Carpal ossification: six centres (normal eight to ten centres).

Case 9. P. M. Male, aged six and a half years. Complaint: swelling in the neck and difficulty in swallowing. History: recurrent attacks of swelling in the neck, sometimes with dysphagia, since the age of three years. Examination: weight 23.6 kgm. (normal 22 kgm.); height 124 cm. (normal 115 cm.); well-developed child; thyroid gland enlarged and firm, especially the isthmus; slight exophthalmos; definite fine tremor of hands; pulse rate not increased. Died of diphtheria nine months after the investigations were made.

Case 10. E. C. Female, aged ten years four months. Complaint: nervousness and excitability. History: for a year her eyes had gradually increased in prominence, and for a month nervousness had been extreme. Examination: weight 24.2 kgm. (normal 30 kgm.); height 131 cm. (normal 133 cm.); well developed but thin child; highly emotional and nervous; severe exophthalmos; sweating marked; moderate uniform enlargement of thyroid gland; pulse rate 110 to 140 per minute; tremor of hands; basal metabolic rate: +78 per cent.

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