T H E S I S

NITROGEN ABSORPTION CURVES in HEALTH AND DISEASE

by

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This investigation was carried out in the wards and biochemical laboratory of the Royal Hospital for Sick Children, Glasgow, during the tenure of a Muirhead Scholarship at the instigation of Professor G.B. Fleming and Dr Noah Morris. I am deeply indebted to Professor Fleming for the stimulus of his continued interest and criticism, and to Dr Morris for many suggestions which have proved most valuable. It is a pleasure also to express my thanks to Dr Stanley Graham and Mr Matthew White for granting me facilities for examining cases in their wards.

I N T R O D U C T I O N

From the work of physiologists it is established that, after ingestion, protein substances are broken down into primary and secondary proteoses, later into peptone, and ultimately into amino-acids in which form they are absorbed and thus enter the portal circulation. The constituents of which the tissues are capable of making use are distributed by the blood stream to various parts of the body, while those which are not utilised are carried to the kidney where they are removed from the circulation and excreted in the urine. The major portion of this nitrogen found in the urine is composed of urea, ammonium salts and creatinin. Thus far, the processes at work have been extensively investigated and the results obtained have been well substantiated. Much less work has, however, been carried out on the intermediate metabolism of nitrogen. It would appear that a hiatus exists in our knowledge regarding the part played by the liver in these processes. It is said that deaminisation of the amino-acids occurs in the liver resulting in the formation of urea, but the actual mechanism of the next step is uncertain. After the liver manufactures the urea does it immediately enter the circulation with a view to excretion by the urine as expeditiously as possible? Or, is it possible that the urea may

be stored by the liver and only allowed to escape gradually into the blood stream? Lastly, the hypothesis has been brought forward that the urea may be actually resynthetised into protein.

The present investigation was undertaken with a view to following the changes in blood non-protein nitrogen which occurred in health and in disease after the ingestion of urea. It was also decided to study the effect of various foodstuffs on the non-protein nitrogen of the blood.

The work has accordingly been divided into the following sections:-

1. A summary of our present knowledge of the non-protein nitrogen of the blood considered from a historical standpoint along with some remarks on the absorption of urea.

2. The influence of (a) a prolonged abstention from food and (b) various foodstuffs, alone and in combination, on the non-protein nitrogen of the blood.

3. A study of the effect of the ingestion of urea on the non-protein nitrogen of the blood in healthy or convalescent children.

4. The influence of the ingestion of urea on the blood non-protein nitrogen in cases where disease of the liver is known or suspected to exist.

5. The effect of the ingestion of urea on the non-protein nitrogen of the blood in diseases of the muscles.

6. The effect of the ingestion of urea on the non-protein nitrogen of the blood in children who were the subjects of rheumatic infection.

7. The effect of the ingestion of urea on the non-protein nitrogen of the blood in cases of renal disease.

8. The influence of the ingestion of urea on the non-protein nitrogen of the blood in cases of coeliac disease.

9. Summary and conclusions.

SECTION I.

A Summary of our present knowledge of the non-protein nitrogen of the blood along with some remarks on the absorption of urea.

The non-protein nitrogen of the blood is variously described as the incoagulable nitrogen, filtrate, rest, waste or residual nitrogen. It is composed of the nitrogen derived from - urea, uric acid, amino acids, creatin, creatinin and a small proportion of undetermined substances, The urea nitrogen is the most important.

Although Wöhler in 1828 succeeded in producing a synthetic preparation of urea and the following year Christison[1] demonstrated an increase in serum urea in cases of nephritis, it was not until 1899 that the non-protein nitrogen of the blood was determined. Schondorff[2] was amongst the first to carry out this estimation. From these early beginnings a great deal of information regarding the metabolism of the non-protein nitrogen of the blood and of its principal constituent, urea, has accumulated.

The formation of urea.

It is now generally believed that urea is manufactured mainly in the liver and that most of it is excreted by the kidneys. In proof of this it has been demonstrated that after complete removal of the liver in a normal animal, always provided that the urinary apparatus has been left intact, the blood urea gradually falls. If, on the other hand, anuria exists, the level of urea in the blood remains constant. If the kidneys are removed in a normal animal the blood urea rises steadily. Should

the liver be next removed the blood urea remains at the level which it had reached immediately prior to the second operation.

The amount of non-protein nitrogen found in the blood of normal individuals.

Naturally the height of the non-protein nitrogen and urea of the blood depends on the rate of formation of urea as well as upon the rate of excretion. The former varies with the amount of protein in the diet as well as with the rate of protein catabolism (MacKay and MacKay)[3] the latter according to the findings of Addis[4] & Drury is conditioned by many factors.

It is now definitely established that any value for the non-protein nitrogen of the blood lying between 15-40 mg. p.100 ccs. is physiological. The earlier workers for the most part found definitely higher values. Some of these investigators concentrated on the hypo-bromite method, which was not sufficiently accurate to afford results of value. The principal exponents of the subject differed greatly as to the actual physiological range of the non-protein nitrogen of the blood. Some of the results recorded between 1913-1915 may be summarised as follows:-

Name		% N.P.N. in 100 ccs. blood.
Rowntree & Fitz	(5)	50-60
Farr & Austin	(6)	15-43
Agnew	(7)	50
Rowntree	(8)	50
Frothingham & Smellie	(9)	20-30
Tileston & Comfort	(10)	30
Foster	(11)	20-40

With the view of endeavouring to clear up the differences found by various workers, Farr & Austin[9] carried out a series of experiments on the values observed using whole blood and serum. The results they obtained led them to the conclusion that with a reliable method and a careful technique there should be no difference of any consequence between the non-protein nitrogen of whole blood and that of serum.

As has been shown by MacKay & MacKay[3] Archer & Robb[12] and others, physiological variations occur within the 24 hours. The value is found to be higher during the day - that is, during activity than during the night-period of rest. That these changes are not entirely due to changes in renal activity is clearly shown by the fact that the urinary urea is also distinctly lower by night than by day. This fact has led MacKay & MacKay[3], Addis & Watanabe[13] and others to conclude that the explanation may lie in changes in the metabolic rate. The decreased values by night would then coincide with a depressed metabolism. The day rise can, of course, naturally be partially attributed to the ingestion of food. Addis & Watanabe[13] have shown that a change from a diet composed mainly of carbohydrate to one rich in protein may cause a rise in blood urea of from 58-250%. MacKay & MacKay[14] state that a single meal rich in protein has little effect on the blood urea, but they agree that if such a diet is continued for

several days an appreciable rise results. From this they conclude that it is unnecessary to pay undue attention to the time of day at which the blood for the estimations is withdrawn. This agrees with the findings of Forsgren[15] who found no characteristic relationship between the height of the non-protein nitrogen and the ingestion of food. In his opinion the fasting non-protein nitrogen estimated in the morning is not necessarily the lowest in the 24 hours. He regards it as possible that these variations may have some connection with hepatic activity. MacKay & MacKay[16] believe that there is less variation in specimens of blood withdrawn at the same hour each day than at different hours on the same day. These workers have produced results which show that the urea of the blood tends to be definitely higher in men than in women by about 35%. This investigation has shown that there is a tendency for the value to increase with age.

It is generally acknowledged that abnormally high non-protein nitrogen and urea values may be obtained in cases where the kidneys at autopsy show no evidence of disease. Amongst such conditions may be mentioned high intestinal obstruction and dehydration from any cause. In some of the acute fevers also higher values than normal may occur.

Tileston & Comfort[10] were apparently the first investigators to demonstrate an increased non-protein nitrogen of the blood in acute intestinal obstruction. In four of their

cases the fasting levels were 76, 92, 150 and 169 mg. per 100 ccs. respectively. Their findings were confirmed by Schwartz & McGill[17]. It was suggested by Addis & Watanabe[13] that the abnormal values in this condition may be accounted for by increased catabolism. Foster[12] demonstrated a rise in cholera which he regarded as a result of the oligaemia. In his cases of pneumonia a rise beyond the normal was exceptional, only occurring in cases showing evidence of cardiac embarrassment. This finding led him to carry out non-protein nitrogen estimations in cases of decompensation, with the result that in 8 patients between the ages of 18-26 years he found an average reading of 61 mg. p. 100 ccs.

In acute infections Tileston & Comfort[10] found that their highest non-protein nitrogen value did not exceed 50 mg. p.100 ccs. In patients suffering from hypertrophy of the prostate complicated by hydronephrosis as a result of backward pressure the urea value of the blood is often higher than in cases of genuine nephritis. These facts point to the advisability, or perhaps rather the necessity, of a urea concentration or other renal function test being carried out before a diagnosis of nephritis is given on the strength of an abnormal blood non-protein nitrogen or urea estimation.

<u>The absorption of urea.</u>

Folin[18] has shown that after ingestion most of the urea is absorbed from the small intestine although a certain

amount of absorption does occur from both the stomach and the large intestine.

By means of their new micro method Folin & Denis[19] in 1912 were able to examine the blood in animals after the ingestion of urea. They took samples of blood and removed the gracilis muscle from one leg, they then introduced a solution containing urea into a ligatured loop of intestine. Specimens of blood were withdrawn at various intervals during the experiment, and at the close the gracilis from the other leg was also removed. The determination of the non-protein nitrogen and urea from the specimens of blood and muscle thus obtained showed that there had been a rapid absorption of urea from the intestine and that it had entered into the circulation unchanged and had actually accumulated in the muscle.

The effect of urea on Nitrogen Metabolism.

We are indebted to Graefe[20] for his work on this subject. His experiments were most carefully planned. On account of the readiness with which pigs partook of the diet he decided that they were the animals best suited for the experiments. The animals were prepared by a preliminary fast extending over a few days, followed by a pre-period in which the diet was rich in carbohydrate and fat, but nitrogen-free. Then, during a further pre-period he continued this diet with the addition of protein equal in amount to about $^{2}/_{3}$ of the maintenance minimum. This

protein was also given during the principal period when urea or urea plus ammonium citrate was added to the diet. The nitrogen balance remained negative during the pre-period, in spite of the protein added to the diet during the second stage, but it became definitely positive during the principal period showing that a certain amount of nitrogen had actually been retained. As a result of these experiments Graefe came to the conclusion that there were three possibilities regarding the fate of this nitrogen namely -

1. It may be retained as ammonia.
2. It may be changed into some nitrogenous compound other than protein.
3. It may actually spare body protein by conversion into some protein-like body.

He decided in favour of the last suggestion, but he does not appear to have been thoroughly satisfied with the results of his investigations.

Henriques & Andersen[21] repeated Graefe's work by means of intravenous injections in goats. There was a daily injection of 2 litres of a solution containing glucose and salts in a pre- and a post-period separated by a principal period during which urea or an ammonium salt was added to the injected fluid. Although the negative nitrogen balance was definitely reduced during the principal period the retention of nitrogen was only temporary as it was followed later by a washing out.

Marshall & Davies[22] also injected fluid containing

urea in considerable quantities but found no evidence of any change into any other substance.

In 1916 Abderhalden[23] in view of the rather conflicting results obtained by other investigators surveyed the whole question. He reached the general conclusion that the nitrogen balance alone could not give much information regarding protein metabolism.

Abderhalden pointed out that the mere addition of ballast to the food in the form of cellulose may convert a positive nitrogen balance into a negative one, through the increased removal of nitrogen by way of the intestine. Working along with Hirsch[24] and Lampé[25] he came to the conclusion that any retention of nitrogen following the absorption of urea was followed later by a washing out. These workers admitted that ammonium salts did act as protein-sparers, but they were of the opinion that the most reasonable explanation of the results was that the nitrogen was retained in some non-protein form. They were in entire disagreement with the theory of resynthesis of protein. Dogs were used for their experiments. G.D.Cathcart[26] and Barnett & Addis[27] have shown that the blood ammonia content may rise after giving urea. This fact really places urea in the same category as the ammonium salts.

Six years later Cathcart[28] stated that in his opinion, even if the body can synthetize amino-acids and eventually protein

from urea or ammonium salts, administered along with carbohydrates and fats, it does not readily do so.

Moore[29] and his co-workers fed normal individuals on urea in quantities varying from 35 to 52 g. as an addition to their usual diet. They carried out estimations of the non-protein nitrogen of the blood and investigated the nitrogen metabolism. They found that a certain proportion of the nitrogen was completely lost trace of. They were, however, quite unable to furnish any explanation of their results. Similar investigations carried out earlier by these same workers using patients suffering from nephritis produced almost identical results.

Cathcart and Green[30] kept a normal adult on a butter and potato diet for some days and then added a single dose of 12g. urea. Within 48 hours they were able to recover 95% of the urea.

As may be observed from this summary our knowledge of the subject is still defective on certain important points one of which is the fate of urea nitrogen between absorption and excretion.

SECTION 2.

The influence of -

(a) prolonged abstention from food and

(b) various foodstuffs on the non-protein nitrogen of the blood.

Between 1911 and 1917 Van Slyke studied the relationship of the liver to urea formation[31a] and determined the blood urea curve after an ample meal of meat. By means of X-ray photographs he was able to show that the blood urea rose directly the first particle of food entered the duodenum - that is to say, before amino-acid formation had taken place. As it had been suggested that the formation of urea by the liver is not the specific result of the presence of protein in the alimentary tract, but might follow the stimulus of the ingestion of any type of food Cohen & Levin[32] began to study the effect of the ingestion of glucose on the blood urea. They performed the test at intervals of 2 and 4 hours after the glucose had been taken, but they found no change in the level of the urea of the blood. From their results they concluded that the presence of the amino-acid molecule in the intestinal tract has the faculty of stimulating the deaminizing power of the liver before there is any increase in the amino-acid content of the blood. With a view to confirming, and if possible supplementing the work of Cohen & Levin the following series of cases was examined. The ages of the children ranged from 7 to 11 years, and they were convalescing from various conditions including chorea, simple endocarditis, fibrosis of lung, renal calculi, and convalescent enteritis. The first specimen of blood was taken at 9 a.m. when the child had been fasting for at least 12 hours. The blood was obtained from

a needle puncture of the thumb. After the fasting sample had been withdrawn the child was given on different days the following -

1. Nothing - i.e. the fast was continued.
2. 150ccs water.
3. 150ccs water containing an amount of glucose equivalent to 1g. per kilog. of body weight.
4. Glucose solution as before with the addition of 100 cc. 40% cream.
5. Glucose solution as before with the addition of 15g. plasmon.
6. Glucose soln. + fat + plasmon.
7. 100ccs cream.

Samples of blood were withdrawn thereafter at intervals of 30, 60, 90 and 120 minutes from the time the fasting specimen was taken.

The results. (Tables 1-8)

In group 1, that is during the continued fast, it was found that there was an average fall in value of 16% from the fasting level during the two hours which the investigation continued. This is in accordance with what one would anticipate, as urea is being continuously excreted by the kidney but no exogenous nitrogen is being added to make good this loss. This is somewhat comparable to the well recognised fall in the value of the blood-sugar which occurs during fasting.

In group 2, where 150ccs. water was given a loss amounting to 30% was observed.

The results obtained in group 3, following the administration of glucose solution were for all practical purposes the same as those found in group 2. They make it apparent that glucose does not act as a stimulant to nitrogen metabolism. In this finding they agree with those of Cohen and Levin whose work has been already mentioned. In place of the non-protein nitrogen made use of in the present investigation they estimated the urea of the blood. These workers appear however only to have examined the blood 2 hours and 4 hours after the glucose had been given. Considering the rapid rate of absorption of glucose it is possible that had a rise occurred it would have subsided by the end of two hours and would thus have been missed by these workers.

In group 4, 100ccs. fat in the form of cream was added to the glucose solution and a curve almost identical with that obtained in groups 2 and 3 was found. From these results it is evident that carbohydrate and fat together exert no influence on the non-protein nitrogen content of the blood.

In group 5, protein in the form of plasmon was added to the glucose solution. As a result of the added protein a definite rise in the non-protein nitrogen curve was anticipated. The composite curve however showed a rise of only 6% occurring within the first half-hour. Thereafter the curve subsided and

had by the end of two hours reached a rather lower level than was found in the fasting state. Of the 5 cases investigated 2 showed a definite rise occurring within 130 minutes of the administration of the fluid - namely cases 1 and 3. Case 1 in fact, had not regained the fasting level 2 hours after the ingestion of the liquid. The remaining 3 cases on the other hand showed fairly definite continuous losses in value.

In group 6 where fat and protein in the same quantities as before were added to the glucose solution the composite curve showed a loss of 23%. In none of the 4 cases included in this series was there any definite attempt at an increase in value.

Group 7 contained only one child who was given 100ccs. cream. In this curve also there was a fall of 12mg. below the fasting value with no attempt at a rise in any of the specimens.

From a study of these groups it is clear that neither glucose or fat, alone or in combination possess the property of stimulating nitrogen metabolism. It was to be expected that the addition of protein in the form of plasmon would cause a definite increase in the non-protein nitrogen value; this however did not occur. Two possibilities may be considered by way of explanation. 1st, the amount of protein actually contained in the plasmon may not have been sufficient to counterbalance the fall which is shown by group 1 to occur normally in the absence of food.
2nd, sufficient time may not have elapsed during the course of

TABLE I.

THE INFLUENCE of a CONTINUED FAST on the N.P.N. CURVE.

Number of case	Age in years	Disease	% of N.P.N. in the blood.				in mgms.
			Fasting	½ hour	1 hour	1½ hours	2 hours
3	11	Convalescent chorea.	30.6	31.8	21.0	-	30.2
4	10	Renal Calculi	29.2	28.4	27.7	20.0	18.8
5	7	Convalescent chorea.	39.0	39.3	36.7	47.1	35.0

TABLE II.

THE INFLUENCE of 150ccs. WATER on the N.P.N. CURVE.

Number of case	Age in years	Disease	% of N.P.N. in the blood, in mgms. Hours after ingestion of water.				
			Fasting Level	½ hour	1 hour	1½ hours	2 hours
1	10	Valvular disease of the heart.	40.9	25.6	23.1	25	-
2	10	Fibrosis of Lungs	46.7	48.0	30.	37.6	40
6	9	Convalescent Enteritis	21.7	20.3	24.3	24.4	23

3)109.3
36.4

3)77.4
25.8

TABLE III.

THE INFLUENCE of GLUCOSE SOLUTION on the N.P.N. CURVE.

Number of case	Age in Years	Disease	% of N.P.N. in the blood, in mgms.				
			Fasting Level	Hours after ingestion of glucose solution			
				½ hour	1 hour	1½ hours	2 hours
1	10	Valvular Disease of the heart	44.0	37.9	30.8	30.0	23.1
2	10	Fibrosis of the lungs	33.3	33.3	28.0	28.0	-
3	11	Convalescent Chorea	44.6	32.4	30.0	25.0	20.0
4	10	Renal Calculi	35.2	27.3	29.2	34.0	25.5
5	7	Convalescent Chorea	51.0	37.0	35.0	33.7	37.0
6	9	Convalescent Enteritis	25.6	21.7	26.2	22.4	25.

TABLE IV.

THE INFLUENCE of GLUCOSE SOLUTION & CREAM on the N.P.N.CURVE

No. of Case.	Age in Years	Disease	% N.P.N. in the Blood, in mgms.				
			Fasting Level	Hours after ingestion of glucose & fat			
				½ hour	1 hour	1½ hours	2 hours
1.	11	Valvular disease of the Heart.....	43.4	33.3	33.3	40.0	30.0
2.	10	Fibrosis of the Lungs...	35.0	30.6	27.0	22.7	21.7
3.	10	Convalescent Chorea.....	32.4	25.7	20.0	19.0	16.9
4.	10	Renal Calculi	34.4	25.5	26.6	27.0	27.0
5.	7	Convalescent Chorea.....	29.0	27,3	26.8	27.0	24.1
6.	9	Convalescent Enteritis...	36.0	32.4	23.0	21.4	15.4

TABLE V.

THE INFLUENCE of GLUCOSE SOLUTION & PROTEIN on the N.P.N.CURVE

No. of Case	Age in Years.	Disease	% N.P.N. in the Blood, in mgms.				
			Fasting Level	Hours after ingestion of glucose & Protein			
				½ hour	1 hour	1½ hours	2 hours
1.	10	Valvular Disease of the Heart.	41.3	58.1	35.0	46.7	34.5
2.	10	Fibrosis of the Lungs.	36.0	47.6	73.5	52.6	52.6
3.	11	Convalescent Chorea.	35.0	26.8	18.0	21.7	26.3
4.	10	Renal Calculi.	39.8	30.8	28.9	40.	36.7
6.	9	Convalescent Enteritis.	25.5	19.6	20.7	18.0	15.0

TABLE VI.

THE INFLUENCE of GLUCOSE, CREAM & PROTEIN on the N.P.N. CURVE.

No.of Case.	Age in Years	Disease	% N.P.N. in the Blood, in mgms.				
			Fasting Level	Hours after ingestion of Solution.			
				½ hour	1 hour	1½ hours	2 hours
1.	10	Valvular disease of the Heart.	40.2	36.6	27.8	27.6	27.0
2.	10	Fibrosis of the Lungs.	34.2	20.0	20.3	32.	24.4
3.	11	Convalescent Chorea.	32.0	23.2	28.8	29.0	38.4
6.	9	Convalescent Enteritis.	18.2	21.4	20.6	15.4	15.3

TABLE VII.

THE INFLUENCE of FAT on the N.P.N. CURVE

No. of Case	Age in Years	Disease	Fasting Level	% N.P.N. in the blood in mgms. Hours after ingestion of Cream.			
				½ hour	1 hour	1½ hrs	2 hrs
4.	10	Renal Calculi.	31.8	19.6	19.8	19.8	22.0

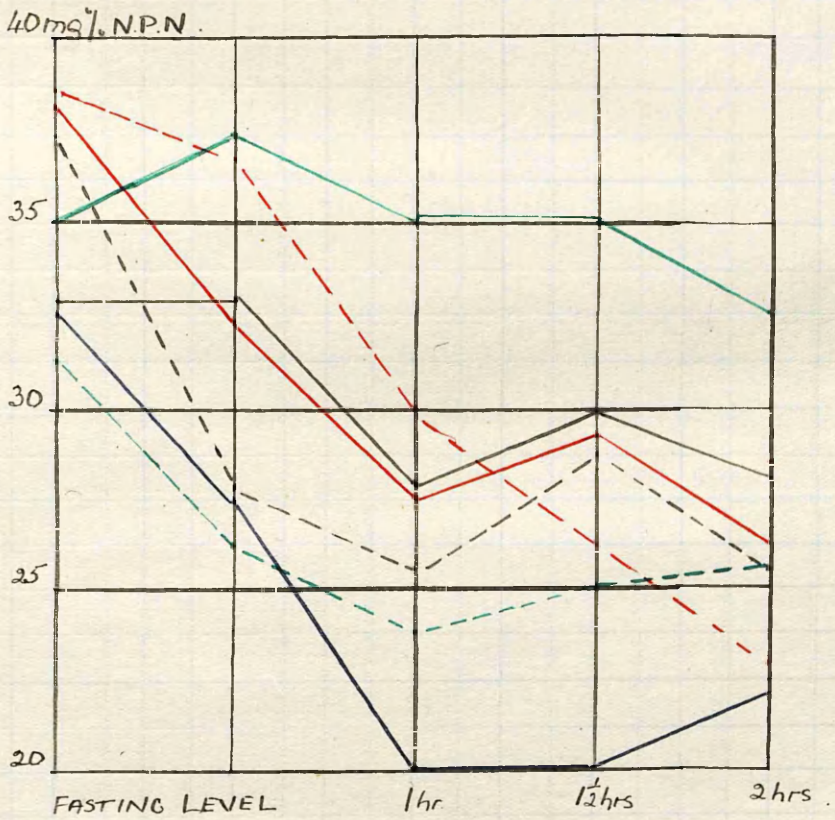
TABLE VIII.

COMPOSITE CURVES SHOWING the EFFECT of VARIOUS FOODSTUFFS on the N.P.N.CURVE

Group No.	Substance given	% variation in Value	% N.P.N. in the Blood, in mgms.				
			Fasting Level	Hours after substance had been given			
				½ hour	1 hour	1½ hours	2 hours
1.	Nil.	- 16	33	33	28	30	28
2.	150 ccs.Water	- 30	37	28	26	29	29
3.	Glucose solution	- 32	38	32	30	29	26
4.	Glucose solution and cream.	- 33	35	29	26	26	23
5.	Glucose solution and protein.	+ 6	35	38	35	36	33
6.	Glucose solution and protein and fat.	- 23	31	25	24	26	26
7.	Cream.	- 37	32	20	20	20	22

FIGURE No.1.

THE EFFECT of FASTING & of VARIOUS FOODSTUFFS
on the N.P.N. of the BLOOD.



NOTHING GIVEN. ———————

150 ccs. WATER. - - - - - - -

GLUCOSE SOLUTION. ———————

" " +CREAM. - - - - - - -

" " +PROTEIN. ———————

" " " " +CREAM. - - - - - -

CREAM. ———————

the curve to allow of the protein being deaminised and entering the general circulation as non-protein nitrogen. Against this theory is the work of Van Slyke of which mention has already been made. He found that the blood urea rose as soon as the first particle of food entered the duodenum - that is, before deamination could have taken place. In favour of this suggestion, on the other hand is the work of Cohen[32] and Levin. They fed children on protein in the form of breast of chicken at the rate of 1g. per kilog. of body weight and found that in normal cases the maximum blood urea concentration was not obtained until four hours after the meal had been taken. Any increase exceeding 50% they regarded as normal. In children who were the subjects of liver disease the increase did not exceed 25%. These writers put forward this test founded on the deaminising power of the liver as being of value in the diagnosis of hepatic inefficiency. Witts[33] in 1928 studied the effect of the ingestion of glycine on the non-protein nitrogen and urea of the blood and found in health a rise ranging between 50 and 113% above the fasting level. The maximum value however was not attained until 6 hours after ingestion.

On comparing groups 1 and 2 where the diminution of values below the fasting levels are 16% and 30% respectively, it was thought possible that the difference could be explained by the diuretic action of the water causing a washing out of nitro-

genous waste products. That this theory was unsound was shown by group 7 where an even more pronounced loss followed the ingestion of fat alone.

SUMMARY

The effect of fasting and of various foodstuffs on the non-protein nitrogen has been studied.

The findings are as follows:-

1. Non-protein nitrogen tends to fall as fasting progresses.
2. This fall continues in spite of the ingestion.of glucose solution or fat, alone or in combination, also following a mixture of carbohydrate, protein and fat.
3. When glucose and protein are administered together there is a slight transient rise in non-protein nitrogen value.

Therefore glucose and fat do not affect nitrogen metabolism.

SECTION 3.

A study of the effect of the ingestion of 15g. urea on the non-protein nitrogen of the blood in healthy children.

In spite of the fact that the urea concentration test is in daily use very few data are available as to the effect of a single dose of urea on the blood urea or non-protein nitrogen when given to a fasting individual.

In 1924 Archer and Robb[12] studied the effect of a single dose of urea on the urea of the blood. Bearing in mind the use of the glucose tolerance test in the diagnosis of diabetes they endeavoured to devise a method whereby nephritis could be diagnosed following the ingestion of urea. They chose four presumably normal individuals and having withdrawn a specimen of fasting blood administered 15g. urea in 120 of water. Samples of blood were examined after intervals of 15, 30, 60, 120, 180 and 300 minutes and the urea estimated by the micro-Archer method. One of the cases had the test performed on 6 occasions. The fasting-levels were found to vary between 21-38 mg. p.100ccs. After the ingestion of the urea, the blood urea increased in amount, the maximum value being reached usually within the first half hour. Sometimes the peak was not attained until an hour after the urea had been given. The authors, however, laid no stress on the delay attributing it to slow absorption.

50mg% was the highest value attained after 25g urea.
48 " " " " " " " 15g "

The actual increase averaged 15 mg. with 25g urea.
" " " " 10 mg. " 15g "

They concluded that after a dose of 15g. urea there was return of the blood urea content to the fasting level within 2 hours, if an

allowance of 6mg. was made for the normal hourly fluctuation. One exception to this rule occurred in their series of normal subjects. It was a case in which after the 15g. urea had been given the original value had not been regained even 3 hours after the ingestion of the urea. With a dose of 25g urea on the other hand recovery was only beginning between 3 and 4 hours after the urea had been given and was incomplete even after 5 hours. In all, 6 estimations were made with 15g urea in 4 adults and 3 estimations following 25g. urea in one adult. It would seem hardly justifiable to base a standard of normality on such a small number of cases.

As regards nephritis these workers diagnosed renal inefficiency when there was failure on the part of the curve to return to the fasting level within 2 hours. They studied 8 cases of nephritis - in one of these the test was performed twice. They stated that of these, 4 were so obviously defective in renal function that bio-chemical aids were unnecessary for diagnosis. Out of 9 blood urea estimations carried out when the patients were fasting, two only were within normal limits, two were slightly elevated, while the remaining 5 gave definitely high values. The urea concentration test gave 1 normal result while 8 were abnormal. In one case only was the curve continuing to rise at 2 hours after the urea. In all the others it was either falling or tending to

do so but in none had the fasting level been regained within two hours. In each of these cases renal inefficiency was diagnosed.

As has been noted these workers estimated the blood urea. Opinion is still divided as to whether the non-protein nitrogen or urea estimation is of the greater value. Were the ratio of the one to the other found to be constant the problem would be non-existent. That such is not the case was, however, demonstrated by Schondorff[2] in 1899 and this finding was later confirmed by other investigators including Farr & Austin[34]. Schondorff regarded 50% as being an average proportion and in this he was supported by Tileston and Comfort[10]. They found however that in pathological conditions this proportion might increase to 70%. Agnew[7] tried to find some connection between the ratio of urea to the total non-protein nitrogen and various types of nephritis but his results were not very convincing. Rowntree[35], Marshall and Bactzer regard the two tests as being of equal importance. Tileston & Comfort[10] put greater value on the non-protein nitrogen while Myers[36] et alii prefer the urea estimation.

In the opinion of Seelig & Pronell[37] the non-protein nitrogen estimation is of the greater value on account of the possibility of changes occurring in ingested urea in the intestine prior to absorption. They have shown that in hepatic disease, for

example, the ingestion of urea leads to an increased output of ammonia because the urea is split up in the gut and is not re-synthetised in the liver.

Accordingly, when all the facts had been considered it was decided that for the present investigation the non-protein nitrogen estimation would appear to be the one of election. It was therefore determined to observe the effect of the ingestion of 15g. urea on the blood non-protein nitrogen of presumably healthy or convalescent children.

General Procedure.

A specimen of blood was withdrawn from the thumb at 9.30 a.m., the children having had nothing to eat or drink since before midnight. In one or two instances the sample was taken from a vein. This was done when blood was required for some other estimation, at the same time to eliminate the necessity of two pricks. Johnstone[38] found no appreciable difference in venous and capillary blood. In each case whole blood was used. 15g. urea flavoured with syrup of lemon and made up with water to 120ccs. was then administered. The drink was taken readily by most of the children. In cases where there was any difficulty a stomach tube was used. In no case did vomiting or any other symptom follow the ingestion of the urea. The blood non-protein nitrogen was estimated at intervals of 30, 60 and 120

minutes after the administration of the urea, as a routine measure. On some occasions it was possible to continue the test for three hours, and in one or two cases for five hours. Owing to the number of estimations necessary and taking into account the ages of the subjects it was decided to use Folins Micro-Method[39] for the estimation of the non-protein nitrogen.

When specimens of urine could be obtained a simultaneous urea concentration test was carried out by the urease method. This was done with a view to gauging the renal efficiency.

The normal non-protein nitrogen curve: (Table 9).

This group consisted of 12 children convalescent from various diseases and injuries. None had suffered from any renal or hepatic disorder or showed any evidence of rheumatic infection. In none of the cases was there any reason to suspect the presence of any metabolic disorder. None of them had been recently anaesthetised and no drugs were being administered. The ages ranged from 4 to 11 years.

The fasting non-protein nitrogen value was found to lie between 18 and 40mg% with an average value of 32mg%. In all the cases a definite rise was observed within half an hour of the ingestion of the urea. The smallest increase noted was 4.6mg% and the largest 33mg% while the maximum level reached was 62.5mg%.

TABLE 9.

NORMAL NON-PROTEIN NITROGEN CURVES FOLLOWING THE INGESTION of 15 GRM. UREA.

No. of Case.	Age in Years.	Disease	Percentage of N.P.N. in blood: mgrm. per cent			
			Fasting level	Hours after the ingestion of urea		
				½ hr.	1 hr.	2 hrs.
1	4	Pulmonary fibrosis.	38.1	60.9	74.5	62.5
2	11	Neurosis.....	26.7	59.5	34.7	31.2
3	9	Spastic diplegia...	18.0	32.6	46.8	38.3
4	8	Convalescent ileo-colitis.....	35.0	38.0	45.0	35.0
5	8	Convalescent purpura	31.3	42.3	30.5	30.0
6	11	Fracture.....	38.0	-	66.0	60.0
7	10	Convalescent appendicitis.....	37.0	49.0	57.4	49.0
8	6	Fracture.....	33.1	50.0	52.6	50.0
9	10	Convalescent chest wound.....	40.0	44.6	54.2	42.3
10	4	Convalescent scalp wound.....	37.1	46.3	55.5	46.3
11	4	Mental deficiency..	38.0	62.5	47.2	46.3
12	4	Convalescent ileo-colitis.....	19.0	44.4	52.6	47.6

1 hour after the urea had been given 9 of the curves were continuing to ascend. The most marked increase from the previous specimen was 14mg. while the smallest was 2.6mg and the highest value attained was 74.5mg%. Three curves (cases 2, 5 and 11) had by this time begun to return towards the fasting level. Two hours after the urea had been taken all the curves were on the downward trend, 3 had fallen to within 2 or 3 mg. of the fasting level, 6 had fallen to within 20mg. of the fasting level, and the remaining 3 were still more than 20mg. above it. It is interesting to note that in both the oldest and the youngest of the group the apex of the curve had been reached within half an hour of the administration of the urea. This would suggest that the size of the dose in relationship to the age of the child is of no practical importance. Taking these 12 cases into consideration it appears that the normal curve may be described as follows - a curve reaching its maximum point within 2 hours of the ingestion of 15g. urea.

SECTION 4.

The non-protein nitrogen curve following the ingestion of 15g. urea in cases where disease of the liver is known or suspected to exist.

Considering that the liver is the main manufacturer of urea in the body it is reasonable to expect that in pathological or functional conditions affecting this organ, disturbance of the metabolism of urea might occur. With a view to demonstrating the effect of the ingestion of urea on the non-protein nitrogen curve in cases where disease of the liver was known or suspected to exist the following investigation has been undertaken.

This series consisted of 19 children whose ages ranged from 6 weeks to 10 years. Two of them had the test repeated on a second occasion. While all of them showed some degree of liver disturbance the conditions were varied. Eight suffered from simple catarrhal jaundice while in 3 of the children the condition was diagnosed as Banti's Disease. There was one case of each of the following diseases - cholecystitis, biliary cirrhosis, amyloid disease, icterus gravis, and a malignant tumour of lung with hepatic involvement. The remaining three patients in this group presented no subjective symptoms but on routine examination enlargement of the liver was found. Summaries of the case histories are given in protocols. Appendix, Section A. The same procedure as before was carried out. The results are shown in Table 10. The fasting non-protein nitrogen was found to lie between 26.7 and 66.6mg% with an average of 40mg%. 30 minutes after the ingestion of the urea all the curves, with the exception of one

TABLE NO.10

NON-PROTEIN NITROGEN CURVES in HEPATIC DISEASE FOLLOWING THE INGESTION of 15g UREA. and UREA CONCENTRATION TESTS

No. of Case	Age in Years	Diagnosis	% N.P.N. in blood in mgms.							% urea in urine in gms.		
			Fasting level	Hours after ingestion of urea						Fasting level	1 Hr.	2 Hrs.
				½ Hr.	1 Hr.	2 Hrs	3 Hrs	4 Hrs	5 Hrs			
1	3½	Catarrhal Jaundice	30.0	36.2	39.3	79.1	-	-	-	-	-	-
2	8	"	47.6	47.6	51.0	57.4	66.6	-	-	1.82	2.00	2.18
2	8	"	42.7	52.6	67.5	67.5	70.0	62.5	52.6	-	-	-
3	5	"	49.0	-	67.5	-	72.5	-	-	2.18	4.02	3.99
4	8	"	35.0	50.7	58.9	68.5	55.0	-	-	2.74	3.93	3.33
4	8	"	34.2	52.6	65.8	77.0	-	-	-	-	-	-
5	5	"	40.0	51.9	50.1	69.4	74.0	-	-	-	-	-
6	1 4/12	"	52.6	54.3	59.5	69.4	-	-	-	-	-	-
7	2½	"	45.4	55.5	66.6	80.0	-	-	-	-	-	-
8	6	"	-	30.8	42.3	62.5	-	-	-	-	-	-
9	4	Chole-cystitis.	26.7	50.0	52.5	71.4	-	-	-	-	-	-
10	1 1/12	Biliary Cirrhosis.	34.0	44.6	44.0	52.6	44.0	34.7	29.4	2.82	2.37	2.68

TABLE NO.10 (Contd)

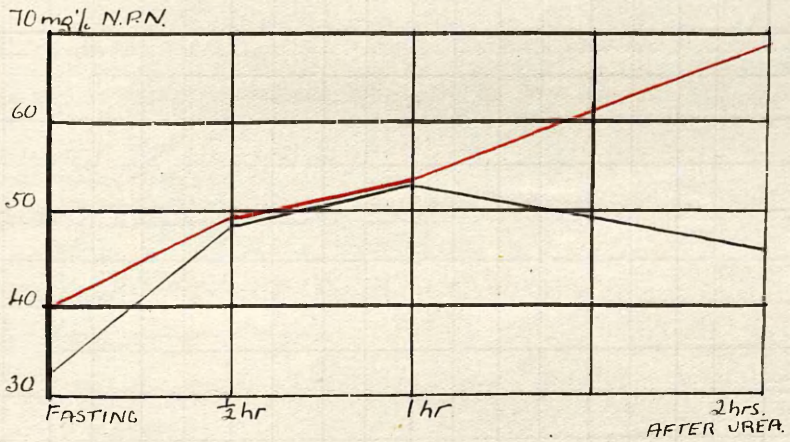
NON-PROTEIN NITROGEN CURVES in HEPATIC DISEASE FOLLOWING THE INGESTION of 15g. UREA. and UREA CONCENTRATION TESTS

No. of Case	Age in Years	Diagnosis	% N.P.N. in blood in mgms.							% urea in urine in gms.		
			Fasting level	Hours after ingestion of urea						Fasting level	1 Hr.	2 Hrs.
				½ Hr.	1 Hr.	2 Hrs	3 Hrs	4 Hrs	5 Hrs			
11	2½	Neoplasm	66.6	82.0	83.3	96.1	-	-	-	1.88	2.43	1.46
12	9	Hepatic enlargement.	47.1	56.8	56.0	74.6	74.0	55.5	-	-	-	-
13	3	" "	34.2	-	60.0	91.0	-	-	-	1.86	2.73	3.14
14	8	" "	-	37.2	45.4	60.0	65.2	-	-	1.23	2.05	2.96
15	6	Amyloid Disease.	47.8	58.1	90.5	91.0	86.2	-	-	1.35	1.91	2.05
16	8	Bantis Disease.	45.4	50.0	50.4	76.0	-	-	-	-	-	-
17	10	" "	35.2	44.6	-	52.6	50.0	52.3	40.0	3.69	3.79	3.56
18	9	" "	48.5	49.5	52.6	70.1	-	-	-	-	-	-
19	6/52	Icterus Gravis.	49.5	74.6	92.6	136.2	108.7	-	-	-	-	-

FIGURE No.2.

COMPOSITE CURVE

THE EFFECT of the INGESTION of UREA on the N.P.N. of the BLOOD in HEALTH and in HEPATIC DISEASE.



NORMAL CURVE.

CURVE IN HEPATIC DISEASE

which remained stationary, were tending upwards. The rise at this stage was very much less marked than that which occurred in the normal cases at the same stage, the average rise in this group being 8mg. as compared with 16mg. in the normal cases. One hour after the urea had been taken most of the values remained at more or less the same levels as in the previous specimens. In only five cases was there a rise of more than 10mg. Two hours after the administration of the urea all the curves were continuing to ascend, the greatest increase from the previous specimen was found in Case 19 where there was a rise of 44mg. during the hour, the value reached being 136.2mg%. Six other curves showed an increase of 20mg or more, while the remainder were mounting to a lesser degree.

Three hours after the urea had been given 4 curves were continuing their ascent. After the elapse of 4 hours from the ingestion of the urea all the curves estimated were beginning to descend, while those in which the test was carried on for a further hour showed that the return towards the fasting level was continuing.

From a study of these results it is readily observed that the non-protein nitrogen curves obtained following the administration of urea in hepatic disease differ in 3 main points from the curves found in normal individuals. These are -

1. The higher average fasting non-protein nitrogen. 2. The slow rise and 3. the height and prolongation of the curve. On account of the high average fasting non-protein nitrogen it might be suggested that some disorder of the kidneys was responsible for the abnormal curves. In order to eliminate this possibility urea concentration tests were carried out on 9 of the patients. The results which are shown in Table 10 were satisfactory in all the cases. The lowest fasting value was 1.35g% and the lowest level reached after the ingestion of the urea was 2g% while the majority were considerably higher. In Case 3 where the fasting non-protein nitrogen was 49mg%. the urinary urea rose from 2.18g. to 4.02g.% after the urea had been given. From this example it would appear that inefficiency in excreting urea is not a factor in the causation of the high fasting non-protein nitrogen or of the abnormal curve. Some other explanation must therefore be looked for.

The view is generally held that urea, which is manufactured chiefly by the liver is a waste substance, which is removed from the general circulation by the kidneys and excreted in the urine as rapidly as possible. It has been thought that the liver acts merely as a filter for ingested urea. If that then is the actual process involved one would expect to find a normal curve after the ingestion of urea in all cases where the kidneys were acting physiologically. In none of these cases of

hepatic disease with abnormal curves, however, could any renal lesion be recognised either clinically or biochemically.

As will be shown later in some cases where the kidney substance is acutely involved and where by means of a urea concentration test the renal function is shown to be markedly impaired the non-protein nitrogen curve after the ingestion of urea is normal. From these results one is forced to turn for an explanation away from the kidneys to the liver.

To G.D. Cathcart[26] we are indebted for much of our knowledge regarding the part played by the liver in the metabolism of urea. Using anaesthetised dogs she exposed the jugular vein and then removed one hind leg and two or three lobes of the liver. This having been done a cannula was inserted into the jugular vein and fluid containing various amino-acids or urea was slowly introduced from a burette. The animal was killed by bleeding some ten minutes after cessation of the injection and then the other hind leg was amputated and the remainder of the liver was removed. The muscles and the liver in the fresh and dried states were then examined. One of the most interesting findings was the effect of the urea on the amide-nitrogen. The results were as follows -

	Liver	Muscle
Before urea.....	50.7mg%	45.8mg%
After urea.....	126.6 "	96. "
% increase.....	149. "	106. "

The increase in ammonia was also of interest as showing that the urea had undergone deaminisation:-

	Liver		Muscle	
	1st dog	2nd dog	1st dog	2nd dog
Before urea... After urea....	9 mg% 11.6mg%	8.6mg% 9.4mg%	11.9mg% 12.6mg%	12.4mg% 12.7mg%
% Increase....	13 mg%	9 mg%	6 mg%	2 mg%

The non-protein nitrogen values also showed an increase -

	Liver		Muscle	
	1st dog	2nd dog	1st dog	2nd dog
Before urea... After urea....	33.4mg% 38.7mg%	29.1mg% 31.7mg%	41.0mg% 47.0mg%	39.3mg% 43.9mg%
% Increase....	16 mg%	10 mg%	14 mg%	11 mg%

From these results she concluded that the injection of urea causes an accumulation of that substance unchanged in the liver and to a lesser extent in the muscles. She decided that there was no evidence of its synthesis into protein but there was abundant proof or its further metabolism particularly in the liver where it is deaminised. In a much lesser proportion the

muscles apparently also take part in the deaminising process.

In view of the results of this investigation the problem of finding an explanation of the normal and abnormal non-protein nitrogen curves appears less formidable. It would appear that here we are dealing with curves somewhat analogous to the ordinary blood sugar curves of the normal and abnormal type. It is known that in normal people the sugar content of the blood rises within half an hour of the ingestion of glucose and that within an hour the curve has reached its peak. By the end of two hours the value has more or less regained the fasting level. In the case of the diabetic, on the other hand, at the end of 2 hours we expect to see the curve if not actually continuing to ascend at least still remaining well above its original value. As we can understand the process in the normal subject we believe that the glucose is rapidly absorbed from the alimentary tract and carried in the blood stream to the liver where part of it, at least, is converted into glycogen and stored. As soon as the glycogen forming capacity of the liver comes into action, the blood sugar quickly falls (in spite of the fact that glucose is still being absorbed from the intestinal tract) and regains its fasting level within two hours. In the case of the diabetic however this glycogenic function of the liver is in abeyance and thus the sugar content of the blood continues to increase until absorption is complete. It is not, of course, permissible to stress the

SECTION 5.

The non-protein nitrogen curve following the ingestion of urea in children suffering from disease of the muscular system.

similarity of the blood sugar and non-protein nitrogen curves too far as in the former we are dealing with a threshold substance and with the latter we are not. In spite of this proviso it seems to me reasonable in the light of G.D. Cathcart's work to suppose that in the non-protein nitrogen curve we are dealing with a mechanism somewhat on the same lines - that is to say that in the liver we have some process or other whereby any excess of urea is removed from the blood and stored either unchanged or in some altered form. The normal non-protein nitrogen curve could then be explained as follows:- after ingestion and absorption from the gastro-intestinal tract the urea is carried to the liver by the portal vein. As the concentration of non-protein nitrogen in the blood increases the liver storage mechanism comes into action and the non-protein nitrogen value gradually descends towards the fasting level, although urea is still being absorbed from the alimentary tract.

In cases of hepatic inefficiency, on the other hand, this function is in abeyance and the non-protein nitrogen curve continues to rise until absorption from the gut is complete. The most plausible explanation of the high fasting non-protein nitrogen in the cases of hepatic inefficiency appears to be that the liver is unable to retain the end-products of endogenous nitrogen metabolism which thus accumulate in the blood.

The delayed rise in the curve may be the result of some

defect in absorption from the bowel, possibly due to absence of or alteration in, the constitution of the bile.

SECTION 5.

The non-protein nitrogen curve following the ingestion of urea in children suffering from disease of the muscular system.

Returning again to a study of G.D. Cathcart's[26] work it is noteworthy to observe that she found that following absorption urea was stored partly in the liver and partly in the muscles. As was shown in the previous section this power of storage by the liver is apparently lost or diminished in cases where there is impairment of hepatic function. From this finding it would not be unreasonable to expect a similar state of affairs in cases where there is disease of the muscular system. Accordingly, it was decided to determine in such conditions the non-protein nitrogen curve after the ingestion of urea. Unfortunately, owing to the comparative rarity of genuine affections of the muscular system only 5 suitable patients were found in the course of the two years during which the investigation lasted. On two of the children the test was repeated on a second occasion. Case 3 gave a rather ambiguous result and a second curve was about to be done when the child became a chicken-pox contact and had to be dismissed. Four of the patients in this group were boys and one was a girl while their ages ranged from 7 to 12 years. The first four were typical cases of pseudo-hypertrophic paralysis. The fifth, while undoubtedly a marked case of muscular dystrophy, did not fall into any of the well-recognised groups of diseases of the muscular system. Summaries of the case-histories are given in protocols. Appendix, Section B. The procedure was similar to that carried out in the previous groups. The fasting

levels of the non-protein nitrogen of the blood lay between 26.2 and 43.4mg% as shown in Table 11. All the curves (with the exception of Case 1 which remained practically stationary) had begun to ascend within 30 minutes of the ingestion of the urea. The greatest increase was 22mg (Case 3) while 61mg% was the maximum concentration reached. One hour after the urea had been taken all the curves were definitely mounting. 16mg was the greatest increase in value over the previous estimations and occurred in Case 5 (1st curve). 65.8mg% was the maximum concentration attained and was found in the repeat curve of Case 5. Two hours after the urea had been taken none of the curves showed the marked fall in non-protein nitrogen value which was found in the group of healthy children already described. Case 4 had risen from 50.1 to 96.1mg%. In three cases the rise while quite definite was not so marked and in the remaining 3 no change in value had taken place since the previous specimens of blood had been withdrawn. Five estimations were carried out 3 hours after the urea had been administered. Two of the curves had begun to return towards the fasting level, and one remained stationary. Of the two which were continuing to ascend one showed a gain of 8mg and the other had risen 50mg. In only one case was the test continued for a further hour. The estimation showed that there was definite evidence of return towards the fasting level.

Urea concentration tests were carried out on 3 of the

TABLE XI.

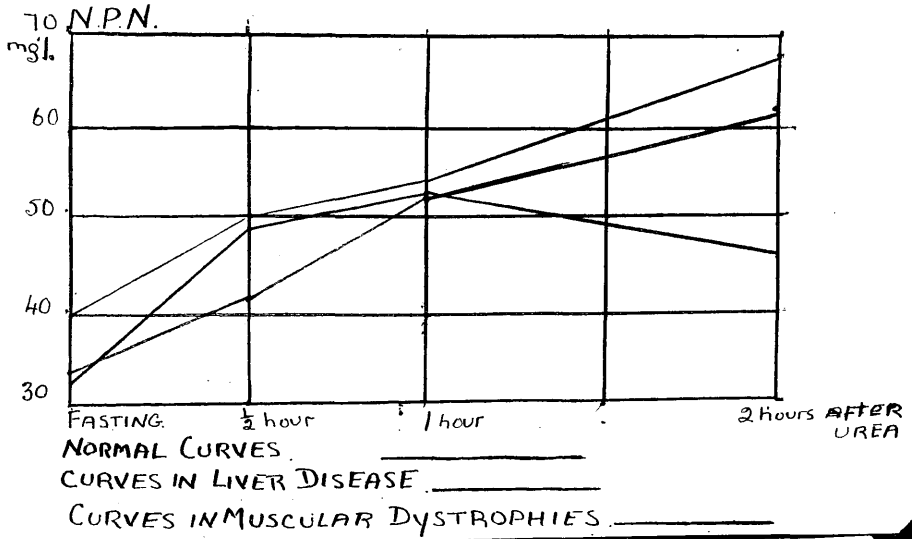
N.P.N. CURVES in DISEASES of the MUSCLES following the INGESTION of 15 g. UREA.

with UREA CONCENTRATION TESTS

No. of Case	Age in Years	Fasting Level	% N.P.N. in the Blood. in mgms. Hours after ingestion of Urea.						% Urinary Urea in gms		
			½ hour	1 hour	2 hours	3 hours	4 hours	5 hours	Fasting Level	Hours after ingestion of urea 1 hour	2 hours
1.	8	39.0	37.6	43.8	46.1	54.3	-	-	-	-	-
2.	10	26.2	30.0	34.6	48.1	-	-	-	2.81	2.73	3.15
2.	10	29.4	32.5	45.4	62.5	51.5	38.3		-	-	-
3.	12	28.4	50.0	62.5	62.3	55.5	-		1.23	2.33	3.25
4.	11	32.0	40.6	50.1	96.1	94.3	-		-	-	-
5.	7	33.4	37.2	63.3	63.0	-	-		2.35	3.22	3.57
5.	7	43.4	61.0	65.8	64.1	115.2	-		-	-	-

FIGURE No.3.

COMPOSITE CURVE SHOWING the EFFECT of the INGESTION of UREA in NORMAL CHILDREN and those SUFFERING from DISEASES of the MUSCULAR SYSTEM.



children, and the results showed that in each case the kidneys were capable of concentrating urea in a satisfactory manner.

Discussion.

It will be remembered that the curves found in normal children and in those who are the subjects of liver disease differed on three main points, namely, -

1st, high fasting non-protein nitrogen of the blood.
2nd, slow rise of the curve.
3rd, height and prolongation of the curve.

Applying those same headings to the children belonging to this section it will be observed that the fasting level of non-protein nitrogen agrees with that found in the normal group (Figure No.3). On the other hand the curve does not ascend as rapidly as in the control section.

Commencing, as has been noted, with an almost identical average fasting level, namely 32 and 33mg% respectively, the curve in the myopathies only reaches 41mg% within half an hour of the ingestion of the urea, whereas in the healthy children 49mg% is attained. 30 minutes later, however, the levels in the two groups are equal. Thereafter the normal group begins to descend while in the case of the abnormal the ascent is continued. A comparison of the composite curves obtained in children suffering from hepatic inefficiency and in those the subjects of muscular dystrophy shows a striking resemblance. The actual increase in value however which occurs in the interval between the hourly and

two hourly specimens is not so marked in the section of muscular diseases. Four of the cases - namely, Nos.1, 3, 5, and 5_2 are practically stationary during that time, but two of these (Nos. 1 and 5_2) rise briskly in the following specimens which were examined three hours after the ingestion of the urea. Those results correspond quite satisfactorily with those of G.D. Cathcart who found that in normal animals the increase of amide nitrogen following on the absorption of urea was 149% in the liver but only 106% in the muscle. Her figures for ammonia, also showed an average increase of 22% in the liver substance but only 8% in muscle. The average increase in non-protein nitrogen value was 26% and 24% respectively. As the muscles therefore in health do not store as much nitrogen as the liver it is natural that disease of the muscles does not produce as marked an abnormality of the non-protein nitrogen curve following the ingestion of urea as does hepatic inefficiency.

From these results it would appear that one is entitled to state that in cases of disease of the muscular system there is definite abnormality in the metabolism of urea and that possibly this defect takes the form of inability on the part of the muscles to provide storage for the urea.

SECTION 6.

The blood non-protein nitrogen curve following the ingestion of urea in children suffering from the various manifestations of rheumatism.

In view of the fact that Chadwick[40] and Brown[41] (to whose work reference will be made later) found hepatic inefficiency, as demonstrated by the laevulose tolerance test, in certain cases of rheumatism in children it was decided to investigate a series of these children making use of the non-protein nitrogen curve following the ingestion of urea. It was further determined to carry out a laevulose tolerance test the following day in a proportion of the patients. This was done with the object of finding out if the nitrogen metabolism was upset in rheumatism and if so whether or not this defect ran parallel with a disturbance of carbohydrate metabolism.

The Laevulose Tolerance Test.

The earliest work on the subject of laevulose tolerance appears to be that of Strauss[42] in 1901. He found that in 10% of apparently normal individuals laevulosuria followed a dose of laevulose. If, however, it was administered to patients known to be suffering from some liver disorder the percentage showing laevulose in the urine rose to 90. On these findings he based a test for liver function. His work was later refuted by various investigators including Worner & Reiss[43] and Churchmann[44]. Spence & Brett[45] in particular mentioned that as the renal threshold for laevulose in normal people varied within such wide limits the presence or absence of laevulosuria could not be

regarded as giving any reliable information as to the condition of liver function. According to those workers the renal threshold lay between 115-130 mg%.

Shirokauer[46] in 1912 was the first to try the effect of laevulose on the blood sugar curve. The laevulose test as now in use was first worked out in this country by McLean & de Wesselow[47] in 1919 and later by Spence and Brett[45] and many other investigators. The test depends on the fact brought out by McLean & de Wesselow[47] that laevulose taken by mouth in doses of 30-50g. does not cause any appreciable rise in the blood sugar curve of ordinary individuals, whereas a considerable and more or less constant rise occurs in those who are affected with any disorder of the liver. Working through a series of the various sugars McLean & de Wesselow found that laevulose was the only one which exhibited this phenomenon. The reason of this finding is rather obscure. According to Winter & Smith[48] glucose and laevulose are not found in the blood as such. They were of the opinion that sugar normally circulates in the blood in the form of what they termed Y glucose. They believed that it was their change into this new compound which prevented them being detected in their original form. It is generally acknowledged that after absorption from the alimentary tract laevulose is carried by the portal vein direct to the liver where it is con-

verted first into glucose, then into glycogen and eventually stored. In this way, provided the liver mechanism is intact, it does not enter the general circulation in sufficient quantities to cause any appreciable rise in the blood sugar value. It has also been stated that the reason attached to the more or less flat blood sugar curve which it normally produces is due to very rapid absorption and assimilation. Tallermann[49] in 1923 suggested that it was the slowness of those two functions following the ingestion of glucose which allowed it to circulate freely in the blood stream and thus caused the characteristic curve.

Folin and Berglund[50] in their work took up a rather different attitude. They attributed the very small rise in the blood sugar value after laevulose to the fact that while the tissues are saturated with glucose they are practically free of laevulose and therefore absorb it readily. They could not agree with some writers that the flat curve is the result of a rapid formation of glycogen. This is directly against the views of Joliffe[51] who argued that the flat curve was easily accounted for by the rapidity with which laevulose was oxidised and converted into glycogen.

Cathcart & Markowitz[52] have found that laevulose must be converted into glucose before it is possible for it to be absorbed by the tissues.

Great differences of opinion exist among the various

authorities as to the type of curve which is to be regarded as normal and the various points of difference which may render it abnormal. Some, such as Joliffe[51] for example, take a definite value and if at any point the blood sugar curve following the administration of laevulose, reaches or excedes that figure they consider that they have definite evidence of liver damage. Joliffe has mentioned 125mg% as the uppermost level of normality. Others put most emphasis on the duration of any hyperglycaemia by taking as definitely abnormal any curve which has not returned to its fasting level within 1½ or 2 hours. Others do not accept as pathological any curve which has not reached a definite percentage above the initial figure. Just what the minimum percentage rise which is indicative of liver damage actually is still a matter of controversy. Elmer & Scheps[53] regard a rise of more than 20% as abnormal, and look upon minor variations as being due to faulty absorption or impure laevulose. Hurst[54] addressing a meeting of the London Medical Society in the autumn of 1931 agreed with these findings. He thought that a failure to return to the fasting level within two hours was pathological. Tallermann[49] in 1923 stated that any reading which after the administration of laevulose exceeded 135mg% or any curve which rose more than 30mg from the fasting value, gave presumptive evidence of hepatic derangement. In his opinion a high blood sugar value at the end of one and a half hours was strongly in favour of liver inefficiency. His theory that the

actual height of the curve was largely dependent on the fasting level was later confirmed by Joliffe[51] they believed that if the initial value was low the rise would be great, but that if the fasting level were high the increase would not be so marked. Spence & Brett[45] believed that the height and duration of the curve obtained gave an estimate of the amount of liver damage. This claim however was not sustained by the work of Brown[55].

Chadwick[40] by means of the laevulose tolerance test appears to have been the first worker to demonstrate disordered function of the liver in certain cases of rheumatic infection in children. He found that those suffering from simple chorea without carditis showed no hepatic inefficiency. On the other hand, he was able to show that patients who had chorea with cardiac involvement did suffer from a degree of liver disturbance. Similar results were found where the rheumatic infection took the form of an active arthritis with or without carditis. He was able to show that this defect disappeared as clinical improvement took place. He was unable to correlate his results with any particular valvular lesion but he was of the opinion that the deciding factor was the tone of the heart muscle rather than the competence or incompetence of the valves. He believed that the liver disturbance was caused by the absorption of toxins from some focus of infection. He did not think that the origin

of the sepsis could be successfully traced to either the tonsils or the alimentary tract.

The following year Brown[41] published a paper on the same subject. She also found hepatic inefficiency in certain rheumatic and choreic children but her results led her to the conclusion that the laevulose tolerance test gave no consistent evidence of derangement of the liver in cases of rheumatic infection. Her only exception being that cases of convalescent chorea with or without carditis invariably gave normal blood sugar curves following the ingestion of laevulose. She believed that the solution of the problem lay in a pathological condition of the myocardium causing passive congestion of the liver which was naturally followed by impaired function. She judged it possible that in chorea there might be present overstimulation of the sympathetic nervous system with a consequent disturbance of carbohydrate metabolism.

Personal results.

The non-protein nitrogen curve after the ingestion of urea was carried out on 19 children who were the subjects of rheumatism. The procedure was the same as in the various other groups with the exception of the fact that 13 of the children were being given sodium salicylate and 3 were having nirvanol administered. The case-histories are given in protocols, Appendix, Section C. The results are shown in Tables 12 and 13. The ages

of the patients ranged from 4 to 12 years. On 7 of the children laevulose curves were carried out the following day, and the results are shown in Table 14. Of the 19 children tested 9 gave a perfectly normal curve while the remaining 10 gave results which were distinctly abnormal.

The normal curves.

This group contained 9 children. Two of them (Nos.5 and 9) had the test repeated on a second occasion with similar results to the first examination. The ages ranged from 7 to 12 years. 7 were cases of chorea, 1 suffered from acute arthritis and 1 from a transient attack of pericarditis. Of these 9 children 4 suffered from definite mitral lesions although none of them showed the slightest tendency to loss of compensation. There were no cases of aortic disease. The fasting non-protein nitrogen values lay between 29-47 mgrm% with an average of 37mg%. Within 30 minutes of the ingestion of the urea all the curves showed a definite rise. The smallest increase in value was 5mgrm and the largest was 23mg. The highest value attained was 60.2mg%. In the next specimens, which were withdrawn one hour after the urea had been taken, 8 of the curves were continuing their ascent but the remaining 3 (Nos.4, 5 and 6) had already begun to return towards the fasting level. The most marked increase in value from the previous sample of blood was 20mg while the highest non-protein nitrogen concentration reached was 63.4mg%.

TABLE XII.

NORMAL N.P.N. CURVES & UREA CONCENTRATION TESTS in RHEUMATISM after the INGESTION of 15g. UREA.

No. of Case	Age in Years	Diagnosis	% N.P.N. in the Blood in mgs				% Urea in urine in gms.		
			Fasting level	Hours after the ingestion of the Urea ½ hour	1 hour	2 hours	Fasting level.	1 hour	2 hours
1.	12	Chorea.	28.9	39.6	51.5	37.0	.94	1.6	2.83
2.	12	Do.	31.4	40.0	58.2	50.1	1.65	2.10	2.92
3.	9	Do.	30.7	40.6	53.2	49.0			
4.	9	Do.	47.6	60.2	58.8	46.3	1.26	2.28	3.12
5.	7(1)	Chorea and Valvular disease of the heart.	34.9	41.2	34.3	23.1	1.53	1.68	2.65
	(2)		38.5	43.5	63.4	42.3			
6.	11	Do. do.	42.2	57.6	49.6	49.4	.85	2.03	2.03
7.	8	Do. do.	38.5	43.5	63.4	42.3			
8.	7	Pericarditis	34.2	56.8	58.1	49.5			
9.	12(1)	Arthritis & Valvular disease of the heart.	35.7	47.6	53.2	51.0			
	(2)		40.3	45.4	48.0	44.2			

TABLE XIII.

ABNORMAL N.P.N. CURVES in RHEUMATISM following the INGESTION of 15g. UREA with UREA CONCENTRATION TEST.

No. of Case	Age in Years	Diagnosis	% N.P.N. in the Blood.in mgs.							% Urea in Urine in gms.		
			Fasting level	Hours after ingestion of Urea						Fasting level	Hours after Urea	
				½ hr	1 hr	2 hrs	3 hrs	4 hrs	5 hrs		1 hr	2 hrs
10.	5	Chorea. V.D.H.	30.5	34.4	37.8	72.4	80.6	66.6	56.6	-	-	-
11.	7	Chorea. Valvular disease of the heart.	25.0	30.7	40.7	43.9	75.4	68.5	53.8	-	-	-
12.	10	Do. do.	49.0	42.3	47.2	48.4	55.5	55.5	58.1	-	-	-
13.	5	Do. do.	31.2	46.5	53.8	68.5	-	-	-	-	-	-
14.	7	Do. do.	50.0	56.2	62.3	61.5	76.2	-	-	1.39	1.98	2.04
15.	10	Do. do.	34.1	-	46.0	58.2	40.3	-	-	3.19	2.50	3.89
16.	10	Do. do.	38.2	37.4	38.3	62.5	-	-	-	-	-	-
17.	4	Scarlatinal Arthritis.	40.8	47.1	60.9	66.4	-	-	-	1.07	2.80	3.63
18.	9	Arthritis.Valvular disease of the heart.	25.5	42.3	-	65.1	-	-	-	1.32	1.92	2.88
19.	11	Do. do.	40.2	43.8	46.7	57.5	-	-	-	-	-	-

TABLE XIV.

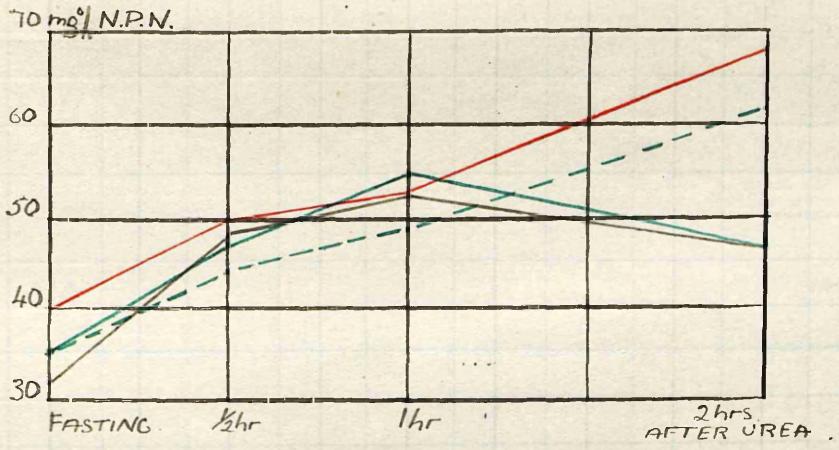
BLOOD SUGAR CURVES in CASES of RHEUMATISM after the INGESTION of LAEVULOSE

No. of Case.	Age in Years	% Sugar in the Blood in mgms.					% increase in value.
		Fasting level	Hours after ingestion of laevulose				
			½ hour	1 hour	1½ hours	2 hours	
3.	9	108.1	129.0	129.2	121.4	120.2	20
9.	12	78.1	84.0	95.2	87.4	81.3	21.
10.	5	61.2	59.3	57.4	64.0	61.3	5
11.	7	57.5	74.6	88.5	56.7	56.7	55.
12.	10	60.2	62.5	80.0	60.2	73.1	33
14.	7(1)	100.2	125.4	87.6	84.6	71.4	25.
	(2)	88.2	93.4	84.0	92.1	93.3	5
15.	10	103.0	131.2	115.3	112.6	116.4	27

FIGURE No.4.

COMPOSITE CURVE

A COMPARISON of the EFFECT of the INGESTION of UREA in HEALTH, in HEPATIC DISEASE and in RHEUMATISM.



NORMAL CURVES. ———————

NORMAL CURVES IN RHEUMATISM. ———————

ABNORMAL CURVES IN RHEUMATISM. - - - - - - -

CURVES IN HEPATIC DISEASE. ———————

After the lapse of two hours from the ingestion of the urea all the curves were on the downward trend. 4 of the values had returned to within 3 or 4 mg of the fasting level. Case 5 began with a fasting value of 34.9mg% and 2 hours after the ingestion of the urea the level was 23mg%. This reminds one of the hypoglycaemia so frequently found in the blood sugar curve after the administration of glucose. Urea concentration tests were carried out on 5 of these cases, and in each the result showed that as far as the concentration of urea was concerned the kidneys were functioning satisfactorily. It will be seen therefore from a comparison of the composite curve obtained in the control children of group 1 and the composite curve obtained in the present series how closely they resemble one another (Figure 4). It is surely permissible therefore to state that the children in the group presently under consideration did not give any indication of hepatic inefficiency. Only two laevulose tolerance tests were carried out on these children but they too failed to demonstrate any loss of function on the part of the liver.

The abnormal curves.

This group was composed of 10 children whose ages ranged from 4 to 11 years. 7 were cases of chorea and the remaining 3 suffered from arthritis. All of them with the exception of two had definite mitral disease, but none of them showed

the slightest tendency to decompensation. Aortic disease was not diagnosed in any of this series.

The fasting non-protein nitrogen ranged from 25 to 50 mg% with an average of 37mg%. Half an hour after the urea had been given all the curves with the exception of two had begun to ascend. The smallest rise was 3mg and the largest 16 mg while the greatest height attained at this stage of the test was 56mg%. Case 16 showed a loss of 1mg and case 12 a loss of 7mg. 30 minutes later, that is 1 hour after the urea had been taken all the curves were steadily mounting. The least increase over the previous specimen was 1mg, the greatest was 16mg, and the highest non-protein nitrogen concentration reached was 62mg. After an interval of two hours from the ingestion of the urea all the curves were rising steadily. The maximum non-protein nitrogen value attained was 72mg%, the minimum was 44 mg% and the average was 61mg%. In the 5 children who had the test carried on until an interval of 3 hours after the administration of the urea had elapsed 4 of the curves showed a further increase in value but one was definitely falling (Case No.15). Of the 3 cases examined 4 and 5 hours respectively after the urea had been t aken two were returning towards the fasting level. The remaining curve, case No.12 was, however, still showing a slight but quite definite tendency to ascend. This curve displayed peculiar features from the beginning. As was already observed there was a fall in value of 7mg. during

the first half hour after the urea had been taken and this was followed by a very slow but quite distinct rise which was even continuing when the last sample of blood was with-drawn. This result would suggest that apparently the absorption had been greatly delayed.

4 of the children in this section had the urea concentration test carried out at the same time. In each case the urinary output of urea was thoroughly satisfactory and it showed that the kidneys were functioning well.

5 of the cases had a laevulose tolerance test performed the following day. Table No.14. Two of the curves obtained were distinctly abnormal showing an increase of blood sugar value after the administration of the laevulose, amounting to 55% and 33% respectively. (Cases 11 and 12). Two other curves (Nos.14 & 15) rose 25% and 27%. The former had a repeat test done one week later when the increase in value was negligible. The remaining case showed practically no change after the ingestion of the laevulose.

Discussion

It will be seen that the curve obtained in cases 1-9 is, apart from the slightly higher fasting level, almost similar to the curve which was found in the group of control children. Where as the curve found in cases 10-19 differs in no essential particular form the curve which occurs in hepatic inefficiency.

One might therefore with a fair measure of confidence state that in a proportion of cases of rheumatic disease there is a degree of liver disturbance present.

The problem then arose for solution as to whether or not it would be possible to correlate liver disturbance with any particular clinical findings. The following points presented themselves for discussion.

1. The ages of the children in the normal section lay between 7 and 12 years, with an average of 9.4 years, while in the abnormal group the ages ranged from 4 to 11 years with an average of 7.4 years. This difference is obviously too slight to be of any significance.

2. As regards the sex of the children it was found that in the normal section there were 6 girls and 3 boys, while the abnormal group contained 7 girls and 3 boys. It is, therefore, evident that the question of sex does not enter into the discussion.

3. On considering the previous history of the children (excluding any of the manifestations of rheumatism) no facts of importance came to light. In the normal section case 4 had a history of cervical adinitis of 4 years duration and case 7 had had an appendicectomy performed three months prior to the present admission. While in the abnormal group Case 13 had suffered from a cervical adinitis for 6 weeks before being admitted to Hospital.

A consideration of the previous rheumatic history showed

that only 2 children in the normal group and none at all in the abnormal group gave a history of sore throats. Two of the abnormal and 1 of the normal series had suffered from scarlet fever. As regards a history of growing pains or previous arthritis it was found that only 1 child in the normal section had once had vague pains in the limbs. Things were discovered to be very different however in the abnormal section. It was found that, leaving out of consideration the 3 cases of acute arthritis, 4 others had had rheumatic pains at some time or another.

Case 16 had suffered from joint pains 3 months prior to admission. Six weeks before coming to Hospital case 13 had been confined to bed for 10 days with pains in the arms and legs. Case 14 had had acute rheumatism 9 months before the present attack of chorea. Case 15 had had pains in the legs a couple of months before his present illness.

4. Coming to the length of time since the first manifestation of rheumatism it was found that no information of interest could be elicited. Case 3 with a rheumatic history of 3 years duration had a normal curve similar to that obtained in Case 9 where the test was carried out within a week of the onset of the first symptom of rheumatism. Considering the abnormal group Case 10 had a rheumatic history of less than 5 weeks duration while in Case 12, the history dated back fully five years. Of the 9 cases in the normal group 7 gave a total rheumatic history of less than

three months, while one had had attacks of chorea at varying intervals for 3 years and 1 had had an attack of chorea one year before the present admission. In the abnormal group also 7 had shown no definite tendency to rheumatism until about three months ago. 1 had had an attack of chorea with cardiac involvement 5 years previously and 1 had had recurrent attacks of chorea for 3 years.

5. The form in which the rheumatic infection showed itself was next investigated. In the normal group 1 case of acute arthritis occurred. This child (No.9) gave a similar curve when the test was repeated about 2 weeks later. This group also contained one case of pericarditis (8). Definite friction was present, but there was no evidence of any effusion into the pericardial sac. On examination 3 months later no abnormality of the heart was found. The remaining 7 children of this series were cases of chorea. In the abnormal group 3 cases of arthritis occurred while here again there were 7 cases of chorea. No conclusions could thus be drawn from these facts.

6. It was then thought that perhaps the stage of the disease at which the test was carried out might influence the curve. It seemed possible that hepatic inefficiency might be most marked during the acute phase of the disease and that it might diminish and ultimately disappear as convalescence progressed. Case 9 was examined during the height of an attack of acute arthritis and

again a couple of weeks later when all obvious signs of rheumatism had disappeared. A normal curve was obtained on both occasions. Case 19 gave an abnormal curve during an acute arthritis. Case 17 gave an abnormal curve 5 months after the onset of an acute scarlatinal arthritis.

Case 7 an active chorea gave a normal curve similar to that obtained in case 2 where all twitchings had ceased. Thus it will be seen that the stage of the disease does not appear to influence the curve.

7. In the presence or absence of carditis it was confidently anticipated that the answer to the problem might be found but such was not found to be the case. In 5 out of the 9 cases exhibiting normal curves no organic cardiac involvement was diagnosed while 2 showed minor degrees of mitral incompetence and in 2 mitral stenosis was developing.

In the abnormal group 8 of the children showed definite mitral incompetence. In the remaining 2 of this series systolic murmurs were heard but they were probably of functional origin. None of the children in this group showed any signs of incipient mitral stenosis. In neither group was aortic disease present nor was there the slightest evidence of any tendency towards decompensation.

8. In two of the children in the normal group nodules were present, but none were found in any of the abnormal cases.

9. That salicylate therapy does not affect the curves was clearly shown. 6 of the children exhibiting a normal urea tolerance, and 7 of those showing an abnormal tolerance had been having sodium salocylate administered. The 3 children who had been taking nirvanol were also found in the normal section.

10. It was considered possible that disturbed carbohydrate metabolism, as shown by an abnormal tolerance to laevulose, might run parallel to an abnormal non-protein nitrogen curve. Accordingly 7 laevulose tolerance tests were carried out. The two tests which were done in the normal group (Nos.3 and 9) gave a normal blood sugar curve after the ingestion of the laevulose. In the abnormal group 3 out of the 5 estimations performed gave a normal result, thus showing that while deranged carbohydrate and protein metabolism may co-exist, they do not necessarily do so.

From a study of these 10 points we are left with only one which would seem to be of any importance in determining the type of non-protein nitrogen curve likely to result after the ingestion of urea - namely, the actual presence or a history of arthritis or growing pains. In only 2 out of the 9 children in the normal group could any such history be obtained whereas in 7 out of the 10 abnormal cases examined definite pains and joint swellings were a feature of the complaint.

As the proportion of children known to suffer from

carditis as the result of chorea is less than the proportion left with damaged hearts after arthritis and growing pains it is not surprising to find a greater number of children with valvular disease of the heart in the abnormal group. That it is not the actual valvular lesion itself which is responsible for the abnormal curve is shown by the fact that case 17 gave an abnormal curve while Case 5 who had a definite mitral stenosis gave a normal result. At the time of examination Case 17 had a systolic murmur all over the praccordium which was probably best heard at the base. A few months later, however, when the heart was again examined it was found that the sounds were of good quality and that there were no murmurs present. These findings would appear to refute Brown's suggestion that diminished hepatic efficiency in rheumatic cases is dependent on passive congestion of the liver secondary to cardiac involvement. The presence or absence of a murmur, of course, gives no indication of the state of the myocardium but it is difficult to believe that in a case such as No.17 the heart muscle could be sufficiently damaged, in the absence of all symptoms, to cause passive congestion of the liver. The explanation proffered by Chadwick that in rheumatism one is dealing with the results of absorption from a septic focus is more attractive. It would appear that in some cases of rheumatism disturbance of carbohydrate and protein metabolism co-exist, while in others the latter only is involved. It may be

that the metabolism of urea is the more delicate mechanism and therefore the more easily put out of action.

SUMMARY

In certain cases of rheumatic infection there is impairment of hepatic efficiency as demonstrated by the non-protein nitrogen curve after the ingestion of urea. It is impossible to correlate the results found in any particular type examined at any particular stage of the illness. It would appear that the liver is less likely to escape damage in cases where the rheumatic infection has manifested itself in the form of arthritis or growing pains. As a natural sequence it follows that liver disturbance does not occur so frequently in the absence of carditis.

SECTION 7.

The effect of the ingestion of urea on the non-protein nitrogen curve in children who were the subjects of renal disease.

Part I.

Nephritis.

Although more than a century has elapsed since Bright[56] published his classical description of nephritis, and in spite of the fact that much careful work has been done and many laborious investigations have been carried out, our knowledge of the chemical pathology is still defective. Attention from a biochemical standpoint at least, has been focussed mainly on the nitrogen metabolism. That the non-protein nitrogen of the blood is raised in certain forms of nephritis is common knowledge but a conclusive statement as to the actual mechanism of this phenomenon has not so far been produced. MacKay & MacKay[3] have shown that in experimental animals half of the kidney substance can be removed without causing any increase in the urea of the blood, It is known that nephritis may be present in quite an advanced stage without showing any marked abnormality in the blood chemistry.

For example, an interstitial nephritis may be well established although the estimation of the non-protein nitrogen gives a figure within physiological limits.

The various constituents of the non-protein nitrogen have been studied separately and in combination and attempts have been made to use the results so obtained in diagnosis and prognosis. Certain authorities have tried to show that in different types of nephritis the ratio of urea to non-protein nitrogen is

constant but their findings have lacked conviction and uniformity. By means of the urea concentration test information is certainly gained as to the capacity which the kidneys possess of concentrating and excreting urea.

It was not until a much later date that investigation into the carbohydrate metabolism in nephritis was commenced.

Carbohydrate Metabolism in Nephritis.

Naubauer(57) in 1910 was the first observer to note an abnormal carbohydrate metabolism in nephritis. He found that in many of his cases of nephritis the fasting blood sugar level was abnormally high and that the curves which resulted from the ingestion of glucose showed a definite hyperglycaemia. These findings were most marked in patients with an increased blood pressure. He attributed both these abnormalities to excessive adrenal activity. In this hypothesis he was supported by Von Noorden(58) but subsequent workers have not accepted it. In 1911 Tachau(59) found four fasting blood sugar values in nephritis ranging from 91 to 104mg%. The values which he obtained in these same cases one hour after the ingestion of 100g. glucose lay between 109 and 216mg%, but in none of these cases was there any glycosuria present.

In 1914 Bing & Jakobsen(60) using Bang's method, confirmed the fact that a hyperglycaemia might be found in nephritis, but they did not support the idea that there was any relationship

between it and the height of the blood pressure.

The following year, Hopkins & Jonas[61] also found an abnormally high curve in nephritis, but while they did not believe that its form was regulated by the height of the blood-pressure, they stated that in their series most of the nephritic patients with a normal blood pressure gave normal curves, following upon the ingestion of glucose. They did not consider that the presence or absence of oedema had any effect on the height or length of the curve. In 8 of their cases with an non-protein nitrogen of over 40mg%, 4 gave a hyperglycaemia. Borchardt & Bennigson[62] had previously demonstrated that an abnormally high blood sugar curve is a frequent accompaniment of a high non-protein nitrogen. O'Hare[63] could not find any correlation between hyperglycaemia and either hypertension or arterio-sclerosis. He stated that in his opinion the cause of the abnormality was entirely unknown. 7 of his cases responded normally but 11 showed hyperglycaemic curves.

Mason[65] has shown a blood sugar curve in acute nephritis rising from a fasting level of 100mg% to 217mg% at the end of two hours from the time the glucose had been taken. Three weeks later in the same patient the values were 100 and 156mg% respectively.

Hopkins[65] was of the opinion that when searching for a solution of the difficulty the slower absorption of elderly

people should not be overlooked. In 1919 Williams & Humphreys[66] mentioned four blood sugar curves in nephritis. The fasting blood sugar levels were 220, 200, 100 and 100mg% and by the end of two hours after the glucose had been taken they had reached the following heights - 280, 360, 290 and 98mg%. These writers were however unable to formulate any theory capable of explaining these results. In the same year Bailey(67)also doing blood sugar estimations in nephritis found a high fasting level and the curve still rising two hours after the glucose had been given. In one of his cases the renal threshold actually reached 290mg%. In 1923 Major[68] studied two cases of chronic nephritis which were clinically similar in all respects. In the one the curve was perfectly normal, while in the other definite hyperglycaemia was present. He examined four cases of acute nephritis and they all showed a hyperglycaemia lasting four hours. Glycosuria was only once found and that was in the three hourly specimen of one patient. The highest blood sugar value obtained was 408mg% one hour after the glucose. The ages of these patients were 11, 40, 33 and 38 years. Hamman and Hirschmann[69] also were among those who found hyperglycaemic curves in certain cases of nephritis, but they were unable to offer any explanation. These writers pointed out that while it was a fact that in some cases of nephritis the renal threshold was raised to some value in the region of 200mg% or more, in other patients, clinically identical,

the threshold lay within normal limits. They mentioned that it had been stated that the hyperglycaemia without glycosuria might be due to renal impermeability, but in view of the general disturbance of carbohydrate metabolism that view was hardly tenable. In their cases these workers also failed to establish any relationship between hyperglycaemia and hypertension. Three of their nephritics with increased blood-pressure values gave typical diabetic curves. By the time Linder, Hillier & Van Slyke[70] published their paper on the subject it was an acknowledged fact that in some cases of nephritis hyperglycaemic curves did follow the administration of glucose but no satisfactory solution was forthcoming. They corroborated the results of previous authorities in failing to find any definite relationship between the height of the blood pressure and the height of the curve. They found however that all their patients with a normal acid base equilibrium had normal blood sugar curves and all but one of those with an abnormal blood sugar curve had some degree of acidosis. They did not consider, however, that the acidosis was a cause of the hyperglycaemia any more than phosphate or urea retention. The estimation of the resperatory quotient following glucose indicated that the combustion of carbohydrate was as rapid in all varieties of nephritis as in normal people. They attributed the prolongation of the curve to some unknown factor such as, for example, retarded glycogen formation. In another

communication these same authors reported observations showing that reducing substances in the blood other than glucose are increased in uraemia. This increase however accounted for only a very small fraction of the total rise, the fermentable sugar being responsible for the greater part.

Hawkins, MacKay & Van Slyke[71] stated that in their investigations they found an increase in the excretion of fermentable sugars in all varieties of nephritis. They were of the opinion, however, that the blood sugar curves were such that the glycosuria was shown to be of the renal rather than of the diabetic type. In spite of this statement, however, they brought forward 10 blood sugar curves performed at various times in the course of attacks of acute nephritis in 10 different patients. In these cases the fasting blood sugar levels lay between 94 and 135mg% and the highest points in the curves ranged from 184 to 261mg%. Of these 10 cases the maximum value in 6 of them was over 218mg%. In degenerative nephritis the lowest fasting level of 6 cases was 80mg% and the highest 143mg%. 4 of these patients gave values of over 200mg% at the peak of the curve. In 3 examples of arterio-sclerotic nephritis the fasting levels were 112, 117 and 118mg% respectively while the highest points reached in the curves were 157, 191 and 201mg%. While not attempting to explain the height of these curves they thought it possible that the glycosuria might be caused by failure of the tubules to re-

absorb glucose from the glomerular filtrate. An argument in favour of this hypothesis is that it is in cases of degenerative nephritis where the tubules are known to be most severely affected that the glycosuria is most marked. In some of these hyperglycaemic curves the question has arisen as to whether we might not be dealing with an accompanying true diabetes. But as McLean[47] has pointed out the high renal threshold found in nephritis disposes of that difficulty.

Spence[70] in 1920 suggested that much of the hyperglycaemia found in nephritis might be due to the high blood sugar value which is physiological in old age.

From the present state of our knowledge therefore we are in a position to state that in certain forms of nephritis there is disorder of the nitrogen metabolism. This is shown by retention of nitrogenous waste products within the body. Whether this is due to an inability of the damaged kidney to excrete or whether it is of the nature of a compensatory phenomenon is, as yet, an unsolved problem. It is also definitely acknowledged that in some cases of nephritis the carbohydrate metabolism may be upset. Several workers have made unsuccessful attempts to correlate defective nitrogen and carbohydrate metabolism.

From a study of these facts it was decided that in this investigation some interesting information might be gained from following the changes occurring in the non-protein nitrogen of

the blood after the ingestion of urea. After several cases had been thus tested it was observed that very conflicting results were being obtained. Bearing in mind, therefore, the facts concerning abnormal carbohydrate metabolism in nephritis it was determined to estimate the tolerance of nephritic children to laevulose. An attempt was then made to correlate abnormal non-protein nitrogen curves after the ingestion of urea, with an abnormal blood sugar curve following on the administration of laevulose.

Accordingly 25 cases of nephritis were examined. Some of the children had the test carried out on more than one occasion. 32 curves in all were performed. Of these 14 gave a normal response to the ingestion of the urea while the remaining 18 gave a curve similar to that which has been already shown to occur in hepatic disease. Summaries of the case-reports are given in protocols. Appendix, Section D. The results are shown in Tables 15 and 16. Taking first of all the normal curves into consideration it was found that the fasting non-protein nitrogen lay between 25.5mg% (Case No.10) and 75mg% (Case No.2). 30 minutes after the urea had been given 2 of the curves showed very little variation from the fasting level, but the others were all beginning to ascend. The greatest increase in value was 30mg (Case 1) while the maximum value reached was 87.7mg% (Case 2). 1 hour after the ingestion of the urea 3 of the curves were already on the downward

TABLE XV.

N.P.N. CURVES in NEPHRITIS following the INGESTION of 15g. UREA.
& UREA CONCENTRATION TESTS

No. of Case	Age in Years	% N.P.N. in the Blood in mg.				% Urea in Urine in g.		
		Fasting level	Hours after ingestion of Urea			Fasting level	Hours after Urea.	
			½ hour	1 hour	2 hours		1 hour	2 hours
0.	8	26.0	31.2	42.1	29.3	-	-	-
1.	9	36.3	58.1	52.6	33.0	1.14	1.86	3.24
1.	9	34.2	64.9	57.4	57.5	1.02	2.46	2.58
2.	$3\frac{4}{12}$	75.1	87.7	120.2	108.3	3.67	3.86	3.68
3.	6	50.2	65.0	62.5	58.8	1.98	2.66	2.28
4.	8	43.4	42.8	87.7	50.1	.80	1.34	1.31
5.	7	53.2	64.1	77.0	69.1	1.89	2.13	2.30
6.	10	58.8	66.6	97.5	73.5	1.65	2.41	2.75
7.	6	36.0	-	70.2	52.5	2.19	2.48	3.25
8.	11	44.2	48.5	52.8	51.0	2.33	2.33	2.50
8.	18	49.0	50.4	52.9	50.2	1.58	4.81	4.69
10.	6	33.5	39.0	45.2	30.6	1.08	1.44	3.6
10.	6	25.5	45.9	47.6	29.4	-	-	-
11.	9	36.8	51.4	62.5	54.0	1.03	2.44	2.98

TABLE XVI.

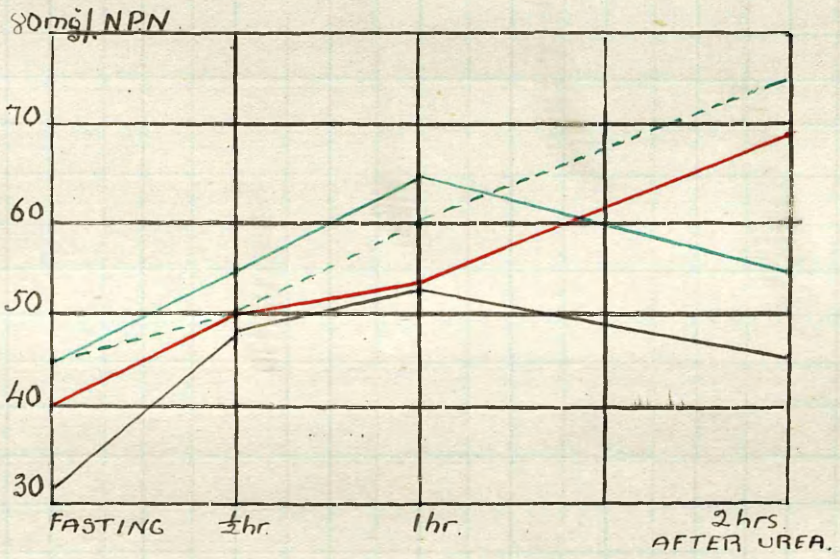
ABNORMAL N.P.N. CURVES in NEPHRITIS following the INGESTION of UREA. & UREA CONCENTRATION TESTS

No. of Case	Age in Years	% N.P.N. in Blood in mg.				% Urea in Urine in gms.		
			Hours after ingestion of Urea				Hours after Urea.	
		Fasting level	½ hour	1 hour	2 hours	Fasting level	1 hour	2 hours
10	6	25.2	25.3	25.6	60.4	1.82	2.20	2.90
11	9	42.0	42.7	58.1	64.3	1.32	2.52	3.06
12	11	50.2	50.2	46.0	76.3	1.39	0.91	2.06
13	4 9/12	35.1	47.6	63.2	70.8	1.73	2.41	2.43
13	4 9/12	30.4	40.6	52.6	73.5	1.34	1.57	1.69
14	10	46.3	66.0	66.4	71.3	0.89	1.58	1.59
15	3	43.1	47.6	54.8	57.4	1.63	1.51	1.81
16	3½	40.9	48.1	66.6	77.1	1.25	2.32	2.55
16	3½	29.4	53.2	66.6	71.4	-	-	-
17	1 8/12	51.5	51.0	52.3	62.5	-	-	-
18	6	84.2	-	90.6	112.4	2.82	2.37	2.68
19	5	49.0	48.8	51.6	64.8	1.06	2.10	2.47
20	7	52.6	67.6	78.0	89.3	-	-	-
21	8	45.8	47.0	52.3	65.4	1.08	1.21	2.56
22	3½	50.4	60.0	61.3	66.5	-	-	-
23	6	69.4	74.1	75.7	89.3	2.46	2.88	3.42
24	3 9/12	33.5	-	67.6	90.9	1.14	1.84	1.45
25	5	31.2	30.8	50.0	66.6	.99	1.25	3.34

FIGURE No.5

COMPOSITE CURVE

A COMPARISON of the EFFECT of the INGESTION of UREA in HEALTH, in HEPATIC DISEASE and in NEPHRITIS.



NORMAL CURVE

NORMAL CURVES IN NEPHRITIS.

ABNORMAL CURVES IN NEPHRITIS.

CURVES IN HEPATIC DISEASE.

trend, while the others were all continuing to ascend. The greatest increase in value over the previous specimen was 45mg. (No.4) while the maximum value reached was 120mg% (No.2). 2 hours after the ingestion of the urea all the curves were returning towards the fasting level. In 4 of the children the values lay within 5mg of the original fasting level, while in the others the degree of recovery was not so complete. Case 2 gave a value of 30mg above the fasting level.

Turning next to the 18 abnormal curves it was found that the fasting non-protein nitrogen values lay between 25.2mg% (Case 10) and 84.2mg% (Case 18). Half an hour after the urea had been given, 6 of the curves showed an alteration of value of less than 5mg from the fasting level, while the others were all definitely ascending. The maximum increase in value during the 30 minutes was 24mg (Case 16) and the highest level reached was 75mg% (No.23). One hour after the urea had been taken 6 of the curves showed little or no increase in value over the preceding samples of blood but the remainder were rising steadily. The greatest increase over the previous specimen was 18mg (No.16) and the maximum height attained was 90mg%. (Case 18).

2 hours after the ingestion of the urea all the curves were definitely ascending. Case 18 gave the highest reading, namely, 112mg% while Case 10 showed the most marked increase in value over the previous specimen namely a rise of 35mg.

The next stage of the investigation was an attempt to determine the nature of the factors at work in nephritis which influenced the response of the non-protein nitrogen of the blood to the ingestion of urea. These were considered under various headings.

As regards age it was observed that in the normal group the youngest child was $3^{4}/_{12}$ years and the oldest was 11 years while the average was 6 years. In the abnormal group the ages ranged from $1^{8}/_{12}$ years to 11 years with an average of 7 years. It is evident therefore that age is not a factor which governs the type of curve obtained. In the abnormal group there were 5 girls and 10 boys. These numbers are however too small to be of any value.

When the previous histories of the two groups were compared no light was thrown on the problem. In the normal group 2 cases (Nos.6 and 9) had a recent history of scarlet fever. Other two of this group (Nos.2 and 3) had suffered from recurrent attacks of tonsillitis. Cases 4 and 6 had had attacks of otorrhoea immediately prior to the onset of the nephritis. Case 5 had had an attack of cervical adenitis one month before the development of the present illness and case 7 had had a bronchiectatic condition for a few years.

Turning one's attention to the group with the abnormal non-protein nitrogen curve a somewhat similar condition of affairs

was found. Case 16 had just recovered from scarlet fever. Case 20 had suffered from enuresis since birth. Case 22 had been receiving treatment for abcesses of the gums for 3 weeks. Case 15 have a history of impetigo of 6 weeks duration. No.14 had suffered from acute rheumatism 1 year previously and for 3 weeks prior to admission had complained of a sore throat and discharging ears.

No help at all was received from a study of the time which had elapsed from the development of the first symptom of nephritis to the date when the test was performed. The average period in the normal group was 3.7 weeks and in the abnormal group 2.7 weeks a difference which was too small to be of much consequence. Normal and abnormal curves were both obtained within a week of the onset of the first symptom of nephritis and similar curves were found in children who had been ill for many weeks. It is interesting however in this connection to make mention of Cases 10 and 11. Case 10 had been a perfectly healthy child until 2 weeks before admission when his face began to swell. A diagnosis of nephritis was made. In spite of rest in bed and suitable diet, however, his condition did not clear up. The oedema&albuminuria varied greatly in amount - sometimes they were practically absent only to return as markedly as ever. At one stage of the illness it was thought possible that the condition might be one of nephrosis, but ultimately macroscopic blood appeared

in the urine, thus disposing of this suggestion. After seven months residence in hospital he was dismissed as a case of chronic nephritis. Three months after the development of the illness the first non-protein nitrogen curve was carried out and a normal result was obtained. A repeat curve was done two weeks later with a similar response. After the elapse of another month the test was again carried out and on this occasion the result was distinctly abnormal. Case 11, on the other hand exhibited a completely different state of affairs. The history was practically the same as in the previous case - a perfectly healthy child until one week before admission when the face began to swell, and there was a complaint of headache. Albuminuria was found and nephritis was diagnosed. After 6 weeks residence in hospital she was dismissed well. 6 weeks later she reported at the Renal Clinic. She looked well and felt well but on examination of the urine it was found to be loaded with albumen. She was re-admitted to hospital but on further investigation it was discovered that the albuminuria was of the orthostatic variety. A non-protein nitrogen curve was done during her first residence in hospital and gave a distinctly abnormal result. A second test was carried out during her second admission and a perfectly normal curve was obtained.

No relationship could be established between the absence, presence or degree of the albuminuria and the type of curve obtained.

As all the children with one exception in both groups presented blood in the urine (microscopic in amount in some but macroscopic in the majority) at one period or another during the illness. no information regarding the curves could be obtained under this heading. The only exception to this finding was case 20 - the renal dwarf - in whose urine neither macroscopic or microscopic blood was ever detected.

Considering the importance of the role played by oedema in the various types of nephritis it was anticipated that its presence or absence might influence the response given to the ingestion of urea. In the normal group 7 of the children suffered from oedema while 3 did not, while in the abnormal group oedema was again absent in 3 but present in 10 of the patients. Those figures are undoubtedly small in number but they would appear to indicate that normal and abnormal curves occur irrespective of the presence or absence of oedema.

The figures obtained from the blood pressure readings bear no relationship to the type of curve which results. The average systolic blood pressure in the normal group was 122 mg.Hg. while that in the abnormal section was 123 mg.Hg.

Having regard to the varying levels of fasting non-protein nitrogen which occur in different types of nephritis the possibility was entertained that in these estimations the solution of the difficulty might be found, but such was not found to be

the case. The average fasting non-protein nitrogen in the normal group was found to be 44mg% while in the abnormal group it was 45mg%.

Coming to a consideration of the urea concentration tests in the two groups it was observed that in the normal section the average fasting urinary urea was 1.66g% while in the abnormal group it was 1.56g%. (Table No.17) One hour after the ingestion of the urea the values had risen to 2.44g and 1.97g% respectively. Two hours after the urea had been taken the figures were 2.98g% for the normal section and 2.43g% for the abnormal. The percentage increase in the urinary urea one hour after the ingestion of the urea was 47 in the normal group and 26 in the abnormal section. One hour later the values in the groups had risen a further 23% and 22% respectively. From a study of these results it is evident that the fasting values in the two groups are for all practical purposes identical. The difference of 21% in the percentage increase 1 hour after the ingestion of the urea would appear to be readily explained by the slower absorption in these cases as is shown by the slowly rising non-protein nitrogen curve. That this difference is not due to defective renal excretion is demonstrated by the fact that the percentage increase in urinary urea which occurs between one hour and 2 hours after the urea had been given is practically the same namely 22 and 23 respectively.

As has already been stated when it was found that a

TABLE XVII.

COMPOSITE TABLE showing RESULTS obtained from the UREA CONCENTRATION TEST in the NORMAL & ABNORMAL GROUPS of NEPHRITIC CHILDREN.

Group	% Urinary Urea in grms.			% increase of Urinary Urea	
	Fasting level	Minutes after Urea		Minutes after Urea	
		60 minutes	120 minutes	Fasting to 60 minutes	60 - 120 minutes.
Normal	1.66	2.44	2.98	47	23
Abnormal	1.56	1.97	2.43	26	22

certain proportion of children suffering from nephritis gave a non-protein nitrogen curve after the ingestion of urea similar to that obtained in cases of hepatic inefficiency it was decided to follow the non-protein nitrogen curve with a laevulose tolerance test the next day. In view of the well-recognised abnormality in carbohydrate metabolism in certain cases of nephritis, it was not unreasonable to anticipate a pathological curve.

Eight laevulose tolerance tests were carried out - 5 of these belonged to the normal non-protein nitrogen group and 3 belonged to the abnormal section (Table No.18).

The following cases were tested in the normal group namely numbers 2, 4, 5, 6, and 7.

The fasting blood sugar levels which were all well within normal limits lay between 85 and 112mg%. Two of the curves (Nos.4 and 6) were perfectly normal but the remaining three (Nos.2, 5 and 7) were definitely pathological showing an increase above the fasting levels of 73, 48 and 68% respectively. Case 5 with a rise of 48% had returned to the original fasting level within 2 hours of the ingestion of the laevulose. Case 7 at the same stage was still 30mg above the level obtained at the commencement of the test. While in Case 2 the curve was still continuing to ascend two hours after the laevulose had been taken.

Of the 3 children (Nos.17, 18 and 19) belonging to the abnormal group who were tested by means of the laevulose curve,

TABLE XVIII.

BLOOD SUGAR CURVES in NEPHRITIS following on the INGESTION of LAEVULOSE.

No. of Case	Age in Years	% of Sugar in the Blood. in gms.					% increase in Value
		Fasting level	Hours after the ingestion of laevulose				
			½ hour	1 hour	1½ hours	2 hours	
2	3 4/12	80.0	93.4	100.2	127.1	138.3	73
4	8	97.8	102.5	108.7	104.0	-	11
5	7	105.2	145.0	156.1	115.2	106.3	48
6	10	112.3	121.3	122.2	100.1	100.0	8
7	6	96.6	108.1	130.2	163.0	129.1	68
17	1 8/12	80.1	78.2	68.3	80.7	74.9	3
18	6	108.1	125.0	133.3	148.4	125.1	37
19	5.	79.1	123.8	87.3	82.3	85.2	57

2 (Nos.18 and 19) gave definitely pathological curves. The percentage increase in value above the fasting level being 37 and 57 respectively, while in the remaining case (No.17) no appreciable increase in blood sugar value followed the ingestion of the laevulose.

From these estimations it is clear that in a certain proportion of cases of nephritis there is a definitely decreased tolerance of laevulose present. From such a small number of cases however it would not be justifiable to attempt to draw any conclusions as to what the factors may be which influence the response given to the ingestion of laevulose.

In view of the fact that normal and abnormal laevulose curves are found in the group giving a normal response to the ingestion of urea as well as in the group where the response is abnormal, it is clear that while disturbance of nitrogen and carbohydrate metabolism may co-exist it is also possible for either the one or the other to occur independently.

The various factors which might be likely to influence the type of curve which would result from the ingestion of urea in cases of nephritis have now been considered. From the results of these investigations it would appear that it is impossible to state what these factors are. All that can be said is that 40% of the cases of nephritis examined gave a curve closely resembling that obtained in the group of healthy children. In the remaining

60% the curve was similar to that found in cases of hepatic inefficiency. This is shown in Figure No.5.

From a study of the whole question it seems justifiable to conclude that in a certain proportion of cases of nephritis, liver disturbance is present. This statement is strengthened by the knowledge that in certain cases of nephritis a decreased tolerance to laevulose is found.

Following on this work which was carried out on nephritic children the second section of this chapter is devoted to similar estimations on children who suffered from disease of the kidneys - other than nephritis.

Part II.

The response of the blood non-protein nitrogen to the ingestion of urea in cases of renal disease - excluding nephritis.

Five children who were the subjects of renal disease - excluding nephritis - were given 15g urea as in the previous groups and the changes in the non-protein nitrogen of the blood observed. The ages ranged from $1^{5}/_{12}$ years to 11 years. Summaries of the case-reports are given in protocols. Appendix, Section E. The results are shown in Table 19. The conditions which came under this heading included pyelitis, tuberculosis of the kidney, and neoplasm of the kidney. In each of these children the response of the blood to the ingestion of the urea was physiological. In the three cases where a simultaneous urea concentration test was performed it was noticed that the kidneys were able to excrete the urea satisfactorily. Two of the cases (Nos.2 and 4) had a laevulose tolerance test carried out and in each a normal curve was obtained. Table No.20. A few weeks later, however, the test was repeated in Case 4, and on this occasion the level of the blood sugar rose 34% after the ingestion of the laevulose and had not returned to the fasting level by the end of two hours. Cases 1 and 2 were examined by means of the phenolphthalein excretion test. The former showed an excretion of 58% of the dye within two hours, but in the latter only 33% was obtained in

the same length of time.

Case 5 was interesting on account of the fact that on clinical examination a greatly enlarged liver was at first diagnosed. This finding was difficult to reconcile with the finding of a normal non-protein nitrogen curve following on the ingestion of urea. At operation, however a very extensive neoplasm of kidney was found, but no abnormality of the liver was detected. Both these observations were sustained at the post-mortem examination which took place a couple of days later.

In Case 4 also the tentative diagnosis of hepatic enlargement was at first made but an exploratory puncture of the tumour revealed a hypernehproma. Unfortunately an autopsy was not permitted.

The fastings levels in these cases ranged from 20.2 to 42.5mg% with an average of 33mg%. Half an hour after the ingestion of the urea all the curves showed a substantial rise. The smallest increase being 7.5mg (Case 4) and the greatest 22.6mg in Case 5. The maximum height attained was 56.8 (Case 5).

One hour after the urea had been taken 4 of the curves were continuing to rise, but one (Case 5) had reached its apex and had already begun to return towards the fasting level. The greatest increase in value noted was 12mg. Case 4, and the maximum concentration attained was 68.5mg% (Case 3).

The specimens withdrawn two hours after the administra-

TABLE XIX.

N.P.N. CURVES in KIDNEY DISEASE following the INGESTION of 15g. UREA.

& UREA CONCENTRATION TESTS.

No. of Case	Age in Years	Diagnosis	% N.P.N. in the Blood in mgms. % Urinary Urea in gms.						
				Hours after ingestion of Urea				Hours after Urea	
			Fasting level	½ hr	1 hr	2 hrs	Fasting level	1 hr	2 hrs
1	11	Tuberculous Kidney.	20.2	33.3	40.0	34.1	1.36	2.60	3.38
2.	6	Tuberculous Kidney.	35.7	52.6	64.2	53.0	1.19	1.41	1.89
3.	10	Pyelitis.	-	51.2	68.5	34.9	1.78	2.24	3.06
4.	$1^{5}/12$	Hyper-nephroma	42.5	50.0	62.5	42.8	-	-	-
5.	$1^{6}/12$	Kidney Neoplasm	34.2	56.8	48.0	47.1	-	-	-

TABLE XX.

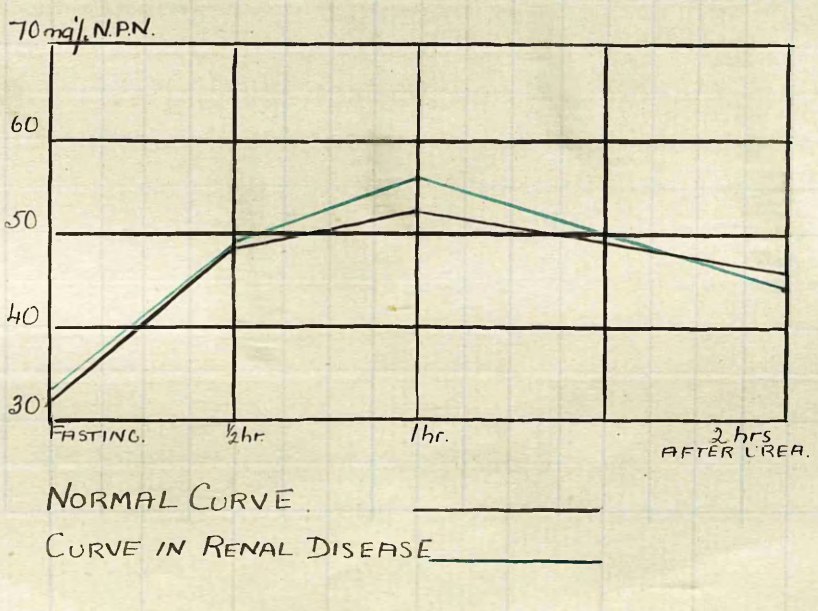
BLOOD SUGAR CURVES in RENAL DISEASE (excluding Nephritis) RESULTING from the INGESTION of LAEVULOSE.

No. of Case	Age in Years	Diagnosis	% of sugar in the Blood. in gms.					% increase in value of blood sugar.
			Fasting level	Minutes after ingestion of laevulose.				
				30 mins.	60 mins.	90 mins.	120 mins.	
2	6	Tuberculosis of Kidney.	142.2	139.9	175.1	123.0	158	
4	$1^{5}/12$	Hyper Nephroma	114.0	124.1	116.2	118.4	110.3	
4	$1^{5}/12$	Do. do.	93.1	111.4	125.0	130.1	116.4	

FIGURE No.6.

COMPOSITE CURVE.

A COMPARISON of the EFFECT of the INGESTION of UREA in HEALTH and in RENAL DISEASE (excluding NEPHRITIS)



tion of the urea showed that all the curves were steadily falling. Case 4, had in fact already reached the original fasting value. It is of interest to point out that this child is one of the youngest in the section. This fact adds support to the statement made in an earlier chapter that the type of curve obtained is independent of the amount of urea given in relationship to the age and size of the child.

A comparison of the composite curves found in this section and of that in the group of healthy children shows that they more or less agree at each stage of the test (Figure No.6.).

From a study of the non-protein nitrogen curves following the ingestion of urea in these five cases it would appear that here there is present strong confirmatory evidence that disease of the kidneys per se is not sufficient to influence the type of non-protein nitrogen curve obtained.

Summary and Conclusions.

The effect of the ingestion of urea on the non-protein nitrogen of the blood in cases of renal disease has been studied.

In 40%of the cases of nephritis investigated the response was normal but in the remaining 60% it was abnormal. All the cases of renal disease - excluding nephritis - showed a normal tolerance to urea.

The conclusion is therefore reached that kidney disease of itself is not sufficient to cause an abnormal curve. When such

a curve does occur it is probably the result of co-existent hepatic inefficiency.

SECTION 8.

The Blood non-protein nitrogen curve following the administration of urea in children suffering from coeliac disease.

Considering the difficulty which children who are the subjects of coeliac disease experience in their efforts to metabolise fats, and the well-recognised abnormalities which characterise their carbohydrate metabolism it was thought that interesting results might follow an investigation into the nitrogen metabolism.

Coeliac disease was first described by Gee in 1888[73] in a paper entitled "On the Coeliac affection". He gave a full account of the symptoms but thought that the causes were obscure. Miller[74] in 1921 published a most exhaustive paper on the literature of the disease. The nomenclature has proved a fruitful source of argument. In this country coeliac disease appears to be the term of choice. On the Continent, however, Lichtenstein[75] agrees with Herter that the name of Intestinal Infantilism is more apt. Miller is of the opinion that the latter only acts as a cloak covering cases varying from true coeliac disease to infantile atrophy. In an autopsy of one case of coeliac infantilism he found no evidence of pathological changes in the intestine pancreas or liver which could possibly account for the protracted symptoms. From this finding he concluded that coeliac disease is independent of structural causative changes. Two years later he confirmed his previous post-mortem observations[76] and stated that we might confidently regard the disease as a digestive disorder affecting fat metabolism and

having no organic origin. He inclined to the opinion that the cause may be found in some defect of the bile salts. Bloch[77] found on microscopic examination a sub-chronic inflammation in the venticle and in the intestines with a great number of mucus cells in the walls of the colon. He thought that from the clinical and anatomical findings the disease must be looked upon as a chronic insufficiency of the digestive glands.

Macrae & Morris[78] have stated "in two of our patients who died the pathological reports (for which we are indebted to Dr J.W.S. Blacklock) indicate that no abnormalities either macro- or microscopic were noted in the gastro-intestinal tract, while in only one was there atrophy of liver and spleen."

In Coeliac Disease the bio-chemist has found a wide field for investigation and many and varied are the theories which have been produced. That the primary fault lies with the metabolism of fats is now generally acknowledged. As regards the metabolism of carbohydrates opinions differ widely. Most workers agree that in the active stages of the disease as manifested clinically and biochemically, the tolerance to carbohydrates is greatly increased. This is shown by the very low or even flat blood sugar curve which results from the ingestion of glucose. So marked and constant is this phenomenon that some authorities go so far as to state that it is pathognomonic of coeliac disease. Svensgaard[79] found this type of curve persisting after a lapse

of months or even years in cases where the stools appeared to be more or less normal.

Many theories have been advanced to account for this peculiarity. It is natural that in the presence of the difficulty which the coeliac child experiences in the absorption of fats attention should be focussed in the direction of absorption of carbohydrates. Macrae & Morris[78] believe that the solution may be found in defective absorption resulting from changes in the physico-chemical constitution of the intestinal contents. They regard it as possible that those alterations may include a shift of the reaction towards the alkaline side accompanied by a deficiency of bile-salts. Svensgaard does not favour slow absorption as a cause of the abnormal curve on account of the fact that glucose and adrenalin combined produce a much greater and more prolonged curve than either glucose or adrenalin separately.

McLean & Sullivan[80] have dismissed the theory of faulty absorption because of the fact that if the blood sugar curve is carried out at intervals of fifteen minutes a short initial rise does occur. They found that a gastric lavage performed two hours after ingestion revealed only a trace of glucose showing that the removal from the stomach was almost complete. In the abnormally flat blood sugar curve which results after intravenous glucose they find another argument against defective absorption.

Turning to the possibility of a defect of liver function being the origin of the abnormal curve we find here also some disagreement. Macrae & Morris do not favour the idea of an increased glycogenic function on the ground that the low curve persists even after some days of a high fat diet. It is generally recognised that such a diet normally increases and prolongs the curve. As an added argument against this theory they mention also that a normal blood sugar curve is obtained in those children following a subcutaneous injection of adrenalin. This fact shows that as far as carbohydrate metabolism is concerned the liver is functioning normally.

Svensgaard also discards the idea of glycogen deficiency on account of the reaction following adrenalin. She does not favour the suggestion of an excessive production of insulin as these children show no tendency to hypoglycaemia. She herself regards the abnormal curve as being due to a secondary result of the disordered fat metabolism. She thinks it possible that as these patients are unable to absorb fat satisfactorily they may exhibit as a compensatory phenomenon a more than normally active carbohydrate metabolism whereby there is an unusually rapid assimilation of glucose. She believes that here we may possibly be dealing with a hormone insufficiency somewhat resembling the condition found in diabetes mellitus. McLean & Sullivan also rather favour the possibility that a solution may be found in

some endocrine deficiency. They consider that the suggestion of a low renal threshold as a cause is untenable owing to the absence of glycosuria. That the bulk of the intestinal contents may be a causative factor has been mentioned, but that this is not the case has been shown by Macrae & Morris who found perfectly normal blood sugar curves in children suffering from non-coeliac steatorrhoea.

This group is comprised of seven children between one and nine years of age of which four were girls and three boys. Summaries of the case reports are given in protocols. Appendix, Section F and the results in Table No.21. All had the symptoms of diarrhoea emaciation & dwarfism. In three of the cases the non-protein nitrogen curve was stopped at two hours after the urea had been given and in one it was carried on for three hours while in the remaining three children the last specimen was not withdrawn until five hours after the urea had been given. The fasting non-protein nitrogen ranged from 27.4 to 52.6mg p.100ccs. In only two cases was there any appreciable rise within the first half hour - cases 3 and 7 which rose from 39 to 50 and 40 to 57.4mg per 100ccs respectively. By the end of one hour Nos.1 and 5 were still more or less at their fasting levels. Nos.3, 4, 6 and 7 were rising steadily while Case 2 had jumped from 58.7 up to 100mg p.100ccs. By the end of 2 hours all the readings were still increasing. Of the four children done at 3 hours three were continuing to climb while the fourth was tending to fall.

TABLE XXI.

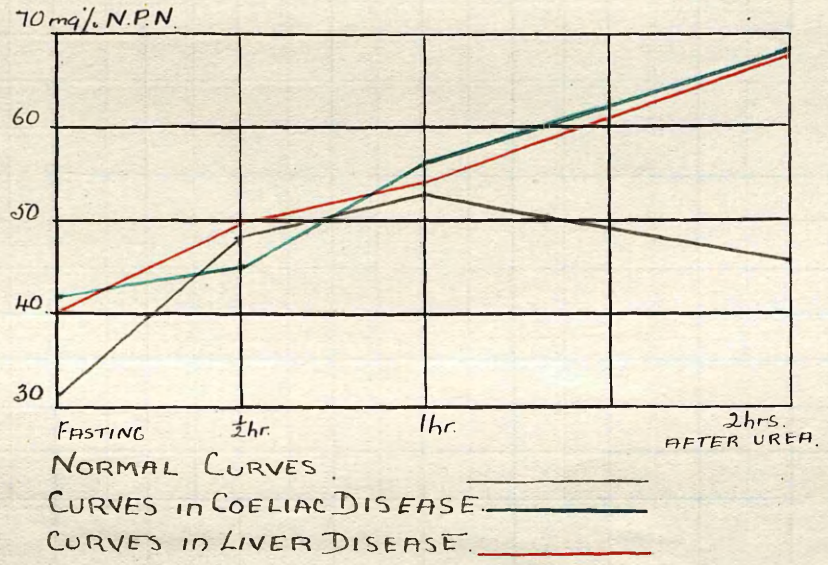
N.P.N. CURVES in COELIAC DISEASE following the INGESTION of 15g UREA.

No. of Case	Age in Years	% N.P.N. in the Blood. in mgms.						
		Fasting level	Hours after ingestion of Urea					
			½ hour	1 hour	2 hours	3 hours	4 hours	5 hours
1	6	49.2	53.1	52	84	-	-	-
2	1 1/12	52.6	58.7	100	-	111	100	100
3	1 9/12	39	50	55	54	93		
4	2	30	31.6	39	47.6	53	53	54
5	1 1/12	50	49	51	90			
6	2 9/12	27.4	27.0	43.4	64	61	61.5	54.3
7	9	40.0	57.4	60.2	97.6	-	-	-

FIGURE No.7.

COMPOSITE CURVE

THE EFFECT of the INGESTION of UREA in HEALTH, in HEPATIC DISEASE, and in COELIAC DISEASE.



By the end of five hours the lowest reading was still 80% above the fasting level while the highest was 100%. It is not easy to find an explanation as to why the curves of these children should differ so materially from those obtained in normal subjects.

Discussion.

A comparison of the normal non-protein nitrogen composite curve following the ingestion of urea, and the composite curve obtained in coeliac children under similar conditions, shows marked differences (Figure No.7). As a beginning we have the contrast of the fasting non-protein nitrogen values - 32mg% in the normal series and 41.3mg% in the coeliac group. The explanation of this difference might be found in a renal lesion. As the children concerned were so young it was only possible to collect specimens of urine for a urea concentration test in two instances. As a result a normal urea output was found. None of the other children showed any evidence of kidney disturbance. The nature of the diet was certainly not calculated to cause any increase in non-protein nitrogen value. Nor could the unusually high value be explained on the ground that the children were dehydrated through loss of fluid by way of the bowel. A further study of the two composite curves shows that in the coeliac children the curve ascends much more gradually, but eventually reaches a higher maximum point. In these cases the peak is not

reached until 3 hours after the urea has been taken, while in the normal children it occurs within 2 hours. As regards the actual height attained we find the average maximum in the normal cases to be 53mg as compared with 80mg. While these results appear definite enough the real difficulty arises when an attempt is made to furnish an explanation. Remembering the difficulty experienced by the coeliac child in absorbing fats, delay in absorption comes naturally to ones mind as a reasonable proposition. Such a theory however is hardly satisfactory. The fact that in the cases where a urea concentration test was carried out, the urinary urea showed such a marked increase following on the ingestion of the urea would appear to negative this idea. The older explanation offered by earlier bio-chemists would without doubt be that in this condition we were dealing with disturbed renal function whereby urea was not being satisfactorily eliminated and was in consequence accumulating in the blood.

Much light however is thrown on the problem by a comparison of the composite non-protein nitrogen curve following urea in coeliac children and the curves obtained in those who show hepatic inefficiency and disease of the muscular system as for all practical purposes they are identical. In the face of these results it would appear that in coeliac disease we are confronted with an actual disturbance of the nitrogen metabolism of the liver or the muscles either alone or in combination. The

fact that no characteristic pathological lesion of the liver is found at autopsy in cases of coeliac disease allied with our knowledge of the characteristic wasting of the glutei makes the suggestion of defective muscular metabolism rather attractive.

SUMMARY

The effect of the ingestion of urea in 7 children who were the subjects of coeliac disease has been studied. The resulting curves were similar to those already obtained in patients who suffered from hepatic inefficiency or disease of the muscular system.

SECTION 9.

Summary and Conclusions.

A resumé regarding the formation, absorption and further metabolism of urea has been given, accompanied by an account of our knowledge regarding the non-protein nitrogen of the blood. The factors likely to influence the non-protein nitrogen of the blood have also been considered. Amongst those investigated have been the effect of prolonged abstention from food and of the administration of foodstuffs containing carbohydrate protein or fat alone or in combination.

The changes occurring in the non-protein nitrogen concentration of the blood after the ingestion of urea have been studied in health and in various pathological conditions.

From the results of these investigations one feels justified in arriving at the following conclusions -

1. Prolonged fasting tends to reduce the non-protein nitrogen concentration of the blood.

2. That neither glucose nor fat singly or in combination, have the power to stimulate nitrogen metabolism was shown by the fact that their administration produced no increase in the value of the blood non-protein nitrogen.

3. The ingestion of urea in health causes an increase in non-protein nitrogen concentration in the blood. The maximum point of the curve is attained within a period of two hours.

4. The ingestion of urea in hepatic disease causes an increase in value in the non-protein nitrogen of the blood which does not

reach its highest point after an interval of 2 hours. The average fasting non-protein nitrogen value is slightly higher than in health and the ascent of the curve is much more gradual than in normal children, but the maximum height ultimately attained is greater.

5. The ingestion of urea in cases of muscular dystrophy produces a curve very similar to that obtained in cases of liver inefficiency.

6. The non-protein nitrogen curve following the ingestion of urea in children who are the subjects of rheumatism shows that half of the patients investigated gave a normal result. In the remainder, however, the curve was similar to that obtained in hepatic disease.

That disturbance of nitrogen and carbohydrate metabolism may or may not co-exist is demonstrated by t he fact that a normal non-protein nitrogen curve may accompany a normal as well as an abnormal laevulose curve.

7. The ingestion of urea in cases of nephritis produces in 40% of the patients a normal non-protein nitrogen curve &in the remaining 60% an abnormal curve resembling that obtained in liver disease. In cases of kidney disease - excluding nephritis - the response to the ingestion of urea was normal in each child, thus showing that renal disease of itself is not sufficient to cause an abnormal non-protein nitrogen curve.

8. The ingestion of urea in cases of coeliac disease presents a curve which differs in no essential particular from that obtained in hepatic inefficiency or in disease of the muscular system.

9. These results appear to give clinical confirmation to the conclusions arrived at by G.D. Cathcart - namely, that in health ingested urea is stored by the liver and the muscles. Apparently in disease of either the former or the latter this function is diminished or lost.

APPENDIX - SECTION A.

SUMMARIES of CASE REPORTS of CHILDREN suffering from HEPATIC DISEASE.

Case 1. Boy 3½ years. Previous history, not important. Vomiting for 9 days, accompanied by dark urine and white stools. Jaundice of 4 days duration. Liver palpable 1½ in. below costal margin. Urine contained bile pigment.

Case 2. Girl 8 years. Previous history, not essential. Nausea and anorexia for 7 weeks. Intermittent jaundice for 4 weeks accompanied by light coloured stools, dark urine and occasional vomiting. Liver 4 in. below costal margin. Wassermann reaction negative. Microscopic blood examination, secondary anaemia. Fragility of red cells normal. Van den Bergh: 32 units, biphasic.

Case 3. Girl 5 years. Previous history, not essential. Loss of appetite and irritable 6 days ago. Next day vomiting began and was accompanied by jaundice, pale stools, dark urine and itchiness of the skin. Liver 2 in. below costal margin. Wassermann reaction negative. Microscopic blood examination, secondary anaemia. Van den Bergh: biphasic reaction, 14 units.

Case 4. Girl 8 years. Previous history, unimportant. Nausea and anorexia for 4 days. Vomiting, constipation and abdominal pain for 3 days. Jaundice for 2 days.

Case 5. Boy 5 years. Previous history, acute rheumatism August 1931. Heart not affected. Jaundice of 4 days duration accompanied by vomiting. Liver border 2 in. below costal margin.

Case 6. Girl 1 year and 4 months. Healthy baby, but always pale. Jaundice for 1 week. Liver palpable but not enlarged. Spleen 2 in. below costal margin. Microscopic blood examination, secondary anaemia. Trace of urobilin in urine. Van den Bergh: direct, negative; indirect, positive.

Case 7. Girl, 2½ years. Previous history not of interest. For 9 days abdominal pain and jaundice have been present, accompanied by clay-coloured stools and dark urine. Examination. Well-marked jaundice. Liver palpable 4" below the costal margin. Spleen palpable. Urine contained urobilin and bile pigment.

Case 8. Boy, 6 years. Previous history not essential. Vomited 3 weeks ago and a few days later jaundice developed. Examination. Marked jaundice. Liver margin palpable 1" below costal margin. Urine contained bile-pigment and the stools were clay-coloured. Van den Bergh Reaction - direct, positive.

Case 9. Boy, 4 years. Healthy until last 5 weeks, when he became listless and lost his appetite. Vomiting and right-sided abdominal pain for 4 days. Motions loose, urine dark. No jaundice. Abdomen tender and resistant. Fever present. At operation, gall bladder greatly distended and liver reached to umbilicus. No stones were found. Urine, no abnormal constituent. Laevulose tolerance test, positive.

Case 10. Boy, 1 year. Diagnosis, biliary cirrhosis. Since birth had had 5 attacks of jaundice, accompanied by light stools and dark urine, which cleared within 1 week. Irritable and loss of appetite for 1 month. Swelling of abdomen noticed 2 weeks ago. Liver and spleen both greatly enlarged. Van den Bergh reaction: direct, negative; biphasic, positive; indirect, 3.5 units of bilirubin. Fragility of red cells, unaltered. Wassermann reaction, negative. Blood picture, secondary anaemia.

Case 11. Girl, 2½ years. Healthy for first 9 months, then diarrhoea developed: 6-7 stools daily containing blood and mucus. Abdomen began to enlarge.
Examination. Chest dull to percussion all over left side of back accompanied by defective R.M. Liver 3" and spleen 1" below costal margin. Paracentesis gave blood. No cancer cells on histological examination. Blood films showed no abnormality.
Diagnosis. Tumour of lung involving liver.

Case 12. Boy, 9 years. Swelling of abdomen dating from infancy. No symptoms. Liver 3 in. below costal margin. Laevulose curve, positive. Fifty per cent rise in blood-sugar value following the ingestion of laevulose.

Case 13. Girl, 4 years. Previous history, pyuria. General health good. Active child. Liver 2 in. below costal margin. Urine clear. Blood urea, 19.1 mgrm. per cent.

Case 14. Girl, 8 years. Healthy until 18 months old when abdomen began to swell: this has continued. Motions became large, soft, foul-smelling and frequent. Periodic attacks of vomiting followed the eating of fatty foods. At 4 years of age she had an attack of jaundice which lasted for three months.
Examination. Liver reached $4\frac{1}{2}$" below the costal margin. Spleen not palpable. Blood examination, normal. Wassermann reaction, negative. Fragility of red cells, normal. Blood sugar curve following the ingestion of glucose, normal. The tolerance to laevulose was decreased.

Case 15. Girl, 6 years. Healthy until 13 months old when diarrhoea developed and has continued, with short remissions, since. Recently severe cough has been present and there has been considerable loss of weight.
Examination. Small, poorly nourished child with protuberant abdomen. Left lung dull to percussion below angle of scapula; respiratory murmur absent: occasional râle. Liver, $5\frac{1}{4}$" and spleen 3" below costal margin. Wassermann Reaction, negative, Fragility of red cells, normal. Blood coagulation period, normal. Blood films: secondary anaemia. Van den Bergh reaction: direct, nil: indirect, 5 units. Sections of liver and spleen showed diffuse amyloid degeneration.

Case 16. Girl, 8 years. Previous history, not important. Intermittent jaundice for 2 years. Constant for 6 months. During attacks stools are white and urine dark. Two months ago abdomen began to swell. Liver and spleen greatly enlarged. Urine: urobilin present, bilirubin absent. Fragility of red cells not increased. Van den Bergh: biphasic reaction, 11 units of bilirubin.

Case 17. Girl, 10 years. Healthy until 7 years of age when in hospital with diphtheria, enlarged spleen found. Child otherwise well. Skin dark, pigmentation of flexures. No jaundice. Liver and spleen both enlarged. No glandular enlargement, Blood picture, secondary anaemia. Fragility of red cells not increased. Urine, no bile pigment. Van den Bergh: direct, negative; indirect, 2 units. Splenic puncture, Banti's disease.

Case 18. Girl, 9 years. Adopted child, previous history unknown. On day of admission headache and vomited about 5 oz. bright red blood followed 2 hours later by vomiting of dark brown material. Physical examination negative. Benzidine test on stool, positive. Laevulose curve, positive.

Case 19. Girl, 6 weeks. Normal pregnancy and labour. Jaundiced at birth - increased for 4 weeks and then very gradually disappeared.
Examination. Skin and conjunctivae markedly jaundiced. Spleen and liver both reached 2" below costal margin. Blood films showed secondary anaemia. Wassermann Reaction - negative. Bile present in urine. Stools white, but later coloured. Van den Bergh reaction - direct, negative: indirect, 3 units.

SECTION B.

SUMMARIES of CASE REPORTS of CHILDREN suffering from DISEASES of the MUSCULAR SYSTEM.

Case 1. Boy, 8 years. Healthy baby. Walked at 1½ years but has always been unsteady and never active; always difficulty in going upstairs or in rising from recumbent position. Can still walk alone for a short distance.
Examination. Generalised weakness of all muscles. Scapulae winged. Hypertrophy of interscapular and lumbar muscles, also of calves and thighs. Rises from the ground by climbing up legs. Blood sugar curve rises 48% following the ingestion of laevulose.

Case 2. Boy, 10 years. Healthy baby. Walked at 1½ years but always appeared to move stiffly. Always been fat and never active. At 6 years definite weakness of muscles developed and has gradually increased. Has difficulty in balancing. Rises from ground by climbing up legs.
Examination. Deltoid, glutei and thigh muscles hypertrophied. Atrophy, if present, is masked by deposits of fat. Scapulae winged. Marked lordosis. Bilateral pes cavus and equinus. Shoulders slip through arms when grasped. Marked weakness of all muscles. Sensation undisturbed.

Case 3. Boy, 12 years. Healthy baby. Remained well until 7 years of age when the legs were noticed to be of a peculiar shape. Condition has gradually progressed.
Examination. Gait unsteady, but with care can walk alone. Marked lordosis. Scapulae winged. Superficial reflexes present. Hypertrophy of supra- and infra- spinati; also of glutei and calf muscles. Thighs atrophied. Bilateral pes cavus and equinus. No Rombergism.

Case 4. Girl, 11 years. Healthy until 6 years old, when began to fall frequently, was not running about, was easily tired and had difficulty in going up stairs.
Examination. Calves much hypertrophied. Slight lordosis. Shoulders slip through hands when lifted. Climbs up her legs on rising. No sensory disturbances.

Case 5. Boy, 7 years. Healthy child. When 4½ years old began to turn in right foot when walking. This was followed by weakness of all the leg muscles.. The condition has gradually progressed until child can only walk alone with great difficulty. Examination. Gross atrophy of glutei, thigh and calve muscles.

SECTION C.

SUMMARIES of CASE SHEETS of CHILDREN suffering from the RHEUMATIC INFECTION

Case 1. Girl, 12 years. Adopted child. Early history unknown. Tonsils and adenoids removed at 5 years. No history of growing pains. Jerky movements present for 4 weeks.
Examination. Chorea present. Heart - Nil.

Case 2. Boy, 10 years. Healthy until 6 weeks ago, when he began to twitch.
Examination. Chorea. Heart, Nil.

Case 3. Boy, 9 years. Attacks of Chorea with carditis when 6, 7, and 8 years of age. Been attending cardiac Clinic for 1 year: during this time heart sounds have been pure. Chorea returned 3 weeks ago.
Examination. Chorea. Heart sounds not good, but no murmurs heard.

Case 4. Girl, 9 years. Cervical adenitis with repeated surgical interference for last 4 years. Chorea for 3 weeks.
Examination. Chorea. Soft V.S. at apex: not conducted.

Case 5. Girl, 7 years. History of recurrent sore throats. Scarlet fever 4 months ago: discharged with cardiac lesion. Since dismissal intermittent chorea.
Examination. Chorea. Sounds at apex of poor quality where V.S. and V.D. murmurs are heard. Nodules present.

Case 6. Boy, 11 years. Healthy until chorea 1 year ago. Has had sore throats since and chorea has recurred.
Examination. Chorea. Heart not enlarged, but V.S., A.S., and V.D. murmurs heard at apex.

Case 7. Girl, aged 8 years. Healthy until appendicectomy three months ago followed by pains in neck and limbs. Chorea for 3 weeks.
Examination. Chorea. Nodules present. Tonsils enlarged. Heart sounds of very poor quality. V.S. at apex.

Case 8. Girl 7 years. Previous history not essential. One week before admission pain in chest, but no joint pains, sore throat or Chorea.
Examination. Pericardial friction and soft V.S. Sounds of fair quality. 3 months after dismissal heart was passed as normal at Cardiac Clinic.

Case 9. Girl, 12 years. Always healthy. Pains in limbs and sore throat for 3 days. Vomited yesterday and ankles began to swell.
Examination. Various joints painful but not swollen. V.S. at apex conducted to axilla.

Case 10. Girl, 5 years. Always healthy. Bronchial catarrh, 5 weeks ago. Chorea for 3 weeks.
Examination. Chorea. V.S. at apex. well conducted to axilla.

Case 11. Girl, 7 years. Had an attack of Chorea at 4 years which lasted for 6 months. Recurred 5 weeks ago.
Examination. Chorea. V.S. at apex conducted to axilla. Heart not enlarged.

Case 12. Girl, 10 years. Had chorea with cardiac involvement at 5 years. Remained well until 1 week ago when chorea re-appeared.
Examination. Chorea. V.S. at apex. conducted to axilla.

Case 13. Girl, 5 years. Well until 6 weeks ago, when cervical adenitis developed. This was followed by pains in arms and legs.
Examination. Slight choreiform movements: no joint swellings or nodules. V.S. at apex conducted to axilla.

Case 14. Boy, 7 years. Well until had acute rheumatism and carditis 9 months ago. Flitting joint swellings have persisted. Twitching of limbs for 8 days.
Examination. Chorea. V.S. at apex: sounds very poor in quality.

Case 15. Boy, 10 years. Healthy until 6 months ago when he had growing pains. Has been twitching for 2 weeks.
Examination. Chorea. Sounds of fair quality: soft apical V.S.

Case 16. Girl, 10 years. Scarlet fever at 6 years. Movements of hands for three months. History of ? nodules and pains in the joints.

Examination. Moderate chorea. No nodules. Tonsils enlarged and unhealthy. Sounds of fair quality: soft V.S. at apex, well conducted to axilla.

Case 17. Girl, 4 years. Healthy until three months ago when she had scarlet fever accompanied by arthritis. Unable to walk on dismissal. Pain and stiffness has continued. Examination. No true limitation of joint movements. V.S. heard all over praecordium.

Case 18. Girl, 9 years. Healthy until 6 weeks ago, when flitting joint pains accompanied by swelling developed. Examination. Arthritis. Sounds of poor quality: loud V.S. conducted to axilla.

Case 19. Boy, 11 years. Previous history not of interest. 2 weeks ago pain and swelling of joints, along with breathlessness on exertion.
Examination. No chorea or arthritis or nodules. V.S. at apex conducted to axilla. Sounds of fair quality.

SECTION D.

SUMMARIES of CASE REPORTS of CHILDREN suffering from RENAL DISEASE.

GROUP I. NEPHRITIS.

Case 0. Boy, 8 years. Previous history not essential. Sore throat 5 days before admission, followed by swelling of face, feet and legs. Urine was red and scanty in amount. Comatose when examined. Lumbar puncture performed. This was followed by convulsions. Transitory blindness on regaining consciousness. Urine contained abundant albumen and blood. Blood pressure not raised.

Case 1. Boy, 9 years. Healthy until 3 days ago, when face began to swell and vomiting took place. Urine said to be scanty and of a dark colour.
Examination. Oedema of feet, legs and lumbar region. Ophthalmoscopic examination showed no abnormality. Urine contained blood and albumen. Systolic and diastolic blood pressure 120 and 80 mg. Hg.

Case 2. Boy $3\frac{4}{12}$ years. Previous history of recurring tonsillitis was given. Sore throat accompanied by fever 10 days ago. Urine scanty and dark in colour for one day.
Examination. No abnormality found. Systolic and diastolic blood pressure 100 and 60 mg.Hg. Urine contained blood and albumen and casts.

Case 3. Boy, 6 years. Tonsillitis occurring at intervals for 3 years. Swelling of face for two days. Urine dark in colour for one day.
Examination. Nil. Systolic and diastolic blood pressure 120 and 80 mg. Hg. Urine contained albumen, blood and casts.

Case 4. Boy, 8 years. Healthy until one week ago when face became puffy. Earache and discharging ears for 5 days. Abdominal pain, vomiting and headache accompanied by fever for one day.
Examination. Boy semi-conscious. Slight lumbar oedema. Tonsils unhealthy. Systolic-diastolic blood pressure 100 and 60 mg.Hg. Urine contained, blood, albumen and casts.

Case 5. Boy, 7 years. Healthy until one month ago, when he developed a cervical adenitis - there was no accompanying sore throat. Ankles swollen for 5 days. Face puffy for one day.
Examination. Oedema of face and legs and some free fluid in abdomen. Systolic and diastolic blood pressure, 140 & 115 mg.Hg. Urine contained albumen, blood and a few casts.

Case 6. Boy, 10 years. Previous history unimportant. 4 weeks ago, rash and fever (but no desquamation) followed by intermittent swelling of face, arms and legs. Otorrhoea for 1 week. Epistaxis, loss of appetite and fever for 2 days. Twitching of limbs for 4 hours before admission.
Examination. Comatose but can be roused with difficulty. Some oedema. Urine contained albumen, blood and casts. Ophthalmoscopic examination, nil.

Case 7. Boy, 6 years. Bronchiectasis for last 3 years. Generalised oedema for 4 days followed by oliguria.
Examination. Systolic and diastolic blood pressure 118 & 80 mg. Hg. Urine contained albumen, blood and casts.

Case 8. Boy, 11 years. Healthy until a fortnight ago, when he became fevered and went off his food. Face puffy and urine dark for 3 days.
Examination. Boy had a few convulsions after admission. No oedema present. Both optic discs slightly blurred at the margins, but no haemorrhages observed. Systolic and diastolic blood pressure 120 & 80 mg. Hg. Urine contained blood and albumen.

Case 9. Girl, 8 years. Scarlatinal nephritis two years ago. Made complete recovery. One year later had a second attack which did not clear up, and child has been more or less an invalid since.
Examination. Tonsils, enlarged and unhealthy. Teeth, carious. Systolic and diastolic blood pressure 134 & 150 mg. Hg. Urine contained abundant albumen and a trace of blood.

Case 10. Boy, 6 years. Always healthy until two weeks ago when face began to swell. There were no other symptoms.
Examination. Marked oedema of legs, lumbar region and face, but no free fluid in the abdomen. Ophthalmoscopic examination negative. Systolic and diastolic blood pressure 80 & 75 mg.Hg. Urine on admission contained abundant albumen and casts. Blood was not present until after the first month of the illness. Child dismissed after seven months in Hospital: albuminuria and oedema were still well-marked.

Case 11. Girl, 9 years. Healthy until one month before admission, when face became puffy & the urine dark in colour. Examination. No oedema present. Urine contained abundant albumen, blood and casts. Ophthalmoscopic examination - negative. Systolic and diastolic blood pressure 132 & 88 mg. Hg. Child was dismissed, well, after six weeks residence in Hospital. Two months later, she reported at the Renal Clinic. She looked well and felt well, but the urine was found to be loaded with albumen. On admission the albuminuria was proved to be of the orthostatic variety.

Case 12. Boy, 11 years. Healthy until two weeks ago, when face began to swell. There were no other symptoms. Examination. Eyes puffy. Ophthalmoscopic examination, nil. Systolic and diastolic blood pressure 156 & 84 mg.Hg. Urine contained albumen and blood.

Case 13. Boy, $4^{9}/12$ years. Always healthy. Two weeks ago vomiting and headache, also swelling of face. Micturition frequent. Urine scanty.
Examination. No oedema. Systolic and diastolic blood pressure 104 and 70 mg. Hg. Urine contained blood and albumen.

Case 14. Boy 10 years. Acute rheumatism one year ago. Sore throat, headache and pains in joints for 3 weeks. Right ear has discharged for 10 days. Face puffy and urine scanty and dark red in colour for 5 days.
Examination. Oedema of legs. Heart slightly enlarged but sounds pure and of good quality. Systolic and diastolic blood pressure 160 and 100 mg. Hg. Urine contained blood and albumen.

Case 15. Girl, 3 years. Always healthy. 6 weeks ago impetigo of scalp. 10 days ago swelling of hands, feet and later of face. Very scanty urine.
Examination. General anasarca. Systolic and diastolic blood pressure 145 and 112 mg. Hg. Urine contained albumen and blood.

Case 16. Girl, $3\frac{1}{2}$ years. Always healthy. 4 weeks ago had sore throat and rash. ? Scarlet fever. Not followed by desquamation admitted two weeks ago with cervical adenitis. Albuminuria was found on routine examination.
Examination. No oedema. Systolic and diastolic blood pressure 109 and 60 mg. Hg. Urine contained albumen, blood and granular casts.

Case 17. Boy $1^{8}/_{12}$. Healthy until 2 weeks ago, when oedema of face developed and gradually spread until the whole body was involved. Oliguria for 1 week. Pneumonia supervened with a fatal result.
Examination. Massive oedema. Ophthalmoscopic examination. Nil. Systolic and diastolic blood pressure 125 and 80 mg. Hg. Urine contained albumen. Trace of blood and granular casts.

Case 18. Girl, 6 years. Always well until yesterday when face began to swell.
Examination. Face puffy. Slight oedema of legs. Ophthalmoscopic examination - nil. Systolic and diastolic blood pressure 100 and 78 mg. Hg. Urine contained albumen, microscopic blood and a few casts.

Case 19. Boy, 5 years. Healthy until four days ago, when face began to swell and urine was dark.
Examination. Oedema of face, lumbar region and feet. Ophthalmoscopic examination - nil. Systolic and diastolic blood pressure 120 and 100 mg. Hg. Urine contained albumen, blood and casts.

Case 20. Boy, 7 years. Enuresis since birth. No growth for last 2 years. Always thirsty. Eats well and looks healthy. Diagnosed as a renal dwarf.
Examination. 2nd aortic sound was accentuated when compared with the second pulmonic. Systolic and diastolic blood pressure 108 and 78 mg.Hg. Ophthalmoscopic examination showed a blurring of the nasal margins of both discs. Urine contained albumen and epithelial casts.

Case 21. Girl, 8 years. Well until 1 year ago, when had acute nephritis and made a complete recovery. No symptoms till yesterday when face began to swell.
Examination. Some oedema of face. Systolic and diastolic blood pressure 116 and 80 mg. Hg. Urine contained albumen and microscopic blood.

Case 22. Boy, $3\frac{1}{2}$ years. Healthy until abscesses of gums developed 3 weeks ago, this was followed by swelling of the face. Urine scanty and highly coloured for four days. Pneumonia supervened and child died.
Examination. Slight oedema of lumbar region. Systolic and diastolic blood pressure 124 and 80 mg. Hg. Urine contained albumen and blood.

Case 23. Boy, 6 years. Always healthy. 7 days ago urine dark. Face puffy for 5 days.
Examination. Slight oedema of feet. Systolic and diastolic blood pressure 105 and 65 mg. Hg. Urine contained albumen, blood and casts.

Case 24. Boy, $3^{9}/12$. Previous history not essential. 3 weeks ago took fainting attacks and was easily tired. 4 days ago swelling of face, arms and legs. Had a convulsion yesterday.
Examination. Impetigo of face which is puffy. Oedema of sacrum and legs. Free fluid in abdomen. Systolic and diastolic blood pressure 100 and 50 mg. Hg. Ophthalmoscopic examination, negative. Urine contains albumen, blood and casts.

Case 25. Boy, 3 years. Healthy until 2 weeks ago when cough and running of the nose developed, - there was no sore throat. Pallor and headache and swelling of the face for one week. Urine noticed to be dark in colour and scanty.
Examination. Oedema. Severe in face, but slight in feet. Systolic and diastolic blood pressure, 116 and 90 mg. Hg. Ophthalmoscopic examination - nil. Urine contained albumen, blood and casts.

SECTION E. GROUP 2.

RENAL DISEASE excluding NEPHRITIS.

Case 1. Boy, 11 years. Healthy baby. Remained well until developed pleurisy, followed by osteo-myelitis. Made good recoveries. Has complained of pain in left hypochondrium for 4 months - usually a couple of attacks each week, each lasting 3 to 4 hours. Nocturnal Enuresis since birth.
Examination. Healthy looking boy. Nothing found on physical examination. Urine contains haze of albumen and pus, but no casts or blood. Tubercle bacilli found.

Case 2. Boy 6 years. Healthy until 8 weeks ago when complained of painful micturition - especially marked at night. Circumcision performed 6 weeks ago, caused no improvement.
Physical Examination: - nil. Urine contains albumen and pus. Tubercle bacilli isolated.

Case 3. Boy, 10 years. Healthy until 2 years ago when spasmodic attacks of pain around the umbilicus developed, accompanied by diurnal frequency. These have continued.
Physical Examination - nil. Urine contains a trace of albumen with white and red cells. Cystoscopy and pyelograms - negative results.

Case 4. Boy, $1^{5}/12$. Healthy baby until 6 weeks ago when he became irritable and went off his food: followed by abdominal pain.
Examination. No jaundice but very pale child. Mass in right flank. Spleen not palpable. Fragility of red cells: normal. Van den Bergh - indirect, 1 unit. Laevulose Tolerance Test - 1st occasion - negative. 2nd - mildly positive. Section of tumour revealed hypernephroma.

Case 5. Girl $1^{6}/12$ years. Healthy baby: remained well until 1 month ago, when she lost her appetite and appeared to have pain on micturition. Has not walked since. 4 days ago swelling of legs noted.
Examination. Fair-sized emaciated child with very large abdomen. Large mass in right flank extending towards and originally thought to be liver. Spleen not palpable.
At operation and also at autopsy a large tumour involving a great part of the right kidney was discovered. Liver was not enlarged and was normal in appearance.

SECTION F.

SUMMARIES of CASE REPORTS of CHILDREN SUFFERING from COELIAC DISEASE.

Case 1. Girl 6 years. Healthy at birth and remained so until 16 months old when diarrhoea developed. This has continued. Motions are large and offensive and like porridge in colour and consistence.
Examination. Small, but fairly well nourished child. Irritable. Urea concentration test - Fasting: 2.82g% 1 hour after Urea: 3.11g% 2 hours after Urea: 4.31g%

Case 2. Girl, $1^{1}/12$ years. Healthy child until 2 months ago when diarrhoea developed and the appetite was lost.
Examination. Small wasted dehydrated child. Blood sugar curve following glucose was abnormally flat.

Case 3. Boy, $1^{9}/12$. Premature birth. Breast for 2 months then milk and water. Never throve satisfactorily. At $1^{4}/12$ began to vomit and to lose weight. This has continued. Very listless and irritable. Makes no attempt to walk.
Examination. Small unhealthy looking child. No organic abnormality found. Motions, large, greenish and offensive. Blood sugar curve does not show any appreciable rise following the ingestion of glucose. Retains 85% ingested fat.

Case 4. Girl, 2 years. Healthy baby. On the breast and Sister Laura's Food until four months and throve well. At that time bowels became loose. At 13 months went off food: the stools became loose and bulky and there was occasional vomiting.
Examination. Small, rather dehydrated child: some atrophy of buttocks present.

Case 5. Boy, $1^{1}/12$ years. Healthy baby. Remained well until 2 months ago, when he became pale and listless. This was followed by severe diarrhoea and occasional vomiting.
Examination. Small, thin child. No organic abnormality found on physical examination.

Case 6. Girl $2^{9}/12$. Adopted child. Early history unknown. Seemed to thrive well until 15 months old when abdomen began to swell and condition gradually deteriorated. Diarrhoea with large bulky offensive stools developed. Always thirsty; very irritable. Unable to talk or walk.

Examination. Small, emaciated child. Liver 1" below costal margin. Fontanelle open. A flat blood sugar curve resulted from the ingestion of glucose.

Case 7. Boy, 9 years. Healthy baby. Throve well for 1 year and then developed diarrhoea which continued for 18 months. Did not walk until 7 years old.
Examination. Very small pale emaciated boy. Bright mentally. Marked knock-knees and curving of forearm bones. Abdomen large. Liver 1" and spleen 1½" below the costal margin. Blood picture showed a secondary anaemia. Urea concentration Test: Fasting level - 1.85g.%: 1 hour after Urea - 2.42g%: 2 hours after Urea - 2.10g.%. The blood sugar curve following the ingestion of glucose was flat. 79.4% fat absorbed.

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