HEPATIC EFFICIENCY : THE VALUE OF THE HÆMOCLASTIC AND THE LÆVULOSE TESTS IN CHILDHOOD.

BY

MURIEL J. BROWN, M.B., CH.B., D.P.H.

(From the Medical Department, Royal Hospital for Sick Children, Glasgow.)

The liver is so complex an organ and has so many functions to perform that no single test can serve as a true index of its efficiency. In consequence several tests have been devised for detecting hepatic disease. The van den Bergh test, and the phenol-tetrachlorophthalein test, are intended to give some indication of the state of the biliary activity of the liver ; while the glycuronic acid test, and Widal's ' hæmoclastic crisis ' have been regarded as of value in estimating the antitoxic function of the liver. For estimating the integrity of glycogenesis the lævulose test has been employed.

The present communication is based upon an investigation of the hæmoclastic crisis and the lævulose test in normal and abnormal conditions of childhood, and was undertaken to determine the value of these tests as indicating disease of the liver.

THE ' HÆMOCLASTIC CRISIS ' IN CHILDHOOD.

This test, which is an application of the physiological digestion leucocytosis, was first employed by Widal¹ in 1920. It consists in determining the number of leucocytes in the blood after fasting, and also 10, 20, 40, and in some cases 60 minutes, after the ingestion of a standard meal (seven ounces of milk). Widal maintained that in health a leucocytosis is invariably obtained, but that when disease of the liver exists the post-prandial leucocytosis is replaced by a leucopenia. This varying reaction he interpreted as evidence of whether peptones are arrested in the liver or not, their presence in the systemic circulation inducing a leucopenia. Moutier and Rachet², however, have brought forward evidence that the phenomenon of " hæmoclasia " is the effect of a physical disturbance of the vasomotor system rather than a chemical reaction connected with the liver.

Some authors like Widal have considered this test as of great value in deciding whether the liver is healthy or not. Wilson³ obtained a leucocytosis in thirty students after the ingestion of milk, a rise of 3,000 or upwards occurring after 20 minutes in more than half of the cases ; only two of the subjects failed to show a rise of more than 1,000. In diseases of the liver, on the other hand, this author obtained an invariable fall. Shaw⁴, on the contrary, performed the test in a large series of healthy individuals and also in cases of hepatic disease, and from his results, totally discounts the value of the test as a means of estimating hepatic efficiency. Schiff and Stransky⁵ obtained a leucopenia in all normal infants as well as in infants with disease of the liver. Misasi and Aiello⁶ state that a leucopenia is normally induced in all children under 10 years of age, but that in digestive disturbances and congenital syphilis a leucocytosis may occur.

Tests in Normal Children.

The leucocytic changes were observed after the ingestion of milk in twenty normal children whose ages ranged from a few weeks to 12 years, and the results are shown in Table I. The amount of milk given varied according to the age of the child, the children under one year receiving an amount equal to their theoretical caloric requirements, while those over one year received 210 c.cm. of milk. In the adjudication of these results a change of less than 10 per cent has been considered within the limits of experimental error.

TABLE I.
THE LEUCOCYTE COUNT IN NORMAL CHILDREN AFTER THE INGESTION OF MILK.

Case No.	Age.	LEUCOCYTE COUNT.					% change in leucocyte count.
		Fasting.	Minutes after feed.				
			10	20	40	60	
1	15 wks.	11,000	9,400	8,500	13,200	—	—14% in 10 min. —22% in 20 min.
2	3 mths.	9,600	12,400	8,500	11,600	—	+28% in 10 min. —11% in 20 min.
3	4 mths.	9,800	7,400	8,600	9,600	—	—24% in 10 min. —12% in 20 min.
4	3 mths.	9,600	12,400	8,500	11,600	—	+29% in 10 min. —12% in 20 min.
5	1½ yrs.	12,000	13,600	12,400	11,200	12,500	+13% in 10 min.
6	2½ yrs.	14,000	12,600	13,800	13,600	14,200	—10% in 10 min.
7	3 yrs.	12,000	11,800	12,900	13,200	13,600	+10% in 40 min.
8	4½ yrs.	8,900	8,400	9,200	8,700	—	No effect.
9	4¾ yrs.	9,400	12,300	10,600	11,200	10,900	+30% in 10 min.
10	5 yrs.	9,400	8,800	7,800	9,200	10,400	—17% in 20 min.
11	5¾ yrs.	8,600	9,500	10,400	10,200	9,800	+21% in 20 min.
12	5 yrs.	10,200	12,400	11,600	10,800	—	+21% in 10 min.
13	6 yrs.	9,800	11,200	8,200	8,400	—	+14% in 10 min. —16% in 20 min.
14	7 yrs.	12,400	13,200	12,600	10,400	—	—32% in 40 min.
15	7 yrs.	12,300	14,000	13,600	12,000	—	+13% in 10 min.
16	8 yrs.	9,420	8,800	10,600	9,780	—	+10% in 20 min.
17	9 yrs.	10,240	12,400	11,200	9,400	—	+21% in 10 min.
18	10 yrs.	9,400	7,100	7,800	—	9,300	—24% in 10 min.
19	11 yrs.	8,600	7,800	9,420	8,400	—	No effect.
20	12 yrs.	7,600	9,240	8,800	9,400	—	+21% in 10 min.

Results.—A leucocytosis varying from 10 per cent. to 30 per cent. was obtained in 45 per cent. of the cases ; a leucopenia varying from 10 per cent. to 32 per cent. in 30 per cent. of the cases ; no change was found in 10 per cent., and a paradoxical result in 15 per cent. In the majority of the cases showing a leucopenia the maximum fall occurred within 10 minutes ; in only one case (No. 14) was the maximum fall not reached until 40 minutes after the ingestion of the milk. In none of the cases did a definite leucocytosis occur later. In the cases showing a post-prandial leucocytosis the maximum rise also occurred within 10 minutes. There was no apparent correlation between the age of the child and the leucocyte count obtained after the ingestion of the milk.

From these observations there is no evidence that in infancy or childhood the ingestion of milk produces a specific effect on the leucocyte count of the peripheral capillary blood, either in the direction of a leucopenia or a leucocytosis.

Tests in Abnormal Children.

In spite of the above conflicting results, however, an attempt was made to see if any consistent effect occurred when there was evidence of hepatic disease. Ten children suffering from unequivocal disease of the liver, and fifteen in whom there existed probable disease of the liver, were investigated. The results are given in Tables II and III.

TABLE II.

THE LEUCOCYTE COUNT AFTER THE INGESTION OF MILK IN CHILDREN WITH LIVER DISEASE.

Case No.	Disease.	LEUCOCYTE COUNT.					% change in leucocyte count.
		Fasting	Minutes after feed.				
			10	20	40	60	
1	Catarrh. jaundice	15,400	14,800	12,400	13,400	—	—19% in 20 mins.
2	„ „ „ ...	14,800	13,920	15,400	14,200	—	No effect.
3	„ „ „ ...	6,800	8,800	8,900	8,600	6,700	+29% in 20 mins.
11	Icterus neonat. ...	10,000	6,600	8,000	9,200	—	—34% in 10 mins.
14	Banti's disease ...	11,200	13,400	8,200	8,000	—	+19% in 10 mins. —44% in 40 mins.
16	„ „ „ ...	11,250	15,937	10,312	10,000	10,937	+41% in 10 mins.
17	Hanot's disease	8,800	6,000	6,400	6,600	8,600	—32% in 10 mins.
18	Hodgkin's disease	8,900	7,250	6,300	7,600	9,750	—29% in 20 mins.
19	Congen. syphilis	10,600	11,200	10,800	10,400	—	No effect.
20	Multilobular cirrhosis ...	18,600	22,800	14,400	13,400	15,400	+40% in 10 mins. —34% in 40 mins.

Results.—It is seen from Table II, in which details of the results in definite hepatic disease are given, that in 40 per cent. of these cases a leucopenia varying in degree from 10 per cent. to 34 per cent. resulted, while in 20 per cent. a marked leucocytosis developed and in 20 per cent. no appreciable change was found.

TABLE III.
THE LEUCOCYTE COUNT AFTER THE INGESTION OF MILK IN CERTAIN
PATHOLOGICAL CONDITIONS.

Case No.	Disease.	LEUCOCYTE COUNT.					% change in leucocyte count.
		Fasting.	Minutes after feed.				
			10	20	40	60	
24	Hodgkin's disease	3,800	4,000	3,800	3,700	—	No effect.
25	Congen. syphilis	12,400	12,900	12,600	12,800	—	No effect.
30	Gaucher's disease	7,600	9,800	11,600	8,000	7,600	+53% in 20 mins.
29	„ „	7,800	8,900	7,700	9,240	—	+19% in 40 mins.
31	„ „	6,000	6,800	5,800	5,800	6,200	No effect.
	„ „	6,900	7,000	7,200	8,400	6,600	+23% in 40 mins.
36	Cœliac disease (?)	6,400	7,800	8,200	5,300	5,800	+28% in 20 mins. —17% in 40 mins.
37	„ „ (?)	10,400	9,260	10,820	11,880	—	—10% in 10 mins. +13% in 40 mins.
28	Wilson's disease	7,800	6,600	6,600	5,400	5,500	—30% in 40 mins.
29	„ „	7,200	7,400	7,400	7,000	7,200	No effect.
26	Acholuric jaundice	10,200	9,600	8,000	7,600	—	—25% in 40 mins.
27	„ „	37,000	22,600	23,800	18,400	17,400	—58% in 60 mins.
32	Gastroenteritis + ketosis ...	12,000	11,000	9,600	10,400	—	—20% in 20 mins.
34	„ „	11,200	11,600	12,800	11,600	—	+14% in 20 mins.
22	Hepatomegaly ...	9,600	12,000	11,600	9,340	—	+33% in 10 mins.
23	„ „ ...	6,600	4,400	4,200	5,800	—	—27% in 20 mins.

From Table III, where details of the test in cases of suspected and probable hepatic disease are given, the results are seen to be equally discordant.

Conclusion.

The hæmoclastic test in our hands has proved to be of no value in estimating the efficiency of the liver.

THE LEVULOSE TEST.

It is usually believed that lævulose after its absorption from the alimentary tract is carried by the portal system direct to the liver and there rapidly converted into glycogen and stored. Cathcart and Markowitz' state that lævulose cannot be oxidized by the tissues, and that it must first be converted into glucose by the liver before being deposited as glycogen. Hence the rationale of the test would seem to be that, in the absence of integrity of hepatic activity,

some of the lævulose ingested will filter through the liver and cause a rise in the blood sugar, and because of the inability of the tissues to utilize it there will ensue a delayed fall.

Straus⁸ in 1901 was the first to draw attention to the different effects of the administration of lævulose and glucose. He regarded the presence of lævulose in the urine as evidence of impaired hepatic efficiency, because he found a lævulosuria after the ingestion of 100 grm. of lævulose in 90% of cases of liver disease, but in only 10% of normal cases. Schirokauer⁹ in 1913 held that periodic examination of the percentage of sugar in the blood after the ingestion of lævulose was a more delicate method of detecting the ability of the liver to metabolize lævulose than its mere presence in the urine. He found that after the ingestion of lævulose in health there resulted practically no rise in the blood-sugar curve, whereas in subjects suffering from hepatic disease a definite rise occurred. Bergmark¹⁰, as also Maclean and De Wesselow¹¹, and Folin and Berglund¹², shortly afterwards confirmed the finding of Schirokauer that in health the blood-sugar level was unaffected by the administration of lævulose. Spence and Brett¹³ though concluding that this test affords a valuable means of estimating the actual degree of liver efficiency, hold that a rise in the blood-sugar content of 20 grm. may be obtained in the normal adult after the ingestion of 50 grm. of lævulose. Tallerman¹⁴ also points out that the absence of any rise in the sugar curve is not as constant in health as had been supposed and that fairly wide variations do occur. Though he considers this test of value in estimating hepatic efficiency he holds that no conclusions can be drawn unless the rise exceeds 30 grm. He also drew attention to prolongation of the curve as strong evidence of some disorder of the liver. Cammidge, Forsyth and Howard¹⁵, on the other hand, found in health a rise of as much as 50% in the blood-sugar content after the ingestion of lævulose. Frank and Melhorn¹⁶ obtained in the normal child after the ingestion of 89 grm. of lævulose in 200 c.cm. of tea, a rapid rise in the blood-sugar with a slow irregular fall.

The possibility that these varying results may be due to variations in the purity of the lævulose employed in the test must not be lost sight of, and will be referred to later.

Method.—The technique employed for the lævulose test is the same as that for the glucose tolerance test. 1 grm. of lævulose per kgrm. of expected body weight was given to children under 12 years of age, and 50 grm. of lævulose to the few adult cases which were investigated. The percentage of sugar in the blood was estimated at half-hourly intervals after the ingestion of the lævulose.

Purity of the Lævulose.—The lævulose used throughout the tests was Merck's pure lævulose. Lævulose obtained from the British Drug House was also tried, but, as is seen from Table IV, the results obtained did not coincide, a higher rise being obtained with the B.D.H. lævulose than with Merck's lævulose.

TABLE IV.
THE BLOOD-SUGAR CONTENT AFTER "MERCK'S" LÆVULOSE AND "B.D.H." LÆVULOSE.

Case No.	Lævulose.	PERCENTAGE OF SUGAR IN THE BLOOD					% Increase in blood sugar.
		Fasting.	Hours after lævulose.				
			$\frac{1}{2}$	1	$1\frac{1}{2}$	2	
1	B.D.H. ...	·098	·125	·118	·106	·093	26
	Merck's ...	·090	·112	·106	·093	—	24
2	B.D.H. ...	·106	·143	·120	·106	—	34
	Merck's ...	·100	·125	·112	·100	·100	25
3	B.D.H. ...	·106	·134	·125	·100	—	26
	Merck's ...	·100	·108	·112	·100	—	12

Because of this discrepancy in the results with the two samples of lævulose Prof. Patterson submitted them to chemical analysis and found the specific rotation for sodium light of the Merck's specimen at a concentration of 10 and at a temperature of 22° C. to be -91.63 ; while the B.D.H. specimen gave a specific rotation of -82.49 . This he concluded indicated an impurity in the B.D.H. lævulose of about 9 per cent. Hence the purity of the lævulose is a factor which should be taken into consideration in judging the normal rise in the blood sugar after the ingestion of lævulose, and a special standard must be set up for each type of lævulose used.

TABLE V.
THE SUGAR CONTENT OF THE BLOOD AFTER THE INGESTION OF LÆVULOSE
IN NORMAL CHILDREN.

Case No.	Age.	Percentage of sugar in the blood				% Inc. in blood sugar.	Disease.
		Fasting.	Hours after lævulose.				
			$\frac{1}{2}$	1	$1\frac{1}{2}$		
1	7 yrs.	·098	·112	·096	·106	13	Conval. lobar pneum.
2	7 yrs.	·106	·098	·112	·100	5	„ „
3	5 yrs.	·086	·098	·106	·084	23	„ „
4	8 yrs.	·106	·112	·094	·100	5	„ „
5	9 yrs.	·108	·112	·098	·100	5	Conval. acute rheum. (no heart lesion).
6	8 yrs.	·086	·100	·098	·098	16	Epilepsy.
7	7 yrs.	·100	·094	·126	·100	26	„
8	12 yrs.	·100	·112	·120	·100	20	„
9	5 wks.	·100	·094	·100	·094	— 6	Incorrect feeding.
10	4 mths.	·075	·081	·096	·081	28	„ „
11	3 mths.	·088	·094	·100	·084	13	Dyspepsia. Vomiting stopped.
12	$1\frac{1}{2}$ yrs.	·100	·125	·112	·106	25	Unresolved pneum.
13	3 yrs.	·098	·088	·100	·100	—10	„ „
14	2 yrs.	·100	·120	·084	·106	20	Rickets.
15	5 yrs.	·084	·100	·106	·090	25	Conval. acute rheum. (no heart lesion).
16	10 yrs.	·098	·120	·125	·100	27	Epilepsy.
17	3 mths.	·088	·094	·100	·084	14	Normal infant.
18	4 mths.	·094	·108	·094	·094	15	Incorrect feeding.
19	11 yrs.	·100	·125	·112	·098	25	Conval. acute rheum. (no heart lesion).
20	8 mths.	·081	·094	·100	·080	23	Incorrect feeding.
Average . . .		·094	·104	·102	·096	15	

Results in Normal Children.

To obtain some idea of the comparative value of this test, its scope and limitations, twenty children who were recuperating from various diseases but in whom there was no suspicion or apparent evidence of disease of the liver were examined (using Merck's preparation of lævulose), and these have been taken as representing the normal. The results are shown in Table V.

A study of the figures obtained furnishes evidence that the average rise in the blood-sugar content is 10 mgrm., the highest being 27 mgrm.; in two cases a fall of 6 and 10 mgrm. respectively was obtained. Calculating the percentage increase, the greatest increase was 28 per cent. with an average of 15 per cent., an increase which is greater than can be allowed for by experimental error. In two of the cases examined no rise in the blood sugar was obtained, but, as previously mentioned, a fall of 6 mgrm. and 10 mgrm. respectively. In all the cases, except Nos. 10 and 15, the blood sugar had returned to the normal fasting level within one and a half hours after the ingestion of the lævulose. In these two cases the blood sugar was tending to fall, but, unfortunately, the result two hours after ingestion was not obtained. Age did not appear to have any effect on the height or duration of the rise.

For the purpose of comparison with the results obtained in pathological conditions we have taken as evidence of liver inefficiency an increase in the blood sugar of more than 30 per cent., and the presence of a prolonged curve, the blood sugar not returning to the normal fasting level within two hours.

Results in Pathological Conditions of Childhood.

The lævulose test was applied to a series of pathological conditions of childhood, and the results obtained are given in Table VI. For the purpose of better evaluation of the test the cases have been divided into three groups. In the first group of cases there was definite evidence of disease of the liver. In the second group there was probable disease of the liver, as evidenced by clinical examination; and in the third group disease of the liver was merely problematical, no evidence of such being present on clinical examination, but the disease present suggesting a possible implication of the organ.

GROUP I.—CASES OF DEFINITE DISEASE OF THE LIVER. In this series are—14 cases of catarrhal jaundice; 5 cases of icterus neonatorum; 1 case of multilobular cirrhosis of the liver; 2 cases of Hodgkin's disease; 2 cases of Banti's disease; 1 case of fatty degeneration of the liver; 1 case of congenital syphilis.

Catarrhal Jaundice.—In all, fourteen cases of catarrhal jaundice were investigated, six of them being children and eight adults. From a survey of the findings it will be seen that the rise in all the cases except three (Nos. 6, 12, and 13) was more marked than in the normal individual. In the majority of the cases the fall also was definitely delayed. In only five of the cases (Nos. 2, 4, 6, 12, and 13) did the blood sugar return to the normal fasting level within two hours of the ingestion of the lævulose.

In the children the increase in the blood sugar varied from 36 per cent. to 63 per cent., with the exception of one case (No. 6), where only a rise of 6 per

cent. was obtained. This very slight rise was obtained in a child in whom the jaundice had disappeared, and the only clinical evidence of disease of the liver at the time was enlargement of that organ. This child had had an attack of catarrhal jaundice two weeks before admission, when he was stated to have been jaundiced and to have passed high-coloured urine and pale motions.

Amongst the adult cases, which were all examined during the first week of illness, the same variations were found to occur, a slight fall being obtained in one case (No. 13), while another (No. 8) gave a rise of 85 per cent. with a definitely delayed fall. The test was repeated in the former case (No. 13) four and also eight days later, when the jaundice was more marked, and yet a negative curve was again obtained. The test was repeated after ten days in Cases 9 and 10, when the jaundice was fading but bile was still present in the urine. In both a normal curve was found, although a definite rise in the blood sugar with a prolonged fall had previously been obtained.

The extent of the rise did not appear to bear any relationship to the severity of the illness. The patient No. 4 appeared as ill as the patient No. 1, yet in the latter a rise of 59 per cent. with a prolongation of the curve was obtained, as compared with a rise of 36 per cent. and a return to the normal fasting level within $1\frac{1}{2}$ hours in the former.

Apart from Case No. 13 these results are in accordance with those obtained by Spence⁷, who found a severe degree of liver inefficiency as evidenced by the lævulose tests during the early stage of catarrhal jaundice. In some cases, however, even before the jaundice had reached its height, a rapid recovery of the hepatic efficiency was indicated by a return to the normal behaviour of the blood sugar.

Icterus Neonatorum.—*Icterus neonatorum* occupies a peculiar place among examples of jaundice as many of the phenomena which are present in other forms of the disease are lacking. The distribution of the pigmentation differs from that in catarrhal jaundice, and there is an absence of clay-coloured fæces and of dissolved bile-pigments in the urine. Five cases of *icterus neonatorum* were examined. Three of these were found to give a positive result, the blood sugar increasing in two of the cases by 38 per cent. and in the other by 41 per cent. This increase, however, was not noted in two of the cases (Nos. 17 and 19) until two hours after the ingestion of the lævulose which probably indicated very slow absorption. Nevertheless the rise at the end of two hours points to definite liver impairment, and, although no distinct rise was obtained in the other two cases (Nos. 15 and 16), it is possible that absorption here may have taken place so slowly that the liver was able to deal with the very small amount of sugar which was carried to it at any one time.

Multilobular Cirrhosis of Liver.—The example of multilobular cirrhosis (No. 20) which was examined gave a positive result at a time when the only clinical evidence of hepatic disease was enlargement of that organ. Five months later yellowness of the skin and conjunctivæ, with the presence of urobilin in the urine, was noted, and on post-mortem examination the liver showed a distinct multilobular cirrhosis with here and there paler areas of "multinodular" hyperplasia.

Hodgkin's Disease.—Although this is not a true affection of the liver, Rolleston¹⁸ states that the liver is involved in 50 per cent. of all examples of the disease coming to post-mortem examination.

Two cases of Hodgkin's disease were examined. One of these (No. 21) showed clinically only slight yellowness of the skin with the presence of urobilin in the urine, but on post-mortem examination the liver was found to be pale, deeply jaundiced and dotted throughout with firm whitish lesions. These areas on histological examination were found to consist of fibro-cellular tissue containing a fair number of large mononuclear cells and suggesting the appearance of lymphadenoma. In this case a rise of 37 per cent. was obtained in the blood sugar after the ingestion of lævulose with, however, a return to the normal fasting level within one and a half hours.

In the other case (No. 30) there was definite clinical evidence of impairment of the liver function as shown by an attack of jaundice six months before admission to hospital. When the case came under observation the liver was enlarged, and urobilin was present in the urine. A gland in the neck was excised and revealed the typical histological picture of lymphadenoma. In this case the lævulose test resulted in an increase in the blood sugar of 50 per cent., with a return to the normal fasting level within two hours.

Banti's Disease.—Two cases of so-called 'Banti's disease' (splenic anæmia) were studied. They both showed progressive enlargement of the spleen, the presence of an anæmia of varying degree with a leucopenia, and free fluid in the abdomen, although in one case (No. 23) this was only noted at the time of the second examination. In both cases the diagnosis was confirmed by splenic puncture. Both gave positive lævulose tests. In one (No. 23) the percentage increase in the blood sugar at the time of the first examination was not more marked than that obtained in a normal child, but the return to the normal fasting level was delayed: this slow fall was again noted two weeks later, with, at this time, a more marked and definitely abnormal increase in the blood-sugar content.

Fatty Degeneration of the Liver.—An increase of 72 per cent. in the blood sugar and a delay in the return to the normal level after the ingestion of lævulose was obtained in one case (No. 24) which at post-mortem examination showed fatty changes in the liver.

Congenital Syphilis.—One case (No. 25) in which there was revealed at post-mortem examination syphilitic cirrhosis of the liver, reacted normally to lævulose. This is not in accordance with the findings of Duzar and Hensch¹⁹ who obtained a positive lævulose test in all their cases of congenital syphilis.

Summary of Results in Group I.—If we summarize the results in the above 25 cases of certain liver disease, we find that 19 (76 per cent.) gave a definitely abnormal increase in the blood sugar after the ingestion of lævulose, and that of these 19 cases 15 (79 per cent.) also showed a delay in the return to the normal fasting level.

GROUP II.—CASES OF PROBABLE DISEASE OF THE LIVER. The second series consists of:—1 case of probable Banti's disease; 3 cases of Gaucher's

disease ; 3 cases of Hanot's hypertrophic cirrhosis of the liver ; 1 case of passive congestion of the liver ; 2 cases of probable Wilson's disease.

Banti's Disease.—In this patient (No. 26) a negative lvulose test was obtained, though the clinical features suggested the diagnosis of Banti's disease. The spleen was palpable one finger-breadth below the costal margin, the liver four finger-breadths below the costal margin, and free fluid was present in the abdomen. There was a definite anmia with a leucopenia, the white cell count numbering 4,685 per c.mm., and the fragility of the red cells was normal. The Wassermann reaction was negative. The child died three weeks after admission to the hospital, but unfortunately no post-mortem examination was obtained, and splenic puncture had not been performed.

Gaucher's Disease.—Splénomegaly of the Gaucher type is of particular interest because the pathogenesis is considered to be of the nature of an overgrowth of the reticulo-endothelial cells, with those in the liver also participating in the change. Three cases (Nos. 27, 28, and 29) were examined in which the spleen, on histological examination, after splenic puncture or splenectomy, showed the characteristic cells of Gaucher's disease. In all the cases the liver was enlarged ; in the first two it was palpable two finger-breadths below the costal margin, and in the other case (No. 29) it was four finger-breadths below the costal margin. In none did the test in any way indicate impairment of the liver function, rises of only 21 per cent. 8 per cent., and 20 per cent. being obtained. In case No. 28 the lvulose test was repeated one month later, and a normal curve was again found.

Hypertrophic Cirrhosis of Liver.—Three cases diagnosed as possibly Hanot's disease on account of the enlarged liver were examined. In two (Nos. 31 and 32) a definite increase of the blood-sugar content was obtained with, however, a return to the normal fasting level within two hours. In the other case (No. 33), although the liver extended at the time of the test to the iliac crest the result was negative, but when repeated 9 months later there resulted a rise of 35 per cent., with a delay in return to the normal fasting level.

Cardiac Failure with Passive Congestion of the Liver.—In a case of severe valvular disease of the heart with cardiac failure and great enlargement of the liver and spleen, the liver extending $3\frac{1}{2}$ inches below the costal margin, the lvulose test was applied on two occasions and resulted in rises of the blood sugar of 43 per cent. and 42 per cent. respectively.

Progressive Lenticular Degeneration.—Two children, aged 12 and 10 years, in whom a clinical diagnosis of Wilson's disease (lenticular degeneration) was made, were examined. Although hepatic cirrhosis is found invariably post mortem in this disease, it is categorically stated by all recent writers that the cirrhosis is latent and gives no evidence (clinical or chemical) of its presence. In one of the cases (No. 36) there resulted a positive lvulose test in so far as the rise (35 per cent.) in the blood sugar was concerned, but the fasting level was reached within two hours. Neither example of the disease was confirmed by post-mortem examination, so that this result cannot be brought forward as a definite exception to the rule above mentioned,

Summary of Results in Group II.—In this group of cases of probable hepatic disease 6 (55 per cent.) gave a definite increase in the blood sugar after lævulose, and of these 6 cases, 2 (36 per cent.) also showed a prolongation of the curve.

GROUP III.—CASES OF PROBLEMATICAL DISEASE OF THE LIVER. The following cases are discussed under this group :—2 cases of acholuric jaundice; 4 of ketosis accompanying gastro-enteritis; 3 of celiac disease.

Acholuric Jaundice.—The jaundice in this disease is extra-hepatic in origin and no special pathological changes have been observed in the liver or bile passages.

Two typical examples of this disease with recurrent attacks of anæmia, enlarged spleen, and increased fragility of the red blood cells were tested. A negative curve was obtained in one (No. 37), but the other (No. 38) gave a rise in the blood sugar of 36 per cent., with a delayed fall. In both children splenectomy was performed. They were seen again one year later, and both appeared very well. The lævulose tests were repeated and negative curves were obtained.

Ketosis accompanying Gastro-enteritis.—The ketone bodies, β -hydroxy-butyric acid, aceto-acetic acid and acetone, which are produced by the breaking down of one part of the fat bodies, are in the normal individual rapidly burned and broken up in the presence of sufficient glucose to maintain combustion into H_2O and CO_2 . It has been suggested that, as a result of fever and toxæmia, the normal reserves of glycogen are depleted, and that the liver loses the power of producing glycogen. Thus there follows an insufficient supply of carbohydrates for the complete combustion of fat with a consequent ketosis. If this hypothesis be correct it would seem possible that in the presence of ketosis produced in this way, the damage to the liver might be revealed by the behaviour of the blood sugar after the administration of lævulose.

Tallerman²⁰ in twelve cases of ketosis accompanying infection found that only one gave a normal blood-sugar curve after the ingestion of lævulose. This he took as an indication of derangement of the carbohydrate metabolism due to hepatic inadequacy.

These results I was unable to confirm in the four cases (Nos. 39, 40, 41, and 42) of acute gastro-enteritis with ketosis which were submitted to the test. In all the cases there were vomiting, diarrhœa, and fever with signs of intoxication, and the presence of a considerable quantity of acetone in the urine. The maximum rise obtained in the blood sugar was 25 per cent., with in all cases a return to the normal fasting blood sugar level one and a half hours after the ingestion of the lævulose.

Celiac Disease.—Some prominence has been given by certain workers to a disturbed function of the liver in this disease. Three cases (Nos. 43, 44, and 45) were examined, but a normal curve was obtained in all. In one a rise of 6 per cent. was obtained, while the other two only gave a rise of 8 per cent.

Summary of Results in Group III.—In the above group of examples of problematical hepatic disease it will be seen that on only one occasion (in a case of acholuric jaundice) was an abnormal curve obtained, and this case, when retested one year later, reacted normally.

TABLE VI.

THE SUGAR CONTENT OF THE BLOOD AFTER THE INGESTION OF LÆVULOSE
IN VARIOUS PATHOLOGICAL CONDITIONS.

Case No.	PERCENTAGE OF SUGAR IN THE BLOOD.					% Increase in blood sugar.	Disease.
	Fasting.	Hours after lævulose.					
		$\frac{1}{2}$	1	$1\frac{1}{2}$	2		
GROUP I							
1	·084	·134	·130	·125	·112	59	Catarrh. jaundice.
2	·093	·132	·108	·098	—	41	" "
3	·100	·112	·154	·134	·125	54	" "
4	·100	·136	·118	·090	·100	36	" "
5	·098	·145	·160	·132	·112	63	" "
6	·100	·108	·106	·100	—	6	" "
7	·100	·165	·150	·134	·112	65	" "
8	·084	·156	·134	·112	·125	85	" "
9	·098	·134	·156	·156	·148	59	" "
10 days later	·100	·125	·125	·118	·100	25	} " "
10	·106	·168	·148	·152	·134	58	
10 days later.	·100	·112	·084	·092	—	12	} " "
11	·118	·156	·162	·137	·132	37	
12	·106	·131	·125	·118	·100	23	" "
13	·125	·118	·118	·118	—	—	" "
4 days later.	·125	·118	·125	·118	—	—	} " "
5 days later.	·118	·125	·118	·125	—	—	
14	·106	·156	·176	·150	·137	70	" "
15	·130	·150	·125	·100	—	15	Icter. neonatorum
16	·086	·081	·093	·081	—	10	" "
17	·081	·093	·093	·112	·112	38	" "
18	·081	·112	·100	·081	—	38	" "
19	·075	·075	·081	·100	·106	41	" "
20	·100	·131	·118	·116	—	31	Multilob. cirrhosis.
21	·098	·135	·125	·096	·100	37	Hodgkin's disease.
GROUP II							
26	·112	·112	·108	·100	—	— 4	Banti's disease.
22	·134	·178	·162	·154	·150	32	" "
23	·115	·140	·137	·125	·120	21	} " "
2 weeks later.	·118	·143	·156	·131	·136	32	
25	·064	·082	·075	·064	—	28	Cong. syph.
24	·081	·112	·150	·132	·112	72	Fatty degeneration.
27	·112	·112	·136	·106	·112	21	Gaucher's disease.
28	·100	·108	·100	·084	—	8	} " "
1 mth. later.	·100	·106	·098	·086	—	6	
29	·088	·076	·094	·106	·080	20	" "
30	·112	·168	·156	·118	·106	50	Hodgkin's disease.
31	·081	·112	·137	·131	—	69	Hanot's disease.
32	·100	·137	·130	·100	·100	37	" "
33	·112	·125	·114	·112	·112	20	} " "
9 mths. later.	·112	·152	·134	·125	·134	35	
34	·112	·150	·125	·118	·112	34	} Hepatomegaly due to passive congestion.
1 week later.	·100	·142	·120	·100	—	42	
35	·106	·100	·112	·094	—	5	Wilson's disease.
36	·086	·118	·098	·086	·090	35	" "

TABLE VI.—*Continued.*

Case No.	PERCENTAGE OF SUGAR IN THE BLOOD.					% Increase in blood sugar.	Disease.
	Fasting.	Hours after lævulose.					
		$\frac{1}{2}$	1	$1\frac{1}{2}$	2		
GROUP III							
37	·098	·126	·106	·096	—	28	} Acholuric jaundice.
1 year later.	·100	·106	·098	·100	—	6	
38	·100	·125	·131	·136	·131	36	} " "
1 year later.	·086	·100	·098	·081	—	20	
39	·075	·094	·075	·081	—	25	} Ketosis and gastro-enteritis.
40	·091	·085	·108	·094	—	19	
41	·112	·126	·124	·106	—	8	" "
42	·084	·098	·093	·084	—	16	" "
43	·100	·106	·100	·098	—	6	Coeliac disease.
44	·098	·106	·100	·100	—	8	" "
45	·087	·085	·094	·080	—	8	" "

DISCUSSION.

A review of all the results of the lævulose test detailed above reveals the fact that so far as the normal child is concerned there was not observed in a single instance a delayed fall in the return to the fasting level of the blood sugar. The level of the blood-sugar curve after the ingestion of lævulose showed, however, as pointed out by Tallerman¹⁴, the greatest variations between a definite fall of 10 per cent. and a rise of 28 per cent. It is suggested that the above range should be taken as representing the normal, a conclusion which gains support from the behaviour of the blood-sugar curve in the examples of definite, probable, and problematical hepatic disease which were examined.

Whether or not one would expect an abnormal behaviour of the blood-sugar curve after the administration of lævulose depends on the manner in which this substance is metabolized. If, as previously suggested, the different behaviour of glucose from lævulose depends on whether or not the liver cells are able to convert lævulose into glucose, then naturally the result of the test will depend on the integrity of the liver cells.

It will no doubt be conceded that the functional activity of the liver varies not only in different cases on account of differences in the size of the organ, but also from time to time in the same individual, because of a varying activity of the cells of which the organ is composed. These factors probably account for the variations observed in different normal individuals.

We know, too, that the functional activity of all organs in health is in excess of their physiological requirements. This is specially true of organs which have the power of undergoing hypertrophy, as, for example, the heart and the kidneys; both of these can be the seat of a moderate amount of disease and yet adequately cope with the physiological needs and thus apparently function normally. Consequently it would not seem surprising that the liver might be the seat of a disease which has destroyed only a certain quota of the liver cells or interfered to a certain extent with the activity of

all the cells, and yet not disclose any deficiency of its powers. In this connection one might contrast multilobular cirrhosis, where extensive bands of fibrous tissue interfere with and replace the true liver tissue, with jaundice from an obstruction of the main ducts, where the bile is dammed throughout the whole organ. In the latter condition any change in the hepatic cells will be generalized, and, as a matter of fact, we find that it is here, where the functional activity of the liver is apparently more widely impaired, that the most marked positive lvulose test is obtained.

It is possible, too—in fact, certain—that other organs in some way influence the activity of the liver, and also that the rate of absorption from the gastro-intestinal tract will play a part, so that extra-hepatic disease may be the cause of an apparent hepatic inefficiency.

In view of all these considerations one must be prepared for great variations in the results of such a functional test, not only in health but also in hepatic disease. Consequently the degree of consistency obtained is remarkable when the patients investigated are grouped, according to whether there is definite, probable, or problematical disease of the liver.

In the cases where from the clinical or post-mortem examination definite evidence of disease of the liver was found, it will be noted that 76 per cent. gave what we consider a definitely pathological increase in the blood sugar, and 79 per cent. of these showed a prolongation of the curve. In no case was a delay in the return to the fasting blood-sugar level noted without at the same time an abnormally increased blood sugar.

In the second group of cases where disease of the liver was probable 55 per cent. gave a definitely abnormal rise and 33 per cent. of these gave also a prolonged fall. One case of possible Hanot's disease which was negative became positive 9 months later, although clinically the condition remained the same.

A certain number of diseased conditions were examined, which presented clinically no evidence of disease of the liver but where from the nature of the illness some impairment of hepatic function might exist. Only one, a case of acholuric jaundice (No. 38) showed a definite abnormal rise, but this patient, examined one year later after splenectomy, gave a normal curve.

CONCLUSIONS.

1. The hmoclastic crisis test performed in 20 normal and 25 abnormal conditions of childhood was found to give inconsistent results.
2. In the normal individual variations in the sugar content of the blood after the ingestion of lvulose range from a fall of 10 mgrm. to a rise of 28 mgrm.
3. These variations could not be accounted for by the age of the child.
4. A rise of more than 30 per cent. in the blood-sugar content after the administration of lvulose is considered evidence of hepatic disease.
5. The purity of the lvulose is a most important element in the test.
6. The lvulose test was positive in the majority of examples of definite hepatic disease.

7. The lævulose test gave no evidence that the liver is affected in ketosis or coeliac disease.

8. In some cases in which the clinical evidence leaves a doubt as to the diagnosis the lævulose test may be of value, a positive curve, i.e., an increase in the blood sugar of more than 30 per cent. with or without a prolonged curve, indicating definite and probably extensive derangement of the function of the liver.

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