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Fatty Liver Disease of Children in Ceylon

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A syndrome consisting of hepatomegaly, oedema and various signs of malnutrition has been described as occurring in infants and young children living in various areas of the tropics. It has been noticed in Africa (Trowell, 1937 ; Gillman and Gillman, 1945c ; Hughes, 1946, etc.), Central America (Gil, 1934 ; Castellanos, 1935 ; *etc.*), and the West Indies (Waterlow, 1948). Different observers have stressed the importance of different signs ; thus Trowell (1941) and Stannus (1934) emphasised the pellagroid skin lesions, Gillman and Gillman (1945a) the enlarged liver with an accompanying fatty infiltration. Most have agreed that the condition was the result of malnutrition ; at various times deficiencies in nicotinic acid, riboflavin, protein, vitamin A, etc., have been implicated in the causation by different workers. As Waterlow (*loc. cit.*) has suggested it is probable that the various syndromes described in different parts of the world are essentially varying pictures of the same disease, giving the more or less constant signs of an enlarged, fatty liver and oedema with differing signs of a multiple dietary deficiency superimposed.

Trowell and Muwazi (1945) suggested that the disease was commoner in peoples of African stock but it does occur among children from other ethnic groups, although few cases have been reported as occurring in Asia. Williams (1946) has stated that the disease is very rare in Malaya, while it is often claimed that the syndrome has not been described as occurring in India. In the latter country young children with enlarged livers are seen but this sign is often accompanied by an enlarged spleen and jaundice as well as oedema (Tirumurti and Rao, 1934 ; Prabhu, 1940 ; Chaudhuri, 1944), while at autopsy the liver shows cirrhotic changes and not fatty infiltration. Children in Ceylon, however, are often seen with an enlarged liver, oedema and signs of malnourishment, and here the liver does show fatty changes rather than cirrhosis. This syndrome presented by these children in Ceylon is so similar to that described by Trowell (1937), Waterlow (1948), etc., in other parts of the world that a common aetiology and pathology seems likely. Even in India, Achar (1950) has described a syndrome with oedema as the constant sign, but accompanied in many children by gross signs of vitamin A or B group deficiencies and a palpable liver (62 per cent. of cases), this liver, in the fatal cases, showing changes varying from fatty infiltration to diffuse hepatic cirrhosis.

Below are presented the results of a series of simple biochemical tests applied to 40 Ceylonese children who were diagnosed as suffering from 'fatty liver disease'. The overcrowded conditions in Ceylon's hospitals, where the patients may exceed the beds by 100 per cent., prevents any but the simplest procedures being performed. It is only known for certain that excess fat was present in the liver of 8 children (in 4 estimated post-mortem and 4 at liver biopsy), but all the children in the series did show a similar basic syndrome.

A total of 40 children presenting this syndrome have been examined to date; control tests on normal children of a similar age have also been made. The children were examined as soon as possible after admission to hospital (usually within 24 hours) and the investigations made on them included estimations of the plasma alkaline phosphatase (King and Armstrong, 1934), plasma bilirubin (Haslewood and King, 1937), plasma proteins, plasma albumin, fibrinogen (King, Haslewood and Delory, 1937), prothrombin time (Quick, 1943), total fat in faeces with differentiation into neutral fat, fatty acids and soaps, (King, 1940) fasting blood fat (Bloor, 1928a), blood cholesterol (Sachett, 1925), lipide phosphorus (King, 1946), blood haemoglobin (Sahli), blood red cell content, total nitrogen, creatinine and creatine in a 24 hour specimen of urine (Delory, 1948), bromsulphalein clearance, and, in a few cases, analysis after a gastric test meal (Riggs and Stadie, 1943).

As we were interested, at first, in discovering the common biochemical changes all the children were kept on the same treatment, a treatment which previous experience had shown gave the best chance of recovery to date. The therapy consisted first of a basic diet whose main items were bread, a breakfast cereal, rice, butter, eggs, milk, liver, and beef with an oral preparation of a protein hydrolysate twice a day in milk. All children also received a daily intra-gastric drip of a protein hydrolysate, vitamin B complex by tablets or injection, cod liver oil, an iron mixture, and liver extract by injection. Those with open skin lesions had dressings of lanoline or sulphonamide ointments applied. The diarrhoea cases received arrow-root and sulphaguanidine. In addition some of the later cases also received supplements of methionine (5 cases) or dried hog's stomach (1 case) or vitamin B_{12} (2 cases).

All children are not brought to hospital at the same stage of the disease and, therefore, variations in the findings between different patients must be expected. An effort was made by questioning the mother to discover the duration of the illness before entering hospital but different cases vary in the speed of development of the syndrome.

The almost constant presenting symptom was swelling of the limbs and the average duration of the illness before entering hospital was 7 weeks (range 1 week to 1 year). In most of Waterlow's cases there was a history of vomiting, and diarrhoea was much less frequent. Here vomiting was a symptom in only 3 cases while diarrhoea had occurred in 25 of the patients. On examination all cases presented an enlarged, palpable liver which extended between 1 and 4 fingers' breadth below the costal margin. Oedema was present in all but 3 cases, being commonest on the feet and legs and occasionally being present in the eyelids and on the hands. All the children showed lesions of the mucous membranes and, or changes in the skin and hair but these signs varied from patient

to patient. Nineteen children had a xerosis; 19 showed an angular stomatitis; 22 had the dry, scanty, thining hair said to be so typical of infantile pellagra in Africa (Trowell and Muwazi, 1945) although depigmentation was rare; 35 showed changes in the texture and nutrition of the skin. In most of these the skin was just dry and wrinkled but 15 of them showed 'mosaic' patterns on the skin and, in all these cases, patches of skin had broken and peeled to give raw surfaces. These varying muco-cutaneous signs probably merely reflect the differing emphasis of the malnourishment between individual children.

A common complication of this disease is fever due to pulmonary infections. Cases admitted with fever were not investigated but 6 patients developed pulmonary lesions (4 broncho-pneumonia; 2 lobar pneumonia) while in hospital and 4 of these eventually died.

It was not possible to judge from the clinical signs on admission what the ultimate prognosis would be. True all cases with a liver enlarged more than 3 fingers' breadth below the costal margin and also with extensive oedema (involving the face as well as the feet and legs) died, but the two signs did not usually correlate. Some patients with a large liver had little oedema and *vice versa*. Some died with only 1 finger-breadth of liver palpable; others lived with a liver extending 3 fingers' breadth below the ribs. Some died with only slight oedema; others lived after showing a generalised oedema. Death often occurred suddenly and with little warning. In four patients, as stated, it was preceded by pneumonia; in others there may have been a sudden dyspnoea with a rapid, thready pulse but no detectable alteration in the other clinical signs. (It is very difficult to persuade Ceylonese parents to allow autopsies to be performed on their deceased children. Four of the cases were examined post-mortem and all showed very similar findings. The liver was enlarged and yellow in colour and the cut surface was greasy. Histologically there was a marked degree of fatty change which was mainly to be seen at the periphery of the lobule. The veins were congested and there was sinusoidal dilatation. The portal tracts were very cellular, the cells being mainly lymphocytes, fibroblasts and eosinophils. The kidneys were pale and swollen and showed cloudy swelling of the tubular epithelium. The skin exhibited a certain degree of parakeratosis with hyper-pigmentation of the stratum corneum. A part from a small collection of fluid in the peritoneal cavity, no other abnormal findings were reported).

It seemed pertinent to see therefore, whether any simple biochemical tests would give a more reliable estimate of the fate of the child. It is necessary to compare the results of these biochemical tests with those from presumed normal children. Unfortunately such 'normal' or 'average' findings for children are surprisingly scanty in the literature and, in any case, one of the authors has learned by bitter experience that many of the 'normal ranges' of physiological and biochemical tests that he reverred in the Western hemisphere bear little relationship to the range of findings presented by Ceylonese. Therefore similar tests were made on 50 'not-ill' children from a similar age range (1 to 6 years) to that of these patients.

Tests of Liver Function (Table 1):—

TABLE I

The Mean Results from some Biochemical Tests upon Children with Fatty Liver Disease.

	Normal Children	Children with Fatty Liver Disease		
		All Cases 40 Subjects	Surviving Cases 27 Subjects	Cases that Died 13 Subjects
Plasma Alkaline Phosphatase units/100 c.c. ..	21·8 ± 0·80 (9-29)	15·8 ± 0·82 (8·7-39·9)	14·8 ± 1·08 (8·7-35·0)	17·9 ± 2·88 (8·7-39·9)
Plasma Bilirubin—mg./100 c.c. ..	0·88 ± 0·07 (0·44-1·51)	1·05 ± 0·13 (0·18-2·73)	0·88 ± 0·11 (0·18-1·84)	1·32 ± 0·24 (0·44-2·73)
Bromsulphalein Retention- ..	3·5 ± 0·73 (0-5·3)	20·9 ± 2·49 (5·6-71·9)	20·5 ± 3·14 (5·6-71·9)	21·7 ± 4·28 (8·6-37·5)
Prothrombin Time-seconds ..	18·3 ± 0·14 (18-19)	22·0 ± 0·68 (18-25)	22·0 ± 0·50 (18-25)	22·5 ± 2·12 (19-25)
Total Plasma Protein g./100 c.c. ..	7·50 ± 0·24 (5·0-9·6)	5·75 ± 0·23 (2·42-8·89)	5·86 ± 0·25 (2·42-8·19)	5·53 ± 0·48 (2·96-8·89)
Plasma Albumin g./100 c.c. ..	4·25 ± 0·11 (3·4-5·5)	2·80 ± 0·13 (0·30-4·75)	2·92 ± 0·15 (0·30-4·75)	2·55 ± 0·27 (1·35-3·78)
Plasma Fibrinogen g./100 c.c. ..	0·314 ± 0·005 (0·27-0·34)	0·354 ± 0·021	0·340 ± 0·021	0·388 ± 0·045
Albumin/Globulin Ratio ..	1·72 ± 0·09 (0·9-2·7)	1·19 ± 0·14	1·25 ± 0·15	1·05 ± 0·13
Total Fat in Faeces g./100 g. ..	10·0 ± 0·80 (13·3-30·8)	30·6 ± 3·36 (1·6-80·8)	27·2 ± 4·37 (1·6-80·8)	36·9 ± 4·00 (10·6-51·5)
Per cent. Faecal Fat as Soap ..	46·4 ± 2·38 (28·3-77·5)	37·8 ± 2·87 (7·6-77·3)	40·0 ± 3·74 (13·0-64·8)	33·9 ± 3·91 (7·6-77·3)
Per cent. Faecal Fat as Fatty Acids	37·7 ± 1·91 (22·1-49·9)	40·4 ± 2·64	36·6 ± 3·16 (10·8-52·9)	47·4 ± 3·91 (26·8-69·4)
Per cent. Faecal Fat as Neutral Fat ..	15·9 ± 1·40 (0·4-29·0)	22·5 ± 2·46 (0·0-62·8)	24·6 ± 2·95 (0·0-62·8)	18·9 ± 4·25 (7·9-43·0)
Blood Haemoglobin g./100 c.c. ..	10·95 ± 0·29 (8·9-14·8)	8·25 ± 0·35 (3·4-12·3)	7·66 ± 0·41 (3·4-12·3)	9·80 ± 0·39 (8·2-11·2)
Red Blood Cells-millions/c.m.m.	4·09 ± 0·11 (2·94-5·60)	3·01 ± 0·13 (1·07-4·67)	2·88 ± 0·16 (1·07-4·67)	3·33 ± 0·09 (2·86-3·85)

(The figures in parenthesis indicate the range of values obtained in each group).

TABLE 1 (*Contd.*)

The Mean Results from some Biochemical Tests upon Children with Fatty Liver Disease.

	Normal Children	Children with Fatty Liver Disease		
		All Cases 40 Subjects	Surviving Cases 27 Subjects	Cases that Died 13 Subjects
24-hour Urinary Nitrogen—g. ..	1960	1449	1484	1352
24-hour Creatinine m.g./Kg. body wt.	8·02	7·86	7·81	7·95
24-hour Creatinine mg./Kg. body wt.	5·45	4·44	5·15	2·88
Blood Fat mg./ 100 c.c. ..	1740 ± 77·5 (966-2381)	2986 ± 251·6 (939-8183)	2250 ± 171·5 (939-4970)	5103 ± 812·4 (2063-8183)
Blood Cholesterol mg./100 c.c. ..	149·0 ± 5·57 (103-203)	161·6 ± 8·83 (110-341)	171·3 ± 11·58 (110-341)	138·9 ± 8·53 (120-191)
Blood Lipide Phosphorus mg./ 100 c.c.	15·8 ± 0·41 (12·5-19·3)	15·7 ± 1·77 (5·88-50·0)	15·5 ± 1·93 (5·88-50·0)	16·1 ± 3·91 (8·5-41·5)

(The figures in parenthesis indicate the range of values obtained in each group).

(*a*) **Plasma Alkaline Phosphatase.** The mean for the diseased cases was less than the mean for normal children and this difference is significant ($P = 0·001$). Those cases which died gave a greater mean plasma phosphatase than did those which survived although this difference was not significant. During treatment the value declined in one-third of the cases and rose in the rest. In those that died the value increased in half of them and decreased in the others. Therefore this biochemical test would not seem to be a good sign either for prognosis or for the progress of the disease.

(*b*) **Plasma Bilirubin.** The mean for all the diseased cases exceeds the normal mean and the mean of those who died exceeded that of those who survived but these differences were small and not statistically significant. The actual measured values of plasma bilirubin were small and moreover the range of values in the diseased cases overlapped considerably the normal range. Hence the plasma bilirubin is not a good measure for differentiating diseased from normal children although it may help a little in deciding prognosis.

(*c*) **Bromsulphalein Clearance.** This would seem to be a valuable test since in all patients the clearance was definitely delayed. Moreover, during treatment the clearance improved in 6 out of 8 cases which had repeated estimations. Therefore, this test does differentiate the disease cases from normal children and may indicate progress during treatment. However, it gave no help in deciding the prognosis for the child on admission since, although the mean clearance for the surviving cases was greater than that for those who eventually died, there was a considerable degree of overlap for the ranges of the two series.

(*d*) **Prothrombin Time.** This test was only performed on some of the later cases because, although the instructions of Quick (1948) were faithfully repeated, a time of 11-13 seconds could never be obtained in our apparently normal children. Finally it was realised that the prothrombin time in Ceylonese children was always more delayed than the times reported in the literature and a time of 18 or 19 seconds which was invariably obtained in the normal cases, was taken as the standard time. In 13 out of 16 cases tested the prothrombin time exceeded 19 seconds and in 3 out of 4 cases the time decreased with treatment. Only 4 of these 16 patients eventually died and one of these gave a normal prothrombin time. Hence, like the bromsulphalein clearance test, the measurement of prothrombin time is of value in differentiating cases of liver dysfunction from normal children and indicates improvement with treatment but is of doubtful value in deciding prognosis. There was no correlation at all between prothrombin times and the bromsulphalein clearance values but no child with an enlarged liver gave normal results for both tests. The two tests together, therefore, differentiated all the patients from the normal children.

(*e*) **Plasma Protein Estimations.** The mean plasma protein concentration in the normal children was significantly greater than that for the diseased children ($P = 0{\cdot}001$) and the mean value for these children who have survived exceeded that for those who died, but here the difference was not significant. Again the ranges of concentration for each group of children overlapped so that it was impossible to be dogmatic about individual children. Of the 13 children who died, 12 had a plasma protein concentration which was less than the normal mean of 7·5 g./100 c.c. and 6 gave a value below the minimum for the normal range (5·0 g./100 c.c.).

The plasma albumin concentration is probably of more value in these patients than the total plasma protein concentration. The albumin concentration was significantly less ($P = 0{\cdot}001$) and in only 6 out of 40 did the value extend into our normal range. In general, therefore, there was a good differentiation by this test of the diseased cases from the normal. Of the 27 patients in the series who survived all but one had a plasma albumin concentration below the normal mean (4·3 g./100 c.c.) and 25 had a concentration below the minimum of the normal range (3·4 g./100 c.c.). Of the nine cases, on whom repeat estimations were possible, four showed substantial increases during treatment. Moreover, the mean concentration for the children who died was less than that of the survivors although this difference was not significant and the ranges of concentrations overlapped. All of the 13 dying patients had an albumin below the mean normal concentration and for 10 of them this concentration was below the minimum of the normal range. The lower the plasma albumin concentration, therefore, the worse the prognosis.

Estimations of the plasma fibrinogen were also made. The results did not reveal any significant differences between the ill-children and the normal group nor were there any consistent trends in the deviations of the concentrations, the mean of the survivors being higher than the normal mean while the mean of those who died was less than normal.

The mean albumin/globulin ratio was less in the ill-children than in the normal group ($P = 0{\cdot}001$) and less in those who died than in the survivors. In all but one

of the dying patients the ratio was less than the normal mean, although in only 4 was it below the minimum of the normal range (0·9).

The Fat Content of the Faeces. Steatorrhoea has been reported in the majority of infants suffering from kwashiorkor (Trowell, 1937 ; Gillman and Gillman, 1945b) or fatty liver disease (Waterlow, 1948). In these children in Ceylon, too, there was a higher mean total fat content of the faeces than in normal children ($P = 0·001$) and there was only a slight overlapping of the normal and the diseased ranges of fat content. The children who died showed a greater mean faeces fat content than did those who survived. The difference was not significant and the ranges overlapped but in all but 2 of the dying cases the fat content of the faeces definitely exceeded the maximum of the normal range.

Of the types of fat present in the faeces, the patients had a lower proportion of soap in the faeces ($P = 0·05$), those children who died having the lower mean content. All but two of the dying children gave faeces with a proportion of soap which was lower than the mean for normal children, but of the surviving children half of them gave a lower and half a higher than the normal mean faeces soap content.

The average proportion of neutral fat in the faeces was higher than the normal mean ($P = 0.05$). The fatty acid content was about the same in the surviving, diseased children and the normal children although those who died had a higher percentage ($P = 0·05$).

Therefore, this condition is distinguished by a high fat content in the faeces and a lower proportion than normal of this fat is present as soap. The greater the faeces fat concentration and the lower the soap content then the worse is the prognosis.

The Fat Content of the Blood. This was increased in most of the patients, and the difference between the means of the diseased and the normal children was significant ($P = 0·001$). The blood fat concentration was greatest of all in the dying and in all these cases it exceeded the maximum for the normal range. In the 7 children upon whom further estimations during treatment were made, 4 showed a decrease in their blood fat.

This lipaemia was accompanied by a higher than normal mean blood cholesterol content, although the difference was not significant and those children who eventually died showed a lower than normal mean value.

The blood lipide phosphorus tended to be high in those who died but the mean value for all the diseased was the same as that for normal subjects.

The Blood Haemoglobin Concentration was significantly less in the diseased children than in the normal children ($P = 0·001$) and, curiously, less in the survivors than in those who died ($P = 0·01$). Of the 13 who died, 4 showed a higher blood haemoglobin content than the normal average, but all showed a lower red blood cell count than normal ($P = 0·001$).

Total Nitrogen in the Urine. Because of the difficulties of collecting 24-hour-specimens of urine from infants and young children, only some of the older boys could be examined for this factor. The few results available do suggest that the excretion of nitrogen in the urine is less in the ill-children than in the normal children

and is probably least of all in those dying from this condition. When related to body weight (without correction for the oedema), the urinary nitrogen was still less than in the normal children, although now the dying cases gave a higher mean than the survivors.

The creatinine excretion was similar to that occurring in normal children but the creatine output was less in the dying children. (Our 'normal' creatine values are less than those reported in the literature; Harding and Gaebler, 1922 and 1923). No correction has been made for the weight of the oedema fluid and it is possible, therefore, that the creatinine and creatine excretions may be much reduced if related to the metabolically active body weight and the low creatine output in those children who died may be due to the small skeletal muscle mass following the wasting illness.

The urine contained no albumin or bile pigments nor was there any excess of urobilinogen.

Fat and Phospholipide Content of Liver. Only four of the children who died could be examined post-mortem, but all four showed higher than normal liver fat contents. The normal phospholipid content of the liver is uncertain but the values here are probably lower than normal. (Bloor, 1928, says beef liver contains 10-12 g. phospholipid per 100 g. fat-free dry weight). The iodine value of the liver fat was also low, e.g.

Case Number	Total Fat g./100 g. wet weight	Phospholipid mg./100 g. fat-free dry weight	Iodine Value of Liver Fat	Nitrogen Content g./100 g. wet weight
8	31·3	688	63	4·46
9	29·3	529	59	1·97
41	14·0	579	66	—
44	16·4	435	65	1·13

Gastric Analysis. On only eight of the cases were test-meal gastric analyses performed. They all showed practically complete absence of free HCl and low total acid values. The peptic activities were probably normal (Table 2).

Gillman and Gillman (1945b) have also reported evidence of gastric dysfunction in their cases in Africa although Waterlow (1948) found that the West Indian children showed normal or hyper-acidity of the gastric juice. In our series the only case with a marked acid secretion (case 44) died but so did two others with low total acid secretions.

Fat Balance Studies. In view of the steatorrhoea that was discovered, crude fat balance studies were done on 10 of the patients and on 7 normal children. Duplicate samples of the food eaten were collected for 3 consecutive days and analysed for total fat. The first and last meals of this period were coloured with carmine so that the corresponding faeces collections were facilitated. The patients had a greater proportion of their fat intake present in the faeces, but the values overlapped and the differences were not marked (Table 3). This is not necessarily evidence in

TABLE 2

Gastric Test Meal Results in Fatty Liver Disease.

Case Number	Gastric Function	Time in Minutes					
		Z	30	60	90	120	150
42 (died)	Free Acid	0	0	0	0	0	—
	Total Acid	1·2	7·3	8·6	12·6	13·5	—
	Peptic Activity	7·6	7·2	20·9	5·7	3·4	—
43	Free Acid	0	0	2·4	0	0	0
	Total Acid	2·5	8·7	15·6	8·7	17·5	12·0
	Peptic Activity	23·0	20·9	31·1	14·1	34·6	—
44 (died)	Free Acid	0	0	46·0	50·0	2·5	—
	Total Acid	18·1	37·5	75·6	92·5	13·3	—
	Peptic Activity	19·3	19·6	3·7	9·1	6·0	—
45	Free Acid	0	0	0	0	0	0
	Total Acid	6·2	17·5	20·0	4·4	8·7	18·1
	Peptic Activity	18·9	27·1	22·8	30·9	19·3	18·9
47 (died)	Free Acid	0	0	0	0	0	—
	Total Acid	2·9	3·8	7·6	2·5	2·5	—
	Peptic Activity	23·7	13·9	19·7	6·5	3·6	—
48	Free Acid	0	0	0	0	0	0
	Total Acid	3·6	7·5	13·3	6·9	5·0	5·6
	Peptic Activity	13·7	13·9	36·5	20·0	9·8	9·8
50	Free Acid	0	0	0	2·5	0	2·5
	Total Acid	2·5	10·0	4·6	10·0	13·8	10·9
	Peptic Activity	40·0	19·1	35·6	13·9	15·0	9·3
51	Free Acid	0	3·5	4·5	5·0	2·5	0
	Total Acid	5·0	9·8	10·3	11·0	17·8	9·5
	Peptic Activity	18·9	36·1	10·7	11·3	18·6	0·5

Acid values are given as ml. N/10 HCl. per 100 ml.

Peptic activity as velocity constant of the protein hydrolysis $\times 10^3$.

favour of diminished fat absorption since faecal fat comprises both unabsorbed and excreted fat (Shapiro *et al*, 1936) and steatorrhoea may occur on a fat-free diet (Gillman and Gillman, 1945b).

TABLE 3

Fat Balance Studies on Ceylon Children.

Case Number	Age in months	Sex	Total Fat in Food g.	Total Fat in Faeces g.	Faeces Fat as per cent. of Fat Intake
11 (died)	28	F	82·39	2·14	2·60
16	12	F	99·99	4·95	4·95
17	60	M	190·65	20·00	10·50
23 (died)	36	M	136·84	12·30	9·00
43	18	F	60·85	14·50	23·90
44 (died)	60	M	100·63	2·18	2·16
45	84	F	64·03	1·83	2·85
52	36		92·06	0·13	0·15
54 (died)	36	M	45·81	3·86	8·45
55	15	M	47·29	1·42	3·00
Average of Disease Cases	—	—	—	—	—
Normal 34	—	F	156·15	3·94	2·52
Normal 35	84	F	210·17	3·83	1·82
Normal 36	48	M	180·08	3·76	2·09
Normal	60	M	347·12	22·60	6·50
Normal	36	M	290·41	1·90	0·54
Normal	22	M	283·03	11·04	3·91
Normal	60	M	362·49	10·18	2·81
Average of Normal Cases	—	—	—	—	—

The normal children had, in general, a greater fat intake than the patients, who were on a standardized diet. The children who died had low proportions of the fat intake in their faeces so that this dysfunction is probably not important from the point of view of prognosis.

Other Findings. Eleven of the children showed round—or hook-worms in their faeces. One child had a positive malaria blood-smear.

Biochemical Findings in the Dying Patients. Only five biochemical tests gave consistent findings in those patients who eventually died. These were an increased bromsulphalein retention, a decreased plasma albumin concentration, an increased prothrombin time, an increased blood fat concentration and a decreased

red blood cell count. Seventeen of the survivors gave similar results so that patients presenting this combination of findings have about a 40 per cent. chance of dying.

Age Incidence. The children varied in age from 9 months up to 7 years. The average of Waterlow's cases in the West Indies was 10½ months, although children in Africa usually exhibit this syndrome after the age of 18 months. Because of the extensive age range of our cases, the question arises as to whether we are dealing with the same syndrome in all children. The group has, therefore, been divided into 3 smaller groups, viz., those aged up to and including 18 months (roughly corresponding with the West Indies series—up to 16 months), those over 18 months and up to 36 months of age (corresponding to most of the African cases) and those over 36 months of age. The main signs and symptoms presented by these 3 groups can be compared (Table 4).

TABLE 4

The Main Signs, Symptoms and Biochemical Findings in Cases of Fatty-Liver Disease, classified by age-group.

Age of Children in Months	9-18	19-36	37-84
Number of Cases	14	16	10
Duration of Symptoms (weeks)	3·1	10·6	4·9
Vomiting	2	1	0
Diarrhoea	9	9	7
Oedema	14	15	9
Enlarged, palpable Liver	14	16	10
Angular Stomatitis	8	9	1
Xerosis	3	9	6
Skin Lesions—total	13	13	9
Skin Lesions, pealing with raw surfaces	3	9	1
Hair, dry, scanty	8	9	5
Deaths	4	6	3
Bromsulphalein Retention-	17·8	19·7	22·8
Plasma Protein—g./100 c.c.	6·01	5·77	5·76
Faeces Fat—g./100 c.	33·6	39·8	18·3
Blood Fat mg./100 c.c.	1980	3037	3330
Blood Cholesterol mg./100 c.c.	165·8	140·3	173·0
Blood Lipide Phosphorus mg./100 c.c.	14·9	18·1	15·2
Blood Haemoglobin g./100 c.c.	8·88	8·17	8·19

The main signs and symptoms have a similar incidence in each group although the muco-cutaneous manifestations of malnourishment do vary. Xerosis is least

common in the youngest group; perhaps there has not been time for the signs to develop. Angular stomatitis, by contrast, is uncommon in the eldest group and skin signs, which have the same frequency in each group, are more often of the pealing variety in the intermediate group. It is impossible to say why there should be these differences in the cutaneous clinical signs. The death rate in the three age-groups is probably the same and it would appear that main syndrome is common to all age groups.

Waterlow (1948) has suggested that the condition may be associated with the change of diet occurring at weaning, with an interval of 2 to 6 months between weaning and the onset of symptoms. The occurrence of cases in children of up to 7 years of age is evidence against weaning being a cause. In the 3 age-groups the interval since weaning will obviously increase with increasing age of the child, e.g. mean time since weaning in the

9 to 18 months age-group was 5·8 months,
19 to 36 months age-group was 12·2 months,
and in the 37 to 84 months age-group was 39·7 months.

Although weaning did occur earlier in the youngest group, in the other two groups weaning occurred at a similar age, e.g. mean time of weaning in the

9 to 18 months age-group was 9·6 months,
19 to 36 months age-group was 15·8 months,
and in the 37 to 84 months age-group was 15·7 months.

An attempt was made to obtain the dietary history since weaning but only rough indications of the qualitative values of the diets could be elicited. The age of the child at weaning did not affect its chance of receiving milk in its new diet. About half the children in each age-group received milk, although only in the youngest group did any children receive only milk on weaning. In the two older groups half the children received diets of rice, vegetables and milk and the other half ate rice and vegetables only. Judging from the results of our nutrition surveys in Ceylon (Cullumbine *et al*, 1950) these diets indicate a high carbohydrate and a low protein intake by these children. Waterlow (1948) has described similar qualities in the diets of the West Indian children.

The mean biochemical findings for the three age-groups showed slight but often insignificant differences. Thus the bromsulphalein clearance tended to be more delayed in the older group but the differences are not significant. The mean total plasma protein concentration was less in the older group but again the variation was not significant. The faeces fat content, in the other hand, was significantly less in the older group, while the blood total fat concentration increased with age and was significantly less in the youngest group. The blood cholesterol and the blood lipide phosphorus contents showed no significant changes between the various age groups and neither did the haemoglobin concentration although this tended to be higher in the youngest group. The apparent duration of the illness before reporting to hospital did not vary between the groups.

Discussion

The syndrome in Ceylon is characterized, therefore, by biochemical findings which indicate a low plasma alkaline phosphatase, a delayed bromsulphalein clearance, a delayed prothrombin time, a low plasma protein, and especially albumin, content,

a low blood haemoglobin concentration, a low red cell count, diminished urinary total nitrogen, a high fat content in the faeces, this fat tending to show a lower proportion of soap and a higher proportion of neutral fat than normal, and a high blood fat concentration.

The low plasma phosphatase is difficult to understand since it should be increased with hepatic disorders (Greene *et al*, 1934). It is said to be lower in hypothyroidism (Talbot *et al*, 1941). The delayed bromsulphalein clearance and prothrombin time have been reported by Trowell (1937) and Waterlow (*loc. cit.*), as have the lowered plasma protein—and the especially low plasma albumin—concentrations. The former results are indicative of impaired hepatic function and the hypoproteinaemia may also be due to the liver damage. It is more likely to be nutritional in origin in view of the suggestive dietary history and low urinary nitrogen outputs.

Other observers have also commented on the moderate hypochromic anaemia and the steatorrhoea (the latter may be the cause of the former, see Hawking *et al*, 1950) which may occur in these children, but the high blood total fat content has not been remarked upon previously. The values reported for normal Ceylonese children are higher than those given for American children (Erichson *et al*, 1937) and the inconstant variation of the blood total cholesterol and lipide phosphorus contents makes difficult the interpretation of this result. The blood lipides are increased in conditions such as diabetes, leukaemia, severe haemolytic anaemias, nephrosis (Thomas, 1943) and in carbohydrate starvation (McQuarrie *et al*, 1933). The diets of these patients in Ceylon suggested a disproportionately high carbohydrate content in their diets. The total calorie values of the diets are not known, however, and they may have been deficient. Waterlow described the diseased babies in the West Indies as being well covered with subcutaneous fat, but this is not true of the Ceylonese children, who showed both loss of their fat depots and muscular wasting. In other words there was undernourishment as well as malnourishment. Undernourishment will reduce both subcutaneous and liver fat and probably the lipaemia is indicative of the drain on the subcutaneous stores. The hepatic dysfunction may prevent a high proportion of this fat being utilised so that accumulation occurs in the liver.

In animals the distribution of fat in the liver varies with the source of the fat (Best, 1950). In starvation the excess fat is deposited in the periphary of the liver lobule and, here in these Ceylon children, examination of both post-mortem liver sections and liver biopsy material invariably showed an accumulation of fat in the periphary of the lobule. This is strongly suggestive evidence in favour of the liver fat being of depot origin and not being due to a deficiency of the lipotropic agents where fat first accumulates in the centre of the liver lobule. The low iodine value of the liver fat, which seems to be chiefly neutral fat, supports this interpretation. Waterlow (1948) also reported a low iodine value for the liver fat, although the fat contents of the livers of his patients tended to be higher than those reported here. Perhaps in Ceylon, as suggested, there is undernourishment as well as malnourishment in these children; the two together should produce a lower amount of liver fat than malnourishment alone.

These preliminary observations were only intended to define the biochemical picture presented by children with enlarged and fatty livers in Ceylon so that any lengthy discussion as to aetiology would be premature. Other observers have

commented on the lack of response to treatment with choline and methionine (Gillman and Gillman, 1945d ; Waterlow, 1948) which fact suggests that deficiency of lipotopic agents may not be a fundamental causative factor. This is supported by the distribution of the fat in the livers of the cases reported here. Five of the cases did actually receive supplements of methionine and one of these eventually died. This is a better death-rate than that for the whole group but the numbers are too small to be of value. Gillman *et al*, (1944) report good results with dried stomach preparations as a therapy and Trowell (1946) confirmed this. Only one of the Ceylon children in this series received dried stomach and this case died.

Those patients who did respond to the standard treatment of an adequate calorie—high protein—and multiple vitamin—containing diet showed a progressively increasing alertness, and the skin lesions healed, the oedema disappeared and the liver gradually receded. The liver was always the slowest to respond and, when all else appeared normal, the liver might still be easily palpable. Others have noticed that the liver lesion is refractory to therapy. The disappearance of the oedema did not always correspond with a rise in the plasma protein or albumin concentration and all cases of oedema did not have a low plasma albumin content. There was no biochemical evidence of renal insufficiency and no other signs of vitamin B_1 deficiency. Both the oedema and the hypoproteinaemia may be due to a low protein diet and both did eventually respond to an increased protein intake but the interrelationships between undernourishment, hypoproteinaemia and oedema have still to be adequately defined (Keys *et al*, 1945).

Riboflavin deficiency (Lillie and Selnell, 1933), pantothenic acid deficiency (Schaeffer *et al*, 1942) and nicotinic acid deficiency (Denton, 1925) have each, at various times, been described as causing fatty changes in the liver. Signs of vitamin deficiency do occur in these children but the signs are not constant from patient to patient and therapy with any of these vitamins alone is said to be ineffective in curing the liver lesions (Waterlow, 1948).

There is some evidence of dysfunction of the alimentary canal in these children. Diarrhoea was common as it is in similar cases in Africa (Trowell, 1937 ; Gillman and Gillman, 1945b), but it was not a prominent feature of the syndrome in the West Indies (Waterlow, 1948), Steatorrhoea, low gastric acidity and possibly a slightly reduced fat absorption were also found. The significance of these observations is again difficult to define and none of them were of value in assessing prognosis. Radiological changes in the intestine have been described by Scott Brown and Trowell (1944) in children with kwashiorkor and Waterlow (1948) noted evidence of pancreatic atrophy at autopsy. The latter was not seen in these cases in Ceylon, although the steatorrhoea with the tendency to increased neutral fat in the faeces may be due to pancreatic insufficiency.

The confusing picture is one of many suggestive dysfunctions and multiple nutritional deficiencies, the only constant feature being the enlarged and fatty liver. The precise aetiology of this lesion has still to be defined.

Summary

Forty Ceylonese children, aged 9 to 84 months, with enlarged livers, oedema and other signs of malnourishment have been investigated and the biochemical findings compared with the results of similar tests on fifty normal children

The diseased children present, in general, a low plasma alkaline phosphatase, a delayed bromsulphalein clearance, a delayed prothrombin time, a low plasma protein (and especially albumin) content, a low blood haemoglobin concentration, a low red cell count, diminished urinary nitrogen, a high fat content in the faeces with a higher proportion than normal of this fat as neutral fat, a high blood fat concentration, and a low gastric acidity.

The fat in the liver is increased in quantity and is mainly neutral fat, has a low iodine value and is distributed at the periphary of the liver lobule. It has probably been transferred from the fat depots.

The children all gave a dietary history which was suggestive of low protein and high carbohydrate intakes.

The basic syndrome is probably the same as that described as occurring in children in Africa, Central America and the West Indies, though the picture is confused by the varying accompanying signs of multiple dietary deficiencies.

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