between 35 and 140 μ in diameter, but a few thrombi were seen in interlobular arterioles. The glomerular arterioles were rarely affected, but a few were found in which the thrombus extended into the glomerular hilum; it was not possible to say whether it was the afferent or efferent arteriole that was affected. In consequence of this relative immunity of arterioles the glomeruli were nearly all normal.

A remarkable degree of atrophy was present, however, in the tubules, with ischaemic fibrosis (Fig. 2). As the ischaemia was due to venous rather than to arterial obstruction, the pattern was entirely different from that seen in arteriosclerosis, and the ischaemic areas were scattered irregularly over the cortex.

Most of the thrombi showed signs of organization, and invasion by spindle cells, with formation of reticulin fibrils in the more recent, while the older showed collagenous scarring. Similar thrombi were to be seen in the arterioles and venules of the hepatic portal systems.

These microscopical findings are fairly typical of this disease. The two unusual features in this case are the thrombosis of venules rather than arterioles and the ischaemic fibrosis of the renal cortex. Symmers (1952) says that it is exceptional to find thrombi in venules, and that some authors claim that the supposed venules are dilated arterioles which have been misidentified. That cannot be so in the present case, as only a few of the thrombosed vessels are so far dilated as to make their identity doubtful. The relative paucity of ischaemic lesions is usually explained by the incomplete occlusion of many affected vessels. In this case, also, many vessels only seem to have been partially occluded by thrombus, but the ischaemic fibrosis is obvious. The haphazard distribution of the ischaemic areas is additional evidence that it is not mainly arterioles that have been obstructed.

Discussion

The correct diagnosis was not made during life, owing to lack of knowledge of the syndrome. There can be little difficulty otherwise in recognizing the fully developed case, with its four cardinal clinical features of haemolytic anaemia, thrombocytopenic purpura, fever, and terminal neurological signs.

In discussing the differential diagnosis, Symmers (1952) has stressed that thrombotic purpura must be considered wherever haemolytic anaemia and thrombocytopenic purpura are associated. Only thus can the diagnosis be made before the appearance of the essentially terminal neurological signs. Biopsy has an obvious place in diagnosis and, although the haemorrhagic tendency must limit the procedures undertaken, successes have been recorded with both skin and muscle specimens. Cooper *et al.* (1952) demonstrated the typical lesions in paraffin sections of aspirated bone marrow in both of their cases, but this is contrary to all previous experience.

In the above case the haemolytic origin of the jaundice was overlooked in the early stages. Its depth, the presence of bile in the urine and the absence of urobilin, and the positive flocculation tests suggested some form of hepatitis. Hirsch and Dameshek (1951) have stressed the frequency with which virus infections precede the onset of the acute form of thrombocytopenic purpura, and it was thought conceivable that a virus hepatitis could behave in this way. Furthermore, neurological signs are a recognized occurrence in liver failure (Walshe, 1951).

The only apparent therapeutic success is that of Meacham *et al.* (1951). In their case splenectomy was performed after an unusually early diagnosis, and was followed by a remission of three years' duration. No other patient has survived for more than ten months. Splenectomy has conspicuously failed in other cases, and the same applies to A.C.T.H., cortisone, various antibiotics, and repeated blood transfusions. Mepacrine has so far not been employed in the treatment of thrombotic thrombocytopenic purpura, but a trial of its effect seems justifiable, on empirical grounds, in view of the possible relationship between this disease and disseminated lupus erythematosus (Editorial, 1952; Symmers, 1952; Barondess, 1952). Page (1951) has reported the value of mepacrine in the treatment of some cases of the latter disease.

Summary

A case of thrombotic thrombocytopenic purpura is reported.

The characteristic thrombotic lesions were found in the renal cortex and hepatic portal systems.

The principal vessels affected were the venules. This is in contrast to previous reports, in which the changes have been found only in capillaries and terminal arterioles, and their occurrence in venules disputed.

Ischaemic fibrosis of the renal cortex was more evident than is usual.

I wish to thank Professor C. Bruce Perry for suggesting that this case should be reported, and Dr. D. W. Pugh for permission to publish and for criticism and advice.

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GALACTOSAEMIA

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[WITH SPECIAL PLATE]

Children with galactosaemia are unable from birth to metabolize galactose normally. Galactose, derived from lactose in milk, accumulates in the blood and gives rise to enlargement of the liver, often jaundice, and commonly death in early infancy. The survivors develop cataracts, and are mentally deficient. Although this is a rare condition it is important that those who care for newborn babies should be familiar with it; with early treatment life can be saved, and a normal child may result. Diagnosis is thus more urgent than in most congenital metabolic anomalies.

The first clear account of this condition was published by Goppert (1917), although the case described by Von Reuss (1908) may also have been an example. Mason and Turner (1935) published the first American case report, and 12 others have since appeared, including papers by Townsend *et al.* (1951) and Donnell and Lann (1951) which incorporated reviews of the literature. Görter (1951) and De Haas (1951) have given brief accounts of three affected Dutch families. The first report from Great Britain is that of Bray *et al.* (1952).

Twenty-five proved cases have been found in the literature up to the end of 1952, and there are others in which the diagnosis is very likely. The object of this paper is to report a further six cases from three affected families, to describe the clinical picture, and to discuss the practical aspects of diagnosis and management of the condition.

Family I

The parents were unrelated; both were Rh-positive. The maternal Wassermann reaction and Kahn test were negative. The galactose-tolerance of the parents and surviving healthy child was normal.

Pregnancies:—Miscarriage. 1942: boy (Case 1); died aged 2 months. 1944: boy, normal child. 1946: girl (Case 2); died aged 39 days. 1949: boy (Case 3); surviving treated case. 1951: miscarriage.

Case 1

The patient, a male child, was born in 1942 following a normal pregnancy; birth weight 7 lb. 14 oz. (3.6 kg.). He was breast-fed. At the age of 2 months he was admitted to the Hospital for Sick Children with the history that from the beginning he had fed reluctantly, vomited frequently, and failed to gain weight; for three days his abdomen had been swollen and he had been lethargic and ill.

Examination revealed a pallid drowsy baby with generalized oedema, slight jaundice, and a distended abdomen with prominent superficial veins. The liver was palpable two fingerbreadths below the costal margin. The urine contained albumin ++, sugar ++++, no acetone, and no R.B.C., W.B.C., or casts. No further study of the urinary sugar was made. The child died early the next day following a series of fits.

Necropsy showed diffuse hepatic fibrosis, but no changes of importance in other organs; sections are no longer available.

Case 2

The patient, a female child, was born in 1946 following a normal pregnancy; birth weight 8 lb. 14 oz. (4 kg.). Her blood group was O Rh-positive (age 11 days). Direct and indirect Coombs tests were negative. She was admitted at the age of 8 days with the history that she had become jaundiced on the fourth day, and was losing weight.

On admission she was jaundiced and weighed 7 lb. 8 oz. (3.4 kg.); the liver was enlarged, the spleen was not. The right ear-drum was inflamed and the umbilicus was moist. The stools were normal in colour. The urine contained albumin 55 mg. per 100 ml., sugar +++, and a deposit of amorphous debris, with an occasional R.B.C., W.B.C., and epithelial cell.

Signs of sepsis disappeared following treatment with penicillin, but she failed to thrive, and the jaundice, after a temporary improvement, deepened. The alkaline serum phosphatase was 85 units, and the Takata–Ara test was negative (age 30 days). On the thirty-sixth day she developed diarrhoea and vomiting, and later vomited blood; the fontanelle was bulging and lumbar puncture yielded hazy xanthochromic fluid containing protein, 55 mg. per 100 ml.; sugar, 137 mg. per 100 ml.; chlorides, 710 mg. per 100 ml.; R.B.C., 2,405; W.B.C., 11. She died on the thirty-ninth day.

Necropsy.—The brain showed haemorrhage into the lateral ventricles and over the occipital lobes. The liver weighed 210 g. and was firm, with a finely granular surface. Histologically, there was gross disorganization of the liver pattern, with necrosis and fatty change of the liver cells, together with well-established mainly perilobular fibrosis. The pancreas showed marked islet-cell hyperplasia.

Case 3

The patient, a male child, was born on January 17, 1949; birth weight 8 lb. 3 oz (3.7 kg.). Initially he was breast-fed, and, like Cases 1 and 2, sucked poorly and failed to gain weight. Jaundice appeared on the seventh day and deepened gradually until his admission at the age of 2 weeks. He then weighed 7 lb. 1½ oz. (3.2 kg.); the abdomen was not distended, but showed dilated superficial veins; the liver was felt two fingerbreadths below the costal margin; and the spleen was not palpable. The stools were normal. The urine contained albumin 140 mg. per 100 ml. and a deposit of amorphous debris with a few R.B.C.s. The direct Coombs test was negative (age 2 weeks). The jaundice faded during the following fortnight but he did not thrive. Owing to difficulty in feeding, he was changed at 1 month from the breast to a half-cream dried milk; he promptly gained 1 lb. (450 g.) in the course of five days. As the mother's milk supply was good, this sudden improvement may well have been due to the lower lactose content of the dried milk. His weight then remained stationary in spite of several changes of feed.

During the following year feeding difficulty persisted; he had bouts of vomiting, and gained weight very slowly. When he was about 1 year he had several slight fits, and at this time he was first noticed to have a squint. The liver remained enlarged to about 5 cm. below the costal margin, and the serum alkaline phosphatase was persistently raised (50–60 K.A. units); other liver function tests were normal. A liver biopsy (Mr. Denis Browne) at the age of 16 months showed a slight to moderate degree of perilobular fibrosis and fatty infiltration. Albuminuria continued, and the urine sometimes contained a few W.B.C.s and granular casts: the blood urea was slightly raised (55 mg. per 100 ml.).

At the age of 18 months the urine was found consistently to reduce Benedict's solution to red, and bilateral cataracts were noted. The suspicion that the urinary sugar might be galactose was confirmed by paper chromatography (Dr. Woolf); this showed a galactose content of about 1% in a morning specimen. Blood sugars were as follows:—fasting (12 hours): glucose 65 mg., galactose 33 mg., total 98 mg. per 100 ml. One hour after 8-oz. (230-ml.) milk feed: glucose 84 mg., galactose 41 mg., total 125 mg. per 100 ml. C.S.F.: glucose 103 mg., galactose 49 mg., total 152 mg. per 100 ml. A galactose-tolerance test showed a prolonged rise in blood galactose and moderate depression of blood glucose. About half the test dose was excreted in the urine (Fig. A).

The patient's developmental age at this point (age 18 months) was thought to be less than 6 months. There was gross retardation of growth, and the liver was still enlarged 5 cm. below the costal margin.

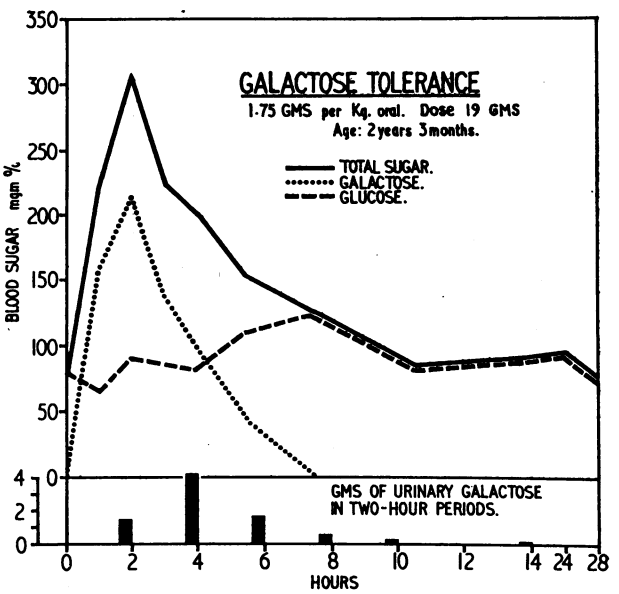

FIG. A.—Case 3. Galactose-tolerance test, showing blood total sugar, galactose, and glucose.

On August 25, 1950, he was started on a "lactose-free" diet (see discussion below). Sugar disappeared from the urine at once, and his albuminuria also diminished rapidly. Within a few days there was a striking improvement in his general condition: he became more alert and responsive and lost his previous anxious appearance. He did not gain weight during the first fortnight, but in the following six weeks he gained 4 lb. (1.8 kg.).

During the next year he made rapid progress in intelligence and physical development. Fig. B, his weight chart from birth, illustrates the striking effect of treatment and shows that between the ages of 18 months and 2½ years his weight was doubled; although remaining slightly below normal weight and height he has continued to gain steadily. A gradual decrease in the size of his liver was noted within a few weeks, and six months after the beginning of treatment this appeared normal, the edge being just palpable at the level of the costal margin. At the age of 2 years and 3 months his developmental age was regarded as about 9–12 months, and at 3 years and 4 months it was 15–18 months on the Gesell scale; at 4 years and 4 months his mental age (Merrill–Palmer scale) was 2 years and 5 months. At the age of 2 years and 3 months intermittent haematuria was noticed. This proved to be due to small renal calculi, lying probably in the minor calices of each kidney. The appearance did not suggest nephrocalcinosis. The calculi have not increased in size, and there is no impairment of renal function.

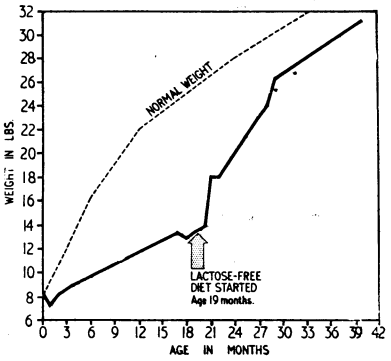

FIG. B.—Case 3. Weight chart, showing the effect of treatment.

After eight months on the lactose-free diet there was no change in the appearance of the cataracts, and in May, 1951, Mr. Doggart carried out discission of both lenses. The operation has since been repeated and the ocular media are clear, the child's sight with glasses being moderately satisfactory.

Family II

The parents were unrelated. The mother was O Rh-positive, Wassermann reaction negative; the father O Rh-negative.

Pregnancies:—1942: girl, normal child. 1946: girl (Case 4); died aged 27 days. 1951: girl (Case 5); died aged 8 weeks.

Case 4

The patient, a female child, was born in hospital following a normal pregnancy; birth weight 7 lb. 13 oz. (3.5 kg.). She was noted to be unduly sleepy by the fifth day of life, and by the sixth day was reluctant to feed and vomited frequently. She was subject to bouts of crying and head retraction. The abdomen became increasingly distended, and by the ninth day the liver edge had descended to the level of the umbilicus. Mild jaundice was then evident, the urine was bile-stained, and the stools were loose but well coloured.

Artificial feeding was first introduced on the eighth day, but breast milk was not entirely discontinued until the twelfth day of life, when also the appetite improved and vomiting ceased (cf. Case 3). Her weight gradually increased during the third week of life, but fell in the fourth week until death on the twenty-eighth day. The liver remained grossly enlarged, the edge extending to the level of the umbilicus, and there was also moderate ascites, with slight pitting oedema of the legs. A single observation of reducing substances, albumin, and bilirubin in the urine was recorded, but the nature of the sugar was not investigated.

Necropsy.—There was bile-stained ascites. The enlarged liver was olive green in colour and the histological picture was similar to that in Case 2. There was disorganization of the liver pattern by widespread necrosis, with gross fatty change in the surviving liver cells, and early fibrosis (Plate, Fig. 1).

Case 5

The patient, a female child, was born in 1951 in hospital; birth weight 7 lb. 2 oz. (3.2 kg.). Pregnancy had been complicated by hydramnios. At birth the infant was seen to have an extensive naevus on the outer aspect of the right thigh, which proved to be associated with absence of the internal saphenous vein on that side. By the end of the first week there had been a weight loss of 12 oz. (340 g.). She had become unduly drowsy, with vomiting and reluctance to feed, and there was mild dehydration. The liver margin descended progressively, reaching below the umbilicus by the twelfth day. The spleen was impalpable. Jaundice was absent throughout.

Urine examination on the twelfth day disclosed a reducing substance, maintained in consecutive specimens between 2 and 3%, and identified by paper chromatography as galactose. Fouchet's test for bilirubin was positive. No ketonuria was present. There was a slight general increase in amino-acid excretion, tyrosine, leucine, and proline being the most prominent.

Serial estimations of the blood-sugar levels before and after a 2½-oz. (70-ml.) breast-milk feed gave the following figures:

	Glucose	Galactose
Fasting	23 mg. per 100 ml.	130 mg. per 100 ml.
½ hour	58 " " " "	146 " " " "
1 "	46 " " " "	194 " " " "
1½ hours	58 " " " "	162 " " " "
2 "	46 " " " "	194 " " " "

The C.S.F. sugar was 111 mg. per 100 ml., of which 70 mg. was galactose and 41 mg. glucose.

From the fifteenth day a lactose-free feed was given. Galactose disappeared from the urine within 48 hours, and after a week clinical improvement was undeniable; appetite and vigour had both increased, vomiting had ceased, and she was no longer dehydrated. Most striking was the softening in the consistence of the liver, which diminished in size at first rapidly and then slowly, to reach half-way between the ribs and umbilicus four weeks after the exclusion of lactose. At the end of the first month of life the weight had mounted to 6 lb. 8 oz. (2.9 kg.), but from that time she did not thrive in spite of a generous calorie intake. Anorexia and occasional vomiting returned, and the stools were often undigested and loose. The liver again increased in size, and the infant died at the age of 8 weeks.

Necropsy.—The organs apart from the liver appeared essentially normal. The liver was enlarged (204 g.) and of a uniform yellow colour. Histological examination showed gross fatty infiltration, some necrosis, with only minimal disorganization of the liver pattern, and mild perilobular cirrhosis (Fig. 2).

Family III

Case 6

The patient, a male child, was born in hospital; birth weight 9 lb. 3 oz. (4.2 kg.). There was no parental consanguinity. The mother was group O Rh-positive and her blood Wassermann reaction was negative. There are two normal siblings aged 6 and 5 years.

The infant first caused concern on her fifth day of life by vomiting and passing loose green stools. These symptoms continued, with a resultant failure to gain weight. On the ninth day the conjunctivae appeared jaundiced, and bilirubin was detected in the urine. On the tenth day a brisk venous haemorrhage occurred from the umbilicus. The liver, which was readily palpable on the fifth day, had now enlarged half-way towards the umbilicus, and prominent veins had appeared over the upper abdomen. The spleen was not

felt at this time or subsequently. By the twelfth day the jaundice was deeper and there were signs of ascites. Spider naevi appeared on the inner aspects of the knees, but these did not persist beyond the third week.

Reducing substances were detected in the urine (2.5 g.%) on the fourteenth day. The sugar was identified as galactose by paper chromatography. The total blood sugar ranged from 240 to 151 mg. per 100 ml., about 70% of which was non-fermentable. There was considerable depression of blood glucose, to levels ranging from 17 to 54 mg. per 100 ml. Later (age 6 weeks) a typical galactose-tolerance curve was obtained. Feeding was exclusively by breast milk until transfer to a paediatric ward on the twenty-second day.

Laparotomy, with liver biopsy, was then undertaken immediately. The enlargement of the liver and the presence of ascites were confirmed. Histological examination showed considerable fatty change, with destruction of the lobular architecture and early fibrosis (Fig. 3).

A lactose-free feed was accepted readily from the beginning; vomiting and drowsiness ceased and the stools became normal. After two weeks the liver margin had ascended 1 in. (2.5 cm.), with resolution of the ascites and disappearance of the prominent abdominal veins, and the infant appeared altogether more vigorous. In spite of this initial encouragement there followed a gradual decline, with terminal new enlargement of the liver, anaemia, and convulsive movements (with normal blood calcium, CO_2 combining power, and blood sugar). Death occurred on March 18, 1953—that is, eight weeks after omitting lactose from the feeds.

Liver-function Studies.—Gross bilirubinuria, hyperbilirubinaemia, and a diminution of pigment in the stools were noted from the twelfth day. Within 12 days of lactose omission, bilirubin was no longer demonstrable in the urine, and did not reappear. The serum bilirubin fell more rapidly, to remain under 1 mg. per 100 ml. Bromsulphthalein excretion was initially grossly impaired (61% of dye still present after 45 minutes at 3 weeks of age), but this gradually approached normal, 16% and 11% remaining at 45 minutes, four weeks and six weeks respectively after lactose omission. Thus there was gradual improvement in liver function up to the time of the final relapse.

Amino-aciduria.—A gross excess of amino-acids was detected in the urine on the fourteenth day of life. This continued to the same degree (150–200 mg. per 100 ml.) until death, being unaffected by the withdrawal of lactose.

Necropsy.—The liver was fatty in appearance and weighed 180 g. Histologically, the liver lesion showed evidence of repair since the biopsy eight weeks before. There was still considerable fatty infiltration, but the lobular pattern was less disorganized and fibrosis had not extended (Fig. 4).

Clinical Picture

These three families illustrate well the clinical picture of the disease. Typically the infant, normal at birth, does not thrive from the first few days of life and is slow to regain its birth weight. There is great difficulty in feeding, with alternate lethargy and irritability, and often vomiting.

Wasting and mild dehydration are usual, but there may be oedema and ascites. Enlargement of the liver is the most constant sign; it appears during the first week of life, and may be accompanied by a palpable spleen. Jaundice is common (Cases 2, 3, 4, and 5); it was present in 14 out of 25 previously reported cases, being usually of short duration but occasionally lasting several months, as in Goppert's original case. Examination of the urine reveals a heavy reduction of Benedict's solution and usually albuminuria, often with a few cells and casts. The infant is at this stage very likely to die, either from infection or more directly from the effects of the disease. If this period is survived subsequent progress is slow and erratic; feeding difficulty continues and there is gross retardation of growth and mental development. Hepatic enlargement and glycosuria persist, and recurrent bouts of fever are common. Spontaneous bleeding may occur during the early weeks.

Cataract.—This was present in 15 out of 25 previously published cases; in those in which treatment was started before the age of 8 to 10 weeks changes in the lens were either absent or early and reversible, but all those above that age had definite cataracts at the time of diagnosis, with the exception of two infants aged 5 months. Similar cataracts are produced in young rats fed on a diet containing a high proportion of lactose or galactose (Mitchell and Dodge, 1935).

Cerebral Damage.—In addition to mental retardation there may be other evidence of cerebral dysfunction: our Case 3 exhibited fits, and later an unusual form of nystagmus which could not be explained entirely on the basis of ocular disease; one of the cases reported by Goldbloom and Brickman (1946) showed a transitory choreiform disturbance some years after starting treatment. Raised intracranial pressure due to cerebral oedema may be a feature in the newborn period (Case 1).

Amino-aciduria.—The urine was studied by paper chromatography in Cases 3, 5, and 6. While still on a milk diet all three showed a general increase in amino-acid excretion: in Cases 3 and 5 this was slight, but in Case 6 it was more considerable, amounting to 150–200 mg. per 100 ml. In Case 3 the amino-aciduria decreased rapidly when treatment was begun; in Cases 5 and 6, however, it persisted up to the time of death. This amino-aciduria probably reflects impairment of liver function, but it is not yet possible to define a consistent pattern and a renal origin has not been excluded.

Cerebrospinal Fluid.—Attention is drawn to the high C.S.F. sugars in Cases 2, 3, and 5. Figures of this magnitude are uncommon in infancy, and may provide a clue to the diagnosis in an unsuspected case.

Diagnosis

Galactosaemia must be diagnosed during the first few weeks of life if the infant is to have a chance of developing normally. Provided the urine of all sick infants is tested with Benedict's solution, cases in hospital at least will not be missed; it is important that this simple procedure, regarded as a matter of routine in older children, should not be neglected owing to practical difficulties. The condition should be suspected particularly in the presence of jaundice, hepatic enlargement, or a suggestive family history.

Consistent glycosuria is uncommon in infancy and should prompt a query regarding the nature of the reducing substance present. The most elegant and conclusive answer is given by paper chromatography, which was used to identify the sugar in our Cases 3, 5, and 6. When this technique is not available identification starts with the observation that the sugar is not fermented by yeast, thus excluding glucose and fructose; the osazone, mucic acid, and other chemical tests for galactose should then suffice for identification, although individually they are often inconclusive.

Galactose is sometimes found in the urine of other infants with liver disease, but it is then usually excreted only in small amounts, and often intermittently. Should the diagnosis be in doubt the persistently high blood galactose level, characteristic galactose-tolerance curve, and rapid response to treatment will differentiate the case of galactosaemia.

The condition should also be suspected in older children suffering from mental defect associated with cataract or liver disease (Fanconi, 1933; Bray *et al.*, 1952); if they are no longer on a milk diet galactosuria may be slight and intermittent, and a galactose-tolerance test should be done. There is no evidence so far that the metabolic error occurs in mild or incomplete forms, but should this be the case diagnosis might well be more difficult.

Treatment

The essential measure is the exclusion of lactose and galactose from the diet, and for infants a lactose-free milk must be contrived. We have used milk protein in the form of "casilan" mixed with coconut oil and arachis oil,

sucrose, and water. Butter contains lactose and is not suitable. Margarine can be used, but produces a less stable emulsion. In addition to vitamins it is necessary to add potassium, sodium, and iron salts, as casilan is deficient in these, but contains an adequate amount of calcium and phosphorus. Casilan contains about 1% of lactose, giving about 12 mg. of lactose (equivalent to 6 mg. of galactose) in each ounce of the feed referred to in our case reports as "lactose free." "Nutramigen" and soya milk, however, the lactose-free feeds recommended by previous authors, also include traces of galactose-containing sugars. A sample of "amigen," the amino-acid component of nutramigen, studied for us by Dr. Woolf, contained 0.7% of lactose, and a sample of soya milk contained stachyose and about 0.2% of raffinose, both of which contain galactose in the molecule, though it is not known whether galactose is liberated in the body.

Our three treated Cases (Nos. 3, 5, and 6) showed an almost immediate improvement in their general condition, with cessation of galactosuria and rapid decrease in size of the liver when the lactose-free diet was started. Case 3 continued to make good progress. Cases 5 and 6, however, both relapsed and died within a few weeks, with a terminal recurrence of gross liver enlargement.

This difference from published experience, which had led us to anticipate an uninterrupted recovery, may be due in part to selection. It is likely that cases have more often remained undiagnosed and unreported when the infants have died in the early weeks of life with severe liver damage than when they have survived to present a clinical problem over a long period, as in Case 3 and in many reports in the literature. Possibly treatment must be started earlier than two to three weeks after birth, which is the best that we have achieved, if survival is to be assured in every case.

On the other hand, the fatal outcome might be attributed to our inclusion of traces of lactose in the diet. Amino-aciduria is probably a sensitive indicator of impaired liver or kidney function in this disease; it is known that the addition of only 2 g. of lactose daily to the special diet may cause its return (Holzel *et al.*, 1952). In Case 3, an older child, amino-aciduria ceased when the casilan diet was started, while in Cases 5 and 6 it continued unabated until death. It may be that in a newborn infant the small quantity of lactose (about 200 mg. a day) included in our casilan diet was enough to prevent recovery, but we think this unlikely. It is possible, moreover, that traces of galactose are necessary in order to meet the body's requirements in the synthesis of essential compounds such as the cerebrosides and mucoids. Further information is needed on the effect of small quantities of galactose before these questions can be answered and a definite conclusion reached regarding the optimum diet for these infants.

As the child grows older it is probable that some milk-containing foods can be introduced into the diet without adverse effect (Townsend *et al.*, 1951), but it would be wise to prohibit the drinking of milk.

Prognosis

Without treatment survival is unlikely and mental defect is probably the rule. It might be expected that if lactose were removed from the diet soon after birth normal development would follow, but evidence for this is lacking. In only one recorded case has treatment been started in the first few days of life, and this child became mentally defective (Townsend *et al.*, 1951, Case T.F.). Nine other previously recorded cases have been followed for long periods (Norman and Fashena, 1943; Bruck and Rapoport, 1945; Mellinkoff *et al.*, 1945; Goldbloom and Brickman, 1946; Goldstein and Ennis, 1948; Townsend *et al.*, 1951): in these children treatment was delayed for periods ranging from seven weeks to two years, and all are mentally retarded or of borderline low intelligence except Bruck and Rapoport's patient, who was treated from the age of 2½ months, and was thought to be normal when 4 years old. In addition, there are several reports of apparently normal progress in infants still too young to be assessed with certainty.

It will be necessary to see the result of early diagnosis and treatment in many more cases before it can be decided whether the mental retardation is in fact due to cerebral damage occurring in the early weeks of life and resulting from the high concentration of galactose in the blood or to some other factor which is less amenable to treatment.

Genetics

The families reported by Goppert (1917), Fanconi (1933), Ellenburg and Peterson (1951), Görter (1951), and De Haas (1951) have been excluded from this discussion owing to lack of detailed information. The three families described above, together with the remaining published cases, give a total of 27 affected children in 17 families.

There is no known instance of cases occurring in more than one generation, and the few galactose-tolerance tests which have been performed on the parents of affected children have been normal. The familial incidence in this group, calculated from the ratio between affected siblings and total siblings after exclusion of the index cases, is 9 out of 31, or about 1 in 3.5. No instance of parental consanguinity has been reported, but unfortunately most authors have not mentioned this question. These limited figures, although naturally inconclusive, are consistent with a recessive mode of inheritance.

Morbid Anatomy

Patients with galactosaemia dying early in infancy usually show oedema of the brain, kidneys, and other viscera, but the only consistent change of importance is in the liver. The histology of the liver has been studied in biopsy or post-mortem material from five of our six cases, as described in the reports above. Our findings are similar to those in the seven previous cases in which the liver has been studied.

These twelve cases can be divided into two groups. In the first group of eight cases the age at the time of death or biopsy ranged from 8 days to 2 months (Bell *et al.*, 1950; Donnell and Lann, 1951; Edmonds *et al.*, 1952; and our Cases 2, 4, 5, and 6). These cases showed varying degrees of parenchymal necrosis and fatty change, with consequent disorganization of the liver pattern and abnormal arrangement of surviving cells, often in an alveolar type of grouping. The older members of the group also showed early hepatic fibrosis. The case described by Edmonds *et al.* (1952) is unusual in that the liver contained three isolated large nodules composed of glycogen-rich cells; the liver changes otherwise seem typical. The second group consists of four cases (Ellenburg and Peterson, 1951; Townsend *et al.*, 1951; Bray *et al.*, 1952; and our Case 3) examined at 4 years, 1 year, 1 year, and 18 months respectively. The livers of these older children showed only diffuse fibrosis and mild fatty infiltration, although the early clinical histories had been similar to those of the first group and, with the exception of the case of Townsend *et al.*, the diet contained lactose up to the time of examination.

It is evident that considerable liver damage occurs at an early age, probably during the first week of life; the severity of this damage may determine whether or not the child survives, but following this critical period repair occurs even though lactose is not removed from the diet. The liver lesion in older children is thus milder and perhaps non-progressive.

The reason for this contrast between the two age groups may lie in the immaturity of the liver in the younger infants, together with the higher concentration of galactose in the blood at this age. Comparison of the specimens from Cases 4 and 5 and of the two from Case 6 reveals differences which may be related to the effect of treatment rather than primarily to the differences according to age which are described above. Disorganization of the hepatic

parenchyma was more considerable in Case 4, who died untreated at 28 days (Plate, Fig. 1) than in Case 5, of the same family, who died at 8 weeks, six weeks after treatment was started (Fig. 2). Similarly in Case 6 considerable repair of the liver occurred in the course of eight weeks' treatment, as shown by comparison of the biopsy and necropsy specimens (Figs. 3 and 4). It is likely that the process of repair had initially progressed much further than the necropsy specimens suggest, since in both cases an unexplained relapse of liver enlargement and failure preceded death.

Biochemistry

The subject of normal galactose metabolism was last reviewed comprehensively by Deuel (1936). Galactose, together with glucose, is formed in the intestine by hydrolysis of the lactose in milk, and in normal milk-fed infants it is present in the blood only for short periods after feeds, although the concentration may then reach 20–30 mg. per 100 ml. (Hartmann *et al.*, 1953). Similarly, if a dose of 40 g. of galactose is given by mouth to a fasting adult (or 1.75 g. per kg. to a child) the concentration of galactose in the blood usually reaches 30–40 mg. per 100 ml. within an hour and falls to zero within two hours (Maclagan, 1940). Although the renal threshold for galactose is extremely low the total urinary excretion in this period does not normally exceed 2–3 g. (Shay and Fieman, 1937), because the galactose is removed rapidly from the blood by the liver (Bollman *et al.*, 1935). This observation forms the basis for the use of galactose tolerance as a test of liver function. Galactose is also utilized, although more slowly, by other tissues with the probable exception of those of the brain.

Direct evidence of the path of metabolism in the liver is lacking, but a speculative scheme can now be constructed (Kosterlitz, 1943 ; Caputto *et al.*, 1950 ; Garner and Grannis, 1951 ; Topper and Stetten, 1951). The first stage is phosphorylation by the enzyme galactokinase to form galactose-1-phosphate ; the latter is converted to glucose-1-phosphate, this process involving an enzyme "phospho-galactoisomerase" ; glucose-1-phosphate is then converted into glycogen.

In children with galactosaemia utilization of galactose is greatly impaired, possibly owing to the absence or inhibition of one of these enzymes. A galactose-tolerance test shows a high and prolonged rise in blood galactose with depression of blood glucose, and while the child is on normal milk feeds the blood galactose remains high throughout the day and galactose is excreted in the urine. The rapid relief obtained when lactose is omitted from the feeds suggests that these children's symptoms are due chiefly to the toxic effect of this high blood galactose concentration, although the depression of blood glucose which also occurs (as in Cases 3, 5, and 6) may play a part. Mason and Turner (1935) suggested that the depression of blood glucose results from overproduction of insulin in response to the high blood galactose, which itself is unaffected by the insulin produced. In this connexion it is interesting that the pancreas from Case 2 showed striking islet-cell hyperplasia ; unfortunately we have no information about the blood sugar in this infant, and changes in the pancreas do not seem to be the rule ; in Cases 5 and 6 the pancreas was normal, and in our other cases it was not examined.

Galactose is an essential cell constituent, in particular as a component of the cerebrosides of nervous tissue and of the mucoids, and possibly plays some part in the metabolism of fat (Richter, 1948). It is not known whether these and other ill-understood functions of galactose are also disordered in children with galactosaemia.

Summary

The possibility of galactosaemia should be considered in infants who fail to thrive from birth and develop enlargement of the liver, with or without jaundice.

A provisional diagnosis can usually be made by testing the urine with Benedict's solution.

Early treatment may save life and prevent the development of cataract and mental defect.

Six cases are reported ; the histology of the liver was studied in five.

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CONGENITAL GALACTOSAEMIA

REPORT OF A CASE

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Since Von Reuss (1908) described this condition some 30 cases have been recorded, principally in America and Germany. Bray *et al.* (1952) have reviewed the literature in presenting three cases in Britain. We report this further case not only because of the comparative rarity of the condition but because of its association with some unusual biochemical findings. The importance of early recognition of the disease as a cause of failure to thrive in infants must be emphasized, for it is capable of cure, but if treatment be delayed blindness, mental defect, or death may ensue.

P. J. N. COX AND R. J. P. PUGH: CHRONIC GALACTOSAEMIA

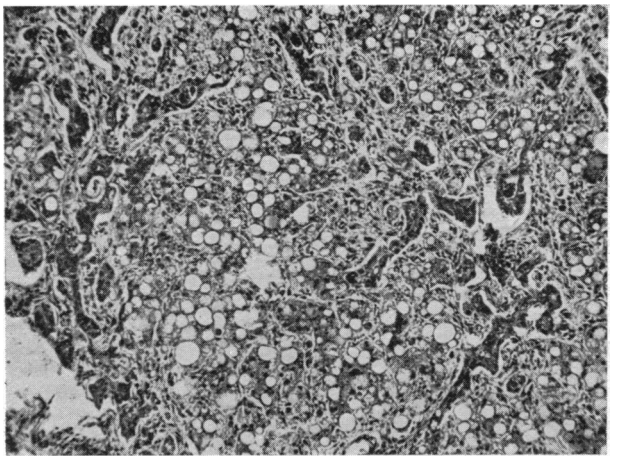

FIG. 1.—Case 4. Liver at necropsy. Fatty change, necrosis, and disorganization of parenchyma.

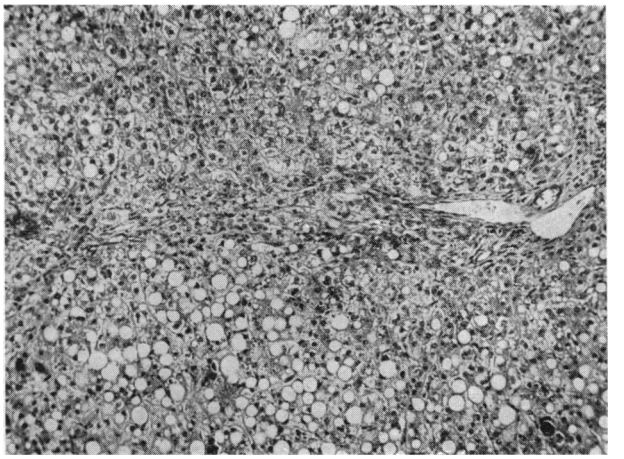

FIG. 2.—Case 5. Liver at necropsy. Gross fatty infiltration but less necrosis and disorganization than in Case 4.

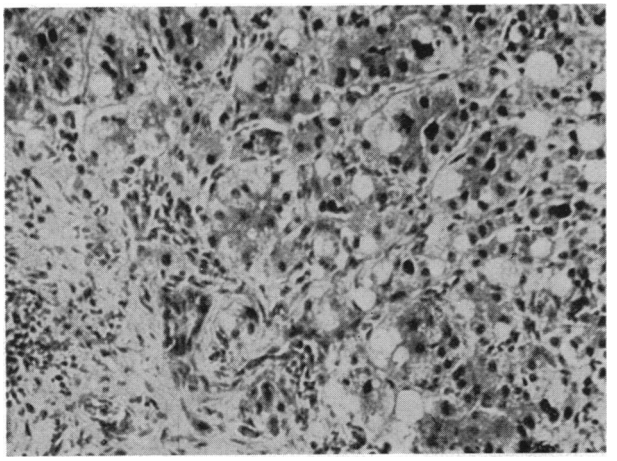

FIG. 3.—Case 6. Aged 3 weeks. Liver biopsy. Fatty change, necrosis, and early fibrosis.

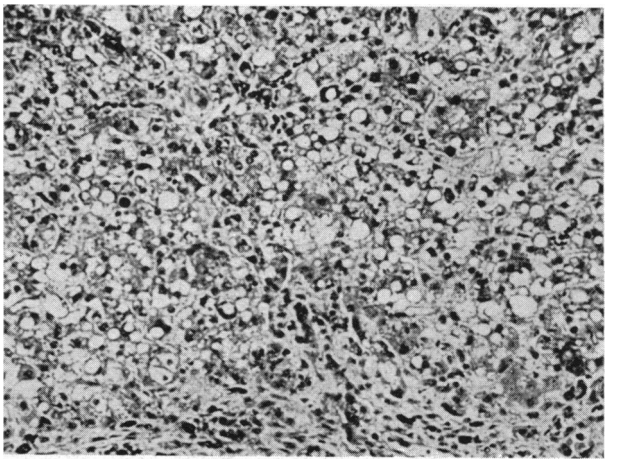

FIG. 4.—Case 6. Aged 11 weeks. Liver at necropsy. Fatty infiltration persists, but necrosis and fibrosis are less obvious.

D. J. ELLISON AND O. C. LLOYD: THROMBOTIC THROMBOCYTOPENIC PURPURA

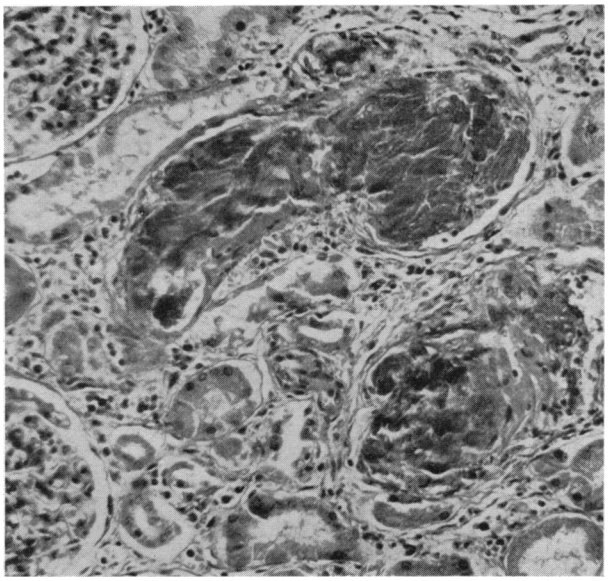

FIG. 1.—Organizing thrombus in two larger vessels, apparently venules. (Stained blue trichrome. ×150.)

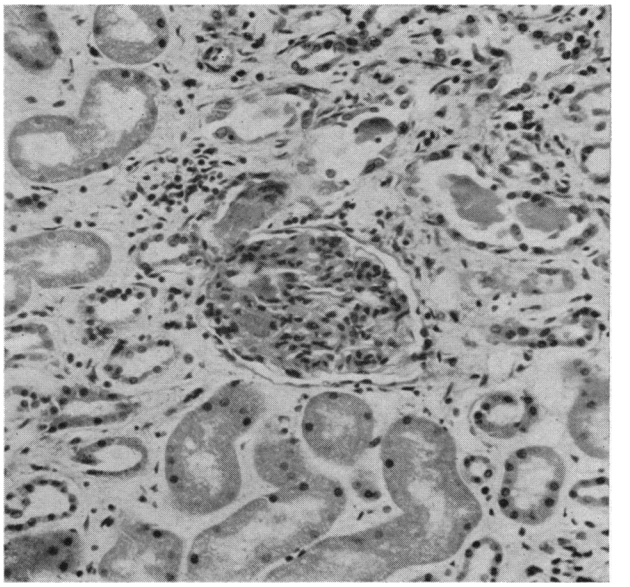

FIG. 2.—A glomerulus with thrombosis of one of its arterioles and some of its capillaries. Some of the neighbouring tubules are atrophied and there is interstitial fibrosis. (H. and E. ×150.)