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.

We are indebted to Professor W. S. Craig and Professor Alan Moncrieff for permission to report these cases, and to Dr. W. W. Payne, Dr. L. I. Woolf, and Mr. F. J. N. Powell for advice and for the biochemical estimations. Dr. Martin Bodian and Dr. W. G. Goldie examined the livers of these infants, and Dr. C. O. Carter helped in the diagnosis and in the discussion on genetics. Dr. Katharine Dodd, Professor Gladys Fashena, Dr. Alton Goldbloom, and Dr. Eugene Goldstein kindly provided information on the progress of cases previously reported elsewhere.

REFERENCES

Bell, L. S., Blair, W. C., Lindsay, S., and Watson, S. J. (1950). *Arch. Path., Chicago*, **49**, 393.
Bollmann, J. L., Mann, F. C., and Power, M. H. (1935). *Amer. J. Physiol.*, **111**, 483.
Bray, P. T., Isaac, R. J., and Watkins, A. G. (1952). *Arch. Dis. Childh.*, **27**, 341.
Bruck, E., and Rapoport, S. (1945). *Amer. J. Dis. Child.*, **70**, 267.
Caputto, R., Leloir, L. F., Cardini, C. E., and Paladini, A. C. (1950). *J. biol. Chem.*, **184**, 333.
De Haas, P. K. (1951). *Maandschr. Kindergeneesk.*, **19**, 304.
Deuel, H. J. (1936). *Physiol. Rev.*, **16**, 173.
Donnell, G. N., and Lann, S. H. (1951). *Pediatrics*, **7**, 503.
Edmonds, A. M., Hennigar, G. R., and Crooks, R. (1952). Ibid., **10**, 40.
Ellenburg, L. L., and Peterson, J. C. (1951). *Amer. Practit., Philad.*, **2**, 602.
Fanconi, G. (1933). *Jb. Kinderheilk.*, **138**, 1.
Garner, R. L., and Grannis, G. F. (1951). *Science*, **114**, 501.
Goldbloom, A., and Brickman, H. F. (1946). *J. Pediat.*, **28**, 674.
Goldstein, E. O., and Ennis, J. M. (1948). Ibid., **33**, 147.
Goppert, F. (1917). *Berl. klin. Wschr.*, **54**, 473.
Görter, E. (1951). *Arch. Dis. Childh.*, **26**, 271.
Hartmann, A. F., Grünwaldt, E., and James, D. H. (1953). *J. Pediat.*, **43**, 1.
Holzel, A., Komrower, G. M., and Wilson, V. K. (1952). *British Medical Journal*, **1**, 194.
Kosterlitz, H. W. (1943). *Biochem. J.*, **37**, 318.
Maclagan, N. F. (1940). *Quart. J. Med.*, **9**, 151.
Mason, H. H., and Turner, M. E. (1935). *Amer. J. Dis. Child.*, **50**, 359.
Mellinkoff, S., Roth, B., and MacLaggan, J. (1945). *J. Pediat.*, **27**, 338.
Mitchell, H. S., and Dodge, W. M. (1935). *J. Nutr.*, **9**, 37.
Norman, F. A., and Fashena, G. J. (1943). *Amer. J. Dis. Child.*, **66**, 531.
Richter, C. P. (1948). *Science*, **108**, 449.
Shay, H., and Fieman, P. (1937). *Ann. intern. Med.*, **10**, 1297.
Topper, Y. J., and Stetten, D. (1951). *J. biol. Chem.*, **193**, 149.
Townsend, E. H., Mason, H. H., and Strong, P. S. (1951). *Pediatrics*, **7**, 760.
Von Reuss, A. (1908). *Wien. med. Wschr.*, **58**, 799.

CONGENITAL GALACTOSAEMIA

REPORT OF A CASE

BY

M. W. ARTHURTON, M.D., M.R.C.P., D.C.H.

Consultant Paediatrician, Dewsbury, Batley, and Mirfield Hospital Group ; formerly Senior Registrar, Westminster Children's Hospital

AND

B. W. MEADE, M.D.

Senior Registrar and Pathological Tutor, Department of Chemical Pathology, Westminster Medical School

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.

Case History

A male infant 4 weeks old was admitted under the care of Dr. I. M. Anderson on September 9, 1952, from a neighbouring maternity unit because of failure to thrive. His birth weight was 6 lb. 12 oz. (3.1 kg.), following a normal pregnancy and delivery. Jaundice of moderate severity, first noted on the third day of life, persisted for two weeks in association with pallor and hepatomegaly. From the fourth day a varying degree of lassitude and anorexia was observed and the weight gain was poor and erratic. The mother's lactation failed on the ninth day, so full-cream National dried milk was substituted.

Family History.—Parents and three sibs were well. In 1946 a premature baby weighing 4 lb. 4 oz. (1.9 kg.) died aged 3 weeks of undetermined cause, although the symptomatology resembled that of the present case. (Unfortunately no case notes are available.) There was no history of consanguineous marriages.

On examination his weight was 6 lb. 8 oz. (2.9 kg.). He was afebrile, pale, and wasted. The head circumference was 13½ in. (34 cm.). The liver and spleen were palpable 6 cm. and 1 cm. respectively below the costal margin. The urine contained a trace of albumin. No other abnormal clinical findings were noted on admission. The provisional diagnoses considered at this time were: (1) A chronic infection, possibly renal; but none could be detected, and microscopically the urine was normal. (2) Congenital syphilis. The negative serology in mother and infant and the absence of clinical evidence of the disease apart from hepatosplenomegaly were against this diagnosis. (3) Erythroblastosis foetalis with secondary cirrhosis of the liver. This possibility was supported by the initial haematological examination (Dr. K. Goldsmith), which showed: Hb, 79%; blood group A, Rh positive; direct Coombs test, weakly positive. The maternal blood was group O, Rh positive. Serum examination showed an anti-A titre 1/64; after suitable absorption immune anti-A titre 1/16. Haemolysin was present to a titre of 1/8. "These findings strongly suggested that the child was affected by an immune anti-A antibody developed by the mother, probably as a result of her pregnancy."

Examination of the urine with Benedict's solution, however, yielded an orange precipitate, but tests for ketone bodies were negative. A provisional diagnosis of galactosaemia was made, and this was confirmed biochemically. The relevant laboratory data were as follows:—*Blood* (three hours after feeding): fermentable sugar, 52 mg. per 100 ml.; non-fermentable sugar, 205 mg. per 100 ml.; serum sodium, 144 mEq/litre; serum potassium, 5.1 mEq/litre; plasma inorganic phosphate, 4 mg. per 100 ml.; alkali reserve, 15.5 mEq/litre; chlorides, 126 mEq/litre; total bilirubin, 1.4 mg. per 100 ml.; plasma amino-acid nitrogen, 5.2 mg. per 100 ml. Other liver-function tests, including alkaline phosphatase and turbidity tests, were within normal limits for a child of this age. *Urine:* albumin, 38 mg. per 100 ml.; *p*H, 8; yeast fermentation test, negative; mucic acid test, positive; total "non-fermentable" sugar, 1.62 g. per 100 ml.; paper chromatography (C. H. Bowden), reducing substance behaved as galactose; two-dimensional paper chromatography revealed alanine, glycine, and serine spots of normal intensity. The urine of both parents and all siblings failed to reduce Benedict's solution on two separate occasions.

Mr. Trevor Roper reported "striate opacity in both lenses."

On September 22 a daily formula was started of "casilan," 1 oz. (31 mg.), glucose, 2 oz. (62 mg.), arachis oil, ¾ oz. (21 ml.), made up to 24 oz. (680 ml.) with boiled water. This diet was supplemented with iron and vitamins, and in view of the laboratory evidence of acidosis 4 g. of sodium citrate was also given daily for seven days. The synthetic feed was well taken and tolerated, and within 24 hours of its institution the blood and urine chemistry returned to normal. After a week the child had gained 7 oz. (200 g.), the liver was felt only 4 cm. below the costal margin, and the lens opacities showed marked regression.

Further progress was unfortunately interrupted by the development of a severe gastro-enteritis of undetermined aetiology, necessitating intravenous therapy.

The lactose-free formula was recommenced on October 9, and was altered to contain casilan 20%, olive oil 18%, arrowroot starch 10%, dextri-maltose 48.5%, calcium gluconate 3.5%. In addition sodium chloride, 1 g., and potassium chloride, 1 g., were given each day. Subsequent progress was excellent until December 23, when the patient weighed 10 lb. 5 oz. (4.7 kg.). Thereafter there was a slow fall in weight, for which no cause could be discovered. The serum potassium level remained steady, however, at approximately 5.7 mEq/litre, and hence on January 10, 1953, the potassium supplement was discontinued. Instead of improving, the patient became more apathetic, and three weeks later the serum potassium had fallen to 1.9 mEq/litre. Daily supplements of 1 g. of potassium chloride were restarted with dramatically good results, but the weight gain, despite normal blood chemistry, was disappointing except when Darrow's solution was given orally in addition to the other supplements. On February 24 potassium citrate, 0.7 g. daily, was accordingly substituted for potassium chloride, and thereafter the weight gain was satisfactory. Oedema appeared on March 16, but was dispelled by the reduction of daily NaCl supplement to 0.75 g.

On April 1 mixed feeding was slowly introduced. In order to facilitate food preparation by the mother after the child's discharge from the hospital, the synthetic formula was replaced by "nutramigen" (a product containing dextri-maltose 42%, co-nutren 20%, corn oil 18%, arrowroot starch 10%, calcium gluconate 3.5%, other salts 3.2%), of which he received 16½ measures (each of 5-ml. capacity) daily in 22 oz. (625 ml.) of water with 3 dr. (12 g.) of added sugar. He was receiving, in addition, a full toddler diet with a daily supplement of 0.75 g. of sodium chloride. A galactose-tolerance test on April 16 gave a grossly abnormal result, as follows (dose 1.75 mg. per kg.): ½ hour 24 mg., 1 hour 72 mg., 1½ hours 80 mg. per 100 ml.

When the patient was discharged on June 11, at the age of 10 months, his condition was as follows: weight, 18 lb. 1 oz. (8.2 kg.); head circumference, 17¾ in. (45 cm.); crown–heel length, 28 in. (71 cm.); six teeth present; liver 2½ cm. below costal margin, smooth but firmer than normal; unable to sit up unaided; mental age estimated at approximately 5 months.

Mr. Trevor Roper reported persistence of the small opacity in the posterior pole of the left lens. The blood sugar, alkali reserve, plasma chlorides, serum sodium, and potassium were all within normal limits.

When he was seen after discharge from the hospital, at the age of 12 months, the findings were: weight, 20 lb. 10½ oz. (9.4 kg.); crown–heel length, 31 in. (79 cm.); head circumference, 18¾ in. (47.5 cm.); 10 teeth present; liver soft, smooth, and only just palpable; remained sitting when assisted into upright position; not yet crawling; sees and hears normally; mental age assessed at 8 months. Mr. Trevor Roper reported that the small central opacity in the left lens was still present, but that it would not affect the child's vision.

Discussion

Studies on galactose-fermenting yeasts have suggested that the probable metabolic route of galactose is:

(A) Galactose+adenosine triphosphate→galactose-1-phosphate
(B) Galactose-1-phosphate→glucose-1-phosphate.

As demonstrated by Trucco *et al.* (1948), reaction A is catalysed by the enzyme galactokinase, whilst B involves the enzyme phosphogalactoisomerase, which has been isolated from adapted strains of *Saccharomyces fragilis* by Garner and Grannis (1951), and the co-enzyme uridine-diphosphate glucose demonstrated by Caputto *et al.* (1950) not only in yeast preparations but also in rat kidney, brain, muscle, and to a less extent liver.

From the glucose-1-phosphate stage the metabolism is probably that of glucose. This proposed sequence of events

is supported by the observations of Topper and Stetten (1951), who fed D-galactose-1-C^{14} to rats and recovered glycogen from the liver which, on hydrolysis, yielded glucose having 90% of its isotope content in position 1. Thus inhibition or lack of any of the enzyme systems involved in reactions A or B would appear a possible lesion in these children. That disease may arise from such a lack of a specific enzyme system has been elegantly established by Cori and Cori (1952), who demonstrated lack of glucose-6-phosphatase activity in liver homogenates from certain cases of glycogen storage disease.

Alternatively the galactosaemia could arise as a result of hepatic damage, following immunization. The galactose-tolerance tests would offer no help in differentiating this secondary defect and the primary defect mentioned above. Bessis (1947) demonstrated profound histological changes in the liver in cases of fatal icterus gravis, but Gerrard (1952) could detect no significant residual hepatic damage in cases surviving Rh sensitization. Gorter (1951) reported galactosuria occurring in association with A–O blood group incompatibility, and in the mother of the present case an anti-A agglutinin was detected. However, Townsend *et al.* (1951), reviewing the relationship between galactosuria and Laennec's cirrhosis, concluded that the defect of galactose metabolism was primary and that the cirrhosis was secondary. This conclusion is supported by the normal liver-function tests in our case.

Bray *et al.* (1952) detected an excess aminoaciduria in two of their cases, but no observations were recorded on the blood amino-acid nitrogen. We were unable to detect this urinary abnormality on two separate occasions. Such an aminoaciduria might result either from liver damage or from renal tubular deficiency. It is noteworthy that the initial biochemical findings in our case resembled those of infantile renal acidosis. Latner and Burnard (1950) have ascribed this condition to failure of the proximal renal tubule to reabsorb bicarbonate ions.

It is conceivable that both these tubular lesions causing excess aminoaciduria and failure of bicarbonate resorption have arisen as toxic manifestations of the galactosaemia, but it must be admitted that we need to study many more such cases before any final conclusion can be reached, and that the association of the acidosis and galactosaemia may be fortuitous.

Summary

The clinical and pathological findings and response to treatment of a case of galactosaemia associated with hyperchloraemic renal acidosis and haemolytic disease of the newborn is described.

It is thought that galactosaemia arises as a congenital condition due to a specific lack of enzymes involved in the metabolism of galactose.

The possibility that the renal acidosis arose as a result of the toxic effect of galactose on the renal tubules is considered.

We are indebted to Dr. I. M. Anderson, whose case this was, and Professor N. F. Maclagan for their advice, help, and criticism in the preparation of this paper, and to Dr. K. Goldsmith for the haematological investigations.

REFERENCES

Bessis, M. (1947). *La Maladie Hémolytique du Nouveau Né*. p. 69. Masson, Paris.
Bray, P. T., Isaac, R. J., and Watkins, A. G. (1952). *Arch. Dis. Childh.*, **27**, 341.
Caputto, R., Leloir, L. F., Cardini, C. E., and Paladini, A. C. (1950). *J. biol. Chem.*, **184**, 333.
Cori, G. T., and Cori, C. F. (1952). Ibid., **199**, 661.
Garner, R. L., and Grannis, G. F. (1951). *Science*, **114**, 501.
Gerrard, J. (1952). *British Medical Journal*, **1**, 1385.
Gorter, E. (1951). *Arch. Dis. Childh.*, **26**, 271.
Latner, A. L., and Burnard, E. D. (1950). *Quart. J. Med.*, **19**, 285.
Reuss, A. Von (1908). *Wien. med. Wschr.*, **58**, 799.
Topper, Y. J., and Stetten, DeW. (1951). *J. biol. Chem.*, **193**, 149.
Townsend, E. H., Mason, H. H., and Strong, P. S. (1951). *Pediatrics*, **7**, 760.
Trucco, R. E., Caputto, R., Leloir, L. F., and Mittelman, N. (1948). *Arch. Biochem.*, **18**, 137.

OPERATIVE CHOLANGIOGRAPHY

BY

E. S. R. HUGHES, M.S., F.R.C.S., F.R.A.C.S.
Assistant Surgeon, Royal Melbourne Hospital

AND

R. H. KERNUTT, M.S., F.R.A.C.S.
Surgical Registrar, Royal Melbourne Hospital

Surgeons are divided in their opinions concerning the value of radiology in the detection of stones in the common bile duct despite the unreliability of the usual surgical methods. Some have come to regard operative cholangiography as indispensable in the surgery of the biliary tract (Mallet-Guy *et al.*, 1947; Mirizzi, 1948; Hicken *et al.*, 1950; McNeill Love, 1952); others have criticized the investigation as being cumbersome, unnecessary (Maingot, 1952), and unsatisfactory because of a susceptibility to appreciable error in interpreting the films at the time of the operation (Waugh *et al.*, 1952).

The bile ducts can be visualized radiologically only after they have been filled by a direct injection of radio-opaque medium. Attempts have been made to do this before operation, but as yet there is no satisfactory standard method.*

Diagnostic Operative Cholangiogram.—The injection into the common bile duct is made after the abdomen is opened and just before the dissection on the biliary tract is begun. The film is developed at once; a stone will be visible as a filling defect.

Control Operative Cholangiogram.—When the common bile duct is opened it is customary after exploration to insert a tube into the duct for the purpose of external biliary drainage. Before the abdominal cavity is closed opaque medium can be injected down the tube into the duct and a further film taken. If an overlooked stone is disclosed the duct is re-explored.

Present Investigation

Operative cholangiography has been performed in a series of 50 patients subjected to operation on account of gall-stones. The investigation was conducted with a view to ascertaining the practicability or otherwise of operative cholangiography as a routine procedure; the value or otherwise of operative cholangiography in the diagnosis of stones in the common bile duct; the apparent advantages of control operative cholangiography over post-operative cholangiography; and the place of operative cholangiography in the recognition of disorders of the biliary tract coexisting with gall-stones.

Technique

Three ureteric catheters (sizes 4 F., 5 F., and 6 F.) and a 20-ml. syringe with blunt needles fitting the corresponding catheters are needed. The medium used is a 35% solution of diodone ("pyelosil 35"). A 50% solution ("pyelosil 50") has been employed in the more obese without ill effect. Diodone contains 49.8% by weight of iodine. It is comparatively free from tissue irritation.

The middle segment of the rubber mattress on the operating table is replaced by a flat tunnel constructed of three-ply wood. The tunnel is long enough to take an *x*-ray plate 11 by 14 in. (28 by 35.5 cm.) and to allow for some readjustment to bring it to lie under the biliary tract, and high enough to accommodate the cassette and Lysholm

*This paper was prepared just prior to experiments with intravenous cholangiography; results have been encouraging.