to operate. No great difference, either in the level at which patency is established or in the appearance of tubal-contraction waves, is usually seen when insufflation is repeated even after several months. Rubin (1939) maintains that the tracings can be correlated with phases of endometrial or ovarian activity. I have not been able to confirm this. More active or more frequent peristalsis may be seen at various stages of the menstrual cycle and spasm may also be exhibited for no apparent reason. Moreover, if two or three insufflations are performed on the one day—that is, within a few hours of one another—the tracings obtained need not be closely similar.

Summary

Some of the more important lessons gained from just over 4,000 utero-tubal insufflations during the past 25 years are:

(1) Practice bears out the theoretical advantages of carbon dioxide. There were only five cases of infection and no deaths.

(2) Two or more tests, with the pressure advanced to 250 mm. Hg, one at least without anaesthesia, provide a reliable diagnosis of non-patency.

(3) Primary sterility patients numbering 902 were traced for 12 months; 30% became pregnant. In a group of 253 patients in whom a uterine sound was passed, only 17.7% became pregnant within twelve months.

(4) The kymograph is a useful adjunct.

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"Arterial Grafting" was the subject of a meeting of the Section of Surgery of the Manchester Medical Society at which Professor C. G. Rob spoke on December 12, 1953. He began by outlining the history of the subject. In 1912 Carrel had been awarded the Nobel Prize for his researches on blood vessel grafting and the transplantation of tissues and organs; in 1913 Lexer reported that he had resected three aneurysms of peripheral arteries and restored continuity with an autogenous vein graft. The first successful arterial graft in man was inserted by Gross in 1947; he established an artery bank based on the principles elaborated by Carrel. The indications for blood vessel grafting included congenital abnormalities, such as certain coarctations of the aorta, some aneurysms and arterio-venous fistulae, wounds, primary thromboses, after some emboli, occasionally in malignant disease, and in arteriosclerosis after very careful selection. Most of these indications were obvious, but the question of arterial grafting in patients with arteriosclerotic occlusion of major vessels was debatable. These patients had a general disease; the arteriogram often showed a lesion anatomically suitable for grafting, but one was treating a patient and not an arteriogram. In all Professor Rob had grafted 35 arteries, but had treated in this way less than 3% of patients with arteriosclerosis who presented with the complaint of intermittent claudication.

DIAGNOSIS AND TREATMENT OF GALACTOSAEMIA

BY

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Galactose, formed during the metabolism of lactose, is normally converted into glycogen in the liver. In the condition known as galactosaemia this process is defective, resulting in a high concentration of galactose in the blood and its excretion in the urine. It is probable that galactose in such concentrations is toxic to some tissues and is itself responsible for the main pathological changes, but the exact pathogenesis is still uncertain. This disease is of more than academic interest because prompt treatment may bring excellent results. The original clinical description was by von Reuss (1908). Göppert (1917) was the first to report a familial incidence. Articles on the subject have appeared with increasing frequency in the past seven years, mainly in American paediatric journals. Gorter (1951) gave an account of the disease at a meeting of the British Paediatric Association, but no cases were reported in this country until Bray, Isaac, and Watkins (1952) published three and gave a full review of the literature. We know of other cases that have been diagnosed in this country, but we feel sure that knowledge of the disease is not yet widespread enough. An increased awareness will lead to earlier and more frequent detection of the disease.

The earliest signs appear in the neonatal period. The infant is reluctant to feed, may vomit occasionally, and is slow to gain weight. Jaundice is common but varies in intensity. In the most severe cases deep jaundice and ascites develop in 4 to 5 weeks and the infant dies from hepatic failure. In milder cases the infants pass gradually into a state of marasmus, and at 6 months may be only a few ounces over their birth weight. Enlargement of the liver is a constant physical finding, the edge being firm and extending nearly to the umbilicus. The spleen may be palpable. Lamellar cataracts are often found, but are not easy to detect in the early stages. Mental retardation is usually obvious by the end of the first year. Early routine investigations should reveal albumin and a reducing substance in the urine. The latter must be identified as galactose to establish the diagnosis.

Basically the treatment consists in removing lactose from the diet. When this is done rapid improvement may follow. The appetite returns, the weight increases, and the liver edge gradually recedes. Galactose disappears from the urine in one to two days and albumin a few days later. Cataracts may disappear in cases in which treatment is started early, in others needling may be necessary. Mental impairment has persisted in many

published cases, but further observation is needed to show whether early treatment will prevent this. The galactose-tolerance test is likely to remain permanently abnormal. Two patients at the ages of 18 years (Townsend, Mason, and Strong, 1951) and 7 years (Bray, Isaac, and Watkins, 1952) have been able to take some lactose in the diet without excreting galactose in the urine. Experience of the disease is still too limited for an accurate assessment of the prognosis following treatment. Reports of four recent cases are given below.

Case 1

A full-term male infant weighing 7 lb. (3,175 g.) was born on February 2, 1952. Two siblings were said to have died from pneumonia, one at 3 months and the other at 11 months. It was not possible to obtain information from the mother on the question of consanguinity.

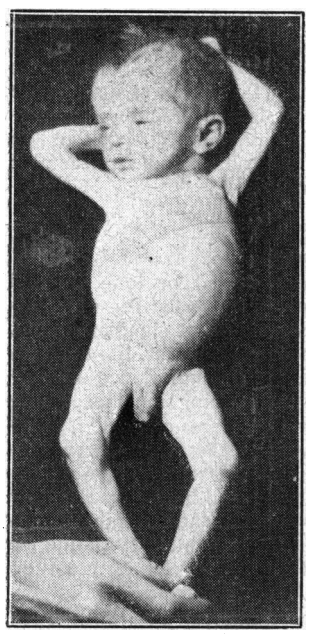

FIG. 1.—Case 1 on admission, aged 3 months.

Early feeding difficulties and poor home conditions necessitated several admissions to hospital and then to a residential nursery. When 3 months old he was transferred to Whiston County Hospital under the care of one of us (R. H. W.-J.). Because of the disproportionate size of his head to his wasted body he was sent in with a provisional diagnosis of hydrocephalus. His weight was 8 lb. (3,630 g.) and his head circumference 15 in. (38 cm.). He was emaciated and miserable (Fig. 1). His heart and lungs were normal; his liver was enlarged, the edge being firm and palpable four fingerbreadths below the costal margin. Because of a wide and rather tense fontanelle a lumbar puncture was performed. The sugar content of the C.S.F. was 222 mg. per 100 ml. (as glucose), the other constituents being normal. This was the first clue to the correct diagnosis. The urine contained albumin but no casts. A reducing substance was present. The latter was thought to be galactose because mucic acid crystals were formed and Tollen's test was negative for pentose and glycuronic acid but positive for galactose. The fasting blood sugar was 190 mg. per 100 ml. (as glucose), and the glucose-tolerance curve was abnormal, rising to 285 mg. after one hour. A paper chromatogram of the urine before starting treatment showed a normal amino-acid pattern.

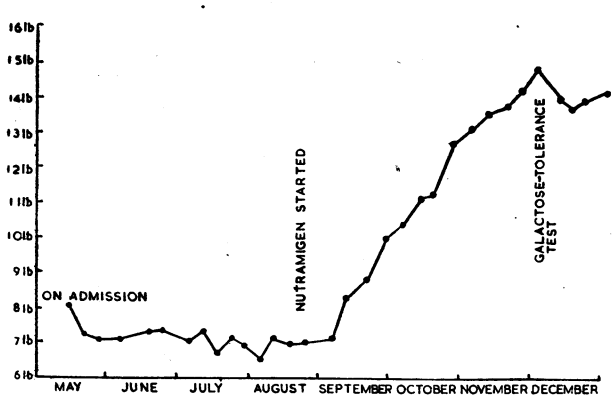

FIG. 2.—Case 1. Weight curve.

The mother's Wassermann reaction was negative. The patient's Wassermann reaction was negative; blood urea, 47 mg. per 100 ml.; haemoglobin, 8.9 g. per 100 ml.; thymol turbidity, 3 units; alkaline phosphatase, 6.6 units per 100 ml. serum (King–Armstrong). *X*-ray films of the skull and long bones showed slight generalized osteoporosis. Mr. J. M. Broderick (ophthalmic surgeon) reported fine but distinct lineal opacities towards the periphery of each lens which were thought to be early lamellar cataracts.

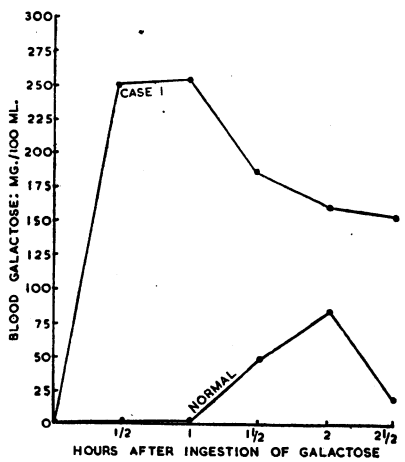

FIG. 3.—Case 1. Galactose-tolerance curves (1.75 g. galactose per kg. body weight).

From the time of admission the baby was reluctant to take feeds of dried milk and sometimes vomited. In the first week he lost 1 lb. (454 g.) in weight. A formula containing lactose-free protein, "dextri-maltose," and fat was given, but this was persistently refused and it was necessary to return to unmodified dried milk. When "nutramigen" was obtained the effect was dramatic. From the first feed the baby took well, and the weight, which had remained at about 7 lb., began to rise steeply and continued to do so (Fig. 2). The liver gradually returned to normal size, the cataracts disappeared, and the urine remained free from reducing substances. A galactose-tolerance test (Fig. 3) was performed when the baby weighed 15 lb. (6,800 g.). This helped to confirm the diagnosis, but for two weeks afterwards he was apathetic and listless, and lost weight. When 11 months old his condition had greatly improved (Fig. 4); he could raise his head from the pillow, smile, recognize people, and play with a rattle. He continued to take nutramigen well, and later had a lactose-free mixed diet.

Case 2

This infant, the first baby of healthy and unrelated parents, was born in 1949. She weighed 6 lb. 8 oz. (2,948 g.) at birth, and was delivered spontaneously after an uneventful pregnancy which went to term. Slight jaundice was present on the sixth day. It was deeper on the ninth day, and as she was feeding badly she was admitted to Alder Hey Children's Hospital. She was afebrile, the um-

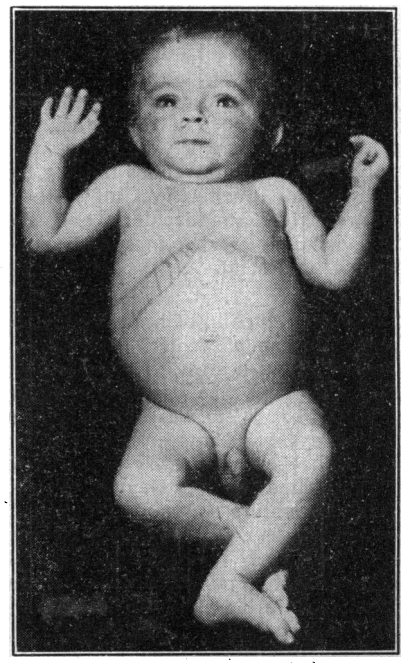

FIG. 4.—Case 1 aged 8 months.

bilicus was slightly infected, and there was oral thrush. The liver was felt one fingerbreadth below the rib margin. A few days later there was severe haemorrhage from the umbilicus; the jaundice was deeper and the liver larger. Her urine contained albumin and bile, but there is no record that it was ever tested for reducing substances. The Wassermann reaction was negative and there was no evidence of haemolytic disease of the newborn. The presumptive diagnosis was septicaemia and hepatitis due to umbilical infection. Treatment with penicillin and streptomycin had no effect, and she died 46 days after birth.

Case 3

A sister of Case 2 was born in 1952, after an uneventful pregnancy which went to term. She had a healthy brother, born in 1950. Her birth weight was 6 lb. (2,720 g.). Jaundice was noticed when she was 5 days old; it became deeper and she was admitted to Alder Hey Children's Hospital on the tenth day. She was then a vigorous infant ½ lb. (227 g.) below her birth weight. There was deep jaundice, and a little blood-stained discharge from the umbilicus. The liver edge was firm and reached 1 in. (2.5 cm.) below the costal margin. Breast-feeding was continued after admission. The provisional diagnosis was congenital familial cirrhosis of the liver, but antibiotics were given because of umbilical sepsis. Four days after admission, when jaundice was deeper and the infant was lethargic and feeding badly, a reducing substance was found in the urine. Very early lamellar cataracts were then discovered. Laboratory investigations at this stage gave the following results:—Urine: a large amount of albumin, bile salts, and pigments present; acetone absent; a reducing non-fermentable sugar present, confirmed as galactose by paper chromatography. Faeces: bilirubin present. Serum: thymol turbidity, 1.3 units; thymol flocculation negative; colloidal gold, 0; alkaline phosphatase, 46.5 K.-A. units per 100 ml.; bilirubin, 23.6 mg. per 100 ml. Blood: Wassermann reaction negative; group O Rh positive (mother: group A Rh positive); sugar, 230 mg. per 100 ml. (as glucose), 200 mg. per 100 ml. being a non-fermentable sugar.

As soon as galactosaemia was suspected breast-feeding was stopped and 5% glucose-saline with added "casinal" (a calcium salt of casein, 90% protein) was given by bottle. After six days she had gained 9 oz. (255 g.) in weight and her appetite and vigour had improved, her liver was smaller and the jaundice was less. Investigations now showed the urine to contain a little albumin but no galactose; blood sugar, 95 mg. per 100 ml.; serum: thymol turbidity, 0; alkaline phosphatase, 11.5 K.-A. units per 100 ml.; bilirubin, 8.6 mg. per 100 ml. A lactose-free peptone was then substituted for the casinal and a few days later a little emulsified butter was added to the feed. Sixteen days after admission she developed a respiratory infection and diarrhoea. She became extremely acidotic and failed to respond to antibiotics and intravenous therapy, dying when 26 days old. Subsequent investigations of earlier specimens of urine showed gross aminoaciduria and, though this persisted, it was definitely weaker in specimens collected after eighteen days of treatment.

Case 4

The second child of healthy unrelated parents was born at term after an uneventful pregnancy. The first child was 7 years old and healthy. The patient's birth weight was 7 lb. 6 oz. (3,245 g.). She was breast-fed for two weeks, then given dried milk. There was mild jaundice from the fifth to the ninth days. She appeared well until the twenty-third day, when she became drowsy and was reluctant to feed. She was admitted to Alder Hey Children's Hospital the next day. Her temperature was normal but she looked very ill. Her abdomen was distended, free fluid was present, and the liver was moderately enlarged. She died 12 hours after admission. Lumbar puncture was performed soon after admission; the turbid fluid obtained yielded a growth of *Str. pneumoniae*. The total sugar was 280 mg. per 100 ml., of which 210 mg. per 100 ml. was non-fermentable sugar. Chromatography confirmed the presence of galactose.

Post-mortem Findings

The following is a brief summary of the pathological findings; a detailed report will be published elsewhere (B. G. Ockenden).

In all three cases the livers were enlarged, firm, and dark green in colour, with finely granular or wrinkled surfaces. Histological examination showed a uniform diffuse fibrosis, mainly periportal, proliferation of the smaller bile ducts, loss of the normal liver pattern, and an alveolar arrangement of the liver cells. In the two untreated cases the liver cells were vacuolated and contained lipoid; in the treated case only traces of fat were present.

The kidneys of Case 2 were enlarged. Those of Cases 3 and 4 were of normal size and showed no macroscopic abnormality, but histological examination showed marked dilatation of the proximal convoluted tubules.

Final Pathological Diagnoses.—Case 2: A diagnosis of cirrhosis of the liver of unknown aetiology was made until 1952, when a sibling (Case 3) was found to have galactosaemia. Despite the complete lack of biochemical evidence, the similarity of the gross and microscopical findings in the liver was such that we are certain that this was also a case of galactosaemia. *Case 3:* Acidosis and uraemia; haemorrhagic bronchopneumonia; galactosaemia; cirrhosis of the liver. *Case 4:* Pneumococcal peritonitis and septicaemia; galactosaemia; cirrhosis of the liver.

Discussion

Diagnosis

The diagnosis has often been missed or long delayed simply because the urine has not been tested for sugar, or if a reducing substance has been found its significance has not been appreciated. It is not always easy to obtain a sample of urine from an infant, but the importance of early treatment in galactosaemia makes the omission inexcusable when investigating neonatal jaundice, marasmus, and hepatomegaly. Once melituria and hyperglycaemia have been confirmed rapid identification of galactose must follow. Fermentation tests applied to both urine and blood should show that the reducing substance in the former and a high proportion of it in the latter are non-fermentable. It should be borne in mind, however, that some samples of yeast do ferment galactose.

Until the advent of chromatography the identification of this non-fermentable reducing substance as galactose depended on chemical tests. Some of these—for example, Barfoed's test (for monosaccharides), mucic acid production (lactose or galactose), and Bial's test (to exclude pentosuria)—may work well enough when sufficient reducing substance is present, but others—for example, osazone production—give inconclusive results when applied to relatively small amounts of complex biological fluids. Paper chromatography used in conjunction with the fermentation methods will give an answer overnight with a high degree of accuracy. Galactose is easily distinguished from three of the other sugars most likely to be found in urine (pentose, lactose, and fructose), either by differences in rate of movement or by the use of selected spraying agents. The distinction from glucose, however, is not so easy. Glucose and galactose have similar rates of movement in butanol-acetic-acid mixture and other common solvents used for sugar chromatography. The only distinguishing feature between them brought out by spraying agents is by the use of phloroglucinol when galactose turns a faint brown and glucose remains colourless. Three-day runs in butanol-acetic-acid mixture are reported to give sufficient separation. For rapid (overnight) identification it is best to make two separate runs in different solvents—for example, butanol-acetic-acid mixture and *p*-cresol; in the former the glucose spot (rf 0.19) runs a shade further than the galactose one (rf 0.17); in the latter solvent the positions are reversed.

Secondary biochemical investigations are concentrated on the detection and assessment of possible liver damage. These involve the usual liver-function tests—for example, examination for bile pigments in urine and faeces, estima-

tion of serum bilirubin and alkaline phosphatase, flocculation tests, etc. A galactose-tolerance test helps in diagnosis, but its performance is not without danger. When the blood galactose rises there may be a brief but serious fall in blood glucose, while the galactose deliberately given may aggravate the symptoms of the disease, as occurred in Case 1.

Gross aminoaciduria is usually detectable in untreated cases of galactosaemia, and here again chromatography is of great value. Amino-acids were not found, however, in Case 1, even before treatment was started. In Case 3 16 or more amino-acids were present, including cystine, tyrosine, aspartic acid, glutamine, serine, glycine, lysine, taurine, alanine, threonine, and possibly citrulline. The total amino-acid nitrogen in the blood was 4.8 mg. per 100 ml. In cases reported by Holzel *et al.* (1952) there was less aminoaciduria after treatment, but Bickel and Hickmans (1952) found it undiminished after a period on a lactose-free diet.

In Case 4 galactosaemia was not suspected until sections of the liver were examined. Only 2 ml. of C.S.F. was then available, but this proved sufficient to confirm the diagnosis; chemical estimation showed a high percentage of non-fermentable sugar confirmed as galactose by paper chromatography.

Treatment

The essential treatment is to remove lactose from the diet. It is not easy to provide a suitable substitute for whole milk for an infant. Case 1 was first offered a formula containing "pronutrin" (an enzymatic hydrolysate of casein), dextri-maltose, brewer's yeast, and water, and later this was replaced by lactose-free peptone, dextri-maltose, cod-liver oil, and water. Both feeds were often refused and had to be abandoned, presumably because they were not palatable. In cases reported by DuShane and Hartman (1951) and by Townsend, Mason, and Strong (1951), a soya bean formula was tried but not tolerated. Goldbloom and Brickman (1946) found such a formula suitable for one baby but not for another. In a number of other cases in which the outcome was satisfactory, nutramigen was used. This preparation consists of dextri-maltose 45.2%, amigen 20% (a non-antigenic pancreatic digest of casein consisting of amino-acids and short-chain polypeptides), corn oil 18%, arrowroot starch 10%, calcium gluconate 3.5%, other mineral substances 3.2%, crystalline vitamins 0.6%, calories 130 to the ounce. It has to be imported from America because no lactose-free infant food is made in this country. Supplies arrived too late for Case 3, but when used for Case 1 the results were most gratifying.

It is possible that the diarrhoea which developed in Case 3 was of infective origin, but it might have been due to the metabolic disturbances of the disease and the feeding difficulties. In the early stages of treatment, particularly in the neonatal period, the infant should be in hospital, where biochemical facilities are available for the control of treatment.

The problem of avoiding lactose becomes much simpler when mixed feeding is introduced, while later in childhood small quantities may be harmless.

Inheritance

From the literature so far published it is not possible to be sure how often the disease affects siblings or what proportion of them will be involved in any one family. Retrospective inquiry often gives a history suggesting that galactosaemia has caused the death in infancy of other members of the family, but proof is impossible. The question of consanguinity of the parents is rarely mentioned. Professor L. S. Penrose (personal communication) suggests that the disease may be due to a recessive gene in homozygous form. If so, the chance of a child in an affected family showing the disease would be one in four. The incidence in the family histories reported by Göppert (1917), Donnell and Lann (1951), and Gorter (1951) would, however, be higher than this, if suspected cases could have been confirmed.

ADDENDUM.—Since the paper was completed the mother of Case 1 has given birth to a girl who after six weeks has shown no reducing substances in the urine. She appears to be healthy. The mother of Cases 2 and 3 has had binovular twin boys (there were two separate placentae). The infants were breast-fed for two and a half weeks, and then took half-cream National dried milk. Samples of urine were examined daily for the first 12 days. Several specimens from each infant contained a reducing substance (up to 0.4 g.%, as glucose). Paper chromatography revealed the presence of a little galactose on four occasions. When the infants were 4 weeks old no reducing substances were found in one specimen of urine from each. Amino-acids in the urine did not differ from those to be expected in the newborn. Both infants appeared to be quite healthy and were gaining weight very well when 6 weeks old.

We wish to thank Dr. R. M. Todd for permission to include Case 4; Dr. F. Fletcher, of Bengers Ltd., for a supply of lactose-free peptone; Dr. C. E. Dent for confirming the aminoaciduria in Case 3; and Dr. R. W. Brookfield and Dr. E. G. Hall for criticism and advice.

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GALACTOSE DIABETES

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Galactose diabetes is a rare inborn error of galactose metabolism. Although originally described by von Reuss in 1908, the condition does not seem to have been reported in this country until Holzel and others (1952) described two cases associated with aminoaciduria.

The essential features of the disease are failure to thrive dating from the neonatal period, hepatomegaly, albuminuria, and galactosuria. In addition, the serum bilirubin is commonly elevated and jaundice may even be detected clinically. The liver-function tests may be abnormal. Nuclear cataracts sometimes occur and mental deficiency may appear in those surviving infancy. Occasionally the disease is familial.

In the case here described bouts of remittent pyrexia occurred, the duration of the fever varying from two to seven days. On two occasions there was an associated upper respiratory infection, but on the other six occasions no satisfactory explanation of the pyrexia could be found. Blood cultures were repeatedly negative and there was no response to sulphonamide, penicillin, or aureomycin therapy. Similar periods of pyrexia have been mentioned in previous case reports, and they would seem to form an integral part of the syndrome.

Treatment consists in the exclusion of galactose from the diet, and this is achieved in infancy by feeding a lactose-free milk substitute. If this therapy is instituted early, the manifestations of the disease are largely reversible, but if diagnosis is delayed the prognosis is poor.