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

BY

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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.

Case Report

A male infant aged 4 months was admitted to hospital on August 30, 1951, because of failure to thrive. He was born at term, weighing 7 lb. 10 oz. (3.5 kg.). The labour was normal. His mother thought that he was a little jaundiced for a few days after birth. Breast feeding was not attempted and the baby was fed on a proprietary food until admission to hospital. Although he took his feeds eagerly and neither vomited nor had diarrhoea, he did not thrive prior to admission to hospital. His mother, father, and brother aged 4 years were stated to be in good health. The brother was examined clinically and no abnormality was detected.

On admission the infant did not look ill but was obviously underweight. His weight was 8 lb. 9 oz. (3.9 kg.), temperature 98° F. (36.7° C.), pulse 146, and respirations 30. On clinical examination the only abnormality was a firm enlargement of the liver to three fingerbreadths below the costal margin. The haemoglobin was 80% Sahli, the white blood cells numbered 21,000 per c.mm., and his blood was group O Rh-positive. The mother's blood was group O Rh-positive. On chemical examination of the urine no albumin or sugar was detected and microscopically no white blood cells or red blood cells were seen. Urine culture gave a light growth of *Streptococcus faecalis* and *Bact. coli*. The stools appeared to be normal, and on culture no pathogens were obtained. The Mantoux reaction (1 : 1,000) was negative. The Wassermann reaction was negative.

The infant fed well on full-cream National dried milk, but did not gain weight. Throughout the course of his illness bouts of pyrexia, as described above, occurred. The urine was repeatedly found to be normal, both chemically and microscopically, until the 35th day after admission, when a trace of albumin was detected. This albuminuria persisted, and on the 46th day Benedict's test became positive. Further laboratory investigation (see below) showed this reducing substance to be galactose. On the 97th day the infant was put on a lactose-free soya-flour mixture, which he took well. This resulted in the urine becoming sugar-free within 48 hours. He started to gain weight and his general condition improved, although there was no change in the size of his liver. A return to milk feeding for 24 hours resulted in the reappearance of a positive Benedict's test and the development of slight pitting oedema. However, these both disappeared when a lactose-free diet was recommenced. On the 147th day he developed an upper respiratory infection with pyrexia, vomiting, and diarrhoea. Chloramphenicol therapy was instituted. His condition appeared to be improving, when on the 156th day he collapsed suddenly after a feed and died within a few seconds.

Biochemical Investigations

Urine.—Chemical and microscopical examinations for cystine were negative on four occasions (October 17 and 25, and November 2 and 19). Amino-acid nitrogen on October 17, 23, and 31, and November 2 and 19 was 60, 116, 35, 40, and 30 mg. per 100 ml. respectively.

Blood.—September 6: serum proteins, 5.5 g. per 100 ml.; serum albumin, 4.2 g. per 100 ml.; serum globulin, 1.3 g. per 100 ml.; serum bilirubin, 0.5 mg. per 100 ml.; serum alkaline phosphatase, 42.1 units per 100 ml.; thymol turbidity, 3 units. October 16: blood urea, 31 mg. per 100 ml.; blood cholesterol, 140 mg. per 100 ml. October 17: serum alkaline phosphatase, 23.5 units per 100 ml. October 26: serum proteins, 6.25 g. per 100 ml.; serum albumin, 4 g. per 100 ml.; serum globulin, 2.25 g. per 100 ml.; serum bilirubin, 1.4 mg. per 100 ml.; serum alkaline phosphatase, 15 units per 100 ml.; thymol turbidity, 3 units. November 9: blood-sugar curve after 20 g. glucose orally was: fasting specimen, 110 mg.; ½ hour after 20 g. of glucose orally, 194 mg.; 1 hour after, 206 mg.; 1½ hours after, 183 mg.; 2 hours after, 181 mg. per 100 ml. (Further investigations were planned—for example, galactose-tolerance test—but owing to the clinical condition of the patient these were not carried out.)

Identification of the Reducing Substance in the Urine.—The reducing substance present was provisionally identified as galactose on the following grounds; it was not fermented by yeast; Bial's test for pentose was negative; Tollens's phloroglucinol test was positive on prolonged boiling, as with pure galactose. The osazone was identical in crystalline form and in melting-point with that prepared from galactose. No depression of melting-point was produced on mixing the osazone isolated from the urine with known galactosazone. Mr. A. P. Kenny kindly confirmed the identification of the reducing substance in the urine by means of paper partition chromatography. He reported that the conclusion to be drawn from the chromatograms was that the principal reducing sugar in the urine was galactose, with a possible trace of free amino-sugar in certain specimens.

Aminoaciduria.—In no specimen of urine was the gross aminoaciduria recorded by Holzel *et al.* observed. Dr. H. Ellis C. Wilson kindly carried out two-way paper chromatograms of the urinary amino-acids. No gross aminoaciduria was observed. The following amino-acids were identified: glutamic acid, glycine, threonine, glutamine, alanine, phenylalanine, valine, histidine, oxyproline and nephrosis peptide.

Post-mortem Examination

The liver was regularly enlarged and of normal contour. On section there was marked pallor of the parenchyma with blurring of the lobular markings in places, giving a homogeneous appearance to the liver tissue. The lungs showed superficial areas of collapse in both lower lobes and there was congestion of all lobes, most marked basally. There was also marked pallor of the renal parenchyma and of the bowel mucosa.

Histology

The liver showed a diffuse monolobular cirrhosis with early fibrosis, formation of new bile ducts, and round-cell infiltration in the portal tracts. A few foci of round cells were seen among the liver cells. There was no glycogen present in the sections of liver examined. The ileum showed congestion of Peyer's patches with some lymphoid hyperplasia and slight round-cell infiltration in the villi. The mesenteric glands showed sinus hyperplasia. The spleen showed congestion of the pulp with reticulo-endothelial hyperplasia.

Discussion

Portal cirrhosis is a recognized complication of galactose diabetes, and although several theories have been advanced to explain its occurence none has gained general acceptance. One theory is that the portal cirrhosis is due to galactose being directly toxic to the liver; another that it results from the absolute or relative hypoglucosaemia which accompanies galactosaemia; while a third suggests that an inadequate diet leads to a deficiency of lipotrophic substances.

The discovery by Holzel *et al.* of aminoaciduria in two patients suffering from galactose diabetes suggested a further possible explanation—namely, that a deficiency of lipotrophic substances results from an excessive urinary loss of these. Such a mechanism has previously been suggested by Himsworth (1950) to explain the cirrhosis of the liver present in hepato-lenticular degeneration and Fanconi's syndrome, in both of which aminoaciduria occurs.

In the present case cirrhosis of the liver developed, although there was no gross aminoaciduria. However, the work of Bickel and Hickmans (1952) suggests that some of the amino-acids found do not occur in normal urine.

Summary

A case of galactose diabetes complicated by cirrhosis of the liver is described. The biochemical investigations are detailed with special reference to the identification of galactose in the urine and to the detection of the amino-acids in the urine. The pathogenesis of the cirrhosis of the liver is discussed.

We are indebted to Dr. J. B. McMillan, of Stobhill Hospital, Glasgow, for the pathological report; and to Dr. H. Ellis C.

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ACRODYNIA ASSOCIATED WITH EXCESSIVE INTAKE OF MERCURY

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Acrodynia is a disease of comparatively recent recognition, being first described in detail by Swift (1914) in Australia, and not reported in England before 1922. Since these earlier descriptions the disease has been recognized with increasing frequency in Europe and America as well as Australia, and in England it appears to be particularly prevalent in the neighbourhood of large industrial towns and cities of the North and Midlands—a distribution which may be of some significance, as is shown later. Another feature of some possible significance is the rather unusual fact that this disease is exceptional in that it affects breast-fed just as readily as artificially fed infants.

It being accepted that the cause and pathogenesis of acrodynia are unknown, it is not surprising that there have arisen a number of theories as to its origin, none of which is proved or even generally accepted. Warkany and Hubbard (1948) recorded several cases in which they suggested that the cause might be chronic metallic poisoning, incriminating mercury, and, in particular, the mercury administered so often to infants in the form of teething powders.

Bivings (1949) summarized all the recorded cases of acrodynia and found that mercury had been present in the urine of 28 out of 31 patients examined. He recorded also that of 15 patients treated with dimercaprol at least 11 showed prompt improvement or recovery; that is to say, these patients responded to the accepted treatment for mercurial poisoning.

There have been other brief references to the association of acrodynia with high levels of mercury in the urine, notably by Gaisford (1949), who states that in Manchester, where the condition is common, there is in almost every case a history of the ingestion of mercury, usually as calomel in teething powders. He states later (1950) that the general consensus of opinion appears to be that acrodynia is a general reaction to some poison in an infant hypersensitive to the offending substance, in most cases mercury. This opinion has been made widely known to chemists, being quoted in full in the *Extra Pharmacopoeia*, 1952.

Wilson, Thomson, and Holzel (1952), in describing five cases of nephrosis due to mercurial ingestion, urged that mercurial compounds should be eliminated from all teething powders, and that other mercurial compounds, such as grey pills, be used with care, and prolonged administration be avoided in young children. Less than a month later Holzel and James (1952) described 176 cases of acrodynia, over 50% of which gave a history of ingestion of teething powders, whereas of 1,561 healthy infants in the same area only 109, or 6.9%, were habitually given these powders.

Despite these numerous warnings of the potential danger of the administration of calomel to young infants, Miss Hornsby-Smith, replying on behalf of the Minister of Health to a question in the House of Commons in April, 1952, stated: "Inquiries are already in progress at various children's hospitals. Although indiscriminate use of teething powders is clearly undesirable, there is not yet definite evidence to justify general publicity."

Twenty months after that statement it does not appear that the results of the inquiries to which she referred have been made public, nor does it appear that physicians in general as yet regard the theory of Warkany and Hubbard as having been fully substantiated; for no concerted effort seems to have been directed towards the elimination of mercury from teething powders, or even towards the education of the public in the possible harmful results that may follow their administration.

The experience gained from a study of this disease in one of the industrial areas of the North Midlands, where acrodynia is particularly common, emphasizes the need for such action.

Case 1

A male child aged 9 months was seen at his home on August 6, 1952, because he was showing increasing irritability and loss of appetite. He had photophobia, was restless and miserable, sweating, had lost weight, and his hands and feet were puffy and peeling. He had marked tachycardia, and a slight sweat-rash was seen about the trunk—in fact, he presented the typical picture of acrodynia. He had been given teething powders on alternate days for the preceding three months.

On admission to hospital his urine was found to contain 1,450 μg. of mercury per litre. *X*-ray examination showed that his chest was free from disease and his Mantoux reaction was negative.

Treatment with dimercaprol was begun: 34 mg. for the first dose, followed by 17 mg. four hours later, and 17 mg. twice daily for a further two days. Ephedrine sulphate, 25 mg., was given orally before each injection.

By the fourth day after the starting of treatment the child seemed much happier, and the photophobia was less. After this course of treatment the urinary mercury dropped to 860 μg. per litre. A further course was given, using the same dosage of dimercaprol, following which his urinary mercury dropped to 300 μg. per litre.

At this stage the child became feverish, although his general condition was vastly improved, and an *x*-ray film showed an opacity in the right upper lobe. This took several weeks to resolve, not responding to antibiotics at all. At the same time radiographs of his long bones showed no abnormality; his serum calcium was 10 mg. and phosphorus 4.3 mg. per 100 ml.

A month later *x*-ray examination showed extensive decalcification of the long bones. As a result of this he was given "sterogyl," 300,000 units monthly, with calcium and phosphates by mouth daily, and it was decided not to give a further course of treatment with dimercaprol. A series of *x*-ray examinations showed that the decalcification had been arrested. Some six months from his admission to hospital his urinary mercury was down to 90 μg. per litre, his skeleton presented normal radiological appearances, and his general condition was satisfactory.

Case 2

A male child aged 10 months was admitted to hospital presenting the typical picture of acrodynia, except for the absence of any photophobia, and with a history of having been given teething powders on alternate days for a period