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L'action du "Sintrom" est assez brève, disparaissant dans les 48 à 72 heures qui suivent l'arrêt de la thérapie. Aucune complication hémorragique ou thrombo-embolique ne survint pendant son emploi, et le temps de coagulation fut presque toujours maintenu dans les limites que l'on accepte comme valables en thérapeutique.

Les auteurs en ont dirigé l'administration d'après les résultats du temps de coagulation déterminé par une méthode décrite antérieurement et standardisée selon des techniques maintenues rigoureusement identiques. Mayer et Connell semblent convaincus de la supériorité de cette méthode par rapport à la méthode en un temps de Quick pour la détermination du temps de prothrombine. Ils n'ont d'ailleurs obtenu aucune corrélation quantitative entre les deux genres de détermination. D'après eux, le "Sintrom" se classerait comme un anticoagulant oral satisfaisant dans les traitements à courte échéance.

M.R.D.

GALACTOSÆMIA*

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GALACTOSÆMIA — COMMONER THAN WE THINK?

GALACTOSÆMIA or galactose diabetes is a congenital familial inborn error of metabolism characterized by an inability to metabolize lactose and galactose normally. To the infant this is a major catastrophe since his diet consists almost entirely of milk — the only important source of these substances.

The essential features of the resulting syndrome are: severe malnutrition, hepatomegaly and the presence of a reducing substance (galactose), often with albumin and casts, in the urine. Lamellar cataracts have been present in many of the reported cases when carefully searched for with a slit lamp. Mental retardation may occur. Jaundice is being reported in an increasingly large proportion of the cases, and failure to report it in others is probably due to the fact that it is confused with physiological icterus of the newborn. Various types of liver lesion have been recorded in autopsy cases.

By simply removing milk from the diet of these affected infants, the entire process is halted or reversed, and a slowly or rapidly fatal illness becomes merely an inconvenience—the inconvenience of supplying a milk substitute.

REVIEW OF LITERATURE

The syndrome was first described in 1908 by von Reuss.[1] Göppert[2] in 1917 reported the familial nature of the condition. Little appeared in the literature until 1934 and 1935 when Unshelm[3] and then Mason and Turner[4] reported cases. Norman and Fashena[5] added a case in 1943, as did Mellinkoff[6] and his colleagues in 1945.

Bruck and Rapoport,[7] also in 1945, reported a case in a seven-week-old infant and suggested that the various manifestations were due to a direct toxic effect of galactose on the tissues.

Goldbloom and Brickman[8] reported two cases in 1946, with observations on the effect of insulin.

Goldstein and Ennis[9] in 1948 reported a case with abnormal liver function tests. In the same year, Greenman and Rathbun[10] demonstrated improvement in galactose tolerance (as evidenced by intravenous galactose administration) by administering insulin and/or glucose, and advised the use of a high carbohydrate diet.

Bell *et al.*[11, 12] in 1950 reported two affected sibs, with a discussion of pathological studies of the liver as well as liver function tests.

Townsend, Mason and Strong[13] in 1951 added five additional cases and postulated a relationship of the liver changes to Laennec's cirrhosis. They presented also a 10-year follow-up on the case reported by Mason and Turner. In the same year, Donnell and Lann[14] reported four cases, with comments on pathology and genetic aspects.

Bray, Isaac and Watkins[15] in 1952 presented three cases from the English literature, with observations on liver pathology and urine amino acid studies.

One purpose of the present paper is to suggest that galactosæmia is, in reality, relatively common, and that the diagnosis is missed for several very good reasons:

(1) Failure to obtain a urine specimen while the infant is on a milk feeding.

(2) Failure to consider the diagnosis in all dystrophic and marasmic infants.

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(3) Failure to consider the diagnosis in all atypical cases of jaundice in the newborn period.

Eight cases have been diagnosed at The Hospital for Sick Children, Toronto—seven in a three-year period. It has been possible to carry out considerable investigation in these cases, especially liver function tests and genetic studies.

Confirmation of our impression, that cases of galactosæmia are frequently misdiagnosed, came upon reassessing the clinical history and autopsy record of a sib of one of our recent patients, who had died of "biliary cirrhosis" in 1941. Since the correct diagnosis was undoubtedly galactosæmia, all autopsy records of "cirrhosis" in infants under six months of age for a 15-year period were reviewed. The results of this review are discussed later. Briefly, of 16 such cases in which an etiological diagnosis had not been established, there was definite evidence in three and suggestive evidence in six others, that a diagnosis of galactosæmia had been missed.

CLINICAL FEATURES (Eight Cases)

1. *Age at time of diagnosis:* This ranged from seven days to nine and one-half months, the ages of the remaining patients being four months, 51 days, 48 days, 18 days and 17 days. One patient died at one month of age, undiagnosed.

2. *Malnutrition:* Except for two patients in whom the diagnosis was made during the first 17 days of life, malnutrition was present in all, usually to a severe degree. Frequently the baby was referred by the family physician for investigation of dystrophy.

3. *Jaundice:* Seven of the eight patients were either jaundiced on admission or gave a history of jaundice in the newborn period. The earliest onset was at three days of age, the latest at three weeks (discovered by the family doctor and probably present before this) and frequently was between the fifth and twelfth days. The only patient who had never shown jaundice was nine months old at the time of diagnosis and, although markedly malnourished, probably represents a milder form of the condition. Six patients were jaundiced on admission and the jaundice faded within a few days after institution of milk-free diet in four, but persisted and deepened in the two fatal cases (one untreated). In one (J.C.) the jaundice appeared at six days of age, deepened for two days and disappeared after seven days despite the fact that he was still receiving milk. The stools were usually green or yellow and the urine dark. Because of this high incidence of jaundice the referring diagnosis was frequently congenital atresia of the bile ducts, erythroblastosis fetalis, or biliary cirrhosis.

4. *Gastro-intestinal disturbances* were common. Six patients had frequent stools in the newborn period. These were usually loose or watery and three were stated to be green, two yellow and one "darker than normal". It was interesting that frequent green loose stools usually occurred in the breast-fed patients and necessitated a change of formula which frequently improved the diarrhœa. In this regard, it is known that breast milk contains considerably more lactose than cow's milk formulæ. None of the patients had pale or white stools.

All were poor feeders, refusing feedings regularly. Four had frank vomiting.

5. *Drowsiness* was a leading complaint in two but was probably due to the general malaise.

6. *Fever:* An unexplained low-grade fever was a prominent feature in one patient, and although it did not disappear during the first month of Nutramigen feeding, it has not been present on follow-up examinations.

7. *Hepatomegaly* was present in six patients at the time of diagnosis, but was not evident in the two patients diagnosed during the first few days of life. Liver enlargement seemed to be directly correlated with the duration of illness before diagnosis and also with the severity of the illness. In three patients the liver extended to the iliac crest or umbilical level. In only two was comment made on the firmness of the liver. With treatment the liver gradually receded to normal size and consistency, usually in a matter of weeks, but in one patient (nine months' duration of illness at time of diagnosis) the liver did not become normal clinically until about one and one-half to two years after treatment was instituted.

8. *Splenomegaly* was present in five patients but never was more than two fingerbreadths below the left costal margin. In each case it receded with treatment.

9. *Cataracts* were searched for in six patients and found in the three who had had their illness for nine months, three months and one month respectively. In the first-mentioned patient early cortical cataractous changes were discovered 11 days before mullsoy feedings were started. De-

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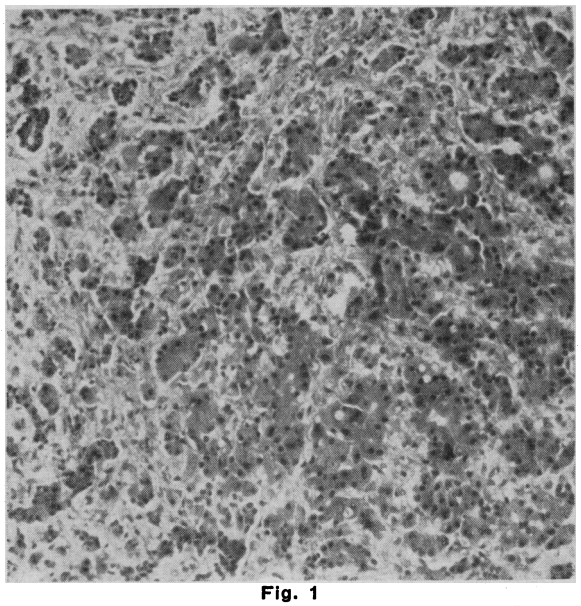

Fig. 1

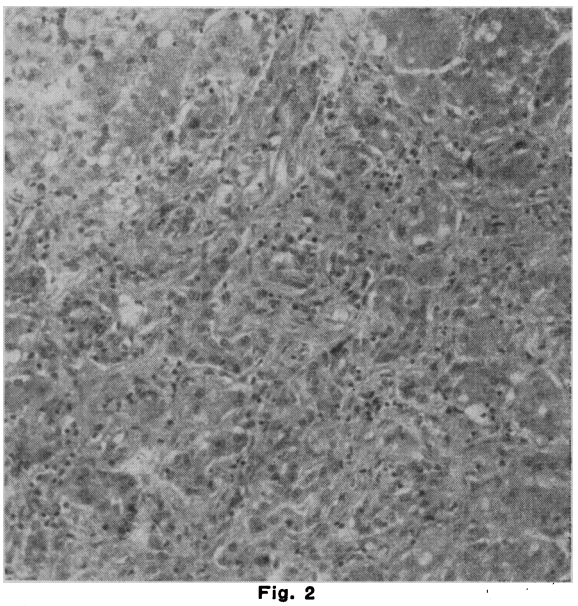

Fig. 2

Fig. 1. (Case 1).—Diffuse hepatic fibrosis with some of the parenchymal cells forming tubular structures. Hæmatoxylin and eosin. Fig. 2. (Case 2).—Diffuse hepatic fibrosis. The pattern is similar to that of Case 1 but more parenchymal cells remain. Hæmatoxylin and eosin.

spite the change of treatment, the cataract changes progressed rapidly over the next six weeks until no fundus detail could be seen. These cataracts have had to be needled twice and at present the patient wears 10 dioptre lenses and has good vision.

In the second patient the cataracts, which were in the posterior subcapsular area and of a minor degree, have remained unchanged after one and one-half years. In the third patient there has been no follow-up.

10. *Family history:* A familial incidence has been a prominent feature. Each of three families has had two affected children. In one family a third sib died at nine days of age with what was almost certainly galactosæmia.

LABORATORY INVESTIGATION

1. *Urinalysis: Reducing substance* was present in the urine of seven patients. The eighth patient was a sib of one of the cases and although he had clinical and pathological findings compatible with the diagnosis, a urine specimen was not obtained while he was receiving milk feedings. Benedict's test showed positive reduction of 3+ to 4+ degree on numerous occasions but only when the patients were receiving milk feedings. In the first three cases the reducing substance was identified as galactose by means of laborious chemical procedures (i.e. fermentation tests, preparation of galactose osazone, etc.) and thereafter by the simple technique of paper chromatography.

Albuminuria was present in all, varying from 1+ to 3+. This disappeared almost immediately on a milk-free diet.

Granular and cellular casts with occasional red and white blood cells were present in five patients and quickly disappeared on a milk-free diet.

Amino aciduria: Amino acid chromatography was carried out on only one patient before cessation of milk feedings and showed a markedly abnormal pattern with 14 abnormal amino acids in varying concentrations. Unfortunately serum amino acid chromatography was not done, so we are unable to answer definitely the question whether the amino aciduria was renal or hepatic in origin. This patient died. However, serum amino acid chromatography was done on another patient at the height of his illness and was normal. Urine amino acid chromatograms, done on three patients several months after institution of milk-free diet, were also all normal. Although this suggests (a) a renal origin and (b) complete reversibility following treatment, still the problem is not settled.

Bile and urobilin were present in the urine during the phase of jaundice and the stools were always coloured.

Blood: Anæmia was present in five at the time of diagnosis, with hæmoglobin value less than 10 g. %. Results of bone marrow examinations on three patients were normal. The red cells showed some anisocytosis and hypochromasia. Coombs tests were negative in all; red cell

fragility was normal in two tests. Platelet and white cell counts were normal, although the latter were frequently elevated to 10-14,000.

GALACTOSE TOLERANCE TESTS

Galactose tolerance tests, using 1.75 g. galactose per kilogram, were carried out on four patients at the time of diagnosis and a fifth (P.A.C.) four months after treatment was instituted. Tests were repeated on two patients, H.L. and J.C., one year after treatment was begun. Briefly, all had grossly abnormal galactose tolerance tests, and in the two on whom repeat tests were done the results were even more abnormal after one year on a milk-free diet. This is not in keeping with the experience of others, who have found an increase in galactose tolerance after treatment.

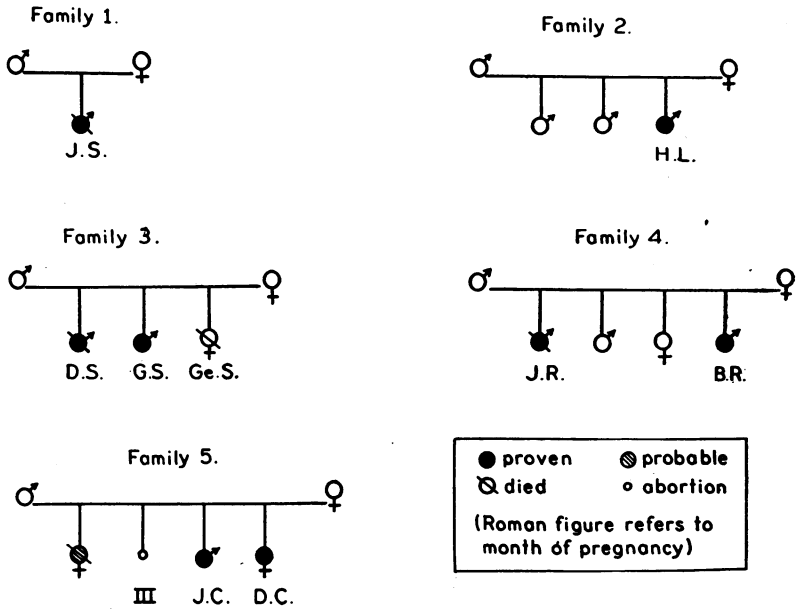

Fig. 3.—Pedigrees of the immediate families of the eight proven cases of galactosæmia.

MISCELLANEOUS TESTS (Before Treatment)

Blood Wassermann and blood cholesterol tests were done on four patients, and results were normal. Adrenaline tolerance was normal in one patient tested, blood glycogen normal in two tested. Non-protein nitrogen was at the high limit of normal in three. Of two patients who had lumbar punctures, C.S.F. protein was 65 mg. % in one, Pandy 1+ in another.

Urine ketones.—It has frequently been noted that, unlike von Gierke's disease, galactosæmia is not accompanied by ketonuria. In fact, ketonuria has never been reported. It has been suggested that hepatotoxic agents may prevent ketone formation and, in this regard, galactose may be acting as an hepatotoxin. In only one of our patients (H.L.) were urinary ketones present, on four occasions, in amounts varying from trace to 2+. This patient was the oldest (10 months) in the series and, although not jaundiced, had the largest liver and spleen and the most abnormal tests of liver function, and took the longest for these tests to return to normal.

LIVER FUNCTION STUDIES

Since all of our patients have shown evidence of disturbed liver function beginning at an early stage of their disease, special efforts were made to carry out tests of liver function, before and after institution of therapy. The results of these tests are shown in Table I.

The upper line opposite the initials of each patient gives the results of tests done while the patient was still receiving galactose; subsequent lines give the results on a galactose-free regimen.

RESULTS OF TESTS BEFORE THERAPY

(a) *Serum bilirubin.*—Four of six patients tested had elevated serum bilirubin levels; the remaining two were not seen until age four months and nine and one-half months respectively. One of the latter had had clinical jaundice from age five days to age 19 days. In the four patients with elevated serum bilirubin levels, both the direct and indirect reacting fractions were elevated, the direct comprising more than 30% of the total. Bilirubin was present in the urine. These findings point to a regurgitation type of jaundice, but none of the four patients had complete biliary obstruction at any stage of their disease. The stools were always coloured and the urine always contained urobilin in varying amounts. With these results, the differentiation of jaundice due to galactosæmia from that due to congenital atresia of the bile duct, or so-called physiological jaundice of the newborn, should not be difficult.

(b) *Flocculation tests.*—Five out of six patients tested showed 2-4+ positive cephalin cholesterol

TABLE I.—LIVER FUNCTION STUDIES

Name	Age when tested	Duration of therapy	Serum bilirubin mg. % Dir.	Indir.	CCF	Thymol turb. units	Thymol flocc.	Total prot.	Serum proteins Albumin	Total globulin	Gamma globulin
G.S.	2½ wks.	0	4.85	15.00	neg.	1.05	neg.	5.80 (4.7-6.4)	2.85 (2.9-4.0)	2.95 (1.3-2.5)	——
	4½ wks.	2 wks.	——	——	neg.	——	neg.	5.15 (4.9-6.0)	2.80 (3.0-4.2)	2.35 (1.2-2.4)	0.44 (0.2-0.5)
B.R.	2½ wks.	0	3.5	5.5	2+	1.3	neg.	5.10 (4.7-6.7)	3.13 (2.9-4.0)	1.97 (1.3-2.5)	0.41 (0.2-0.6)
J.S.	7 wks.	0	7.85	12.0	3+	——	neg.	4.40 (4.9-6.0)	2.75 (3.0-4.2)	1.65 (1.2-2.4)	0.59 (0.2-0.5)
	8 wks.	1 wk.	4.30	6.0	——	——	——	——	——	——	——
	9 wks.	2 wks.	——	——	neg.	——	neg.	4.15 (4.9-6.0)	1.86 (3.0-4.2)	2.29 (1.2-2.4)	0.57 (0.2-0.5)
	2½ mos.	1 mon.	0.6	1.0	neg.	——	neg.	6.04 (4.9-6.0)	3.86 (3.0-4.2)	2.18 (1.2-2.4)	0.40 (0.2-0.5)
D.S.	2 mos.	0	3.75	7.45	3+	4.6	2+	6.04 (4.9-6.0)	3.59 (3.0-4.2)	2.45 (1.2-2.4)	1.28 (0.2-0.6)
J.C.	4 mos.	0	norm.	norm.	3+	——	neg.	6.62 (5.5-6.6)	3.58 (3.6-4.8)	3.04 (1.7-2.9)	0.59 (0.3-0.6)
	4½ mos.	2 wks.	——	0.25	3+	——	——	6.60 (5.5-6.6)	3.25 (3.6-4.8)	2.35 (1.7-2.9)	0.72 (0.3-0.6)
	21 mos.	7 mos.	——	——	neg.	——	——	7.20 (6.5-7.7)	4.92 (3.7-4.9)	2.28 (2.3-3.3)	——
H.L.	9½ mos.	0	norm.	norm.	4+	——	2+	6.35 (5.9-4.8)	2.62 (3.6-4.8)	3.73 (1.7-2.4)	1.22 (0.4-0.7)
	10½ mos.	1 mon.	0.24	0.5	2+	——	——	6.78 (5.9-6.8)	3.81 (3.6-4.8)	2.97 (1.7-2.9)	1.25 (0.4-0.7)
	11 mos.	1½ mos.	——	——	neg.	——	——	7.02 (5.9-6.8)	4.10 (4.0-5.0)	2.92 (1.7-2.9)	0.91 (0.4-0.7)
	15½ mos.	6 mos.	——	——	neg.	1.5	1+	7.31 (6.3-7.6)	4.01 (3.6-4.8)	3.30 (2.1-3.1)	1.18 (0.4-0.8)
	22 mos.	11 mos.	——	——	neg.	3.4	3+	7.26 (6.5-7.7)	4.70 (4.0-5.0)	2.56 (2.3-3.3)	0.78 (0.7-1.3)
	30 mos.	21 mos.	——	——	neg.	1.6	neg.	6.98 (6.5-7.7)	4.77 (4.0-5.0)	2.21 (2.3-3.3)	0.87 (0.7-1.3)

flocculation tests. There appeared to be increasing positivity with longer duration of milk feedings before diagnosis. This test is usually negative in cases of so-called infantile hepatitis and other types of parenchymal liver disease in this age group.

The incidence of positive thymol turbidity and flocculation tests was much lower, only one patient showing more than 4 unit turbidity and two patients a positive flocculation. These last two patients were the oldest at the time of diagnosis.

(c) *Serum proteins.* — Total serum protein levels were within the normal range in all save one which was low.

The albumin fraction, however, showed a marked tendency to low levels and only two patients had levels within the range of normal. The patient with the longest duration of disease before diagnosis (H.L.) had the lowest level. Normal values (shown in parentheses) were obtained using the same method in a group of 140 normal infants from birth to two years of age, and the range represents ± twice the standard deviation for each age group.

Total globulin levels were elevated in most, paralleling the decrease in albumin levels. This elevation was due, in the main, to an increase in gamma globulins as measured by the salt precipitation method of Jager and Nickerson. Gamma globulin was elevated in 4 of 5 cases tested, and in 2 cases was increased to more than twice the normal figure for age. One of these was the most severe case and died shortly after a galactose-free regimen was instituted. The other had received milk feedings for 9½ months before the diagnosis was established. The only normal level was found in a young infant diagnosed at 18 days of age.

On the galactose-free regimen the results of the various tests approached normal levels after a variable length of time, but, generally speaking, the earlier treatment was started the faster was the return to normal levels.

The cephalin cholesterol flocculation test in a baby 17 days old when taken off milk reverted to normal in two weeks (patient G.S.). In another one, 4 months old at the time of diagnosis, there was no change in two weeks, but after one month the test was negative. In a third patient (H.L.), who was 9½ months old when diagnosed, the test was still 2+ positive after a month on galactose-free feedings.

In one patient (H.L.) who had a positive thymol flocculation test at the time therapy started, the test was still positive a year later, followed by a negative result after 21 months. Seemingly the results of the thymol test return to normal much more slowly than those of cephalin cholesterol flocculation. This is also seen in infectious hepatitis.

The serum protein values were similarly quite slow in returning to normal levels.

The pathological findings in two fatal cases are now described.

CASE 1 (B.S.)

A poorly developed, emaciated white male of 8½ weeks (length 53.0 cm., wt. 4000 g.). There was moderate jaundice. The peritoneal cavity contained 100 ml. of slightly turbid fluid. The liver (154 g.) was enlarged with the anterior border 4.0 cm. below the costal margin; it was dark green, smooth and firm and the cut surface was not nodular. The gall-bladder contained what appeared to be normal bile, and the bile passages were patent. The spleen (46 g.) was three times the average size but otherwise normal. An acute erosion of the lower

end of the œsophagus was the only other abnormal finding. There were no lens opacities. A heavy growth of *E. coli* was cultured from the peritoneal cavity, and microscopic evidence of an acute omphalitis and early peritonitis was found. Sections of the liver showed complete disruption of the liver cell plates and no recognizable lobular pattern (Fig. 1). There was extensive loss of parenchymal cells with collapse and condensation of the reticular framework. The surviving cells were arranged in short columns and sometimes formed distinct tubular structures. No multinucleate cells were seen and there were no mitoses. In the portal areas many cholangioles and small bile ducts were seen, some plugged with bile. The larger bile ducts were empty. Many of the liver cells contained a single small vacuole. Fat stains on frozen sections revealed very little fat in these cells and chemical analysis showed that the liver contained only 1.3% fat (wet weight). The over-all picture was that of a diffuse hepatic fibrosis, an almost pericellular cirrhosis affecting both lobes equally. No inflammatory cells were seen. The blood vessels were normal. The kidney showed only some protein casts in the tubules. The remaining tissues were normal.

CASE 2

This was a sib of one of the recent cases (J.R.). He died in 1941 at the age of 7 weeks and the diagnosis made at that time was congenital biliary cirrhosis. The body was fairly well developed and nourished. There was moderate jaundice. The peritoneal cavity contained 25 ml. of clear yellow fluid. The liver (not weighed) was enlarged and the anterior border was 4.0 cm. below the costal margin; it was firm, smooth and dark green in colour. The gall-bladder and bile passages were normal. There were no other abnormal findings. Microscopic examination showed an early bronchopneumonia. The liver changes were similar to those described in the first case but the process of cell destruction and stromal collapse was not as far advanced (Fig. 2). There were many more surviving parenchymal cells although most of them showed degenerative changes with greatly swollen, granular, eosinophilic cytoplasm. Many showed a single large vacuole. Bile plugging was limited to canaliculi and cholangioles; the larger vessels were empty. Some of the cells appeared to be grouped around a single vacuolated cell whilst others were arranged in a tubular manner. Between the short columns and groups of cells there were thin bands of mature collagen fibres and no lobular pattern was recognizable. The other tissues were normal.

When the above two cases were recognized, a survey of all autopsy cases of hepatic cirrhosis in children under the age of 6 months was undertaken. Between 1938 and 1952 there were 46 cases of cirrhosis diagnosed at autopsy. Most of them were due to extrahepatic biliary atresia. A miscellaneous group of 16 cases, in which no such cause for the cirrhosis could be found, was analyzed and in nine the diagnosis of galactosæmia was considered likely. All nine had clinical and pathological evidence compatible with a diagnosis of galactosæmia. Three had reducing substance in the urine. Unfortunately the urine in the remaining six was not tested for reducing substance while the patients were receiving milk feedings. These nine cases had been labelled variously as intrahepatic biliary atresia, neonatal cirrhosis, congenital cirrhosis, etc. They all showed liver changes similar to those described in the two known cases and it is very likely that they were examples of galactosæmia. The histological findings in this condition are probably not specific but we think that a presumptive diagnosis of galactosæmia may be made from the microscopic examination of the liver.

DISCUSSION

1. *Why Cases Are Missed*

Primarily, the diagnosis of galactosæmia is missed because it is not considered in cases of unexplained dystrophy, jaundice, anæmia, hepatomegaly with or without splenomegaly, and glycosuria.

The essential clue, of course, is the presence of reducing substance (galactose) in the urine. However, galactosuria is present *only* if the child is ingesting milk. Invariably these infants are not referred to hospital until their clinical condition precludes the possibility of feeding milk. On admission they are given some form of glucose drink and the initial urinalysis is negative. A second one is rarely done after the infant has resumed feedings. If jaundice is the problem, frequent subsequent urinalyses may be done for bile and urobilin, but the test for sugar is rarely repeated. Even if a baby has been receiving milk up until the time of admission, in which case his urine will show reducing substances, this is frequently attributed to the sugar solution or intravenous glucose given in the hospital.

It is therefore imperative that all infants presenting with any of the above signs or symptoms have a urinalysis while milk feedings are being ingested and retained. It is also essential to keep in mind that glycosuria is rare in early infancy except as caused by galactosæmia.

2. *Etiology*

It is generally agreed that a specific gene necessary for proper galactose metabolism is absent or altered, so that utilization of galactose is partially or completely impaired. Similar situations are seen in alkaptonuria, where one of the enzymes necessary for the conversion of tyrosine to aceto-acetic acid is absent, and as a result the end product is homogentisic acid, and in von Gierke's glycogen storage disease, where the metabolic defect is felt to be the absence of glucose-6-phosphatase which is necessary for the conversion of glucose-6-phosphate to glucose.

Normally, lactose is split into galactose and glucose in the small intestine. Galactose is absorbed as quickly as glucose but is metabolized less rapidly and less completely. The liver is almost entirely responsible for galactose metabolism although some workers believe that a little peripheral utilization is possible. In eviscerated and nephrectomized dogs, injected galactose persists for long periods almost unchanged, in the blood stream. Unlike glucose, galactose

cannot be directly utilized by the brain and will not relieve the symptoms of hypoglycæmia.

In the liver, galactose combines first with phosphate from adenosine triphosphoric acid (A.T.P.) under the influence of an enzyme, galactokinase. The resulting galactose-1-phosphate is then converted to glucose-1-phosphate under the influence of galactowaldenase, uridindiphospho-glucose being necessary as a coenzyme. It is felt that the metabolic defect is an impaired function or absence of one of these enzyme systems.

3. *Pathogenesis*

The mechanism by which abnormal galactose metabolism can cause such diversified effects as liver damage and jaundice, cataracts, mental retardation and kidney damage is the subject of some controversy.

It is known that the high blood galactose levels in untreated patients are sometimes associated with low blood glucose levels, which Mason and Turner[4] felt was due to excessive hepatic conversion of glucose to glycogen. Several authors have felt that the various manifestations were due to relative glucose starvation of the tissues and organs involved. However, such manifestations are not seen in hyperinsulinism or von Gierke's glycogen storage disease, both of which are associated with low blood glucose levels. Also hypoglycæmic signs and symptoms have not been noted in galactosæmia patients, even during the course of galactose tolerance tests.

Bell and his co-workers[12] feel that the inability to metabolize galactose normally, results in fatty infiltration of the liver, in a manner similar to that seen in poorly controlled diabetics. They suggest that this fatty infiltration of the liver then results in an even more severe inability to metabolize galactose. They also feel that, if the condition is untreated, cirrhosis may follow this infiltration with fat.

Bruck and Rapoport[7] found that galactose diffuses freely into the cerebrospinal fluid and felt that it likely diffuses freely into all body tissues. They therefore postulated that the various manifestations were best explained as being due to a direct toxic effect of high levels of galactose. In this regard it has been shown that rats fed on a diet containing 70% galactose develop cataracts which are reversible in the early stages.[16] The changes in the liver are more difficult to explain. Crooks was unable to produce liver damage in rabbits by the administration of large amounts of galactose both intravenously and orally, continuously for 21 days.

It is our feeling that the most logical explanation of the liver damage is that it is caused by a direct toxic action of galactose. That such damage cannot be produced in rabbits by the administration of large amounts of galactose is understandable, since the normal liver is able to metabolize galactose and therefore high levels of galactose might not occur at the metabolic site, in the liver cells. In fact, the galactose level at the conversion site might be the lowest of any site in the body. However, in galactosæmia, the liver cells are unable to metabolize galactose and it is reasonable to postulate that the galactose concentration in these defective liver cells may be just as high as at any other site in the body, resulting in a direct toxic action of galactose on the liver parenchymal cells.

The kidney damage, as evidenced by albumin and casts in the urine, is also best explained on the basis of a direct toxic action of galactose.

GENETICS

The eight proven cases of galactosæmia here presented belong to five families (Fig. 3). In two families there was an affected child (1 and 2); in two families there were two proven cases (3 and 4); while in the remaining family (5) there were two proven cases and a third probable case. The latter was the first-born child who died at 9 days with signs and symptoms identical with those of the two affected sibs, i.e. diarrhœa, vomiting and severe jaundice.

The recurrence of the disease among sibs in three families suggests the possibility of a genetic factor. As one test for single recessive inheritance, appropriate biochemical tests (galactose tolerance tests) were carried out on the parents and normal sibs, but all proved to be negative. Thus carriers were not detected. The condition may, nevertheless, depend upon a rare recessive gene or upon multiple genes, but until many complete and proven pedigrees have been assembled it is impossible to test further for a mode of inheritance. The low incidence of galactosæmia indicates that the recurrence among sibs is not due to chance clusterings of

cases in these families. Several etiological factors were investigated, such as consanguinity, maternal-fetal incompatibility (all known blood groups), prenatal disturbance of growth (as recorded by dermatoglyphics), and parental age, but all proved negative.

SUMMARY AND CONCLUSIONS

1. Galactosæmia is a congenital, familial inborn error of metabolism characterized by severe malnutrition, hepatomegaly, presence of reducing substance (galactose) in urine, and, perhaps, jaundice, cataracts, and mental retardation.

2. Cases are frequently missed because of failure to consider the diagnosis in all cases of jaundice and dystrophy in young infants and failure to test urine for reducing substance while the patient is receiving milk feedings.

3. It is felt that all of the various manifestations are best explained by direct toxic action of galactose, and a theory as to the pathogenesis of liver damage is presented.

4. All signs and symptoms, except perhaps cataracts and mental retardation, are reversed when milk products are removed from the diet.

5. Results of various laboratory tests, especially those of liver function, are presented.

6. Genetic aspects are discussed.

7. Detailed pathology of two cases is presented.

8. It is suggested that undiagnosed cases will be found in a review of case histories of autopsy cases of "cirrhosis" in early infancy.

REFERENCES

1. VON REUSS, A.: Zuckerausscheidung im Sauglingsalter, *Wien. med. Wchnschr.*, **58**: 799, 1908.
2. GÖPPERT, F.: *Berl. klin. Wchnschr.*, 54: 473, 1917.
3. UNSHELM, E.: *Deutsch. med. Wchnschr.*, **60**: 633, 1934.
4. MASON, H. H. AND TURNER, M. E.: *Am. J. Dis Child.*, **50**: 359, 1935.
5. NORMAN, F. A. AND FASHENA, G. J.: *Ibid.*, **66**: 531, 1943.
6. MELLINKOFF, S., ROTH, B. AND MACLAGGAN, J.: *J. Pediat.*, **27**: 338, 1945.
7. BRUCK, E. AND RAPOPORT, S.: *Am. J. Dis. Child.*, **70**: 267, 1945.
8. GOLDBLOOM, A. AND BRICKMAN, H. F.: *J. Pediat.*, **28**: 674, 1946.
9. GOLDSTEIN, E. O. AND ENNIS, J. M.: *Ibid.*, **33**: 147, 1948.
10. GREENMAN, L. AND RATHBUN, J. C.: *Pediatrics*, **2**: 666, 1948.
11. BELL, L. S. *et al.*: *Arch. Path.*, **49**: 393, 1950.
12. *Idem*: *J. Pediat.*, **36**: 427, 1950.
13. TOWNSEND, E. H. JR., MASON, H. H. AND STRONG, P. S.: *Pediatrics*, **7**: 760, 1951.
14. DONNELL, G. N. AND LANN, S. H.: *Ibid.*, **7**: 503, 1951.
15. BRAY, P. T., ISAAC, R. J. AND WATKINS, A. G.: *Arch. Dis. Childhood*, **27**: 341, 1952.
16. MITCHELL, H. S. AND DODGE, W. M.: *J. Nutrition*, **9**: 37, 1935.

RÉSUMÉ

La galactosémie est la manifestation d'un vice métabolique par lequel le malade ne peut assimiler le lactose et le galactose. Cette anomalie congénitale et apparemment familiale pose un problème d'une importance capitale pour le nourrisson dont la diète se compose entièrement de lait. Les manifestations cliniques de cette maladie comprennent: une mauvaise nutrition pouvant aller jusqu'à la cachexie, la présence de galactose dans l'urine, accompagnée souvent d'albumine et de cylindres, une hépatomégalie proportionnelle à la durée de la maladie, de l'anémie, des cataractes zonulaires, de la jaunisse et de l'arriération mentale.

D'après les auteurs de cet article, la galactosémie est plus répandue qu'on est porté à le croire, mais comme les cliniciens ne la gardent pas à la mémoire, elle passe souvent inaperçue et peut être prise pour de la cirrhose biliaire, une atrésie congénitale des voies biliaires, de l'érythroblastose fétale ou une dystrophie quelconque.

En plus des constatations cliniques déjà notées, les huit cas sur lesquels est basé ce travail présentaient les caractéristiques clinicopathologiques suivantes: l'utilisation du galactose dans la galactosémie provoquée, déjà mauvaise à l'époque où fut posé le diagnostic, l'était encore davantage après un an de traitement; les selles étaient toujours colorées, l'urine contenait de la bilirubine et de l'urobiline, mais rarement de l'acétone. Le diagnostic fut toujours signé par l'identification de la substance réductrice dans l'urine; cette opération est maintenant simplifiée de beaucoup grâce à la chromatographie sur papier. L'altération de la fonction hépatique fut mise en évidence par les résultats positifs de la céphaline cholestérol et l'élévation des gamma globulines.

Le facteur étiologique semble résider dans l'absence ou le mauvais fonctionnement d'un système enzymatique. Le taux élevé de galactose dans le sang pourrait être la cause de l'infiltration graisseuse du foie et de la cirrhose qui s'en suit, de même, que des signes de toxicité que l'on observe au niveau des différents tissus. Bien que cette élévation du galactose sanguin soit souvent accompagnée d'un abaissement du glucose, on n'a jamais observé de manifestations d'hypoglycémie dans la galactosémie. Les considérations génétiques restent encore obscures.

M.R.D.

RENAL BIOPSIES FROM PATIENTS WITH "TOXÆMIA OF PREGNANCY"

Renal biopsies were obtained by Dieckman and his associates (*Am. J. Obst. & Gynec.*, 73: 1, 1957) from 26 primiparas and 44 multiparas during or at the termination of pregnancy and in one non-pregnant multipara. A moderate or severe change (2+ or 3+) in renal glomeruli consisting of thickening of the basement membrane, the presence of fibrils in endothelial cells, and narrowing of glomerular capillaries was present in all of 11 primiparas with a clinical diagnosis of pre-eclampsia, in 2 of 3 with eclampsia and in 5 of 7 with a diagnosis of hypertensive disease.

It is concluded that this lesion may occur in patients with any variety of toxæmia of pregnancy, but that it is most constant in primiparas with a diagnosis of pre-eclampsia. There is no evidence that it persists to be responsible for permanent kidney damage.

A mild change (1+), consisting of slight thickening of basement membranes, slight fibrillation in endothelial cells, and little reduction in capillary lumina, was found in one primipara with eclampsia and in 3 primiparas with a clinical diagnosis of glomerulo-nephritis, and in 13 multiparas with a diagnosis of hypertensive disease and 4 with normal pregnancies. It is concluded that so mild a lesion rarely occurs in pre-eclampsia but is moderately frequent in multiparas with hypertensive disease.