

THE GENETIC MECHANISM OF GALACTOSAEMIA*

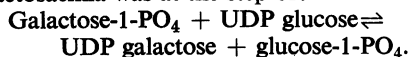
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Galactosaemia is a heredity disease of carbohydrate metabolism characterized by a failure to thrive, vomiting and jaundice in early infancy. Babies with this condition usually present with these symptoms and they are found to have enlarged firm livers, which soon become cirrhotic; this has been borne out by autopsy reports. They may be oedematous and have a tendency to bleed easily. Cataracts and mental retardation are common complications. The diagnosis can be confirmed by a markedly elevated galactose tolerance test and the finding of galactose in the urine. Schwarz, Golberg, Komrower and Holzel (1956) showed that galactose-1-phosphate accumulated in the erythrocytes of galactosaemic children if they were given galactose or milk. This indicated that galactokinase, which is the enzyme that converts galactose to galactose-1-phosphate, must be present in such individuals. In the same year, Isselbacher, Anderson, Kurahashi and Kalckar (1956) demonstrated a deficiency of galactose-1-phosphate uridyl transferase in the red blood cells of these children. This indicated that the site of the metabolic block in galactosaemia was at the step of:



It is now generally agreed that galactosaemia is transmitted by a Mendelian autosomal recessive gene. This is because of its frequent occurrence amongst siblings, its equal distribution in both sexes and the increased incidence of consanguineous matings amongst the parents of these children. Holzel and Komrower (1955) attempted to study the genetics of this condition by subjecting the parents of galactosaemic children to a galactose tolerance test. In only one family were they able to show that both parents were abnormal. In each of the four other families tested only one of the

parents gave an abnormal result; Durand and Semach (1955) found an abnormal galactose tolerance test in one parent; Bray, Isaac and Watkins (1952); Bain, Bowden, Chute, Jackson, Sass-Kortsak and Walker (1957); Schreier, Acker and Henckel (1957); and Bennett (1958) failed to demonstrate any abnormalities in the parents they tested. Hsia, Huang and Driscoll (1958) have since shown that a group of heterozygotes can be detected by estimating the blood level of galactose-1-phosphate uridyl transferase. This is discussed in more detail later.

The purpose of this paper is to present a complete family with galactosaemia and to give evidence that the disease is transmitted by a Mendelian autosomal recessive gene; it also sets out to show how enzyme studies in this family confirm the recessive mode of inheritance, that heterozygotes as a group can be detected and finally it demonstrates that galactosaemia can be present in a relatively unaffected adult.

Clinical Description of Family J

This family came to our notice from a genetic point of view as a family suffering from renal glycosuria. On investigation it was found that the reducing substance in the urine was galactose and as a result, all available members of the family have been studied. The pedigree is given in Fig. 1 and clinical details below:

- I₁ R.W., born 1894, had been thought to have diabetes mellitus for 16 years but has never needed insulin. The reducing substance in his urine has recently been shown to be galactose. Now he is in reasonably good health attending to his office business daily, and he is of above average intelligence. His eyesight is impaired because of cataracts and also he has an enlarged firm liver.
- I₂ B.W., born 1900, is healthy and has no reducing substance in her urine.
- II₁ R.W., born 1925, was known to have had a reducing substance in his urine since the age of 11 and to have a normal glucose tolerance test. He was healthy but not robust, and when put on an ulcer regime containing one or two pints of milk a day he found

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that he felt quite ill and so stopped it himself. He has five children, all of whom are well.

- II₂ A.J., born 1926, had been thought to have renal glycosuria for the past 10 years and when the diagnosis had been established in her children, it was found that the reducing substance in her urine was also galactose. She prefers to avoid milk, and has had much less intermittent diarrhoea, fewer headaches and has felt generally in better health since being on a milk-free diet.
- II₃ K.M., born 1928, has remained in reasonable health but had a reducing substance in her urine when she was pregnant. She has had one miscarriage and two healthy children.
- II₄ W.W., born 1931, was discharged from the services because a reducing substance was persistently found in his urine. Otherwise he was healthy.
- II₅ H.F., born 1935, has never been robust; she looks unwell with a rather pale translucent skin. She has had five pregnancies; two ended in miscarriages, two were premature births, the babies dying, and one a healthy child. She felt ill when pregnant, and was known to have a reducing substance in the urine at those times.
- II₆ S.C., born 1937, was in good health and has no reducing substance in her urine.
- II₁₁ J.J., born in 1920, admitted to no ill health and came from a large healthy family.
- III₁ T.J., born in 1948 at term by caesarean section because of a transverse lie, weighed 6 lb. 14½ oz. Although not particularly jaundiced at birth, he was an extremely difficult baby to feed because of vomiting. None of the usual artificial feeds suited him. In spite of his not regaining his birth weight until he was 1 month old, he was always an active baby. He smiled at 5 weeks, had some control of his head at 8 weeks, sat in a high chair at 5 months, pulled himself up to stand at 6 months, walked with

support at 11 months and by himself at 1 year. He could say single words at 15 months and talked at 22 months. Hence, there has been no evidence of any mental retardation and his subsequent progress at school has always been more than satisfactory. At about the age of 9 months, his mother took him off regular milk because she felt it did not suit him, and his condition subsequently improved. Since the age of about 1 year, he has complained of headaches and his mother correlated these with the taking of milk. He has had many unpleasant ill-defined episodes, which culminated in an alarming attack, in which he shook violently, had blurred vision, profuse sweating and almost lost consciousness. This attack had occurred after gulping a large bowl of milk and cereal at breakfast and was relieved by taking a sugar drink. At this time he was known to have a reducing substance in his urine with a normal glucose tolerance curve. It was the investigation of this presumed hypoglycaemic attack that led to the establishment of the diagnosis of galactosaemia. Examination now revealed him to be a tall, thin boy, of 9 years old, weight 65 lb., height 55 in. He has red hair and a rather translucent skin, bilateral cataracts and pale retinae; the liver and spleen were not palpable, and there were no other abnormal physical findings. The reducing substance in his urine was shown to be galactose by its failure to ferment with yeast; this was confirmed by the osazone test. Other laboratory data are given in Table 1. Since being on a milk-free diet, he has grown 1 in. and gained 3½ lb. in six months. He has been free of headaches, has felt much better and, instead of being a rather docile apprehensive boy, he has more energy and is full of spirit; in addition, his scholastic attainments have improved. Any relaxation of his diet, however, brought back the headaches and symptoms reminiscent of the hypoglycaemic attack.

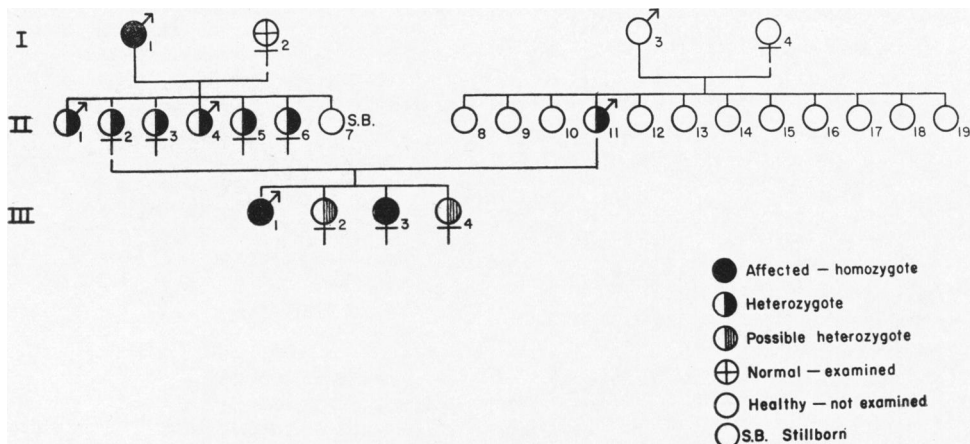


FIG. 1.—Pedigree on Family J.

TABLE 1
LABORATORY AND BRIEF CLINICAL DATA ON FAMILY J

		Gal-1-P Uridyl Transferase Level (units/g. Hb)				Galactose Level (mg./100 ml. blood)			Cataracts	I.Q.	Probable Genetic Status
		Mean	S.D.	Range		No value should be more than 50; reading should return to fasting level in 2 hrs					
Values for Normals		4.13	±1.4	2.8-7.0 (16)*		Usually normal					
Values for Heterozygotes		2.9	±1.1	1.1-5.5 (23)*		Values more than 50 mg.					
Values for Affected		0.6	±0.47	0 - 1.1 (16)*							
PEDIGREE Ref. No.	Initials	Random	Fasting	1 hr	2 hrs	Fasting	1 hr	2 hrs			
I 1	R.W.		0.9			59	115	42	+	N	Homozygote
I 2	B.W.	3.4								N	Unaffected
II 2	A.J.		1.7	1.8	1.7	8	28	6		N	Heterozygote
II 11	J.J.		1.8	1.0	0.9	7	31	10		N	Heterozygote
III 1	T.J.		0.6	0.6	0.4	7	86	54	+	N	Homozygote
III 2	M.J.		1.8	2.0	2.0	11	49	4		N	Possible heterozygote
III 3	S.J.		1.0	0.8	0.5	10	45	10	+	N	Homozygote
III 4	B.J.		2.5	2.4	—	10	83	—		N	Possible heterozygote
II 1	R.W.	1.1									Heterozygote
II 3	K.M.	3.4									Heterozygote
II 4	W.W.	2.1									Heterozygote
II 5	H.F.	2.5									Heterozygote
II 6	S.C.	4.1									Heterozygote

* Number of cases of which mean is recorded.

III₂ M.J. was born in 1950. Although her mother had some hypoglycaemic episodes during this pregnancy, she was born at term by caesarean section weighing 7 lb. 9 oz. She was breast fed for four months, thrived well from the beginning and has always been healthy, although she had an intussusception at the age of 4 months. She passed her milestones normally and is now a healthy intelligent girl.

III₃ S.J., born 1953, at term by caesarean section, weighing 6 lb. 14 oz. Vomited constantly from birth and had intermittent diarrhoea. When mother's milk failed she was extremely difficult to feed on cow's milk. When first admitted to the hospital at 3 months with a tentative diagnosis of congenital hypertrophic pyloric stenosis she weighed only 8 lb. Every type of milk feed was tried, but all were vomited. At 7 months of age she had a convulsion, which was thought to be related to an attack of pyelitis; at this time she only weighed 10 lb. She passed her milestones normally, sat at 6 months, walked between 10 and 11 months and was talking at the age of 2 years. She had frequent headaches, a poor appetite and 'chills' after drinking milk.

On examination she was found to be 39½ in. tall and weighed 28 lb. She, too, has red hair and a pale translucent skin unlike her two unaffected siblings. She had a palpable liver and bilateral cataracts but was otherwise normal. When the diagnosis was established in her brother T.J., her mother realized that she too was suffering from the same disease and enzyme studies confirmed this. Since then she has been on a milk-free diet, has grown 1½ in. and gained 5 lb. in six months. She has been free of headaches, felt better and done better in school though perhaps not quite so dramatically as her brother. Neither T.J. nor S.J. can

tolerate more than 1 oz. of milk on alternate days without the recurrence of symptoms.

III₄ B.J. was born in 1955, three weeks prematurely, by caesarean section because of a transverse lie. She weighed 7 lb. 11 oz. at birth and has thrived ever since. There were no feeding difficulties but a congenitally dislocated hip was diagnosed when she was 4 months old. It has been satisfactorily treated with splints and she stood at 7 months, walked at 13 months and is now a bright alert little girl.

Laboratory Data

Methods and Results. Galactose tolerance tests were done in the usual manner after an overnight fast. *D*-galactose was given orally in doses of 40 g. for adults, 1.25 g./kg. body weight for children and 1.75 g./kg. body weight for infants. A fasting blood sample, and others, one and two hours after taking the galactose, were collected in heparinized tubes and packed in ice until they were brought to the laboratory, the same samples being used both for the galactose determinations and the enzyme assays.

Blood galactose was determined by removing the glucose with glucose oxidase and estimating the remaining reducing substances by the Nelson Somogyi method.

Galactose-1-phosphate uridyl transferase was estimated by the method originally described by Anderson, Kalckar, Kurahashi and Isselbacher (1957). The method depends upon incubating a haemolysate of the red cells which contain the enzyme with known amounts of galactose-1-phosphate and uridine diphosphoglucose (UDPG). The reaction then proceeds from left to right as shown by the equation above. A unit of enzyme is that amount which will convert one micromole of UDPG to UDPGalactose in an hour. After the incubation period the remaining UDPG is estimated by means of uridine diphosphoglucose dehydrogenase in

TABLE 2
DETAILS ON PUBLISHED CASES OF GALACTOSAEMIA

Author	Case No.	Details of Families	Author	Case No.	Details of Families
Von Reuss (1908)		●	Patz (1953)	1	○ ○ ●
Goppert (1917)		♂♂♂♂		2	●
Fanconi (1933)	+	○○○○○○○○○○ order not stated	Fox, Fyfe and Mollison (1954)		♂♂
Boer (1932)		●●	LoPresti, Itani and Rice (1952)		♀♂♂
Mason and Turner (1935)		♀♂♀♂♂	Lockhart and Roboz (1954)		As LoPresti et al. (1952)-
Norman and Fashena (1943)		○♂	Bickel and Thursby-Pelham (1954)		♂♂
Mellinkoff, Roth and MacLaggan (1945)		♂	Hudson et al. (1954)	1	○ ○ ♂ ♀
Bruck and Rapoport (1945)		♂		2	♀ ♂ ♀ ♂
Goldbloom and Brickman (1946)	1	○♂		3	○ ●
	2	♂	Arthurton and Meade (1954)		○ ♂ ○ ○
Goldstein and Ennis (1948)		○○♂ order not stated	Cox and Pugh (1954)	1	◇ ♂ ♂ ♀ ♂ ◇
Greenman and Rathbun (1948)		♂		2	♀ ♀ ♀
Bell, Blai., Lindsay and Watson (1950)		♀♂		3	○ ○ ♂
Donnell and Lann (1951)	1	♀	Hartmann, McCoy, Swarm and Nakasato (1954)		♂
	2	◇♂♂♂	Lodding (1954)	+	♀
DuShane and Hartmann (1951)		○○○○♂	Jeune, Charrat and Loaec (1954)		♂ ♂ ♀ ♂ ♀ ♀ ♂
Townsend, Mason and Strong (1951)	1	○♂	Holzel and Komrower (1955)	1	♂♂♂
	2	◇♂♂♀		2	♀
	3	○○♂		3	♂♂♀♂
	4	●		4	♂♂
Ellenburg and Peterson (1951)		♀♂♂♂		5	+ ♂♂♂♂
Gorter (1951)	1	○○♂	Clay and Potter (1955)		●
	2	●	Mortensen and Sondergaard (1955)		♀
McCue (1951)		♂	Ritter and Cannon (1955)		♀
De Haas (1951)		○○○○○○○○●●	Durand and Semach (1955)		♂♂♂
Enns (1951)		♂	Rathbun (1955)		♀
Falls, Lowrey and Anderson (1951)		♀	Flury and Berger (1955)	+	♀ ♀ ♂
Edmonds, Hennigar and Crooks (1952)		♀ ○ ○ ○ ○ ○ ○	Haas and Newman (1955)		♂
Langewisch and Bigler (1952)		♂	Salt, Ross and Gerrard (1955)		♂
Bray, Isaac and Watkins (1952)	1	♂	Smith (1955)		♂♂♂♂
	2	♂	Kalckar, Anderson and Isselbacher (1956)	1	♀ ♂♂♂
	3	◇♂		2	♂
Brodie, J. L. (1952)		♂♂♂♂♂♂		3	♂♂
(1958)		As Brodie (1952)	Komrower, Schwarz, Holzel and Golberg (1956)	1	◇◇◇♂♂♂
Pitt (1952)		♂		2	●
Reiter and Lasky (1952)		♂	Turnbull (1956)		♂ ○ ♂
Johns (1953)		♂♂♂	Clément, Combes-Hamelle and Saada (1956)		○ ○ ○ ♂ ○ ○ ○
Hsia (unpublished data) (1952)	1	♀♂♂			order not stated
	2	♀●	Rodier (1957)		♀
	3	♀	Gillot, Schaeffer and Dalaut (1957)		♂
Maris and Valcke (1953)		♂♂	Bain, Bowden, Chute, Jackson, Sass-Kortsak and Walker (1957)	1	♂
Birdsong and Wood (1953)		○ ○ ♂		2	♂♂♂
Hartmann, Grunwaldt and James (1953)		♂		3	♂♂
Johnson (1953)	1	○○○♂♂♂		4	♂♂♂♂
	2	♀♂♂		5	◇◇♂♂
	3	♂			

TABLE 2 (continued)

Author	Case No.	Details of Families
Schultze-Jena and Schafer (1957)	1	◇ ○ ♂♂
	2	○ ○ ♂♂♂♂
Schreier, Acker and Henckel (1957)		○ ○ ♀
Wilhelm (1957)		♂
Bennett (1958)		○ ♂

KEY

Male	♂
Female	♀
Sex not recorded	○
Miscarriage or stillbirth	◇
Cataracts	⊙
Cirrhosis	⊚
Reducing substance in urine	⊖
Trace of reducing substance in urine	⊕
Abnormal galactose tolerance test	⊕
Galactosaemia	●
Consanguinity	†

the presence of DPN. The amount of haemoglobin in the haemolysate is calculated and the enzyme expressed as units per g. of Hb. Huang, Hugh-Jones and Hsia (1959) have described these methods in detail.

Using these methods the results obtained in this family are given in Table 1. Normal values for this laboratory are given at the top of the Table. The grandfather, who clinically had had a reducing substance in his urine for years (recently proven to be galactose), a large liver and cataracts, was found to have an abnor-

mal galactose tolerance test and an enzyme level within the affected range. The two of his grandchildren, who had typical histories of galactosaemia, also had enzyme levels within the affected range. The enzyme determinations on the grandfather's six children showed them, as a group, to be heterozygotes and the only one who was free of symptoms had the highest enzyme level.

Genetic Analysis of Literature

All the available published literature on galactosaemia has been reviewed. All families containing a case of galactosaemia have been tabulated (Table 2). For a case to be accepted as one of galactosaemia it must have had the typical clinical history of failure to thrive and feeding difficulties since birth, jaundice and an enlarged liver, a reducing substance in the urine after the first week of life and albuminuria. The reducing substance must have been proven to be galactose either by (1) its failure to ferment with yeast, (2) positive mucic acid test, (3) osazone crystal formation or (4) by paper chromatography. Many cases also had cataracts, were oedematous in the first week of life and had a tendency to bleed. Once a case had been diagnosed in a family others were quite often diagnosed retrospectively. These have been accepted provided they had three of the four following findings: typical history, cirrhosis, a reducing substance in the urine and cataracts. Using these criteria all the families, except those containing only one child, have been tabulated in Table 3.

Clinically, as had already been mentioned, it seems likely that galactosaemia is transmitted as a recessive gene. To confirm this the family data collected from the literature have been analysed

TABLE 3
ANALYSIS OF THE 57 SIBSHIPS WITH ONE OR MORE CASES OF GALACTOSAEMIA, COLLECTED FROM THE LITERATURE, BY THE A PRIORI METHOD (ONE CHILD FAMILIES OMITTED)

Family Size	No. of Families	Observed No. of Cases				Expected No. of Cases	Variance
		Male	Female	Not Stated	Total		
2	15	9	6	5	20	17.142	1.83
3	20	16	13	3	32	25.946	5.26
4	10	12	4	2	18	14.628	4.20
5	4	5	1	—	6	6.556	2.37
6	2	2	3	—	5	3.650	1.55
7	4	3	1	—	4	8.078	3.88
9	1	—	—	2	2	2.433	1.38
11	1	1	—	—	1	2.871	1.805
	57	48	28	12	88	81.304	22.275

Standard deviation = 4.72
 Observed cases, excluding cases from families of size one = 88
 Expected number of cases = 81
 $t = \frac{\text{difference between the observed and expected number of cases}}{\text{standard deviation}} = \frac{7}{4.72} = 1.5$
 7 degrees of freedom
 $p > 0.05$

by two methods. In each instance it has been shown that the observed frequency of cases was not significantly different from the theoretical incidence calculated for a recessive mode of inheritance.

In the first instance the data was analysed using the Weinberg sib method (Schultz, 1936). The formula for a recessive mode of transmission is:

$$\frac{Ta-P}{T-P} \text{ Should equal } 0.25$$

$$SE = \sqrt{\frac{pq}{T-P}}$$

Where: Ta = Total affected children in all the families
 T = Total children in all the families
 P = Probands
 p = Expected frequency of affected
 q = Expected frequency of remainder

There were 36 families with only one child, of which 18 were males, 12 females and in six the sex was unrecorded; when these were added to the data from Table 3, the formula became:

$$\frac{124-93}{246-93} = 0.2 \quad SE = \frac{0.25 \times 0.75}{153} = 0.035$$

Thus, the difference between the observed and expected value was not significant.

The data were also analysed by the 'a priori' or Apert's method. Calculating the expected number of children to be affected from Hogben's tables reproduced by Neel and Schull (1954) it will be seen from Table 3 that in these 57 families (families with only one child were omitted in these calculations) there should have been 81.3 affected children. The number observed was 88. The standard deviation is the square root of the sum of the variances. The difference between the observed and expected was 7; this divided by the standard deviation gave a 't' value of 1.5 which for 7 degrees of freedom was not significant. Therefore, the difference between the observed and expected number of affected children was again not significant.

In the total series, where the sex had been recorded, there were 66 males to 40 females. From Table 2 the sex of the unaffected siblings, where recorded, gave a ratio of 32 males to 25 females. There was obviously no significant difference between these two figures. Many of these galactosaemic children had died within the first month of life; therefore, as another comparison, the sex ratio at birth of the large Birmingham series reported by Crosse (1949) has been used. In this series of over 19,000 births there were 53% males and 47% females. This gave a calculated incidence of 56 males to 50 females for this series. Using the χ^2 test between the observed and calculated values $t = 1.92$; 1 d.f.; $p > 0.05$. So there was no statistical evidence to suggest that this difference in sex incidence was of significance. These statistical analyses confirm the clinical impression that galactosaemia is transmitted by a Mendelian autosomal recessive gene.

Discussion

As has already been mentioned, attempts to detect the heterozygous carriers of this condition

by stressing them with galactose tolerance tests have not been sufficiently precise to be successful.

During the past year three groups of workers have been able to demonstrate an abnormality amongst the heterozygous carriers of galactosaemia. Originally Hsia *et al.* (1958) reported a reduction of the enzyme galactose-1-phosphate uridyl transferase in the red cells of a group of 12 heterozygotes as compared with 11 normal controls. Bretthauer, Hansen, Donnell and Bergren (1959) modified the original method of assaying the enzyme and found that they were able to detect the heterozygous group with less overlap of the results between carriers and controls than the previous worker. Kirkman and colleagues (Kirkman and Kalckar, 1958; Kirkman and Bynum, 1959), have reported a more refined technique of enzyme assay using oxygen consumption and by this method have also shown a decrease of enzymatic activity amongst the relatives of galactosaemic individuals. The first study has been enlarged upon by the addition of further data, and also by a second attempt to detect the carrier state by measuring the accumulation of hexose-1-phosphate in the red cells under the stress of a galactose tolerance test (Huang *et al.*, 1959). The results of these enzyme assays have been analysed and are included at the top of Table 1. Although it may be difficult to evaluate the significance of the results from an individual, the difference between the enzyme levels of the normal group and the heterozygous carriers gave a value for 't' of 3.0 with 37 degrees of freedom (16 normal controls and a group of heterozygotes consisting of 18 parents and five offspring of galactosaemic patients). This difference was highly significant ($p < 0.005$). That the value for heterozygotes with one abnormal gene fell between the normals with no abnormal genes and the homozygotes with two abnormal genes lent further support to the recessive mode of transmission.

The interest in this family lay in the chance discovery of an affected adult who had affected grandchildren. From our genetic analysis of the literature we would have expected him to have two abnormal genes for galactosaemia and therefore, for him to have handed on one of the abnormal genes to each of his children. This has been elegantly confirmed by doing the enzyme levels in this family; the average enzyme level for his six children was 2.5, which was well within the heterozygous range. That one of his daughters should have married another unrelated heterozygous carrier for galactosaemia was a chance of fate, but of great academic interest. That the father of these grandchildren was a heterozygote was confirmed by th

enzyme studies. Therefore, in this family study, there was a clear confirmation of the recessive mode of inheritance and a demonstration of the laboratory techniques for detecting heterozygotes. In addition, the use of enzyme determinations was shown in confirming the clinical diagnosis.

It was not generally known that a person with galactosaemia could live to be an adult in reasonable health without treatment. One other adult case has been found by this laboratory. There were three cases in the literature reported by Ritter and Cannon (1955) and by Durand and Semach (1955), who were not diagnosed until the ages of 5, 14 and 8 years respectively. They showed little ill effects other than cataracts and no doubt could have lived normally with no more serious effects than had the grandfather I_1 R.W. Presumably his two grandchildren who were not diagnosed until the ages of 9 and 5 years could also have survived. Mason and Turner's (1935) original case is now in his late 20's but he is severely retarded.

Another unusual feature in this family was the symptomatology among the heterozygotes. II_{1-6} were all heterozygotes because their father I_1 was a homozygote. This has been confirmed by the enzyme studies. Three of his four daughters felt unwell when pregnant and had mellituria; in one II_2 , this has been proven to be galactose. His two sons had mellituria and after reducing their intake of milk their conditions improved. The only child in this family who did not have symptoms had an enzyme level at the upper end of the heterozygous range. Ellenburg and Peterson (1951) and Hudson, Ireland, Ockenden and White-Jones (1954) have reported siblings of affected cases who showed a trace of reducing substance in the urine. LoPresti, Itani and Rice (1952) and Kalckar, Anderson and Isselbacher (1956) each record a paternal grandfather who was intolerant of milk; Holzel and Komrower (1955) state that one of the fathers of their patients became ill after taking 30 g. of galactose daily. Abnormal galactose tolerance tests have been demonstrated in some parents and siblings though not regularly (Brodie, 1952; Holzel and Komrower, 1955; Durand and Semach, 1955; Komrower, Schwarz, Holzel and Golberg, 1956). This was not surprising once it was realized that the heterozygote has less enzyme available than normal and in some cases this was nearly as little as in affected individuals.

Summary

A family is presented in which the grandfather was proven to have galactosaemia by galactose tolerance tests and by the determination of the

enzyme galactose-1-phosphate uridyl transferase level in his blood. His six children were shown by similar enzyme studies to be heterozygous carriers of the condition and one of these married another unrelated heterozygous carrier and they had two affected children in their family of four. A complete review of the literature is given and genetic analysis of the data collected strongly suggests that galactosaemia is transmitted as a Mendelian autosomal recessive gene. The results of our laboratory studies in the detection of the heterozygous carrier in galactosaemia are given and these confirm, in this family, this mode of transmission.

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