

A STUDY OF THE GENETICS OF GALACTOSAEMIA

BY

A. HOLZEL and G. M. KOMROWER

From the Department of Child Health, University of Manchester

(RECEIVED FOR PUBLICATION NOVEMBER 19, 1954)

The medical world, of recent years, has shown an increasing interest in the hereditary metabolic disorders and considerable research has been undertaken in an endeavour to follow the physical and biochemical problems involved. It is generally accepted that both the presence and absence of enzymes or enzyme functions are determined genetically, but it is not yet known whether a single gene, the specific unit of heredity, is responsible for a single or for several enzymes. It is most probable that the capacity for a definite enzyme reaction is inherited as a dominant characteristic, whereas its absence is likely to be of a recessive nature.

Harris (1953), in his *Introduction to Human Biochemical Genetics*, pointed out that in 1923 Garrod had put forward the hypothesis of congenital absence of a certain enzyme (or enzymes) leading to a block in the chain of metabolic reactions and that by careful examination of the individual stages it should be possible to trace the faulty link. This conception of metabolic blocks has therefore opened up a new and promising line of research into both genetics and biochemistry.

Galactosaemia, a disease which recently has attracted a great deal of attention, has been known to occur in more than one sibling of a family, but its mode of inheritance has been a matter of speculation. Up to the present no special techniques have been consistently employed by which one could recognize the specific trait, if present, in clinically unaffected members of the families in which cases of the disease have been found. Göppert (1917) was the first to note the familial incidence of galactosaemia, though he established the diagnosis beyond doubt in only one case. The medical history of the three other siblings made it more than likely that they also suffered from the same inborn error of metabolism. Bell, Blair, Lindsay and Watson (1950) mention its occurrence in two siblings. Donnell and Lann (1951) report the disease in three siblings; after having recognized it in the youngest they diagnosed it retrospectively in the two others. Townsend, Mason and Strong (1951) described among their six cases two siblings with galactosaemia,

while the third child of the same parents seemed entirely normal though she gained weight slowly. The authors point out that theirs is the first record of a family where the disorder existed in two siblings but not in the third. They had not, however, examined the third child's response to a galactose tolerance test. Gorter (1951) gave a short account of familial galactosaemia, but the available data were incomplete. Hudson, Ireland, Ockenden and White-Jones (1954), reporting four cases, found the disturbance in two siblings, but in one it was assumed on retrospective evaluation of the case history; the mother of these children later gave birth to binovular twin boys who have remained healthy. Cox and Pugh (1954), in a communication on six cases, found three in one family and two affected siblings in a second. Three of the cases again were diagnosed in retrospect only. Consanguinity in the parents of proven cases of the disease has not yet been commented upon in the literature.

Between May, 1951, and April, 1954, five cases of galactosaemia came under our observation. They occurred in four families, were clinically typical, and in each case the diagnosis was confirmed by the isolation of galactose in the urine and by the presence of significant levels of this sugar in the blood. The galactose tolerance tests carried out in four of the patients were grossly abnormal, the fifth child dying before the investigation could be undertaken. (Details of the case histories will be discussed elsewhere.)

The galactose tolerance test, although not specific, is regularly and persistently abnormal in cases of galactosaemia, even when the active phase of the disease has long since abated, either spontaneously in the milder forms or on milk-free diets in the treated. For these reasons it was decided to use this technique in an attempt to study the genetics of the condition.

Following a preliminary clinical examination to exclude other causes of galactose intolerance (such as liver disease) the test was carried out on as many relatives of the patients as agreed to submit to it.

TABLE 1
GALACTOSE TOLERANCE TESTS ON THE FAMILIES OF CASES OF CLINICAL GALACTOSAEMIA

	0 hr.	½ hr.	1 hr.	1½ hr.	2 hr.	Index	
<i>Family F.</i>							
H.F. (father)	0	60	133	98	33	324	1 proven case of galactosaemia, 1 likely case
F. (mother)	0	25	48	52	0	125	
M.F. (grandmother)	0	40	65	5	0	110	
A.F. (brother)	0	52	72	68	30	222	
L.F. (uncle)	0	84	57	38	33	212	
M.F. (cousin)	0	48	64	73	10	195	
A.G. (aunt)	0	30	55	30	10	125	
<i>Family K.</i>							
M.K. (father)	0	105	85	25	10	225	1 proven case
W.K. (mother)	0	10	55	65	60	190	
<i>Family G.</i>							
G. (father)	0	25	40	48	58	171	2 proven cases
G. (mother)	0	16	37	4	0	57	
J.G. (brother)	0	42	45	0	0	87	
W.G. (sister)	0		Traces only		0	—	
<i>Family S.</i>							
R.S. (father)	0	43	83	42	0	168	1 proven case
S. (mother)	0	15	60	47	13	135	
R.S. (brother)			Traces only				
<i>Family L.</i>							
L. (father)	0	38	32	20	0	90	2 probable cases
L. (mother)	0	230	60	78	38	406	
L.L. (sister)	0	30	40	190	100	360	
E.L. (sister)	0	10	58	134	130	332	

Adults were given a total dose of 40 g. of galactose, and older children were given 1.25 g. and infants 1.75 g. per kg. body weight. The determination of the galactose in the blood was made by the method of Maclagan (1940). The galactose index is the sum of the half-hourly blood galactose values up to two hours expressed in milligrams per 100 ml. after the ingestion of galactose; the index is of little use in children. With the 40-g. dose in adults the average normal value is 68 with an upper limit of 160. The galactose tolerance test was regarded as normal if the blood galactose values returned to the fasting level within two hours and in adults the galactose index did not exceed 160. Table 1 gives the results obtained in testing the relatives of the galactosaemic patients. It shows that in each family at least one parent reacted abnormally to the galactose tolerance test; the figures also reveal many instances of an abnormal galactose index in other relatives, who had no clinical manifestations of the disease, although in some of the individuals concerned there was a history of feeding difficulties in early infancy.

The family trees of the galactosaemic patients are presented in Figs. 1, 2, 3 and 4. They were computed on the basis of the test findings.

Family F. (Fig. 1)

In addition to the patient, who is now a healthy, active girl of 3 years of age, there was a second female sibling who died aged 11 days of an illness which in retrospect has been diagnosed as galactosaemia. The third child, a boy, as well as the

father, uncle and cousin, have abnormal galactose tolerance curves.

Family K. (Fig. 2)

Both parents show abnormal tests; the patient is developing normally both physically and mentally.

Family G. (Fig. 3)

There were four siblings in this family. The first baby died of pneumonia at the age of 8 months; his history was typical of galactosaemia and on his admission to hospital he was found to excrete a reducing substance in the urine which was identified as galactose, but unfortunately too late to undertake any therapeutic steps. The second child was seen for the first time at the age of 3 years with fully developed cataracts, mental retardation and slight liver enlargement. Galactosuria was not present, but his galactose tolerance was greatly reduced. Two other children, a brother and sister, are perfectly healthy and have normal galactose tolerance tests, which, in the case of the father, is abnormal.

Family S. and Family L. (Fig. 4)

The father of the patient produced an only slightly abnormal response to the tolerance test, but on adding 30 g. of galactose daily to his normal diet, he developed nausea and vomiting within three days, as well as an irritating scaly rash of the face which subsided a fortnight after he ceased to take the additional galactose.

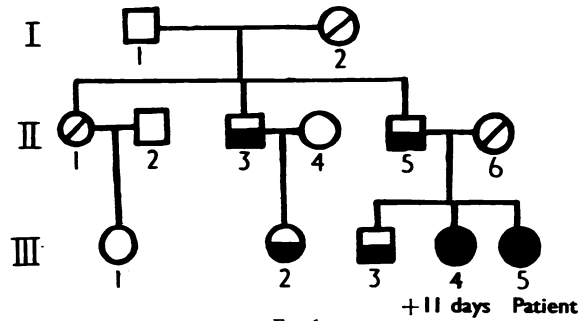


FIG. 1.

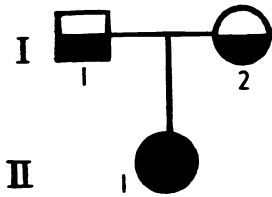


FIG. 2.

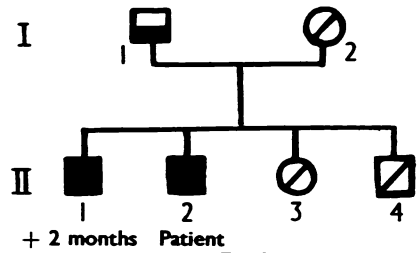


FIG. 3.

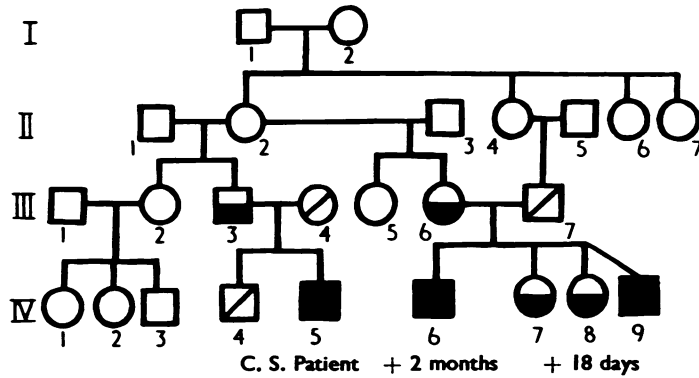
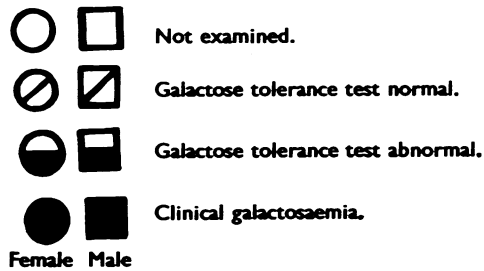


FIG. 4.



The results of the investigations on the other members of the family were normal and the patient, now aged $3\frac{1}{2}$ years, is developing normally. The father's half-sister, an offspring of his mother's second marriage, married a first cousin (a son of her mother's sister).

Four children were born to these consanguineous parents. The first child died at the age of 2 months at the Royal Hospital for Sick Children, Edinburgh, 24 hours after admission. The history was characteristic, and Dr. Agnes Macgregor, after reviewing the morbid histology, wrote in a personal communication (1953) that there was no reasonable doubt that this was a case of galactosaemia. The next child, a girl, seemed to develop normally. Then followed a twin birth; the male infant died aged 18 days at the Doncaster Royal Infirmary, and again the history was in keeping with galactosaemia, while the other twin, a girl, developed normally. Galactose tolerance tests showed grossly abnormal curves for mother and both daughters, while that of the father was within normal limits.

Although the diagnosis in the dead siblings is one of probability only, it would appear justifiable to regard these cases as galactosaemia and therefore the first recorded in the offspring of consanguineous parents.

Discussion

Haldane (1954) expressed the opinion that galactosaemia is probably due to the inheritance of a recessive gene as did Penrose in a personal communication quoted by Hudson *et al.* (1954). If this is the case one would expect such a recessive Mendelian character to show two very distinctive features: first, a relatively high frequency of the condition among siblings of affected individuals and only rarely among their parents, children or more distant relatives; secondly, a higher number of consanguineous marriages among the parents of the cases than in the general population (Harris, 1953). The first of these postulates seems to be fulfilled in the reports published on the familial occurrence of galactosaemia. Consanguinity of the parents has, however, not been noticed previously and this single observation is inadequate to offer any foundation for a firm conclusion on the second point.

Using the galactose tolerance test as a screening technique it is only in the Family K that this method seems to reveal abnormal tolerance as a recessive trait. But, reviewing the findings in the members of the other four families, it immediately becomes obvious that reduced tolerance for galactose as revealed in the test is found in at least one parent of every child with clinical galactosaemia and, as seen

in the Family F., in the more remote relatives. Although in the Family L. the parents are first cousins, only the mother and the surviving two children had abnormal galactose tolerance tests. This indicates that abnormal galactose tolerance without clinical manifestations is probably inherited as a heterozygous character, i.e., dominant. The individuals who develop the active overt form of the disease may be homozygous for the same gene, or there may be other factors that accentuate the condition.

Thalassaemia provides a comparable distribution of genetic factors. This form of haemolytic anaemia, which is due to a hereditary defect of haemoglobin synthesis, can be transmitted as a heterozygous dominant gene and individuals carrying it are clinically well but show characteristic blood changes. This subclinical form has been described as thalassaemia minor. The homozygous offspring of two parents with thalassaemia minor present more pronounced haematological changes accompanied by severe clinical manifestations and often succumb to the disease; this is thalassaemia major. Family K., where both the parents show marked abnormal galactose tolerance, offers itself readily for comparison.

This study has shown that the abnormal galactose tolerance factor is much more common than originally suspected and that it is likely to become more widespread. There is as yet no information available as to the presence of the disease in children of treated or untreated and surviving patients suffering from galactosaemia, but there is little doubt that with earlier diagnosis a much larger number of galactosaemic babies will remain alive, grow, mature and procreate, and it is likely that galactose diabetes will have to play a more important part in diagnostic considerations than heretofore.

Summary

Galactose tolerance tests carried out in members of five families in which cases of galactosaemia occurred showed a reduced tolerance for galactose in at least one parent as well as in other relatives of the patients.

In one family the parents were first cousins. Two siblings died of galactosaemia; two surviving children as well as the mother have a grossly abnormal galactose tolerance.

This is the first record of galactosaemia in the offspring of a consanguineous marriage.

It is concluded that abnormal galactose tolerance without clinical manifestations is inherited as a heterozygous character, while clinical galactosaemia

may be transmitted as a homozygous recessive gene.

We are greatly indebted to Mr. H. Varley, biochemist at the Manchester Royal Infirmary, and Dr. H. Lederer, pathologist at Doncaster Royal Infirmary, for carrying out the galactose tolerance tests on the relatives of our patients, and to Dr. Agnes Macgregor for reviewing the necropsy findings in one of the cases. Our special thanks are due to Dr. H. Harris, lecturer in biochemistry in the London Hospital Medical College, for his considered advice and most helpful criticism, and to Professor Wilfrid Gaisford for his unfailing interest.

REFERENCES

- Bell, L. S., Blair, W. C., Lindsay, S. and Watson, S. J. (1950). *J. Pediat.*, **36**, 427.
- Cox, P. J. N. and Pugh, R. J. P. (1954). *Brit. med. J.*, **2**, 613.
- Donnell, G. N. and Lann, S. H. (1951). *Pediatrics*, **7**, 503.
- Garrod, A. E. (1923). *Inborn Errors of Metabolism*, 2nd ed. London.
- Göppert, F. (1917). *Berl. klin. Wschr.*, **54**, 473.
- Gorter, E. (1951). *Archives of Disease in Childhood*, **26**, 271.
- Haldane, J. B. S. (1954). *The Biochemistry of Genetics*. London.
- Harris, H. (1953). *An Introduction to Human Biochemical Genetics*. Eugenics Laboratory Memoirs (37). Cambridge University Press.
- Hudson, F. P., Ireland, J. T., Ockenden, B. G. and White-Jones, R. H. (1954). *Brit. med. J.*, **1**, 242.
- Macgregor, A. (1953). Personal communication.
- MacLagan, N. F. (1940). *Quart. J. Med.*, **9**, 151.
- Townsend, E. H., Mason, H. H. and Strong, P. S. (1951). *Pediatrics*, **7**, 760.