

Long-term Follow-up of Galactosaemia*

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Komrower, G. M., and Lee, D. H. (1970). *Archives of Disease in Childhood*, **45**, 367. **Long-term follow-up of galactosaemia.** A study of 60 galactosaemic children was carried out in order to assess their physical and mental development on a galactose-low diet. The physical health of the group was good but the mental development fell below that of the average population and there was a significant incidence of psychological disturbance.

Galactosaemia is an inborn error of galactose metabolism in which the affected subject is unable to convert galactose to glucose due to the absence of activity of the enzyme galactose-1-phosphate (gal-1-p) uridyl transferase. This enzyme facilitates the conversion of gal-1-p to glucose-1-phosphate (glu-1-p). The untreated infant fails to thrive; jaundice, hepatomegaly sometimes with splenomegaly, and ascites are found, and he becomes seriously ill and may die. If he survives, cataracts may develop and there is mental retardation, usually severe; in some cases also cirrhosis of the liver is found. The signs and symptoms regress quickly after the removal of galactose from the diet.

The object of this clinical study was to review all possible cases of galactosaemia in Great Britain, in particular those in which the diagnosis had been established by Dr. V. Schwarz of the Department of Medical Biochemistry, University of Manchester, with a view to establishing their present clinical condition and psychological and emotional state. In addition it was hoped to obtain evidence concerning the total effect of dietary therapy and the time for relaxing this regimen.

Material and Methods

Sixty children, 22 boys and 38 girls, with galactosaemia were studied, each receiving a detailed psychometric examination. The physical examination in 24 cases was made in Manchester, but in 36 cases reports were accepted from the local paediatricians who gave information concerning the present condition of the children, the most recent liver function tests, and the erythrocyte gal-1-p estimations when these were done.

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The gal-1-p tests were available only in 40% of cases, and then with varying degrees of regularity. In addition to this information the local paediatrician gave a personal estimate of dietary control. The psychometric examination was made by one person (D.H.L.), who saw the children either in Manchester or in their own homes or local hospital.

Physically, the group were healthy, and with one exception there was no indication of any serious disease. The exception was a child with portal hypertension who had been followed from 12 days of age when the diagnosis had been made, and in whom good dietary control had been established. Significantly, for the past 18 months there had been some concern about the increasing gal-1-p level in the red cells. The parents were certain that the child had not taken any quantity of galactose in her diet. In the light of this observation two other apparently healthy children have been seen who have a rise in the red cell gal-1-p level in spite of good dietary control, and one wonders whether this finding might be an index of subclinical liver damage (liver biopsy has not been performed). In the other 57 children the liver function tests were normal and when the gal-1-p levels were done they were largely below 50 $\mu\text{g./ml.}$ packed red cells; this is a level which is considered to imply satisfactory dietary control. In fact, only three children had levels that were above 60 $\mu\text{g./ml.}$ packed red cells, one being the child with portal hypertension mentioned above.

Eight children had residual cataracts with impairment of vision varying from minimal disturbance caused by a small residual remnant in one eye to significant handicap because of bilateral cataracts requiring surgical treatment in two children. Of the six children who were treated expectantly, two had small central cataracts, two had bilateral residual remnants, and two had small unilateral remnants. Four girls and four boys were affected; the IQ score in this group varied from 46 to 107 (average 78).

Psychological testing. Three Intelligence Scales

were found useful. The Griffiths Developmental Scale was used for children with a mental age below 2 years (Griffiths, 1954); this scale is based essentially on that of Gesell and Amatruda (1941) which was the one used in a survey by Fishler and his colleagues (1966). The Stanford-Binet (LM Revision) (Terman and Merrill, 1961) was used in children with a mental age above 2 and below 10 years, and in general children above this mental age were assessed on the Weschler Intelligence Scale for Children (WISC) (Weschler, 1949).

Parental socio-economic and intellectual status was determined by asking the consultant in charge to grade the family on a five-point scale, and following this a similar assessment was made independently by D.H.L. when he carried out psychological testing. Agreement was found to be sufficiently close to allow the two observations to be scored as one. The standard of dietary control was determined by the physician in charge and a further assessment was made by the psychologist when he saw the parents and child.

The two main dietary groups were classified as 'good' or 'moderate to poor'. Good control (32 cases) demanded a similar assessment by the physician and psychologist when they carried out their respective examinations, together with a satisfactory level of gal-l-p in the red cells when this investigation was performed. 'Moderate to poor' control (22 cases) indicated that these indices were less satisfactorily maintained. These judgements were used to assess the possible effects of diet and environment on the intellectual status of the children.

Results

Intelligence. The scores of intelligence for the whole group ranged from 30-118, with a mean of 80. The boys (2 2/12-13 11/12 years) averaged 89 and the girls (2 4/12-17 2/12 years) 73. Two extremely handicapped girls contributed in some measure to this disparity.

A progressively lower IQ was obtained in each of the age-groups 0-5 years, 5-10 years, and over 10 years, the figures being 90 (61-118), 79 (30-112), and 70 (45-107), respectively (Table I). This experience is similar to, if perhaps a little more marked, than that reported in an American survey (Fishler *et al.*, 1966).

TABLE I
Intelligence Scores in Three Age-groups from 0-15 Years

Age-group (yr.)	No.	Mean Age (yr.)	Mean IQ	Range
0-5	21	3 4/12	90	61-118
5-10	25	8 3/12	79	30-112
10-15	14	13 7/12	70	45-107

There are a number of factors that might have contributed to the lower IQ in the older children. In the first place, more extensive investigations were carried out because the disorder was relatively new. In addition there had to be in the early years some experimentation with the diet as there was a lack of suitable preparations. As a result some children had a low protein intake early in infancy, while the galactose intake was greater than one would have desired. Finally, lack of experience meant that the babies were kept in hospital and away from their mothers for considerably longer periods than would obtain today. For these reasons these children could have been disturbed both physically and emotionally.

Growth. The heights of the children in the survey were below average, most being below the 50th centile, with 17 below the 10th centile (Fig. 1 and 2). The latter children had the lower IQ scores, with 12 of the 17 less than 70: there seems to be some association between small stature and intelligence, the Rank Order correlation coefficient being 0.61 ($p > 0.01$). This is in excess of that reported for the normal child population by Douglas, Ross, and Simpson (1968).

When the birthweights were considered, only 18 of the 60 were below 3200 g. Two of this group had IQ scores below 50: one of these had not been diagnosed until 18 months of age and the second child, who was illegitimate and had been abandoned, had spent most of her life in institutions; in addition her dietary control had always been poor. The IQ scores of the remaining 16 ranged between 57 and 106 with an average of 80. Low birthweight and subsequent intelligence showed no correlation.

Effect of diet. The IQ scoring for the children in the 'good control' group was 84 (average) compared with 77 for the 'moderate to poor' group ($p > 0.1$) (the ranges being 51-118 and 51-107) (Table II). The 'moderate to poor' control group was considered to have only one family in the 'above average' category for intelligence and none for socio-economic status, whereas the 'good' control

TABLE II
Effect of Diet on Subsequent Intelligence

	Control of Diet	
	Good (n = 32)	Moderate or Poor (n = 22)
Mean IQ	84	77
Mean age (yr.)	6 8/12	8 9/12

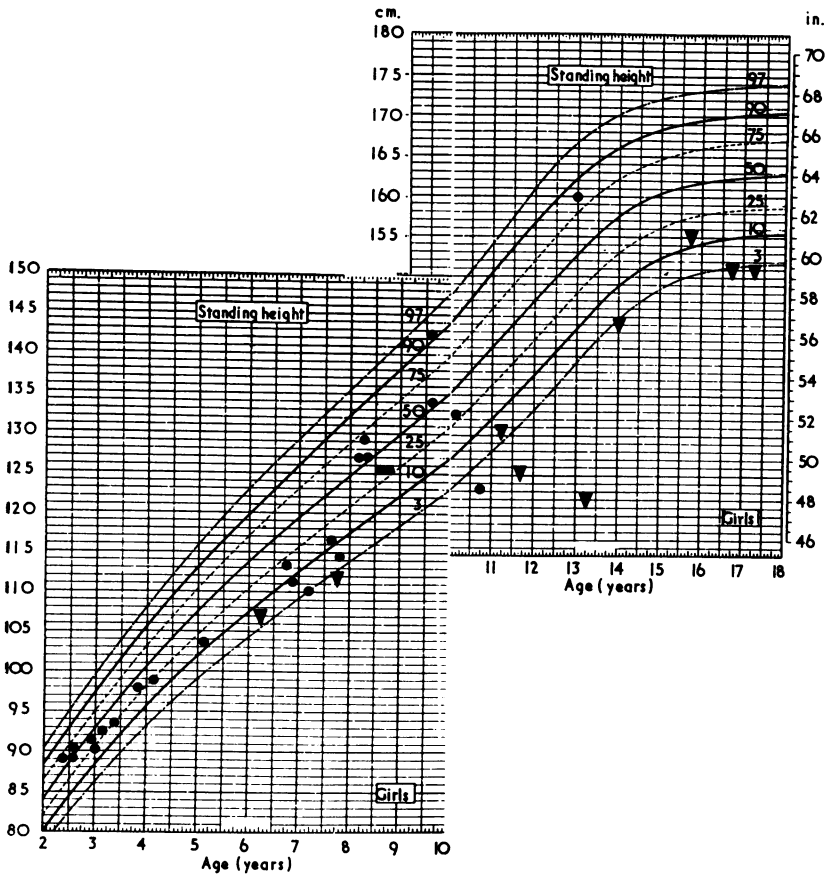


FIG. 1.—Height of girls plotted on a standard centile chart. ● IQ score > 70; ▼ IQ score < 70.

group had 10 families 'above average' intellectually and 9 socio-economically. This fact clouds any significance of the difference in the mean IQs of the two groups.

A very small group (6) of children was diagnosed late between 13 months and 6 years of age, and with two exceptions the subsequent dietary treatment was good. The mean IQ score for the group was 48—with figures ranging from 30 to 70.

Analysis of intelligence test results. It was not feasible to isolate patterns of successes and failures with either the Griffiths or Stanford-Binet Scale. In the first of these scales the group tested was both too small and too young for such an analysis to have meaning, and the nature of the second scale does not allow such analysis because it gives a global figure of intellectual functioning (McNemar, 1942). Only the group of children tested on the

WISC were subjected to test analysis. This test has two major divisions (Verbal and Performance) for which separate scores are obtained and then averaged. Twenty-one (21) children had the test, 8 being boys. The scores for the latter children were similar (Verbal 89—Performance 89), whereas the 13 girls showed 7 points higher on the verbal scale (Verbal 71—Performance 64). On the breakdown of the performance scale no difference was observed between the scores for Block Design and Object Assembly compared with Picture Arrangement, Coding, and Picture Completion, there being no supporting evidence of a specific visuo-motor handicap. The most obvious and consistent feature of the test results is that the boys produced better scores in all items than did the girls.

Additional information on the intellectual development of these children was sought by using the

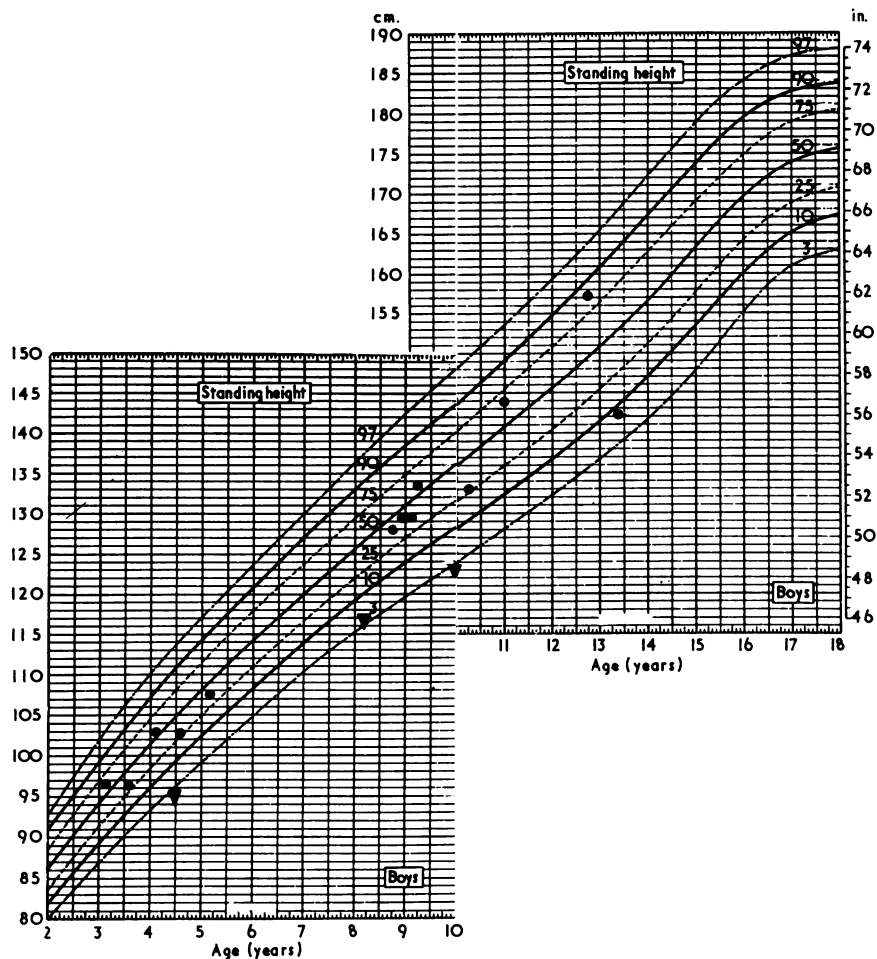


FIG. 2.—Height of boys plotted on a standard centile chart. ● IQ score > 70; ▼ IQ score < 70.

Bender-Gestalt drawing test (Bender, 1938). 23 children were tested, all more than 7 years of age. Of these 23, 18 (78%) produced distorted copies of the test figures. They had a mean IQ of 67, while the 5 children producing normal figures had a mean IQ of 101. The two groups were of similar age. Only 8 of the children were boys (35%), similar to the proportion (37%) noted in the whole group of children studied. The mean ages of boys and girls with 'abnormal' ratings were similar (10 years 7 months) and the IQ scores: girls 64 and boys 77. The mean IQ for children with 'normal' Bender figures was 99 for girls and 103 for boys.

The degree and nature of the distortion of the Bender figures varied considerably. The most common type of difficulty, however, was irregularity

of line and size such as may arise in children with known co-ordinative handicaps, for example, severe epilepsy or brain-injured children. Other types of error, such as in relative positioning, distortions of angulation and simplification or fragmentation of the whole figure (Gestalt) are present in most cases and suggest more subtle difficulties of perception either of spatial relations, or of pictorial images, or both (Fig. 3a-d).

Social adjustment. The Bristol Social Adjustment Guide was used to study the reaction of the children to a particular social environment, the school. The Guide which is a well-standardized technique that can be applied at different age levels (Stott, 1965) was sent to the schools of 30 children

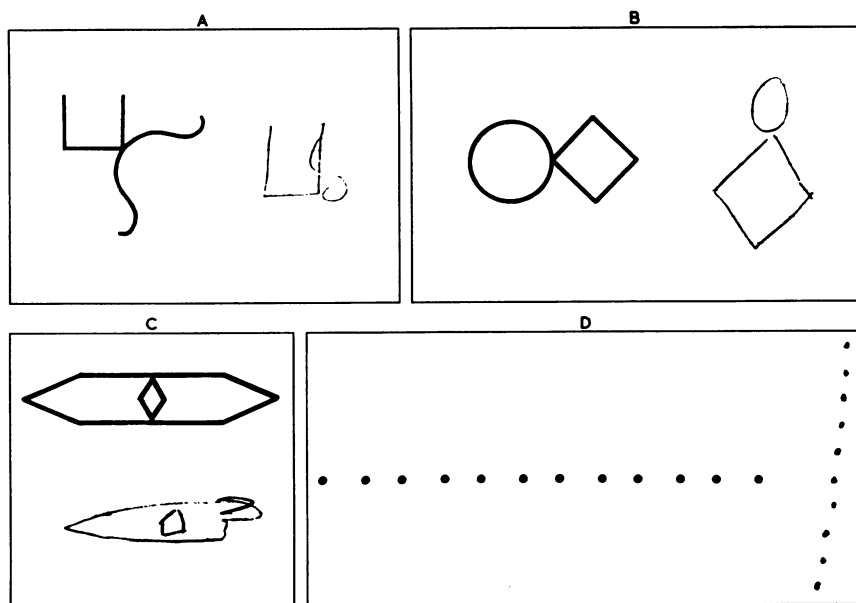


FIG. 3a-d.—Examples of the degree and nature of the distortion of the Bender figure.

(18 being girls). 20 of these children were attending normal schools and of the remaining 10, 5 attended schools for ESN pupils, 3 went to schools for physically handicapped children and 2 went to private schools. Their mean age was 9 years 10 months and average IQ was 80 (range 46 to 112).

The Guide provides information in nine main areas of children's psychological reactions to environment (Table III). Each area or variable is represented as a numerical scale on a 'diagnostic' form, and each item marked on the returned form scores one point.

Of the nine main variables of social adjustment provided by the Scale, the galactosaemic children scored heavily on three (Table III). These were

TABLE III

Stott Variables of Social Adjustment for 30 Galactosaemic Children. Items D, U, and HA Score Very High

	D	U	W	XA	HA	K	XC	HC	R
Total points scored	53	64	19	29	43	28	12	9	37

Key: D, depression; U, unforthcomingness (effectance deficit); W, withdrawal; XA, anxiety towards adults; HA, hostility towards adults; K, knavery; XC, anxiety towards children; HC, hostility towards children; R, restlessness.

Higher point scores indicate a greater tendency towards maladjustment in this group of children.

the factors of 'unforthcomingness' (or effectance deficit), 'hostility to adults', and 'depression'. The first of these is considered by Stott to be a symptom of inadequate drive. It was found in a large proportion of the 60 galactosaemic children studied and is supported by parental opinion. A standard and, it is hoped, objective pattern of questions concerning the children's temperaments was put to the parents during their interview with the psychologist and led to such typical comments as 'He's always been very sensitive', and 'She's shy and has difficulty making friends'.

The second of the strongly emphasized variables was 'hostility to adults'; and this seems to have two possible components. It is a continuation of the child's tendency to withdraw from any kind of conflict situation, seen in this case through the eyes of a teacher, and may also be a reflection of the galactosaemic child's poor academic record (24 of the 30 children for whom the Guide was returned were retarded in reading and 16 of these were retarded also in arithmetic). Though Stott envisages the hostility mainly as a reaction to the threat of parental rejection, the fact that it is noticeable in these school-based records does seem to indicate some connexion with failure in academic attainment.

'Depression', in the sense used by Stott, is characterized by fluctuating attention-span and

listlessness, and it is these symptoms of the 'depression variable' which are most frequently emphasized in the Bristol Guide returned from the schools. Notes made when the intelligence test was in progress support these findings, suggesting that a large proportion of the children showed similar signs of restlessness and difficulties of concentration during the interview with the psychologist.

Discussion

The fact that small numbers of children were involved in the administration of each of the test procedures makes it difficult to form firm conclusions from this descriptive study: in the case of the WISC only 21 children were studied. In addition, repeated attempts over the years to relate the separate WISC subtests to known mental abilities such as spatial skills or verbal reasoning have met with limited success (Anastasi, 1961). Nevertheless one must re-emphasize the small difference between the mean IQ scores on the Verbal and Performance scales of the WISC and the similarity of the scores of the subtests within the Performance Scale.

A further indication of the non-specific nature of the perceptual disorders in these galactosaemic children was obtained in the results of the Bender-Gestalt drawing test, with the recording of a low average IQ in the group producing the distorted copies. It is true that the 'global' type of intelligence tests used to obtain the mean IQ scores contain items similar to the Bender drawing test and there is the probability that the same perceptual handicap influences the drawing of the Bender figure and the performance in the IQ test. Nevertheless the cross-over effect is not likely to be the sole cause of the difference of 34 IQ points noted between the mean scores of the 'normal' and 'abnormal' Bender groups for both males and females, there being a genuine disparity of intellectual ability. These findings make it impossible to confirm the previously recorded finding that these children show a specific visuo-motor disorder (Fishler *et al.*, 1966).

The observations made during the intelligence testing (D.H.L.) together with the results of the Bristol Social Adjustment Guide are in line with those recorded in Fishler's study though the results are expressed somewhat differently.

The children in this study also are timid and lack assertiveness; in addition they are withdrawn and anxious about their relationship with the adult world. They are academically inferior, which is to be expected in view of their lower general intelligence. This poor scholastic progress coupled with

their insecurity is the probable reason for the lack of motivation in a learning situation, a point that was repeatedly underlined during their intelligence assessments.

These findings are a cause for some concern. Could they be the result of early and sometimes frequent hospital admission? Is it possible that the rigid dietary regimen which demands careful control by the parents has encouraged the symptom of withdrawal and hostility? There is no doubt that the parents of children with inborn metabolic errors are considerably disturbed by the situation. Generally they become overprotective, but occasionally they reject the child emotionally while still maintaining good general care. Finally, could this disturbed psychological and learning pattern be the result in part of an intrauterine insult?

Conclusions

The general health of these galactosaemic children has been good. They are small but do not suffer infections or other ailments to any greater extent than the average child. One child has developed portal hypertension; she had a raised erythrocyte gal-1-p level before there were clinical signs of cirrhosis of the liver. Two other children have raised gal-1-p levels in spite of careful galactose restriction, with no evidence of obvious illness. This may indicate parenchymal liver damage.

The intelligence of the early diagnosed and well-treated children is below the average for the normal population though it lies within the educable range.

From the information obtained it appears that provided treatment is started early and maintained satisfactorily during the first two years of life, subsequent *rigid* dietary control does not play a significant beneficial role in respect of intelligence and intellectual development.

There is a recurrent pattern of learning difficulties and psychological upset which may in part be environmental but may be inherent in the disorder.

The above finding taken in conjunction with the raised gal-1-p levels in cord blood reported in the literature suggest the possibility of some intrauterine disturbance.

The results of this review suggest the following.

(1) The diagnosis should be made as early as possible and treatment started in order to save life, minimize the possibility of any permanent liver damage, and allow of reasonable intelligence.

(2) Efficient dietary therapy should be introduced and carefully maintained for at least two years.

(3) There might well be some reasonable easing of the diet before the child starts at school, for example, milk, cheese, and butter could be used

in cooking and in the diet, but it is felt that no milk as such, no butter in excess, or raw cheese should be given.

We thank Dr. Schwarz of the University of Manchester, Department of Medical Biochemistry, for the information concerning the children he had tested at birth; the paediatricians and general practitioners for their generous help; the parents and the children who co-operated with us; Miss Naomi Simpson for her help in carrying out the galactose-1-phosphate estimations; and the Medical Research Council for their financial assistance to Mr. Lee.

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