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# Variations in Intelligence in Phenylketonuria

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PHENYLKETONURIA was originally called imbecilitas phenylpyruvica, phenylpyruvic amentia or phenylpyruvic oligophrenia. In time it was realized that although the great majority of patients with phenylketonuria are mentally retarded, a small proportion have normal or near normal intelligence. Furthermore it is now evident that the early treatment of the disease by a low phenylalanine diet will often prevent the appearance of mental retardation.[1] Since not all patients with this disease are necessarily retarded and since they all have a similar metabolic disorder characterized by the excretion of phenylketones in the urine, phenylketonuria seems the most appropriate title.[2]

This paper describes the variations in intelligence of a series of 75 patients with untreated phenylketonuria, including an adult with normal intelligence. Some observations on the effect of a low phenylalanine diet in 12 children are also presented.

## MATERIAL AND METHODS

The series consists of 87 patients with phenylketonuria. They were either inpatients at the Ontario Hospital Schools at Orillia and Smiths Falls or patients under the care of the Hospital for Sick Children, Toronto.

The intelligence tests of the patients in the Ontario Hospital Schools were made by a number of different observers using different methods. The intelligence tests of the children on dietary treatment were all made by the same observer using the Cattell infant intelligence scale and, where appropriate, the Stanford-Binet intelligence scale (Form L-M).

Plasma phenylalanine and tyrosine levels were measured by the methods of Udenfriend and Cooper.[3, 4] Phenylalanine load tests were carried out according to the method of Hsia;[5] blood was taken after an overnight fast and then again one hour after an oral dose of 0.1 g. of L-phenylalanine per kg. body weight.

Certain observations on some of these patients have been published previously.[6, 7]

## UNTREATED PHENYLKETONURIA

Table I shows the variation in intelligence of 75 patients aged 2 years or more with untreated phenylketonuria. The measurement of intelligence in severely retarded patients (or young children) is not a very accurate procedure, so that no attempt was made to place the patients on a continuous scale of intelligence quotients (I.Q). Instead, the I.Q. scale was divided into five parts (0-20, 21-40, 41-60, 61-80, 81 and over) and, after assessment, the patient was allotted to one or other level. These particular levels were chosen so that this group of patients could be compared with the large series collected by Knox[1] (Table I, column 4). Alternatively, the patient's intelligence was described as low, medium or high-grade mental deficiency, and borderline, dull normal or normal. These two scales of measurement are shown in parallel in Fig. 1.

TABLE I.—DISTRIBUTION OF INTELLIGENCE OF 75 PATIENTS OVER THE AGE OF TWO YEARS WITH UNTREATED PHENYLKETONURIA

| *I.Q. level* | *Number of cases* | *Per cent of total* | *Per cent distribution of 466 cases reviewed by Knox*[1] |
|---|---|---|---|
| 0 - 20 | 46 | 61.3 | 64.4 |
| 21 - 40 | 20 | 26.7 | 23.2 |
| 41 - 60 | 4 | 5.3 | 9.7 |
| 61 - 80 | 4 | 5.3 | 1.9 |
| 81+ | 1 | 1.3 | 0.6 |

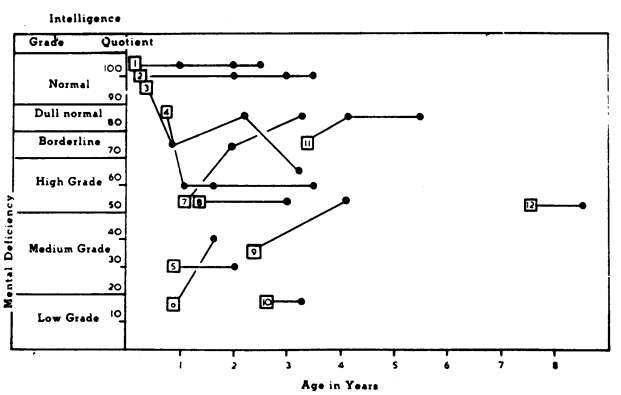


Fig. 1.—Changes in intelligence of 12 patients with phenylketonuria treated by means of a low phenylalanine diet for nine months or more. Each box represents one patient; the left-hand edge of the box corresponds to the age at which dietary treatment was started. Each dot represents subsequent intelligence ratings. Biochemical control of the disease was "good" in 1, 2, 3, 7, 9, 10, 11 and 12, "fair" in 4, 5 and 8 and "poor" in 6 (see text).

It can be seen (Table I) that the distribution of intelligence in the two series of patients was closely similar. In both series, over 90% of the patients had an I.Q. of 60 or less, which means that they were classed as idiots and imbeciles or as low-grade and medium-grade defectives.

Fasting plasma phenylalanine levels were measured in 51 cases. These are shown in Fig. 3 in relation to the intelligence of the patient. As found by others,[8, 9] there was no obvious correlation between the two measurements when the patient's intelligence was low. However, the three patients with comparatively high intelligence had fasting plasma phenylalanine levels that were low com-

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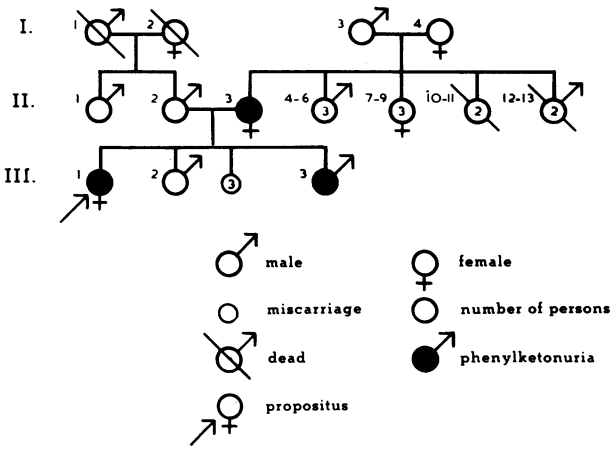


Fig. 2.—Pedigree of the patient with untreated phenylketonuria and normal intelligence (II, 3).

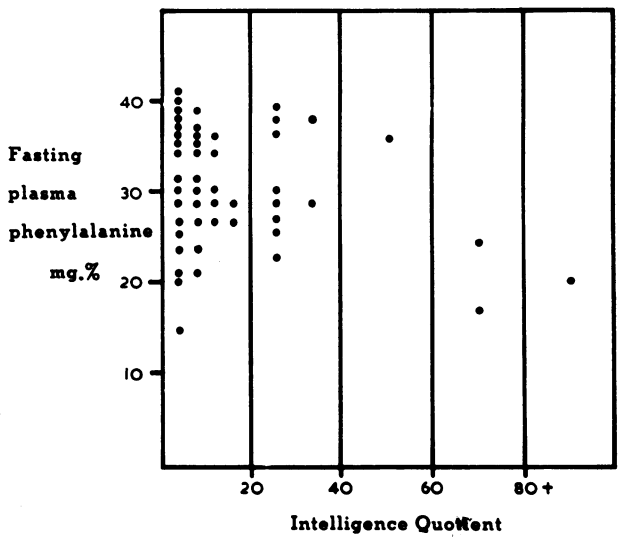


Fig. 3.—The fasting plasma phenylalanine level of 51 patients over the age of two years with untreated phenylketonuria related to the intelligence of the patient.

pared with the group as a whole. The converse was not true; several other patients with low plasma phenylalanine levels were also severely retarded. This tendency for the untreated phenylketonuric patient with relatively high intelligence to have relatively low blood phenylalanine levels has been noted by other workers.[10-12]

Phenylalanine load tests were carried out on 34 patients. The results are shown in Table II. There were no significant differences between the load tests on the three patients with comparatively high intelligence (Table II, and subject No. 1 in Table III) and the rest of the group (Table II).

Two of the more intelligent patients with phenylketonuria are described briefly. The third patient and her family are described in some detail.

TABLE II.—PHENYLALANINE LOAD TESTS ON TWO PATIENTS WITH UNTREATED PHENYLKETONURIA AND RELATIVELY HIGH INTELLIGENCE

| | | | | *Plasma values in mg.%* | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | *Fasting* | | *One hour after load* | | |
| *Subject* | *I.Q.* | *No. of patients* | *Age in years* | *Phenylalanine* | *Tyrosine* | *No. of patients* | *Phenylalanine* | *Tyrosine* |
| M.C. | 60 - 70 | 1 | 2.25 | 24.5 | 0.91 | 1 | 33.8 | 1.17 |
| E.R. | 74 | 1 | 10.0 | 14.7 | 1.33 | 1 | 34.0 | 1.40 |
| Untreated phenylketonurics | <60 | 48 | 15.2 (11.3)* | 30.8 (7.7) | 1.19 (0.36) | 34 | 44.6 (8.1) | 1.24 (0.35) |

*Figures in parentheses are standard deviations.

M.C., aged 2 years.—This boy was tested for phenylketonuria because his younger sister was found to suffer from the disease. His mother had not suspected mental retardation, although his developmental progress had been slow. He was found to have a high-grade mental deficiency with an I.Q. between 60 and 70. Urinary tests with 10% ferric chloride and Phenistix reagent strips (Ames) were positive. His fasting plasma phenylalanine level was 24.5 mg. % on one occasion and 23.1 mg. % on another.

E.R., aged 10 years.—This boy had been an inpatient at an Ontario Hospital School for three years. There was a history of slow development since early life. On admission to hospital he had been shy and seclusive, with poor speech and occasional emotional outbursts. He had improved with time and, at the age of 10, his I.Q. was 74. His urine gave a faint green colour with ferric chloride; with Phenistix there was less than "15 mg. % of phenylpyruvic acid", according to the chart supplied by the makers. At this time his fasting plasma phenylalanine level was 14.7 mg. %; six months later it was 19.6 mg. %.

## PHENYLKETONURIA WITH NORMAL INTELLIGENCE

This patient and her family have been reported on very briefly on a previous occasion.[7] The pedigree is shown in Fig. 2, and other data are given in Table III. Three members of the family had phenylketonuria. The propositus was a 13-year-old retarded child in an Ontario Hospital School. Her youngest sibling, a four-month-old boy, was similarly affected. Her mother, a woman of normal intelligence, was also found to have phenylketonuria.

The propositus (III, 1 in Fig. 2) was aged 13 years. She had been born at term on February 2, 1948, after a normal pregnancy and delivery. Her birth weight was 4 lb. 9 oz. (2.2 kg.). Her early feeding and general development had been normal, but her mother suspected mental retardation at the age of two years. About this time she had become an extremely irritable and difficult child. Development had been slow but she had learned a few words, had become toilet trained and would help a little in the house. At the age of 12

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TABLE III.—PHENYLALANINE LOAD TESTS ON THE PATIENT WITH UNTREATED PHENYLKETONURIA AND NORMAL INTELLIGENCE, AND HER FAMILY

| | | | | | Plasma values in mg.% | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fasting | | One hour after load | | |
| *Subject* | *Place in pedigree* | ‡ *I.Q.* | *Age in years* | *Date* | *Phenylalanine* | *Tyrosine* | *Phenylalanine* | *Tyrosine* | *Phenylalanine/-tyrosine* ratio* |
| Grandfather | I, 3 | N | 82 | 16/11/61 | 1.8 | 1.33 | 23.0 | 1.86 | 13.6 |
| Grandmother | I, 4 | N | 77 | 16/11/61 | 1.7 | 1.72 | 14.5 | 2.46 | 6.5 |
| Uncle | II, 4 | N | 54 | 16/11/61 | 0.9 | 1.49 | 19.8 | 2.34 | 9.3 |
| Mother | II, 3 | 102 | 36 | 25/10/60 | 20.6 | 0.96 | 37.2 | 0.93 | 43.9 |
| | | | | 13/12/60 | 20.8 | 0.75 | 38.0 | 1.01 | 41.3 |
| Father | II, 2 | N | 38 | 25/10/60 | 1.4 | 0.93 | 16.5 | 1.20 | 15.1 |
| Propositus | III, 1 | 15 | 13 | 7/10/60 | 35.8 | 0.91 | — | — | — |
| Brother | III, 2 | 103 | 9 | 25/10/60 | 1.4 | 1.16 | — | — | — |
| Brother | III, 3 | R | 0.33 | 4/10/60 | >35.0§ | 1.04 | 49.2 | 0.97 | 55.6 |
| 10 normal persons | | N | 34.1 (0.29)† | — | 1.29 (0.5) | 1.51 (0.26) | 12.1 (3.5) | 2.8 (0.83) | 5.0 (2.1) |
| 20 heterozygotes¶ | | N | 35.7 (6.27) | — | 1.39 (0.44) | 1.30 (0.36) | 14.8 (3.7) | 1.8 (0.36) | 8.9 (1.9) |

*—Ratio of values at one hour, both expressed in μM/100 ml.
†—Figures in parentheses are standard deviations.
‡—N = normal, R = retarded..
§—Not accurate for technical reasons.
¶—Parents of phenylketonurics.

years she was admitted to an Ontario Hospital School and a diagnosis of phenylketonuria was made. Her height then was 4 ft. 7 in. (1.4 m.); weight 80 lb. (3.4 kg.) and head circumference 19½ in. (50 cm.). There were no abnormal physical signs except for short big toes and partial syndactyly of the second and third toes. She was thought to behave at the idiot level with an I.Q. of 15. Urinary tests with ferric chloride and Phenistix were positive. Her fasting plasma phenylalanine was 35.8 mg. % (Table III).

The youngest brother (III, 3) was born on November 11, 1960. The pregnancy was normal but the delivery had been difficult. The birth weight was 5 lb. 9 oz. (2.5 kg.). The neonatal period had been normal. At the age of three months his urine was tested with ferric chloride and found to be positive. He was admitted to the Hospital for Sick Children at the age of four months. He was a fair-haired, blue-eyed child with no abnormal signs except for brisk tendon jerks and a small skull. The head circumference was 14 in. (35.5 cm.) and the anterior fontanelle was closed. Radiographs of the skull showed "a microcephalic skull of normal shape and contour". An electroencephalogram showed a possible epileptogenic focus in the right parietal area. It was thought that he was probably mentally retarded with a developmental quotient (D.Q.) of about 50. Urinary tests with ferric chloride and Phenistix were positive. The fasting plasma phenylalanine was raised. He was treated with a low phenylalanine diet. He was last seen at the age of 1 year, when progress had been good and his D.Q. was thought to be about 75. His head circumference was 16½ in. (41.5 cm.).

The mother of the propositus (II, 3) was aged 36 years. She was a bright, able woman, who had coped well with her family's illnesses. She had reached Grade VIII at school and, before marriage, worked as a weaver in a wool mill. She had had difficulty in reading at school which had continued to the present day. She had suffered no major illnesses except for three miscarriages. Her hair and eyes were brown. Her intelligence was normal as indicated by the following levels attained on the Wechsler adult intelligence scale:

| | *I.Q.* |
|---|---|
| Verbal scale | 106 |
| Performance scale | 96 |
| Full scale | 102 |

The psychologist thought that she had a mild reading disability.

Her urine was tested and found to be negative to ferric chloride and faintly positive with Phenistix. Both tests became strongly positive after a phenylalanine load. Her fasting plasma phenylalanine level was raised (Table III).

The father (II, 2) was aged 38 years. He was a friendly, mildly euphoric man with apparently normal intelligence. He had reached Grade VIII at school, spent four years in the Army and had then become a foreman in a paper-box factory. His plasma phenylalanine and tyrosine levels are shown in Table III.

The elder son (III, 3) was aged 9 years. He had had no major illnesses, his developmental progress had been normal and he was in Grade IV at school. His I.Q. was estimated at 103. His fasting plasma phenylalanine level was normal.

There was no consanguinity between the parents. The mother (II, 3) had 10 siblings. Four of these had died when less than six months old from "acute indigestion". The remaining six siblings were of apparently normal intelligence. One brother (II, 6), aged 41 years, has recently died of long-standing diabetes mellitus and renal failure.

The fasting plasma phenylalanine levels (Table III) of the mother (II, 3) and two of her children (III, 1 and III, 3) were diagnostic of phenylketonuria. Phenylalanine load tests on two of these three subjects were no different from those found in other patients with phenylketonuria (Table II). The father's (II, 2) fasting plasma phenylalanine level was within the normal range, but after an oral load of phenylalanine it rose higher than expected in normal subjects. The corresponding plasma tyrosine values were somewhat low, so that his phenylalanine/tyrosine ratio one hour after the phenylalanine load was high (15.1). According to Hsia,[5] and our own observations, these results suggest that he was heterozygous for phenylketonuria. In the same way, the grandfather (I, 3) and one of the mother's brothers (II, 4) also appeared to be heterozygotes. The grandmother (I, 4) had a phenylalanine/tyrosine ratio of 6.5, which lies in the area of overlap between heterozygotes

and normals. No load test was carried out on the elder son (III, 3), but his fasting plasma phenylalanine level was within normal limits.

### RETARDED SIBLINGS

Since phenylketonuria is inherited as a Mendelian recessive it would be expected that the mentally retarded sibling of a known phenylketonuric patient would suffer from the same disease. This is not always the case, however. In this series three patients with phenylketonuria in three different families had retarded siblings who did not have phenylketonuria.

Family 1. — The youngest child was discovered to have phenylketonuria at the age of nine months because of the findings of mental retardation, slight eczema, a positive urine test with ferric chloride and a raised plasma phenylalanine level. There were seven other siblings. One sibling had died of pneumonia at the age of 13 months and another had died at birth. The remaining children appeared normal except for the eldest, aged 15 years. This boy had always been slow mentally. He was in an opportunity class (Grade V) at school. His urine was negative to ferric chloride, and his fasting plasma phenylalanine was 1.48 mg. %.

Family 2. — There were three siblings. The youngest child was recognized to have phenylketonuria by urine tests with ferric chloride at the age of 3 years. She was grossly retarded (I.Q. 16) and had a history of infantile eczema. She was admitted to an Ontario Hospital School. She died of lobar pneumonia at the age of four years. The eldest sister was normal, but the second sister, aged 12 years, was a behaviour problem and suffered grand-mal seizures. Her I.Q. was 75. Her fasting plasma phenylalanine level was 2.88 mg. %, rising to 9.29 mg. % after a phenylalanine load. The corresponding tyrosine values were 2.58 mg. % and 2.52 mg. %. The phenylalanine/tyrosine ratio at one hour was 4.0.

Family 3.—There were six siblings. The third eldest child had had epilepsy and gross mental retardation. He was diagnosed as having phenylketonuria by urinary tests after admission to an Ontario Hospital School. He died of lobar pneumonia at the age of eight years. The youngest sibling was found to have phenylketonuria at the age of ten months; her fasting plasma phenylalanine level was 51 mg. %. Three of the remaining siblings were of normal intelligence and had normal plasma phenylalanine levels. The eldest child, a boy of 12 years, was mentally retarded. He was in Grade III at school and subject to unwarranted outbursts of temper. His plasma phenylalanine level was normal. A phenylalanine load test on this subject was normal. Similar tests on two other siblings were also normal but that on the father suggested heterozygosity (Table IV).

None of these three retarded siblings were grossly defective, but two had behaviour problems and one had epilepsy. On the history alone, phenylketonuria was strongly suspected. Two of the children had normal plasma phenylalanine levels. The third child (from Family 2) had a high fasting phenylalanine level, but a phenylalanine load test did not suggest that she was a heterozygote. A similar test on the retarded sibling from Family 3 was also normal.

TABLE IV.—PHENYLALANINE LOAD TESTS ON A PATIENT WITH PHENYLKETONURIA AND HER FAMILY (FAMILY 3)

| | | | | *Plasma values in mg.%* | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | *Fasting* | | *One hour after load* | | |
| *Subject* | *Sex* | *I.Q.** | *Age in years* | *Phenylalanine* | *Tyrosine* | *Phenylalanine* | *Tyrosine* | *Phenylalanine/-tyrosine† ratio* |
| Father | M | N | 38 | 0.84 | 1.12 | 14.5 | 1.94 | 8.2 |
| Mother | F | N | 33 | 0.84 | 1.38 | — | 1.67 | — |
| Sibling | M | R | 12 | 1.46 | 1.56 | 5.92 | 1.86 | 3.5 |
| Sibling | F | N | 10 | 1.46 | 1.86 | 9.31 | 2.13 | 4.8 |
| Sibling | F | N | 5 | 1.46 | 1.38 | — | — | — |
| Sibling | F | N | 2 | 1.30 | 1.75 | 6.69 | 1.66 | 4.4 |
| Patient | F | R | 0.82 | 51.00 | 2.68 | 68.4 | 1.56 | 44.6 |

*N = normal, R = retarded.
†Ratio of values at one hour, both expressed as $\mu$M/100 ml.

### THE EFFECT OF A LOW PHENYLALANINE DIET

A properly controlled, low phenylalanine diet in phenylketonuria will lower the plasma phenylalanine to normal, stop the excretion of phenylpyruvic acid and other abnormal metabolites in the urine and allow normal growth to occur. A number of phenylketonuric children have now been treated from the early weeks of life with this diet and have apparently maintained a normal intelligence.[13, 14] The results in older patients have been less spectacular.[9] The diet may ameliorate such symptoms as seizures, eczema and irritability, but no striking improvement in intelligence is usually seen.

There are difficulties in interpreting the effects of a low phenylalanine diet on the intelligence. In particular, the assessment of intelligence in young children is not precise, and there is also considerable variation in the final intelligence of untreated patients (Table I). It is possible that some of the treated patients who have done well would have done well without a special diet. However, as Knox[1] has pointed out, it should be possible to form some idea of the efficacy of a low phenylalanine diet by comparing the distribution of I.Q. among treated patients with that found in untreated patients.

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Twelve children with phenylketonuria under the care of this hospital have been treated with a low phenylalanine diet for nine months to three years. Lofenalac (Mead Johnson Ltd.) was used as the basis of the diet. These patients have been seen routinely every three months and the fasting plasma phenylalanine has been measured. The degree of biochemical control of the disease was arbitrarily divided into three categories. "Good" control was taken to indicate that one month after the diet had been started all measurements of the fasting plasma phenylalanine were below 10 mg. %. "Fair" control meant that not more than one in four fasting plasma phenylalanine levels was above 10 mg. %, and "poor" implied all degrees of control worse than this.

in each case and the initial and final intelligence levels. Cases 1 and 2 (Patricia and Kevin McG.) were originally under the care of Dr. W. R. Centerwall in Los Angeles. He supplied details of their early life, and has recently published full accounts of them (Cases $B_1$ and $B_2$ in reference 15). In Cases 3 and 4, first diagnosed at the age of nine weeks and seven months, respectively, the initial assessments of I.Q. may have been over-optimistic, so that it is not certain that there has been a real decline of intelligence whilst on dietary treatment. In Case 3, biochemical control was good, but it was only fair in Case 4. Cases 5, 8, 10 and 12 showed no change in intelligence level after dietary treatment. In the first two cases biochemical control was fair; in the last two it was good. Cases 6, 7, 9

TABLE V.—COMPARISON OF THE I.Q. DISTRIBUTION OF THE UNTREATED GROUP OF PATIENTS WITH PHENYLKETONURIA WITH THAT OF THE TREATED GROUP

| *Group* | *Number of patients* | *Age in years* Mean | Range | *I.Q. level* 0-20, | 21-40, | 41-60, | 61-80, | 81+ |
|---|---|---|---|---|---|---|---|---|
| I. Untreated | 75 | 16.25 | 2.0-54 | 46 | 20 | 4 | 4 | 1 |
| II. Treated: | | | | | | | | |
| (a) before treatment | 12 | 1.63 | 0.03 - 7.42 | 2 | 2 | 3 | 1 | 4 |
| (b) after treatment | 12 | 3.66 | 1.58 - 8.50 | 1 | 2 | 3 | 2 | 4 |

$\chi^2$ between Group I and Group II,a = 16.89
$\chi^2$ between Group I and Group II,b = 18.40
} d.f. = 4; $p > .01$.

Table V shows the distribution of intelligence of the 12 patients before treatment. Comparison with the I.Q. distribution of the untreated series showed a significant difference. This was to be expected for two probably interrelated reasons. In the first place, the patients in the untreated group were all aged two years and over, whereas most of those in the treated group were aged less than two years when the first I.Q. assessment was made. Since it is thought that patients with phenylketonuria are born with normal intelligence and become retarded during the first two or three years of life, it would be expected that the untreated, younger group would have the better I.Q. distribution. In the second place, the untreated group were mostly long-stay inpatients at the Ontario Hospital Schools whereas the treated group were all outpatients of a general children's hospital.

Table V also shows the I.Q. distribution of the 12 patients after a minimum period of nine months' dietary treatment. Comparison with the I.Q. distribution before treatment showed a slight, but not significant, improvement. In other words, the difference between the I.Q. distribution of the treated group and that of the untreated group had not changed. If treatment had had no beneficial effect, it would be expected that this difference would have decreased, i.e. with increasing age the I.Q. distribution of the treated group should have approximated more to that found in the older, untreated group.

The same data are set forth graphically in Fig. 1. This shows the individual cases, the age at which treatment was started, the duration of treatment and 11 all showed some improvement in intelligence after dietary treatment. Biochemical control was poor in Case 6, but good in the rest. However, in three of these patients (Cases 6, 9 and 11) the improvement was only from one intelligence grade to the next, so that it is difficult to be sure of its significance. One child appeared to show a real increase in intelligence.

D.C.[6] was first found to have phenylketonuria at the age of 11 months. There had been a history of vomiting starting in the second week of life, irritability and an offensive odour to the urine. At 11 months he was apathetic, took little notice of his surroundings and tended to lie still in his cot all day. He could sit unsupported, but made no effort to sit up on his own. He could not roll from prone to supine, but did transfer an object from one hand to the other. He co-operated well with testing and he was thought to be a high-grade mental defective (I.Q. 50 to 70). He was put on to a low phenylalanine diet. Biochemical control was good.

His intelligence was reassessed one year later. He again co-operated well, and this time he was thought to function at the borderline level (I.Q. 70 to 80). He was tested again at the age of three years and three months. Further improvement had occurred and he was able to do some tests at the 3-year-old level on the Stanford-Binet scale. His intelligence was graded as dull normal (I.Q. 80 to 90).

In summary, most of the patients with phenylketonuria showed little or no significant change in intelligence while on a low phenylalanine diet. Two children appeared to deteriorate from relatively normal intelligence to high-grade mental

deficiency, and one child improved from high-grade mental deficiency to the dull-normal level. It was not possible to correlate any changes in intelligence with the degree of biochemical control of the disease.

## DISCUSSION

The distribution of intelligence in this series of patients with untreated phenylketonuria was similar to that found by others[1, 16] and indicates the severity of the disease. However, these series were, for the most part, collected through surveys of hospitals for retarded children and so are bound to reflect the worst aspects of the disease. It is possible that the true distribution of intelligence in untreated phenylketonuria is not quite as bad as these surveys suggest. A number of untreated patients with phenylketonuria who have normal or slightly impaired intelligence exist in the general population, but it is not known what proportion of the total population of persons with phenylketonuria these subjects represent. Knox[1] concludes from the ratio of phenylketonuric patients with low intelligence to those with relatively high intelligence reported in the literature, and the distribution of I.Q. amongst this latter group, that the true incidence of high intelligence in untreated phenylketonuria is no more than 5%.

The situation is complicated by the possibility that large surveys of subjects with normal or slightly impaired intelligence[17] may miss cases of phenylketonuria even if they are present. The urinary test for phenylketonuria depends on the amount of phenylpyruvic acid in the urine, which in turn depends on the level of phenylalanine in the blood.[18] In general, if the serum or plasma phenylalanine level is below 15 mg. %, no phenylpyruvic acid appears in the urine. Above this level phenylpyruvic acid is excreted in the urine, and the amount excreted is proportional to the amount of phenylalanine in the plasma. There are exceptions to this rule; for example, in the newborn period there may be very high plasma phenylalanine levels (50-60 mg. %) and no phenylpyruvic acid in the urine. There also seems to be some variation in the threshold value of plasma phenylalanine from subject to subject and even from time to time in the same subject. Nevertheless, the relationship appears to hold in a general way.

It follows that if it is true that those patients with untreated phenylketonuria and relatively high intelligence tend to have comparatively low plasma phenylalanine levels, it would be expected that a number of them would be missed by urinary surveys. The patient with normal intelligence in this series excreted urine which was negative to the ferric chloride test although her plasma phenylalanine level at the time was 20.6 mg. %. On this specimen alone, and with this test, she certainly would have been missed in a urinary survey. The patient E.R., with an I.Q. of 74, also had a low fasting plasma phenylalanine level and only a faintly positive urine test with 10% ferric chloride. A clearer picture of the incidence of relatively high intelligence in untreated phenylketonuria may emerge as time goes by and the relatives of phenylketonuric patients are studied more closely.

A phenylketonuric patient with a relatively low fasting plasma phenylalanine level is presumably better able to metabolize phenylalanine than one with a high fasting plasma phenylalanine level, provided the dietary intake of phenylalanine is comparable. A low fasting plasma phenylalanine could be due to a less severe deficiency of phenylalanine hydroxylase (the basic lesion in phenylketonuria), or else to the development of more efficient alternative metabolic pathways. The former explanation is not supported by the results of the phenylalanine load tests (Table II), since those patients with relatively high intelligence showed no greater rise in plasma tyrosine one hour after a phenylalanine load than the group of patients with phenylketonuria and low intelligence. Other attempts to demonstrate a biochemical difference in the metabolism of these two types of phenylketonuric patients have not been successful, except to show a rough inverse correlation between the intelligence and the amount of phenylpyruvic acid excreted in the urine;[18, 19] the latter is itself a function of the blood phenylalanine level.[18] It is possible that minor differences in phenylalanine metabolism between patients might be brought out by detailed comparative quantitative analyses, or "profiles", of all the abnormal urinary constituents found in this disease.[20]

Phenylketonuria is inherited as a Mendelian recessive. Theoretically, the phenylketonuric mother (II, 3) of the two phenylketonuric children could have been either homozygous for phenylketonuria or else a heterozygote in whom the single abnormal gene had unusual penetrance. Testing her parents (I, 3, 4) with phenylalanine loads might have clarified the situation, since it might have been possible to show that only one was a heterozygote. In this case their daughter could have inherited only one abnormal gene and so would herself be heterozygous. In the event (Table III), although the grandfather (I, 3) clearly appeared to be heterozygous, the result of the load test on the grandmother (I, 4) was equivocal, so the matter is still not decided.

Allen and Gibson[21] have recently described a boy with untreated phenylketonuria and an I.Q. between 105 and 110. The serum phenylalanine level was 19 to 25 mg. %. A paternal aunt and uncle also had phenylketonuria, and phenylalanine load tests on the parents suggested that only the father was heterozygous for the disease. For this reason it was suggested that the patient himself might be a phenylketonuric heterozygote.

This raises the intriguing possibility that all those phenylketonuric patients with high-grade intelligence and relatively low blood phenylalanine levels

(e.g. E.R., Cowie and Brandon's patient,[11] the boy with muscular dystrophy and phenylketonuria described by Coates, Norman and Woolf[22]) are, in fact, heterozygotes in which the single abnormal gene is particularly penetrant. This might explain why, as judged by the fasting plasma or serum phenylalanine levels, these patients have a relatively mild metabolic lesion. If it were true, however, that the penetrance of the single phenylketonuric gene does vary widely, one would expect to find a correspondingly wide variation in the blood phenylalanine levels of presumed heterozygotes (i.e. the parents of patients with phenylketonuria). In fact this is not the case. On the average, presumed heterozygotes do have raised fasting blood phenylalanine levels compared with normal subjects, but these elevations are up to twice the normal level, not 15 or 20 times as high, and intermediate values (e.g. 5 to 15 mg. %) are not reported.[23]

In either case, whether the mother (II, 3) was homozygous or heterozygous for phenylketonuria, she must have mated with a heterozygote partner in order to have produced a homozygous child. The phenylalanine load test on the father in the present family (Table III) strongly suggests that he was in fact a heterozygote. Two similar families in which the father was the presumed phenylketonuric homozygote and the mother the heterozygote have been reported.[24, 25]

The present phenylketonuric mother gave birth not only to two phenylketonuric children but also to a normal child. No phenylalanine load has been given to this child but, in theory, he should be heterozygous for phenylketonuria. Jervis[26] has under his care a mother with phenylketonuria and an I.Q. between 40 and 50, who has had two children (now aged 5 and 12 years) whose I.Q.s are both within the normal range. The same author, on a previous occasion,[27] has reported another phenylketonuric mother with two normal children. It is of some interest to speculate how it is possible for a mother with untreated phenylketonuria to give birth to a normal child. Current theory suggests that the maximum amount of brain damage in phenylketonuria occurs in the first year of life. This time is regarded as a crucial or critical period during which the growing brain is peculiarly vulnerable to the abnormal biochemical environment. Presumably the fetal brain would have a similar vulnerability. It seems likely that phenylalanine can cross the placental barrier freely because the phenylalanine level of umbilical cord blood in a phenylketonuric baby born of a heterozygous mother is normal or only very slightly raised.[28, 29] Furthermore, in a pregnant, untreated phenylketonuric woman (also with normal intelligence and a comparatively low fasting blood phenylalanine level who had given birth to normal children) recently followed by Woolf *et al.*,[30] it was shown at term that the amniotic fluid, cord blood and first urine specimen of the baby all contained high concentrations of phenylalanine. It follows that the fetus of a mother who herself has untreated phenylketonuria may well be exposed to high blood phenylalanine levels. If this is true, one would expect that all her children, with or without phenylketonuria, would be born with some evidence of brain damage. In the present family such theorizing seemed to provide a plausible explanation for the youngest child's (III, 3) microcephaly, but it does not explain the normal sibling (III, 2).

There are a number of possible explanations. For example, the fetal liver might develop phenylalanine hydroxylase activity of its own in response to the high maternal blood phenylalanine levels. In this case it would be of great interest to know the plasma phenylalanine levels of the mother before, during and after pregnancy. Alternatively, the crucial period during which brain damage occurs in the phenylketonuric child may be strictly limited to a particular time in postnatal life. Another possibility is that the degree of brain damage may be entirely a function of the degree of abnormality of the biochemical environment and not related to any critical stage in cerebral development. It is known that in the first year of life, when the maximum brain damage occurs in untreated phenylketonuria, the blood phenylalanine level is far higher than at any other age.[18, 29] A fasting plasma phenylalanine level of 50 to 80 mg. % may imply a far greater degree of cerebral damage than a fasting plasma phenylalanine level of 20 mg. %, at whatever age the brain is exposed to it. This might explain why, after the age of 5 or 6 years, when the untreated phenylketonuric patient's average fasting plasma phenylalanine level is 30 mg. % or less, there is apparently little or no further cerebral deterioration.[16, 23] This might also explain why the untreated phenylketonuric patients with relatively high intelligence have relatively low blood phenylalanine levels, why the efficacy of dietary treatment is not obviously related to the degree of biochemical control of the disease,[1] and how the second child of the untreated phenylketonuric mother in this present series escaped brain damage.

Clearly more information is needed before this concept can be judged. It should be pointed out, however, that this hypothesis implies that it may not be necessary to maintain scrupulously normal blood phenylalanine levels in the treatment of phenylketonuria, but that the main point of treatment is to avoid excessively high blood phenylalanine levels.

Experience with this small series of treated patients corresponds broadly with that of others.[9, 13, 15, 31] The main beneficial effect of treatment appeared to be the prevention of mental deterioration. Most of the patients after nine months or more of dietary treatment had the same intelligence rating as that with which they started. The changes in intelligence observed were difficult to

assess either because they were small or else the initial assessment had been made when the child was very young (and was, therefore, not very reliable).[31] The two children with the highest final intelligence had been started on a low phenylalanine diet at the age of ten days and six weeks, respectively. It seems likely that until a greater number of patients have been treated with diet from this early age, the full benefits of treatment will not be known.

## SUMMARY

The distribution of intelligence among 75 patients, aged two years or more, with untreated phenylketonuria is presented. Fasting plasma phenylalanine levels were measured in 51 patients and phenylalanine load tests were carried out in 34. No correlation was found between the intelligence level and the biochemical tests except that three patients with comparatively high intelligence (I.Q.>60) had comparatively low fasting plasma phenylalanine levels (<25 mg. %).

A patient with untreated phenylketonuria and normal intelligence (I.Q. 102) is reported. Her family and three children (two with phenylketonuria and one normal) are described.

Three families are presented to demonstrate that mental retardation in the sibling of a patient with phenylketonuria is not necessarily due to phenylketonuria.

Some observations on the effect of a low phenylalanine diet on the intelligence of 12 patients with phenylketonuria are briefly described.

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## PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

### PELLAGRA

Until more recent years pellagra was looked upon as a rarity upon this continent. Of late, however, the number of recognized cases has increased to an alarming extent, some observers estimating the number of cases in the United States to be as high as fifty thousand. As a result of this rapid rise in the importance of the condition, much space has been devoted to it in the medical journals of the republic. In brief, pellagra is a disease characterized by various affections of the epithelium lined surfaces of the body and of the nervous system. Enteritis, cystitis, vaginitis, and stomatitis are commonly present at some time during the course of the disease in addition to the characteristic dermatitis. With the exception of the skin manifestations no lesion presents any pathologic peculiarity characteristic of pellagra. The skin lesion which appears on the extremities, and somewhat less frequently upon the face and neck, begins as an erythema with, or without, bullae formation. In general, the lesion is similar to a severe erythema solare, but is followed by a more intense pigmentation and epithelial proliferation or hyperkeratosis. The histological appearance of the lesion is similar to that of x-ray dermatitis, and in view of this fact, as well as the clinical observation with reference to its development upon exposed parts of the body, there seems little doubt that the direct cause is sunlight, acting upon skin surfaces whose normal resistance to the sun's rays has been depressed. Intertrigo in the usual situations is commonly associated with other evidence of reduced epithelial resistance. The nervous manifestations consist of pain in the extremities, mental dullness, apathy, and not infrequently pronounced melancholia or mania.

At the present time no pathology of pellagra can be said to exist. There is no characteristic lesion, nor is the etiological factor by any means determined. In so far as is known at present it would appear that, as the result of some factor whose nature is still problematic, there is induced a state of lessened resistance of the epithelial structures of the body, whereby they are rendered more susceptible to the action of irritants to which they are normally subjected. Lombroso, whose observations upon pellagra were very extensive and carefully carried out, believed that the ingestion of corn or other cereal improperly prepared accounted for the disease. At the present time, probably the majority of writers on pellagra believe that it is caused by the presence in spoiled corn, or other similar food-stuff, of certain moulds which produced a toxin similar to ergot.—Fraser B. Gurd: *Canad. Med. Ass. J.*, 2: 303, 1912.