THE DIETARY TREATMENT OF PHENYLKETONURIA

BY

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Phenylketonuria is an inborn error of the metabolism of phenylalanine associated almost invariably with grave mental deficiency, and often with epilepsy resembling petit mal. It was suggested that the mental deficiency was due to an intoxication by phenylalanine or one of its metabolites and might be relieved by feeding a diet low in phenylalanine (Woolf and Vulliamy, 1951). An economically practicable form of such a diet, based on a charcoal-treated casein acid hydrolysate, was devised by one of us (L.I.W.) and first fed to a phenylketonuric child by Bickel, Gerrard and Hickmans (1953).* They reported a dramatic improvement in mentality in their patient and Woolf, Griffiths and Moncrieff (1955), using objective psychometric methods, found a marked improvement in three other cases. Since then there have been a number of reports of the successful application of the dietary treatment of phenylketonuria (*e.g.*, Armstrong and Tyler, 1955; Braude, 1956; Horner and Streamer, 1956; Blainey and Gulliford, 1956), and it is evidently being widely adopted. We are reporting here our experiences both with the original three patients (now followed for a further 32 months) and with a further seven phenylketonuric children who have been treated on the diet for periods varying from 11 to 34 months. One of these has been treated from the age of a few weeks for over two years, and has remained in the normal range of intelligence. Another, treated from the age of 4 months, has not shown the further deterioration in intelligence which would be expected if untreated. The rest have all improved in intelligence rating; in two of the four cases with fits these ceased soon after the children were placed on the diet, and the E.E.G. became nearly normal (*cf.* Wolf, 1956).

Of the children who have been or are being treated with the diet at this hospital, all but eight are reported here. Of these eight, one lives at a considerable distance, while the other seven have been treated for too short a time to enable any conclusions to be drawn.

Clinical Summaries

Case 1. This child, a sibling of Case 9, was born in February, 1955, weighing 6 lb. 3 oz. (her twin sister, born first, weighed 7 lb. 10 oz. at birth). Urine obtained on the seventeenth day of life contained phenylpyruvic acid and both twins were admitted at the age of 3 weeks. Phenylpyruvic acid could not be detected in the urine of the twin sister and paper chromatography showed that her urinary phenylalanine concentration was normal. Dr. Cedric Carter kindly saw them and tests showed conclusively that they were dizygous. The blood group of Case 1 was O, NN, CD (probable genotype R_1R_1) and of the normal twin O, NN, CDc (probable genotype R_1r). Both children appeared normal physically, and clinically about identical in behaviour. Intelligence tests were carried out on both twins and will be discussed later. The affected twin was weaned from the breast and a special synthetic 'milk', low in phenylalanine was started (see page 39), and she was quickly worked up to an intake of 50 calories per lb. per day. She lost a little weight and the intake was increased at first to 60 calories per lb. and then to 70 calories as she appeared to be hungry. The weight increased rather slowly and the amount of cow's milk added to the diet was several times increased, each increase accelerating the weight gain. She became anaemic in appearance, the haemoglobin fell and a blood transfusion was given. Clinically, she did not appear quite as bright as her twin sister but intelligence testing gave a very satisfactory result, showing her to be average at the age of 15 weeks, with a 'general quotient'* (G.Q.) of 99. She was re-admitted with a bad 'cold' at the age of 5 months having continued on her special 'milk' as an out-patient. At the age of 6 months, she weighed 14 lb. 10 oz. and was doing very well physically and mentally. The urine remained free from phenylpyruvic acid. She became difficult over feeds and was re-admitted for weaning on to a more solid diet but this proved an impossible task, and weaning was delayed for a further few months. She was successfully weaned on to solids at 15 months and is now getting a mixed diet like that of her older sister (Case 9). Her mother did not think

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* It was Dr. Bickel who undertook the laborious task of preparing the charcoal-treated casein hydrolysate, now commercially available, and who courageously first gave it to a phenylketonuric patient.

* The G.Q. is derived from a scale (Griffiths, 1954) suitable for testing very young children of low mental age (see page 34).

her progress quite so good as her twin sister's but intelligence tests were satisfactory, the child's G.Q. having reached a 'plateau' of about 88. An E.E.G. was performed on June 13, 1956, and was within normal limits as far as could be ascertained on a short record with the eyes open.

For several months she had very little hair on her head. When it finally grew it was golden, exactly the same colour as her normal twin sister's and unlike the grey-blonde characteristic of phenylketonuria. (The family was fair-haired, see Case 9.)

Case 2. This girl, born on October 9, 1951, was under the care of Dr. P. R. Evans. She originally attended at the age of just over 1 year for muscular weakness and failure to thrive. There had been a few attacks which were possibly 'fits'. The urine was not examined for phenylpyruvic acid at this time. Her retardation was not great and progress continued. She walked at just under 2 years. At this time phenyl-ketonuria was diagnosed but no treatment was instituted. A year later in view of success with the diet in other cases she was admitted, and a phenylalanine-free diet was started in September, 1954. She was at this time a blue-eyed blonde with an I.Q. of 71. There have been no fits since the age of 2 years (on no medicaments). An E.E.G. in 1954, before the condition was first treated, was normal. Her physical development is normal. She had been a contact with a patient with active pulmonary tuberculosis, and her Mantoux reaction became positive in November, 1954, but the child has shown no evidence of the disease. The phenylalanine-free diet has been maintained since the autumn of 1954, though with occasional mild lapses. In the autumn of 1956, her I.Q. having reached the level of 92, she started school, being nearly 5 years old. Her teacher has said, 'She is a normal child, no different from the others.'

Case 3. This child was born on February 17, 1951, and the following is a summary of the previous clinical account (Woolf *et al.*, 1955).

One older brother is a proved phenylketonuric. Case 3 was late in sitting up, standing and walking. She had no illnesses and no fits. Phenylketonuria was discovered at the age of 2 years 7 months and dietary treatment was begun in October, 1953. An E.E.G. was normal and her G.Q. was 42. Her very pale hair became dark under treatment.

CONTINUATION OF HISTORY. She was re-admitted for assessment in January, 1954, and appeared to be pro-gressing. She was more active than before. Phenyl-pyruvic acid was absent from the urine. Similar results were found when admitted in April, 1954, and again in July, 1954. She was admitted to Tadworth Branch Hospital in September, 1954, for three weeks while her parents had a holiday. Her urine remained free from phenylpyruvic acid. She had a slight gastro-intestinal upset in October, 1954. The clinical impression was one of continuing improvement. In April, 1956, it was noted that her parents were inclined to be careless and phenylpyruvic acid was found in the urine on one

occasion. Her I.Q., which had been rising steadily, levelled off at 57, and then slipped back to 52 at this time. The dietary errors were corrected and her I.Q. has risen to 65 (January, 1957). She is now aged 6 years, and has lessons several times a week from a visiting Surrey County Council teacher.

Case 4. This boy was born on February 20, 1951. The following is a summary of a previous clinical account (Woolf *et al.*, 1955).

The milestones were passed late. Fits occurred at 6 months of age. Phenylketonuria was discovered at the age of 2 years and 8 months. An E.E.G. in October, 1953, was abnormal, and diagnostic of epilepsy. The special diet was started in October, 1953. By January, 1954, an E.E.G. showed none of the previously reported abnormal features. A subsequent E.E.G. showed no specific epileptic activity. His ash-blonde hair became darker. Difficulties over the diet at home caused him to be admitted to the branch hospital at Tadworth. During the period September, 1953, to October, 1954, his G.Q. rose from 20 to 31 while he was on the diet.

CONTINUATION OF HISTORY. He was admitted to The Hospital for Sick Children and its country branch from July 28, 1954, to August 3, 1955, mainly because of home difficulties. He had acute appendicitis in January, 1955, but made an uneventful post-operative recovery. Walk-ing improved and he had no fits. The general impression of his last few months at Tadworth in 1955 was that there was no noticeable improvement in physical and mental achievements. He was seen in the Out-patient Depart-ment in September, 1955, at the age of $4\frac{1}{2}$ years. He weighed $17 \cdot 8$ kg. He could walk unaided, though unsteadily, but could not talk and was still doubly incontinent. He had had no fits. After careful con-sideration of his physical state and the results of intelli-gence testing, it was decided to discontinue the special diet, especially in view of recurrent difficulties at home. An E.E.G. in June, 1955, showed in a sleep record evidence of some epileptic activity, with high-voltage spikes and slow components, but it was not strictly comparable with previous records which were taken with the eyes open. Only slight 'fits' have recurred, confined to his waking on occasional mornings three times or so each week. Another E.E.G. in June, 1956, did not show any epileptic outbursts but there were frequent artefacts which makes the record unreliable. Clinically he was still having occasional fits when wakening out of sleep but these were not so severe as previously. He is on no sedative drugs or any special diet now (June, 1956). His mother thinks he is continuing to improve slowly in all he does and is not going back. He actually continues at a low level of G.Q. 20, the same as before treatment was started.

Case 5. This child born on December 13, 1948, was described by Woolf *et al.*, 1955, and the following is a summary:

An older brother is a proved phenylketonuric ament, and there is one normal sister. At the age of 3 months it was thought that she did not recognize her parents.

She could sit by 1 year. At the age of 15 months she began to have fits. An E.E.G. showed spike-and-wave discharges. Her I.Q. was estimated to be about 40 at the age of 20 months. Phenylpyruvic acid was found in the urine. Fits, resembling petit mal, continued but ceased abruptly in December, 1953, on aloxidone and amphetamine sulphate. She could stand with support at 3 years. An E.E.G. in April, 1954, showed slow spike-and-wave complexes during sleep. Dietary treatment began at the age of 5 years 4 months in May, 1954. There was a curious attack of major epilepsy after 25 days of diet with unconsciousness and cardiac failure. Her hair darkened very markedly during treatment.

CONTINUATION OF HISTORY. She was admitted to Tadworth Branch Hospital to give her parents a holiday. The cardiac failure had completely resolved. No fits occurred (she was still on sedatives), but she was still very retarded. She was seen in the Out-patient Department from time to time and also admitted for re-assessment in September, 1954. An E.E.G. in September, 1954, showed very frequent bursts of irregular spike-and-wave complexes in the sleeping record, but no epileptic activity when awake. Later she developed some severe fits. She began to crawl about the end of the year. It was eventually decided to stop the special diet gradually, starting on April 21, 1955, as very little progress was being made. Several severe fits occurred and she was admitted in 'status epilepticus' on May 8, 1955. The fits were controlled with intramuscular paraldehyde followed by aloxidone, and she remained free from fits up to November, 1956, when last seen, continuing treatment by aloxidone. On that date she was still unable to walk alone or to swallow solids. Her mother thinks she has deteriorated and is losing skills she once possessed.

Case 6. This child, born on March 10, 1955, is the second of two children. He was brought to hospital under the care of Dr. P. R. Evans at the age of 16 months with an older backward brother who was found to have phenylketonuria. This child's urine was therefore tested and he was found to have phenylketonuria. He had been thought to be normal up to 8 months of age although he did not hold up his head until 6 months. When first seen he could not crawl or walk and had only been sitting up for two months. He was a fair-haired, blue-eyed child. There was no history of fits but a doubtful episode resembling petit mal occurred while he was an in-patient. The E.E.G. was not abnormal except for tracings from the pre-frontal region which were perhaps abnormally flat. The G.Q. was 57 on the Griffiths scale. A low phenylalanine diet was started. He has attended the Out-patient Department regularly with clinical improvement and only minor difficulties over diet. A second E.E.G. three months after the diet was begun was normal. Clinically he was thought to show some slow improvement but speech was delayed. In January, 1957, his I.Q. was 76 (Merrill-Palmer); on the Griffiths scale his G.Q. was 68 but this was an incomplete test, since he scored the maximum on several items.

Case 7. This child, born on January 6, 1951, was brought to the Out-patient Department at the age of 2½ years because she was not walking. The patient had been slightly backward with her other milestones. Phenylpyruvic acid was discovered in the urine. The parents were uncooperative from the start, refusing to accept that the child was severely retarded. A brief attempt to start a low-phenylalanine diet was abandoned because the child was removed by the parents. The E.E.G. was within normal limits. The G.Q. on the Griffiths scale was 49 (on July 2, 1953, aged 2 years 6½ months) and, on a repeat test, again 49 (August 5). The parents came back to the Out-patient Department some months later but it was decided that lack of cooperation would preclude use of a special diet. Frequent respiratory tract infections led to a further admission at the age of 4½ years when her tonsils were removed. The G.Q. at this time on the Griffiths scale was 35. She continued to attend erratically and physically made reasonable progress. The G.Q. in May, 1956, was 37, and she was being considered for an occupation centre despite her mother's continued opposition to acceptance of the diagnosis. The child never had any fits.

Case 8. This child, born on August 10, 1955, is a sister of a known phenylketonuric boy. When his condition was diagnosed her urine was examined, and she was found also to be passing phenylpyruvic acid. She was then 4 months of age and had been thought by her parents to be normal in her mental development, but clinically she seemed a little retarded. Her G.Q. (Griffith's scale) was 57. She was put on a low phenylalanine diet and proved difficult to feed on this diet. As with Case 1, phenylalanine tended to vanish completely from her blood and so cow's milk was given and increased several times in an effort to restore the blood phenylalanine level to normal. The serum proteins dropped to 4·56 g. per 100 ml., and the blood urea level rose to ·67 mg./100 ml., but both returned to normal when phenylalanine reappeared in the blood in response to an increase in intake of cow's milk. After being stationary for over three weeks, her weight began to rise and she was eventually discharged. Her G.Q. at the age of 6 months was 64. Progress at home continued but seemed to slow up. At the age of 11 months she could sit only with assistance. An E.E.G. was normal. This child emigrated at the age of 14 months, preventing further testing, but the mother reports (January 3, 1957) that, at 16 months, the child stands alone and says a few words.

Case 9. This child is the sister of Case 1. She was born on March 9, 1953, and first attended The Hospital for Sick Children in April, 1954, at the age of 11 months for backwardness. She held up her head at 6 months, and sat alone at 1 year. Minor 'fits' began at about 20 months in which she dropped forward. At this time phenylpyruvic acid was found in the urine and she was admitted for further investigation. She was a typical

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blonde, backward child with a general intelligence quotient of 24 (Griffiths scale). An E.E.G. was severely abnormal with very high voltage, slow delta activity associated with 'sharp' components. A low phenylalanine diet was started. Some initial loss of weight occurred with the diet as usual, but was later made good. Her hair, which had been almost albino, changed to a medium brown colour with a sharp line of demarcation between white and brown. She had no fits while she was in hospital, but no obvious improvement occurred in her mental state. She was discharged home to continue on the diet but re-admitted a few weeks later with an acute respiratory tract infection which yielded to routine treatment. The mother was pleased with progress and the child was crawling. In February, 1956, she was reported to be saying single words and had begun to walk. Aloxidone was being used but the 'fits' were not entirely controlled. Further intelligence testing in May, 1956, gave a G.Q. of 31, an improvement of four points since October, 1955, and of seven points over the lowest score of 24 in March and June, 1955. An E.E.G. on March 14, 1957, showed only doubtful or slight improvement over the one before treatment started, and was still severely abnormal with large irregular sharp waves, spikes, and slow waves, but with an unstable alpha rhythm. It is probable that except for a special feature in this case the special diet might well have been abandoned after about a year's trial but when it was started the mother was again pregnant and gave birth to twins. One of these was affected, with phenylpyruvic acid in the urine, and one was not. This very important pair of twins from the point of view of study merited great care for all the family.

Case 10. This boy (under the care of Dr. P. R. Evans) was born on December 23, 1952, and is an only child. He was said to be normal up to 3 months of age. Minor fits began at 5 months and he has been retarded ever since. The urine was found to contain phenylpyruvic acid at the age of 18 months. The G.Q. was 20 on the Griffiths scale. An E.E.G. showed diffuse epileptic changes. Major epilepsy developed about a month later. A low phenylalanine diet was started in July, 1954. Slight clinical improvement was noted. He was admitted for re-assessment about five months later. The E.E.G. was reported as erratically normal. (He was on phenobarbitone and the improvement could be due to this.) Fits were continuing but less frequently. He was re-admitted six months later. He was now aged 2½ years and for two months he had been standing and walking. There had been no fits for three months (phenobarbitone ½ grain at night). He had some difficulty over solid food. An E.E.G. was reported as 'mildly abnormal'. He has continued to attend as an out-patient. He had no more fits. The G.Q. in August, 1955, was 27 and in May, 1956, it was 34, indicating a very definite intellectual improvement. He has continued throughout on his low phenylalanine diet, but with numerous serious lapses, his mother being apparently unable to keep forbidden foods from him.

Case 11. This child was born on February 7, 1955, and was first seen (under the care of Dr. P. R. Evans) in March, 1956, at the age of 13 months, because his mother thought he ought to be doing more. Phenylpyruvic acid was found in the urine. There were no fits at any time. The G.Q. (Griffiths scale) was 21 in April, 1956. An E.E.G. showed diffuse abnormal bursts of sharp spike-and-wave activity, such as are often associated with the condition of phenylketonuria. A phenylalanine-free diet was begun but, through a manufacturer's error, N-acetyl-DL-tryptophan was fed instead of DL-tryptophan for the first eight weeks. His weight dropped over six days from 11·3 kg. to 11 kg., rose to 11·7 kg. soon after cow's milk was added to the diet, and then dropped steadily to 10·7 kg. During this time the blood phenylalanine level remained high, though phenylpyruvic acid did not reappear in the urine. When tryptophan was added to his diet, his weight began to increase at once, the blood phenylalanine level dropped to normal, and he obviously became much more cheerful. His hair remained the grey-blond colour characteristic of phenylketonuria throughout the period when he was unintentionally deprived of tryptophan; three days after adding tryptophan to his diet the new growth at the base of the hair was almost black, making a striking contrast with the rest of the hair.

His G.Q. (Griffiths scale) on November 8, 1956, was 23, and on April 18, 1957, it was 32. An E.E.G, on April 16, 1957, still showed a generalized abnormality with large amplitude, irregular sharp waves, spikes and slow waves, but there was an improvement over the E.E.G. of April 19, 1956, though the records are not strictly comparable.

Psychological Examinations

Careful psychometry was necessary if we were not to rely on subjective impressions of any improvement on dietary treatment. The test used had to be suitable for children of low mental age. A recently devised test (Griffiths, 1954), which had been standardized by one of us (R.G.) on about 600 children between the ages of 2 weeks and 2 years has been used throughout. The nature of this test provides for very detailed information by virtue of items divided into five sub-scales, each measuring a significant aspect of mental growth and development. This makes it possible to observe from time to time the progress in, *e.g.*, eye-hand coordination, or alertness to sounds. After the second year the scale merges into the Terman-Merrill which was the test used for children of mental age over 2 years, except in Case 6 where the Merrill-Palmer scale was used. The youngest infants were tested every six weeks, the intervals being gradually lengthened to three months during the second year.

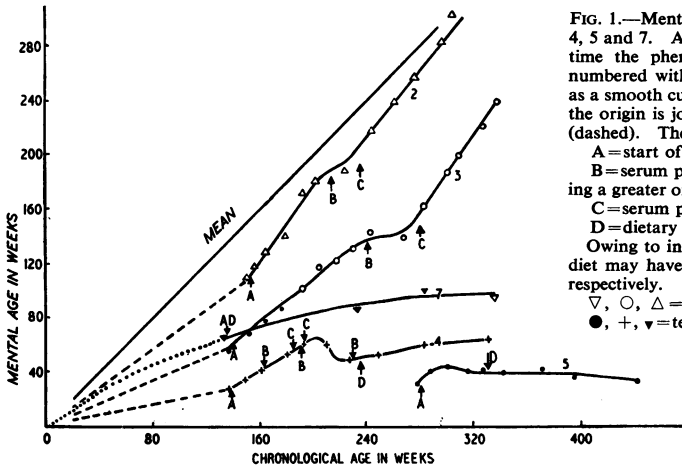The results are best shown in graphs of mental age plotted against chronological age (Figs. 1-4).

FIG. 1.—Mental age plotted against chronological age for Cases 2, 3, 4, 5 and 7. A smoothed curve is drawn through the points from the time the phenylalanine-restricted diet was started (each curve is numbered with the case no.); in Case 7 this line is continued back as a smooth curve (dotted) through the origin and in Cases 2, 3 and 4 the origin is joined to the first point in each curve by a straight line (dashed). The mean for the whole population is also shown.

A = start of the diet low in phenylalanine

B = serum phenylalanine concentration found to be raised, indicating a greater or lesser departure from the diet

C = serum phenylalanine level found to have returned to normal

D = dietary treatment terminated.

Owing to intermittent testing, the departure from or return to the diet may have occurred a little earlier than is indicated by B or C respectively.

▽, ◯, △ = test results obtained on the Terman-Merrill scale.

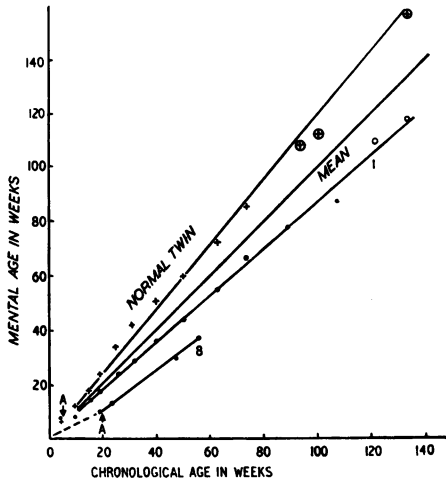●, +, ▼ = test results obtained on the Griffiths scale.

FIG. 2.—Mental age plotted against chronological age for Cases 1, 8 and the normal twin of Case 1. A as in Fig. 1.

◯, ⊗ = test results obtained on the Terman -Merrill scale.

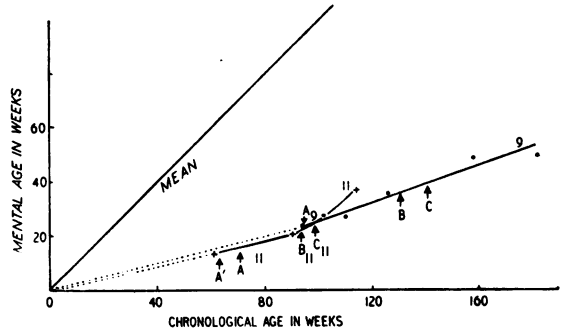●, + = test results obtained on the Griffiths scale.

FIG. 4.—Mental age plotted against chronological age for Cases 9 and 11.

●, + = test results (Griffiths scale).

A′ = phenylalanine and tryptophan-restricted diet started.

A, B and C as in Fig. 1; where confusion might arise, the case no. is added to A, B or C as a subscript.
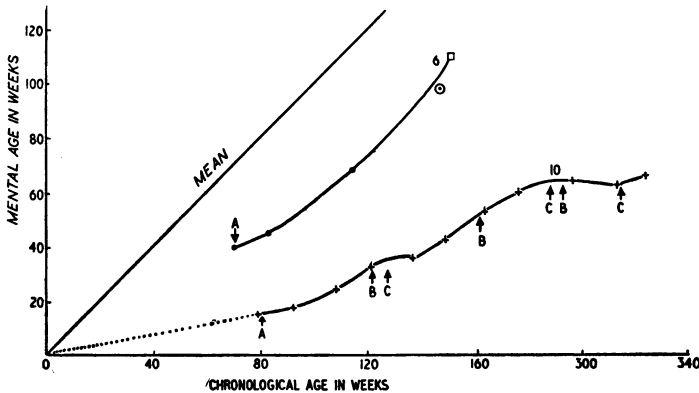

FIG. 3.—Mental age plotted against chronological age for Cases 6 and 10. A, B and C as in Fig. 1.

●, + = test results obtained on the Griffiths scale.

⊙ = result of an incomplete test on the Griffiths scale.

☐ = test result on the Merrill-Palmer scale.

Fig. 5 shows the changing general intelligence quotients as time passes.*

Case 1. When first tested, at the age of 4 weeks, she was more active than her normal twin; in fact she displayed a certain hyperactivity. For example, when placed in the prone position she suddenly lifted head and shoulders well up, turned her head first to the left, then to the right, and then placed her cheek against the pillow again. Apart from this unusual physical activity, her test results were in general and in detail very like her twin sister's, and the two children actually passed and failed exactly the same test items in scales C, D and E. In subsequent tests the healthy twin continued to do well. After one very good test result (119) the G.Q. of Case 1 dropped to a fairly steady level of between 88 and 92. This has been maintained.

Case 2. Even before she went on to the diet, this child had a G.Q. of 71. She was already able to do a few tests

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* The raw quotients and mental ages have been given in Figs. 1-5. Differences in the standard deviations make the quotients slightly different in meaning as one passes from one type of test to another, but these do not obscure the improvement. Dr. J. A. Fraser Roberts advised us that, owing to the doubtful accuracy of the standard deviations for children of such low I.Q., it would be misleading to give the results for most of these children in terms of standard scores at the different ages.

of the Terman-Merrill scale, and this test was used for all subsequent psychological examinations. The child has made steady and quite rapid progress ever since (Fig. 1). Her speech was at first indistinct and largely babble, but this stage has long ago been left behind and her speech is now clear and fluent and developing rapidly.

Case 3. This child has been followed since October, 1953, when her G.Q. was 42. Her intelligence has improved almost continuously. At one stage (see Fig. 1, point B) there was a pause in progress; she did not do so well on tests and much of the restlessness noticed earlier had returned. It was found that the blood phenylalanine level was raised (both in this case and all the others, the blood and urinary phenylalanine levels were not known till after the intelligence testing). The diet has since then been strictly adhered to and the child has not only regained her former position but has advanced still further. When tested in November, 1956, she had reached a new level of 62.

It is highly probable that this child will prove to be educable, at least at an educationally subnormal level, but she will be continually under observation and in another year or so may be found capable of accepting education in a normal school.

Case 4. This child was described in a previous paper as Case 1 (Woolf *et al.*, 1955) as improving quite rapidly
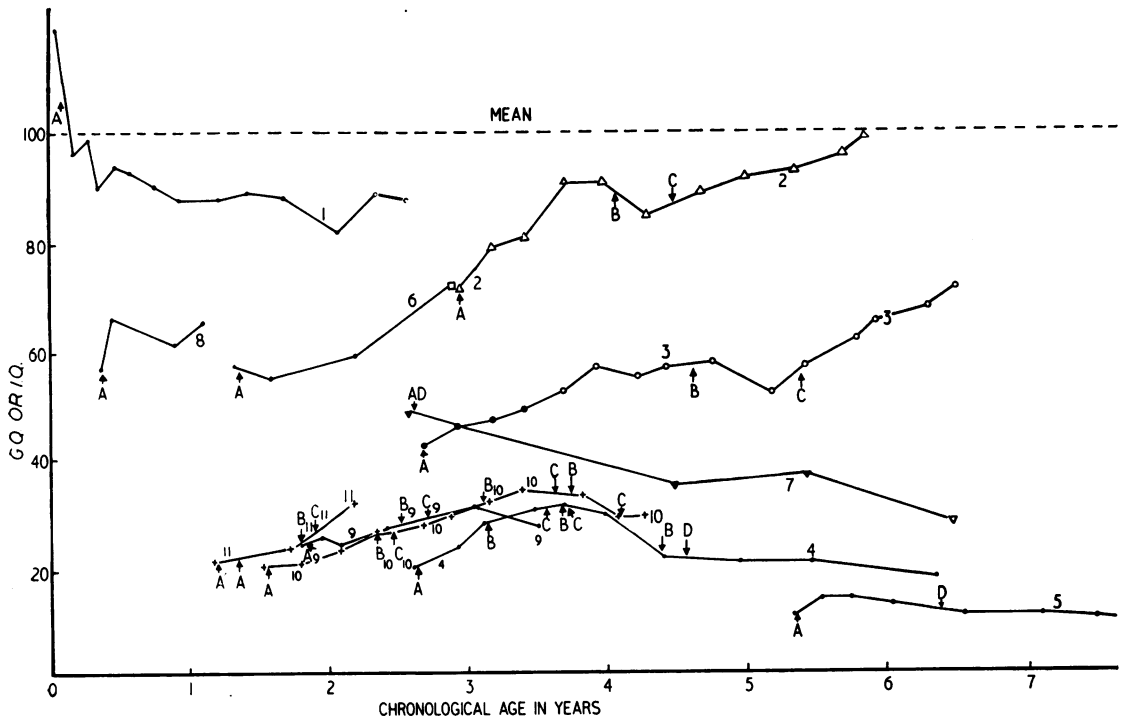

FIG. 5.—Intelligence quotient plotted against chronological age for all 11 cases, A' A, B, C and D as in Figs. 1 to 4.
●, +, ▾ = test results obtained on the Griffiths scale.   ▽, ○, △ = test results obtained on the Terman-Merrill scale.
☐ = test result obtained on the Merrill-Palmer scale.

in all directions, but particularly in regard to speech. On the diet his G.Q. rose from 20 to 30 in 10 months and his speech from Q.C.8 to Q.C.32 during the same period.

Soon after this encouraging progress, however, it was found that the child was not being kept strictly on the diet at home and phenylpyruvic acid was again found in the urine.

The results of a test on March 2, 1955, were surprising, for not only did his mental age remain exactly the same as on the last test, but every item in the test was passed or failed exactly as before. This naturally produced a drop in the G.Q. from 31 to 29. He was content to do various tests, but appeared not to recognize the examiner. He was unsteady on his feet, produced very few sounds, and the nurses reported no speech. He did not laugh or smile. He did not always fixate objects shown to him, and manipulation was vague and momentary, objects being immediately relinquished after handling. He deliberately bumped his head on the floor twice.

On June 29, 1955, he had made no progress in learning; he had in fact deteriorated, failing a few items he could previously do. He walked unsteadily, without direction, round and round in circles, and did not go after toys. He appeared not to make contact with people. Speech had regressed seriously, he had ceased to masticate, and was being fed with a spoon.

It was felt at that time that the child was suffering from a degree of emotional deprivation in this long period (10 months) away from home, sufficient to produce some signs suggestive of an early psychosis and to cause intellectual regression. As the youngest child in the home, he had previously had a good deal of attention and devoted care from his mother. The separation was working against the success of the diet. The child was apparently sent home, but the parents made little attempt to keep to the diet and he was taken off it. He has maintained his level at about G.Q. 21 to 22. He is happy, smiling and laughing, vocalizing and quite different in appearance since he was seen in the summer at Tadworth. He has re-learnt to walk upstairs, holding his mother's hand, can seat himself at table, is less vague, going towards people and after toys on the floor. He produces several clear sounds, e.g., 'me-me, Babby, Dada'. His use of his hands, too, is slightly better.

Case 5. The progress of this child on the diet was slight, her G.Q. rising in the course of 12 months from 11 to 14. No further progress could be obtained. Subsequently she was taken off the diet.

Since the child came off the diet her mental age has actually dropped from 42 weeks in September, 1954, to 38 weeks in June, 1956. This negative progress rate indicates continuing deterioration and her G.Q. has dropped sharply to 10. At 7½ years of age she is intellectually and in all developmental respects like a baby of 8 months.

Case 6. This case is of interest since there was no sharp inflexion at the start of the diet, but the progress rate increased steadily (Fig. 3). During the first 10 months of treatment the G.Q. did not change significantly, but during the next eight months it rose by 17 points on the Merrill-Palmer scale. The Griffiths scale test was not completed, but even in its partial form already showed a rise of eight points. The diet was strictly adhered to throughout.

Case 9. The test results on this child demonstrate the irreversibility of some effects of the phenylketonuria if the child is too old when treatment starts. This girl was 21 months old and her G.Q. was 24; after 20 months o treatment it has only risen to 27, although it did reach a peak of 31.

For the past six months, this child has been showing behaviour which increasingly qualifies to be called psychotic. She does not make any progress in relating to people, and does not look at people. Her increasing motor skill makes more evident the poverty of the content of her thought; she staggers about aimlessly, hurting herself, biting the furniture, completely withdrawn, though her mental age is now about 12 months.

Case 10. The rise in the actual quotient of 13 points, from 20 to 33, is not in itself dramatic, but a slow and steady rise of the quotient by a few points each time is definitely significant. To know this boy, however, is to be aware of a continuous improvement, for, where he previously lay in his cot, contented enough but unable to sit or speak or play, he is now, two years later, walking and trotting about and climbing. He has a small vocabulary of words and can throw a ball and manipulate toys and bricks a little.

When seen on January 30, 1957, he was very restless and miserable and his G.Q. had dropped to 29. His urine and blood, obtained immediately after the intelligence test, contained quite a high concentration of phenylalanine, and his mother was again warned not to depart from the diet. A similar G.Q. was found on April 3, but he was much more cheerful and cooperative; his blood and urinary phenylalanine concentrations were normal.

Case 11. This child went on the diet when he was 1 year and 2 months old. Six months later the quotient had only risen two points, but the diet had not been kept strictly; six months later it had risen 11 points. This child has a persistently unhappy disposition; whenever seen in hospital, he cries continually and inconsolably; no attention his mother gives him is of any help and all activities seem equally distasteful to him. Twice the test had to be abandoned. This crying is very like that seen in a child with cerebral damage, but, on the other hand, the mother says he is not like this at home. She agrees that the home circumstances, necessitating a day nursery, are by no means ideal and may be the cause of the abnormal behaviour.

It is of interest to note that, as these children begin to progress on the diet, improvement in different kinds of activities is not uniform but tends

to accentuate what may be a characteristic profile. The first and most striking observation, patent to everybody concerned, is the increased physical activity with the accompanying progress in loco-motor development. In a few weeks or months, the child may learn to sit, creep, stand and walk. He also shows improved social alertness, enjoying the contact with other people and losing some of the apathy and general mental dullness previously observed. Progress in speech and also in hand-eye coordination is frequently much slower, and manual skill may be delayed for some time. The number of cases studied in this way so far is too few for any statistical evaluation of a characteristic profile to be valid, but it appears that the child, still limited in general mental capacity, tends to concentrate on one type of activity at a time, locomotor improve-ment being at first most strikingly present in the majority of cases.

Feeding more protein than allowed seems, in some cases, to cause restlessness and hyperactivity. The child seems unable to concentrate on the test or to cooperate with the examiner. He seems miserable. On a number of occasions when this type of behaviour was noted, blood obtained immediately after the psychological examination was found to have a raised phenylalanine concentration. Return to the diet (as shown by subsequent chemical investigation) produced a happier, calmer and more cooperative mood.

Chemical Investigations

The diet was controlled, in each case, by repeated chemical investigation of the blood and urine. In the first three cases treated, the daily phenylalanine intake, as milk protein, was at first reduced till phenylpyruvic acid was no longer detectable in the urine, using the direct ferric chloride reaction and the more sensitive method of Berry and Woolf (1952). It was found that the concentration of phenylalanine in the blood and urine, though reduced to about one-third of its former value, was still considerably above normal when phenylpyruvic acid vanished from the urine. The amount of cow's milk fed daily was therefore controlled by keeping the phenylalanine concentration in the blood and urine at the same level as in normal children. This resulted in the milk intake being roughly halved for the first three cases (3, 4 and 5).

Paper chromatography (Woolf, 1951) was used to follow the blood and urinary amino-acids; this enabled the phenylalanine concentration to be com-pared with the concentrations of the other amino-acids and this balance, particularly for the blood, is more nearly related to the body's needs than is a simple determination of phenylalanine. One advan-tage of using this method was that any drop to below normal in blood phenylalanine level could be detected and corrected by increasing the intake of cow's milk, usually by 15 or 30 ml. per day. After each such increase or reduction, the blood phenyl-alanine concentration took about a fortnight to reach a new steady level.

In Case 1, the daily phenylalanine requirements rose steadily between the ages of 5 weeks and 9 months. The blood phenylalanine level was found on several occasions to be very low and there was necessarily a time lag between the subsequent increases in intake of cow's milk and retesting. The infant's growth rate was unsatisfactory at times, probably as a result of this, and on one occasion the blood urea concentration rose to 60 mg. per 100 ml., reflecting the catabolism of the unbalanced amino-acid mixture being fed. Case 8 showed similar effects of too low a phenylalanine intake.

Case 11 ceased to gain weight when placed on the diet and his blood and urinary phenylalanine con-centrations remained raised, though below the point at which phenylpyruvic acid is excreted. This continued for five weeks, in spite of progressively decreasing his intake of cow's milk. His hair remained very fair and did not show the darkening at the roots that appeared so dramatically in most other phenylketonurics when placed on the diet. It was noticed that he was excreting very little tryptophan, and the various components of the diet were examined. It was found that, through an error of the manufacturer, he was being fed acetyl-DL-tryptophan instead of DL-tryptophan. When this was corrected there was a dramatic rise in his weight, his blood and urinary phenylalanine concentrations dropped sharply, and his hair turned dark at the roots within three days.

In every case, the diet did not affect the post-absorptive blood concentrations of any amino-acids except phenylalanine, methionine and α-amino-butyric acid. The blood levels of methionine and α-aminobutyric acid rose slightly when 1 g. of DL-methionine was fed daily. The urinary concen-trations of methionine and tryptophan were very high; presumably the D form of both amino-acids was not appreciably reabsorbed by the kidney tubules and accounted for their high excretion. The urinary excretion of tyrosine, leucine, valine, serine and lysine was also somewhat higher than the average, though far below the levels met in diseases such as cystinosis. Probably feeding the bulk of the dietary nitrogen as a mixture of amino-acids resulted in a higher rate of absorption from the gut than when protein is fed; this would lead to an

unusually high blood amino-acid level and hence to a greater 'overflow' of amino-acids into the urine. The daily intake of casein hydrolysate was kept on the high side to correct for inefficient utilization, and a fairly high calorie intake was maintained by feeding extra carbohydrate, since dietary carbo-hydrate is known to affect the utilization of amino-acids (Harris and Harris, 1947; Munro and Thom-son, 1953).

In every case, within a few days of starting the diet, the previously normal urinary taurine concen-tration fell to an extremely low level and taurine sometimes vanished from the urine. It was thought that sulphur-containing amino-acids might be deficient in the diet and so DL-methionine was added (1 g. per day for children over 1 year). This raised the urinary taurine excretion very slightly in a few cases, but had no effect at all in most, even though the urinary cystine excretion rose markedly in all cases. L-cystine was fed to Case 1 to see whether the slow absorption of this amino-acid from the gut was necessary for the production of taurine (*cf.* the anomalous effect of feeding cystine to cystinurics), but no extra taurine was excreted. Pyridoxine may be necessary for converting cystine to taurine (Blaschko, Datta and Harris, 1953) and 25 mg. extra pyridoxine was fed daily to Case 1 for three days, but there was no increase in taurine excretion. Acid hydrolysis of urine showed that taurine was not present in conjugated form except in traces; the quantity of conjugated taurine adsorbed by the acid resin, Zeo-Karb 225, was normal (*cf.* Woolf and Norman, 1957). The con-centration of taurine in the blood was normal, or even above normal when the urinary concentration rose slightly; taurine in the blood was identified as in Woolf and Norman's (1957) analysis. The only conclusion is that in some unexplained way the diet increases the renal tubular reabsorption of taurine.

In Case 1 the urinary excretion of hydroxyproline, previously marked (*cf.* Woolf and Norman, 1957), fell almost to zero as soon as the diet was started. The excretion of proline and of all other amino-acids was unaffected except as discussed above.

Indolyllactic acid was present in all the specimens of urine examined before the children were placed on the diet, and indolylacetic acid could be detected in about half of them (*cf.* Armstrong and Robinson, 1954). Within a few days of starting the diet neither acid could be detected in the urine, in spite of the large amount of DL-tryptophan being given. Phenyllactic acid and the unidentified reducing keto-acid (Berry and Woolf, 1952) also vanished from the urine shortly after starting treatment, while the concentrations of phenolic acids and phenylacetyl-glutamine dropped to normal values.

The Diet

Basically the diet has differed very little from that described by Woolf *et al.* (1955). The major differences have been: (*a*) The reduction in the intake of cow's milk when the blood phenylalanine level, rather than urinary phenylpyruvic acid, was made the criterion (the amount of casein hydrolysate fed was raised to compensate for the diminished protein intake); (*b*) the adaptation of the diet for a very young infant; (*c*) modifications as the patients got older; (*d*) the addition of methionine.

The daily intake of cow's milk was between 60 and 120 ml. per day, providing an estimated 100 to 200 mg. of phenylalanine daily for children over 18 months of age. The daily requirements were higher during the first 18 months. Afterwards changes in phenylalanine requirement were slow for any given child, but there was some variation between one child and another. Potatoes were given to the older children in strictly controlled amounts, 2 oz. mashed potato being taken as equivalent to 1 oz. cow's milk in phenylalanine content.

Cases 1 and 8 presented a special problem as they were only 17 days old and 4 months old respectively when treatment was decided on. The soup, vegetables, bread, etc., of the older children had to be replaced by a thin liquid which had to contain, as far as possible, all the nutrients of human milk, except phenylalanine, in their correct concentrations. The greatest difficulty was in incorporating the fat; experiments with coconut oil and glyceryl mono-stearate were unsuccessful, the emulsion invariably breaking when the mixture with amino-acids, sugar, salts, etc. was sterilized. Eventually the fat was added as double cream and this was completely successful. The composition of the 'milk' is shown in Table 1 (Appendix).

The thick cream supplied a proportion of the protein required (for phenylalanine) and the rest was supplied by the cow's milk. A diet completely free from phenylalanine was never given to these very young infants, in contrast to the older phenylketo-nurics who were given a phenylalanine-free diet for a few days to bring the blood phenylalanine level down quickly before adding cow's milk. The amount of cow's milk fed to the young infants had to be increased frequently as it was repeatedly found insufficient to keep the blood phenylalanine level up to normal. At its maximum, when Case 8 was 7 months old and weighed 7·4 kg., the daily intake of cow's milk was 120 ml. in addition to 90 ml. of double cream, and slightly less for Case 1. Another

case, not reported here in detail, at 11 months required 200 ml. of cow's milk and 100 ml. of double cream daily to keep the blood phenylalanine level normal. After the eleventh month the phenylalanine requirements began to drop. Inositol and choline were given in such large amounts because they are present in milk (Robinson, 1951) though of unknown function. The salts were also added to give a mixture resembling the inorganic constituents of human milk and of the same pH, though the calcium phosphate had to be in suspension. Vitamin B_{12} was added as 'cytagon' oral syrup in preference to crude liver extract, and folic acid was added to the vitamin tablets (cf. Collins, Harper, Schreiber and Elvehjem, 1951).

As the children got older and could take a more solid diet than the original soup, some variety was introduced. The cow's milk was omitted from the soup, and was given with a cereal at breakfast. The 'soup' was made thicker, flavoured with tomato and given at the mid-day meal only, sometimes poured over potatoes, swedes, cabbage, etc., but more often as a separate course. Vegetables (except potatoes and pulses) were allowed freely. Stewed fruit, or a pudding (made from cornflour or sago with sugar, flavouring and colouring) followed; the parents were given a number of recipes. Bread, made from gluten-free wheat starch, with margarine and honey or jam was given at teatime and at other meals as required. Biscuits made from wheat starch, fat, sugar and flavouring were allowed freely, as were oranges and apples and sugar confectionery.

It is difficult to get much variety into the menu since all forms of protein are almost wholly barred. In spite of all efforts it is impossible to disguise completely the taste of the casein hydrolysate. It is remarkable that the children have taken the diet so well; there has been very little difficulty in getting any child to accept the diet in the first place, and they mostly continue to take it without any trouble —even the older children of fairly high I.Q. Some difficulty has sometimes arisen where a normal child in the same family awakens the phenylketonuric to the fact that her food differs from the normal sibling's, but this has always been smoothed over by the exercise of a little tact. A number of commercial firms have become interested in supplying a casein hydrolysate of better flavour, or in providing a ready mixed 'soup' powder, containing all the ingredients of the diet, to which the mother need only add hot water and flavouring.

DL-methionine was added to the children's diets when it was suspected that they were getting insufficient sulphur-containing amino-acids. Although this was shown to be a misinterpretation of the facts,

DL-methionine is still added to the diet, a child over 1 year of age getting 1 g. daily. Casein is not very rich in sulphur-containing amino-acids, and hydrolysis and charcoal treatment removes the cystine; it seemed logical to provide an additional source of sulphur. Methionine was chosen in preference to cystine because methionine can replace cystine in the diet but not vice versa.

After the first few weeks the patients were all treated at home. The parents showed varying degrees of ability to cope with the special diet. Of the 11 patients, the parents of eight were fully cooperative. The parents of Case 7 refused to cooperate. In Case 4 there was very little attempt to keep to the diet. In Case 10 the child was quite obviously given forbidden foods on many occasions; a talk with the mother would result in a temporary drop in the urinary phenylalanine concentration, but sooner or later she lapsed. Case 2 also had an occasional lapse, shown by a temporary rise in urinary phenylalanine excretion; the child may have been taking food from the larder herself. Case 3 showed at one time a moderate rise in phenylalanine excretion that persisted and even increased in spite of cutting down her daily allowance of cow's milk and potatoes. Eventually phenylpyruvic acid appeared in the urine and her I.Q. remained stationary for six months, i.e., progress, previously marked, ceased. It was only after close questioning that the parents, who were intelligent and cooperative, mentioned that the child was very fond of tea, drinking several cups a day. Each cup contained perhaps 60 ml. of milk. As soon as this beverage was omitted, phenylalanine excretion fell to normal and her I.Q. started to rise. In the other seven cases the parents seemed well able to make up the diet and repeated checks showed it was being adhered to. Thus in only two out of 10 cases did the parents seriously fail to keep to the diet.

Discussion

When Fölling (1934) first described phenylketonuria it was immediately apparent that this condition was an inborn error of metabolism closely analogous to those described by Garrod (1908, 1923). It has since been shown by Jervis (1953) that the enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine in the normal liver, is absent from the liver of phenylketonurics. The simplest hypothesis is that in phenylketonurics the gene normally responsible for an essential stage in the synthesis of phenylalanine hydroxylase is replaced by a mutant gene incapable of this synthesis. Thus the inheritance of phenylketonuria as a recessive character is explicable if the patient

is assumed to be homozygous for the mutant gene. Probably all the abnormal biochemistry of phenylketonuria results from the absence of phenylalanine hydroxylase.

The almost invariable association of severe mental defect with phenylketonuria, and its frequent association with epilepsy, have been explained as being due to either a pleiotropic effect of the same recessive gene, or an intoxication by phenylalanine or one of its metabolites, or a deficiency of tyrosine due to its not having been formed from phenylalanine. All three theories have been put forward at various times and, to some extent, investigated, *e.g.*, by Jervis (1937, 1950), Borek, Brecher, Jervis and Waelsch (1950), Woolf *et al.* (1955), Cowie (1951a) and Woolf and Vulliamy (1951).

If the mental deficiency is due to an intoxication, whether by phenylalanine or by one of its abnormal metabolites formed as a result of a high concentration of phenylalanine in the cells, it might be reversible by giving a diet low in phenylalanine unless permanent mental damage has occurred. The success attending the giving of such a diet is reported above and confirms and extends previous reports of success (Woolf *et al.*, 1955; Bickel *et al.*, 1953; Armstrong and Tyler, 1955; Braude, 1956; Blainey and Gulliford, 1956; Horner and Streamer, 1956). This improvement in the mental state is evidence of the correctness of the intoxication hypothesis.

The clearest evidence of a mental effect of the diet is given by the curves of mental age plotted against chronological age (Figs. 1-4). The slope of this line at any given point is the progress rate of the child at that time (Woolf *et al.*, 1955). In most cases there was a sharp inflexion upwards as soon as the low-phenylalanine diet was started. This improvement has been maintained while the child stayed on the diet, *i.e.*, the curve did not return to its original slope, although often the slope has remained well below the mean for the population as a whole. This finding can be explained only as an effect of restricting the phenylalanine intake.

There is no evidence of a spontaneous increase in progress rate or intelligence quotient in untreated phenylketonuria; in fact all the evidence is that there is a steady decline in both, rapid at first and gradual later (*e.g.*, Cases 5 and 7). These children are normal at birth and signs of mental deficiency are usually first noted at an age of 6 months or later. By about 1 year the child is usually an idiot, and mental deterioration seems to continue thereafter at a reduced rate. It is estimated that the majority of all older untreated phenylketonurics have intelligence quotients below 30 and fewer than 1%

have intelligence quotients over 70 (Penrose, 1951). The probability of finding a phenylketonuric of average intelligence is very low indeed. Apart from the cases reported above and others treated elsewhere, only two cases have come to our notice, one of a boy aged 6 with an I.Q. of 103, who will be reported elsewhere (Coates, Norman and Woolf, 1957), and one of a 6-year-old boy who scored 94 on some intelligence tests (Cowie, 1951b). It is unlikely that any considerable number of phenylketonurics of normal intelligence are not being detected because: (*a*) the ferric chloride test has been so widely used for urinary 'acetone bodies', it is unlikely that a strong green coloration would be overlooked or not reported, and (*b*) the shape of the distribution curve of intelligence quotient among phenylketonurics, with its mode at 10, indicates (unless it is bimodal) that very few indeed would come within the normal range (*cf.*, Larson, 1956). Thus there is only a very low probability that in Cases 1 or 2 the intelligence would be at its present level if untreated.

In addition to the effect on the intelligence, with all that this implies, the electroencephalogram has become more nearly normal in two cases after the child was placed on the diet and epileptic fits have ceased (Cases 4 and 10). The epilepsy, often closely resembling petit mal, which occurs in a proportion of phenylketonurics is unusually resistant to drug therapy and the success of the low-phenylalanine diet in controlling it is all the more striking. However, in Case 9 the diet did not control the fits and the E.E.G. showed little improvement. In Case 5, starting the phenylalanine-restricted diet seemed to cause major epilepsy leading to status epilepticus, and the return to a normal diet seemed to have the same effect, in each case two to four weeks after the change in the diet. Both these cases showed evidence of mental deterioration even while they were on the diet; the continuing epilepsy may well be partly or wholly responsible for this. Epilepsy is more common in phenylketonurics of low I.Q. than in high-grade ones, and the intellectual defect may be partly due to the epilepsy in these cases or both may be the expression of more severe intoxication. As in other causes of epilepsy, once the condition is well established it appears to be not always controlled by removal of the precipitating agent.

Among minor effects of the diet, the eczema-like skin condition frequently found in phenylketonurics clears up rapidly. The dramatic darkening of the hair is one of the most striking effects of the diet. The relative deficiency of melanin in hair, skin and eyes in phenylketonuria is well known (*cf.*, Cowie

and Penrose, 1951), and it has recently been shown that this is probably due to competitive inhibition of tyrosine oxidase by phenylalanine (Dancis and Balis, 1955). The inhibition is reversible *in vivo* by giving massive doses of tyrosine (Snyderman, Norton and Holt, 1955). It is not unexpected that the inhibition should also be reversible by reducing the phenylalanine concentration in the body by dietary means; the amounts of tyrosine given by us were insufficient of themselves to account for the hair darkening.

It is tempting to try to link this inhibition by phenylalanine of the formation of dihydroxyphenylalanine with the effects on the central nervous system, adrenaline and noradrenaline being synaptic transmission agents chemically related to dihydroxyphenylalanine. In fact, Weil-Malherbe (1955) has found that the concentrations of adrenaline and noradrenaline in the blood are unusually low in phenylketonuria. However, Pare, Sandler and Stacey (1957) have found that the serum concentration of 5-hydroxytryptamine, a neurohumoral agent chemically unrelated to dihydroxyphenylalanine, is also low in phenylketonuria and rises when a low phenylalanine diet is fed (Sandler and Stacey, 1957, private communication). It may be that the low blood concentrations of adrenaline, noradrenaline and 5-hydroxytryptamine are merely a reflection of a lowered level of activity of the central nervous system, and not due to a direct chemical inhibition of their formation.

In phenylketonuria the effects of the intoxication are not completely reversible. In almost every case the progress rate, although accelerated once the child was put on a low-phenylalanine diet, has been less than 100, suggesting that there is an irreversible component, as well as a reversible one, in the mental deterioration. Nor is this unexpected: from the age of a very few days the child has been subjected to the continuous action of a depressant substance—the period when the normal child is acquiring its first knowledge of the outer world, its first mastery of itself and its environment, is spent in a 'drugged' state. However completely the intoxicant is later removed, the effects of this time lost at a vital period will show in later years.

The brain is undergoing continuous structural development in the early months of life. (It is noteworthy that no consistent morphological changes in the brain have been reported to be associated with phenylketonuria.) It has been suggested (Hebb, 1949) that the neural mechanisms necessary for the earlier steps in learning may be altered by normal growth and development in such a way that they are not so readily available to an older child. This may explain why, in most of the cases considered here, although the brain has been restored to physiological normality by removal of an intoxicant, there is some impairment of the ability to learn. The lowering of the intelligence quotient in phenylketonuria is due to two factors: this irreversible component, and the immediate effect of the intoxication.

In Figs. 1-4 it can be seen that the slope of the curve of mental age plotted against chronological age is less than the average normal even after treatment has started. This reflects the permanent element of the mental deterioration. The time lag when treatment is started, *i.e.*, the difference between chronological and mental ages, is due to both temporary and permanent factors; it represents a gap between normal and phenylketonuric that may never be closed. From Fig. 1, curves 2 and 3, a temporary departure from the diet appears to result in a temporary flattening of the curve, but the slope returns to its previous value on resumption of the diet. We may tentatively conclude that a fairly short period of intoxication at the age of 4 or 5 years causes a reversible mental deterioration; nonetheless the time lag has been increased and the I.Q. consequently may always be lower than it would otherwise have been. Earlier in life, a period of intoxication increases the degree of permanent mental damage as is shown by the slope of the curve.

Cases 4 and 9 raise two interesting and perhaps related problems. Both children showed behaviour which could be called psychotic. In Case 4 this withdrawal most probably was the result of the 10 months in hospital, since on his return home he became more normal in his play and relationships. This withdrawal coincided with, and perhaps produced, a period when the mental age remained stationary though the diet was being kept to. The return to more normal behaviour at home led to a renewed but slow rise in mental age even though the diet was abandoned. Periods in hospital are known in general to depress the mental development of children (*e.g.*, Spitz, 1955). The deterioration in Case 9's emotional relationship seems to have a different origin. There have been no prolonged periods of separation from the mother, though the birth of twins has absorbed the mother's attention to some extent. The quality of the behaviour is more like that of a child with psychotic behaviour of organic origin. This observation can, perhaps, be correlated with the fact that the E.E.G. in Case 9 has remained abnormal, though in Case 4 it returned to normal on the diet. It seems possible that Case 4 may have suffered from a temporary psychosis of psychological origin, and Case 9 may have a

permanent psychotic condition, additional to the lowering of the intelligence, following brain damage which is observable also on the E.E.G. Case 11 is the only other case with an E.E.G. which has remained abnormal, though there have been no fits, and it is interesting that he has always cried and been very actively miserable on every visit to the hospital.

The mental deterioration in untreated phenylketonurics follows an approximately exponential curve; it is most rapid during the first few months of life, e.g., Case 8, I.Q. 57 at 4 months, higher than the great majority of older phenylketonurics; after the second year it proceeds more slowly, but still measurably, e.g., Case 7. Even in Case 1, where the diet low in phenylalanine was started by the fifth week, some slight degree of mental deterioration had already occurred and appears to have been arrested but not reversed. In Case 8 the diet, started at 4 months, appears to have prevented further deterioration though there is as yet no significant rise in the G.Q. As one would expect, the younger the child and the less the degree of mental damage (as measured by the I.Q.), the greater the effect of the diet. This indicates the necessity for diagnosing phenylketonuria and instituting treatment as early in life as possible. The test for phenylpyruvic acid in the urine is extremely simple,* and the implications of a positive result are most important.

We advocate that every child's urine should be tested at the age of 21 days. In the light of further experience it may be possible to shorten this period between birth and testing. The urine of a sib of a known case of phenylketonuria should be examined daily, as far as possible, from birth up to at least 3 weeks of age (perhaps using paper chromatography as well as the ferric chloride test) both for his own sake and to help to close a gap in our knowledge, since there is a one in four chance that he will be affected, and we know neither the age at which the blood phenylalanine level begins to rise nor the age at which phenylpyruvic acid first appears in the urine in affected cases.

If this scheme is followed, all future cases of phenylketonuria will be detected and treatment begun before the fifth week of life. We estimate that from 20 to 40 new cases are born every year in Great Britain, basing this on Munro's (1947) figure of two to six cases of phenylketonuria per 100,000

population, and the 600,000 live births every year. It is probable that the incidence is rather higher than Munro estimated, because his figures are based on the population of institutions for low-grade mental defectives and their relatives, and there is a small but appreciable number of phenylketonurics of too high a grade to be admitted to institutions (e.g., Case 2; cf. Coates et al., 1957). The local health authorities should work out the necessary administrative measures to see that health visitors collect and test the urine of every baby. A coloured card with instructions as to testing is being prepared.† Already one large local authority has asked one of us to talk on the subject to health visitors and midwives in the area.

Even in older children a worthwhile improvement often results from dietary treatment. It is obviously a gain even if a child's mental rating is raised only from idiot to imbecile level. As a rough guide we consider treatment worth initiating if the child is 2 years old or under and the G.Q. not less than 20, or 3 years old with a G.Q. of 30 or over, or 4 years old with a G.Q. of 40 or over. In any border-line cases it is probably wise to try six months' treatment with careful psychological testing at the beginning, at 3 months and at the end of this period. A decision would then be reached in the light of any improvement effected. It is also important to rule out any other form of brain disease. For example, in the presence of spasticity or any suggestion of birth trauma in the widest sense, investigations such as air studies should be undertaken to eliminate the possibility of structural brain damage of a gross type.

We do not know for how long the diet must be strictly adhered to. It may be impossible to relax it throughout life. On the other hand, once development of the brain has reached a stage where permanent mental damage is unlikely, a certain degree of intoxication resulting from some relaxation of the diet may be tolerable. However, from Case 3, it appears that 5 years is too early an age for this.

The effects of giving a normal diet, after the child had been on a low-phenylalanine intake, have been reported by Bickel et al. (1953) and by Armstrong and Tyler (1955). They both noted reversal of the previous improvement. In Case 5 above, the mental age actually started to decline, causing a marked decrease in I.Q., when her diet was changed from one low in phenylalanine to a normal one; previously her I.Q. had been maintained at a steady though very low level. Somewhat similar findings were noted in Case 4, but here

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* To a fresh specimen of urine is added a little 5% ferric chloride solution. A green coloration, reaching a maximum within five minutes and fading only slowly, constitutes a positive result. Acidification is unnecessary and can invalidate the test. The ferric chloride can be spotted on to a wet napkin but this is much less reliable than the test-tube method.

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† This may be obtained from the Secretary, The Hospital for Sick Children, Great Ormond Street, London, W.C.1, price 6d.

the results are complicated by other psychological factors.

None of the children considered here has been given any psychological treatment or tuition likely to affect the score in intelligence tests. All, except Case 4, have been treated at home and received the ordinary attention a child receives from parents who have not been instructed in any special teaching or training. Only one child, Case 3, has received part-time tuition from a trained teacher, and this for a limited period. Thus we can eliminate disturbing factors in evaluating the effect of the diet on mentality.

These children have special educational problems. As the child emerges from his semi-intoxicated state and begins to function more normally in the intellectual sphere, his capacity to learn is accelerated. Learning takes time, and his climb to a state nearer to his innate level will take several years and may involve some strain. Thus the child of imbecile level with a rising I.Q. may eventually need, not an occupation centre, but a school for educationally subnormal children, and even here full justice may require an open mind, for the child may be capable of travelling still further, in fact to the normal school. Each case should therefore be considered individually and sympathetically by education authorities, and re-assessed frequently so that suitable adjustments can be made in the type of education available to him.

A further question is whether definite psychological help, other than periodic testing of intelligence, should not be seriously considered. These children, while improving rapidly, need sympathetic handling. Some of them tend to be nervous and, having much to catch up educationally, and socially may need individual tuition, or remedial education, or even psychotherapy. It is possible that even more rapid progress might be obtained through attendance at a child guidance clinic or other centre for individual or group play therapy.

Summary

The results of treating 10 phenylketonurics with a diet low in phenylalanine are described.

In almost every case there was a sharp and significant rise in I.Q. The I.Q. continued to rise, the mental age plotted against chronological age showing a point of inflexion at the time the diet was started.

An infant treated from the age of 5 weeks has remained at I.Q. 88 for nearly two years, indicating that relatively slight deterioration had occurred during the five weeks before treatment. Mental deterioration (dementia) proceeds most rapidly in untreated cases during the first weeks of life, then gradually slows down, but is still continuing appreciably at 2 years of age.

As it seems likely that mental deterioration in this condition can be prevented by early treatment, we suggest that every infant's urine be tested with ferric chloride at the age of 21 days (though this age may have to be modified), and treatment instituted immediately if a positive reaction is obtained.

It is important to keep the blood phenylalanine concentration at the normal level. If it is too high the child's progress slows down measurably, if too low, the child ceases to grow or thrive. The diet must supply all essential nutrients.

The success attending the use of this diet confirms the theory that the mental deficiency in phenylketonuria is the result of intoxication by phenylalanine or one of its abnormal metabolites.

REFERENCES

Armstrong, M. D. and Robinson, R. S. (1954). *Arch. Biochem. Biophys.*, 52, 287.
—— and Tyler, F. H. (1955). *J. clin. Invest.*, 34, 565.
Berry, J. P. and Woolf, L. I. (1952). *Nature (Lond.)*, 169, 202.
Bickel, H., Gerrard, J. and Hickmans, E. M. (1953). *Lancet*, 2, 812.
Blainey, J. D. and Gulliford, R. (1956). *Arch. Dis. Childh.*, 31, 452.
Blaschko, H., Datta, S. P. and Harris, H. (1953). *Brit. J. Nutr.*, 7, 364.
Borek, E., Brecher, A., Jervis, G. A. and Waelsch, H. (1950). *Proc. Soc. exp. Biol. (N.Y.)*, 75, 86.
Braude, H. (1956). *S. Afr. med. J.*, 30, 83.
Coates, S., Norman, A. P. and Woolf, L. I. (1958). *Arch. Dis. Childh.*, 32, 313.
Collins, R. A., Harper, A. E., Schreiber, M. and Elvehjem, C. A. (1951). *J. Nutr.*, 43, 313.
Cowie, V. (1951a). *J. ment. Sci.*, 97, 505.
—— (1951b). *Lancet*, 1, 272.
—— and Penrose, L. S. (1951). *Ann. Eugen. (Camb.)*, 15, 297.
Dancis, J. and Balis, M. E. (1955). *Pediatrics*, 15, 63.
Fölling, A. (1934). *Hoppe-Seyl. Z. physiol. Chem.*, 227, 169.
Garrod, A. E. (1908). *Lancet*, 2, 1, 73, 142, 214.
—— (1923). *Inborn Errors of Metabolism*, 2nd ed. London.
Griffiths, R. (1954). *The Abilities of Babies.* London.
Harris, M. M. and Harris, R. S. (1947). *Proc. Soc. exp. Biol. (N.Y.)*, 64, 471.
Hebb, D. O. (1949). *The Organization of Behaviour.* New York.
Horner, F. A. and Streamer, C. W. (1956). *J. Amer. med. Ass.*, 161, 1628.
Jervis, G. A. (1937). *Arch. Neurol. Psychiat. (Chicago)*, 38, 944.
—— (1950). *Proc. Soc. exp. Biol. (N.Y.)*, 75, 83.
—— (1953). *Ibid.*, 82, 514
Larson, C. A. (1956). Gedda's *Novant'anni delle Legge Mendeliane*, Rome.
Munro, H. N. and Thomson, W. S. T. (1953). *Metabolism*, 2, 354.
Munro, T. A. (1947). *Ann. Eugen (Camb.)*, 14, 60.
Pare, C. M. B., Sandler, M. and Stacey, R. S. (1957). *Lancet*, 1, 551.
Penrose, L. S. (1951). *Ann. Eugen. (Camb.)* 16, 134.
Robinson, F. A. (1951). *The Vitamin B Complex.* London.
Sandler, M. and Stacey, R. S. (1957). Personal communication.
Snyderman, S. E., Norton, P. and Holt, L. E. Jr. (1955). *Fed. Proc.*, 14, 450.
Spitz, R. (1955). In *Mental Health and Infant Development*, ed. K. Soddy, Vol. 1. London.
Weil-Malherbe, H. (1955). In *Biochemistry of the Developing Nervous System*: Proc. 1st int. Neurochemical Symposium, Oxford, 1954, ed. H. Waelsch   New York.
Wolf, H. (1956). *Medizinische*, 883.
Woolf, L. I. (1951). *Gt Ormond Str. J.*, 1, 61.
—— and Norman, A. P. (1957). *J. Pediat.*, 50, 271.
—— and Vulliamy, D. G. (1951). *Arch. Dis. Childh.*, 26, 487.
——, Griffiths, R. and Moncrieff, A. (1955). *Brit. med. J.*, 1, 57

Addendum

In November, 1957, Case 9 had an attack of tonsillitis and refused all food for five days. At the end of this period her urine was found to contain phenylpyruvic acid in a concentration approaching that found in untreated cases of phenylketonuria, and her blood phenylalanine level was also very high.

The most likely explanation is that phenylalanine was released in the proportion relative to the other amino-acids in which it occurs in the tissue proteins which are spontaneously breaking down. This would be, of course, the ideally balanced amino-acid mixture for a normal person (and is approached by ordinary dietary proteins), but the phenylketonuric, owing to the absence of the enzyme phenylalanine hydroxylase, cannot catabolize the phenylalanine released from the tissues and therefore, in the fasting state, it accumulates in the blood and tissues. The low phenylalanine diet provides the other amino-acids in proportions giving a balanced mixture for a phenylketonuric, permitting all the phenylalanine released by tissue breakdown to be used in the synthesis of new tissue protein, and allowing for growth and for the small loss of phenylalanine in the urine and by reactions not involving phenylalanine hydroxylase.

APPENDIX

The following items of the diet can be provided by the National Health Service: Casein hydrolysate, tyrosine, tryptophan, methionine, calcium hydrogen phosphate, the items listed in Table 2, a mixture of salts in solution, namely, potassium chloride, sodium chloride,* magnesium sulphate, potassium iodide,* sodium citrate,* citric acid.*

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* Only in the case of infants under 1 year old.

The parents have to buy sucrose, cow's milk, gluten-free wheat starch, kosher margarine, double cream, iodized salt, tomato juice, fruit, cornflour, sago, flavourings, vegetables, breakfast cereal, honey, jam and sweets.

TABLE 1

COMPOSITION OF 'MILK' GIVEN TO CASES 1 AND 8

Ingredient	Daily Intake
Casein hydrolysate*	24 g.
L-Tyrosine	2 g.
DL-Tryptophan	1 g.
DL-Methionine	1 g.
Sucrose	90 g.
Cow's milk	0 to 200 ml.
Double cream†	85 ml.
Calcium hydrogen phosphate	0·71 g.
Potassium chloride	0·65 g.
Sodium chloride	0·016 g.
Magnesium sulphate	0·165 g.
Sodium citrate	0·177 g.
Potassium iodide	0·00013 g.
Citric acid	0·08 g.
Water ..	to 850 ml.

* Acid hydrolysed casein passed through charcoal to remove phenylalanine and tyrosine.
† 48% fat, 1·7% protein.

TABLE 2

DAILY INTAKE OF SUPPLEMENTS TO ABOVE 'MILK'

Ingredient	Daily Intake
Choline chloride	100 mg.
Inositol	216 mg.
Vitamin B$_{12}$	4 µg.
Aneurine hydrochloride	0·5 mg.
Riboflavine	0·5 mg.
Pyridoxine	0·33 mg.
Nicotinamide	3·33 mg.
Ascorbic acid	40 mg.
α-Tocopherol	0·33 mg.
Acetomenaphthone	0·5 mg.
Biotin ..	0·17 mg.
Folic acid	0·25 mg.
Vitamin A	3,000 I.U.
Vitamin D	500 I.U.
Ferrous sulphate	0·15 g.
Manganous sulphate	0·0008 g.
Zinc sulphate	0·0014 g.
Cupric sulphate	0·003 g.