TREATMENT OF PHENYLKETONURIA WITH A DIET LOW IN PHENYLALANINE

BY

L. I. WOOLF, Ph.D., B.Sc. RUTH GRIFFITHS, M.A., Ph.D.

AND

ALAN MONCRIEFF, C.B.E., M.D., F.R.C.P.

(From The Hospital for Sick Children, Great Ormond Street, London)

Phenylketonuria is one of the very few conditions in which mental deficiency is associated with a demonstrable metabolic error. It has been suggested that the mental defect is due to an intoxication by phenylalanine or one of its metabolites, and that the mental deficiency may be relieved by feeding a diet low in phenylalanine (Woolf and Vulliamy, 1951). Such a diet must be adequate to permit normal health and growth.

All dietary proteins are about equally rich in phenylalanine (Block and Bolling, 1951), and a suitable diet can therefore be devised only by supplying the bulk of the nitrogen as a mixture of amino-acids. While it would be possible to mix pure amino-acids to obtain such a diet, the cost would render any long-term treatment of even a few cases impossible. Protein hydrolysates have been commercially available for some years, and it is known that they can be freed from phenylalanine, tyrosine, and tryptophan by passing through a column of charcoal (Schramm and Primosigh, 1943). It seemed likely that a suitable amino-acid mixture could be obtained at a reasonable cost by passing an acid hydrolysate of casein through charcoal and adding tyrosine and tryptophan. This was suggested by one of us (L. I. W.) to Dr. H. Bickel, who at that time had a suitable phenylketonuric patient under his care. Bickel carried out the preparation of the suggested diet, fed his patient on it, and reported a very marked improvement in the child's mental condition (Bickel, Gerrard, and Hickmans, 1953). No psychometric measurements were made, and it seemed worth while repeating this work, making as objective and as accurate measurements as possible of intelligence level before feeding the diet and at intervals after. Electroencephalograms were used as a second objective measurement.

The findings are described for two children, both aged 2 years 8 months at the start, who have been fed a diet low in phenylalanine for nine and ten months respectively; marked intellectual improvement resulted, and the E.E.G. became normal in the one case in which it was previously abnormal. A third child, aged 5 years 5 months, has been fed this diet for a shorter period, but presents interesting features, and the preliminary finding of intellectual improvement is described.

Diet

The major dietary components (Table I) were fed as a soup made by cooking the starch in the milk and water,

adding the other components, and homogenizing. In the first stage (till the urine was free from phenylpyruvic acid, two to ten days) milk was omitted and the other ingredients were increased. In the second stage the amount of milk fed was gradually raised till phenylpyruvic acid became just

TABLE I.—Daily Dietary Intake for a 3-year-old

Casein hydrolysate*	26.5 g.
DL-Tryptophan	1 "
L-Tyrosine	5 "
Wheat starch	28 "
Glucose	85 "
Calcium hydrogen phosphate (CaHPO ₄)	1 "
Iodized salt (NaCl)	2 "
Kosher vegetarian margarine	70 "
Arachis oil	3.5 ml.
Milk	240 "
Water	300 "

* Low in phenylalanine, tyrosine, and tryptophan.

TABLE II.—Daily Vitamin Intake

As tablets:	
Aneurine hydrochloride	1.5 mg.
Riboflavin	1.5 "
Pyridoxine	1 "
Nicotinamide	10 "
Calcium pantothenate	3.5 "
Ascorbic acid	50 "
α -Tocopherol	1 "
Acetomenaphthone	1.5 "
Meso-inositol	50 "
Biotin	0.5 "
Lactose	q.s.
As liquid:	
Crude liver extract	6 ml.
Choline chloride	25 mg.
"Adexolin"	10 drops

TABLE III.—Daily Mineral Intake

Potassium chloride (KCl)	1.5 g.
Magnesium sulphate (MgSO ₄ .7H ₂ O)	0.324 g.
Zinc sulphate (ZnSO ₄ .7H ₂ O)	0.0017 g.
Ferrons sulphate (FeSO ₄ .7H ₂ O)	0.069 g.
Manganous sulphate (MnSO ₄ .4H ₂ O)	0.0011 g.
Cupric sulphate (CuSO ₄ .5H ₂ O)	0.00393 g.
Hypophosphorous acid	0.05 ml.
Water	11 ml.

detectable in the urine; then it was dropped to a level at which no more phenylpyruvic acid was excreted. The wheat-starch is a protein-free preparation as fed to children with coeliac disease. The soup was fed in divided feeds four or five times daily.

Vitamins were added in tablet form, made up in the pharmacy of The Hospital for Sick Children, supplemented by a liquid crude liver extract containing added choline chloride and by an oily solution of vitamins A and D (Table II). Minerals (other than calcium phosphate, sodium chloride, and iodine) were added as an aqueous solution (Table III).

Water, orange juice, and glucose water were allowed *ad lib*. Biscuits, composed of wheat starch, kosher margarine, sugar, and flavouring, were also allowed up to 50 g. a day.

Clinical Summaries

Case 1

The parents of this child are Irish and unrelated. Five elder brothers and both parents are normal and have no phenylpyruvic acid in the urine. Pregnancy was normal except that the mother had high blood pressure; the birth was rapid but otherwise normal; he was jaundiced for about a week. His "milestones" were all passed late; he did not hold up his head until he was 6 months old. He began to have "fits" at the age of 6 months, and at 19 months was thought to be deaf by his parents; this led to a medical examination, when his mental retardation was noted, but he had had otitis media, which might have contributed to his deafness. At 2 years 3 months his "fits" had increased in frequency, and his backwardness was more obvious; he could not stand by himself, was incontinent of urine and faeces, and made only unintelligible sounds. Phenylpyruvic acid was found in his urine and he was admitted for dietary treatment when 2 years 8 months old.

Physical examination showed a slightly small skull, 18 in. (46 cm.) in circumference. There were no signs of abnormality in the cranial nerves or central nervous system and the disks were normal. The Wassermann reaction was negative. His "fits" consisted of transient losses of consciousness when, if sitting up, he fell forward.

An E.E.G. on October 2, 1953 (before starting the diet), was reported as "abnormal and diagnostic of epilepsy." There were frequent sustained outbursts, bilateral and synchronous, consisting of irregular high-voltage slow activity associated with spikes. The special diet was started on October 9. His weight then was 31 lb. (14 kg.) and there was some initial loss, but within three weeks the weight curve was climbing steadily.

He was readmitted on January 18, 1954. No "fits" were seen and an E.E.G. showed "none of the previously recorded high-amplitude slow wave and spike." His weight was 32 lb. 8 oz. (14.7 kg.).

In May an E.E.G. showed "a medium-voltage dominant rhythm of about 5 cycles per second. From this background occasional brief high-voltage specific epileptic outbursts occurred, having generalized distribution and consisting of slow waves associated with spikes. There was considerable general improvement over the first record of October 2, 1953."

An E.E.G. on August 3, 1954, showed a medium-voltage activity of 5 cycles per second dominant, but no well-sustained rhythmical runs of activity. No specific epileptic activity was seen. The weight was only 32 lb. 8 oz. (14.7 kg.) and there had been some difficulties at home. On ward "discipline" he gained nearly 2 lb. (0.9 kg.) in a few days, and was later transferred to the branch hospital at Tadworth, where a further weight gain was recorded.

An interesting observation was that his hair, which was almost ash-blond when he was admitted, became noticeably darker during the special diet period.

Case 2

One older brother of this child is a proved phenylketonuric ament. The parents are of normal intelligence, do not excrete phenylpyruvic acid, and are unrelated; one parent comes from Yorkshire and the other from Cheshire. The pregnancy was normal and delivery normal at full-term. The child appeared to recognize her mother at the age of 6 to 8 weeks. She was 1 year of age before sitting up, stood at 2 years, and walked at 2 years 4 months. She had had no illnesses and there had been no fits.

At the age of 2 years 7 months the state of mental retardation was confirmed, phenylpyruvic acid was found in the urine, and she was admitted for dietary treatment. This was started on October 21, 1953, when her weight was 33 lb. 4 oz. (15.1 kg.). There was a slight initial loss, which was quickly regained. Nearly a year later, after a continuous period of the special diet, she weighed 38 lb. 11 oz. (17.5 kg.).

The skull was a trifle small, measuring 19 in. (48 cm.) in circumference; the fontanelle was closed. There was no evidence of disease in the central nervous system other than the mental backwardness. The disks were normal. An E.E.G. was considered to be within normal limits; there was no evidence of epilepsy.

The hair, very pale originally, became darker during the year of treatment.

Case 3

One older brother of this child is a proved phenylketonuric ament, an older sister is mentally normal and does not excrete phenylpyruvic acid. The parents are Irish, unrelated, of normal intelligence, and do not excrete phenylpyruvic acid. The pregnancy was normal and delivery normal at full-term. Nothing abnormal was noted during the first three months of life and then it was thought the child did not recognize her parents. She could sit unsupported by 1 year, and by 15 months showed signs of recognizing her parents.

At this time (1951) she started having "fits" of a petit-mal type and occasional major attacks in which she screamed and fell forward unconscious, the attack lasting two or three minutes. Phenylpyruvic acid was found in her urine. The Wassermann reaction was negative. An E.E.G. showed generalized spike-and-wave discharges.

At the age of 18 months an attempt was made to assess her intelligence in Guy's Hospital, and her mental age was put at 8 months. She was given a trial of glutamic acid for six months, but showed no improvement (Woolf and Vulliamy, 1951). Aloxidone was given for the fits, resulting in partial control, but the fits ceased abruptly when amphetamine sulphate was added in December, 1953. At the age of 3 years she could stand when holding a support. She was admitted for dietary treatment at the age of 5 years 4 months.

Physical examination showed that she was well developed for her age. She would not sit erect and preferred a flexed posture, making frequent rocking movements and dribbling saliva. There was a divergent strabismus, but no other signs of abnormality in the cranial nerves or central nervous system. An E.E.G. on April 30, 1954, showed, when sleeping, generalized slow spike-and-wave complexes.

The phenylalanine-free diet was started on May 3, when her weight was 35 lb. (15.9 kg.). There was an immediate gain, followed by a steep fall. Then she showed a steady gain except during the acute episodes described later. On September 16 she weighed 40 lb. (18.1 kg.).

After 25 days on the diet low in phenylalanine (May 28) she had a curious attack of unconsciousness with severe twitchings of arms and neck. Similar episodes lasting an hour or so at a time continued for three days, and cardiac failure then developed with persistent tachycardia. Digoxin, primidone, aloxidone, and amphetamine sulphate were given, the fits came under control, the general condition of the heart and circulation gradually returned to normal, and digoxin was stopped.

This child's hair also darkened considerably during the period of the special diet—even more so than in the other two patients.

Psychological Observations

The scale of tests used for these investigations is the "Griffiths mental development scale for testing infants from birth to 2 years." This scale was recently devised and standardized on a fairly representative sample of about 600 babies ranging in age from 2 weeks to 2 years (Griffiths, 1954). The severe retardation of the cases to be studied brings them well within the range of these tests in spite of their higher chronological ages. The scale consists of 260 finely graded items placed in strict order of difficulty on a percentage basis. The items are classified and divided into five subscales which measure separately five significant aspects of development: A, locomotor-development; B, personal-social development; C, hearing and speech

development; D, hand and eye co-ordination; and E, performance. These five subscales are very closely equal in difficulty at each month of age throughout the scale. It is therefore possible to compare a child's level of attainment in several directions at once and watch the changing development as the child's interests swing from one aspect of learning to another.

Case 1

First Test

October 6, 1953, and before treatment began. Chronological age (C.A.), 137½ weeks; mental age (M.A.), 27½ weeks; general quotient (G.Q.), 20.

The child was excessively fatigable, and could concentrate for only very brief periods.

The profile, with the trough at C (Table IV), is suggestive of deafness. The child made no responses to auditory stimuli—bells, tuning-fork, the human voice. Subsequent results go to show, however, that this boy now hears quite well, and we can safely regard this early lack of response to sounds as functional rather than organic. All the results at this time showed a low-grade defective level with general quotient 20.

The child could sit in his cot among pillows and take his weight a little when held on his feet, but could not lift his head when lying in the dorsal position, roll from back to stomach, or make any attempt towards crawling. (Q.A. 21.)

He could smile and laugh, recognize his mother, stop crying when talked to, look at himself in a mirror, etc. (Q.B. 20.)

There was some slight vocalization and one-syllable cooing, but no definite response to auditory stimuli. (Q.C. 8.)

He was somewhat better at manipulation, but thumb opposition was not yet complete and he could manipulate only one object at a time; when offered a second, he immediately relinquished the first. He could pass a cube from one hand to the other, and did this continually with objects given to him. He played with paper. (Q.D. 25; Q.E. 25.)

Second Test

January 20, 1954, three months after diet was started. (C.A., 151½ weeks; M.A., 34½ weeks; G.Q. 23.)

As before, there was very slight ability to respond or concentrate. Some progress in the total result had been achieved, particularly in the direction of speech (Table IV). The total quotient had risen by three points to 23 and the profile had become more even, the trough at C being very largely corrected.

Some slight progress was recorded in regard to locomotor development. His lower limbs were still feeble and underdeveloped; there was no attempt at crawling. He could lift head and shoulders in the dorsal position, sit alone on the floor, make stepping movements when held up, and almost stand when held. (Q.A. 24.)

He was taking more notice of people, beginning to return affection, and responding more definitely to situations. (Q.B. 23.)

Quite remarkable progress had taken place in the direction of speech. He was now able to shout, make sing-

ing noises, respond and listen to sounds (bell, tuning-fork, stop-watch). He was making more noises but no clear syllables yet. (Q.C. 21.)

There was practically no progress yet in scales D or E. (Q.D. 24, Q.E. 22.)

Third Test

April 7, 1954, six months after diet was begun. (C.A., 162 weeks; M.A., 44½ weeks; G.Q. 28.)

This test indicated definite progress in each of the five scales. The improvement at speech was being maintained and accelerated. Also scales D and E showed definite movement forward (Table IV).

The total quotient had risen by five points, to 28, since the previous test. Considerable progress had been made all round. Manipulation of objects was increasing and becoming more effective.

At this time the child could sit himself up from both prone and dorsal positions, walk round the railings of his cot and playpen holding on, pivot on the floor, and roll over to get about. He was not yet crawling. (Q.A. 29.)

The child was also reacting more normally to the presence of people; he looked at them more definitely and co-operated in activities better. (He gave the impression that he had "become a human being.") (Q.B. 26.)

At speech he was making slow but definite progress. Most significant was the improved capacity to attend to sounds (active listening). (Q.C. 25.)

A gain of as much as six and seven points was recorded in scales D and E respectively. Thumb opposition had become complete. He showed preference for the right hand and was handling toys and materials with more interest and more efficiently. (Q.D. 30; Q.E. 29.)

Fourth Test

August 4, 1954, ten months after diet was begun. (C.A., 179½ weeks; M.A., 53½ weeks; G.Q. 30.)

This test showed quite dramatic progress in this child on scales A, B, and C, but practically no movement on scales D and E, on which he made such remarkable improvement between the second and third tests. This produced again a changing profile (Table IV).

The total quotient had again risen somewhat, though not so much as during the previous period. None the less, the results suggest that further and most important stages had been reached in several directions.

The boy could not only balance on his feet and stand alone but had begun to walk alone. He demonstrated this by taking half a dozen steps between the mother and the psychologist in the ward. This brought him well into the second year for locomotor development. From this time on he no longer sat endlessly in his cot, but was eager to be moving about the room. (Q.A. 33.)

He was much more alert and aware of people. He obeyed simple commands, played pat-a-cake, and tried to "help" with dressing. His facial expression had become quite different, alive, watching people, laughing at the examiner's approach, and wanting to be lifted up. He accepted and returned affection. He helped to hold the cup when drinking, but could not yet manage a spoon to feed himself. (Q.B. 29.)

TABLE IV.—Case 1

Test No.	Chronological Age (Weeks)	Mental Age (Weeks)	General Intelligence Quotient	Subscale A Locomotor		Subscale B Personal-Social		Subscale C Hearing and Speech		Subscale D Hand and Eye		Subscale E Performance	
				Mental Age (Weeks)	Q.A.*	Mental Age (Weeks)	Q.B.*	Mental Age (Weeks)	Q.C.*	Mental Age (Weeks)	Q.D.*	Mental Age (Weeks)	Q.E.*
1	137½	27½	20	28½	21	26½	20	11½	8	35	25	35	25
2	151½	34½	23	36½	24	35	23	31½	21	36½	24	33½	23
3	162	44½	28	46½	29	41½	26	40	25	49	30	47½	29
4	179½	53½	30	59½	33	52½	29	57½	32	49	27	49	27

* Q.A., Q.B., Q.C., Q.D., and Q.E. are the intelligence quotients (subquotients) calculated on subscales A, B, C, D, and E respectively.

Speech showed improvement greater than in any other direction. He could say two clear words and produced much meaningful babble. He tried to sing, knew his own name, and enjoyed and recognized familiar rhymes. (Q.C. 32.)

At the sitting stage he had made a remarkable spurt in scales D and E (between the second and third tests), but now that he was on his feet this new activity claimed his interest, together with his newly found skill at verbal expression. (Q.D. 27; Q.E. 27.)

Case 2

First Test

October 16, 1953, immediately before the diet was started. (C.A., 138½ weeks; M.A., 58½ weeks; G.Q. 42.)

The child was much less severely retarded than Case 1 and was already walking. As with Case 1 this child showed great fatigability and sleepiness.

The results produce an unusual profile (see Table V). The child did best at locomotor development. She was walking alone but with an unusual gait, her feet rather wide apart and swaying from side to side, like a child of 14 to 15 months just learning to walk. (Q.A. 54.)

She showed friendliness and liked attention from adults, but became easily excited when noticed. An affectionate child, she put her face up to her mother, but, like a 12-months-old baby, she was unable to kiss. She could hold a cup for drinking, take off her shoes and socks, etc. She liked her mother to show pictures to her, but was not able to recognize objects in pictures. (Q.B. 49.)

Her level at speech was very low. The mother reported that the child used to say one or two words but had ceased to do so. There was no indication of deafness. She enjoyed rhymes and responded to auditory tests including the voice. (Q.C. 36.)

Her hands were developed only to a 12-months level. She could point with her index finger, and thumb opposition was complete. She held a pencil and made a slight mark with it. (Q.D. 39.)

At performance she did poorly. She could rattle a box and crumple paper, but had no other interest in objects except to carry them to her mouth or send them to the floor. (Q.E. 32.)

Second Test

January 18, 1954, three months after diet was started. (C.A., 152 weeks; M.A., 70½ weeks; G.Q. 46.)

Genuine improvement in the child's condition had taken place since she was first seen. Although progress was slow, it was definite and noticed in all directions. She was more active and alert, and firmer on her feet. The general quotient had risen by four points to 46.

Locomotor development was at this time still somewhat ahead of the other scales. She was trotting about like a child of 18 months, able to climb into chairs and climb up stairs (but not down), and had improved in balance and liked pushing a pram, etc. (Q.A. 52.)

In personal-social development she "showed shoes" on request, pointed out "hair" and "hands," and had begun to use a spoon. Her relationship to people was developing. (Q.B. 47.) Speech, still poor, was developing very slowly. (Q.C. 38.) At manipulation, considerable improvement was

shown. She had learnt to roll and throw a ball, to scribble on paper, and to play a little with toys, pushing cars, etc. (Q.D. 51.) At performance she not only rattled the boxes, but opened them and explored the contents, and did the first two items of the form-board series. (Q.E. 44.)

In this case, as with the first, the profile is seen to change as the child begins to progress and take interest in her surroundings.

Third Test

April 14, 1954, six months after diet was started. (C.A., 164 weeks; M.A., 77 weeks; G.Q. 47.)

The third test showed the child maintaining progress at her new level and developing more in relation to speech, the general quotient remaining approximately the same. The profile has become more even (see Table V).

Only slight progress was made in regard to walking. She was at this stage more competent on stairs and climbing about more. (Q.A. 50.) In social development also there were very few gains, only five weeks' progress being achieved in the three months. (Q.B. 47.) At speech, however, very great progress was made, 16½ weeks' progress being recorded. At this stage she had a vocabulary of about 10 words, clearly and consistently used, and could identify objects by name. (Q.C. 45.)

Only slight progress was recorded on scales D and E. (Q.D. 47; Q.E. 44.)

Fourth Test

July 14, 1954, nine months after dietetic treatment began. (C.A., 177 weeks; M.A., 86½ weeks; G.Q. 49.)

This examination showed the child maintaining the improvement achieved earlier, and the general quotient was again slightly improved (Table V). The general shape of the profile is much as it was in the previous test, and is still fairly even, except that scales A and B still tend to be somewhat higher than the other scales.

The child had ceased to climb stairs on hands and knees and was able to walk up and down holding the banisters. She could run and jump. (Q.A. 53.) She was learning self-help to some extent, could open doors, feed herself with a spoon more competently, and point out three parts of the body. (Q.B. 51.) She had a vocabulary of about 16 words, recognized pictures, and was beginning to name them. (Q.C. 48.) Only slight progress could be reported on scale D. (Q.D. 45.) She showed more definite interest in performance material. She did form-boards and brick boxes to a 20-months level. (Q.E. 48.)

Case 3

This little 5-year-old girl was seen before treatment was started, and given the Griffiths scale. She was seen again after periods of 9 weeks and 21 weeks on the diet. This child being older than either of the other two cases, the severe retardation produces a still lower quotient.

First Test

April 21, 1954. (C.A., 278½ weeks; M.A., 30½ weeks; G.Q. 11.)

When seen in April this child was in most respects like a child of about 7 months' mental development (see Table VI). She was somewhat more advanced than this in locomotor development and less advanced in regard to hearing and speech.

TABLE V.—Case 2

Test No.	Chronological Age (Weeks)	Mental Age (Weeks)	General Intelligence Quotient	Subscale A Locomotor		Subscale B Personal-Social		Subscale C Hearing and Speech		Subscale D Hand and Eye		Subscale E Performance	
				Mental Age (Weeks)	Q.A.*	Mental Age (Weeks)	Q.B.*	Mental Age (Weeks)	Q.C.*	Mental Age (Weeks)	Q.D.*	Mental Age (Weeks)	Q.E.*
1	138½	58½	42	74½	54	68½	49	50	36	54	39	45	32
2	152	70½	46	79½	52	72	47	58	38	77	51	67	44
3	164	77	47	82	50	77	47	74½	45	77	47	72	44
4	177	86½	49	94½	53	89½	51	84½	48	79½	45	84½	48

* Q.A., Q.B., Q.C., Q.D., and Q.E. are the intelligence quotients (subquotients) calculated on subscales A, B, C, D, and E respectively.

The child could sit alone, and sat rocking back and forth in the cot. She twisted her rather thin limbs about in unusual positions. She could roll over and turn around on the floor, but could not crawl. She could not pull herself up to stand, or balance holding on to a support. She could make stepping movements when held in a standing position and encouraged to try to walk (an eighth-months item). (Q.A. 14.)

She appeared indifferent to strangers, but gradually began to co-operate to some extent in the examination. She reacted to her mirror image, smiling and turning the mirror over as if in search of the child in it. She was not yet drinking from a cup but was still on the bottle. (Q.B. 10.)

She could make a few vague noises and blow bubbles like a young baby. She had a vocabulary of four vague sounds (er-er, ah, m-m-m, g-g-g). She listened to the tests with bells, tuning-fork, and voice. (Q.C. 8.)

Manipulation was very poor. She could attend to only one small object at a time. She could not retain two cubes; when offered a second one she invariably dropped the first. She could pass a toy from one hand to the other, and did this continually. Thumb opposition was complete. (Q.D. 11; Q.E. 11.)

Second Test

June 23, 1954, nine weeks after treatment started. (C.A., 287½ weeks; M.A., 40½ weeks; G.Q. 14.)

The child showed marked improvement in appearance. She seemed to be more active mentally, and definitely more able to co-operate. Dropping of saliva had ceased. She looked at the examiner and appeared to remember (see Table VI).

Some slight progress had been made in locomotor development, the child being more active on the floor, rolling, lying, and sitting, frequently changing her position in order to secure toys beyond her reach, but without actually crawling. She could still not pull herself to standing. (Q.A. 15.)

Social progress was quite good. She had learned to drink from a cup instead of the bottle previously used. She turned her head to people talking and took more interest in her surroundings. (Q.B. 13.)

The child was now able to pay better attention to sounds—bells, tuning-fork, watch, etc.—and listened to the voice of the examiner, but the simpler, clearer sounds of the instruments gave definite pleasure. She herself could make many sounds and noises; no definite speech, nor prolonged babble, but crooning, cooing, squeaking noises, much like a young baby makes. She tried to sing. (Q.C. 12.)

On the manipulative scales D and E progress was most pronounced. The right hand had become dominant. She was handling objects more freely, still spending much time passing toys from hand to hand and back again. She accepted the third cube, and watched the scribble but did not handle the pencil. She could take the lids off the test boxes and remove the bricks. She did not understand the first form-board. (Q.D. 15; Q.E. 16.)

Third Test

September 15, 1954, 21 weeks after start of diet. (C.A., 299½ weeks; M.A., 42½ weeks; G.Q. 14.)

The child's reactions during this third test were very similar to those made at the second test. She passed only

six new items. After the rapid progress made between the first and second tests, there was in this second period a slowing up of development. At the same time there was no deterioration. On the contrary, her progress was sufficient to maintain the slightly higher quotient that she showed at the second test. Her progress rate over the entire period of 4½ months was 55.5.

At locomotor development she had gained two points (Q.A. 15). No progress can be reported on scales B (Q.B. 12) or C (Q.C. 12), where her mental ages remained the same; but slight gains were made on scale D, hand and eye development (Q.D. 16) and scale E, performance (Q.E. 16).

[NOTE ADDED DECEMBER 16, 1954.—The three children continue to progress: Case 1, at C.A. 44½ months, had M.A. 14 months, G.Q. 31, and no epileptic activity; while Case 2, at C.A. 191 weeks, had M.A. 100 weeks, and G.Q. 52.]

Chemical Investigations

In each case at least one 24-hour specimen of urine and a corresponding specimen of blood were obtained before starting the diet. Once the child was placed on the diet single specimens of urine were obtained daily until it went home, in addition to one or more complete 24-hour specimens of urine and corresponding blood specimens once the diet was stabilized. At home the parents collected single specimens of urine at weekly intervals and sent them, preserved with chlorbutol and acetic acid, to the laboratory. Every three months, when the child returned for an intelligence test, a complete 24-hour urine specimen and a specimen of blood were obtained.

The blood specimens and the 24-hour urine specimens were examined by paper chromatography for amino-acids (Woolf, 1951b). In addition there was determined, on the 24-hour specimens of urine, phenylpyruvic acid (Berry and Woolf, 1952), phenylacetylglutamine (Woolf, 1951a), and phenylalanine and phenyllactic acid (Kapeller-Adler, 1932; Woolf, unpublished). The daily or weekly single specimens of urine were used for a qualitative ferric chloride test for phenylpyruvic acid.

In Cases 1 and 2 phenylpyruvic acid could no longer be detected in the urine by the tenth day after starting a completely phenylalanine-free diet. Then 8 oz. (230 ml.) of milk was added daily for nineteen days; no phenylpyruvic acid could be detected in the urine either by the direct ferric chloride test or by the far more sensitive method of Berry and Woolf (1952). The milk was increased to 10 oz. (285 ml.) daily, phenylpyruvic acid remaining undetectable in the urine for 28 days, when it became just detectable by the direct ferric chloride method. The milk was then dropped to 8 oz. (230 ml.) daily and kept there, no more phenylpyruvic acid appearing in Case 2. In Case 1 occasional weak positive reactions and, later, strong ones were obtained from urine specimens sent from his home. The mother admitted that he had occasionally been fed food not included in the diet.

On the diet phenylalanine quickly dropped to a low level in both blood and urine, but remained a little above the normal; phenyllactic acid, and the unidentified phenolic keto-acid (Berry and Woolf, 1952) vanished, and phenylacetylglutamine dropped to the normal level.

TABLE VI.—Case 3

Test No.	Chronological Age (Weeks)	Mental Age (Weeks)	General Intelligence Quotient	Subscale A Locomotor		Subscale B Personal-Social		Subscale C Hearing and Speech		Subscale D Hand and Eye		Subscale E Performance	
				Mental Age (Weeks)	Q.A.*	Mental Age (Weeks)	Q.B.*	Mental Age (Weeks)	Q.C.*	Mental Age (Weeks)	Q.D.*	Mental Age (Weeks)	Q.E.*
1	278½	30½	11	40	14	28½	10	23½	8	31½	11	30	11
2	287½	40½	14	41½	15	36½	13	36	12	42½	15	45	16
3	299½	42½	14	45	15	36½	12	36	12	47½	16	46½	16

* Q.A., Q.B., Q.C. Q.D., and Q.E. are the intelligence quotients (sub-quotients) calculated on subscales A, B, C, D, and E respectively.

In Case 3 the withdrawal of phenylalanine from the diet produced more dramatic results, all phenylpyruvic acid vanishing from the urine by the third day. Milk (10 oz. (285 ml.) daily) was added to her diet on the fourth day, but phenylpyruvic acid did not reappear in the urine. The blood phenylalanine level dropped to normal by the third day after withdrawal of phenylalanine and continued to drop, being below normal by the eighteenth day and completely absent on the twenty-eighth day, in spite of the presence of phenylalanine in the diet; later the phenylalanine levels in blood and urine returned to normal. Phenyl-lactic acid, phenylacetylglutamine, and the phenolic keto-acid had dropped to normal levels by the tenth day after starting the diet.

Discussion

The results of the psychological testing prove conclusively that there is at least in some cases considerable intellectual improvement in phenylketonurics fed a diet low in phenylalanine. The increase in the general intelligence quotient, from 20 to 30, in ten months in Case 1 is highly significant, as is that in Case 2 (from 42 to 49 in nine months). It is extremely unlikely that such an improvement, as indicated by mental testing, would ever occur spontaneously in children with phenylketonuria. The changes in these two children have been dramatic. The boy (Case 1) lay inert, sleepy, unaware of much that was going on around him and subject to frequent slight epileptic attacks. Unable to do more than sit among pillows, and endlessly finger-fanning or twisting his limbs about, with eyes half-closed, unable to roll over or sit himself up, with no speech other than the murmured vocalization of a very young baby, his general level was that of a child of 6 months. After ten months of treatment he is upon his feet, walking, has begun to talk, and is developing in all directions. This development goes forward irregularly, swinging now in one direction and now in another, but the total quotient shows the degree of mental growth that is definitely taking place. The girl (Case 2), not quite so severely handicapped, just beginning to walk when treatment was started, and without speech other than a few babbled phrases, is now able to run about more normally and has a small vocabulary of clearly spoken words, and has also developed socially.

Mental age plotted against chronological age for Cases 1 (J. J.) and 2 (G. W.). For discussion see text. (O) = Result of test on the Griffiths scale. ↑ = Point at which diet was started.

This improvement could result only if the mental deficiency were due to an intoxication by phenylalanine or one of its metabolites; there is evidence that the toxic agent is not phenylalanine itself (Woolf and Vulliamy, 1951), but more work is needed to prove its identity.

The concept of progress rate is particularly useful in evaluating the results of the diet. The progress rate is the increase in mental age divided by the increase in chronological age between tests multiplied by 100. Thus over a period of 43 weeks the mental age of Case 1 increased from 27½ weeks to 53½ weeks; his progress rate over the period is $\frac{53\frac{1}{2} - 27\frac{1}{2}}{43} \times 100 = 60$. The progress rate can be defined as the slope of the curve of mental age plotted against chronological age and multiplied by 100 (see Chart). In the majority of children in whom the quotient is constant, the

progress rate is equal to the I.Q. and does not vary with time. An increase in progress rate to a new steady level indicates a mind that has improved and is maintaining its improvement. In such a case the new progress rate will be higher than the intelligence quotient, which will steadily rise. The I.Q., being a ratio, is always affected by the magnitude of the chronological age at the beginning of treatment.

The notation of the infinitesimal calculus can be used with advantage; if M represents the mental age, Q the intelligence quotient, t the chronological age, and R the progress rate,

$$\text{then } Q/100 = M/t$$

$$\text{and } R/100 = dM/dt;$$

$$\text{therefore } M = 1/100 \int_0^t R \cdot dt$$

$$\text{and } Q = 1/t \int_0^t R \cdot dt.$$

$$\text{If } dR/dt = 0, \text{ then } Q = R.$$

If, at a chronological age t_1 , the progress rate changes from R_1 to R_2 , and these are constant from birth to t_1 and from t_1 to t_2 respectively, then, at the age of t_2 ,

$$Q = 100.M/t_2 = 1/t_2 \left(\int_0^{t_1} R_1 \cdot dt + \int_{t_1}^{t_2} R_2 \cdot dt \right)$$

$$\text{Therefore } Q = 1/t_2 (R_1 t_1 + R_2 (t_2 - t_1))$$

In the Chart the mental ages of Cases 1 and 2 are plotted against chronological age. It is assumed that the progress rate was steady from birth (when the mental age was presumably zero, these children being normal at birth) to the time of withdrawing phenylalanine from the diet immediately after the first psychological test; it is not unlikely that the curve should be convex to the abscissa over this period—that is, decreasing progress rate—but we have no evidence in these or other cases that it should be concave or irregular. The three determinations of mental age after starting the diet in each case clearly lie on a new straight line of slope—that is, progress rate—considerably greater than that before the diet. The kink in each curve is sharp and would be even sharper if the curve before starting the diet were convex to the abscissa; it occurs at the time of starting the diet. From the curves the progress rate in Case 1 has increased from the assumed consistent value of 20 to 64, and in Case 2 from 42 to 76. The actual ratio between the total increase of mental and chronological age between the first and the fourth test gives a progress rate of 60 in Case 1 and 71 in Case 2.

The intellectual improvement has been maintained at a fairly steady rate over nine and ten months respectively and is therefore not a matter of a sudden spurt followed by a return to the previous rate. This sudden jump in progress rate to a high but fairly steady level and the consequent steady improvement in the intelligence level is just what would be expected if the brain were continuously under the action of a depressant that did not cause any irreversible damage to the brain tissue. It must be remembered that post-mortem examinations have failed to show any consistent changes in the brains of phenylketonurics (Corseilis, 1953).

In Case 3, though the result can only be regarded as preliminary, the initial improvement in progress rate, even though this dropped again, is so striking that it strongly suggests that even at the age of 5 years the brain has suffered relatively little permanent damage. The appearance, for the first time, of major epilepsy soon after this child was placed on the diet is unlikely to be due to coincidence. A possible explanation is that the cerebral cortex, for over five years under the action of a depressant, began functioning more actively once this agent was withdrawn, and at first cortical activity was poorly co-ordinated. This child is of interest for another reason: she shows clear evidence of a deterioration in intelligence before being placed on the diet. When first seen she was 15 months old and had an estimated mental age between 6 and 9 months (Woolf and

Vulliamy, 1951, Case 5), and her mental age was assessed at 8 months when she was 18 months old. Her mental age had not increased when seen at the age of 5 years 5 months, and her I.Q. has therefore dropped very considerably.

Petit mal is far more frequent among phenylketonurics than among the population as a whole, and an association of petit mal with phenylketonuria is generally accepted. The cessation of attacks of petit mal (formerly very frequent) in Case 1 and the change of the E.E.G. from a typical spike-and-wave pattern to a normal pattern when placed on a diet low in phenylalanine is particularly interesting; it suggests that the petit mal is due to the same intoxication as the mental deficiency and, like it, yields to withdrawal of the toxic agent.

In Case 1 the diet was not very strictly adhered to at home, particularly from the sixth to the tenth month. It seems probable that the reversion of the E.E.G. from normal to a rather improved epileptic pattern, and the decrease in the progress rate over this period, are associated with these dietary indiscretions.

The profile varies in an interesting way from test to test and from child to child. It is as though the small amount of mental energy available to these children becomes, at a particular stage, almost completely absorbed in one dominant phase of development.

The prognosis for these three children can be made only tentatively. If the intoxication theory is correct the improved progress rate may be maintained. The I.Q. at the age of 14 would then be about 70 for Case 2, and about 60 for Case 1. Either of these children may eventually reach an educable level. It may be possible to improve the diet in such a way as to raise the progress rate still further. However, the present progress rate, being below 100, may possibly indicate true, though relatively slight, long-term damage to the functioning of the brain. Only repeated psychological testing throughout childhood can settle this point.

The difference in final I.Q. tentatively predicted for the two children is the result of their differing progress rates, and their different mental and chronological ages when placed on the diet. These differences are in themselves interesting; presumably the children, had they not had this error of metabolism, would have had differences in innate intelligence—that is, different progress rates; the differences in mental age are, however, far greater than those to be expected for individuals chosen at random, and it is necessary to postulate a difference in degree of intoxication, whether due to differing concentrations of the toxic agent or to differing susceptibilities.

The difference between the mental and the chronological age at the time treatment is started is a "time lag" that may never be made good. The child who at 5 years has the mental age of a 7-months-old infant has to learn to babble and then to speak, to crawl, and then to walk, omitting nothing of the developmental sequences before babyhood is passed. Even if, as the result of treatment, his progress rate became 100 at this age, this would enable him to make the same amount of progress in a year as would be made by a normal baby between 7 and 19 months of age. Then at 7 years his mental age would still be only $2\frac{1}{2}$; only at $9\frac{1}{2}$ would he reach a mental age of 5 years and be ready to start formal education, and then he would presumably progress at the normal rate for a 5-year-old. This raises special educational problems, such a child being clearly distinguished on the one hand from children of similarly low intelligence whose progress rate is constant and as low as their I.Q., and on the other from normal children. His educability should not be judged on the basis of his I.Q. but on his progress rate, starting formal education at a mental age of 5 years so far as administrative difficulties allow. Of course the progress rate of Case 1 is only 64, and that of Case 2 76, but their educability should have been more accurately assessed by the time these children reach a mental age of 5 years. It is, at present, useless to speculate

on the mechanism of learning for a brain structurally more mature than one corresponding to its mental age, or on the more distant problem of the age at which increase in mental age will cease.

Presumably the improvement in intelligence in these patients can be maintained only while a diet low in phenylalanine is adhered to, and any return to a normal diet would be likely to lead to re-intoxication. The economic aspects of this form of "treatment" must be considered. It has been estimated that the incidence of phenylketonuric amentia is about 4 for every 100,000 of the population. This gives a figure of about 1,600 patients for England and Wales—and without treatment most of these will eventually reach an institution, where the cost each week is said to average at least £5. The special dietary constituents—casein hydrolysate, tryptophan, tyrosine, the vitamin tablets (made in the pharmacy of The Hospital for Sick Children), the liver extract and choline (see Tables I and II)—cost 10s. 9d. a day at present prices. If all the phenylketonuric aments came under "treatment" and some form of central manufacture of the special diet ingredients could be organized, the cost would fall considerably.* The grades of many of these patients might be raised so that the ineducable become educationally subnormal and the E.S.N. group might get accepted at ordinary schools, thus saving the cost of institutional care. Later on, society may gain productive members. These financial considerations must, however, not be allowed to influence decisions on the treatment of afflicted individuals. The most important point is that if costly treatment is to be justified it must be started early. *This means that the urine of every baby or young child in whom there is the slightest suspicion of mental retardation must be tested for phenylpyruvic acid.* This is an extremely easy screening method: a few drops of 5% ferric chloride solution are added to the fresh urine; the appearance of a deep green colour (sometimes an opaque deep blue-grey owing to precipitated phosphates) within five minutes is a positive result. In phenylketonuric aments the test should be positive by the age of 3 weeks at latest.

The Diet

The diet has to supply adequate amounts of total nitrogen, the essential amino-acids, carbohydrates, fats, minerals, and vitamins. The bulk of the nitrogen is supplied as the charcoal-treated casein acid hydrolysate (hereafter called casein hydrolysate) now commercially available as a dry powder. Casein is a protein of quite high biological value—that is, it contains adequate amounts of all the essential amino-acids; an acid hydrolysate, unlike an enzymatic hydrolysate, is free from peptides which might complicate the removal of phenylalanine. L-Tyrosine and DL-tryptophan are added to the casein hydrolysate; L-tyrosine is not normally an essential amino-acid, but, since in phenylketonuria phenylalanine cannot, or can only very slowly, be converted to tyrosine (Jervis, 1947, 1953; Udenfriend and Bessman, 1953), tyrosine should be an essential amino-acid in phenylketonuria. DL-Tryptophan is harmless, has about 70% of the dietary value of L-tryptophan, and costs only one-tenth as much.

Phenylalanine is an essential amino-acid, the minimum requirement for a normal adult being 1.4 g. a day (Harte and Travers, 1947). A diet containing less than this causes a negative nitrogen balance, loss of appetite, and rapid loss of weight. The minimum daily requirement of phenylalanine for a young child is unknown. Phenylalanine is very rapidly converted to tyrosine in normal individuals (Woolf and Edmunds, 1950), but since this metabolic path is closed in phenylketonuria, less dietary phenylalanine should be required for anabolism by a phenylketonuric than by a normal person. The success of the diet depends wholly on this point; in effect an "unbalanced protein" with a deficiency of phenylalanine is being fed, and in a normal

* Reductions in the prices of the casein hydrolysate and of the other amino-acids had reduced the daily cost to 7s. 4d. at the time when proofs of this article were received.

individual this would result in reduced protein utilization and excessive nitrogen excretion, but the dietary amino-acids are balanced for a phenylketonuric. It follows that the best daily intake of phenylalanine in our cases could only be determined empirically. Phenylalanine is added in the form of whole milk, which contains 42 mg. of phenylalanine per oz. (1.35 mg. per g.) (Block and Bolling, 1951).

Since the diet is almost entirely synthetic, it seemed advisable to feed a salt mixture (similar to that fed by Rose, Johnson, and Haines, 1950), a comprehensive selection of vitamins as well as a liver extract, and arachis oil to supply arachidonic acid. *p*-Aminobenzoic acid was originally included in the vitamin mixture, but later excluded on the grounds that there was no proof that it played any part in human nutrition, and it might, at some future date, have complicated the sulphonamide treatment of an acquired infection. Tomato purée and agar-agar (to supply "bulk") were at one stage included in the diet, but they appeared to have no beneficial effect.

The mental ages of all three children being initially below 1 year, the diet was fed in the form of a soup. As their mental ages increased some of the starch, sugar, and fat was presented as biscuits or bread. Our latest patient (not included in this paper), with a mental age of over 2 years, has potatoes, carrots, and cabbage with, instead of the soup, a thick gravy flavoured with tomato purée; the phenylalanine in the vegetables is allowed for by reducing the amount of milk, which she has separately with a breakfast cereal; she eats fruit, jam tarts, and bread with butter and honey (both made with protein-free wheat starch), and even an egg may be allowed occasionally if the amount of other protein is correspondingly reduced.

The amount fed was varied with age according to the accepted desirable intakes of calories and protein nitrogen.

A careful watch was kept for any signs of incompleteness of the diet. While the children were in hospital they were weighed daily and their appetites watched. Their blood haemoglobin content and erythrocyte count were determined fairly often. Only when it was considered that they were thriving satisfactorily on the diet were they sent home, and they returned for examination at intervals. The weight loss while on a diet completely free from phenylalanine was expected; once phenylalanine was added to the diet (as milk) the children started gaining weight satisfactorily and their blood haemoglobin levels remained normal. It appears that the diet is adequate in all respects for normal health and development.

Choice of Subjects

Two factors suggested that children should be as young as possible when placed on the diet low in phenylalanine: (a) if the mental deficiency is due to an intoxication starting in the neonatal period and continuing throughout life, the brain may possibly become permanently damaged by prolonged exposure to the toxic agent; and (b) removal of the intoxicant would probably result, at best, in a child with the ability to learn and the intellectual content of a normal infant of the same mental age. There are, however, considerable difficulties in detecting mental retardation in the very young. It is worth emphasizing again that in every instance of mental retardation the urine should be tested for phenylpyruvic acid.

It may be argued that if a patient of initially relatively high level of intelligence is chosen, a socially useful person is more likely to result. On the other hand, a patient of initially low level would be expected to show a more clear-cut and dramatic effect. In practice, however, the number of children under 3 years of age in whom phenylketonuria is diagnosed is so small that there is little opportunity for choosing them on other grounds.

Where experimental therapy is prolonged, as in this case, the child will, in general, have to be treated at home. The parents must be able and willing to feed the child this rather complicated diet, and in accepting a child for treatment this had to be taken into account.

Summary

An economically practicable diet low in phenylalanine has been devised.

Three phenylketonurics (two idiots and one imbecile) have been fed this diet for four and a half to ten months. Their mental ages have been measured before and at intervals after starting the diet.

The rate of increase of mental age of all three rose markedly on the diet, their I.Q.s have risen, and they may reach educable levels.

One child ceased having attacks of petit mal and his E.E.G. became normal soon after starting the diet.

The other child with petit mal developed major epilepsy and status epilepticus on the diet, but later improved.

Otherwise normal physical health and growth were maintained.

It is concluded that the mental deficiency in phenylketonuria is due to intoxication by phenylalanine or one of its metabolites and can be relieved by decreasing the dietary content of phenylalanine. The petit mal may also be due to this intoxication.

We wish to thank Dr. P. R. Evans for permission to quote Case 3; Miss Dilliston for working out details of the diets; Dr. W. W. Payne, Mr. Rae, and Mr. Philips for helpful discussions; Mrs. S. Zisman and Mr. A. Jarrett for technical assistance with the laboratory investigations; Dr. D. A. Pond and Dr. C. C. Evans for the E.E.G. reports; the nursing staff for their intelligent co-operation; and the Research Committee of The Hospital for Sick Children for financial support.

REFERENCES

- Berry, J. P., and Woolf, L. I. (1952). *Nature (Lond.)*, **169**, 202.
 Bickel, H., Gerrard, J., and Hickmans, E. M. (1953). *Lancet*, **2**, 812.
 Block, R. J., and Bolling, D. (1951). *The Amino-acid Composition of Proteins and Foods*, 2nd ed. Thomas, Springfield, Illinois.
 Corsellis, J. A. H. (1953). *J. Neurol. Neurosurg. Psychiat.*, **16**, 139.
 Griffiths, R. (1954). *The Abilities of Babies*. Univ. of London Press, London.
 Harte, R. A., and Travers, J. J. (1947). *Science*, **105**, 15.
 Jervis, G. A. (1947). *J. biol. Chem.*, **169**, 651.
 — (1953). *Proc. Soc. exp. Biol. (N.Y.)*, **82**, 514.
 Kapeller-Adler, R. (1932). *Biochem. Z.*, **252**, 185.
 Rose, W. C., Johnson, J. E., and Haines, W. J. (1950). *J. biol. Chem.*, **182**, 541.
 Schramm, G., and Primosigh, J. (1943). *Ber. dtsh. chem. Ges.*, **76**, 373.
 Udenfriend, S., and Besman, S. P. (1953). *J. biol. Chem.*, **203**, 961.
 Woolf, L. I. (1951a). *Biochem. J.*, **49**, ix.
 — (1951b). *Gt Ormond St J.*, **1**, 61.
 — and Edmunds, M. B. (1950). *Biochem. J.*, **47**, 630.
 — and Vulliamy, D. G. (1951). *Arch. Dis. Childh.*, **26**, 487.

Delivering the Florence Blair Memorial Lecture before the Liverpool Medical Institution on December 1, 1954, Sir CHARLES DODDS, F.R.S., spoke on two human menaces— infection and cancer. After briefly reviewing current theories on cancer, Sir Charles turned to the question of infection, a hundred years ago a scourge of equal mystery and seriousness to cancer. He wondered whether a lesson could be learnt from that study. The problem of infection had been solved by Pasteur's realization that the question of spontaneous generation must be settled finally before a real advance in biology could take place. It was his demonstration that the development in broths, etc., of living creatures was due not to their spontaneous generation but to their introduction from outside. This fact, that the air contained living organisms, was the basis of Lister's work which indicated clearly that infection of wounds came from outside. It might well be, Sir Charles continued, that a solution of the cancer problem would come from the application of some principle discovered as a result of general research. Also the possibility of what might be termed "a piece of luck" should not be entirely lost sight of.