Studies on Phenylketonuria

IX. FURTHER OBSERVATIONS ON THE EFFECT OF PHENYLALANINE-RESTRICTED DIET ON PATIENTS WITH PHENYLKETONURIA

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Recently there have been reports from several laboratories concerning the effects obtained by administering phenylalanine-restricted diets to patients with phenylketonuria.1–4 This type of regimen has been found to correct the major biochemical abnormalities which are present in phenylketonuria. In addition it has been apparent that improvement has occurred in the clinical condition of some, though not all, of the patients who have been studied. The purpose of the present publication is to present follow-up studies on patients reported previously,2 to record observations on new patients, and to discuss the observations with regard to the possible manner of development of the mental and neurological impairment present in phenylketonuria.

Dietary Management

For the clinical studies subsequent to those previously reported,2 a properly supplemented phenylalanine-deficient casein hydrolysate has been used, rather than a mixture of pure amino acids. The major differences between the composition of the amino acid mixture3 and the supplemented casein hydrolysate are that in the latter there are: (1) the presence of a relatively lower amount of aspartic acid (rather than asparagine), (2) the presence of proline and serine, (3) altered relative levels of many amino acids, and (4) the inclusion of both DL-tryptophan and L-tyrosine at considerably higher levels. The basal mix prepared from the supplemented casein hydrolysate contained appropriate minerals, but no water-soluble vitamins; these were administered daily in the form of commercial preparations. Proportions of amino acids, carbohydrates, fat and total calories were adjusted as described earlier.3

Nutritional difficulties which arise from continued use of the synthetic diet were minimized by allowing higher blood levels of phenylalanine than were maintained during the previous study. After the initial depletion period, an estimated 25 mg of phenylalanine per kg body weight per day in the form of natural protein has been found to result in a serum phenylalanine level of 4 to 8 mg per 100 ml for most cases.4 This level of phenylalanine is well below that which leads to the formation of phenylpyruvic acid in amounts large enough to be detected in the urine.5 Since the earlier detailed studies had demonstrated that it is possible to maintain low blood phenylalanine levels and to eliminate the abnormal urinary metabolites, frequent analytic data were not obtained with the present cases. After the appropriate intake of natural protein had been established with each patient, measurements of blood phenylalanine levels were made at intervals of a month or longer. Further and

* It should be noted that the modification of the method of Kapeller-Adler used in this laboratory4 does not give accurate values. The same reproducible procedure has been used throughout this work, however, and the values are consistent.
more detailed information on the dietary management of patients will be reported elsewhere.

**CLINICAL PROCEDURES**

In general pediatric observations, the patients were found to demonstrate essentially normal somatic growth and gross bodily proportions, aside from relative microcrania in one infant, and occasional distortions of head and trunk which probably had resulted from general bodily immobility. The skin was found to be soft and the subcutaneous lax. A chronic, superficial inflammatory reaction demonstrated by erythema and fine scaling was apparent in some children. This inflammatory reaction was increased in areas of abrasion, such as the cheeks, and in areas of chemical irritation, as under the diaper. Plethora of palms and soles was of normal distribution but diminished in degree. There was commonly a fine vascular motting of the skin of the trunk and extremities. No abnormality of nasal, oral, or pharyngeal mucosae was seen. The skin and subcutaneous of the trunk and limbs were readily penetrated by a Number 22 or 24 needle and the limb veins tore easily incident to venipuncture, so that ecchymosis occurred commonly. The musculature was diminished in mass, soft and lax, and articular support was generally deficient.

For an evaluation of the initial neurologic effects of dietary therapy on these subjects, observations of their seizure disorder were of special importance. In addition, their duration of attention, irritability, or calmness under stimulation, and their effective response were found to be useful criteria. For the periodic observations made during prolonged dietary therapy, particular increments of achievement were noted and the general developmental level was estimated.

The seizure disorder of the infant subjects was manifested most commonly by the comparatively subtle clinical phenomena of lapses and brief jerks, variably distributed in the trunk and extremities, which have been termed "infantile spasms." This form of seizure disorder, which is commonly overlooked clinically, is found not infrequently in infants and small children who suffer diffuse neurologic impairment. It is associated characteristically with hypsarhythmia, as described by Gibbs et al., in the electroencephalogram. The frequent occurrence of seizures in phenylketonuria, particularly in infants, has been pointed out previously by Ford and by Low et al.

**PATIENT DATA**

**F. D. (Case 1, Case 6.** (Born Nov. 13, 1947.) This was the case of a red-haired, blue-eyed girl who was able to sit without support at one year and started walking at two years. She is said to have used a few words at one year but to have lost that ability during her second year. At age four and one-half years she was given a phenylalanine-restricted diet for 12 weeks. After a seeming initial improvement in attention span, she regressed to the same level of behavior and activity after three months as before treatment was started. During that period, however, her eczema disappeared. When her diet was discontinued, the eczema recurred but no other striking changes were observed. She was admitted to the Utah State Training School in 1956. At the present time she is a stout girl who has mild eczema in the flexor areas and at the ankles. She walks with poor balance and a wide-based gait. She can repeat a few single words in a parrot-like fashion. She is still very distractible and spends much of her time sitting on the floor, grinning or shouting. In general, she appears to have progressed at a consistently slow rate after the first year or two of life. The degree of retardation did not appear to be so severe during the first year.

**A. Du. (Case 2, Case D.** (Born July 8, 1948.) This boy apparently developed normally for the first five months of life; regression of performance became apparent after an ear infection at that age. When seven months old he began to have frequent seizures. He continued to have a severe seizure disorder and made little neurologic progress. At the age of 48 months he showed increased muscular tone and his tendon reflexes were hyperactive and equal; he did not have eczema. He paid no attention to persons or objects, and was not able to sit up. Phenylalanine-restriction was then commenced. While he was receiving the diet, and with no anticonvulsant medication, his seizures stopped; phenobarbital had not controlled them previously. His EEG became normal and remained so for some time after the diet was discontinued. His seizures have not recurred although the EEG again showed seizure discharges. The restricted diet diminished his tremor when excited, improved his neurologic abnormalities, and improved his attention span.

During the succeeding four years he has continued to develop at an extremely slow rate. Now, at the age of eight and one-half years, he has begun to pull himself into a standing position in his crib. He still shows no affective response to persons and no interest in objects. He spends most of his time in bed in grotesque positions, chewing, biting, and drooling.
J. Du. (Case 3, Case C.) (Born July 3, 1951.) This child, a sister of A. Du, developed eczema at the age of five months which is still present at five and one-half years of age. She sat without support when six months old, pulled herself to standing when 10 months old, and walked with slight support at the age of one year. A marked tremor was apparent before she was one year old, particularly when she was excited or tired. She was maintained on a phenylalanine-restricted regimen from the age 13 to 23 months. During this 10-month period she appeared to develop at a fairly normal rate. Her eczema was absent during that period. Her tremors diminished. At the age of 23 months psychometric evaluation (Kuhlman test) indicated a mental age of 18 months (I. Q. 78). For a few months after treatment was discontinued she seemed to maintain her abilities, but after 14 months she was estimated to have gained only five months of mental age (I. Q. 67); in retrospect, it was suggested that the testing circumstances had not been favorable. When 47 months old she was estimated by the same psychologist, this time with the Stanford-Binet test, to perform at a 38-month level (I. Q. 83).

In February 1957 (age five years, seven months), the child was re-examined. Her speech was somewhat infantile, although her vocabulary corresponded to her chronologic age. She dressed herself completely, except for tying her shoes and tying a bow on the back of her dress. Psychologic evaluation showed her to have a development quotient of 97. Although she could draw pictures and geometric patterns spontaneously on the five to six year level, she was unable to copy the same patterns when presented with a sample. No tremors were observed on that visit.

The only EEG recorded, when patient was three years of age, showed a few parietal and occipital spikes.

This child suffered less neurologic damage at an early age than did the other patients in this series. There was no evidence of deterioration after the first two years of life, but rather an apparent increase in intellectual ability, as indicated by psychometric evaluation.

M. J. (Case 4, Case A.) (Born August 9, 1953.) This girl was first seen at the age of nine and one-half months. She had been hospitalized at the Colorado General Hospital when approximately three months of age because of a severe acute illness with pneumonia, diarrhea, dehydration, and acidosis. At that time she had been observed to be neurologically prostrated and had had a prolonged left-sided convulsion. Her cerebrospinal fluid protein at the time of acute illness varied from 96 to 136 mg/100 ml. Her cranial circumference at five months of age was 34.5 cm. A psychologic evaluation at that time estimated her motor development to be at the 12-week level, and her language-social functioning at the four-week level. The infant was maintained in the Metabolic Ward, Salt Lake County General Hospital, for approximately ten months, beginning at nine and one-half months of age. At admission she was small, with a cranial circumference of 39 cm. She was pale, blond, had lax skin, and generally poor muscle tone.

The infant had numerous infantile spasms consisting of abrupt, single jerks of varied distribution within trunk or extremities. Her orientation to personal and object environment was insignificant. Motions of neck, trunk, face, tongue, and extremities were random in character and commonly repetitive. Limb motions were undirected and ineffectual except for the performance of repetitive clenches of fists. The general level of orientation of the infant was equivalent to that of two to three months of normal schedule of development, though in a distorted pattern. Eye coordination was essentially binocular. Posture of head upon shoulder was poor. Biceps and triceps reflexes were normal and symmetrical. Patellar reflexes were increased without elicitation of clonus. The plantar reflexes were in extensor pattern. Suckle and swallow were accomplished in normal fashion, and there was no pharyngeal pool. An EEG obtained at this time demonstrated continuous hypsarhythmia.

The infantile spasms became progressively less evident, and she became more active and vigorous after initiation of the phenylalanine-restricted diet. She responded to attention and demonstrated an elementary smile. After three weeks she reached for objects and minimal posture was developed in the neck and upper trunk. She showed increasing visual attention and would follow objects carried into the superior visual field. With acquisition of visual attention a convergent strabismus was noted for the first time. The plantar reflexes became asymmetrical three weeks after the diet was initiated, the left converting to flexor and the right persisting in extensor pattern.

As reported heretofore, the infant's accelerated progress continued during the first three months of phenylalanine restriction. In the following weeks, however, it became apparent that this rate of development was not being maintained. She remained consistently free of outward signs of seizures and her EEG was improved, but it continued to show intermittent hypsarhythmia. After five months she showed questionable recognition of a ward aide who gave her much attention. Her responsive smile continued to be vague, and was supplemented with minimal simple phonations which were similar to those she uttered spontaneously when alone. She began to show visual awareness of objects and occasionally studied her hands. She would grasp objects and hold them in an unpurposive manner before discarding them. At this time she was able to raise herself from supporting surface on hand and pelvis and could sit with support. Startle reactions continued to be marked and the infant would assume an opisthotonic position on abrupt stimulation. Patellar reflexes continued to be maximal and occasionally a brief clonus was elicitable.

Since it became apparent that this infant was not showing the sustained progress that R. Du. maintained, and that she probably had suffered extensive irreversible damage, the effect of restoring her previous high blood phenylalanine level was tested. At the age of 15 months, after five months of phenylalanine restric-
tion, an EEG was made while patient was sleeping and while awake, 4 g of L-phenylalanine was given to her via stomach tube, and the EEG was recorded for the ensuing four hours. Her serum phenylalanine level was 7 mg/100 ml just prior to administration of the phenylalanine and 63 mg/100 ml 90 minutes after it was given. No significant change in the EEG was noted during the entire period nor the following day. For the next six weeks 2.4 g of L-phenylalanine was added to her diet daily. Her fasting serum phenylalanine level was 61 mg/100 ml. At the end of this time no striking deterioration had occurred, but she had lost some of her previous attainments; i.e., no longer attempted to stand on her head or sit up, seemed crosser and less alert, and demonstrated some tremulousness of her hands.

Her daily intake of L-phenylalanine was then increased to 5 g; this led to a serum phenylalanine level of 80 mg/100 ml. With this higher intake of phenylalanine her condition worsened rapidly. After five weeks she was very pale, lay immobile and almost comatose, with neck and trunk stiff, and with motion, when undisturbed, limited to arms and hands. Her EEG became markedly worse, but outward signs of seizure did not reappear.

Phenylalanine was again withdrawn from the child's diet at the age of 17 months; in 2 weeks the serum phenylalanine decreased from 80 to 2 mg/100 ml. She recovered very rapidly from the deteriorated condition, and within ten days appeared to be as alert and to have as many capabilities as at 14 months, when phenylalanine had been restored to her diet. She was maintained on a phenylalanine-restricted diet for the following three months in Salt Lake City and in Denver, Colorado. Little further change in her condition was observed during this time, and the restricted regimen was discontinued.

The patient was lost to follow up for 18 months, but then had a psychologic evaluation at the University of Colorado Medical Center in September 1956, at the age of 37 months. At that time she functioned at an eight to nine month level in all four areas of development according to the Gesell Scale. She was able to sit up but made no attempt to support herself when put into a standing position. She showed no interest in people; she could hold her bottle and feed herself crackers. According to her mother, she could say "mama" and "dada." Her fasting serum phenylalanine level at that time was 50 mg/100 ml.

This child had suffered extensive brain damage before dietary treatment was initiated. This severe neurologic involvement was evidenced by microcere, convulsions, and elevated cerebrospinal fluid protein. Whether this initial disease was related to phenylketonuria or not is not clear, but it limited any possible improvement that could be obtained on the phenylalanine-restricted regimen.

R. Du. (Case 5, Case B.) (Born Sept. 12, 1953). A brother of A. Du and J. Du, the development of this boy for the first seven months of life was considered essentially normal with good quality of alertness interpersonal recognition and discrimination, appropriate phonation, intra-oral manipulation, reach, grasp, and posture. The first evidences of simple tonic seizures were detected incident to an illness in the seventh month. These progressed within a few days to repetitive grand mal episodes. There was coincident indolence, diminution in interpersonal recognition and response, and loss of motor achievement. An EEG at that time demonstrated continuous hypsarrhythmia (Fig. 2). A phenylalanine-restricted diet was initiated at seven and one-half months of age. The minor motor seizure phenomena became less frequent, but typical major grand mal pattern appeared; these major seizures occurred approximately three to five per day the first week following initiation of diet and subsequently diminished progressively to termination within three weeks. Coincident with this change in seizure pattern the boy became more alert and calm and graduated more stably into and from sleep. At the end of one month the first evidences of return of affection response appeared. Gross motor achievement progressed rapidly from his immediate pretherapy status of comparative neurologic failure. Within three weeks of initiation of the diet he sat with support of his hands and attempted to crawl; coincidentally, muscular tightness observed in the neck and trunk were relieved without other therapy. Binocular following of large test object increased in range to far lateralward gaze toward either side. Motions of extremities retained an abnormal abrupt and irregular quality. The EEG improved steadily and after five weeks showed no signs of abnormality (Fig. 3).

Because of the striking improvement in seizure disorder and EEG, the effect on the EEG of restoring a high blood level of phenylalanine was tested. A control EEG was recorded, 6 g of L-phenylalanine was administered by stomach tube, and the record was continued for four hours. Serum phenylalanine level was 2 mg/100 ml before, and 88 mg/100 ml 90 minutes after administration of the amino acid. There were no significant alterations in his EEG either immediately or during the following two weeks. During this time he received 0.85 g of L-phenylalanine daily and had a fasting serum phenylalanine level of 35 mg/100 ml. His behavior during this period has been described earlier. The phenylalanine-restricted diet was resumed, beginning again when patient was 10 months old and continuing until the age of 29 months. The adequacy of the dietary regimen in controlling serum phenylalanine was established by frequent assays of urine samples for o-hydroxy-phenylacetic acid, and less frequently by direct measurements of serum phenylalanine. The child maintained levels of less than 10 mg/100 ml of phenylalanine except on two occasions, at the age of 12 and 29 months, when 15 mg/100 ml was observed. No phenylpyruvic acid could be detected in his urine during the entire period. His health remained good,
and he gained in weight from 19 lb to 281/2 lb, in height from 381/2 in. to 35 in. and in cranial circumference from 44.5 cm to 47 cm.

Developmentally, the child followed an almost normal pattern, lagging behind slightly. At the age of 12 months he walked with support and at 14 months of age he walked without help; he also employed meaningful sounds. When 16 months old he engaged in mimicry, talked, climbed adately, and had manual dexterity equivalent to 14 months of usual schedule. A psychometric examination at the age of 25 months (Stanford-Binet, Cattell) indicated an I. Q. of 82, and another when 29 months old, I. Q. 80. The EEG at 29 months appeared to be normal.

At this time the restricted regimen was discontinued and the boy was allowed to eat a natural diet. He continued to develop at the same slightly retarded schedule for the next year. Psychometric evaluation showed an I. Q. of 86 at 33 months and 83 at 42 months. The EEG showed a few spikes at 33 months, but a waking and sleep record at 42 months was normal. There has been no indication of deterioration in the year he has been receiving a natural diet. When 30 months old, his fasting serum phenylalanine was 46 mg/100 ml.

S. L. (Case H.)10 (Born Jan. 15, 1952.) This girl was born of normal pregnancy and delivery and appeared to be normal in the period immediately following birth. Her early developmental progress was on a retarded schedule; the mother first realized the child was retarded at the age of approximately six months. She sat without support at approximately 11 months of age. Since she attained the age of 12 months, she had episodes of "staring," but had no overt grand mal seizures.

Upon initial observation at the age of 35 months this child was seen to have episodes of lapses of awareness. Her general level of performance was equivalent to that of 11 to 12 months of the usual schedule of development. She was able to distinguish her mother from others. She did not participate in dressing. She showed only minimal interest in objects, which included a familiar doll. She was able to sit without support but required help to stand or walk. Her mouth was relatively pendant with oral pool and intermittent drooling. Intracranial manipulation was crude. There was a small variety of phonations. Her EEG showed frontal and parietal spikes.13 Fasting serum phenylalanine level was 32 mg/100 ml.

A phenylalanine-restricted diet was initiated at the age of 36 months. The parents noted a distinct improvement in alertness and in general quality of activity for the first two weeks, but relatively little subsequent improvement. When she was next seen at the age of 42 months, there had been little change in quality of attention and no distinguishable improvement in affective response. She could sit more stably but stance and gait still required support. Variety of phonations was slightly increased. There was no distinct change in manual manipulation. There was no improvement in the EEG.

When seen again at 48 months of age, she demonstrated increased interpersonal discrimination and preference of a familiar toy. She had developed an increased empathic relationship with her mother with moderate resistance at times. She was able to raise herself to a standing position, but still required support in gait. There was a further increase in variety of phonations and she had one word of consistent meaning. Manual manipulation had improved somewhat and she would use one object to impel another. Her jaw remained relatively pendant. The clinical impression that this child underwent little change in her mental status was borne out by the result of psychometric testing. Results obtained with a battery of tests at 36, 42, 48, and 52 months showed developmental quotients of 24 to 25, 22 to 24, 21 to 23, and 18, respectively.

N. P. (Case 6.13) (Born Sept. 2, 1953.) This boy was born at term of a normal pregnancy and delivery. His performance was considered to be entirely normal for the first month of life, but in the second and third months he became increasingly indolent, and markedly obese. At the age of eight months he was unable to sit and would not hold objects in his hand. At this time the mother first noticed seizures in the form of abrupt flexion of the trunk on occasions of startle. When 13 months old the seizures became more frequent and prolonged and were associated with up-turning of the eyes. An EEG revealed hypsarhythmia. Subsequent development was at a very slow rate. At the age of 20 months he was able to raise himself to sitting position and to sit without support.

Initial observation by this group was when the patient was 26 months old. This child was found to demonstrate little somatic abnormality aside from symmetrically muscular stiffness in trunk and limbs. He was extremely pale and was continually restless and irritable. Interpersonal and object discrimination was poor. He was able to sit very briefly and precariously without support. He demonstrated minimal co-operation in feeding. There were few intentional phonations and there was no distinguishable utilization of hands. General level of performance was appropriate to five to seven months of usual schedule of maturation. The EEG showed continuous hypsarhythmia. Fasting serum phenylalanine level was 87 mg/100 ml.

A phenylalanine-restricted regimen was initiated at 27 months of age. He was seen again nine days later. The parents reported that he had become more calm, consistent, and responsive, and that gradation into sleep was accomplished more stably. On observation, the infant was found to be less irritable. He demonstrated an improved affective relationship with his mother. The originally noted tightness in limbs was diminished. Motor tonus was improved in neck and upper trunk, and there was noted a greater awareness of objects placed in his hands. There was also a greater variety of elementary sounds.

At the next observation, age 281/2 months, the parents reported that the boy had continued to have three
to four grand mal seizures per day which were characteristically brief; in addition, he had 12 to 20 infantile spasms daily. There was no further increment in improvement beyond that observed at the previous visit.

Five months later he was able to sit without support but with the back and shoulders rounded. He had generalized convulsions approximately every two to three weeks and a few infantile spasms daily. He reached for objects held before him but did not grasp them. He paid no more attention to people than previously. His EEG was unimproved. The restricted diet was discontinued at the age of 34½ months.

In the next seven months he gained seven pounds. After he was taken off the diet, he continued to have four to five convulsions every three to four weeks and his minor motor seizures were observed many times daily. At the age of 41 months he still made no attempt to support himself on his legs; he reached for toys and touched them but did not grasp or pick them up. The EEG showed multiple spike foci and definite petit mal variant, especially in the frontal areas, in addition to hypersynchronous seizure discharges. At age 42 months his fasting serum phenylalanine level was 39 mg/100 ml; the decrease in blood phenylalanine with increasing age has been commented upon elsewhere.19

This child showed only slight improvement during the first weeks after treatment had been started at 27 months. No appreciable improvement, beyond the one expected without the restricted diet, was noted during the last six months on the regimen.

D. W. (Case E.19) (Born Nov. 5, 1953.) This girl was born at term, of a normal pregnancy. When two weeks old the mother had noticed some rigidity during feeding; this persisted for several months and was of sufficient degree to occasion difficulty in dressing the baby. This infant's retardation was first suspected by the mother at five months of age, and she was taken to a pediatrician when nine and one-half months old. He observed the infant's performance at that time to be equivalent to approximately six months of usual development; there was little further increment in achievement at the age of 11 months. The child sat without support when 16 months old; when 17 months old her physician considered her performance equivalent to that of an infant seven to eight months of age of usual schedule of maturation. The mother had observed that at ten months the eyes occasionally turned abruptly upward but there was no other suggestion of recognized seizures.

She was first seen at the age of 22 months. General examination showed no significant evidence of abnormality other than neurologic impairment. The general level of orientation and response was equivalent to approximately eight months of usual schedule of maturation. There was little interpersonal discrimination. Attention to a test object was brief, and she preferred with arc-like raking motions. There was no discrete thumb-finger prehension. Intra-oral manipulation was minimal, and there was no distinguishable bite. An EEG showed multiple spike foci. The diagnosis of phenylketonuria was made at this time; fasting serum phenylalanine level was 70 mg/100 ml.

A phenylalanine-restricted diet was initiated at the age of 22 months. In the succeeding three weeks, interpersonal orientation increased strikingly and responses of displeasure appeared. Object orientation and toy handling increased slightly. There was an increasing variety of phonations but they were still in elementary pattern. Posture stability increased and she was able to sit without support but was not able to bring herself into sitting position.

When the patient was 26 months old slight further improvement was evident as demonstrated by increased duration of attention and greater variety of empathic responses. She repetitively handled simple noise making toys. Posture achievement increased somewhat in that she was able to rise to sitting position and attempted to walk when supported.

At the age of 29 months, further increment in orientation was manifested in that she was able to recognize her mother and was aware of her absence when she was away from home. She now had favorite toys, her attention was more prolonged, and she laughed. Discrete intramanual coordination had further matured and was equivalent to 15 to 18 months of usual schedule of maturation. Posture achievement was increased and she was able to raise herself to standing and to walk better, though she still required support.

When 32 months of age, the patient enjoyed toys more than she had before, and when played with laughed frequently. She had started mimicking various actions, such as coughing and blowing the nose. She attempted to make appropriate use of a hairbrush or a handkerchief. She walked around furniture without help and along the wall, putting her hands flat against the wall. Her vocabulary at that time consisted of the words "hi" and "go." She smiled when the examiner whistled, cried when touched by the examiner, and resisted being measured and weighed. She grasped tongue blades or reflex hammer with four fingers and threw them away immediately.

At 35½ months of age, no further increase in accomplishments was noted although the serum phenylalanine level had been maintained at 5 to 7 mg/100 ml. She weighed 27 lb 6½ oz, her height was 35 in., her head circumference was 48 cm, and chest circumference was 48 cm. She showed affection to her parents and resentment to the examiner. Her muscular development in her extremities, especially in her legs, had improved. After the phenylalanine-restricted diet was started, all EEG were normal except the one at 35½ months of age when there was a suggestion of some four per second spike and wave complexes in light sleep.

The phenylalanine-restricted diet was discontinued at 35½ months. Four and one-half months later, no evidence of regression was evident. During that time she had learned to feed herself in a poor fashion, and
she would remove and replace pegs in a peg-board.

This child showed improvement while receiving the phenylalanine-restricted diet. At first the improvement was marked; toward the end of the treatment it was slower, and by the time the patient reached three years of age no further relative improvement was evident. No regression had occurred four and one-half months after the restricted diet was discontinued.

**C. M.** (Case F.3) (Born Feb. 13, 1953.) This girl was born at term after a long labor and weighed 7 lb 14 oz. She suffered from intermittent eczema from early infancy, frequently had petechiae around the eyes, and bruised easily from very slight trauma. She was able to sit without support when eight months of age. At the age of 14 months, she started to have frequent seizures daily; these consisted of throwing up the arms, stiffening and jerking for about a second.

At time of first examination in this study, when 15 months old, she could not pull herself up but was able to remain in a standing position while holding on to furniture. When the child was supine and a diaper was placed over her face, she made no attempt to remove it. At that time, no eczema was observed and general physical examination was normal. The extremities had flabby musculature which was less well developed peripherally than proximally. The tendon reflexes in the upper extremities were 2 plus, in the lower extremities 1 plus, and the Babinski sign was negative bilaterally.

Diagnosis of phenylketonuria was made at that time. Her serum phenylalanine level was 61 mg/100 ml. An EEG showed typical continuous hypsarrhythmia without periods of normalcy.13

Ten days after the phenylalanine-restricted diet was started, the phenylalanine level had decreased to 7 mg/100 ml; the seizures were milder and were restricted to periods immediately following awakening. Three weeks after the initiation of the dietary regimen, the seizures had decreased further in frequency and severity and the EEG showed periods of normalcy up to 10 to 15 seconds between seizure discharges. At the age of 20 months, the child laughed when entertained and showed normal affective response to her relatives and the examiner. She was able to "pat-a-cake" and play like a 15-month-old child; she walked well without support. After she had been on the restricted diet for five months, no more seizures were observed. At 24 months of age, the child's motor functions corresponded to those expected at the age of 21 months, her adaptive behavior and language were on the level of a child 15 to 18 months of age, and her personal and social level on a par with that of a child up to 18 months. Her EEG was normal while she was awake and during sleep.

Her actions and behavior responded to the diet rather promptly; the seizures improved markedly within three weeks but did not stop entirely until she had been on the diet for five months. The rate of improvement is less at the present time than during the first few months after treatment was initiated.

**W. S.** (Born March 15, 1953.) This boy was the second child of a second marriage, his full sibling and three half-siblings being normal. He first sat at nine months and walked unassisted at 19 months of age. His mother's chief complaints were that he engaged in fighting and screaming without provocation. He scratched objects, banged his head against the wall or furniture, and could not be let out of the house alone because he would run into the street and try to touch moving cars. He would defecate all over the house but not in his bed.

On initial examination, age 421/2 months, he weighed 32 lb 13 oz, his head measured 49 cm, and the chest 55 cm in circumference. His hair was blond, his eyes dark brown, and there was no history or evidence of eczema. There were no abnormal findings on general physical examination. His deep tendon reflexes were 2 plus to 3 plus and symmetrical, and the Babinski sign was bilaterally negative. The EEG showed a few occipital and generalized spikes while awake and during sleep; there was a negative seizure history. His fasting serum phenylalanine level was 43 mg/100 ml.

A phenylalanine-restricted regimen was started at age 43 months. After two weeks the serum phenylalanine level had decreased to 4 mg/100 ml. The mother reported the following changes: He now showed appropriate fear of moving cars, sought his mother's company, and for the first time showed an affective response to her.

At the time of his fourth birthday, his hair had become noticeably darker, his disposition had improved, and he displayed many activities typical of a three-year-old child.

An EEG at this time showed no evidence of abnormality while the patient was awake or during sleep. The dietary regimen was continued.

**M. Y.* (Born Nov. 15, 1953.) This boy was born at term of an uneventful pregnancy. He appeared to be completely normal when examined at three weeks of age. Because he had an older brother with diagnosed phenylketonuria, his urine was tested with ferric chloride at this time for the presence of phenylpyruvic acid, with negative results. At the age of eight weeks he developed a persistent eczema. When the patient was 17 weeks old the ferric chloride test was repeated and this time was positive. At the age of 18 weeks, his fasting serum phenylalanine level was 99 mg/100 ml. At this time he reached and grasped and seemed to have developed normally, but was noted to startle and cry easily, and to sleep restlessly. Height 241/2 in.; weight 13 lb 13 oz; head circumference 39.5 cm. A phenylalanine-restricted regimen was started at 19 weeks. Although the infant had seemed to be normal, the mother reported that shortly after commencing the diet he seemed to be calmer and slept better. He has continued to follow a normal pattern of development.

* The two patients, M. Y. and S. R., were cared for by Dr. P. R. Vandeman, Memorial Clinic, Olympia, Washington, and the recorded observations are his.
on the phenylalanine-restricted diet; at 21 weeks of age he attempted to roll over, when seven and one-half months old he sat alone and played, and at 11 months crawled, pulled up, and cruised, at 14 1/2 months he walked alone and began to say “bye-bye” and “daddy.” He had gained in height to 31 in. in weight to 26 lb, and in head circumference to 40 cm. His anterior fontanel closed at seven months, yet head continued to grow normally. He successfully withstood several infectious illnesses during this period. This child differed from the pattern usually shown by phenylketonuric infants in requiring a considerably higher intake of natural protein in order to maintain an adequate serum phenylalanine level (4 to 8 mg/100 ml). On 5 g natural protein per day (estimated 250 mg phenylalanine, corresponding to 25 mg phenylalanine per kg body weight), he consistently had less than 1 mg/100 ml of serum phenylalanine. His daily allowance of natural protein was doubled (50 mg phenylalanine per kg body weight per day) and he then maintained four to eight mg/100 ml serum phenylalanine.

S. R.* (Born Nov. 19, 1956.) This child was born at term of an uneventful pregnancy. He seemed to be normal during the postnatal period and was seen at the age of three weeks for the complaint of a severe eczema. A positive phenylpyruvic acid test was obtained with his urine, and a fasting serum phenylalanine determination at four weeks showed 83 mg/100 ml. A phenylalanine-deficient regimen was commenced at this time. He continued to develop normally. At the age of three months he was alert and responsive, and at five months he smiled, was alert and happy, and could roll over both ways. From the age of 1 month to five months he gained in height from 21 1/4 in. to 25 3/4 in., in weight from 8 lb 12 oz to 14 lb 11 oz, and in head circumference from 37 cm to 42 cm.

**DISCUSSION**

The observations presented here and by other laboratories confirm the previous suggestion that some of the pathologic symptoms in phenylketonuria occur as the result of a deleterious effect of some substance present in phenylketonuria. In addition, further inferences concerning the manner of development of the mental and neurologic impairments may now be made.

A new aspect of interest regarding the disorder arises from the finding that many patients with phenylketonuria appear to be normal at birth and during the neonatal period. They then develop pathologic signs, in the form of sudden onset of seizures or signs of retardation, and undergo deterioration. The deterioration appears to involve all demonstrated functions including orientation, affect, and motor abilities; it is coincident with frequent infantile spasms. This impairment of previous ability was first suspected as a result of examination of the application forms of some of the phenylketonuric patients admitted to the Utah State Training School; it was reported that these patients had performed better at an early age than when examined at the institution in the course of these studies. History taken from parents of other phenylketonuric children confirmed this impression.

By now several phenylketonuric infants who have been subjected to expert appraisal have been found to exhibit no signs of neurologic abnormality or retardation. This is true of J. Du, M. Y., and S. R. of the cases described herein, Cases III and VI (the newborn infant described previously) of Horner et al., and the case of Berendes. In addition, the observations stated herein indicate that F. D., A. Du, R. Du, and D. W. probably progressed more rapidly for the first few months of life than later. The fact that children with phenylketonuria are normal at birth and appear to develop normally for a period after birth offers additional encouragement for the hope that a dietary regimen may provide an adequate therapeutic procedure for averting the mental retardation, since a normal, rather than an already damaged, nervous system would be present.

A possible explanation for delay in the development of pathologic symptoms in phenylketonuria has been afforded by the finding that there may be delay in the development of full biochemical abnormalities. This had been anticipated by Delay et al., who reported that an infant whose urine showed only a doubtful positive test for phenylpyruvic acid at two months of age later developed typical phenylketonuria; and by Case 3 of Horner and Streamer whose urine did not contain phenylpyruvic acid during the newborn period, by M. Y., in this paper, whose urine contained no phenylpyruvic acid at three weeks, by Case 6 of Blainey and Gulliford whose urine did not contain phenylpyruvic acid at two weeks of age, and by the newborn infant studied in detail, who did not excrete a detectable amount of phenylpyruvic acid until 34 days of...
age. These findings suggest that phenylpyruvic acid is metabolically more closely related to the damaging agent than is phenylalanine.

The suggestion that there are individual variations in the time phenylpyruvic acid first appears in the urine of phenylketonuric infants has been substantiated by observations on another newborn infant with phenylketonuria studied in collaboration with Drs. W. B. Weil, Jr., W. M. Wallace, and J. E. McClelland, University Hospitals of Cleveland, Ohio. This second infant first excreted a barely detectable amount of phenylpyruvic acid at the age of six days, and a readily detectable amount at seven days of age.\(^*\)

The results now available on the therapeutic effect of phenylalanine restriction in phenylketonuria indicate that children younger than two to three years of age may be remarkably benefited by this type of treatment. The infants reported here who were started on a phenylalanine-restricted regimen before any signs of pathologic changes developed, or immediately after the first signs of abnormality, seem to be developing normally or nearly so. Thus, R. Du is only slightly behind normal, and M. Y. and S. R. show no signs of retardation. Cases III and VI reported by Horner et al.\(^*\) and the infant described by Berendes,\(^*\) all of whom were started on the restricted diet at a very early age, seem to be developing normally. The older infants reported here, C. M. and D. W., progressed more rapidly for a time after initiation of the diet than later. M. J., on the other hand, had severe seizures for several months before the restricted diet was initiated, and, although she seemed to have been benefited, remained very retarded.

The effect of dietary treatment of patients older than two to three years of age has been difficult to evaluate. The observations made here and drawn from other reports, however, may be interpreted as indicating that the improvement which is occasionally seen occurs secondarily to the relief of neurologic abnormalities as manifested by seizure disability, which is frequently present. Of the 12 patients described here, five had passed their second birthday when the dietary regimen was commenced. All five of these showed some initial signs of improvement. Four of these patients had seizure disorders, as manifested by abnormal EEG, with or without overt signs of seizures. The EEG of two of these four (S. L. and N. P.) were not markedly improved by the restricted diet; little sustained change in their behavior was observed. The EEG improved and seizures disappeared in the other two (A. Du and W. S.). The regimen was continued only three months with A. Du; with W. S., however, after five months considerable improvement in behavior could be observed.

Other groups have reported improvement, ranging from slight to extensive, in the mentality of older children maintained on restricted diet. Woolf et al.\(^*\) described two 32-month-old children and one five and one-half year old child. After the age of 10 months one of the younger children improved from I. Q. 20 to 30; a markedly abnormal EEG at the beginning of the experimental period became essentially normal after 3 months and remained so. The other of the younger children had improved from I. Q. 42 to 49, a less significant change, after ten months; her EEG was considered essentially normal at the beginning of the dietary test. The oldest child did not improve greatly, but it was not reported whether the seizure disorder which was present was greatly benefited by the dietary regimen. Bickel et al.\(^*\) reported changes in the mental development of one two-year-old and three older children, without details. Horner and Streamer and collaborators\(^*\) reported results with two four-year-old children who demonstrated remarkable improvement as assessed by psychological testing. A boy increased from an I. Q. of 35 at 49 months to 69 at six years; there was no comment concerning his EEG. A girl improved in I. Q. from 37 at four and one-half years to 70 at six years of age; a seizure dis-

\(*\) Added in proof. Another newborn infant with phenylketonuria, studied in collaboration with Drs. F. A. Horner and C. W. Streamer, University of Colorado Medical Center, Denver, first excreted a barely detectable amount of phenylpyruvic acid at the age of seven days, and a readily detectable amount at nine days of age.
order present at the beginning of the dietary regimen apparently was improved after only one month. Blainey and Gulliford7 described their experiences with six older children; these children were followed closely with psychometric testing. Only one of their patients showed significantly increased mental ability as revealed by the testing. It is of interest that their series of patients contained the first case reported by Bickel et al.,1 in whom striking improvement was reported to have occurred by the use of a phenylalanine-restricted diet. Despite the improvement the child was said to have made at that time, the results of the psychometric testing reported by Blainey and Gulliford showed that she had remained at a very low level.

Thus, in nearly all of the cases in whom apparent marked improvement in mental functioning has been observed, there has been an accompanying improvement in seizure disability. Convincing evidence of better mental performance in older patients receiving phenylalanine-restricted diets will have to take into account not only progress occurring as the result of improvement of seizure disorders, but that following increased attention and better acceptance by parents. A further difficulty in clinical evaluation of diet effects lies in the spontaneous improvement which might occur coincidentally with, but not because of, a dietary treatment. The improvement shown by Patient J. Du off the diet provides an excellent example that this possibility can occur.

The presence in phenylketonuria of some substance with a deleterious effect on the nervous system was well demonstrated by the observations reported here. When the blood phenylalanine level is decreased to the near normal range, the secondary biochemical abnormalities present in phenylketonuria are corrected. In all the patients studied there were marked, though not objectively measurable, changes which accompanied the initiation of the phenylalanine-restricted regimen. Among these were the improved attention span, calmer behavior, and improvement in neurological signs and, usually, improvement in EEG, when abnormal to begin with. Woolf et al.2 described the changes of this sort in one of their patients by stating, "He gave the impression that he had 'become a human being.' " The pathologic signs accompanying high blood phenylalanine levels also were well demonstrated by the behavior of R. Du during the two weeks phenylalanine was returned to his diet, and by the behavior of M. J. during the period she was given phenylalanine. It has been noteworthy, however, in all the patients who have been maintained on restricted diets and then again given natural diets that there has not been a sudden, but a very gradual, return of these signs.

Previous studies, carried out with older patients, failed to show any correlation between biochemical abnormalities and the degree of mental impairment. The recent opportunity for dietary treatment of phenylketonuria has stimulated detection and observations on infants much younger than any included in the earlier reports. As a result of the current studies, the suggestion may be made that two factors influence the mental level of older patients with phenylketonuria. The first is the amount of permanent damage the central nervous system has suffered. This damage occurs in the first two or three years of life either because of an accentuation of the biochemical abnormalities at this age, a greater susceptibility of the rapidly developing nervous system to damaging agents, or a combination of the two. The extent of the damage is dependent upon the age at onset of pathologic signs, and the degree of the biochemical abnormalities. The second factor influencing the observed status of older patients is the continuing presence of some neurotoxic agent(s). The rapid initial improvement observed in patients given a phenylalanine-restricted diet would be regarded as occurring as a result of the removal of the toxic agent(s). This would allow the brain to function at a level conditioned by the extent of the damage previously suffered during the first two or three years. The probability that the extent of early damage influences the effect of the deleterious metabolites is indicated by the fact that older, untreated phenylketonurics, with typical biochemical abnormalities, can be mentally normal.18
The presence of an upper age limit of two to three years after which no further damage occurs is suggested by (1) the previous observation that further mental deterioration is not usually observed in older patients,7 and (2) by the absence of consistent improvement in older patients, in conjunction with the improvement observed in children less than two years old under the influence of a phenylalanine-restricted diet. The likelihood that there is this upper age limit after which severe damage to the nervous system no longer occurs is of considerable practical importance. Since phenylketonuria in older children is not incompatible with normal or near normal intelligence,8 it might not be necessary to continue feeding phenylketonuric children the synthetic diet, with its attendant nutritional difficulties, after they attain this age. As a corollary, it would follow that it would be of little advantage to try to maintain older patients on the dietary regimen unless they have seizures or are extremely hyperactive.

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