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Phenylketonuria

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PHENYLKETONURIA

A Special Studies Paper Prepared For

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by

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Great strides have been made in improving and safeguarding the health of mothers and children of this country. The risks of pregnancy have been considerably reduced. Many of the threats to the lives of newborn babies have been removed, and more infants survive today than ever before.

Among those who survive, however, are some who are not fully equipped to grow and develop normally. At birth, some have defects which we have been unable to prevent. Correction and prevention of these defects are among the most challenging frontiers in medical research today.

For my special studies this semester, I have chosen to report on one such defect--phenylketonuria. I have studied the causes, the effects, the symptoms, the detection, the treatment, and the laws related to detection and treatment. While it affects only a small number of infants born each year, if untreated, the condition results in the tragic destruction of the mind of the child, although he may have been born with normal mental potential.

Phenylketonuria is (in simplest terms) an inherited metabolic disorder associated with mental retardation. Phenylketonuria (PKU) holds a unique position in the field of mental deficiency. It is unique because it is easily detected and when diagnosed early the mental deficiency of this disorder can be prevented or favorably modified by special dietary management.

The history of PKU dates back to the early 1930's to a family in Norway with two retarded children. The mother was haunted by the notion that these children

had a peculiar odor. Her efforts to get help for her children and to learn the cause of this odor (the odor is present when phenylacetic acid is secreted in the perspiration and urine of persons with PKU; the distinctive odor of this compound is described as "musty", "horsy", or "barnlike".) led her from doctor to doctor over a period of years. Finally she interested a Norwegian physician and biochemist, Dr. Ashborn Fölling.

In the process of examining the children, Dr. Fölling discovered that the urines of both reacted with ferric chloride to give an unuaual, green color. This he proved was due to the presence of phenylpyruvic acid, which he was able to crystallize in pure form from the urine samples. The same simple ferric chloride urine test and modifications thereof and newer simplified blood test such as that developed by Robert Guthrie make early diagnosis of PKU possible today.

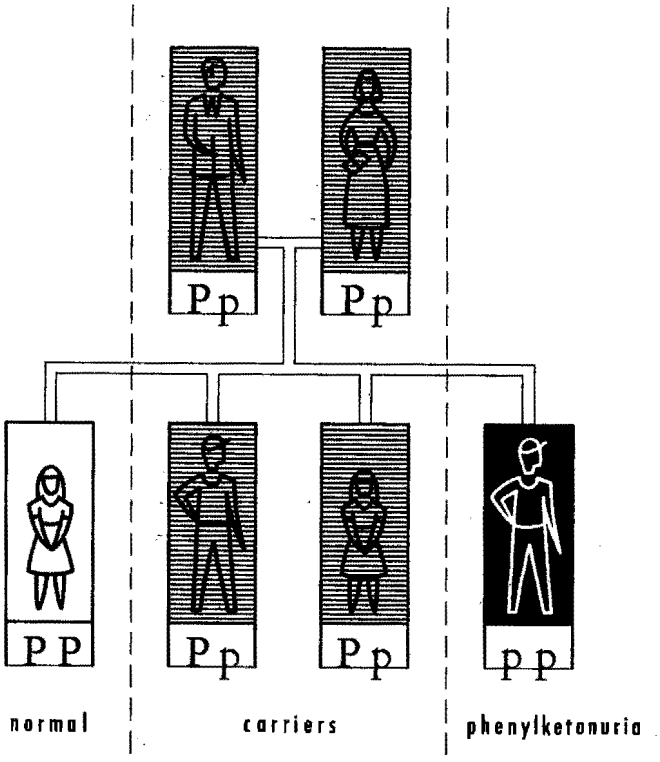
(Note: The designation "phenylketonuria" or "PKU" refrers to the urinary excretion of phenylpyruvic acid.)

As news of this newly discovered disease spread, patients in institutions for the mentally retarded in many countries were similarly tested. Out of such studies came figures for incidence, determinations of type of inheritance, and a fairly complete clinical picture of the disease. Study of these patients also provided information by which much of the metabolic error eventually was mapped out. Because phenylpyruvic acid, the substance responsible for the green color reaction with ferric chloride in the urine, is a phenylketone, the name phenylketonuria, or PKU, was suggested for this disease. To date, this is the name of preference although other names have been suggested.

It was soon discovered that PKU is found on the average in one-half of 1 percent to 1 percent of institutionalized mental defectives. Interpolating from this prevalence, it was estimated that PKU occurs once in every 20,000 to 40,000 live births. A comparison of birth statistics and causes of PKU discovered over

a 10-year period in Utah suggested that the incidence must be somewhat more than 1 in 20,000. Extensive mass testing of blood phenylalanine levels of newborns in the United States suggests that the incidence is in the neighborhood of 1 in 10,000 live births. Sexes are essentially equally affected and all races appear to be involved. However, the incidence is relatively higher in people of European stock and is particularly low in people of Askenazi Jewish and Negro ancestry. It has been reported from India (hindu and Muslim) and from the Orient (Japan and China).

Because PKU often involves more than one child in a family, it was recognized from the beginning as a familial disorder. When it was determined that the parents were normal and that approximately 1 in 4 children in the involved families had PKU, it was concluded that PKU was inherited by a simple, autosomal, recessive gene. The following diagram represents the mode of inheritance in a classical PKU family.



In this situation the normal parents are each carriers (Pp) of the defective gene for PKU. The children from two such parents can be noncarriers (PP) or carriers like the parents (Pp), or have two abnormal genes (pp) and have phenylketonuria (PKU). Thus each pregnancy of such parents has a 1 in 4 chance of resulting in a PKU child (pp) and a 3 in 4 chance of resulting in a phenotypically normal child (PP and Pp).

If we assume that the incidence of PKU in the general population is 1 in 10,000 then it can be determined that 1 in 50 of the general population is a carrier of this disease. (This figure is derived by multiplying 1:10,000 by 4 and then taking the square root.) To better understand this figure, one can calculate in reverse that the chance of two such carriers in the general population marrying each other would be 1/50 x 1/50 or once in 2,500 marriages. If each of these 2,500 couples, including the "carrier" couple, had four children, then one of the 10,000 offspring would be expected to have PKU. Since PKU is transmitted by inheritance of an autosomal, recessive gene, homozygous phenylketonurics rarely mate. As more widespread success in the dietary management of this genetic disorder is achieved, however, the incidence of marriage by mentally normal adults with phenylketonuria will increase. All children of such a union will be phenylketonuric.

It should be realized that the exact incidence of PKU and thus the incidence of carriers is as yet unknown. This fact will not be determined until there are more wide scale screening programs of the general population and more extensive use is made of improved methods for "carrier" detection. Earlier proposed means of determining "carriers," although useful, have some limitations in clinical application--mainly because of overlap between normal and "carrier" results. Newer approaches have not successfully reduced discrimination below 4 percent.

Phenylketonuria is known as an inborn error of metabolism. The basic defect caused by the PKU gene is lack of the enzyme phenylalanine hydroxylase which normally changes the essential amino acid phenylalanine to tyrosine. If PKU is permitted to progress, brain development is arrested and severe mental deficiency results.

If the mother has essentially normal metabolism, the baby seems to be protected before birth. As soon as a newborn baby with PKU begins to take milk (breast milk or cow's milk), phenylalanine, which constitutes approximately 5 percent of all proteins, is absorbed. Blocked in its normal metabolic pathway, the phenylalanine builds up to serum levels of about 20 times the normal. This takes place fairly rapidly. By the time the infant is 1 to 6 weeks of age, abnormal byproducts of this high serum phenylalanine begin to appear in the urine. It is believed that the continued high level of phenylalanine or its related metabolites is responsible directly or indirectly for the mental retardation. This view is amply confirmed by the fact that low phenylalanine diets started on PKU infants in the early months of life (so that serum phenylalanine levels remain within the normal or near-normal range), have resulted in normal mental development. (If a newborn PKU infant doesn't receive milk (proteins) the serum phenylalanine level still will show some rise within a few days due to catabolism of body proteins.)

Although the mechanism of the adverse effect of elevated levels of phenylalanine or abnormal metabolites of phenylalanine metabolism has not been clarified, some facts are beginning to emerge. There is experimental evidence of an inhibitory effect on enzyme systems active in significant metabolic and transport processes. It is known that there is a significant inhibition of serotonin products in untreated patients with PKU which can be normalized under therapeutic dietary control. Also, there is evidence of failure of myelination or loss of myelin in about a third of PKU patients examined histologically. A rare case of PKU now and then is reported to have developed normal mentality without any treatment. Still many questions remain yet unanswered about the mechanism of the adverse effect in PKU.

The untreated PKU patient is born apparently normal but begins to show retardation early in life. At about 3 or 4 months of age, a subtle change may be noticed. The infant begins to lose interest in his surroundings, and thereafter

development is slowed down or arrested until by 2 or 3 years of age most are in the below "50 I.Q." range of mental deficiency. Of the known untreated cases in institutions, 90 percent fall into this bracket. Occasional untreated cases (perhaps 10 percent) are only mildly retarded and a few cases (less than one-half percent) have been reported with normal mentality.

PKU children usually are fairly well developed physically and have no truly diagnostic stigmata other than the characteristic musty odor. Older children may exhibit slight stunting of height and some have smaller than average head sizes. Patients with PKU may have blue eyes, blonde hair, and fair skin when compared to their parents and normal siblings. Although there are many exceptions, approximately 80 percent are blonder than their parents and normal siblings.

The average age of untreated PKU children for sitting alone is from 12 to 15 months; the average age for walking is 2½ years, for talking 3½ years. Some never learn to walk; many nver learn to talk. Behavior patterns are frequently autistic, hyperirritable, and destructive. About 80 percent have abnormal EEG's (electroenecphalographs) and approximately 25 percent have convulsions. (Convulsions are uncommon after 10 years of age.) The more severely involved cases may show signs of upper motor neuron damage such as positive Babinski and ankle clonus. About 25 percent of PKU patients have eczema, which is pruritic and not limited to any specific areas of the body and which may have its onset within the first few months of life. Although not reversible, this process can be arrested by proper dietary management. Clinical signs such as vomiting, eczema, and urine should be stressed.

There are two basic types of programs in use for the screening of babies. Historically, the first of these was one of the ferric-salt urine tests performed on babies between 1 and 2 months of age, at the time when phenylpyruvic acid ordinarily appears in the urine of an affected child. When using the urine test it is best to repeat this test three times on each child at each of the first three

A classical setting for PKU: The one child in four involved with PKU is severely mentally retarded, has a disturbed behavior pattern, had a history of convulsions earlier in life, and is blonder than his parents and normal brother and sisters. Phenylalanine tolerance studies revealed that the parents and two of the three normal children are "carriers" of the PKU gene.

well-baby checkups.

In the United States, where the majority of babies are born in hospitals, the Guthrie inhibition assay blood test is recommended on the third day of life. This test is simple, inexpensive, and can be performed in large numbers. Public health departments in many states have been setting the example through pioneering such screening programs for PKU. Followup blood testing by this method is recommended at 1-2 months of age. If two successive serum phenylalanine levels are normal, PKU can be safely ruled out.

The inhibition assay blood test can be performed on specimens collected simply by placing a drop of blood dried on a piece of filter paper. It is known that in a phenylketonuric baby the blood level of phenylalanine rises rapidly after birth, and blook taken on the third day of life will usually reveal the disease. The great advantage of this type of test is the possibility of systematically testing practically all babies. Extensive screening trials using this method on newborn babies in the United States have resulted in detection of cases at a twofold to fourfold higher incidence than the previously estimated frequency for PKU, which has been 1:20,000 to 1:40,000.

The screening of mentally retarded populations for PKU has been done for many years in a good number of institutions for the retarded, whereas in many others such detection efforts are more recent. Although it is unlikely that the intelligence of children picked up by this method can be improved very much by dietary control, diagnosing older children is such an important way to protect subsequent siblings and other related infants with PKU that routine screening for the retarded, in all institutions, schools, or classes, both public and private is strongly recommended.

The success of such programs will depend on many cooperating organizations. Case finding will have to be followed systematically into the homes of the families in a way somewhat similar to screening families in which an active case of tuberculosis has been found.

A home survey of the siblings of 20 PKU patients at an institution of 3,000 population uncovered three previously undiagnosed cases. Two of these were still young enough to receive benefit from treatment. On the basis of this experience, several recommendations have been made for followup work with families of PKU patients:

1. The families should be carefully oriented and counseled as soon as possible. The orientation should also include an explanatory letter or literature that describes the problem. The information should also be forwarded to the family physician. Information pamphlets for parents are now available.

2. All siblings should be screened as soon as possible, even if the parents do not think they are retarded. Sometimes retardation in young children is unsuspected by the parents.

3. All newborn siblings should have serum phenylalanine determinations just prior to discharge from the newborn nurseries (at 3 or more days of age). If this is not possible, they should have urine tests at 2, 4, 6, 8, and 12 weeks of age. As an extra precaution, it is advisable to do similar followup urine tests, even on newborn siblings who have had a normal serum level.

4. The families should be encouraged to notify other relatives so that young cousins, second cousins, nieces, and nephews can be tested for PKU during early infancy.

Because of the sometimes associated findings of behavior disturbances, convulsions, cerebral palsy, and eczema in PKU patients, it is advisable to screen children presenting such problems in clinics, medical centers, or in private practice, including those with or without mental retardation. In addition, mothers of retarded children should be screened. Maternal PKU has been reported as a cause of mental retardation in non-PKU offspring, due to the damaging effect to the foetus before birth caused by the mother's high phenylalanine blood levels.

Now we shall examine the different types of tests used in detection of PKU. There are two broad categories of tests--blood tests and urine tests. First, let's look at the blood tests for phenylalanine.

Screening test. This test which was developed by Guthrie is called the inhibition assay method of determining phenylalanine in the blood. Only a small

amount of blood is needed, which can be obtained easily by heel puncture and collected on a filter paper. The test is based on the fact that the inhibition of the growth of Bacillus subtilis by beta-2-thienylalanine is prevented by phenylalanine, phenylpyruvic acid, and phenyllactic acid. With cautious training of technicians to impose judicious control of procedures the incidence of false positives can be held to a practical level. Some workers have reported excellent results with the use of the Guthrie method for diet regulation. The method, however, is subject to a greater chance for error in carrier studies than the biochemical methods which measure only phenylalanine rise after an oral load.

Earlier methods of determining serum phenylalanine required from 2 to 5 cc. of blood and thus were not suitable for screening small babies. The Guthrie procedure is a simple and inexpensive test and can be performed in large volume. The blood-saturated filter paper can be sent through the mails for analysis in a centralized laboratory. A blood-saturated filter paper can remain at room temperature for several days without significantly affecting the test results. (See following pages for examples.)

Confirmatory tests. Quantitative serum phenylalanine determinations are used for final confirmation of the diagnosis of PKU in cases seemingly positive by urine tests and the inhibition assay blood test, and for clinical care. Also it might be advisable to determine the serum phenylalanine level on a child who seems to suggest strongly the diagnosis of PKU but whose urine tests are negative; there are instances of PKU in which serum phenylalanine levels, although definitely elevated above normal, are just at the renal threshold level so that excretion of metabolites into the urine is inconsistent. No infant or child should be started on the long-term program of a low-phenylalanine diet without blood-test confirmation of the disease. The serum specimen (2 cc.) can be safely stored in

BLOOD SCREENING FOR PHENYLKETONURIA

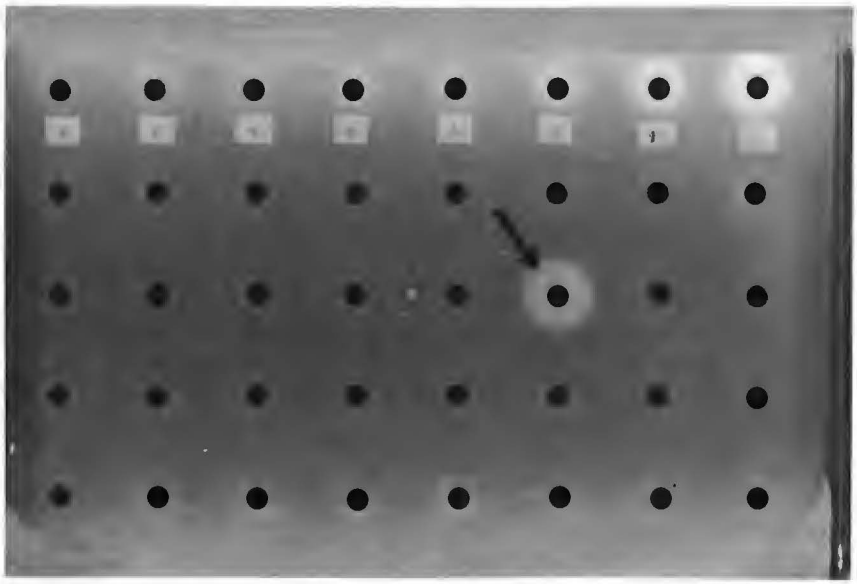
Robert Guthrie and Ada Susi

1. After puncture the baby's heel is touched to the filter paper. The specimens are then mailed to the lab.

2. After autoclaving, a small disk is punched out of each blood spot.

3. The melted agar culture medium, containing the phenylalanine antagonist β-2-thienylalanine, is inoculated with *Bacillus subtilis* spores, poured into flat dishes and allowed to solidify.

4. The blood paper disks from as many as 100 patients are, in addition to 8 control disks, placed upon the agar surface in rows, and after overnight incubation, the results are observed.



5. An indication of PKU is a blood disk producing a growth halo corresponding to any of the 4 highest control disks. This indication is then confirmed by a quantitative blood determination. The control disks are prepared from blood containing phenylalanine in the following concentrations: 2,4,4,6,6,8,12 and 20 milligram per 100 ml.

PKU BLOOD TEST

Laboratory No. _____

Patient's identification:

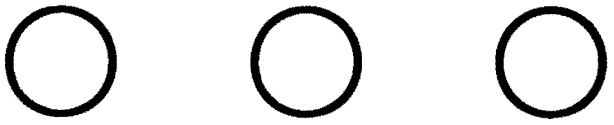
Date of specimen _____

Date first milk feeding _____

Bottle ☐ Breast ☐ Both ☐

Date of birth _____

FILL ALL CIRCLES WITH BLOOD



Filter paper used for collecting specimen from heel puncture. Blank space in center is for hospital's identification on specimen.

HOSPITAL PKU BLOOD TEST

Fill in all information with *pencil* only:

HOSPITAL

_____

Baby's Name

_____

Date of birth _____

Date 1st feeding _____

Bottle ☐; Breast ☐; Both ☐

Date of Sample _____

Premature? Yes ☐; No ☐

Baby's Doctor

_____

Doctor's Address:

FILL 3 CIRCLES WITH BLOOD
(Be sure blood soaks through.)

4 WEEKS PKU BLOOD TEST

DOCTOR FILLS 3 CIRCLES WITH BLOOD — *must soak through.* Write with *pencil* only:

BABY'S NAME

_____

Date of birth _____

Date of Sample _____

Hospital

_____

Baby's Doctor

_____

Doctor's Address:

This part mailed in by the hospital.

This part torn off for the mother to give to the baby's doctor for use at the 4 to 6 weeks routine visit to the doctor.

a freezer and tested later if an immediate serum phenylalanine determination is unavailable. In this way there need be no long delay in initiating dietary treatment because of local lack of certain laboratory facilities.

There are other indications as well for the use of the serum phenylalanine level. Subsequent siblings born into a family where PKU is present in an older child have a 25 percent chance of also having PKU. Cord levels of newborn infants with this disorder are not sufficiently elevated to establish the diagnosos. Cord levels are somewhat higher than maternal levels. By 2 or 3 days postnatally, however, the serum phenylalanine has risen to abnormally high levels (10 to 15 mg.); a blood specimen at this time usually is adequate to make the diagnosis except in the premature. In the latter, caution must be exercised because of immature enzyme systems causing temporary elevations of serum phenylalanine. It takes a week or longer (rarely up to six weeks) before phenylpruvic acid can be detected in the urine. Thus, newborn siblings of known PKU children should be fed a milk formula until blood specimens are obtained on the third or fourth day of life. Serum phenylalanine determinations are now sufficiently simple and in such widespread use that there should be little delay in clarification of the zygosity of the infant. If for some reason clarification is delayed, the infant may be temporarily placed on a low-phenylalanine diet. Then, if the serum value is elevated the diet is continued; if normal, a regular diet is initiated.

The PKU infant or child on a low-phenylalanine diet should have periodic determinations of his or her serum phenylalanine levels. Several methods for determining serum phenylalanine levels are quantitatively sensitive enough for this purpose and for research and other investigative efforts such as phenylalanine tolerance tests for detection of carriers of the PKU gene.

The various methods fro determining serum phenylalanines are too comples for description in this brief report. Many medical school centers and some research centers and commercial laboratories are able to do these determinations.

Urine tests for phenylpyruvic acid. Several urine tests and modifications of urine tests are available for the identification of PKU. A study was done at the College of Medical Evangelists School of Medicine, Los Angeles, California, (now the Loma Linda University School of Medicine) to try to determine the advantages or disadvantages of the various urine tests for screening purposes. In this study several thousand evaluations were made on 132 consecutive urine samples taken from 20 untreated institutionalized cases of PKU. The effects of many factors on the urine tests were measured, such as pH, specific gravity, turbidity, a.m. and p.m. voiding, age and sex of patients, hours of standing after voiding, etc.

The most important variable which affected all the tests was the freshness of the urine sample. Unless the urine has been frozen or a preservative added, it should be freshly voided for accurate results. Although deterioration is less rapid when the urine is dried on filter paper, 10 percent will no longer test positive after 3 days. Factors such as cost of the test and ease of administration were also compared. All the tests studied were comparable in accuracy, and each had enough specific merits to make that test valuable under certain circumstances.

It was found that in each of these tests the value is dependent on some simple but specific precautions which if not understood and appreciated can easily cut the efficiency of that test considerably. On rare occasions PKU patients fail to excrete phenylpyruvic acid; therefore, the possibility of this disease can not be excluded on the basis of one negative urine test. Because the diagnosis is of great concern to the family and involves an expensive, long-term treatment, all positive urine tests should be confirmed with a serum phenylalanine level before

the diagnosis of PKU is established and treatment begun. In a rare circumstance, when a serum phenylalanine level can not be obtained within a week, treatment may be started on a presumptive diagnosis of two confirmatory urine tests, for example, ferric chloride and dinitrophenylhydrazine. In such a case, however, a sample of pretreatment serum should be frozen for later phenylalanine determination.

Ferric salt tests. The test-tube test with ferric chloride is the oldest, best known, most widely used of any of the urine tests for PKU and it is the only one I will attempt to cover in my report. The color reaction of ferric chloride with phenylpyruvic acid is practically pathognomonic. Immediately there is a medium-dark, blue-green to gray-green color which fades in a matter of seconds, or minutes, depending upon the concentration of the phenylpyruvic acid in the urine and the strength of the ferric chloride solution being used. This fading of the color back to a neutral or negative urine color is most useful in differentiating the true phenylpyruvic acid reaction from most so-called false-positive reactions. Ingested salicylates, for example, will give the urine a blue-purple color upon application of ferric chloride. Unlike the phenylpyruvic acid reaction, however, this color does not fade away. Some of the color responses obtained when a ferric chloride solution is added to urine samples are: green from bile, homogentisic acid (alcaptonuria), the catecholamines (pheochromocytoma), and the urine of maple syrup disease, red brown from diacetic acid, gray from melanin, light violet from chlorpromazine ingestion, and purple from proclorperazine ingestion. Color reactions are fairly stable except with homogentisic acid. In this case the green color is extremely fleeting, disappearing within a second or two. The fact that the ferric chloride reagent will demonstrate the presence of various drugs and unusual metabolites other that

phenylpyruvic acid does not impair the values of this test but rather makes it more interesting and more valuable. For example, the first cases of histidinemia were discovered by finding individuals with positive ferric chloried urine test but normal serum phenylalanine content.

The ferric chloride solution is very inexpensive and when made with distilled water and stored in polyethylene bottles it is stable indefinitely. A 10 percent solution is preferred because of its quick, intense color reaction. When a few drops are added to a small amount (1 cc.) of urine, it has been found unnecessary to add acid first because the ferric chloride solution is itself very acid.

The diaper test is a modification of the ferric chloride test-tube test. A drop of 10 percent ferric chloride is placed on a baby's wet diaper (or even if the diaper has dried since being wet), and a blue-green to gray-green color appears immediately. The concomitant use of a drop of acid is neither necessary nor desirable. As with the test-tube test, the color is transient. Many times a definitely positive test will fade in less than half a minute. Such fading starts in the center of the spot, and the last to fade is the green-rimmed periphery. Whether positive or negative, the spot on the diaper leaves a permanent stain. This is perhaps worth mentioning to the mother. Although thousands of infants have been tested there has been no real complaints from the mothers.

The same false-positive reactions occur with the diaper test as with the test-tube test. The test has proved to be inexpensive and simple to perform. One penny's worth of solution can test several hundred infants. Of 104 PKU urine specimens allowed to stand at room temperature for 4 hours, 97 (or 93 percent) still definitely tested positive with ferric chloride.

In practice it was found that in a considerable number of cases the infant did not have a wet diaper, and the mother had no wet diaper with her. For this reason, mothers are instructed to bring along with them on the initial and subsequent clinic visits the most recently wet diaper. In this way approximately 30 percent additional infants may be tested who would otherwise be missed. False-negative tests unfortunately do occur and this test is not as reliable as the ferric chloride test-tube test.

The dinitrophenylhdrazine test-tube test. Properly prepared and used, the dinitrophenylhydrazine (DNPH) reagent is the most sensitive and reliable of the various urine tests for PKU. False-negative test reactions using DNPH on known untreated cases of PKU are rare (less than 1 percent). Because other substances rarely found in urine will react to give a positive test with the DNPH, any positive test should be cross-checked with a ferric chloride test.

Dietary treatment for PKU was first described in the early 1950's and has since been reported in enough cases to establish its efficacy in the treatment of infants and small children. When the diet has been started in the first several months of life, significant mental deficiency is thought to be prevented. The rate and irreversibility of the deterioration are somewhat variable; however, it is generally felt that the diet should be tried on all children under 3 years of age and that many of these may be significantly improved. The cases of children above 3 years of age have to be considered individually. It is felt by some workers in this field that older PKU children who are only mildly retarded or who have marked behavioral or convulsive disorders are more likely to show benefit from diet management than others in the same age group.

The purpose of the diet is to lower the blood phenylalanine from the abnor-

mally high levels caused by the disease (15-60 mg. per 100 ml. of serum) to near normal levels (1-3 mg.) while promoting normal body growth by the provision of all essentials for good nutrition. Because all proteins in normally available foods are 4 to 6 percent phenylalanine, it is impossible to devise a diet from such foods that will lower the phenylalanine level and still provide sufficient protein for growth and repair. Therefore, all low phenylalaning diets are based on synthetic foods with provide amino acids with little phenylalanine. Most of these synthetic foods have been made with a modified casein hydrolysate. Several products have been available commercially in the United States and Europe. Actually, these special products are so low in phenylalanine that if given by themselves they would produce a phenylalanine deficiency, including poor growth and a paradoxical rise in serum phenylalanine due to catabolism of body protein. Phenylalanine is an essential amino acid and the body requires a certain minimal daily amount. An opportunity is thus provided for varying the diet by the addition of low protein vegetables and fruits--with the goal of maintaining a serum level of from 2 to 6 mg. of phenylalanine per 100 ml. of serum. (These are believed to be the safe levels. How high the phenylalanine can be kept and still get the best results has not been determined.) The serum level of phenylalanine at which phenylpyruvic acid will begin to appear in the urine is between 10 and 15 mg. per 100 ml. Urine tests are inadequate as checks of dietary control. There is need of periodic serum phenylalanine level determinations. It is advised that these serum levels be obtained at intervals not less than every 2 to 4 months while a child is on the low-phenylalanine diet. (And tests should be run even more frequently during the early months of control.) The serum levels are necessary to detect both excesses and deficiencies of phenylalanine so the diet can be adjusted accordingly.

In the United States experience has largely been with an American-made product,

Lofenalac®. Lofenalac® has fat, carbohydrate, and certain minerals and vitamins incorporated with the low-phenylalanine casein hydrolysate. One measure (tablespoon) of Lofenalac® powder has approximately 1½ gm. of protein equivalent, with 7½ mg. of phenylalanine. One measure (tablespoon) added to 2 ounces of water makes a 20 calorie to the ounce formula which has almost the same consistency, appearance, and components as milk minus 90 percent of its phenylalanine. It has a nutlike flavor which has been well accepted by almost all patients. Most of the children have taken it as a beverage either standard strength or somewhat concentrated. Several have preferred to take it mixed directly into their low-protein foods. The powder can also be utilized in special low-phenylalanine recipes for pastries, breads, puddings, ice creams, and sauces. Realization on the part of the mother or others responsible for feeding a child, of how the diet can be varied and still meet the child's needs will lead to easier control and success with the diet. Quite naturally it is easier to introduce this new diet to a small baby than to an older child.

In the early months of life, the baby's low-phenylalanine formula may be supplemented with a small quantity of milk plus extra vitamins and iron. As the baby grows older, all varieties of fruits and certain low protein vegetables, such as carrots, beets, string beans, squash, turnips, tomatoes, etc., are added. These low protein foods continue to form the basis of the food supplements and later, depending on the amount of phenylalanine allowed and the child's preference, two or three small servings of cereal, potato or cookies may be added to the daily menu. Small doses of supplementary vitamins and iron may be given as an extra precautionary measure, although with the recent inclusion of vitamin C, the Lofenalac formula is probably adequate in these factors. Sample diets for infants and young children are given in the table on the following page.

Age and weight	Formula	Breakfast	Midmorning	Dinner	Midafternoon	Supper	Bedtime
2 months (10 lbs.)	15 measures Lofenalac® 2 oz. milk 26 oz. water	Five or six 5–6 ounce feeding of formula					
8 months (18 lbs.)	22 measures Lofenalac® 2 oz. milk 25 oz. water	½ cup chopped peaches 8 oz. formula		½ cup chopped carrots 8 oz. formula		½ cup chopped pears 8 oz. formula	8 oz. formula
2 yrs. (26 lbs.)	26 measures Lofenalac® 1 oz. milk 20 oz. water	½ cup dried rice cereal* with 3 oz. formula with sugar ⅓ cup orange sections 6 oz. formula		½ cup cooked carrots 2½ tbsp. mashed potato made with formula and 1 tsp. butter ½ cup apple sauce 6 oz. formula	2 animal cookies 6 oz. formula	3 tbsp. of green beans 3 pear halves 6 oz. formula	
4 yrs. (36 lbs.)	27 measures Lofenalac® 25 oz. water	½ cup dried rice cereal* with 2–3 oz. formula 1 small orange 8 oz. formula	wedges of apple	½ cup cabbage and carrot salad with vinegar and oil dressing ½ cup homemade vegetable soup 1 peach half 8 oz. formula	3 animal cookies 4 oz. formula	½ banana ½ cup tapioca pudding made with pineapple juice 8 oz. formula.	Synthetic fruit flavored drink

1 measure = 1 tablespoon 16 tablespoons = 1 cup *Do not use any "protein fortified" cereals

From these sample menus, a handy rule of thumb should be noticed. Children about 1 year of age need approximately 1 measure (tablespoon) of Lofenalac® per pound of body weight each day. For younger infants the need is proportionately greater, and for older children, it is proportionately less.

One of the means of helping parents is to provide them the food lists and special recipes that have been devised for low-phenylalanine diets. The food lists give the equivalent amounts of food that provide 15 mg. of phenylalanine, called one "equivalent" according to one plan that has been devised. By substituting equivalents of various foods, the parents can easily vary the diet and still keep within the prescribed amount of phenylalanine.

It should be noted that every child will not take to a low-phenylalanine diet without any difficulty. Depending on this personality, the older the child is, the more he will miss his previous diet, and the more resistance he will put up to the new diet. But experience has shown that the difficulties that were encountered with older mixtures have not been a problem. Within a week, even two and three year olds have been drinking the Lofenalac® and liking it--and without the use of special flavoring or sweetening.

Any physician who starts and supervised this diet must be prepared to spend extra time with the family. Public health nurses, nutritionists, and social workers are valuable assistants in this field. Conscientious, continued follow-up guidance and counseling are essential for long-range success of the program.

The length of time that a child should be kept on the diet to obtain optimal and permanent benefit has been the subject of much interesting discussion. In the natural course of the disease, it seems that deterioration does not continue much beyond three years of age and this has been quoted as the age after which the special diet may not be necessary. The issue has been confused by the fact that

a few PKU children who were not treated until after three years have shown good improvement. At the present time, scattered experiences are indicating that children over three years are maintaining their I.Q.'s off the diet. However, since it seems to be true that the adverse personality effects of phenylketonuria as well as mental deficiency respond somewhat to the low-phenylalanine diet, it will be interesting to see whether this will be a factor in the duration of treatment. Some believe that discontinuance of the diet should occur in adolescence rather than at three to four years of age. In fact, recent evidence suggests that female phenylketonurics who are desirous of pregnancy may have to be on a low-phenylalanine diet during the entire pregnancy. The reports of retarded children being born to PKU mothers suggests that elevated maternal serum phenylalanine may cause foetal damage in utero. On the other hand, there have been reports of women with PKU producing normal children. It will take a few more years of research and study to be certain of the long-term effects of diet treatment on both mentality and personality.

It should be emphasized that the child must be under a doctor's care at all times while on the diet to assure the maintenance of prescribed levels of phenylalanine both for maximal benefit to the child's mentality and to prevent dietary deficiency.

It has been shown that the mental deficiency of phenylketonuria (PKU) can be prevented or favorable modified if a speical low-phenylalanine diet is started early in life. Those concerned with child health are faced with the challenge of finding these children during infancy.

As of November 1966, thirty-seven of the fifty states in the United States had passed laws and these laws were in effect pertaining to phenylketonuria. These thirty-seven states are Alabama, Alaska, California, Colorado, Connecticut,

Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusett, Michigan, Minnesota, Missouri, Montana, New Hampshire, New Jersey, New Mexico, New York, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Texas, Utah, Virginia, West Virginia, and Wisconsin. These laws all require that all infants be tested for phenylketonuria.

On the whole, it has been may observation, that the majority of the American people seem to be extremely apathetic in regard to phenylketonuria. In fact, during the eighteen week period of my research in this area, I have run across a very few people who even know what PKU is and/or have ever heard of it. This is an extremely grave situation when we stop to realize that these apathetic and "ignorant" (on this subject) people are future parents, if not parents all ready!

If this situation weren't sad enough, it seems that some of our "influential and prominent" elected legislators have gone on record as being opposed to any type of legislation that would insure that each child be tested for PKU--a step that, in my opinion, could be nothing but beneficial not only for the children affected but for all Americans. (For more in depth study on this aspect see Saturday Review, June 3, 1967, p. 56 +).

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