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A Growth Study on Phenylketonurics

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A Growth Study on Phenylketonurics

by

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A Thesis in Partial Fulfillment

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————

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Each person whose signature appears below certifies that he has read this thesis and that in his opinion it is adequate, in scope and quality, as a thesis for the degree of Master of Science.

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THE PROBLEM

Many facets of phenylketonuria have been studied since the discovery of the disease in 1934. Outstanding among these is the mental retardation associated with the untreated condition. Since 1953, treatment of this metabolic disease with diet therapy has become increasingly successful in alleviation of the mental retardation. However, at the present time very few reports are available on the influence of a phenylalanine-restricted diet on the growth of phenylketonuric children.

I. THE PROBLEM

Statement of the Problem

It was the purpose of this study:

1. To compare the mean height of male and female heterozygotes (parents of phenylketonuric patients) with the mean of the normal male and female adult population.

2. To determine if treated phenylketonuric children differed in stature from the norms established in the general population.

3. To determine if there was a significant difference between stature of treated phenylketonuric patients with "good" control (defined as serum phenylalanine levels equal to or less than 4 milligrams per cent) versus those with "poor" control, when age of beginning treatment was considered.

4. To determine the phenylalanine, protein, and caloric intake of phenylketonuric patients with good control (defined as serum phenylalanine levels equal to or less than 6 milligrams per cent) and compare this intake with protein and calorie intakes recommended by the National Research Council.

Importance of the Study

Those treating the disease have observed that the children were of smaller stature than normal children and smaller than untreated phenylketonuric children. Searching the literature for growth studies on the phenylketonuric revealed only one report.[31] There have been some general references suggesting that stature is smaller,[25, 26, 79] yet others have made statements that treatment allowed for normal physical and mental growth.[15, 26] Centerwall stated that both the treated and untreated phenylketonuric tends to be smaller than average so that "it appears the low phenylalanine diet may have little effect on the usual pattern of physical growth."[25]

If the phenylketonuric children were found to be of significantly smaller stature than the normal, particularly if parents compared well with the norms, a basis would be laid for further research. On the other hand, if the study showed that the treated children were of normal size, concerns related to adequacy of the casein hydrolysate to support growth would be relieved.

II. LIMITATIONS OF THE STUDY

Since phenylketonuria is a relatively rare disease the sample available for this study was small. Another limiting factor was the lack of pre-prepared protocol on what, how and when to collect growth and nutritional data.

There were inherent inaccuracies in the nutritional data brought about by the human element as well as a lack of nutritional data in some instances because the parents did not keep a three day diet record as requested before each serum phenylalanine determination. Complete phenylalanine analyses were lacking and those available had been based on few samples and old techniques so that in calculation of the phenylalanine content of the diet, phenylalanine as five per cent of total protein was used until some time in 1965.

CHAPTER II

REVIEW OF THE LITERATURE

Research on phenylketonuria has intensified during
the past few years, and much has been published in regard
to this metabolic disease. Only a brief summary of
related research will be presented.

Many growth studies have been reported, particu-
larly during the first thirty to forty years of this
century. Literature on growth will be cited only as it
has a bearing on standards used for comparing the growth
of the children and as it relates to conditions which
affect growth in general.

I. LITERATURE ON PHENYLKETONURIA

History, Incidence and Etiology

In the spring of 1934 a young mother brought her
two children to Dr. Asbjorn Folling, a Norwegian
physician and biochemist, for an examination. They were
both mentally retarded and had a peculiar odor. When
Dr. Folling added ferric chloride to their urine, a green
color appeared which he identified as being caused by
phenylpyruvic acid. He hypothesized that the disease
"represented a disturbance in the metabolism of the amino
acid phenylalanine . . . and that this same abnormality
might be causing the retardation in these two children
and perhaps in other mental defectives."[23] In five

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months' time he had identified eight other cases and had ready for publication a scholarly report on a new metabolic disease which he called "imbecillitas phenylpyruvica."[22, 23]

It is the opinion of Guthrie and Hsia that the condition arises once in every 10,000 births in the United States,[40, 43] however, an incidence greater than this has been reported in some screening programs.[5, 66, 81]

The disease occurs equally in both sexes and is found in most races, but is more common in the people of Northern European and Japanese origin. It is rarely found among Negroes and Jews.[34, 67]

Phenylketonuria is a metabolic disease of genetic origin. Jervis has shown that the disease is transmitted by a single autosomal recessive gene. Both parents are normal because the recessive gene cannot gain expression unless it pairs up with another similar gene to form the homozygote recessive state. In the parents, the normal gene suppresses the one recessive gene for phenylketonuria and this condition is described as heterozygote. When two parents mate who both have a recessive gene for phenylketonuria, conditions are such that both may pair and produce offspring with the disease.[50, 95]

The genetic status of children born from marriage of two heterozygote parents shows a Mendelian distribution: 1 entirely normal, 2 heterozygote carriers (clinically normal), 1 phenylketonuric. It should be emphasized, however, that this 1:2:1 ratio is statistical and that in these families each birth involves a 1 in 4 chance that the child will have phenylketonuria.[89]

The recessive trait is carried by about one in fifty to seventy persons in the general population.[69, 78]

Clinical Findings in the Untreated

Most infants with phenylketonuria are brought to medical attention because of delayed development in one or more areas. The mothers notice the children do not sit, stand, walk, or talk at the time normally expected.

Mental manifestations. The most striking clinical feature of the untreated phenylketonuric is mental retardation, evident at four to six months of age.[17,43,94] The large majority of the patients are low grade defectives.[43, 67] Twenty-five or so atypical phenylketonurics with normal or near normal intelligence have been found.

Body size, height and weight. References in the literature relative to size of phenylketonurics either before or after treatment are rare. One of the first reports stated "the patients are usually well built."[17] Centerwall,[25] Cheek,[26] and Paine[79] noted the children were smaller than the average normal child. Jervis found these patients somewhat smaller than normal individuals, but when compared with the average defective individual, they might appear larger and taller.[72] Obesity is a characteristic of the infant with phenylketonuria and this sometimes leads to a mistaken diagnosis of hypothyroidism.[60]

Neurological abnormalities. Abnormal electroencephalograms and other neurological manifestations such as convulsions, epileptic seizures, irritability, tremors of the hands, increase in reflexes, temper tantrums and hand posturing may occur with varying degrees of severity.[43, 67, 78, 93]

Extraneural manifestations. Eczema has been reported frequently,[89] vomiting in early life is common.[80] Phenylketonurics are often lighter in color than their parents or siblings.[43, 67] Japanese patients have brown hair instead of black.[34] A peculiar musty, mousey odor is noticed in the urine and sweat and was one of the first characteristic symptoms noted.

There is delayed dentition and enamel hypoplasia[94]

with wide spacing of the upper incisors in some patients.[67]
Feinberg and Fisch described the presence of calcified
spicules projecting into the epiphyseal area of the long
bones.[37]

Biochemistry

Normal phenylalanine metabolism. Phenylalanine is
an essential amino acid in that the benzene ring cannot be
synthesized in the body. In normal individuals, ingested
phenylalanine is used for protein synthesis and the remainder
(the greatest part) is hydroxylated to tyrosine by the
action of liver phenylalanine hydroxylase. This is an
irreversible reaction; two enzymes, triphosphopyridine
nucleotide (TPNH), molecular oxygen, ferrous ion, and a
pteridine like cofactor are required. The metabolic end
products of tyrosine are thyroxine, epinephrine (adrena-
line), fumaric acid, acetoacetic acid and melanin. Some
transamination of phenylalanine to phenylpyruvic acid and
thus to phenyllactic acid takes place, but these reactions
are reversible and usually end with further catabolism
through phenylalanine. Traces of phenylpyruvic acid may
be decarboxylated to phenylacetic acid. Tyrosine exerts
a sparing action on phenylalanine to the extent of about
one-half the daily requirement for growth and three-fourths
of the requirement for nitrogen equilibrium, since most
of the functions of phenylalanine are performed subsequent
to its conversion to tyrosine.[21, 70, 87, 100]

Two enzymes are involved in the phenylalanine hydroxylase system, which catalyzes the oxidation of phenylalanine to tyrosine. Enzyme I is a labile enzyme which has been purified from rat liver and requires DPNH; enzyme II is a stable enzyme and requires oxygen, TPNH and tetrahydropteridines. This second enzyme is not involved in the hydroxylation reaction, but merely catalyzes a reaction which keeps the coenzyme in an active form so that the hydroxylation can take place.[34]

In Figure I the usual pathways for phenylalanine and tyrosine metabolism are outlined.

Jervis demonstrated that the inability of the phenylketonuric to metabolize phenylalanine was due to a defective oxidizing system for converting phenylalanine to tyrosine.[52] Later he showed that phenylalanine hydroxylase activity is not present in the liver of patients with phenylketonuria.[51] By the use of radio-active phenylalanine, it was found that the phenylketo-nuric could oxidize phenylalanine to tyrosine about five per cent as well as normal individuals.[16, 98] Armstrong states that ten per cent of the phenylalanine is oxidized to tyrosine.[67] It is now known that phenylketonuria is caused by a deficiency of Enzyme I.[34] Regarding the hereditary enzyme defect, Hsia states:

> All we can say is that the enzyme . . . does not appear to be working properly (the enzyme has not been crystallized, and there is no physical means of showing whether it is present or absent).
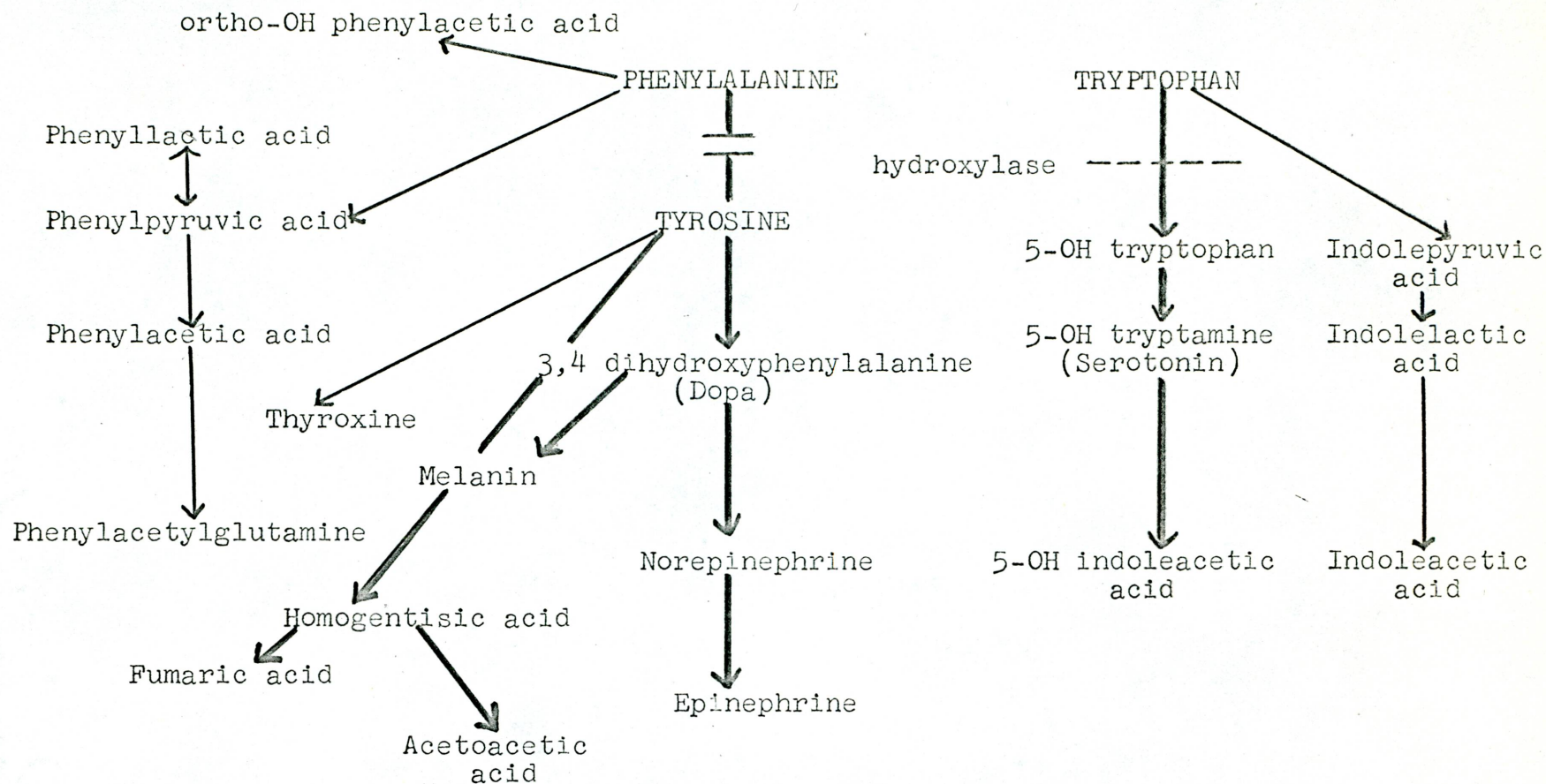
FIGURE 1

METABOLISM OF PHENYLALANINE, TYROSINE, AND TRYPTOPHAN SHOWING
BLOCKS THAT OCCUR IN PHENYLKETONURIA

This can occur because the enzyme molecule is completely absent and hence is unable to do its work. More likely, the protein molecule is present but there is a genetically determined mutation at the reactive site. It is probable that, as in the abnormal hemoglobins, there has been an amino acid substitution so that the enzyme-substrate reaction cannot take place properly, and one is given the impression that we are dealing with an inactive enzyme. Finally, it is possible that the enzyme could be both present and structurally normal but unable to function properly in the environment because of alterations in the host or within the cells. A deficiency of cofactors or the presence of inhibitors could produce such an effect.[43]

In the absence of phenylalanine hydroxylase activity, a group of minor pathways of phenylalanine metabolism, little used in normal individuals, become prominent. Transamination of phenylalanine yields phenylpyruvic acid (which forms the green color in the presence of ferric chloride). Accumulation of this product leads to formation and excretion of phenyllactic acid, ortho-hydroxyphenylacetic acid, and phenylacetic acid (responsible for the odor associated with the disease, the latter appearing in the urine as phenylacetylglutamine). Phenylalanine and phenylpyruvic acid (this usually predominates) are also excreted in the urine. A normal excretory product, metahydroxyphenylacetic acid, is absent or greatly diminished in quantity.[13, 21, 34, 70, 94, 100]

There are increased amounts of indolelactic, indoleacetic and indolepyruvic acids in the urine indicating that a disturbance of tryptophan metabolism is associated with phenylketonuria. The serum level of serotonin, five-hydroxy-indoleacetic acid and other hydroxylated deriva-

tives of tryptophan are lower in the untreated phenylketonuric, showing a close inter-relationship in the hydroxylation of aromatic amino acids.[68, 70, 94, 101] It has been found that the same enzyme which hydroxylates phenylalanine also hydroxylates tryptophan to five-hydroxytryptophan, the precursor of serotonin.[16, 70] Phenylalanine metabolites have an inhibitory effect on five-hydroxytryptophan decarboxylase.[34]

The decreased pigmentation in phenylketonuria results from the competitive inhibition of phenylalanine on the tyrosinase system which catalyzes the first step and accelerates the second step in the metabolism of tyrosine to melanin. If the intake of tyrosine is increased or the intake of phenylalanine lowered (as in treated patients) the hair and skin become darker.[34, 67, 94]

There are no detectable abnormalities in the amino acid composition of proteins of various tissues, or serum proteins, or of hemoglobin in the phenylketonuric.[15, 34, 67] The phenylalanine level in the cerebrospinal fluid is one-fourth of that in the plasma.[94] There is an altered pattern of plasma amino acids; the alpha amino nitrogen of the phenylalanine found in phenylketonuria is about half of the normal total alpha amino nitrogen of plasma, yet the total alpha amino nitrogen in the plasma is not substantially higher than normal. The high phenylalanine content evidently causes a depression of the concentration of most other amino acids. Glycine is present at a

normal level and histidine at an increased level.[70, 89, 94]

Figure I, page 10, shows the main alterations of metabolism of phenylalanine and tryptophan in the phenylketonuric.

Treatment

Since the clinical symptoms of phenylketonuria result from the accumulation of phenylalanine and its metabolites in the body, treatment is aimed at reducing these biochemical compounds. This is accomplished by the use of a phenylalanine-restricted diet.

Bickel and coworkers (1952) were the first to devise a low phenylalanine diet which they administered to a phenylketonuric. Blood phenylalanine was reduced and phenylpyruvic acid in the urine disappeared.[17]

Early diagnosis and dietary treatment are of utmost importance in preventing the associated mental changes.[58, 61] In older children, increase in intelligence cannot be expected, but clinical symptoms improve.[18, 45, 67]

The major source of nutrients in the phenylalanine-restricted diet is supplied by the use of a specially processed protein hydrolysate, low in phenylalanine. This amino acid is purposely low so that the phenylalanine requirements may be adjusted to meet the individual's requirements for growth. This is accomplished by the judicious addition of a wide variety of natural foods,

thus allowing the phenylketonuric's diet to be as near normal as possible.[14, 61, 67, 99]

<u>The diet and its nutrients</u>. The optimal daily intake of phenylalanine for the phenylketonuric infant has been estimated to be forty to twenty milligrams per pound each day, with a gradual decrease of requirements on a weight basis with increasing age in each child.[1, 2, 24] The phenylalanine requirement for the normal infant is forty-one milligrams per pound per day.[92] Others have reported considerable variation in the amount of phenylalanine needed by phenylketonurics during the first year of life, both from infant to infant, and at different times in the same infant.[56, 100] Two and a half to seven milligrams per pound per day has been set as the possible daily needs of a fifteen year old phenylketonuric boy.[2]

> Phenylalanine requirements vary but rise to a maximum when body protein is being formed at the highest rate. This parallels rapid growth which occurs during the first year of life. The time and degree of this peak varies from infant to infant. Older children usually have a relatively lower requirement, but their tolerances are variable also . . . All low-phenylalanine diets must be tailored and altered according to the individual child's tolerances and requirements.[99]

The protein need of phenylketonurics may be higher than for the normal child since the protein is in the form of a casein hydrolysate. At the present time one and three fourths to two grams of protein per pound is recommended for the infant up to three months of age and

one and a half grams for the infant from four months to
a year.[89]   These recommendations are higher than those
for the normal baby.

Caloric intakes of phenylketonuric children on the
low phenylalanine diet have been higher than the National
Research Council recommends.[47, 84, 100]   Centerwall
suggested sixty to sixty-five calories per pound per day
for the infant with phenylketonuria.[24]

Treatment and growth.   Very little appears in the
literature with the exception of general statements that
a phenylalanine level should be maintained which will
allow for satisfactory growth and that if this level is
too low, growth responses will be inadequate.   Centerwall
stated "the children generally had somewhat slow growth
patterns but were well nourished for their heights."[25]
Of the six children who were started on the low phenylala-
nine diet after eight months of age, five maintained a
growth pattern similar to that of the pre-diet period.
He reported significant drops in percentile levels in the
babies who were started on treatment before two months of
age.   In conclusion he wrote:

> Observations on physical growth show that the
> children's heights tend to be below average, but
> their weights have been in good proportion to
> their heights.   In that untreated children with
> phenylketonuria also tend to be smaller than
> average, it appears that the low phenylalanine
> diet may have little effect on the usual pattern
> of physical growth.[25]

On the other hand, Cheek stated that the use of the low phenylalanine diet (improved both mental and physical status,[26]) and Bessman says "the majority of the cases found and placed on the diet grow normally, both physically and mentally."[15]

A German scientist observed significant retardation of growth in children suffering from phenylketonuria and treated with a low phenylalanine diet, compared with untreated phenylketonurics. There was a retardation of bone age and a thickening of the metaphyseal plate, which he felt was due to changes in amino acid balance.[31] This same author reported that growing rats fed with protein hydrolysate low in phenylalanine showed definite growth inhibition, but with the addition of phenylalanine and tyrosine, retardation of growth was prevented. Further studies on the rats "revealed definite structural and biochemical changes mostly in the epiphyseal growth area."[32]

That there may be definite changes in bone growth has been shown by others. Feinberg and Fisch studied a group of thirty-three patients at the University of Minnesota Hospitals; five in the younger age group showed unusual bone changes in growing long bones. Serum calcium, phosphorus and alkaline phosphatase were in the normal range and they did not think that diet was related to the cause of changes in the long bones.[37] However, Murdock and Holman followed two phenylketonurics from infancy and found a direct correlation between diet,

serum alkaline phosphatase, and epiphyseal spiculation.
"Both patients exhibited subnormal bone growth, decreased
weight gain, and lowered serum alkaline phosphatase
levels, corrected by increasing dietary phenylalanine."[77]
Hsia states that calcified spicules have been found to
project into the epiphyseal area of long bones and
cupping occurs in the metaphyseal plate, along with
osteoporosis which he attributed to protein mal-
nutrition.[46]

Termination of dietary treatment. Various ages
have been proposed as to time the diet might be
discontinued.[4, 22, 102] Horner reported termination of
dietary treatment at four years of age on three children
with phenylketonuria, treated from earliest infancy, and
found no deterioration of mental development.[42] However,
Koch cites a case which had been treated from sixteen
months to four years of age. At age six and a half the
child was brought to his clinic when she began to
experience psychomotor seizures. He states that dis-
continuance of diet therapy may be hazardous and
recommends caution when considering it.[89] At the present,
both Koch and Bickel continue diet therapy at least
until adolescence.[59, 60, 67]

II. LITERATURE ON GROWTH

Today there is no lack of literature on growth and its many aspects. In fact, the "pediatrician and his ancillary colleagues may well be overwhelmed by the quantity of data, charts and grids concerning growth that have appeared in the last 20 years."[35]

Assessment of Growth

Ideally, growth and development are assessed through observations and measurements obtained from pediatric examinations, health and dietary records, x-rays, anthropometric measurements, dental examinations, measures and observations on the skin, hair, muscle and subcutaneous fat, observations of sexual maturation and biochemical tests. Practically, the investigator usually has to settle for those observations and measures which are directly concerned with his purpose for the research. Since this study is concerned with anthropometric measurements and dietary records, the discussion will be limited to these phases.

Anthropometric measurements. There is a minimum of lengths and circumferences which should be maintained in any growth study. Garn has slightly modified those which were recommended by the Committee on Nutritional Anthropometry, Food and Nutrition Board, National Research Council in 1956.[28] In the listing, the

measurements are rated from A (absolutely essential)
through E (desireable but rarely practical in the field).
This listing follows:[38]

Birth and 1 month

A. Length (crown-heel and crown-rump) and weight.
B. Head circumference, chest circumference.
C. Bicristal diameter.
D. Fat-folds at triceps, below the scapula and
on the chest at the mid-axillary line.

During the first year

A. Lengths (including stem length) and weight.
B. Head, chest, arm, calf circumference.
C. Bicristal diameter.
D. Fat-folds.
E. Postero-anterior hand x-ray.

1-6 years

A. Lengths, standing height and weight.
B. Circumferences, excepting head after 3 years.
C. Bicristal and bisocromial diameters.
D. Fat folds.
E. Hand x-ray.

From 7 years on.

A. Lengths, height and weight. Ratings of sexual
maturation.
B. Chest, arm and calf circumference.
C. Bicristal and bisacromial diameters.
D. Fat folds.
E. Hand x-ray.

Reasonable care should be exercised that these
measures be taken with accurate, readable scales, calipers,
and tapes. Weight should be taken after the bladder has
been emptied, clothing should not be a variable factor.[38]

In order that there may be an accurate comparison
with established norms, measurements and observations
should be made at constant intervals,[7] ideally on the

subject's birthday or half-birthday or at other pre-determined ages. However, this is usually not possible and it is reasonable to allow for small tolerances. Garn suggests plus or minus 1 day until 3 months, 2 days at six months, 4 days at one year, etc., ending with plus or minus 25 days at 7 years of age.[38] Interpolations are not the best as velocity of growth varies with age and also with adverse influences.[71] The children in the Brush Foundation Study were measured within a week of their birthday.[91]

As an indicator of growth, height is fairly stable, whereas weight is influenced by many factors and may fluctuate greatly. A weight measure can be lost in disease, malnutrition or dieting, whereas height is not. It is necessary to know whether weight represents water, muscle, bone or fat.[35] Simmons states that "as a measure of growth, stature is superior to weight."[91] Holt[41] and Lowe[65] state that weight gain is adequate for assessing nutrition.

X-rays. The use of x-rays to determine skeletal maturity is a relatively simple and effective tool in assessing growth and is reasonably independent of body size.[39] It is the most widely used method of determining biological age.[54, 62]

The Atlas of Greulich and Pyle[39] is the standard of reference generally used in the United States for

the determination of bone age.[53] An x-ray of the left
hand is made and the number of calcified centers and the
amount of calcification is matched with a standard set of
films, each representing an average child at a particular
age.[35] When the nearest matching film has been found, the
age from this film becomes the "bone age" of the child
whose skeletal maturity is being assessed. Growth time
available to the child is related directly to the degree
of skeletal maturity exhibited.[11, 53]

One measure or film will give the status of the
child at that time and has some use, but rate of progress
seen through successive films is of more value in evaluation of growth.[54]

Dietary records. Nutrition is an important factor
for investigation in relationship to the various aspects
of growth, development, and health of children. Dietary
records should be both qualitative and quantitative, and
"should be made in conjunction with a competent nutritionist, preferably one with research training and field
experience."[38]

Growth Studies

Ideal patterns of growth for healthy children are
not known, though many studies provide data for growth on
selected populations.

The Iowa growth charts used regularly in pediatricians' offices were based on 13,000 cross sectional

height and 11,000 weight observations of Iowa city boys and girls between 1920 and 1940. The majority came from the higher socio-economic group.[49]

The Brush Foundation Study (1931-1942) was longitudinal in nature. The 999 children studied were a sampling of the Greater Cleveland child population selected on the following basis: 1) voluntary participation, 2) agreement to continued participation, and 3) freedom from gross physical and mental defects. The parents were from above average economic and educational status, all white, and of North European ancestry. The children were measured while dressed in indoor clothing with shoes removed.[90] This is the study on which Greulich and Pyle's Atlas was based. Two other well known longitudinal studies are the Harvard and Berkeley studies.[8,9,96,97]

Growth Patterns and Rate of Growth

The growth of normal children is continuous but not necessarily uniform from one age to the next; there are periods of both rapid and slow growth. In general all children grow rapidly the first year, slowly from then until the pre-adolescent growth spurt.

At birth and during the first year of life, boys are slightly heavier and taller than girls.[41] Sex differences tend to be negligible from about three years through ten to eleven years,[90] when girls exceed boys in stature.[41] From this age until thirteen, the girls

are taller, after which the boys catch up and pass. Boys
mature approximately two years later than girls with the
pre-adolescent growth spurt coming between the ages of
eleven to fourteen. This growth spurt manifests itself
between ages nine to twelve in girls.[41, 90] If there is
an unfavorable environment for growth, there is a lagging
rate of skeletal maturation. Males are more subject to
this maturation lag than females.[33, 53, 62]

There are two sets of growth factors, one which
determines the ultimate size of the individual and one
which determines the speed at which the individual will
attain this size.[53] The extra tall girl may be closer
to maturity than the shorter one or she may have a much
greater growth potential.

The growth curves for height and weight have been
derived from averages of the measurements of large
numbers of children at each age. For children under nine
years, this method is acceptable, but after this age,
comparing an individual child with the average can be
very misleading since the prepubertal growth spurt can
come very early or very late (and yet be very normal for
this individual) and this spurt is much more rapid than
is indicated by the curves of averages.[9]

Reed and Stuart report a wide range of variation
observed in the growth curves of height and weight in
their series of 134 children. They found that "the rate

of growth during early childhood, i.e., before 6 years of age was associated with, but not specifically predictive of, size at maturity and timing of the adolescent growth spurt. Individuals with rapid growth before 6 years of age tend to have large mature size and early adolescent growth spurt."[85]

It has been shown that children shift through more of the stature range during the early period of life and hold their approximate position during the middle period of childhood.[71, 90] Thus, self-predictability of stature is poorest during infancy and can be predicted somewhat more accurately at an age before the pre-adolescent spurt.[90]

In addition to periods of both rapid and slow growth naturally occurring in normal children, there are sudden spurts, often termed "catch up phase of growth" after an adverse circumstance such as illness or malnutrition has been removed.[41, 83] Cravioto found that when young, malnourished children were placed on a good diet, the rate of growth was very fast at the beginning of the rehabilitation period, but slowed later on. The initial rate corresponded to the actual size of the child. However, growth ceased at the usual chronological age, and the child became an undersized adult.[29] This is in line with Mitchell's findings that "full growth potential must be used continuously if full development is to be achieved."[74] However, Holt states that if the duration of growth

arrest has been short, the sudden spurt or "catch up" phase may compensate entirely for the growth arrest.[41]

There has been an increase in stature and weight in many countries during the past hundred years, thus the age at which a child attains a given height or weight has been reduced.[36, 41, 57, 62, 72] However, this secular increase in height and weight seen in the United States during the last century may be at an end. Infants studied recently show the same growth pattern (length and weight) as well cared for infants from the same area thirty years ago.[88]

Factors Which Influence Growth

There are many factors which influence growth and to do a thorough review of all would be quite impossible and much beyond the scope of this present research. Hence, this review will be brief and cover those factors important for this study.

Genetic influences. The rate and pattern of growth and body size an individual attains is determined by genetic and environmental factors.[28] This hereditary background has been estimated to be as much as eighty per cent of all influences.[35] Bayley found that there was an increasing correlation between the child's height and that of the parent of the same sex as the child grew older.[10] Kagan and Moss have cross-validated this parent-child relationship.[55]

Mitchell states that each child inherits genes for height and shortness, but that it is the inheritance from the taller parent that predominates.[75]

X-rays reveal that genetic control is linked not only to variation in ossification patterns but also to the speed at which these develop.[28, 53]

Studies of the relationship of rate of growth and nutrient intake suggest that infants have genetically or physiologically predetermined maximums of statural growth which they could not exceed no matter how much they increased nutrient intake.[88] Thus, it is seen that final stature is limited by heredity, but whether or not the individual realizes his full potential is determined by environmental factors.[28]

Endocrine influences. The anterior pituitary, thyroid, adrenal cortex and gonads secrete hormones which influence the rate and timing of growth. This influence is a very complex one. At the present time very little is known about the factors which control the rate of secretion of the growth hormone, somatotropin, by the pituitary.[41, 49]

Birth weight and subsequent growth. It has been suggested that birth weight may be connected with later growth. "A striking high proportion of children of the smallest birth weight were far below the 'normal' weight in later childhood . . . There were similar but less

striking changes in the mean height of these children at all ages."[48]

Climatic and seasonal influences. An interesting study was reported by Lloyd-Jones. He found Los Angeles Public School children in 1937 to be superior in height and weight to any other group and concluded that this superiority must "in part be put down to environmental influence in that area."[64]

Holt states that season affects growth and he found weight gain to be greater in late summer and fall than in winter, spring or early summer.[41] However, Prader, Tanner and von Harnack report that a minority of children regularly grow faster in height in spring and summer. One child showed a springtime velocity nearly double the autumn rate.[83]

Nutritional influences. The relationship of good nutrition and physical growth has long been recognized. Minimum requirements for many nutrients have been established. In the United States today efforts are being made to establish optimal levels and even maximal levels of nutrient intake compatible with health.[12]

As mentioned previously, the growth of infants now is about the same as twenty years ago for the same area of the United States. This would indicate that with optimal nutrition, there has been no further increase in

growth. The nutrition of these children has allowed them to obtain their genetic potential but increases past this point do not occur.[28, 86, 88]

Arrested growth occurring in conjunction with severe nutritional deficiencies has been noted with increasing frequency in developing countries. However, there must also be a class of children in whom nutritional limitations are such that frank clinical symptoms are absent, yet who do not reach their full growth potential because of these limitations.[74]

The extent to which undernutrition influences the size of an individual depends upon the age at which it occurs, the greatest effect being at the period of maximum growth, and its duration in relation to the total period of growth.[33] Dreizen compared the height and weight of 561 children with chronic nutritive failure with a group of adequately nourished, ethnically comparable children from the same geographic region. The undernourished children showed a substantial lag in height by the third year of age; this lag increased progressively in the boys while it remained constant in the girls.[33]

Several examples of nutritional limitation are cited by Mitchell. Viennese children after World War I were two to three years behind in height and weight. Growth of children in Stuttgart, Germany, was compared and a significant difference was observed between those

from the low income families and from upper income families. In both there was a leveling off or drop in stature after the two world wars and a period of unemployment in the early 1930's. A survey of Guam children in 1947 showed all to be retarded in height, weight, and skeletal maturity.[75]

Japanese data, where heights and weights of all school children had been recorded annually since 1900 showed a steady increase in stature until 1939. When the heights were again recorded after the war (1948), stature at every age was less than it had been in 1939. Since that time, there has been a steady increase in height along with concommitant increase of animal protein consumption. To find whether this increase was due to better nutrition, the author studied data from twenty-two orphanages. These children were smaller in stature than Japanese youth in general. When the nutrients from the foods used in the institutions were calculated, it was found that animal protein was a serious limitation. The Food and Agriculture Organization protein scores varied from sixty-seven to seventy-four in these orphanages. The limiting amino acids were tryptophan, the sulphur-containing amino acids, or both in all the institutions. These findings seem to "corroborate the theory that better nutrition, and particularly more adequate protein, are significant with respect to stature."[75]

A retardation of skeletal age is evident when there is chronic malnutrition;[53] there may also be "a considerable frequency and variety of anomalies in the bones of the hand skeleton."[33] Bone growth depends primarily on the proliferation of cartilage cells before calcified bone can form. This mechanism is very sensitive to both qualitative and quantitative limitations of protein.

> Since cartilage is protein and the growth mechanism is extremely sensitive to a protein limitation, it is understandable that physiologic growth may slow down or stop when the protein supply is limited in quality or quantity . . . The first reaction of young bone to growth-impeding factors is localized in and around the cartilage cells. The number of these cells is reduced as new bone production is limited. Apparently then this mechanism may be affected by a mild protein limitation when there are no other signs of a deficiency.[75]

When malnourished children are treated with protein supplements, epiphyseal calcification progresses more slowly than weight.[65]

The Harvard Growth Study included a nutritional study by Burke.[96] A comparison of her findings with the National Research Council Recommended Allowances showed average values for nutrient intake and especially protein to be higher than those recommended.

> Enormous differences between individuals of the same age and sex are equally obvious in the findings. At every age, for both sexes, and for both calories and protein, there was at least one child whose intake was approximately twice as high as that of one or more other children of the same age and sex . . . It was evident that many children varied widely from the average pattern in both level and rate of change in intake from year to year.[19]

Rueda-Williamson conducted a longitudinal study of sixty-seven infants from two to fifteen months of age; his report relates growth and nutrient intake simultaneously. These infants were from the same geographic area and ethnic groups as those who had participated in the Harvard Studies. The infants had high caloric and very high protein intakes as compared with the National Research Council Recommended Allowances. "The correlation between length increment and calorie or protein intake was not significant. The correlation coefficients between weight increments and calorie intake were significant but low."[88]

Nutritional studies were added to the program of the Denver Longitudinal Study in 1946. Beal presents data on height of these children to show the variety of individual patterns attained. Two boys had a similar caloric intake and weight but the second boy had considerably wider fat layers. Two other boys had similar caloric intake but were alike in height only. The four girls compared varied as much. It was concluded that caloric intake alone "cannot be expected to have a high positive correlation with weight gain."[12]

The dietary pattern of Indian pre-school children was correlated with height and weight. Those receiving the most protein showed the greatest increase in weight. Heights did not differ significantly.[6]

<u>Mental deficiency and retarded growth</u>.   There are
conflicting opinions regarding the relationship between
mental deficiency and physical growth.   Quoting from
Kugel and Mohr: "Many are of the opinion that the
factors which operate to produce mental debility also
seem to produce a general physical inferiority, others
emphatically maintain that this relationship is slight
or even non-existent."[63]

Skeletal age has been found to be closely corre-
lated with chronological age and not delayed in the
mentally retarded.   However, if these patients were
divided into diagnostic categories, those with disorders
of metabolism exhibited the greatest percentage delay in
bone maturation.[82]

Cravioto proposes that malnutrition in the very
young individual may produce mental retardation that
does not repair with dietary restoration.   In five
different communities of Mexico and Guatemala he found
high correlations between deficits in height and weight
and developmental scores.[29]

A recent cross-sectional survey of physical
measurements on Caucasian institutionalized mentally
defective patients showed a positive correlation of
height and weight with intelligence in both sexes.[76]
The fact that these patients were institutionalized
might in itself have had a bearing on their height and
weight.   Some are of the opinion that institutionalization

tends to lower the intelligence quotient due to lack of
stimulus in the social situation and this could be a
factor in appetite. Also, the diets might not be taken
as well due to inability to self-feed. Perhaps nursing
does not have as much time and interest to help the
patient with his food as the interested family members do.
However, research at a Child Development Clinic confirms
the positive correlation of intelligence and physical
growth.

> The degree of physical impairment is related to
> the severity of mental retardation. Regardless of
> the cause of the disorder, the data presented
> support the conclusion that the degree of mental
> retardation and the degree of physical growth
> deficiency are related, and that the greater the
> mental defect, the more checked will be the physical
> growth . . .

> While it is clear from this study and others
> that there is an association between physical
> development and mental development, it is not clear
> whether this is a cause and effect association . . .

> The supposition that brain defect can of
> itself produce physical growth retardation, may
> be a reasonable hypothesis.[63]

Culley found that profoundly retarded children,
with or without motor dysfunction, were shorter and
lighter for their age than higher functional children.[30]
On the other hand, it is reported that Servian children
"who had been seriously undernourished in infancy were
found at schoolage to have normal physical character-
istics but subnormal mental capacity."[20]

Summary

Growth is dependent on a great many genetic and

environmental factors. Control rests in the continuous
interplay of these forces operating through the endocrine
and nervous systems. Harmony among these forces results
in orderly growth progress; disharmony may lead to
bizarre growth disturbances.[33]

CHAPTER III

METHODS OF PROCEDURE

The methods of procedure are discussed under three
general classifications: 1) selection of the subjects
and data, 2) collecting and recording the data, and
3) analysis of the data.

I. SELECTION OF THE SUBJECTS AND DATA

Data utilized for this study was secured from the
medical records of phenylketonuric patients of the Child
Development Clinic of Children's Hospital, Los Angeles,
California. At this clinic the children were seen at
regular intervals on an outpatient basis for evaluation
of medical and developmental status. Data from forty-eight
medical records was used for the statistical analyses and
in some instances this number was further reduced. The
number of cases and/or measures are listed in each table.

The criteria for selection of the subjects for the
growth study were: 1) there must be serial measurements
of patient's height, and 2) there must be serial serum
phenylalanine determinations.

The criteria for selection of the data for the
nutritional study were: 1) the serum phenylalanine level
must be equal to or less than 6 milligrams per cent,

2) records of simultaneous serial phenylalanine, protein
and calorie intakes must be available, and 3) records of
simultaneous weights must be available.

II. COLLECTING AND RECORDING THE DATA

The following data were collected from the medical
records: birth date of the child, serial heights and
weights, bone ages, serial serum phenylalanine levels in
milligrams per cent, intakes of phenylalanine in milli-
grams per day, protein in grams per day, and calories
per day, with the date of each measure and/or observa-
tion. Father's and mother's heights were also recorded.
Age records were to the nearest whole month, inches
were to the nearest one fourth, ounces were to the nearest
tenth of a pound. Height and weight measurements before
2 years of age were made without clothing. After two
years of age, only the shoes were removed. Standing
height was used as soon as the child could stand erect.

Intakes of phenylalanine, protein, and calories
were calculated from three day diet records kept by the
parents immediately before the blood specimen was
obtained for determination of serum phenylalanine. Cal-
culations of protein and calories were based on analyses
listed in Food Values of Portions Commonly Used.[27] Data
for calculation of nutrient content of the casein hydro-
sylate (Lofenalac) was based on manufacturer's analysis.
Previous to July, 1965, phenylalanine was calculated as

five per cent of all protein; after this date, phenylalanine was determined from the analyses listed in <u>Food Values of Portions Commonly Used</u>[27] and <u>Journal of the American Dietetic Association.</u>[73]

III. ANALYSIS OF THE DATA

Parents' Height

Analysis of parents' height consisted of obtaining the mean and comparing this with the mean for the adult white American male and female.[3]

Height of Phenylketonuric Children

Statistical procedures were applied to the following hypotheses as indicated:

Hypothesis I. The mean of the last reported height of phenylketonuric children is less than the mean of the expected heights.

The z test for large sample correlated data was used to test the significance of difference between means of the last recorded height of treated phenylketonuric children and normals. The following formula was applied:

$$Z = \frac{M_1 - M_2}{\sqrt{\sigma_{m_1}^2 + \sigma_{m_2}^2 - 2r_{1\,2}(\sigma m_1)(\sigma m_2)}}$$

Where M_1 = mean height of normals and M_2 = last recorded height of phenylketonuric patients.

Existing norms from the Brush Foundation Study[41] were used as a basis for comparison of the growth data in this hypothesis. Since the children in this study were not measured exactly at ages which correlated with those of the normal growth study, it was necessary to interpolate the norms to arrive at the age on which the measurement used for the analysis was taken.

Hypothesis II. Phenylketonuric children whose treatment was instituted at or before six months of age are shorter than those whose treatment was instituted after six months, when the two groups are made comparable (by covariance) in terms of mean height at time treatment was started.

Hypothesis III. Phenylketonuric children under "good" dietary management are shorter than those under "poor" control when the two groups are made comparable (by covariance) in terms of mean height at time treatment was instituted.

Hypothesis IV. Phenylketonuric children whose treatment was instituted at or before 6 months of age under "good" control and those treated after 6 months of age under "poor" control differ in height from those who were treated at or before 6 months under "poor" control and after 6 months under "good" control.

Hypotheses II, III, and IV were analyzed using the analysis of covariance. The covariate was the height at time treatment started after the data was transformed by the following formula: $(\frac{A - E}{E})$, where A = actual height, E = estimated height, i.e., mean of normative data at same age as case. This was simply a means of making the heights comparable at beginning of treatment through a statistical procedure, so that if there was a later difference, this would have significance.

In testing Hypotheses II, III, and IV, the groups were divided according to control and age. Patients described as having "good" control were those whose serum phenylalanine levels were equal to or less than 4 milligrams per cent, 75 per cent of the time. Those in the "poor" control group had serum phenylalanine levels greater than 4 milligrams per cent greater than 75 per cent of the time. It should be noted the criteria of "good" and "poor" control in the growth section was based on a different serum phenylalanine level than the criteria for selection of the data used in the nutritional section. It is the opinion of some investigators that very low serum phenylalanine levels cause growth retardation. For this reason, a lower level was chosen for this section of the study.

Groups were further divided according to age of beginning treatment; i.e., one group was 6 months of age

or less at beginning of treatment, the other group was over 6 months of age at beginning of treatment. Thus, four groups were formed with 6 patients in the "young-good" group, 6 in the "young-poor" group, 10 in the "old-good" group, and 26 in the "old-poor" group. This method of comparison is illustrated by the following diagram:

		≤ 6 months	> 6 months
C O N T R O L	≤ 4 mg.% 75% of time	1 N=6 "young-good"	3 N=10 "old-good"
	> 4 mg.% 75% of time	2 N=6 "young-poor"	4 N=26 "old-poor"

Nutritional Data

For analysis of the nutritional data, the ages of the patients were divided into intervals by months and nutritional data was obtained (only if the simultaneous serum phenylalanine level was equal to or less than 6 milligrams per cent) for the following groups:

Group 1. $0 \leq 3$ Group 4. $10 \leq 12$ Group 6. $37 \leq 72$

Group 2. $4 \leq 6$ Group 5. $13 \leq 36$ Group 7. $73 \leq 108$

Group 3. $7 \leq 9$

Means and standard deviations of intake of phenylalanine, protein, and calories were obtained. Protein and calorie intake was compared with the National Research Council Recommended Allowances for the various ages.

CHAPTER IV

RESULTS AND DISCUSSION

The results are discussed under two general headings: growth data and nutritional data.

I. GROWTH DATA

Parents' Heights

Since heredity plays such a large part in the stature of an individual, the parents' heights were compared with the mean height for the American white male and female. There were 36 sets of parents' heights available for use in this part of the study. The range of the fathers' heights was 61.50 to 78.00 inches with a mean of 69.83 inches as compared to 69.68[3] inches for the American white male. The range of the mothers' heights was 57.50 to 71.75 inches, with a mean of 64.49 inches as compared to 64.17 inches for the American white female. The mean height of parents of phenylketonuric children was slightly above the mean height for the average white American, though only slightly so.

Hypothesis I.

This hypothesis deals with the comparison of the heights of the treated phenylketonuric children and normal children. The mean height of the research group at time of beginning treatment was 32.55, the mean of normal

children's heights at the same ages was 33.11, a difference of approximately one half inch. The mean of the latest measured height of the research group was 40.96, the mean for the normal children's height was 42.36, with standard deviations of 8.91 and 8.42, respectively. The difference of 1.40 inches would seem to indicate that treated phenylketonuric children were shorter than the general child population. The z test was applied to determine if the difference between the means of the treated phenylketonuric children and the normals was significant. Very significant differences were found. A probability of $\leq$ .001 indicated that the children in this sample could not have been drawn from the normal population more than 1 time in 1,000 if only chance differences were occurring. The conclusion reached was that treated phenylketonuric children were shorter than normal children. This difference in stature could be due to one and/or several unknown factors. The disease itself may cause the growth retardation or there may be diet related factors, one of which could be an amino acid imbalance.

Hypothesis II

When the last recorded heights of the phenylketonuric children were analyzed (by analysis of covariance) considering time of beginning of treatment, i.e., those started on treatment $\leq$ 6 months of age versus those

started on treatment after 6 months, it was found that
there was no significant difference between the two groups
in terms of their last measured height. The conclusion
was that age treatment was instituted in the phenyl-
ketonuric children makes no difference in their later
heights.

Hypothesis III

Hypothesis III evaluated the stature increase of
phenylketonuric children in terms of "control" as
defined in the chapter on methodology. Again the research
hypothesis was rejected as no significant difference was
found between the last measured heights of those under
"good" control and those under "poor" control. Thus, the
state of control of the treated phenylketonuric child
did not make any difference in growth, when height was
the parameter used as a measure.

Hypothesis IV

When the group whose treatment was started at or
before six months of age in "good" control and the group
whose treatment was started after 6 months of age in
"poor" control were compared with those whose treatment
was started at or before six months of age in "poor"
control and those whose treatment was started over six
months of age in "good" control, no significant difference
was found in terms of their last measured height. Again

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phenylketonuric children in terms of "control" as
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found between the last measured heights of those under
"good" control and those under "poor" control. Thus, the
state of control of the treated phenylketonuric child
did not make any difference in growth, when height was
the parameter used as a measure.

Hypothesis IV

When the group whose treatment was started at or
before six months of age in "good" control and the group
whose treatment was started after 6 months of age in
"poor" control were compared with those whose treatment
was started at or before six months of age in "poor"
control and those whose treatment was started over six
months of age in "good" control, no significant difference
was found in terms of their last measured height. Again

it was shown that control and/or time of beginning of treatment had no effect on later height of phenylketonuric children.

Skeletal Age

There were 40 children for whom one or more skeletal ages were available. Of this number, 22 had a normal bone age, 9 had a retarded bone age, and 9 had reports of both normal and retarded bone age. In the latter group, four were retarded at beginning of treatment and later normal, five were normal at beginning of treatment and were later retarded. Three of those who were normal at beginning of treatment and later retarded had returned to normal on a subsequent x-ray. In one child treatment began at 10 months of age but at 3 years 5 months there was a retarded bone age, however, this returned to normal three months later. Another child whose treatment began at 8 months had a retarded bone age at 3 years 9 months; this also returned to normal when he was 4 years 4 months old.

An interesting observation was that those having both normal and retarded bone age ratings fell within the group who were 24 months or younger at time treatment was instituted. This change in skeletal age probably reflects a growth pattern normal for those children. Table I shows the bone age scores on these phenylketonurics.

TABLE I

SKELETAL AGE SCORES ON FORTY
PHENYLKETONURIC CHILDREN

	Number	Per cent
Normal	22	55.00
Retarded	9	22.50
Normal and Retarded	9	22.50
Retarded at beginning of treatment	4	
Normal at beginning of treatment	5*	

*Of this group, 3 had returned to normal on a subsequent measure.

II. NUTRITIONAL DATA

Table II gives the means for serum phenylalanine level, dietary phenylalanine, protein, and caloric intakes for each of the age intervals. In the first interval, the mean age was 2.3 months with a standard deviation of 0.65 indicating that there were no measures for children under approximately six weeks of age. This material is graphically presented in Figures 2, 3, and 4.

Mean serum phenylalanine levels ranged from 1.4 to 2.8 milligrams per cent and indicated that the children were in good control. However, this was inherent in the data selected since the criteria for use of the measure was that serum phenylalanine level be equal to or less

TABLE I I

MEAN SERUM PHENYLALANINE LEVELS AND MEAN PHENYLALANINE, PROTEIN, AND CALORIC INTAKE FOR PHENYLKETONURIC CHILDREN OF VARYING AGES*

N	AGE			MEAN PHENYLALANINE (mgs)							MEAN PROTEIN INTAKE (grams)				MEAN CALORIC INTAKE			
				Serum		Intakes												
	w Months	Mean Age	SD	Mg. %	SD	Per Day	SD	Per lb.	SD	Per Day	SD	Per lb.	SD	Per Day	SD	Per lb.	SD
12	0 ⋜ 3	2.3	0.65	1.9	0.86	227	71	19.3	5.53	20.8	5.88	1.76	0.42	611	182	53.6	14.0
7	4 ⋜ 6	5.1	0.69	2.6	2.40	259	91	16.9	3.89	20.4	4.60	1.18	0.53	664	145	44.7	6.4
11	7 ⋜ 9	8.1	0.94	2.8	2.20	288	57	15.4	3.44	25.4	6.30	1.34	0.28	856	148	45.8	6.8
4	10 ⋜ 12	11.0	1.15	1.4	1.40	271	78	14.3	3.10	25.3	2.50	1.30	0.13	866	126	45.3	5.3
40	13 ⋜ 36	22.9	6.60	2.0	1.75	296	169	12.0	2.87	30.8	8.10	1.25	0.27	1086	274	43.9	9.1
38	37 ⋜ 72	51.1	8.53	2.7	2.10	405	164	10.5[y]	3.50	41.7[y]	10.80	1.10[y]	0.26	1569[z]	312	42.5[z]	6.9
17	73 ⋜ 108	87.0	6.52	2.5	1.90	488	224	9.7[x]	3.91	45.7[x]	12.10	0.95[x]	0.25	1817[x]	465	37.8[x]	8.9

*Data in this table are only for those children who had serum phenylalanine levels less than or equal to six milligrams per cent at the time of the measure.

Note: w Age intervals in months
       x N = 16
       y N = 36
       z N = 37

FIGURE 2

COMPARISON OF MEAN SERUM PHENYLALANINE, AND MEAN INTAKES OF
PHENYLALANINE, PROTEIN, AND CALORIES FROM BIRTH THROUGH
12 MONTHS

FIGURE 3

COMPARISON OF MEAN SERUM PHENYLALANINE, AND MEAN INTAKES
OF PHENYLALANINE, PROTEIN, AND CALORIES WITH NATIONAL
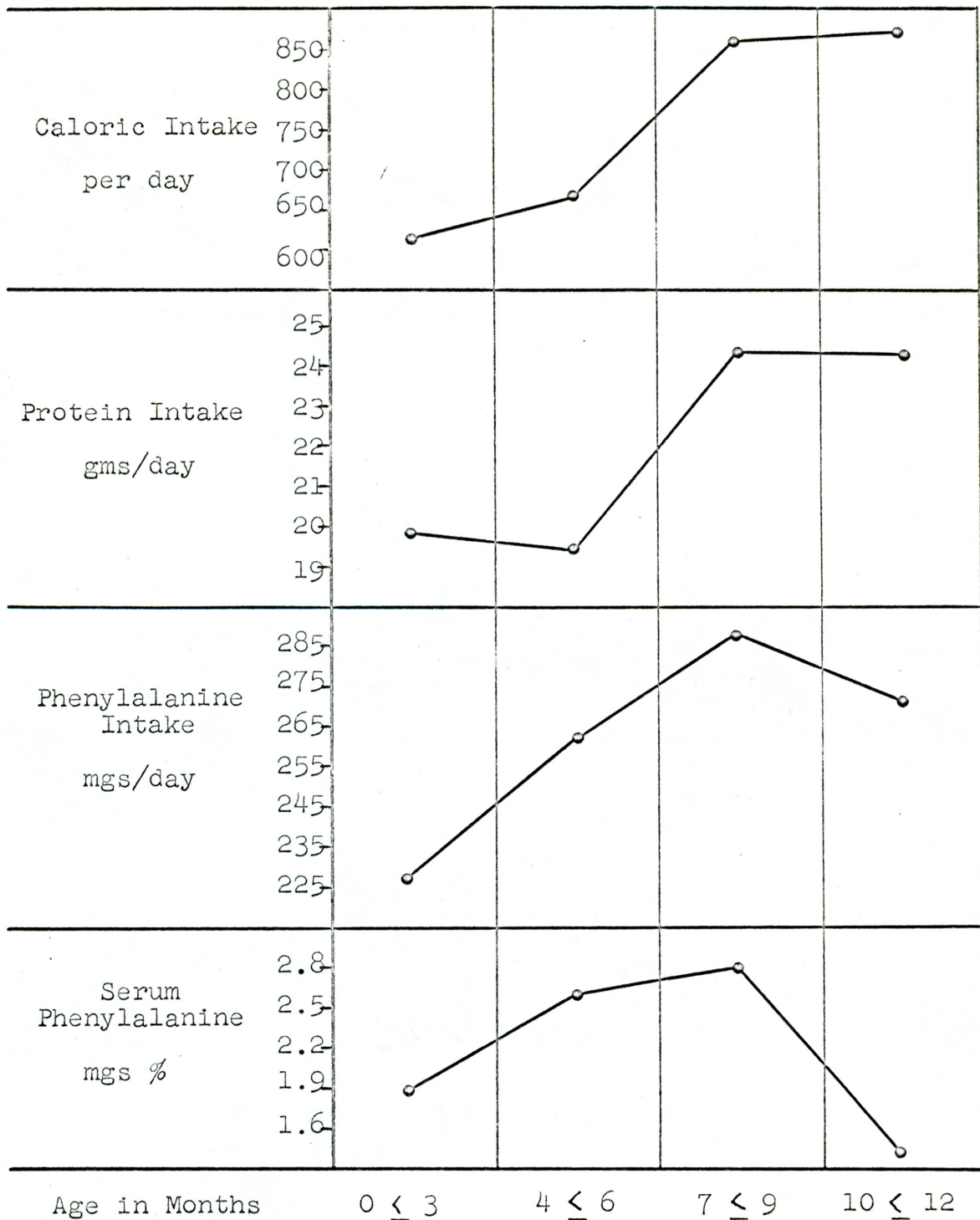RESEARCH COUNCIL RECOMMENDED ALLOWANCES FROM BIRTH
THROUGH 12 MONTHS

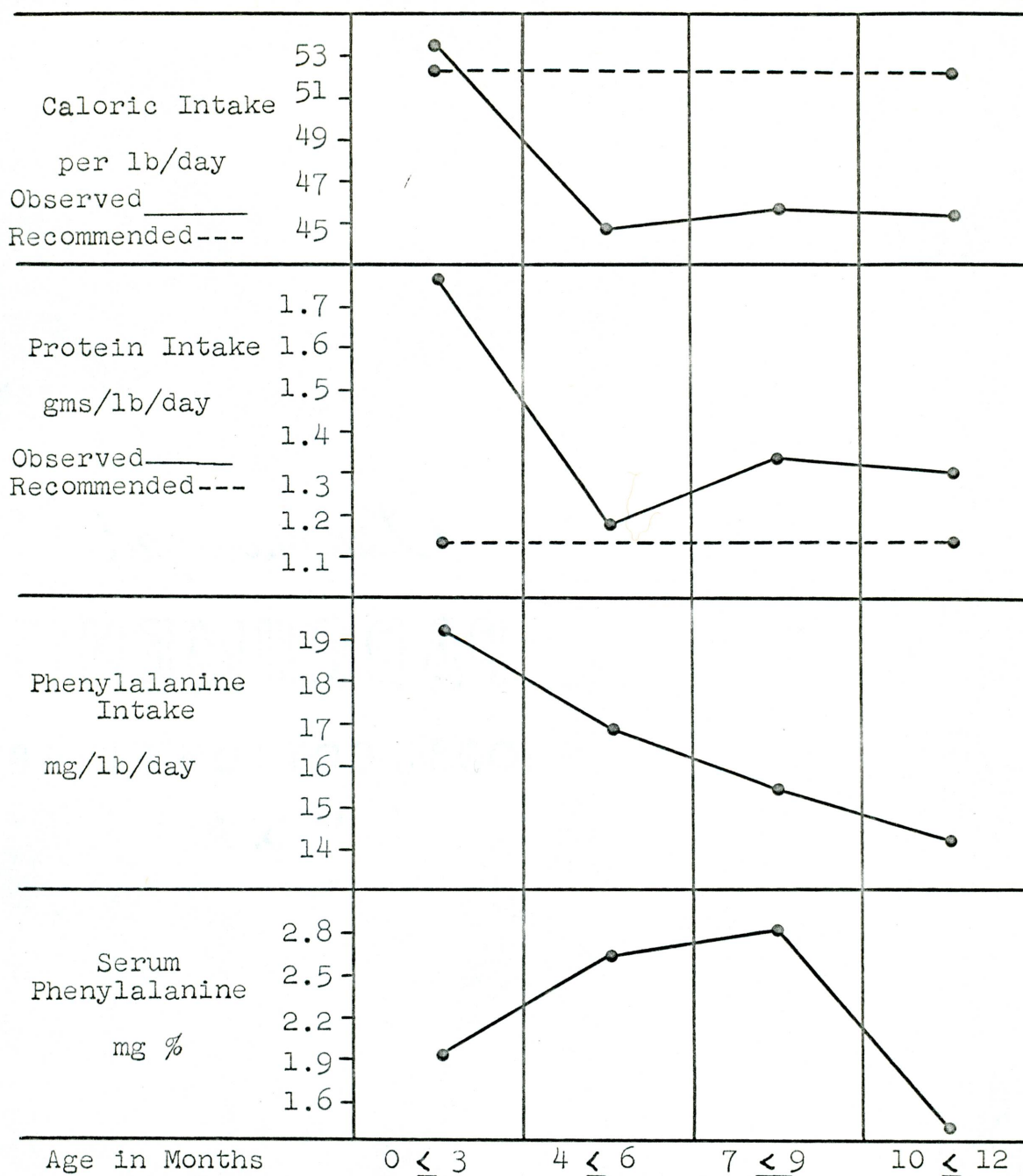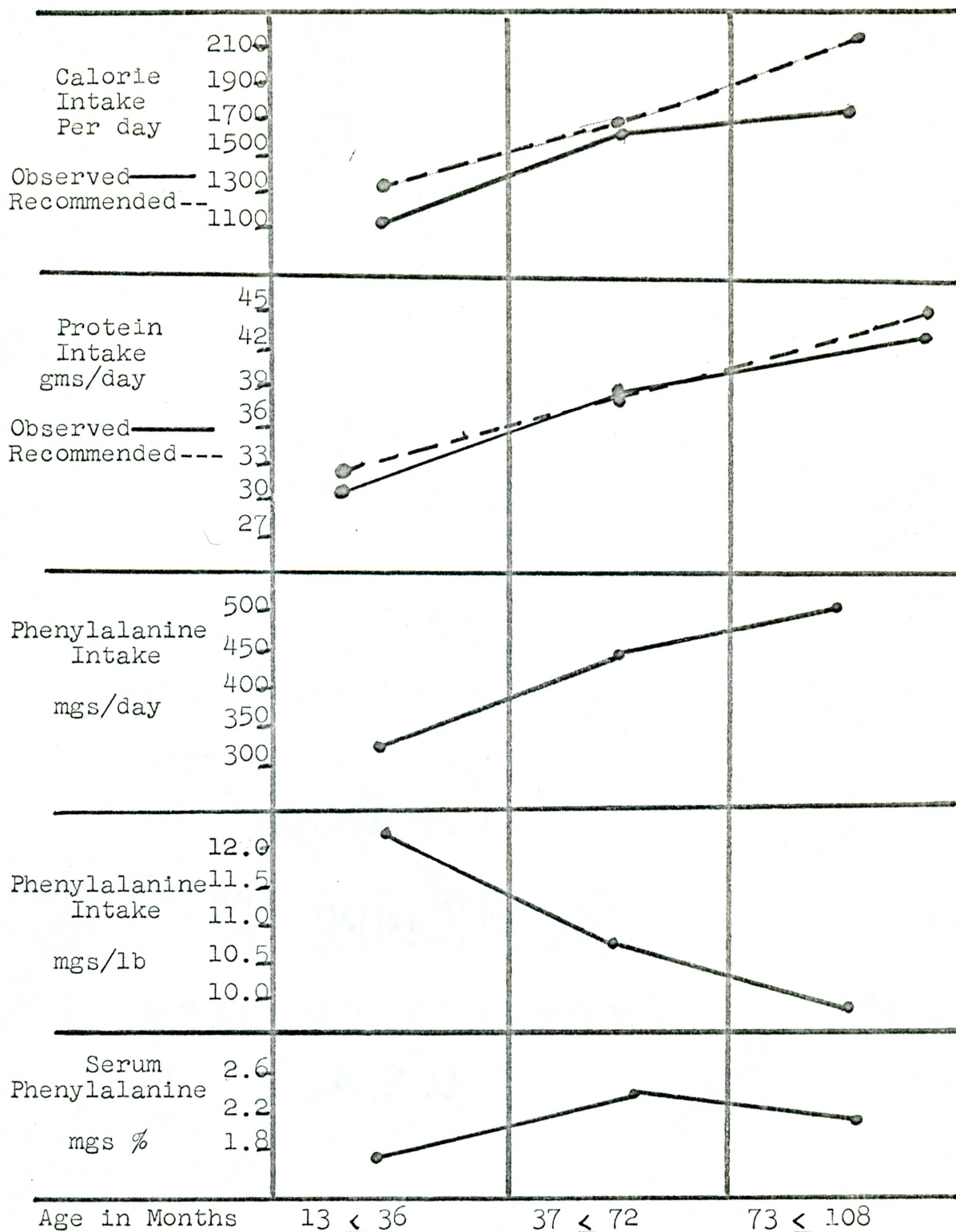FIGURE 4

COMPARISON OF MEAN SERUM PHENYLALANINE, AND MEAN INTAKES OF
PHENYLALANINE, PROTEIN, AND CALORIES WITH NATIONAL RESEARCH
COUNCIL RECOMMENDED ALLOWANCES FROM 13 THROUGH 108 MONTHS

than six milligrams per cent. Mean phenylalanine intakes
were from 227 to 488 milligrams per day with standard
deviations of 57 to 224 milligrams. Phenylalanine
intakes based on the child's weight ranged from 19.3
milligrams per pound each day for Group 1, to a low of
9.7 milligrams per body weight in Group 7. Standard
deviations were greatest in the youngest group. Total
daily phenylalanine intake was greatest in the oldest
children, but the youngest children had the highest
intake when this intake was based on milligrams per pound
of body weight.

The data for protein intake as grams of protein
per day and as grams of protein per pound of body weight
each day is given in Table II. Group 1 had a mean daily
intake of 20.8 grams of protein; Group 2, 20.4; Group 3,
25.4; Group 4, 25.3; Group 5, 30.8; Group 6, 41.7; and
Group 7, 45.7. Standard deviations ranged from 12.1 in
the oldest age group to 2.5 in Group 4, however, this
group had the smallest number of measures. When the
protein intake was figured on the basis of grams per
pound of body weight each day, a high of 1.76 grams was
observed in the youngest age group with a gradual
decrease to 0.95 grams in the oldest age group.

Caloric intake ranged from a high of 1817 calories
each day for ages 73-108 months, to a low of 611 for the
infants as shown in Table II, page 47. Calories per
pound of body weight each day were in inverse order;

the youngest consumed the greatest number per weight
(53.6). Groups 2, 3, 4, 5, and 6 had intakes of 44.7,
45.8, 45.3, 43.9, and 42.5 calories per pound, respect-
ively. The oldest group had an intake of 37.8 calories
for each pound of weight, about 5 calories less than the
group immediately preceeding. The standard deviation
for calories in Group 1 was 14.0 calories per pound each
day. This was in line with other reports in the liter-
ature that there were great differences between individ-
uals of the same age as to caloric consumption.[19] In the
older age groups, the standard deviations were not as
large; this too was in line with previous findings that
there was less change in children from age one year
until the pre-pubertal spurt than in the infant. Probably
none of the children had reached this age, since the data
included only those up to nine years of age.

In Table III, the intake of phenylalanine per
pound of body weight daily was compared with the amounts
recommended by Acosta.[1] The means for Groups 1, 2, and
4 were below her recommended amounts, the means for
Groups 3 and 5 were within the recommended amounts, and
the means for Groups 6 and 7 were slightly higher than
those recommended. However, these two age groups obtained
more protein from sources other than the casein hydrol-
ysate and the method of arriving at this nutrient data
has been changed since July, 1965. If the more recent

TABLE III

MEAN PHENYLALANINE, PROTEIN, AND CALORIC INTAKES COMPARED WITH RECOMMENDED ALLOWANCES*

N	Age Intervals In Months	Phenylalanine mgs./pound		Protein gms./day -		Protein gms./lb./day		Calories per day		Calories/ pound/day	
		Ref. [1]	Study	N R C [89]	Study	N R C	Study	N R C	Study	N R C	Study
12	0 ≷ 3	40 - 20	19.3		20.8	1.14	1.76		611	52.3	53.6
7	4 ≷ 6	40 - 20	16.9		20.4	1.14	1.18		664	52.3	44.7
11	7 ≷ 9	20 - 15	15.4		25.4	1.14	1.34		856	52.3	45.8
4	10 ≷ 12	20 - 15	14.3		25.3	1.14	1.30		866	52.3	45.3
40	13 ≷ 36	15 - 10	12.0	32	30.8		1.25	1300	1086		43.9
36	37 ≷ 72	10 - 7	10.5	40	41.7		1.10	1600	1569[z]		42.5
16	73 ≷ 108	7 - 5	9.7	52	45.7		0.95	2100	1817		37.8

z N = 37

* Data in this table are only for those children who had serum phenylalanine levels less than or equal to 6 milligrams per cent at the time of the measure.

method of calculation had been used throughout it is possible that calculated phenylalanine intake might be lower. The analytical data for phenylalanine content is lower in some foods than originally calculated on the basis that all protein contains five per cent of the amino acid phenylalanine.

The comparison of protein intake for the study group with that recommended by the National Research Council[84] is shown in Table III. The protein intake in the youngest group was considerably higher than the recommended allowances. From the age of three months to one year the intake was higher, though by a fairly small margin. At the age of 13-36 months, the intake was slightly less, being 30.8 grams compared with 32 grams recommended. Those in Group 6 had slightly more than the recommended intakes and Group 7 consumed approximately six grams of protein less than recommended.

Calories per pound of body weight each day for Group 1 was above the National Research Council Recommended Allowances by a slight margin; for all other groups, calories were less than those recommended. Evidently then the phenylketonuric children did not follow the usual pattern of ingesting more calories than recommended by the National Research Council as did the normal children in the studies of Burke[19] and Rueda-Williamson.[88] This might be due to one of many factors. One factor to

be considered was the necessity for strict control of the
diet which would militate against high food consumption
because of less variety and less opportunity for con-
suming high caloric foods due to snacking. Another
factor was that the diet averages of the study were
based on recorded intakes, while those of other studies
have been based on "recall" histories; there could very
well be a difference in the end results due to the two
different methods of securing the data. These data are
graphically presented in Figures 2, 3, and 4, pages 48,
49, and 50. The nutritional data was selected for
inclusion only if the simultaneous serum phenylalanine
was equal to or less than 6 milligrams per cent.

CHAPTER V

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

Forty-eight children treated for phenylketonuria were selected for study to determine if the growth of the children was different from the growth of the normal child population. Since heredity plays such a large part in the stature of an individual, the parents' heights were compared with the adult white American.

The heights of both father and mother were above that of the adult white American, however, the difference was very small, being 0.15 and 0.32 inches, respectively.

The mean of the last reported height for the treated phenylketonuric children compared with the expected mean height for norms showed that the children were 1.4 inches shorter; when this difference was tested statistically for significance, the results showed that there was a probability of only 1:1,000 that the results could have occurred by chance. Thus, it was concluded that treated phenylketonuric children are shorter than normal children. It was also shown that degree of control (of serum phenylalanine level) and the time of beginning treatment had no influence on the last heights of the treated phenylketonuric children.

Phenylalanine intake varied with the children and with the ages of the children. The intake based on body

weight was at a maximum for the early age group. Protein intake in the infant to three months of age was considerably above the National Research Council Recommended Allowances, the intake of 3-12 and the 37-72 month old groups were only slightly above the recommendations, whereas in the ages of 13-36 and 73-108 months, protein intake was somewhat lower than the recommendations. Calorie intake was slightly higher than the recommendations only in the 1-3 month old group.

The following recommendations were made for further research based on the results and limitations of this study:

1. Definite protocol be established regarding techniques to be used in securing the anthropometric measures. Height and/or length should be taken in a specific manner with a fixed age at which to begin using standing height; clothing should not be a factor in the weight measure.

2. In addition to height and weight, stem length, bicristal and bisacromial measures should be taken to allow for the study of the body proportions of the phenyl-ketonuric.

3. Evaluation of the physical status of siblings.

4. Evaluation of anthropometric data on all known untreated phenylketonurics.

5. The anthropometric measurements be taken at constant increments of time and if at all possible, these to be taken on the birthdate, the half year date, etc.

6. Further effort be made to secure more complete data in all areas.

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LOMA LINDA UNIVERSITY

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A Growth Study on Phenylketonurics

by

Emma Johnson Aitken

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An Abstract of a Thesis
in Partial Fulfillment of the Requirements
for the Degree Master of Science in
the Field of Dietetics

————

June, 1966

Data from forty-eight medical records of phenyl-
ketonuric children under treatment were investigated to
determine if growth, as measured by stature, was normal;
and to determine if the state of control or the age at
beginning of treatment had an effect on growth. Mean
intakes of phenylalanine, protein, and calories were
obtained on the nutritional data only if the silumtaneous
serum phenylalanine was equal to or less than 6 milligrams
per cent. These means were grouped according to the age
of the children into 7 groups (0≤3, 4≤6, 7≤9, 10≤12, 13≤36,
37≤72, and 73≤108 months).

The height at beginning of treatment and the last
measured height was compared with established norms of the
Brush Foundation Study. To determine whether the state of
control or age of beginning treatment were factors in
growth, the children were divided into groups according to
(1) age dietary treatment was instituted (equal to or less
than six months and over six months), and (2) state of
control. "Good" control for this part of the study was
having serum phenylalanine levels equal to or less than
4 milligrams per cent 75 per cent of the time, and "poor"
control, those having levels over 4 milligrams per cent
75 per cent of the time.

The mean height of the parents compared favorably
with the mean height for the white American male and
female. At beginning of treatment the children were
approximately half an inch shorter than estimated norms

but at their last measured height they were 1.40 inches shorter. When the last recorded heights of the phenyl-ketonuric children were analyzed considering time of beginning of treatment and state of control during treatment, there was no significant difference between the groups.

The mean phenylalanine intake ranged from 227 to 488 milligrams each day. On a pound basis Group 1 consumed 19.3 milligrams per pound, with a gradual decrease to a low of 9.7 milligrams per pound in the 73 to 108 month age group. Protein intakes ranged from 20.8 grams a day for Group 1 to 45.7 grams each day for Group 7. The protein intake of the youngest group was above that recommended by the National Research Council, Groups 2, 3, 4, and 6 intakes were only slightly above the recommendations, Groups 5 and 7 had a somewhat lower intake than recommended. Mean caloric intake ranged from 611 to 1817 calories each day, increasing with increasing age. Calorie intake in Group 1 was 53.6 calories per pound of body weight. This was slightly higher than the recommended allowances. All other groups had mean calorie intakes less than those the National Research Council recommends.

It was concluded that treated phenylketonuric children are significantly shorter than established norms but that age at beginning of treatment and control during treatment had no influence on the last heights of the children.