In 1934 Gyorgy reported experimental studies on the relation of a dietary factor to rat dermatitis and established this nutrient as a new member of the B-Complex, calling it vitamin B6. The vitamin subsequently isolated and synthesized was found to be 2 methyl-3 hydroxy-4,5 hydroxy methyl pyridine and called pyridoxine.

By means of an elegant series of experiments, Snell discovered that vitamin B6 exists in three interchangeable forms, pyridoxine, pyridoxal, pyridoxamine, all of which are phosphorylated in vivo, as shown in Figure 1. The vitamin is eventually metabolized to pyridoxic acid and excreted in the urine. Pyridoxal phosphate, biochemically the major active form of this group, functions as a coenzyme in virtually all of the reactions involving amino acids, such as transamination, deamination, decarboxylation, racemization, amine oxidation, as well as elimination and additive reactions.

Pyridoxal phosphate is also a significant component of muscle phosphorylase a and b, the enzyme that initiates the first step in glycogenolysis, leading to formation of glucose-1-phosphate. Furthermore, pyridoxal phosphate has been implicated in fat metabolism through its relation to phospholipids and cholesterol esters, fatty acid transport, and control of adipose tissue composition.

Since vitamin B6 is involved in such a large number of crucial biochemical reactions, a variety of metabolic disorders may result from a deficiency of this vitamin. The integrity of each biochemical reaction seems to depend on the individual rank order of affinity of the apoenzyme for pyridoxal phosphate and the avidity of binding with pyridoxal phosphate.

In the disease states referred to as “vitamin B6 dependency,” it has been proposed that an inborn or acquired structural abnormality has changed the binding capacity of the specific B6-dependent apoenzymes to the cofactor and that only larger amounts of pyridoxal phosphate can overcome adverse binding kinetics. Bonner has demonstrated specific mutations affecting the B6 binding site of an apoenzyme. Frimpter recently presented evidence which strongly supports the concept of an altered binding site as the mechanism of B6 dependency. It has also been confirmed that both metabolism and availability of the vitamin are normal in at least one form of B6 dependency.

In an individual with B6 dependency, in contrast to the excessive needs by the abnormal enzymes for pyridoxine, the other enzymatic reactions requiring B6 proceed normally in the presence of the usual concentrations of the vitamin.

**MEASUREMENT**

Since vitamin B6 participates in the many biochemical reactions mentioned above, procedures to detect the effect of the deficiency state on most of these have been developed. One of the most sensitive indicators of pyridoxine deficiency is the increased excretion in urine of xanthurenic acid and related intermediary metabolites following the ingestion of a tryptophan load. Other determinations of diagnostic value include: changes in activity of enzymes, such as glutamic pyruvic transaminase and glutamic oxaloacetic transaminase; excretion in urine of pyridoxic acid; and variations in the levels of vitamin B6 in blood and urine.

Discrepancies in the values reported by different laboratories preclude an accurate compilation of data on the levels of the vitamin.
VITAMIN B6 CONTENT OF VARIOUS TYPES OF FOODS

<table>
<thead>
<tr>
<th>Food</th>
<th>µg/gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milks</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>0.01-0.10</td>
</tr>
<tr>
<td>Cow</td>
<td>0.35-0.60</td>
</tr>
<tr>
<td>Eggs</td>
<td>0.22</td>
</tr>
<tr>
<td>Meats</td>
<td></td>
</tr>
<tr>
<td>Beef liver</td>
<td>7.3</td>
</tr>
<tr>
<td>Beef steak</td>
<td>2.8</td>
</tr>
<tr>
<td>Chicken</td>
<td>1.2</td>
</tr>
<tr>
<td>Pork, Ham</td>
<td>3.9</td>
</tr>
<tr>
<td>Grains</td>
<td></td>
</tr>
<tr>
<td>Wheat</td>
<td>5.8</td>
</tr>
<tr>
<td>Oats</td>
<td>0.92</td>
</tr>
<tr>
<td>Rice</td>
<td>3.4</td>
</tr>
<tr>
<td>Corn</td>
<td>4.9</td>
</tr>
<tr>
<td>Yeast, Brewer's, dry</td>
<td>47.3</td>
</tr>
<tr>
<td>Vegetables</td>
<td></td>
</tr>
<tr>
<td>Bean, lima</td>
<td>6.0</td>
</tr>
<tr>
<td>Carrots</td>
<td>2.1</td>
</tr>
<tr>
<td>Onion</td>
<td>0.68</td>
</tr>
<tr>
<td>Potato, White</td>
<td>1.8</td>
</tr>
<tr>
<td>Soy bean</td>
<td>10.2</td>
</tr>
<tr>
<td>Fruits</td>
<td></td>
</tr>
<tr>
<td>Apple</td>
<td>0.26</td>
</tr>
<tr>
<td>Banana</td>
<td>3.2</td>
</tr>
<tr>
<td>Orange</td>
<td>0.31</td>
</tr>
</tbody>
</table>

* Reported as micrograms of pyridoxine per gram or per milliliter.

Fig. 1. The metabolism of the members of the vitamin B6 group.

three B6 cofactors in either biological samples or food. Microbiological assays employing *Saccharomyces carlsbergensis* have been generally accepted as the standard for estimating total B6 content of foods. Typical data derived from this assay are listed in Table I. It is worth noting that advances in the use of column chromatography for separation of the specific cofactors in the pyridoxine group and the development of methods for spectrophotofluorometric measurement promise to provide more accurate quantitation of each of the specific forms.

In foods of animal origin, particularly milk, most of the vitamin B6 is present as heat-labile pyridoxal and pyridoxine rather than the more heat-stable pyridoxamine. Exposure of foods to temperatures above 100°C during processing may result in destruction of an appreciable portion of naturally occurring vitamin B6. In milk, an inactive disulfide-pyridoxal complex may be formed during heating. The heat lability of the vitamin is a factor to be considered as in the commercial processing of infant formulas containing fluid or skim milk, especially since these preparations are often subjected to additional sterilization by commercial formula services, hospital formula rooms, and at home. Most, if not all, commercially prepared formulas manufactured in the United States are adequately supplemented with pyridoxine to compensate for any such losses.

VITAMIN B6 REQUIREMENTS IN THE NORMAL POPULATION

Although the data on vitamin B6 requirements in man are meager, Table II summarizes estimates of daily requirements.
TABLE II
ESTIMATED VITAMIN B6 REQUIREMENTS FOR VARIOUS AGE GROUPS
(mg/Day)

<table>
<thead>
<tr>
<th>Individual</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>0.10-0.5*</td>
</tr>
<tr>
<td>Child</td>
<td>0.5-1.5</td>
</tr>
<tr>
<td>Adolescent</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>Elderly Adult</td>
<td>2.0-4.0</td>
</tr>
<tr>
<td>Adult</td>
<td>1.5-2.0</td>
</tr>
</tbody>
</table>

* 20 μg/gm protein. These ranges are related to normal ranges of protein intake.

of the vitamin by normal people of various ages. In general the needs are related to levels of protein intake.

Pregnancy
It has been noted that most pregnant women have decreased levels of vitamin B6 in blood and increased urinary excretion of kynurenine, which is observed following a tryptophan load. These findings, generally considered evidence of a B6 deficiency state in nonpregnant subjects, may reflect insufficient intake of the vitamin, an increased urinary excretion of B6 or placental transfer of B6 to the fetus. The placenta actively transports B6 to the fetus to maintain a five-fold concentration gradient favoring the fetus. In the majority of women studied, daily oral doses of 5 to 10 mg of pyridoxine corrected biochemical signs of vitamin B6 deficiency. The exact significance of these biochemical changes in the normal pregnant woman is as yet poorly understood but suggests that needs for pyridoxine are increased during pregnancy.

Newborn Period and Infancy
The normal newborn infant has sufficient tissue stores of vitamin B6 to meet needs during the neonatal period even though the diet may be virtually devoid of the vitamin. The concentration of B6 in human milk is approximately 10 to 20 μg per liter during the first month of lactation, thereafter gradually increasing to 100 μg per liter. While the daily requirements of B6 are met by the consumption of adequate quantities of normal human milk, the relation of vitamin B6 and protein appears to be critical. Cow's milk, which has a higher (3.3%) protein level than human milk, also contains more vitamin B6, 350 to 600 μg per liter. If vitamin B6 concentration fails to rise above 60 to 80 μg per liter in human milk, clinical and biochemical abnormalities characteristic of the deficiency state may occur when protein consumption exceeds the infant's metabolic capacity. The situation is similar to that seen in infants receiving formulas containing inadequate amounts of B6 in whom clinical manifestations of deficiency disappear immediately following the addition of B6-containing solid foods to the diet. Metabolic requirements for B6 are satisfied at 6 months of age if the vitamin is present in amounts of 20 μg per gram of dietary protein. Evaluation of commercially prepared baby foods has shown that in relation to their content of protein they contain more than adequate amounts of vitamin B6.

Childhood
The requirement for vitamin B6 of the older infant and young child, estimated to be 0.5 to 1.0 mg per day, is readily supplied by a suitably balanced diet. In developing countries, where marginal or frankly deficient intakes of B6 are very common, infants and children may have no clinical signs of deficiency, since the amount of protein in the diet is relatively low and individual B6 requiring enzyme systems are usually adapted to a lower level of metabolic activity. Vitamin B6 deficiency, even if not clinically manifest, may have long-term detrimental effects on physical and mental growth and development.

Adolescence and Adult Life
At the present time, available data are insufficient to permit an accurate estimate of the B6 requirement for older children.
and the adolescent, but it is presumably in the range of 1.5 to 2.0 mg daily. Calculations based on "market-basket" types of surveys suggest that if individuals in these age groups ingest the selected diet they can obtain 2.0 to 2.5 mg per day of vitamin B₆; since none of the known deficiency syndromes have been seen in normal people in this age range consuming these diets, such intakes are presumably adequate. Unfortunately, the wide fluctuations in the quantity and quality of food consumed by the adolescent, the lack of information concerning the destructive effects of cooking on the B₆ food content of food, and the absence of adequate measurements of possible biochemical alterations with varying intakes of B₆ during these periods of growth and development preclude making a final statement on the matter.

In considering the vitamin B₆ requirement of older adolescents, it is possible to utilize data from controlled studies of healthy young adult males to estimate needs in relation to level of protein intake. A daily requirement for B₆ of 1.25 to 1.50 mg was established for a low (30 gm/day) protein diet and 1.75 to 2.0 mg for a high (100 gm/day) protein diet.58

**CONDITIONS REQUIRING VITAMIN B₆ SUPPLEMENTATION OR THERAPY**

**Deficiency States**

In 1950, Snyderman, et al.,19 observed biochemical changes in two infants 2 and 8 months of age following ingestion of B₆-free diet for 76 and 120 days, respectively, with ultimate development of anemia in the younger child and convulsions in the older. Each child’s symptoms were relieved and the biochemical alterations corrected after administration of pyridoxine.

In 1954, a number of investigators reported the occurrence of hyperirritability, convulsive seizures, and hyperacusis in infants receiving a prepared milk formula containing 15 gm of protein and 60 µg of vitamin B₆ per liter.60-64 Electroencephalograhic changes and abnormal responses to tryptophan loading were consistently demonstrated, but they were promptly alleviated by administration of vitamin B₆ in appropriate amounts. Similar findings have been described in infants nursing at the breast of mothers whose milk was found to contain less than 100 µg of vitamin B₆ per liter.46

Bessey and co-workers46 evaluated the daily requirements of several infants who developed clinical symptoms of pyridoxine deficiency due to inadequate intakes of vitamin B₆. They found that these infants required between 1.0 to 1.4 mg/day of pyridoxine, a dose somewhat in excess of the usual daily requirements for normal infants. Scriver and Hutchinson65 described a 20-month-old infant with unequivocal stigmata of vitamin B₆ deficiency whose daily maintenance requirement of the vitamin was greater than normal. It is possible that pyridoxine-deficient infants may for unknown reasons become deficient in coenzyme because of some idiosyncrasy of coenzyme metabolism which is similar to or distinct from that seen in the “B₆ dependency state.” Patients with malabsorption syndromes may exhibit laboratory evidence of vitamin B₆ deficiency; the latter is reversed with pyridoxine therapy.66,67

**Miscellaneous Problems**

Vitamin B₆ activity in blood is reduced in a variety of disease states, including leukemia, liver disease, and rheumatic fever.65,69 Isoniazid, used in treatment of tuberculosis, irreversibly combines with B₆ to form an inactive isonicotinic acid hydrazide-pyridoxal phosphate complex. Since continued administration of the drug may lead to symptoms of B₆ deficiency,70 B₆ supplementation is recommended in patients receiving isoniazid and for a similar reason in those under treatment with chelating agents.

Vitamin B₆ has been reported to have some role in antibody response to antigenic stimuli,71 oxalate metabolism,72 dental caries,19 and in various disorders such
as myoclonic epilepsy,\textsuperscript{74,75} phenylketonuria,\textsuperscript{76} and mongolism.\textsuperscript{77-79}

Recently Hagberg, \textit{et al.}\textsuperscript{80,81} reported finding an abnormal urinary excretion of xanthurenic acid following a tryptophan load test in 26 of 43 infants and children who had the clinical symptomatology and the electroencephalographic changes of cryptogenic epilepsy. Although these findings were interpreted as evidence of vitamin B\textsubscript{6} deficiency, the pyridoxal phosphate levels in the blood of these patients were within normal limits. Furthermore, the dose of pyridoxine necessary to correct the excessive xanthurenic acid excretion and to improve clinical and electroencephalographic evidence of cerebral dysfunction was found to be in the range of 160 mg per day, a level far in excess of the daily dose of 1 to 10 mg that ordinarily will restore to normal the patient with the usual forms of B\textsubscript{6} deficiency. As yet it is not possible to determine whether the excessive B\textsubscript{6} requirement of these patients represents an acquired state or is the expression of a genetic abnormality.

\textbf{Dependency States}

In the syndrome(s) referred to as "vitamin B\textsubscript{6} dependency," coenzyme availability is normal and there is no evidence of depletion of the B\textsubscript{6} pool of the body.\textsuperscript{21} The disorder is probably inherited as a recessive condition and may be caused by a modification of the coenzyme binding site in a specific apoenzyme.\textsuperscript{18}

Hunt, \textit{et al.}\textsuperscript{17} described the first individual with vitamin B\textsubscript{6} dependency in 1954.\textsuperscript{17} The patient had repeated convulsive seizures and was mentally retarded. A tryptophan load test was normal. Daily doses of 10 to 25 mg of pyridoxine were necessary to control the seizures. Several additional cases have since been reported by other investigators.\textsuperscript{83-85}

Harris, \textit{et al.}\textsuperscript{86} have described a vitamin B\textsubscript{6} dependency syndrome involving the hematopoietic system that usually appears in early adult life but may be seen in children. Among 72 patients reported to have had a pyridoxine-responsive anemia, four were infants and five were older children.\textsuperscript{87} This anemia is characterized by severe hypochromia, microcytosis, and hyperferremia, and it responds to therapy with vitamin B\textsubscript{6} at levels of 25 mg/day. The patients require maintenance doses at this level to prevent anemia. The defect may be genetically determined, since the disease frequently affects several members of a given family and may be an example of late manifestation of a genetically controlled metabolic defect. In patients with the molecular disease cystathioninuria, the ability of the apoenzyme to bind coenzyme is severely limited, and, therefore, a continuous high intake of vitamin B\textsubscript{6} is required to control the metabolic disturbance.

\textbf{UNTOWARD RESPONSES TO VITAMIN B\textsubscript{6} ADMINISTRATION}

To date there has been no report of deleterious effects associated with daily oral ingestion of large doses of vitamin B\textsubscript{6} (0.2 to 1 gm per day).

There have been a few unpublished reports of the induction of convulsive seizures and at times the occurrence of status epilepticus following rapid parenteral administration of pyridoxine to patients who were pyridoxine-dependent\textsuperscript{15} and to patients receiving isoniazid. While treatment with the vitamin is indicated in these circumstances, it should be administered slowly and with caution.

Undesirable reactions were observed by Hottinger, \textit{et al.}\textsuperscript{88} in a heterogeneous group of patients with central nervous system disorders. They exhibited an abnormal excretory pattern of metabolites in urine following tryptophan load tests. Following therapy with pyridoxine several of these individuals experienced a marked increase in severity of clinical symptoms and showed deterioration of their electroencephalograms. These symptoms disappeared with cessation of pyridoxine therapy.
SUMMARY

Because of the limited information available, it is not possible to derive precise figures for daily requirements of vitamin B₆ in infants and children at this time. Data currently available suggest that the daily need in childhood is 0.5 to 1.5 mg and in adolescence is 1.5 to 2 mg. The requirement in infancy is clearly related to protein intake and is 20 μg/gm of dietary protein.

Requirements of a few individuals will undoubtedly be higher than the estimates for the normal population. Some of these patients will manifest frank biochemical and clinical signs of deficiency which will usually be promptly reversed by administration of small additional amounts of pyridoxine. Another group of patients will require large amounts of the vitamin to balance the heritable alteration in binding properties of a specific apoenzyme requiring pyridoxal phosphate for normal activity.

It would appear that most infants, children, and adults will have little difficulty in achieving an adequate intake of vitamin B₆ if they receive what is considered to be in other respects an adequate diet.

Committee on Nutrition

Charles U. Lowe, M.D., Chairman
David B. Coursin, M.D.
George N. Donnell, M.D.
Felix Heald, M.D.
Malcolm A. Holliday, M.D.
Robert Kaye, M.D.
Donough O'Brien, M.D.
George M. Owen, M.D.
Howard A. Pearson, M.D.
Charles Schiver, M.D.
Michael J. Sweeney, M.D.
L. J. Filer, M.D., Consultant
O. L. Kline, M.D., Consultant

REFERENCES


48. Jarusova, N. S.: New standards for daily vita-

49. Coursin, D. B., and Brown, V. C.: Changes in

50. Wachstein, M., Kellner, J. D., and Ortiz, J. M.: Pyridoxal phosphate in plasma and

51. Wachstein, M., and Lobel, S.: Abnormal


53. Karlin, R.: Sur la teneur en vitamine B,

54. Gregory, M. E.: The microbiological assay of


56. Theron, J. J., and Parmelee, A. H.: Convul-

57. Schaeffer, A.: Personal communication. Sum-

58. Deutsch, M. Jr., and Plonko, M.: Pyridoxine hy-

59. Snvdcman, S. E., Carretero, R., and Holt, L.

60. Hansen, A. E., Wiese, H. F., Adam, D. J. D.,

61. Molony, C. J., and Parmelee, A. H.: Convul-

62. May, C. D.: Vitamin B,


64. Jarusova, N. S.: New standards for daily vita-


66. Scriver, C. R.: Abnormalities of tryptophan


68. Rabe, E. F., and Plonko, M.: Pyridoxine hy-

69. Wachstein, M., and Lobel, S.: Relation be-

70. Beihl, J. P., and Vilter, R. W.: Effects of

71. Hodges, R. E., Bean, W. B., Ohlson, M. A.,

72. Cershoff, S. N., and Prien, E. L.: Excretion of

73. Hillman, R. W., Cabaud, P. C., and Schen-

74. Bower, B. D.: The tryptophan load test in

75. French, J. H., Grueter, B., Druckman, R., and

76. Reichle, P. A., Baldridge, R. C., Dobbs, J.,

and Trompetter, M.: Tryptophan metabo-
VITAMIN B₆ REQUIREMENTS


LETTERS TO THE EDITOR

battered child. It takes no great amount of diagnostic acumen to make a diagnosis of the battered child. It is, therefore, most important that the physicians and pediatricians be alert and conscious of signs diagnostic of the maltreatment syndrome. Only in this way can a battered child possibly be saved from lethal inflicted injuries. Prevention by proper recognition of these more insidious symptoms will lead to the ultimate decreased incidence and eradication of this life-threatening disease.

We have seen many children admitted to The New York Foundling Hospital and St. Vincent’s Hospital and Medical Center who have, perhaps, been saved by prompt recognition by the physician and nursing personnel of the child who has been maltreated.

It is a sad commentary that, in spite of the
**COMMITTEE ON NUTRITION: VITAMIN B6 REQUIREMENTS IN MAN**

*Pediatrics* 1966;38;1068

| Updated Information & Services | including high resolution figures, can be found at:  
| http://pediatrics.aappublications.org/content/38/6/1068 |
| Permissions & Licensing | Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
| https://shop.aap.org/licensing-permissions/ |
| Reprints | Information about ordering reprints can be found online:  
| http://classic.pediatrics.aappublications.org/content/reprints |
COMMITTEE ON NUTRITION: VITAMIN B6 REQUIREMENTS IN MAN

*Pediatrics* 1966;38;1068

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://pediatrics.aappublications.org/content/38/6/1068