# DRUG-INDUCED NUTRITIONAL DEFICIENCIES

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# Foreword

The widespread use of drugs in contemporary society poses challenging problems for the practicing physician and other health professionals. Patients frequently receive therapy with more than one drug, and the side effects of these agents are varied and complicated. When faced with an ailing patient who is taking several medications, it is often difficult for the physician to determine whether he is dealing with the disease itself, or with the treatment for it. At the present time untoward reactions to drugs constitute significant causes of hospitalization in the United States, and often prolong the duration of hospital stay.

In the day-to-day practice of medicine, drug reactions in many instances are recognized readily. Such signs and symptoms as pruritic rash, leukopenia, nausea and vomiting, general malaise, or fever, may be identified easily, and the offending agent promptly discontinued. Drug toxicity may be dramatic in its presentation, e.g. anaphylaxis, and constitute a medical emergency. Toxicity may be observed within minutes or hours after the initiation of drug treatment. In other instances, a longer time is required. It is often impressive to note the extent to which the most striking features of a patient's illness are often related in some measure to the use of pharmacological agents. For example, in certain patients with prolonged fever and rash, discontinuation of all drugs restores body temperature to normal and results in disappearance of the eruption.

Together with the widespread use of drugs has come the gradual but increasing recognition of the significance of interactions between drugs. One drug may interfere with the intestinal absorption or renal excretion of another drug, or block its binding to plasma proteins and tissue receptor sites. Drugs have been reported both to accelerate and to retard the metabolic transformations of other drugs. The finding that certain drugs, such as phenobarbital, are potent inducers of hepatic drug-metabolizing enzymes, has many implications for the practical use of pharmacological agents. It is apparent that the pharmacologist and the clinician must consider drug interactions in order to gain maximal therapeutic effectiveness as well as to minimize the incidence and severity of untoward reactions.

There has also been increasing recognition of the many physiological variables which influence the body responses to drugs. Such

factors as (1) individual differences in the rates of removal of drugs from the body, (2) the presence of alterations of hepatic or renal function, or of acid base balance, (3) the presence of extremes of body weight and fat stores, (4) the status of endocrine function, particularly thyroid, and (5) individual differences in the rates of intestinal absorption or of binding of drugs to plasma proteins, have profound effects upon the results of drug administration. Attention to these matters requires that drug therapy be individualized, and that the special problems posed by each patient be examined separately and carefully. The rapid growth of knowledge and complexity about drug usage has resulted in clinical pharmacology coming into its own as a distinct discipline in internal medicine.

One consequence of the widespread use of drugs is an increase in the diversity of reactions to them. A bewildering array of clinical findings involving virtually every organ system may be attributable to drug therapy. The more subtle manifestations of drug toxicity, particularly those which are not associated with specific symptoms or signs, or those which occur only after extremely prolonged periods of drug administration, may escape notice by the physician. Metabolic complications of drug usage, such as osteoporosis, frequently arise only after long term use of pharmacological agents, and are particularly difficult to detect in the early stages.

An entire category of reactions to drugs which has received only scant attention in clinical practice is the multiplicity of effects upon the nutritional status of the patient. One rarely considers the many ways in which drugs may influence the dietary intake of nutrients, their disposition in the body, and their rates of elimination. The nutritional status of the patient, in turn, may have profound influence upon the therapeutic efficacy of drugs and the likelihood of developing drug toxicity.

As physicians, we often tend to be too simplistic and casual in our approach to evaluating the nutritional status of our patients. In a typical description at the bedside, the patient is considered to be either "well-nourished" or "poorly nourished." This opinion is usually based upon a rapid glance at the patient, and knowledge of the extent to which weight loss or dehydration has occurred during the course of the illness. Because overt signs of certain vitamin deficiencies, such as cheilosis, glossitis, hyperkeratosis and petechial hemorrhages, are only rarely encountered, vitamin status is presumed to be normal. If no specific etiology for anemia can be determined, it is frequently labelled as a "nutritional anemia," with little thought given to its pathogenesis or treatment. Rarely is any

aspect of the patient's nutritional status carefully scrutinized or quantitated.

Much of the thinking we do about the nutrition of patients is superficial, largely because our education in this subject has also been superficial. Few medical schools properly focus on nutrition in their curricula, and many treat the subject with disdain. Nutrition is considered appropriate material for nurses and dieticians, but not for medical students. Under these circumstances, it is not difficult to understand why the physician tends to shed his responsibility for nutritional management to supporting medical personnel, and why he often remains unaware of the implications of drug therapy for nutrition. The need for upgrading the education of physicians in nutrition at the undergraduate and post-graduate levels is urgent.

The present volume is devoted to a systematic examination of the multiplicity of mechanisms by means of which drugs influence the nutritional status of the patient. Some of these mechanisms, such as nausea and vomiting, are obvious ones, but their full significance has often not been appreciated. Nausea and vomiting are such common sequelae of drug ingestion that one tends to focus attention nearly exclusively on what appear to be the critical problems: loss of water and electrolytes, shifts in acid-base balance, and maintenance of blood pressure. The consequences of nausea and vomiting, particularly on a chronic basis, are much more complicated than these, and often lead to depletion of a number of important nutrients. Anorexia due to drugs is a less dramatic symptom than vomiting but may be equally important in reducing dietary intake and thereby producing various nutritional deficiencies.

In addition to influencing dietary intake, drugs affect the metabolism of nutrients at a wide variety of sites, including intestinal absorption, plasma-binding and transport, peripheral utilization, transport across cell membranes, intracellular reactions, storage in tissues, turnover, and elimination and excretion. Knowledge of the multiplicity of these effects should help the physician to provide more appropriate drug therapy. It is evident that drugs are important causes of malnutrition, in addition to their other side effects. This problem must be considered particularly with respect to older individuals, who constitute the largest group of drug users. The economic deprivation of the elderly in our population and their social isolation compound the problem of their already impaired drug-metabolizing and excreting abilities. The enormous physiological changes in organ functions which occur with aging must always be kept in mind when prescribing drugs to older patients.

Suggestions for evaluating and monitoring the nutritional hazards of drugs, and for initiating new research programs are also made in this volume. The issues raised are serious ones, and must be dealt with by various governmental agencies as well as by the medical profession and allied fields. The basic problems remain those of developing awareness of the side effects of drugs, encouraging education about clinical pharmacology and nutrition, and coordinating the activities of industry, medicine and government.

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*February 1976*

# Preface

This book deals with nutritional disorders caused by drugs, a subject of growing importance as new drugs are produced and established drugs are given to larger groups of people either for the prevention and treatment of disease or for population control.

Diverse drug groups, including such widely used medications as anticonvulsants, antimalarials, antituberculous drugs, and contraceptive steroids have been shown to increase nutrient requirements. These drugs, as well as certain antibiotics, sedatives and cholesterol-lowering agents, can cause specific vitamin deficiencies, if the increased vitamin requirements imposed by drug intake are not met by diet or by oral and parenteral vitamin supplements. Stimulants, such as dextroamphetamine, given to control behavioral problems in hyperactive children, have been shown to impair growth. Diuretics and also antacids can produce mineral depletion. Certain drugs given to pregnant women can induce fetal malnutrition which can lead to malformations.

These side effects are brought about because drugs can impair absorption, increase excretion, or decrease nutrient utilization. Certain drugs can also lead to decreased nutrient intake because of attendant anorexia. The risk of drug-induced nutritional deficiencies varies, being highest in those on marginal diets, and in those whose nutritional status is compromised by physiological stress such as pregnancy, or by pre-existent disease. Alcoholics are prone to develop drug-induced malnutrition because their nutritional status is impaired prior to the initiation of therapy using drugs that further deplete the body of specific nutrients.

The reader will be introduced to the subject by a review of basic concepts including nutrient and drug metabolism and drug-nutrient interactions. A survey of the literature pertaining to drug-induced hypovitaminoses and other drug associated nutritional problems in man is given. The bibliography, however, is selective, because the author believes that it is more important to explain the circumstances in which drug-induced malnutrition or drug-induced nutrient depletion occurs, rather than to include very large numbers of case reports extracted from published literature. Discussion of the diagnosis of drug-induced deficiencies has necessitated appraisal of biochemical tests which may not always be available in hospital laboratories.

While it is hoped that biochemical evaluation of nutritional status will soon become generally available to the medical profession, at the present time it is still possible to detect the majority of cases where drugs are causing nutrient depletion through an increased awareness of the risk, and by the performance of such laboratory tests as are presently feasible. Whenever a physician is considering the institution of therapy with a drug known to be capable of impairing nutritional status, appropriate nutrient supplementation should be considered; more especially, if the patient's diet has been inadequate or if he has some disease which has already interfered with nutrient absorption or utilization. If the patient has been on a drug or drug group for a period of time and signs or symptoms develop which are not referable to the primary disease, nor to direct toxic effects of the drug or drugs in use, then the possibility of drug-induced malnutrition should be considered. This book has been written because the author believes that nutritional side effects of drugs are preventable, and that most of them occur because physicians are unaware that they exist.

While the present work is intended primarily for use by physicians, it is hoped that it may also be used as a work of reference by nutritionists, clinical pharmacologists, nurses, and medical students.

The author wishes to acknowledge her indebtedness to associates in the Division of Nutritional Sciences at Cornell University, and more particularly to Dr. Donald B. McCormick who has offered advice and assistance in interpretation of biochemical studies and evaluation of biochemical publications pertinent to the subject. Thanks go also to Mrs. Catherine Brashear who prepared most of the figures for publication. Special thanks go to my secretary, Mrs. Beverly Hastings, who prepared drafts and final copy of the manuscript. Further I would like to express my thanks to Dr. D. K. Tressler and Mr. J. J. O'Neil of the AVI Publishing Company.

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# Contents

# Basic Concepts

## NUTRIENTS AND THEIR INTERACTIONS WITH DRUGS

In order to understand the mechanisms involved in the development of drug-induced nutrient depletion, it is necessary for the reader to review current concepts of nutrition and malnutrition. This exercise is essential to the interpretation of such questions as why drugs interact with certain nutrients more than others, why particular groups of drugs create a limited number of deficiency states, and why patterns of malabsorption occur when specific drugs are taken. Whereas drugs can interfere with the endogenous synthesis of nutrients, or impair the digestion and absorption, or affect nutrient metabolism or excretion, the types of malnutrition so produced are circumscribed. It can be generalized that with the exception of certain vitamin antagonists, drugs in therapeutic dosage interfere to a limited extent with nutrient utilization, having least effect over short periods of time or where the intake of a nutrient exceeds demand, or when nutrient stores are ample. When the effects of drugs on nutritional status are viewed in this light, it is predictable that for any given population, drugs will have most effect in chronic drug users. Within this group, the drugs will emphasize pre-existing nutrient lack, incurred by marginal intakes of nutrients or by disease.

If, for example, we limit our consideration to drug-induced malabsorption, certain drugs will decrease the absorption of macronutrients including sugars, fats, and amino acids, fat- and water-soluble vitamins, and minerals. Whether or not a particular nutritional deficiency supervenes depends not only on the residual absorptive capacity of the small intestine, but also on the prior nutrition of the patient or population. While it is probably true to say that drugs can affect the utilization of any nutrient, whether or not deficiency or depletion results is determined by nutrient availability and the economy of physiological systems concerned with nutrient metabolism. Girdwood (1971) commented that the precise amount of each of the vitamins that is believed to be required by the human male and female at different ages should not concern us as much as the various factors that may affect the actual amount of these vitamins available to the body. Similar comments to those of Girdwood could be made with respect to nutrients other than vitamins.

## Causes of Nutrient Depletion

In the United States and in all other parts of the world in which the food supply is adequate for the needs of most people, the risks of nutrient depletion are related to 1) socioeconomic factors, 2) nutrient losses due to food processing and preparation, 3) food habits, 4) decreased food intake associated with restrictive diets, 5) lack of interest in food, or anorexia, 6) failure to increase nutrient intake with respect to physiological needs, 7) alcoholism, 8) drug addiction, 9) disease, and 10) medications. In western countries, a major factor determining a balanced diet is the proper choice of foods. Since foods vary markedly one from another in their ability to supply essential nutrients, a balanced diet becomes almost synonymous with a varied diet. This does not mean, of course, that a diet containing 20 kinds of crackers would be desirable, but rather that a wide range of foods should be taken, so that the nutrient content of one will complement that of another with respect to requirements of different nutrients. Hansen (1973) has pointed out that foods with a substantial number of important nutrients without excessive calories are of good quality. He suggests a classification of foods according to the nutrient: calorie ratio, those foods having such a ratio greater than 1 being particularly desirable in a population which tends to consume excessive calories. Deliberate omission of certain key sources of nutrients from the diet, such as milk (supplying vitamin A, D and calcium as well as protein), green leafy vegetables (supplying folic acid, vitamin K and carotene), and liver (providing a major source of fat-soluble and B vitamins as well as iron), contributes to the incidence of nutrient depletion in this country. Blood levels of nutrients, particularly vitamins, have been used in recent years as a measure both of dietary intake and of nutritional status.

In the Canadian Nutrition Survey (Nutrition Canada 1973), it was found that in people of all age groups low serum folate values were prevalent. The preliminary data presently available from this study also suggest that in special subgroups of the Canadian population there is a significant incidence of iron deficiency, calcium and vitamin D deficiency, thiamin depletion, and among pregnant women protein depletion. Data derived from nutrition surveys carried out in the last ten years show that malnutrition including avitaminosis is uncommon in industrialized countries except among special groups of the population such as the elderly and those in hospitals (Brocklehurst *et al.* 1968; Leevy *et al.* 1965).

Among hospital patients, hypovitaminemia is far more common than clinical vitamin deficiencies. In the study by Leevy *et al.* (1965) the most common vitamin deficiency encountered was that of folic

acid and this occurred most frequently in alcoholic persons. There was also a frequent occurrence of low-circulating levels of vitamins A, C and $B_6$ in this hospital group.

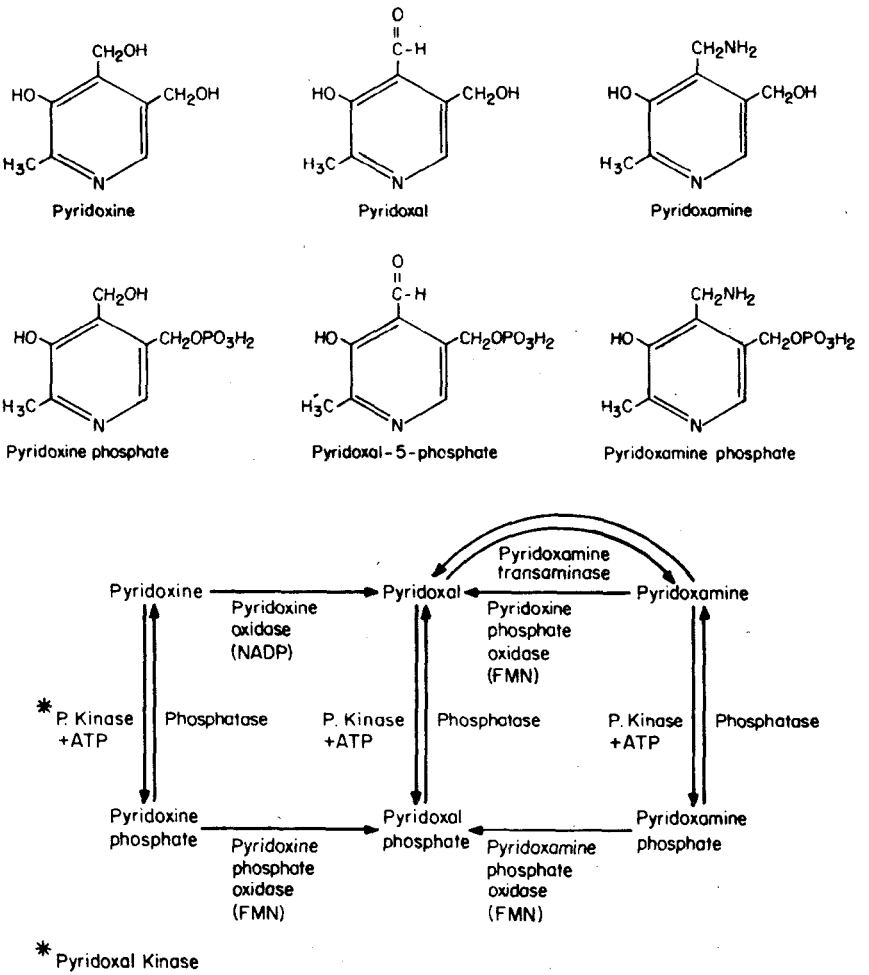
From available information it can be predicted that prevalent forms of nutrient depletion, especially hypovitaminoses, will be those most accentuated by drug ingestion. This may be a partial explanation for the fact that drug-induced folate deficiency is the most frequent form of vitamin depletion due to pharmacological agents which is found in those developed countries from which reports have been published. However, it may be anticipated, in developing countries where endemic malnutrition exists, that ingestion of drugs would also exacerbate other dietary deficiencies.

In order to understand the mechanisms involved in the development of drug-induced nutrient depletion, this review of nutrient sources—their absorption, metabolism and excretion—has been compiled. Detailed discussion of particular nutrients is justified, either on the basis of frequent drug interactions, or because in the clinical sense they are most commonly affected by drug intake. It is important not only to realize how nutritional deficiencies are incurred through drug action, but also how the body is defended against the occurrence of such deficiencies. Varied and multiple nutrient sources, accessory systems of nutrient absorption, as well as metabolic adaptation, contribute to the economy of the body in preserving nutritional status at a reasonable level.

## Water-Soluble Vitamins Significantly Affected by Drugs

**Vitamin $B_6$.**—Sources of $B_6$ vitamers include the pyridoxine present in plant materials and pyridoxal and pyridoxamine, coming from foods of animal origin. The vitamin is present in many foods and the richest sources are liver (beef, calf and pork), herring, salmon, nuts such as walnuts and peanuts, wheat germ, and yeast. While the vitamin is present in significant amounts in meats, fish, fruits, cereals and vegetables, it is present to a lower extent in milk and other dairy products. Since pyridoxal and pyridoxamine are decomposed rapidly at high temperatures and are broken down by autoclaving, there is concern that modern food processing may diminish dietary sources of the vitamin. Evidence presently available suggests that vitamin $B_6$ vitamers are absorbed by simple diffusion across the cells of the small intestinal mucosa (Booth and Brain 1962; Brain and Booth 1964).

Utilization of vitamin $B_6$ depends on conversion of the various forms of the vitamin to a metabolically active coenzyme, pyridoxal phosphate (Fig. 1.1). Pyridoxine and pyridoxamine are phosphorylated by pyridoxal kinase with ATP. Then the resultant pyridoxine




*From Wada and Snell (1961)*

FIG. 1.1. VITAMERS OF $B_6$ AND THE FORMATION OF PYRIDOXAL PHOSPHATE

or pyridoxamine phosphate react with oxidases to form pyridoxal phosphate (Wada and Snell 1961). The latter compound can also be formed directly by phosphorylation of pyridoxal. McCormick *et al.* (1961) showed that the brain, liver and kidney contained the highest concentrations of pyridoxal phosphokinases. Anderson *et al.* (1971) demonstrated that in man pyridoxine can be converted to pyridoxal phosphate in circulating erythrocytes. In an editorial (Nutrition Reviews 1972) discussing the work by Anderson *et al.* (1971) and by others in the same field, it is pointed out that there is evidence that

pyridoxal phosphate can also be converted to pyridoxal in the red cell, and that the pyridoxal passes out into the plasma. Indeed, there is strong evidence that pyridoxal is the major transport form of the vitamin. The editor of this review questions whether pyridoxal in the plasma may enter other tissue cells so that it could be converted to the active coenzyme, pyridoxal phosphate, and also whether pyridoxal can be taken up by the liver cells before conversion to the end product, pyridoxic acid, which can be excreted in the urine.

Pyridoxal phosphate is the key coenzyme in many reactions involving amino acid metabolism. In such reactions an amino acid condenses with pyridoxal phosphate on an enzyme surface and a Schiff base is thus formed. When the Schiff base intermediate is bound to a particular enzyme, the bonds at a specific carbon atom are labelized and reactions are then possible involving a number of different bonds (Larner 1971). Specific enzyme proteins are responsible for particular rearrangements within the Schiff base.

There are three important classes of $B_6$ dependent reactions which will concern us in discussion of the effects of drugs:

1. $B_6$ is necessary to the metabolism of the amino acid, tryptophan, and is required at several steps along the pathway leading from tryptophan to the formation of niacin. It is for this reason that drugs that are vitamin $B_6$ antagonists are capable of inducing frank niacin deficiency (Fig. 1.2).

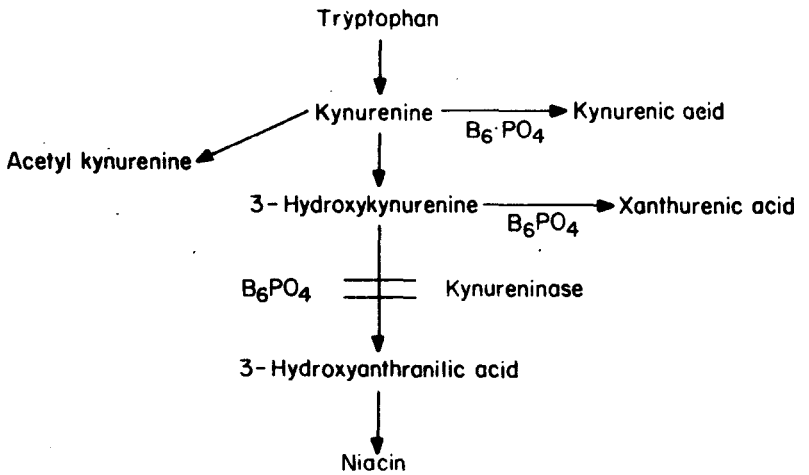
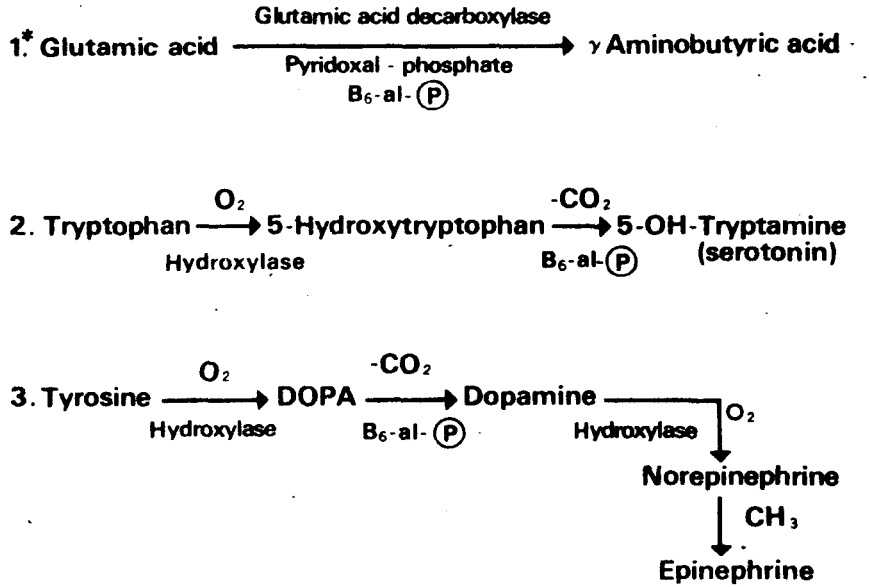



FIG. 1.2. ENDOGENEOUS PATHWAY FOR NIACIN BIOSYNTHESIS FROM TRYPTOPHAN SHOWING VITAMIN $B_6$-DEPENDENT REACTIONS AND STEP PREFERENTIALLY BLOCKED BY $B_6$ ANTAGONISTS



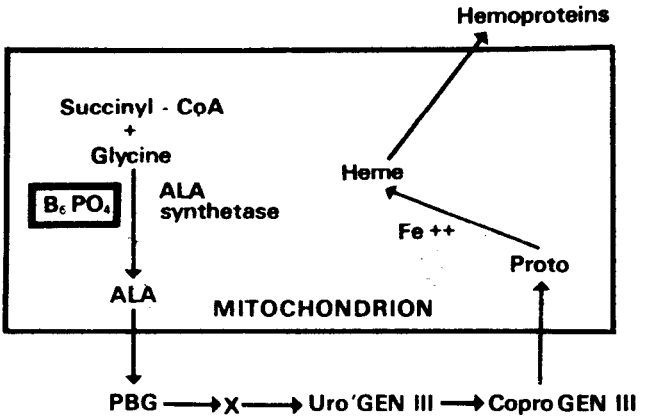

*Convulsions in drug induced $B_6$ deficiency may be associated with decreased function of $B_6$ dependent, glutamic acid decarboxylase

FIG. 1.3. VITAMIN $B_6$ AND THE SYNTHESIS OF NEUROTRANSMITTERS

2. $B_6$ is necessary for the synthesis of a number of neurotransmitters and neurohormones including serotonin, gamma-aminobutyric acid and epinephrine. The fact that these compounds are necessary to neuronal function at many levels explains neurological symptoms associated with drug-induced $B_6$ deficiency (Fig. 1.3).

3. Vitamin $B_6$, in the form of pyridoxal phosphate, is a necessary factor in the synthesis of delta-aminolevulinic acid. The activity of the enzyme Δ-aminolevulinic acid synthetase, which allows condensation of succinyl coenzyme A and glycine to form Δ-aminolevulinic acid, requires $B_6$ for its activity and this synthetase is the rate-limiting enzyme in heme synthesis. Vitamin $B_6$ is also required for globin formation (Fig. 1.4).

It is important to remember that when one speaks of the syndromes of vitamin $B_6$ deficiency caused by drugs, one may refer to an actual deficiency caused by hyperexcretion of the vitamin, or to a lack of




ALA aminolevulinic acid
PBG porphobilinogen
Uro'GEN III uroporphyrinogen III
Copro'GEN III coproporphyrinogen III
Proto protoporphyrin IX
X intermediates
Enzymes catalyzing heme biosynthesis omitted except ALA synthetase

FIG. 1.4. ROLE OF PYRIDOXAL PHOSPHATE IN HEME BIOSYNTHESIS

conversion of the vitamers to the coenzyme form, or to specific defects in $B_6$ dependent apoenzymes (Fig. 1.5).

Syndromes of vitamin $B_6$ deficiency can then be divided into three important groups:

1. Neuropathic, in which there is a sensory neuritis. In this condition there also may be evidence of involvement of the central nervous system and convulsions can occur. In the milder forms of $B_6$ depletion, depression is a common symptom.
2. Anemic, in which hypochromic, sideroblastic anemia develops.
3. Pellagrous, in which cutaneous, gastrointestinal and central nervous system signs and symptoms occur which are identical with those of pellagra. The evolution of these syndromes in patients made $B_6$ deficient by administration of a $B_6$ antagonist were described by Vilter *et al.* (1953).

**Folic Acid (Folacin).**—Folic acid and its derivatives are found in a number of foods, the richest sources being liver, yeast, dark green, leafy vegetables, broccoli, asparagus, legumes, and fruits, more espe-