Changing Patterns of Disease: Some Nutritional Remarks

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In the last century the way of life and the way of death have changed in the United States. Infectious diseases have been replaced by diseases of apparently complex origin. Inborn errors of metabolism are more common than the classical deficiency diseases.

The discovery of vitamins and the essentiality of trace elements occurred in the 20th century. Plenty of characteristics have been identified to assess vitamin nutriture; methods of assessing trace element nutriture are less well developed. Newly discovered aspects of copper physiology are potentially useful in establishing requirements.

Key words: assessment of nutritional status, biotin, copper, epidemiology, history, history of medicine, inborn errors of metabolism, infantile scurvy, lipid metabolism, nutriture, puerperal fever, trace elements, vitamins, zinc

HISTORICAL COMMENTS

A centennial provides an opportunity for reflection on comparisons and contrasts between two eras. The Cincinnati Children’s Hospital, which preceded both the Institut Pasteur and the Johns Hopkins Hospital, was founded the same year that Koch discovered the tubercle bacillus. This discovery provides a proper symbol of subsequent change.

In 1882 Pasteur and Koch were providing observations and developing theory to explain important medical and surgical phenomena. Holmes [1] and Semmelweis [2] already had shown how to avoid puerperal fever. Snow [3] had associated cholera with contaminated drinking water. Daniel Drake [4] and John Lea [3, p. 114], both of Cincinnati, also had written about cholera. Lister [5] had proved the value of carbolic acid in surgery.

Microbiology was transforming medicine at the end of the Victorian era. However, Osler [6] in his new textbook of 1892, referred to influenza as an infectious disease without an identifiable organism. This statement also was applied to syphilis. Electrocardiograms, enzymes, and x-rays still were unknown.

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Physicians and patients in Cincinnati live and die differently now from how they did 100 years ago. In 1900 the leading causes of death in the United States were pneumonia, tuberculosis, and enteric disease [7]. It would be 1910 before deaths from heart disease exceeded those from tuberculosis.

The founders of this hospital dealt largely with infectious disease. Sometimes new problems arise as old problems are solved. In 1898 as pasteurization of milk was becoming more common, infantile scurvy was increasing because the process destroyed ascorbic acid [8, 9]. The modern diseases were not unknown, however. Jenner [10] associated angina pectoris with the coronary arteries over two centuries ago.

It seems that four classes of etiologic agents have been identified as causes of disease. Their chronology is shown in Table 1. Perhaps with the prevalence of chain saws, motorcycles, and oil rigs one should mention trauma—a special type of toxicity, in my opinion. Gradually medicine has moved from dealing with infectious disease to dealing with apparently complex diseases. Some of these have a large nutritional or toxic component in their etiology.

Early in this century new concepts of disease arose. Garrod [11] suggested the concept of inborn errors of metabolism and listed four errors: albinism, alkaptonuria, cystinuria, and pentosuria. In contrast, a recent text [12] contains both a tabular list of inborn errors that fills 21 pages and a separate summary of 167 disorders of specific enzyme deficiency. The editors [12] quote McKusick's enumeration of more than 1,350 human diseases determined by single genes. Although these diseases are individually rare, they are collectively numerous. They may account for 5% of all pediatric hospital admissions [12].

Funk [8] promoted the concept of "vitamines." Vitamins were renamed by the excision of the terminal e and were divided into two classes. These conceptual changes were based on their physical properties (fat-soluble A and water-soluble B [9]) and the realization that not all of them were amines. A baker's dozen of vitamins is well characterized [13].

The classical deficiency diseases (scurvy, beriberi, and pellagra) almost have disappeared from the United States. Among those from Cincinnati who assisted in the eradication of these diseases are Aring, Bean, Blankenhorn, Cogswell, C. Cooper, Evans, Frommeyer, Hamburger, Morey, Ruegsegger, Spies, and the three Vilters [14].

Now there are more patients with specific inborn errors than with classical deficiency disease. For example in 1974 there were three deaths from scurvy in the United States [15]. One can calculate that three people with cystinuria probably are born in Cincinnati each year [16, 17]. Similarly, approximately 450 people with cystinuria are born in the United States annually.

Some scientists believe that the model of disease suggested by Koch or Funk—ie, one agent producing one disease—is not germane to the modern diseases—eg,

### Table 1. Chronology of Etiologic Classes*

<table>
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<tr>
<th>Toxicity (Aristotle, 384–322 BC)</th>
<th>Heredity (The Talmud, AD 50)</th>
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<tbody>
<tr>
<td>Infection (Boccaccio, AD 1353)</td>
<td>Deficiency (Liand, AD 1753)</td>
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*Probably the concepts were known before these dates, which seem to be the first written records.
ischemic heart disease and cancer. Sometime between 1948 and 1966 the term “multifactorial disease” or “disease of multifactorial origin” was introduced into the medical vocabulary [18].

However, all diseases are multifactorial in some respect [19]. Not all victims of tuberculosis have identical signs and symptoms. The organism is the cause; modifying factors exist. Holmes [1] mentioned modifying factors and variable attack rates in puerperal fever, vaccination, scarlet fever, and smallpox.

Before the origin of a disease is known, medical scholars are confronted by a bewildering array of apparently dissimilar observations. Some of the observations are false, some are the result of improper classification of disease, and some are true. Modifying factors at this stage cannot be distinguished from cause. The similarity of the complexities and intricacies of pellagra [20] in 1915 and scurvy [18] in 1772 to those of ischemic heart disease today have been noted.

Unfortunately, in every era, physicians spend most of their time treating patients whose diseases are of obscure origin. That is, when the origins of diseases become known, therapy and prevention become well developed and the diseases almost disappear. Extensive knowledge of pathophysiology is insufficient to eradicate a disease. In contrast, knowledge of etiology is necessary for eradication. In this sense physicians spend most of their time treating diseases they don’t understand.

**requirements and allowances for nutrients**

A substance is considered a nutritional essential for an organism if the organism can neither grow nor complete its life cycle in the absence of the substance. This concept was best outlined by Bowen [21] who extended Arnon’s [22] criteria for plants to animals. It is difficult, perhaps impossible, to obtain evidence in conformity with this rigid definition, even for plants or animals. It is unethical to satisfy this definition by subjecting people to severe experimental conditions. Consequently less rigorous criteria often are acceptable; emphasis frequently is placed on impaired function [23–33].

If a substance has been identified as an essential nutrient, it is important to determine its requirement. Often the experiments that prove essentiality provide the first estimates of requirements.

“Recommended Dietary Allowances (RDA) are the levels of intake of essential nutrients considered, in the judgment of the Committee on Dietary Allowances of the Food and Nutrition Board on the basis of available scientific knowledge, to be adequate to meet the known nutritional needs of practically all healthy persons” [13]. As these allowances are for healthy populations, the effects on requirements of the stress of chemotherapy, sepsis, surgery, trauma, etc are not considered. The Committee considers a wide variety of evidence and is not always in agreement that a requirement has been met. It sets the Allowance as an amount greater than the average value of the requirement. Estimation of requirements is a matter of judgment as data are incomplete for some nutrients. Requirements for a given nutrient vary with the criterion considered [13,32].

**Biotin Nutriture**

According to Murthy and Mistry, the history of biotin began in 1901 [34]. A few years ago I determined the biotin requirement of rats fed egg white [35]. Growth
for 60 days was used as the criterion; it is clear from Figure 1 that 1 mg of biotin per kg of diet was insufficient for optimal growth. In principle, one could define the biotin requirement as the amount necessary to provide a certain activity of an enzyme or a certain concentration of biotin or its metabolites in body fluids. Thoene, Mock, and Kien, et al [36–39] have summarized more than a dozen chemical and physiological changes associated with human biotin depletion that could be used to define the requirement.

Unfortunately, if dose-response curves for biotin intake and all of these characteristics could be drawn, there could be more than a dozen estimates of the requirement. It is unlikely that the estimates would disagree by an order of magnitude, however. Selection of the best estimate would depend on opinions regarding the importance of the characteristic under consideration. In general, there are plenty of characteristics that can be used to assess vitamin nutriture; however, methods of assessing trace element nutriture are less well developed.

![Graph](image)

Fig. 1. This experiment was designed to determine the biotin requirement of growing rats fed egg white. The male rats were fed purified diets based on sucrose (62% by weight), egg white (20%), and corn oil (10%) and containing graded amounts of biotin. Weight of rats fed stock diet (a commercially available diet composed of agricultural products) on the 60th day was assumed to be optimal. Dietary amounts of biotin ranged from 1.00 to 3.00 mg biotin/kg of diet. The graph contains unpublished data from [35], experiment 2. Ten rats per group except for nine in 3.00 mg/kg groups. Circles and triangles indicate the mean weights which determine the curves. Triangles indicate mean weight significantly different (P < 0.05) from the corresponding mean on the curve for rats fed stock diet. The first day for each curve is displaced slightly along the abscissa to prevent overlap. Horizontal arrows indicate the intersection of the curve with the time line indicated by the accompanying number. The growth of rats fed either 1.00 or 3.00 mg/kg was inferior to that of rats fed 2.00 mg/kg. Two mg/kg was taken as the dietary requirement based on these and other data in [35].
Dietary Copper and Copper Balance

A few years ago we observed [40] that hospital diets, and perhaps diets in general, contain less copper and zinc than the amounts thought to be required by adults. The data were consonant with earlier publications and have been confirmed. A short discussion of the possible consequences of the findings was excised from the manuscript by the editors because it was based on data from animals. Table 2 contains a short summary, based on Underwood [32], of the abnormalities found in animals deficient in copper or zinc. The similarities of the findings in animals to those found in some human diseases have been noted [41,42]. Certainly there are many patients whose diseases are of unknown etiology and whose biopsies, chemistry, pathology, and physiology resemble those of animals deficient in copper or zinc.

"The daily American diet contains 2–5 mg of copper." This statement is obsolete; this obsolescence and its origin have been reviewed [20,42]. In brief, the statement is based on a few papers, decades old.

No Allowance has been given for copper; the estimated safe and adequate intake for adults is 2–3 mg per day. This amount is based largely on a graph drawn by Cartwright [43] in 1950; it still is considered a reliable estimate of the amount of copper required (2 mg per day) to compensate for urinary and fecal loss [44]. The numerous articles containing data on daily diets containing less than 2 mg of copper have been reviewed [18,42]. Three are among the more accessible [40,45,46]. I estimate [18,42] that less than 25% of daily diets contain more than 2 mg.

Thus there is a disparity between dietary copper and the copper requirement for adults. Either there is something wrong with usual diets or there is something wrong with available estimates of the copper requirement.

We did a balance study similar to those on which the copper requirement [43,44] is based. The mean amount of copper in a diet of conventional foods necessary to compensate for urinary and fecal loss of men was 1.30 mg/day [47]. We concluded that the data fell within the scatter of the points about the line drawn by Cartwright [43].

As a further refinement of the estimate we measured loss of copper from the surface of the body [48] and evaluated by linear regression the effect of other dietary components on copper balance [49]. The mean daily loss of copper from body surface is 0.3 mg [48]. Dietary zinc is one of the more important dietary components that can affect the copper requirement [49]. Extra zinc increases the copper requirement. An

<table>
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<tr>
<th>TABLE 2. Abnormalities of Copper or Zinc Deficiency in Animals*</th>
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<tr>
<td>Copper</td>
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<tr>
<td>--------</td>
</tr>
<tr>
<td>1. Anemias</td>
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<tr>
<td>2. Defects of connective tissue</td>
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<tr>
<td>a. Arteries</td>
</tr>
<tr>
<td>b. Bone</td>
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<tr>
<td>3. Degeneration of brain and spinal cord</td>
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<td>4. Myocardial degeneration</td>
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*After Underwood [32].
intake of dietary zinc similar to its Recommended Dietary Allowance plus mean surface loss of copper can increase the daily copper requirement to more than 2 mg [49]. The suggested "safe and adequate intake" for copper [13] may be neither safe nor adequate for some people.

**Copper Nutriture: Newer Conceptions**

Until recently, all measurements of the human copper requirement have been made with the balance method. As different methods of assessing requirements can lead to different values for the requirement, we have attempted to measure the requirement of several men by the depletion method. They were fed a diet made of conventional foods and low in copper (about 0.8 mg/day); their requirement exceeded this amount. One man responded with an increase in the concentration of cholesterol in plasma [50]; two others responded [51] with an increase in the height of their glucose tolerance curves. Both of these changes were reversed by supplementation with copper sulfate. None of these men was anemic. Children with Menkes disease, a disease in which intestinal absorption of copper is decreased [52], are both hyperlipidemic and glucose-intolerant [53].

Glucose intolerance in copper-deficient rats was discovered a half century ago [54]. This phenomenon has been rediscovered [55]; there is much current interest. Since the association of copper metabolism with cholesterol metabolism a decade ago [56], the phenomenon has been confirmed in at least four independent laboratories [57-60].

Pharmacologic doses of zinc may be harmful. Young men taking 160 mg zinc per day in addition to dietary amounts had a decrease in the concentration of high-density lipoprotein cholesterol in serum [61]. This effect of zinc probably is not beneficial [62] and probably is the result of an adverse effect on copper metabolism [63]. An increase in plasma cholesterol of rats from the ingestion of a high ratio of zinc to copper was described a decade ago [56].

There is a correlation (r = 0.354) between the ratio of zinc to copper of cow milk available in 47 cities in the United States and the mortality rate for coronary heart disease in the cities [64]. Only ethanol and the ratio of zinc to copper of milk have been associated with risk of death due to heart disease in an epidemiologic study in the continental United States.

Osborne [65] noted that accident victims dead by age 20 had less atherosclerosis of the coronary arteries if they had consumed human milk in infancy. Perhaps the higher ratio of zinc to copper [64] of cow milk (greater than 38) in comparison to human milk (less than 7) contributed to the atherosclerosis. It has been known for more than a half century that animals (other than cows) fed cow milk become deficient in copper [54,66,67]; the cardiovascular damage can be extensive [67].

Anemia was the first aspect of copper deficiency to be recognized [66]. Although Cartwright [68] stated in 1947, "There has been no subject in hematology more controversial than that of copper," I have found [69] no evidence that the controversy — whether or not anemias responsive to copper replacement exist in the free-living population — has been settled. Perhaps the controversy has been forgotten.

Experiments with animals [56,70] and men [50,51] have shown that it is possible to have an abnormality of copper nutriture with minimal or no anemia. For example, in an experiment on copper deficiency hemocrit was decreased by 17% when plasma cholesterol increased 65% [70]. Perhaps hematology doesn't reveal the most sensitive
indicator of low copper status in all situations. Perhaps lipid metabolism is more sensitive than hematocrit to copper depletion. Perhaps use of other criteria of deficiency may be useful in defining the copper requirement.

Measurement of copper in blood plasma or serum (serum values tend to be 7% higher than those of plasma [71]) probably is not helpful if the values are in the normal range [72,73]. This lack of utility is probable for ceruloplasmin, as well. Within the normal range, which is quite wide, higher values may not indicate better nutriture than lower ones. In fact, when the metabolism of copper of calves is inhibited by molybdenum, plasma copper is increased and liver copper is decreased [74]. Measurement of superoxide dismutase in erythrocytes may be useful as low values may indicate low tissue copper [75].

Nutritional research on copper, having been quiescent for a number of years, is in resurgence. In 1983 there was, for the first time in more than a third of a century, a session devoted solely to research on copper metabolism at the annual meeting of the American Institute of Nutrition. The aspects of copper metabolism discussed in the session and included in recent journals represent an almost incredible diversity. Perhaps some of them will be useful in the search for better assessment of nutriture so that requirements can be defined more completely. Experiments with animals may be of guidance in the selection of potential criteria.

There are many new findings related to copper metabolism—eg, catecholamines in brain or abnormalities of pulmonary anatomy—which may not be useful in assessing nutriture in establishing requirements because one is unable to obtain samples during life. Of course if is possible to correlate some of these findings with liver copper after death. Some work [76] on aneurysms of the aorta can be viewed in this way.

Some other characteristics of animals deficient in copper can be sought safely in people. However, after measurements are made interpretation may be difficult. Normal values may be normal only in the sense of being those most frequently found, not in the sense of being optimal. Perhaps one should search for a chemical or physiological change in response to copper supplementation. This approach is more difficult; some aspects of a trial of copper supplementation have been discussed [18].

The hypercholesterolemia and glucose intolerance of animals deficient in copper have been noted above. In addition these animals are hyperuricemic [77], they have decreased activity of lecithin: cholesterol acyltransferase [59,78] and lipoprotein lipase [79] in plasma, and glycosylation of hemoglobin is increased [80]. Abnormal electrocardiograms in copper-deficient rats [81] improve on treatment with copper [82]. It has been suggested that copper deficiency may contribute to the abnormal electrocardiograms associated with consumption of liquid protein diets by humans [83], and that some human arrhythmias may respond favorably to copper supplementation [84].

CONCLUSIONS

Medicine has changed during the last century. Infectious diseases have been replaced by apparently complex diseases of obscure origin as the leading causes of death. Some of the modern diseases have a large nutritional or toxic component in their etiology. Since 1900 the major advances in nutrition have been the discovery and characterization of two groups of micronutrients, the vitamins and trace elements,
and the eradication of the classical deficiency diseases. Inborn errors of metabolism now are more common than scurvy, beriberi and pellagra.

Requirements, and hence Recommended Allowances, for vitamins are reasonably well defined; those for trace elements are uncertain. Traditional assessments of nutriure have relied on the presence or absence of anemia; perhaps hematology is not the most sensitive index of depletion. Recent discoveries on the effects of copper deficiency on animals have provided new characteristics that have potential utility in the assessment of nutriure. If we use this information, perhaps, in the words of Thomas Kuhn [85], we will "see new and different things when looking...in places (we) have looked before."

REFERENCES


69. I have examined the volume indices of the Ann Intern Med, Arch Intern Med, Blood, Br J Haematol, and N Engl J Med from 1946 to 1982 and have found no titles suggesting that the controversy has been studied.


