A CONCEPT OF THE ETIOLOGICAL COMPLEX OF DEFICIENCY STATES WITH ESPECIAL CONSIDERATION OF CONDITIONS

H. D. KRUSE, M.D.

IN a previous paper (1) were presented the nature, forms, qualities, and characteristic behavior of a deficiency process in its development and course in the body. But the cause, conditions, and circumstances responsible for it and determining its qualities and behavior were perforce only briefly mentioned. Such is the scope and complexity of its etiology that the relation and unification of its manifold diverse parts could not there be fully presented. In the present paper is to be considered the etiology of the process. A new concept is evolved embracing the causal complex and particularly integrating the conditions that engender and govern the bodily deficiency and impart to the process its qualities and behavior. Its salient points have already been briefly outlined in a preliminary publication (2).

In the several present-day views on the etiology of deficiency states, diet occupies the paramount position. What has been since 1910 and still is the most prevalent doctrine is simple in essence: faulty diet is the sole cause of deficiency disease. The reason for this view becomes understandable in the light of the development of the newer knowledge of nutrition. It reflects the objectives and particular procedure in the long succession of studies during the past three decades that have been directed foremost upon diet. There were two aims:

1. detection of the number and nature of essential nutrients in foods; and
2. ascertainment of their significance as derived from the effects of deprivation of them upon nutrition.

Particularly sought as part of the latter goal were the separa-

tion and characterization of individual deficiency states and elucidation of their specific etiology. In the accomplishment of these ends the particular procedure of inducing the deficiency diseases in animals through subjecting them unremittingly to a deficient diet exerted a strong influence upon the views of etiology. The preoccupation was with diet and emphasis was on its part in nutrition. Diet was the only variable under study by contrast; all other variables were equalized or minimized. This exclusive study of diet among the variables was bound to make an indelible impress on notions of etiology. Under these circumstances it was therefore entirely natural to ascribe sole and complete causal responsibility for deficiency diseases to diet. All nutritional diseases were reduced to diet, traceable and attributable to it.

At the same time diet came to be regarded as the basis, even the essence, of nutrition. As a further outgrowth their relationship was also viewed as a unity, their separate identities were merged, their connotations were blended, and their differentiation was lost. The two terms came to be used often synonymously with no distinction between them. This practice inviting looseness and vagueness in thought and expression has contributed to confusion. In meaning and usage the two words are to be dissociated; hence it is essential to restore and reassert their differentiation. Actually nutrition is a bodily process; diet, in contradistinction, refers to a regimen of food which supports nutrition.

Upon scrutiny of the procedure by which deficiency states were induced in animals, it is to be noted that variables other than diet were also active. It has been known that growth, reproduction, and lactation increase nutritive requirements, that it is easier to induce acute deficiencies in young, growing than in older animals, that growth is necessary in young animals subjected to an incomplete diet if they are to develop acute deficiency states, and that reproduction and lactation as critical factors can under adverse circumstances precipitate deficiency states. Accordingly, in animal studies these points were turned

to advantage. Also, it is obvious that confinement of the animals limited other variables and their influence. But whether these nondietary influences were used to advantage or were kept at a minimum, their influence was always equalized in groups under study. Hence they were not accorded recognition in the etiological complex. But neither equalization nor minimization excludes them and their influence. Nor does it permit them to be ignored. Consequently, as derived from these studies, the doctrine that diet alone controls nutrition and to all intents and purposes the two are identical, does not embrace all of the many influences other than diet upon nutrition and all of the components, nondietary as well as dietary, that actually entered into the etiology of deficiency states. It is therefore fallacious. Rather, these studies demonstrated that diet was an influence, not the only influence on nutrition; an etiological factor, not the only factor, in the production of deficiency states. It is evident that even in animals under influences limited, controlled, or equalized, the etiology of deficiency diseases is not so simple: it includes nondietary influences.

Compared with animals under the restrictions of study, the situation with man is even more complex. Man has additional environmental influences freely affecting his nutrition. Then too, in studies on man, none of the influences is so readily limited or equalized. What is more, in the course of everyday life the influences are free from such curbs and restraints, however slight, as may be introduced by scientific procedure. Thus, in the natural occurrence of deficiency diseases in man, the influences are not only more numerous but also less restricted. Consequently the etiology of deficiency diseases in man is no less, it can be even more complex than in experimental animals. The doctrine that diet alone controls nutrition, that faulty diet is solely responsible for deficiency diseases, has never been adequate to cover the situation. Many nondietary influences have to be recognized in their relationship to nutrition and accommodated in the etiology of deficiency states. Perhaps partly because they had a greater degree of freedom to affect man and

partly because they were not from the first overshadowed and relegated to obscurity by emphasis on diet in observations on deficiency diseases in man, these nondietary influences have been more easily apprehended in their action on him.

Among the clinicians the view that many influences, nondietary in nature, contribute to the etiology of deficiency diseases is neither new nor isolated. Very early, even before they were identified as nutritional disorders and associated with diet, beriberi, xerophthalmia, scurvy, rickets, and pellagra were each regarded as not having a single causative agency. Their recorded natural history is replete with reports of their arising from various causes among which were cited numerous endogenous and environmental influences. In the mind of at least one physician, these forces were unified in their action. In 1866, long before pellagra was shown to be a nutritional disturbance, Roussel expounded the view that the efficient cause had to be in conjunction with a set of conditions for production of that disease (3). Although his writings understandably do not make a point of it, his examples of conditions are seen to be nondietary influences.

After the nutritional character of these diseases and the significance of diet in relation to them were recognized, clinicians still appreciated that nondietary influences entered into the production, occurrence, or exacerbation of them. McCarrison in 1921, in his book STUDIES IN DEFICIENCY DISEASES, devotes a chapter to "Factors Influencing the Onset of Morbid States Due to Food Deficiency." Among them he lists (4): instinct and appetite; species and race; age; sex; individual idiosyncrasy; segregation; excessive physical exertion; over-work; cold; warmth; rest; fear; mental depression; lack of balance of the food; previous food conditions; infections; over-crowding; and imperfect hygiene. Four years later Jackson (5) in describing the mode of occurrence of nutritional diseases, including deficiency states, classified extrinsic and intrinsic causes or conditions. During this period pellagra following gastro-intestinal lesions or disorders (6, 7, 8) was assigned the name "secon-

dary." In the next decade Strauss (9) treated on the subject of conditions under the pertinent title "The Role of the Gastro-Intestinal Tract in Conditioning Deficiency Diseases." In a later article (10) he described various "mechanisms" that bring about avitaminosis B_1. Writing of beriberi, he stated: "Severely acute cases probably represent acute exacerbations precipitated perhaps by infections or excessive physical activity in persons who have had unrecognized mild symptoms of the disease for some time."

Since these reports, many additional nondietary influences conducive to deficiency states have been recognized so that the list has been much extended. During their long history, these influences have been variously designated as causes, conditions, factors, conditioning factors, contributing, exciting, or precipitating factors. In this discourse the short, precise, and proper term, conditions, will be preferentially used. After a period of eclipse concomitant with the rise to prominence of diet, these nondietary influences have begun to reattract interest and regain recognition. In vivid accounts, Wilbur (11) and McIntosh (12) have each described deficiencies conditioned by gastro-intestinal diseases and digestive disorders. Platt (13) too has taken cognizance of "factors contributing to the clinical expression of nutritional deficiency." Recently, conditions have been the subject of review in special articles (14, 15).

One of the common yet distinguishing characteristics set down about these particular conditions or influences bearing upon nutrition and deficiency states was their nondietary nature. Notwithstanding their renewed recognition, their relation to nutrition, and their precise part in the etiology of deficiency diseases, especially their relative position to diet, have been and still are variously regarded. The writings of McCarrison (4) thirty years ago, when the experimental study of the association between diet and deficiency disease was first gaining momentum, reveal a point of view implicit in his use of the term contributing. From the context it may be gathered that diet was thought to be the main or basic cause, but nondietary

factors may contribute to the production of a deficiency state or aggravate it. This view did not, however, persist.

Instead, two divergent beliefs developed and still prevail. When a nondietary condition is conspicuously associated with a deficiency lesion, sole causality is apt to be attributed to it. Participation of other causal forces may be ignored. Indeed, the condition may be viewed as having no relation to the nutritive system and its effects may not be recognized as conducive to or aggravative of a deficiency state. On the other hand, under similar circumstances, it may be regarded as related to nutrition and productive of deficiency disease. Then, although it is invested with sole causality, it is assigned an etiological plane subordinate to diet and the deficiency disease is sharply distinguished as a type and placed in a subordinate category. It is called a secondary deficiency disease (6, 7, 8). Only those in which diet is found to be prominent as cause are primary. This shade of view reaches its height in public health when if marked dietary deficiency is not found or nondietary conditions seemingly predominate, the deficiency state holds little interest.

Today the views on the etiology of deficiency states reflect the two lines of their historical development with their sharp separation. According to the one, diet is the sole cause. According to the other, one or another nondietary condition may be assigned as the cause. A basic hindrance to harmonizing these beliefs has arisen from the difference in opinion on the relation of nondietary conditions to nutrition. Nor has the exaltation of diet facilitated or encouraged rapport. Furthermore, to relate these conditions with diet has seemed so unnatural and difficult as to be unlikely. These have been obstacles to embracing both nondietary conditions and diet in a unified yet inclusive etiological scheme; consequently they have been treated as insulated items. Despite these impediments, there was an indication of a beginning attempt, unfortunately too indefinite, to encompass the two approaches; but it did not endure, much less come to maturity. Such is the situation that it has led, not to unifica-

tion, but to further division into three views on the etiology of deficiency diseases.

The first two are alike in their conclusions but differ in their arguments. Neither acknowledges a causal complex with multiple members. The one recognizes only diet as the cause of deficiency processes and does not take cognizance of or admit nondietary conditions. The other holds likewise that only diet is the cause of a deficiency process; but while it recognizes nondietary conditions, it does not accept that they can bear upon nutrition or accord them a place in the causal nexus. Thus the one says: all deficiency diseases are due to faulty diet. The other states it negatively: the changes produced by nondietary conditions are not a deficiency process, even though they may be similar to or identical with those produced by inadequate diet. This amounts to saying: nondietary conditions do not produce deficiency processes. The remaining school of thought differs from the preceding in that it recognizes that faulty diet and nondietary conditions may each be conducive to deficiency processes. But it does not visualize that diet and nondietary conditions usually operate jointly. Either diet or a nondietary condition is regarded as the sole, distinct cause. Furthermore, diet is viewed as the main cause of a deficiency disease. If causation is attributed to a nondietary condition, the deficiency disease is regarded as secondary in type. If both faulty diet and a nondietary condition are conspicuous, their concurrence is viewed as a coincidence and two "causes" are accepted.

These views on etiology and conditioning factors have obvious shortcomings in common. In no one view have all the parts in the etiological process been recognized, taken into account, related, and organized. The association of these parts has not been appreciated; no causal combination has been envisioned. Consequently the relative position and contribution of each has been ignored. The result is a set of narrow, exclusive, disjointed, incomplete notions, each of which oversimplifies and misemphasizes one factor and presents, therefore, distorted and inaccurate views. It is interesting that Roussel (3) in

1866 in discussing the etiology of pellagra called attention to the complex character of the formula; pointed out that "conditions" were an indispensable member; and criticized their omission from consideration in the then extant theories and the consequent inadequacy of the latter. Much the same situation prevails today.

What is needed is a complete, comprehensive, and integrated view of the causal nexus with its parts in proper perspective. Such a concept must not only fit but also explain the facts. In the ensuing paragraphs is given a concept in which the etiology of a deficiency disease is visualized in its entirety, and its components are organized and unified. Considered especially are the conditions: their nature, association, action, effects, and significance. In this concept the several aspects previously regarded as unrelated and divergent are harmonized and consolidated.

The Ratio

In essence, nutrition is a process supporting growth and maintenance of tissue. Both growth with its increase in substance, and maintenance with its replacement, are dynamic functions. For its nutrition, tissue must have essential nutrients supplied to it to meet requirements for structure and function. Whether nutrition of the tissue proceeds in a favorable or unfavorable direction turns upon the relation between the supply of nutrients to it and its requirements. Tissue nutrition in respect to the biologically active form of a nutrient depends upon this relationship which may be most simply expressed (Figure 1) as a ratio $\frac{\text{Supply to Tissue}}{\text{Tissue Requirements}}$.

Several terms appearing in association with the ratio should be clarified. For one thing a dietary essential and a tissue essential are to be differentiated. A dietary essential is a nutrient that must be present in the diet if nutrition is to be successful. Included in the class are the fully fabricated forms, variants, and precursors occurring in food. In contradistinction,

FOR THE BIOLOGICALLY ACTIVE FORM OF A NUTRIENT

$$\frac{\textit{SUPPLY TO TISSUE}}{\textit{TISSUE REQUIREMENT}} = \textit{NUTRITIVE BALANCE}$$

Fig. 1. Ratio determining nutritive balance of a tissue in respect to the biologically active form of a nutrient.

a tissue essential is a nutrient that a tissue must receive for its nutrition. More specifically, it is a nutrient in its essential form or forms for the tissue. It would include those capable of being synthesized by the body or its parasites with remote relation or little obvious resemblance to their original materials from food. Some of the amino acids and vitamins synthesized in the body of different species would fall into this category. A disturbance of their synthesis brings out their essentiality. Properly too, this class would embrace the endocrine elaborations. Secondly, tissue essentials would also include those nutrients more readily traceable to kindred substances in food. Even here a nutrient essential to a tissue may not necessarily be identical with the form in food in which it was ingested. Many of the essentials from diet undergo change in the body. Some of the vitamins will serve as examples, although intermediary change, that is metabolism, is by no means limited to them. In the interest of simplicity, illustrations drawn in the presentation of the concept will be limited to the more familiar vitamins and minerals essential to man.

In their chemical reactions in the body some of the vitamins have been shown to undergo transformation and to enter into combinations. These changes may be of several kinds: First, a dietary essential may occur as a provitamin which in the body is converted into the vitamin. For example, β carotene is a pro-

vitamin of vitamin A; 7-dehydrocholesterol is the provitamin of vitamin D. Secondly, a provitamin may occur in closely related multiple forms in food: e.g., α, β, and γ carotenes and kryptoxanthin yield vitamin A. Likewise, a vitamin may occur in closely related multiple forms in foods: a vitamin A_2, as well as vitamin A, is reported; vitamin D_2 and D_3 are recognized as separate entities. With knowledge of the chemical structure of both vitamins and provitamins, closely related compounds such as their analogues, homologues, and derivatives have been synthesized for most of them. The several provitamin forms of a vitamin vary in the maximum amount of the vitamin that they are potentially capable of yielding. Furthermore, the multiple forms of a vitamin, whether natural or synthetic, may vary in their biological activity in one species and from species to species.

Thirdly, several of the vitamins must assume a different chemical form before their catalytic role in metabolism is possible. They enter into a reaction forming a new compound constituting a coenzyme. Thus, niacin is converted to diphosphopyridine nucleotide, known as coenzyme I, and to triphosphopyridine nucleotide, coenzyme II; thiamine is transformed to diphosphothiamine, cocarboxylase; and riboflavin to alloxazine adenine nucleotide. These coenzymes combine with protein to form enzymes instrumental in and essential for intermediary metabolism of amino acids, carbohydrate, and fat. The coenzyme is the prosthetic group of the enzyme; while the vitamin is the key distinctive component of the coenzyme. For all these reasons a nutrient essential to a tissue is not necessarily the same as a dietary essential.

These changes in which the vitamin enters into an enzyme system project a fundamental question. Does an essential tissue nutrient, such as a vitamin, operate in one or several functional, biologically active forms? The answer cannot now be given. Conceivably the free vitamin, like the coenzyme and enzyme, may be a functional form; but it is not known. It is sufficient to emphasize that the terms of the ratio refer to the

biologically active form or forms of the nutrient essential to the tissue.

Then too, for clarification, the supply to a tissue of a needed nutrient should be distinguished from ingestion of food. The latter is, of course, an ultimate source of supply. However, diet is not synonymous with supply of nutrient to a tissue. Several steps, over and beyond those just presented, intervene between them. Food materials must run the gauntlet of digestion, absorption, transport, and utilization. Thus, intake of food containing a dietary essential is not the same as supply to a tissue of a nutrient essential to it.

The ratio takes into account both terms, requirements as well as supply, and their relationship in producing a favorable or unfavorable balance; it summarizes the resultant of this relationship as a causal force for good or poor nutrition. Although precise numerical values cannot yet be assigned to the terms of the ratio, it is clear that a quotient of one or greater indicates activity in a favorable direction. Thus when supply equals or exceeds requirements, the bodily processes operate towards good nutritional status. But when the quotient is less than one through need exceeding supply because the former is high or the latter is low or both, it is adverse on an absolute scale. It represents a deficit or deficiency and the bodily processes operate towards poor nutritional status. This deficiency expressed by an unfavorable ratio conduces to the creation, maintenance or progression of pathological changes in the tissue which constitute a deficiency disease. It is the cause of the deficiency disease.

Parenthetically, it should be noted that for some nutrients the ratio has an optimum zone above which as well as below which it is adverse. For example, a supply of lipogenic nutrients in excess of requirements would be conducive to obesity. But here discussion will be confined to those nutrients which cannot be obtained in injuriously excessive amounts from a diet of natural foods, and which can be taken therapeutically at still higher levels with beneficial, not harmful, effects.

One of the most significant features of the ratio is its dynamic behavior. It reflects the continuous operation of its terms with their capacity to undergo change at any time. The terms and ratio may change in either direction, decrease or increase. They are therefore vector quantities with direction as well as magnitude. Thus by a decrease in supply or an increase in requirements, or both, a satisfactory ratio may be lowered to the point of indicating a deficiency which sets into operation the bodily processes in an adverse direction. Such a change in the ratio is not to be confused with changes in influences on the ratio. For example a dietary inadequacy occurring suddenly does not mean that a satisfactory tissue ratio is at once commensurately disturbed. Compensatory or counteracting influences may delay and cushion the change in the ratio. Manifestly, by an adverse alteration in supply or requirements, a ratio that is already low will reach a still lower point.

Oppositely, by an increase in supply or a decrease in requirements, or both, a low ratio reflecting an unsatisfactory balance increases thereby setting into operation the bodily processes in the more favorable direction. However, it should be stressed that in this situation a large increase in nutrient intake, as in therapy, or a considerable decrease in bodily needs, or both, does not necessarily mean that the ratio for the tissue at once attains or exceeds unity. A nutrient intake and supply that would be sufficient or in excess of needs in the absence of existing, accumulated nutritional pathology in the tissue and would therefore give a ratio greater than 1, does not produce such a ratio in the presence of pathological tissue. Until their disappearance lesions already existing and constituting poor nutritional status raise requirements. Indeed, because of the limited rate at which the cumulative chronic pathology of a deficiency can be liquidated, considerable time elapses before it and the increase in requirements created by it are removed. It is broadly comparable to the financial situation in which a current improvement does not immediately offset an accumulated deficit. It is however, a favorable turn of events.

Then too, a lesser degree of upward change from a quotient of less than unity has its relative effect. If a heavily minus ratio changes to a lesser deficit, specifically to a level that would still be less than one even if the tissues were free of pathological alteration, the new quotient admittedly is still not satisfactory as judged by what it could be, but it represents an improvement. It is a change in the favorable direction.

Certainly the ratio can undergo change at any time, and probably does change frequently or continually, if only to a slight extent. Evidence from persons of all ages indicates a long term trend over a life time with seasonal cycles and intercurrent fluctuation.

By virtue of its capacity to change and the relationship to time, the ratio yields quantities characterizing the governing force over nutrition: intensity, velocity, and duration. Acceleration also enters into the calculations. All except duration are vector quantities. Since a major interest is the pathogenesis of a deficiency disease, for which the deficiency state is responsible, let us assume that a ratio previously above is now below one. Its new absolute value expresses the intensity of the causal force. Obviously the ratio has been brought to this point by change. What the ratio was becomes as important as what it is. Three questions arise: How far did it drop? How fast did it drop? How long has it been at the new level or zone? The answers to these questions further characterize the governing force expressed by the ratio.

As a dynamic process the governing force possesses a velocity. In the example, it was proceeding in a favorable direction. With the drop in the ratio, it changed its direction and velocity. The rapidity of the change which is derived from the extent of change and length of time indicates acceleration. This is the velocity of change which brings the force to a new velocity. Hence, the previous velocity of the force × acceleration = new velocity of the force. From these distinctions, it is obvious that the same ratio expressing intensity may have different velocities; that a less unfavorable ratio may have a higher ve-

locity than does a more unfavorable ratio; and that the same velocity may be reached by rapid or slow acceleration, the latter taking the longer time. Acceleration including deceleration is then a distinctive quantity derived from the ratio, which perforce imparts a different velocity. And it is this consequence, increased or decreased velocity, that is usually more readily recognized.

Finally, the duration of the ratio at its new level below one indicates how long the causal force has been in operation at that plane or in a given zone. Since time is inherent in the acceleration, velocity and duration of the deficiency force, it is seen to be an important element. Expressing a dynamic process the force may change continually and variously in amount, direction and velocity. From the ratio and time may be derived the characteristics of the governing or causal force: intensity, velocity including acceleration and deceleration, and duration.

These quantities characterizing the governing force of nutrition, whether favorable or unfavorable in direction, affect similar quantities in its manifestations in tissue morphology. The latter indicates nutritional status. A deficiency expressed by an unfavorable ratio is the cause of a deficiency disease manifested by morphological changes in the tissue. Moreover, the quantities of the deficiency are reflected in the pathological manifestations in the tissue. Thus the causal force imparts its characteristics to and thereby helps to determine those of the pathological process in the tissue in terms of velocity, intensity and stage.

The farther the ratio drops below one, the more intense is the deficiency disease. A lesser drop would lead to a more moderate or mild outcome. The faster the ratio drops below one, whether it was previously above or under one, the more rapid is the deficiency disease so that it is seen in its acute form. As it later loses velocity, it may proceed at a slower rate that characterizes the chronic form. Or, as happens most frequently, the process may set in at a slow rate. The various possible patterns of

change in intensity and velocity in the course of a deficiency disease, after its inception have previously been outlined (1). In the usual course of events pathology is established; then the ratio may oscillate with the pathology changing in intensity, velocity, and even direction. In its progress the pathology in the tissue exhibits a definite sequence of events. The longer an unfavorable ratio persists, the more advanced the pathology.

The method of defining and classifying the status of pathological manifestations at a particular time in terms of intensity, velocity and duration has already been described (1). Each may be divided and subdivided as much as is necessary yet feasible for particular purposes. By one of the simpler classifications, intensity is expressed as mild, moderate or marked. To convey the zone of velocity, the terms acute, subacute and chronic were adopted. Duration is measured by the stage which the pathology has reached: early, intermediate, late or advanced. These characteristics of the tissue manifestations reflect the behaviour of the ratio.

Undoubtedly changes in the ratio are almost constantly going on, but only the broadest are directly and promptly recognized. For the most part they are apt to be noted in the light of their effects manifested in tissue. Since time is required for production or recession of pathological manifestations, and since the cumulative effect is more readily discernible than its increments, minor changes in the ratio are masked and even major alterations may for a time go unnoted, depending much on the pre-existing nutritional status.

Conditions

It has already been stated that change is an attribute of the ratio. This change, its occasion, kind, and extent is not a spontaneous, inherent property of the terms of the ratio. It is brought about by influences upon the terms. These influences affect both terms i.e., supply and requirements: some act on one; some on the other; some on both. They may change the terms favorably or unfavorably and may likewise change the

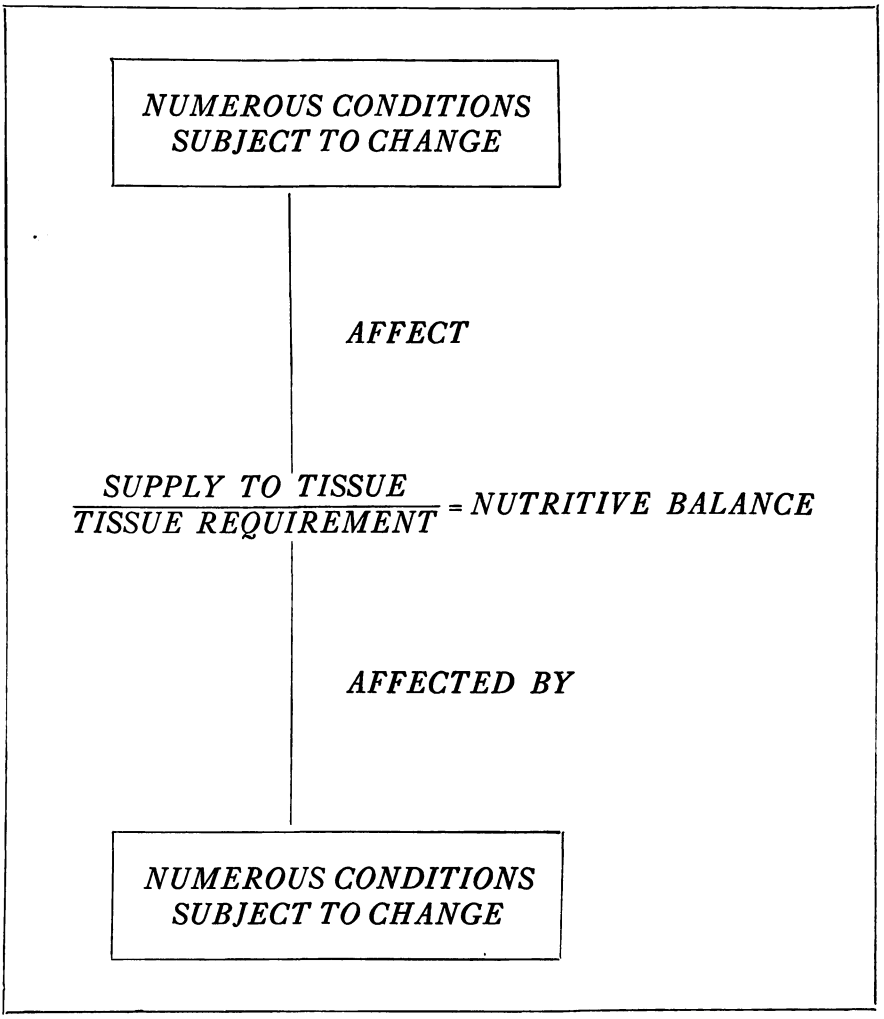

Fig. 2. Action of conditions on members of ratio determining nutritive balance.

ratio. These influences are conditions, a precise yet shorter term than conditioning factors. The ratio and the conditions influencing it constitute a complex (Figure 2). It is to this complex and particularly the conditions operating in it that consideration will now be given.

Their Nature and Multiplicity. All the external and internal environmental as well as hereditary factors that influence either or both members of the ratio in whatever direction are condi-

tions. They are manifold. An extensive but not exhaustive list of these exceedingly numerous conditions is classified in Figure 3 according to their natural location and character which have, however, no necessary bearing on the manner in which they act upon the ratio. Diet, growth, pregnancy, lactation, work, sunlight, climate, toxic material, and disease are just a few of the examples included in the list. It is to be noted particularly that conditions embrace those of a dietary as well as as a non-dietary character.

Not only are the conditions numerous, but they are multiple in operation. In any instance several or many conditions are affecting the ratio and it is their resultant which determines its balance. Furthermore, these conditions are dynamic in nature. According to their nature or circumstances, conditions differ in their schedule of activity or influence. Some are continuous through life, constantly in action. Others impermanent, may occur frequently, occasionally, or only once; and may last a very short or very long time. Of these, some may become active at any time; others, such as growth and pregnancy, are operative only in a definite period of life. In both types, some may last for a definite, others for an indefinite period. Some conditions are inevitable, or so inherent as to be inescapable; others are fortuitous. On the other hand, the influence of a condition for a particular person, not its activity, may begin or cease as he undergoes or passes from exposure to it. In all, there is a variation in the duration of activity or influence of conditions: some continue; others now appear, now disappear. While in operation, a condition may intensify or abate; accelerate or decelerate. Thus not only the cast of conditions but also the degree of influence of any condition may change from time to time. The ratio derives its dynamic behavior from these changing conditions.

Influence and Effects of Conditions on the Terms of the Ratio

These multiple conditions act upon the ratio by influencing

CLASSIFICATION OF CONDITIONS

1. *External Environment*

a. *Socio-Economic*
- Living conditions
- Working conditions
- Available foods
- Ability to seek them
- Income
- Education

b. *Physical and Chemical*
- Radiant energy
  - Light infra-red
  - Ultra-violet, x-ray
  - Radioactive
- Temperature
- Mechanical
  - Trauma
  - Physical movement
  - Pressure; irritation; friction
  - Occlusion
  - Dentures
- Toxicants

c. *Time*

d. *Dietary*
1) Form of nutrient
   - Provitamin: analogue
   - Potential or intrinsic biological activity
2) Level
3) Imbalance—Disproportion
4) Interrelations
   - a. Protein-Carbohydrate-Fat
   - b. Vitamin-Vitamin
   - c. Vitamin { Protein / Carbohydrate / Fat }

2. *Bodily Environment*

a. *Digestive and Metabolic Channels*
- Functional form of nutrient
- Appetite
- Ingestion
- Digestion
- Absorption
- Transport
- Formation of enzyme
- Breakdown of enzyme
- Elaboration, Utilization } Metabolism
- Storage
- Metabolic level
- Excretion
- Biosynthesis
  - Intestinal synthesis
- Biodegradation
  - Intestinal destruction

b. *Functions and Reactions*
- Disease { Degenerative / Neoplastic / Organic / Toxic / Infectious }
- Chemotherapy
- Endocrine relationship
- Nutritional status
  - Morphology and physiology of tissue
- Growth
- Pregnancy
- Lactation
- Work
- Psychobiology
  - Food habits
  - Psychosomatic reactions

c. *Time*

5) Inhibitors—Antagonists
   - Anti-vitamins
6) Enzymatic destruction
7) Autoxidation-rancidity
   - Oxidants-autoxidants
8) Processing of foods
9) Availability of nutrients
   - Precipitation
     - Phytic acid—Iron
     - Oxalic acid—Ca
10) Acceptability—Palatability

3. *Genetic Patterns*

Fig. 3. Classification of conditions affecting the ratio according to their natural location and character. The list is not exhaustive.

both of its terms: some affecting supply, some altering requirements, some modifying both. As a group the conditions have various modes and channels of action in their effect on a nutrient.

On Supply and Responsibility for Deficient Diets. Conditions outside and inside the body affect supply. Because specialization has placed economics, sociology, and agriculture beyond the sphere of competency, although not interest, of the physician, biochemist, and dietitian, usually these conditions are not included in the list. Yet they should be included, for they have a profound effect upon supply, specifically the amount and kind of food. Still other conditions, both external and internal, such as illness, education, intelligence, custom, and habit, affect appetite and choice of food. Thus conditions affect the quantity and quality of the diet, and when acting adversely, become responsible for deficient diets. But supply to tissues extends beyond ingestion of food. Digestion, transport, and metabolic elaboration of nutrients are part of the supply channels, and conditions impairing them interfere with supply. Indeed, interference or failure in supply may occur while a diet adequate for ordinary circumstances is being ingested. Thus a set of conditions may affect another condition, diet, and through it affect supply. It is seen that conditions influence supply on a broad base.

On Requirements. Conditions outside and inside the body likewise affect requirements. Among the external environmental conditions may be mentioned temperature, radiant energy, light, and wind. Bodily conditions include growth, pregnancy, work, toxic material, and disease. In their effects upon requirements these bodily conditions may operate through various channels which are also conditions. Some of these pathways influencing requirements are: utilization, tissue construction and maintenance, metabolic level, excretion, and destruction.

On Supply and Requirements. Some conditions affecting several channels modify both supply and requirements. As an

example, a disease with anorexia, gastrointestinal disturbance, and fever would influence both terms of the ratio.

Opposition and Counterbalance. Conditions that increase the numerator or decrease the denominator tend toward making the ratio favorable; those that operate oppositely conduce to an adverse ratio. By their very nature some conditions only interfere with supply, while others always raise requirements; therefore they would conduce only to a decrease in the ratio and an unfavorable result. Their operation, even at a minimum, tends to lower the ratio. In general they fall into three groups:

1. Those regarded as natural or normal in that they are usually or constantly among the bodily activities or ordinary vicissitudes of life.
2. Some of these in excess or disorder are pathological.
3. Still other conditions are always pathological.

As has been stated, never is one condition responsible for an adverse ratio. That is because, of the many conditions constantly affecting the ratio, a number are natural conditions conducing to lowering it and by their very nature are always in action.

Operating in a favorable direction against depression of the ratio are counteracting conditions. Furthermore, particularly offending or adverse conditions may be removed, controlled, or diminished. The ratio-depressing conditions differ in the ease and readiness with which they may be offset or controlled. The natural conditions can be counterbalanced by equally natural ratio-raising conditions. Because of this, the resultant ratio can, of course, be satisfactory. In contrast, it is less easy to counterbalance the pathological conditions and maintain a proper ratio by ordinary ratio-elevating conditions. Among the pathological group are conditions which may produce a markedly adverse ratio that is resistant to complete correction other than by their abatement. However, their adverse effects on the ratio may be partially overcome by suppression of

another ratio-depressing condition, usually one of the natural type. For example, reduced activity in the form of bed rest is a familiar countermeasure against disease.

If there is deterioration in the function of a pathway of supply from a pathological condition, it may be countered in three ways: (a) removal or control of the offending condition; (b) an alternative route of supply; (c) reduction in requirements by an appropriate change in a condition influencing them. On the other hand, if requirements are unduly high because of some natural condition perhaps temporary, they may be met by increased supply. Increased intake is the obvious step for pregnancy or excessive physical exertion. But if the requirements are elevated because of a pathological condition, the ratio may be kept at a satisfactory or least unfavorable point by removal or control of the offending condition or by suppression of another ratio-depressing condition. For example, measures to terminate an acute infectious disease, together with bed-rest, assuming proper intake, have that effect.

ON THE RATIO AND ON THE PRODUCTION OF DEFICIENCY DISEASES AND THEIR PREVALENCE

Through acting upon supply and requirements, conditions influence the ratio and its effects. They determine whether it is satisfactory or unsatisfactory and in turn affect the nutritional processes. It has been noted that favorable ratio-elevating conditions may balance or overbalance adverse ratio-depressing conditions so that the resulting ratio is 1 or greater. This ratio indicates adequacy and is conducive to a satisfactory nutritional status in the tissue.

But if adverse ratio-depressing conditions come to predominate, the ratio falls below 1, indicating a deficiency of the nutrient in the tissue. That situation arises from decline of ratio-elevating conditions such as diet; ascendency of ratio-depressing conditions, e.g. growth; or activation of impermanent adverse conditions. Any or all of these types of eventualities may occur. Other unchanged ratio-depressing conditions con-

tinue in their effect. When the balance is unfavorable, a deficiency state ensues. This deficiency state leads to pathological changes in the tissues and signs representing a deficiency disease. Through this chain of events, conditions determine the production of a deficiency disease.

In a broad, loose sense, a tissue deficiency indicated by an unfavorable ratio and the combination of conditions responsible for it comprise a complex that can be regarded as the cause of the ensuing deficiency disease. Not only the adverse ratio but also the conditions which brought it about by their effect on supply or requirements are a fundamental consideration in deficiency diseases. But in the interest of clarity and precision in delving into the etiological system, it is essential to draw a distinction between cause and condition.

In one sense, a condition is defined as a cause. In another sense, a cause is the agency producing a result; whereas a condition is something that necessarily precedes a result, but does not produce it. It is a prerequisite to fulfillment. It is helpful to draw this latter distinction. The tissue deficiency state arising from an unfavorable ratio between supply and requirements of the tissue and expressed in the adverse ratio is the primary, direct, immediate cause of the tissue pathology in the deficiency disease; while the combination of conditions influencing the ratio to that end through their control over supply and requirements are secondary, indirect, mediate causes. Conditions are necessary to the occurrence and existence of deficiency states but are not the direct cause. Most simply and accurately designated, the tissue deficiency expressed by the adverse ratio is the cause; the factors responsible for the unfavorable ratio are adverse conditions.

It has already been explained that a combination of conditions are in action at any one time and that it is the net effect of the aggregate that determines the quotient. If the ratio is adverse, a number of conditions are responsible. Never is one solely responsible for an adverse ratio. It follows that at any one time, the influence of each adverse condition and its re-

sponsibility in the production of a deficiency disease is relative. At another time the relative influence of each adverse condition in the composite may have changed or the cast of conditions may have changed. In this change from time to time, the etiological complex exhibits relativity.

More than for satisfaction of intellectual curiosity, rather for working out suitable therapeutic measures, the analysis of the etiology of a deficiency disease in any instance, the ascertainment of the various conditions contributing to it and assessment of their relative weight are practical matters of moment. It will be recalled that in all instances it has been traditional to divide deficiency disease into two groups: primary, those in which faulty diet is demonstrable; and secondary, those attributable to non-dietary means. Here two separate etiologies were recognized and they were regarded as causes, not conditions. Actually they are conditions, not causes; and since numerous adverse conditions operate in any instance, no one is the sole responsible condition. Furthermore, it is scarcely justifiable to single out one condition, e.g., diet, arbitrarily for the sole and universal distinction of primacy when in many instances other conditions may be more influential.

Rather, the relative influence of any condition in the production of a deficiency disease may be various. Adverse conditions may operate towards deficiency states with two outcomes: (1) They may tend and come close to bringing the cause into action, but are over-balanced by favorable conditions with the net result falling short of a deficiency state. Here they are predisposing conditions. (2) They may bring the cause into action. Among the combination of conditions leading to a deficiency state, some may be arbitrarily designated as contributory, others determinative, on the basis of either their relative weight or timing. Of the aggregate of adverse conditions contributing to an unfavorable ratio, one is often decisive in the sense that it adds enough to tip the scale. It may be the exciting, aggravating, or precipitating condition if the

onset is acute. It is not necessarily, however, the major adverse force; rather its timing attracts disproportionate attention to it. Certainly in any assessment of the relative contribution of conditions to etiology in any instance, the condition with the greatest impact is of considerable concern. Whichever it may be in any instance, it might better be called the major rather than the primary condition. Yet, on the other hand, it is conceivable that in some instances no one condition is major; several conditions of nearly equal impact may jointly exert the major influence.

Thus the etiology of a deficiency disease comprises a number of minor conditions; a major condition or a combination of a few minor conditions with major influence; and one or more exciting conditions. The major condition may also be the exciting condition, or a condition of lesser magnitude may serve that end. As for any one condition that may be operating adversely, its relative contribution is referable to a particular instance. For example, at one time it may be the minor; at another, the major condition. Some conditions by nature are unlikely to be other than minor, though in that they are not unimportant; others are more frequently the major condition; still others are more commonly the exciting condition.

It may be helpful to cite a few examples of familiar conditions and the effect of each in the development or accentuation as well as the subsidence of deficiency diseases. It is to be remembered, however, in discussing a single condition that it is never solely responsible for an adverse ratio since other conditions natural in type are intrinsically and inescapably in operation towards depressing the ratio.

A gastro-intestinal disorder may impede absorption and transport of nutrients and thereby interfere with supply to the tissues (8, 9, 11, 12). Decrease in supply diminishing the quotient of the ratio tends to a deficiency state. With abatement or disappearance of the adverse condition, supply and the resulting quotient would increase unless other unfavorable conditions intervened with counteraction.

Acting on the other member of the ratio, growth, pregnancy, and physical labor are conditions conducing to deficiency states by raising the level of requirements. It is a byword that young animals subjected to an incomplete diet must grow if they are to develop acute deficiency states. Growth makes exacting and unyielding nutrient demands which reduce the quotient and accentuate the deficiency state. Arrest of growth with consequent lowering of requirements changes the denominator in the opposite direction. As another example, signs of deficiency states may flare up during pregnancy. That an increase in nutrient requirements is associated with pregnancy is generally accepted; this increase in the divisor of the ratio, operates adversely towards reducing the quotient. With the termination of pregnancy, its effect on the ratio ceases; its particular aliquot of the divisor drops out.

Forced exercise of animals restricted to a diet low in vitamin B-complex has been found to lead much sooner to occurrence of a deficiency sign than did usual activity (16). Similarly, it has been observed (16a) that men engaged in hard physical work while receiving a ration deficient in vitamin B-complex "developed symptoms and definite signs of deterioration far more quickly and more severely than sedentary subjects on a similar diet." Conversely, a pellagrin put to bed, even though continuing to eat a pellagra-conducive diet (17, 18), shows remission for a time. Here the lowering of requirements from reduced activity is tantamount to nutrient therapy; for reducing the denominator has the same mathematical result as increasing the numerator. It has been noted that conditions differ in their efficiency of exercising influence on the ratio. Although it may seem odd, it is nevertheless true that bed-rest is nutrient therapy in highly effective form.

In all three examples, growth, pregnancy, and work, the recognition of increased requirements associated with them is evidenced by larger recommended dietary allowances (19). The attempt is to increase supply to counterbalance the increased requirements. But to repeat, although each of the

three conditions may precipitate an aggravation of deficiency states, it should not be concluded that any of them alone can bring it about. Unless other adverse conditions, such as inferior diet, disease or pre-existing poor nutritional status prevail, growth, pregnancy, or physical exertion does not set off deficiency signs.

Besides these more familiar examples, the list includes several conditions less commonly recognized as related to nutrition. Mechanical stress, a general term covering many specific situations, is a condition affecting the nutrition of tissues. It may be recalled that one of the usual signs of scurvy in the infant is subperiosteal hemorrhage in the thigh, a site of considerable movement. Contrariwise, when the hind leg of a guinea pig on a scurvy-conducive diet is immobilized, acute changes do not occur (20). Similarly, it is probable that movement of the tongue, one of the most active organs in the body, contributes to the acute glossitis of pellagra. In a kindred class is pressure, such as occurs in dental occlusion. In its more severe form of malocclusion even greater pressure is applied on fewer points of contact. It then becomes understandable why the severest changes in gingivitis of avitaminosis C are often located at these sites. Ill-fitting dentures in their effect on the gums and angles of the mouth fall in the same category (21). Another type of condition apt to be overlooked is radiant energy. Intense light or glare aggravates or elicits photophobia and lacrimation in persons affected with ariboflavinosis (22). Conversely, confinement to a dark room or use of dark glasses is a temporary expedient minimizing an aggravating condition. It should be repeated that they are conditions, not causes; that they affect the nutrition of tissues; and that each may contribute to a deficiency state but alone is not responsible for it.

Two of the most influential adverse conditions are infection and existing poor nutritional status. Twenty-five years ago it was vigorously debated whether xerophthalmia was an infection or a deficiency disease. Careful histopathological

studies settled the issue (23): xerophthalmia was shown to be a deficiency disease in which infection usually supervened. Another deficiency state has now been observed to conform to the same pattern (24, 25). At a certain stage in their development, secondary infection of the tissue is almost invariable. As a condition, not a cause, infection aggravates and accentuates existing pathology. Also especially noteworthy among the list of conditions is existing nutritional status. If the tissue is already the site of deficiency pathology, usually chronic, its requirements obviously are raised. One of the outstanding reasons that an acute deficiency sign may be induced in one study but not in another is the initial difference in the nutritional status of the subjects.

It is almost superfluous to point out that time is an important condition constantly in effect and therefore an invariable element in every deficiency process (1). It appears as a component in the velocity and acceleration of the deficiency process. Likewise, it is the essence of duration. The length of time which a ratio prevails above or below 1 and at a particular level is a highly significant condition. It takes time, furthermore, to produce and develop, as well as reverse and remove the pathological expressions of a deficiency disease. And time is a factor in the acuteness or chronicity of the clinical manifestations.

At the risk of seeming to minimize diet, whereas the intent is to bring the ensemble of conditions in proper perspective in which neglected members are elevated to their rightful place, it should be pointed out that poor diet is not the cause of a deficiency disease, but a condition conducive to it. Poor diet alone cannot produce a deficiency disease; for it is never the sole ratio-depressing condition in operation—other conditions intrinsically participate with it. True, in many, if not most, instances of deficiency disease, poor diet is the major adverse condition; but in other instances, it is a minor condition. Indeed, deficiency diseases may even occur when diet is satisfactory to meet usual demands and therefore operating favor-

ably on the ratio. Poor diet is not, therefore, an indispensable condition in the production of a deficiency disease.

The traditional view that poor diet is the cause of deficiency diseases was derived largely from experiments in which they were induced by subjecting animals unremittingly to a diet nearly totally deficient in a nutrient. Since the only variable studied and allowed to differ between the experimental and control groups was diet, it was regarded as the cause of the ensuing deficiency disease. All other variables were equalized and therefore ignored. Yet these conditions were exerting their influence. For example, it is known that acute deficiency diseases can be induced readily in young, growing animals but only with great difficulty if at all except by special measures in adult animals. Here growth is a necessary condition which together with poor diet and other natural conditions tipped the balance towards production of deficiency disease. But the effect of the conditions other than diet were disregarded since they operated in both the experimental and control groups. The additional burden of poor diet in the experimental group was accredited with the full effect of all the conditions and with being the cause. The error lies in attributing the effect of the whole to one of its parts. Even when diet is ostensibly the only etiological factor, it is actually only one of several conditions, and then it is the predominant rather than the sole condition. As a condition, diet is often an important member of the etiological complex, indeed the preponderant influence.

From this reasoning and evidence it may be concluded that conditions determine whether a deficiency state occurs. From the deficiency arises a pathological process in the tissue. Thus, conditions affect the production of a deficiency disease. In addition, through this influence on the production of deficiency diseases, conditions likewise determine their prevalence. When the series of conditions adversely influencing requirements are added to those adversely affecting supply, and their very frequent operation is considered, the possibility, if not proba-

bility of high prevalence of deficiency diseases, however slight some may be, becomes understandable.

ON THE CHARACTER OF A DEFICIENCY DISEASE AND ITS MANIFESTATIONS

Conditions influence not only the production of a deficiency disease but also its character. For, individually and jointly, the conditions display velocity, intensity, and duration. The resultant of these from a complex of conditions is imparted to the ratio. Conditions determine not only the value of the ratio but also the characteristics of the governing force which it expresses. It has already been shown that a ratio indicative of a deficit and therefore causative action brings to bear these characteristics upon the pathological changes of a deficiency disease. Ultimately, then, through this sequence conditions are responsible for the character of the deficiency process and its tissue manifestations in deficiency disease.

Initial Incidence. First to be considered in this relationship to conditions is the character of the deficiency process and its tissue manifestations in their initial occurrence. The deficiency may set in early in life, indeed in utero (26); but whether early or later, the form which it takes depends upon conditions. Let us assume that not only the ratio but also tissue morphology has been satisfactory; and that then the ratio drops below 1. Here is change in direction. In proper time, as the result of the deficiency force if it is sustained, the tissue will exhibit morphological changes. But what will be their character? For an answer, the change in conditions should be examined.

It will be recalled that the ratio is depressed under any or all of three types of change: (1) Weakening of ratio-elevating conditions, such as impairment of dietary pattern. (2) Strengthening of ratio-depressing conditions, such as a spurt in growth. (3) Appearance of a temporary adverse condition, such as infection. From quantitative measures of their changes are derived the characteristics of these conditions, in terms of intensity and velocity.

The first two types of change represent an alteration in intensity of existing conditions, the magnitude depending on the extent of change. *Ipso facto* through its appearance, the adverse condition in the third type takes on an intensity. If unopposed, any or all of these conditions influence the ratio and deficiency with their new intensities. Again if unopposed, the rates of change in these conditions determine their accelerations and velocities as influences. But sooner or later protective counter conditions, as new or pre-existing conditions changed to furnish opposition, set in with their intensities and rates. They may oppose the offending conditions directly or indirectly. Depending on the time of their start or change, magnitude, rate, and duration, these counter conditions may minimize or slacken, or both, the adverse change. The resultants of velocities and intensities derived from changes in adverse and counter together with unaltered conditions influence the rate and severity of the deficiency force and its tissue manifestations in their first occurrence.

Thus from the incidence of new conditions and from alteration in rate and intensity of existing conditions, together with unmodified conditions, the deficiency force takes on characteristics in direction, velocity, and intensity which it transmits to the tissue pathology. In any instance a number of conditions are in operation; it is therefore the net effect of the aggregate of conditions with action in opposing directions at various intensities and velocities which is conveyed through the ratio to the deficiency force and its manifestations in tissue. Reflecting the influence of the conditions through the resultants of characteristics derived from them, the deficiency force and its pathological manifestations in tissue in their onset may occur in a wide range of velocity from very slow to very rapid and intensity from slight to marked. It has already been indicated that, while fine gradations may be established, these ranges may be arbitrarily grouped for convenience into several broad categories. In the last analysis then a combination of conditions determines whether the deficiency force and its

tissue manifestations in their first incidence are slow or rapid, i.e., chronic or acute, and mild or marked in intensity.

Strictly speaking, probably no initial deficiency as manifested in tissue starts suddenly as the acute form. Rather it is the culmination of a rate moving continuously to that end. In its beginning the process passes through a period when its velocity is slow and then at its zenith reaches the acute form by increasing acceleration and velocity. The pattern of increase in acceleration and velocity may vary from a constant, regular build-up to more irregular surges; hence the acute form may develop with various degrees of rapidity. Furthermore, a distinction must be drawn between the deficiency process and its tissue manifestations, for animals may die from initial deficiency, acute at its onset, with a minimum of local pathology.

The most familiar example of an acute onset is that produced so frequently in experimental animals. Young animals on stock diet with good growth and satisfactory nutritional status are suddenly subjected to a diet extremely deficient in one nutrient. It has long been recognized that under such a procedure an animal must eat and grow if an acute deficiency process is to develop. Here appetite, growth, and deficient diet are conditions with major adverse influence on the ratio, though other conditions are as usual depressing it. The drastically impaired dietary introduces a profound change which with rapid growth and other ratio-depressing conditions brings about a change in the direction of the nutritional process with deceleration of the force for satisfactory nutrition and acceleration of the deficiency force. If unopposed, the rapid rate of growth and sudden imposition of the severely deficient diet would greatly accelerate and intensify the deficiency force and its tissue manifestations. Actually, protective counter changes set in. A short list of counter conditions are shown in Table 1. In the present instance, mobilization of stored nutrients counteracts for some time the full effect of the deficient diet, the length depending on the nutrient and the extent of its stores. Later appetite may fall off and growth may slow as reactions to the unfavorable

Ratio-Depressing Conditions	Counter Conditions
Deficient Diet	Mobilization of Nutrient from Stores
	Loss of Appetite
Maintenance of Growth	Retardation or Cessation of Growth
Infection	Bodily Resistance
Ambulation, Work, Exercise	Lessened Physical Activity or Bed Rest
Deficiency Pathology in Tissue	Good Tissue Status

Table 1. Examples of a few ratio-depressing conditions and counter conditions.

ratio. Eventually activity may lessen. These reactions work toward lowering the potential acceleration, velocity, and intensity of the deficiency. Meanwhile the nutrient stores are progressively lowered and the deficiency gains in velocity and intensity, subject to modification as other counter conditions supervene on schedule. Its consequent velocity and intensity are the resultants of these actions and counter actions. If appetite and growth can be maintained, the usual outcome is an acute process in which the pattern has been one of a constant build-up in velocity and intensity. The familiar failure of some animals to show acute manifestations and the more common variation in the time-table of the signs are explained by individual differences in these conditions and counter conditions.

As for the reflection of the acute deficiency in tissue with pathological manifestations, still another counter condition, the existing status of the tissue has a profound effect. Obviously, prior to the initial incidence, the tissue was free of deficiency pathology. Such tissue is more resistant to pathological change than is tissue already altered. Furthermore, development of pathological changes requires time. Under a set of severe conditions it is not uncommon for an animal to die from an extremely acute initial deficiency with a minimum of pathology. The conditions must be within prescribed limits for acute pathology to develop as the culmination of an initial onset.

If, in addition to changes in diet and growth, intercurrent infection also sets in, it marks the appearance of a new condi-

tion. It adds to the intensity of the deficiency force and from its sudden appearance still more to the velocity. In consequence it is likely that the force of the deficiency in its onset will be of rapid velocity. It marks the more precipitate and irregular pattern. With several conditions already adversely in operation, the sudden introduction of another capable of high acceleration tips the balance still further with a strong impact on the velocity of the deficiency and abruptly brings on the acute form. It should not be inferred, however, that a new condition is a prerequisite for an acute process; rapid adverse change in an existing condition will produce it. Nor does intervention of a new condition always produce an acute process That depends upon its characteristics as well as those of other conditions in effect. Acute infection has great power of acceleration.

In reality the most frequent form of the initial deficiency in man is not acute. Rather it is the chronic with its typically slower tempo. As an example, it may be imagined that the dietary pattern shows some gradual deterioration, perhaps seasonal, and a spurt of growth may be in progress. In contrast to conditions in the animal experiments, the change in the diet is more gradual and less severe. Probably counter-conditions set in but at a commensurate rate and level. The net effect on the causal force is slow acceleration and velocity and moderate intensity; assuming sufficient time the effect on tissue manifestations is a chronic process of moderate intensity.

On the Course of the Deficiency and Its Manifestations

Progression. Nutrition is a dynamic process extending throughout life from conception until death. Consequently, nutritional status is of never-ending consideration over this span. For many persons, the first impairment may never be completely rectified; for some it may be corrected only to be followed by later impairment. Whichever way, the several courses which it may pursue are important. With an impaired status, a

definite pattern of events may be repeated endlessly throughout life as the process progresses, stands still, or rarely recedes. In progression or recession a wide range of velocities and intensities may be seen in the tissue process. Just as in its inception, so in the subsequent changes during the course of the deficiency and its manifestations, conditions have a large share of responsibility. Just as they determined whether it first emerged as a chronic or an acute process, conditions influence its course and later characteristics. They impart their velocity and intensity to the deficiency and its tissue manifestations.

Underlying, Progressing Chronic State. To take a common situation, a low-grade chronic process becomes established. It may pursue several courses. It may be continuously or intermittently progressive over a long period, indeed for life, with little change from mild degree and slow velocity. Or it may at one time or another take on added intensity. Or periodically or occasionally it may undergo exacerbation in the form of acceleration with or without increased intensity. But in the long run these events are merely episodes; viewed over the years, the predominant characters of the deficiency are slow velocity with long duration. It constitutes an underlying, progressing chronic state from which transitory acceleration may arise. The factors contributing at any point to this continuation and progressive course may be broadly designated en masse as perpetuating conditions. That is not to say that each of the conditions is perpetual; or that the composition of the group or the relative contribution of each condition does not change over the course.

Actually, the chronicity of a disease in its strict sense denotes its continuation over a long period of time. But inasmuch as a deficiency process of rapid velocity could not endure in the tissue for a protracted period, a slow velocity perforce characterizes the chronic state. Usually it is of long duration. But because conceivably a process of slow rate may be of short duration, i.e., may be terminated, and because the duration of a deficiency process may be measured on the basis of its stage,

it appears to be desirable in the interest of precision to restrict the usage of the term chronic to the expression of slow velocity. In point of fact it is almost always of long duration.

It is informative to look for the reasons why deficiency states over much of their course are chronic in nature and form. Four may be advanced: (1) Certain conditions operating at a rate conducive to the chronic form, such as slightly or moderately deficient diets without sudden change, are common at least in this country. (2) Under adverse conditions that might otherwise lead to an acute form, counteracting conditions maintain the chronic form. (3) The acute form is an extreme state produced by extreme conditions which prevail less frequently. (4) The acute form either undergoes abatement, lapsing into the chronic, or it proves fatal. In a sense, it is self-limiting.

When conditions conducive to a deficiency state operate steadily but gradually without undergoing or building up acceleration of the deficiency process, it is readily understandable that the chronic form will ensue. More complex is the situation where great, even drastic, reduction in total intake or subsistence on a moderately deficient diet occurs suddenly yet also leads to a chronic form when an acute might have been expected. In explanation, as has been noted, counter-conditions tend to offset adverse conditions that become active at a rate conducive to the development of an acute process. By their retarding influence a chronic state is incurred instead. In marked underfeeding, fasting or starvation, the consequent loss in weight, lowered basal metabolism, and restricted activity from weakness lower current bodily requirements. Though these counteracting conditions cannot prevent an adverse shift in the ratio, they lower its intensity and slow its advance thereby warding off a severe acute deficiency state. To the extent that they prevent a wide shift in the ratio, they prevent or mitigate a severe deficiency. Furthermore, this counteraction is a gradual process; hence in the absence of potent exciting conditions, an acute state is likewise prevented or allayed. It has long been known that, barring the intervention of power-

ful, exciting conditions, acute deficiency diseases do not develop during fasting or marked underfeeding. They are moderated to the chronic form. To take another example, with lowered intake of calcium there is impaired growth and more economical and efficient use of the mineral as judged by metabolic balance. This mechanism also holds true for other nutrients. Here again lowered current requirements and more efficient utilization avert the acute though they do not necessarily prevent or pass over the chronic. In avoiding the more critical consequences of an acute process, the body may not escape the chronic. The wide prevalence of chronic states among the populations with various degrees of lowered or inadequate intake attests to this.

It is not to be thought that, because of these types of reactions, the incidence of acute processes is generally prevented. Obviously there are limits to these counter-reactions beyond which critical inanition will ensue if the food supply is pronouncedly inadequate; or acute or subacute deficiency states will break through if nutrient imbalance outweighs an inadequate total intake or potent adverse conditions become uppermost. Overwhelming or unusually numerous adverse conditions conducive to an acute process will be decisive.

Acute State as an Exacerbation. Although the deficiency process in its course in man may persist or progress as a chronic process throughout life and never exceed a slow rate, usually at intervals it undergoes exacerbation. This exacerbation is primarily an acceleration but ordinarily intensification is also associated. Thus the chronic process at times undergoes acceleration of rate, with or without intensification, over a wide range of velocity reaching its peak as a severe, acute process. This exacerbation may be either gradual or precipitate.

It should be stressed that the acute form in man is usually an exacerbation. Because the chronic is much more prevalent than the acute state, because chronic lesions are frequently seen without signs of acuteness but not vice versa, because signs of chronicity may be recognized in an acute lesion, and be-

cause the acute has been seen to emerge from a chronic state and decline into it, it may be stated that in man the acute state arises almost invariably as an exacerbation of an underlying chronic state and subsides into it. True, it is theoretically possible than an acute may occur in the absence or at least with the minimum of a chronic process, in some proportion of the first incidence. But over the life span, usually the acute form in man is an exacerbation of an underlying chronic state.

Yet it is not usually recognized as that. Not uncommonly the chronic deficiency proceeds unnoticed for a long time and the tissue manifestations draw attention only during the exacerbation. Then this exacerbation is erroneously taken to be the onset, whereas in fact it is only the transitory eruption of the underlying preexisting chronic form. The misleading evidence from the senses and its seeming accord with the experience from animals are responsible for the misconception. The chronic form in its course escaped observation. Then, too, in setting and course of events the natural occurrence of the acute form in man is different from its experimental induction in animals. In the latter by design the deficiency is from the first continuously progressive to the acute form. As a condition drastically imposed, diet is as nearly deficient as possible in one nutrient. Only a short part of the animal's life span is covered. None of these circumstances is comparable to those usual for man. Rather, conditions are different for the development of the acute process by exacerbation in man. While the dietary deficiency is ordinarily not so drastic, other conditions assume major weight and decisiveness.

The underlying chronic base in man lends itself readily to exacerbation. It is much easier for an acute to emerge from a chronic process which is already progressing, though at a slow rate or even in virtual suspension, than from a good nutritional status. The existing chronic base is then an important condition toward the exacerbation. The more pronounced the chronic process, the more sensitive and susceptible it is to influences that would exacerbate it.

Besides the existing chronic manifestations in the tissue, other conditions are prominent in favoring an exacerbation. While dietary deficiency may not be so profound, that of lesser degree is not without influence. The lower the level of intake, the less need be the velocity and intensity of nondietary conditions, both exciting and precipitating, to set up an acute process. Oppositely, the more potent and explosive the nondietary conditions, or the more rapidly they build up force, the less deficient need be the level of intake to induce an acute episode. Here the sudden intervention of an additional condition such as intercurrent infection or pregnancy may be decisive. Because of the underlying chronic process, the less forceful need either group of conditions be to bring about an exacerbation into an acute process. Man's life span, as contrasted with the short survival period of animals with experimentally induced acute deficiencies, allows more opportunity for adverse conditions, including poor existing nutritional status, to become operative and set off an exacerbation.

Taking the entire life span of man, acute processes are seldom seen except superimposed on a chronic deficiency state; they are episodic, transitory phenomena in the course of the latter. It is not to be construed and presumed that acute processes occur easily and frequently in man. After all, the acute is an extreme state. It does not persist; it either subsides or is fatal. And there are conditions, already considered, counteracting against it. Whether it occurs hinges upon a set of conditions, among them the preexisting nutritional status.

Finally, the clinical manifestations of the acute form as an exacerbation are not necessarily the same as those of the acute representing the peak of the initial onset. The former can exhibit profound pathology with the acute superimposed upon the chronic. In contrast, animals may die from the acute deficiency induced initially with a minimum of local pathology. The more acute the latter type is, the less pronounced its local manifestations.

Slackening and Abatement of the Deficiency Process. In the

course of the deficiency process, the exacerbation with its heightened speed and intensity undergoes slackening and abatement from a change in conditions. Such subsidence of an acute or subacute process through a favorable turn in conditions changes only the form of the process. The slackening and abating do not mean cessation of the deficiency process. Rather the acute process, as an exacerbation, upon subsidence leaves the underlying chronic state. Or if the acute form is the culmination of a deficiency state in its incidence, it too wanes into a chronic state. Such moderation of an acute process therefore is not to be confused with reversal and recession of an underlying chronic form, or with obliteration of the deficiency state.

Practically the changes in conditions responsible for subsidence of an acute process may be divided into three types: improvement in diet; use of pure nutrients or concentrates; favorable alteration in other conditions. It is a familiar observation that, other conditions permitting, an acute process declines under an improvement in diet. But for such purposes, diet is not the only source of supply. With availability of nutrient concentrates and more recently pure nutrients that allow administration of more potent levels than can be provided in food and admit of either the oral or parenteral route, such preparations have been differentiated from diet.

On numerous occasions subsidence of an acute process has occurred or been induced when the diet or nutrient intake has undergone little or no improvement, while other conditions have or have been altered. This moderation comes about by removal, lessening, or circumvention of conditions, either pathological or normal, that have raised requirements or interfered with supply. Most frequently it is a favorable change toward reducing requirements; but in other instances it may be toward raising supply. Examples are: confinement to dark room instead of exposure to sun; bed-rest instead of full activity; conquest of infection; termination of pregnancy.

Conditions comprised in the three types are seen to differ

in their pathway of action and their effect on the ratio. Because of this and because the acute process may arise from conditions with different mechanisms, ameliorating conditions differ by nature in their appropriateness for a particular instance. The ideal course in controlling an acute process might be rectification, removal, or diminution of a particular dominant or exciting condition; but that is not always possible or desirable. Other courses would be to offset the effect of the adverse condition by changes in other conditions directed towards either reducing requirements or increasing supply, or both. Indeed, under some circumstances the latter measures may be preferable. In any situation the most appropriate course for controlling an acute process depends in part on the nature of the adverse conditions responsible for it. When infection is the exciting condition in an acute process, removal of that deleterious condition may be more effective than increasing the supply of nutrients in moderating the exacerbation. Under many adverse conditions bed-rest may be an effective measure. On the other hand increased provision of nutrients would be indicated for an acute process precipitated during pregnancy. And parenteral administration of nutrients may be indicated to abate an acute process when interference with supply arising from various diseases is to be circumvented.

Conditions also differ in the degree of their influence. Removal of a condition that has raised requirements brings a commensurate change that may be equivalent to a substantial supply of a nutrient. Pure nutrients may be administered in amounts beyond those which diet can provide. It is evident that the effectiveness with which any set of conditions overcomes an acute process depends upon their degree of influence. The potency of ameliorating conditions is then another measure of their appropriateness.

Finally, conditions conducing to moderation of an acute process also differ in their rapidity of action. Removal of adverse conditions usually has an early result, although there are differences in rate depending on the nature of the condition.

Parenteral administration of nutrients has a more rapid effect than oral. For its part, the acute process in its rapidity and intensity may present different degrees of urgency for correction. A florid process may be so extreme that parenteral administration of nutrients at high level may be imperative as an emergency measure; for diet would provide them not only in much less amounts but also too slowly. When prompt effect is essential not only the ability of a change in conditions to bring an acute process under control but also the rapidity of its action is an index of its appropriateness.

All in all, according to their nature, potency and promptness in action, conditions differ in their efficacy and appropriateness in abating the acute process. Quite properly in many instances all three types of moderating conditions are to be applied.

This moderation of an acute process may occur as a result of either inadvertent or intentional change of conditions. When the change is unpremeditated and unwitting, the effect is spontaneous; when it is by design, it is a therapeutic procedure. In the one, conditions change or are removed, or the person is withdrawn from their influence, all unwittingly; in the other, these changes are deliberate and purposeful. Actually whether spontaneous or sought, the effect is the same. All three types of conditions have alleviative action. They differ in their likelihood to be spontaneous; for example, use of pure nutrients is unlikely to be inadvertent. But all can be used by design.

Spontaneous. As an acute or subacute process subsides without intervention, it seemingly slackens and abates spontaneously. Thus a deficiency process may undergo spontaneous remission. Indeed a severe, acute process untreated either leads to death or spontaneously undergoes improvement. In a subacute process a similar subsidence occurs in course though it may be less immediate. Actually conditions operating towards mitigation have gone into operation or have directly or indirectly been called into operation in the natural course of events without personal knowledge or intent. Spontaneous moderation is accomplished by inevitable or chance removal

or cessation of unfavorable conditions; either nondietary or dietary, or both. Thus pellagra may be so severe that the person is driven to bed. This step removing two conditions, physical activity and exposure to sun, may be enough to shift the ratio so that the severe, acute manifestations, are to some extent moderated. An acute cheilosis enkindled after a week-end in the sun subsides in a few days upon return of the affected person to his otherwise indoor life. In both instances the subjects are withdrawn from the offending condition by circumstances. It matters not whether the restraint of ill health or the natural schedule inadvertently brings release of a patient from untoward conditions, the net result is a spontaneous remission. On such occasions spontaneous moderation may occur when diet has undergone little or no improvement.

Both before and since diet has been understood to be related to deficiency states, it is obvious that spontaneous improvement of acute processes, as reflected by their moderation, may in many instances have been due exclusively or largely to seasonal betterment in diet. On the other hand, a counteracting condition which may inadvertently come to mollify an acute deficiency state is diminished intake from underfeeding. Although change in diet may be the sole influence to bring about spontaneous moderation of an acute process, both non-dietary and dietary conditions may be jointly responsible, each to a varying degree, for the amelioration.

By Design. Moderation of the acute or subacute process may be brought about by design by a favorable change in any or all of the three types of conditions as indicated. Much of the early therapy for deficiency diseases, long before their true nature was recognized and pure nutrients were available, was to change or remove non-dietary conditions or withdraw the patient from them. Bed-rest and protection of pellagrins from sunlight; restriction of photophobic persons to a dark room were common measures. Such procedures are still valuable. Among their virtues is the rapidity of their moderating effect. However, there are limitations to the removal of non-dietary

conditions. While it is easy to control some or protect the patient from them, it is inadvisable or difficult to interfere with others. Infection, exposure to radiant energy, physical activity, and chemotherapy may be stopped; but interference with growth or pregnancy is an undesirable step as therapy.

When the character of food was found to be related to deficiency states, improvement of diet upon clinical advice became a customary and familiar step to abate an acute process. More recently as potent concentrates or pure nutrients became available they have been used at therapeutic levels, in conjunction with improvement in diet, to moderate acute states. As has been noted, the severity of the exacerbation and the nature of the dominant and exciting adverse conditions associated with it indicate the types of measures to be applied as the therapeutic procedure. Often for prevention of recurrence as well as most effective therapy all three are indicated.

Ebb and Flow: Recurrence of Exacerbation. What has been and often still is taken to be the incidence of a deficiency disease e.g., beriberi, scurvy, or pellagra, is really the exacerbation of an underlying chronic process. By the same token, therapeutic measures applied until the "deficiency disease" disappeared and presumed to have cured it, actually have brought about subsidence of the exacerbation, i.e., the acute form, and then have been discontinued leaving the underlying chronic state. Or as a self-limiting process, the exacerbation, if not fatal, spontaneously sinks into the chronic process. By whichever course, only abatement of the exacerbation, not reversal of the underlying chronic process, has been the usual eventuality. And the chronic process remaining is subject to later and repeated exacerbations.

As the chronic process persists for years, even a lifetime, there are recurrent exacerbations with abatement. Thus the process ebbs and flows, the acute or subacute emerging from the chronic and subsiding into it, the latter either spontaneously or by limited treatment. Whether the exacerbation is acute or subacute, in perspective it is a short, passing event.

As a transient phenomenon, it shows temporary heightening of tissue signs with symptoms that soon fade back into the chronic process.

Endemic deficiency diseases have been noted for recurrence even after treatment. It is now clear that therapy was continued only until the acute manifestations moderated. The underlying chronic remained to fulminate at a later date with recurrence of the acute process. Thus, actually the deficiency state persisted after the short-term therapy; and it was only the acute manifestations that recurred.

This ebb and flow, the recurrence even after therapy is attributable to conditions. For one thing, it is easier to bring about acceleration of an existing chronic process into an exacerbation than to produce an equally rapid acute process in tissue of satisfactory nutritional status. For another, it is easier to slow down an acute process than to reverse and abolish the underlying chronic. Hence, with these settings many conditions with more limited powers can exert a considerable or even decisive influence toward enkindling or extinguishing an exacerbation; but without the settings, they are neither determinative nor relatively so potent. The chronic process is a principal condition in setting the stage for exciting and precipitating conditions; just as the exacerbation, as an acute process, is for moderating conditions.

Reversal and Recession. Moderation of an exacerbation as an acute process does not eliminate a deficiency state; usually an underlying chronic process remains. This chronic state may follow any of several courses. As previously described, it is subject to recurrent exacerbation with abatement. Less frequently it may progress without exacerbation. Under a favorable turn in conditions inadvertently or designedly, the chronic process shows a favorable change. Depending on the effectiveness of the conditions and the duration of their application, it may be controlled, improved, or removed. As the lowest response, it may undergo arrest. That is not to say that the chronic process becomes inactive; rather it does not progress.

Or even more favorably it may enter into a reversal with incomplete recession. Under conditions sufficiently potent and sustained, complete recession may be attained. This latter eventuality, however, usually occurs only intentionally under therapy.

Because tissue with a chronic deficiency is more susceptible to the effects of adverse conditions and therefore more liable to recurrent exacerbation it is desirable, if for nothing more than protection against this, to dislodge the chronic process. The ultimate is its reversal to extinction. But it is easier to control an acute than to eliminate a chronic process. Whereas treatment of an acute process is mainly a matter of slowing and abating it; eradication of a chronic process is a matter of reversing it and then bringing it to the point of complete recession. More total nutrient and time are required to reverse completely a chronic than to moderate an acute process. The pathology of a chronic process represents the effects of an accumulated deficit. Its development at a slow rate over a long period is reflected in its character, which differs from that of an acute process. Correspondingly, under the most favorable therapeutic conditions, it recedes at a slow rate; consequently, therapy must be extended for a long time. Thus upon administration of therapy, chronic pathology is not at once obliterated and nutritional status does not immediately become satisfactory. To borrow an example from finance, a current improvement in conditions does not quickly discharge an accumulated indebtedness that has a stipulated maximum rate of repayment and minimum date of maturity. Similarly time is necessary to remove completely the chronic pathological manifestations from tissue.

In practice, treatment of a severe acute superimposed on a chronic deficiency process has usually been incomplete in that it is continued only long enough to abate the acute but not to reverse the underlying chronic. Complete correction of a combined acute and chronic process or of chronic alone is a long-time affair. This is true even if the process has not advanced

beyond its early stages; for still later stages, even more time is necessary.

The three types of changes in conditions responsible for subsidence of an acute are also applicable to recession of a chronic process. But because of the more stringent requirements to reverse the pathology of a chronic deficiency, especially to extinction, they differ even more pronouncedly in their efficacy for it. Whether spontaneous or therapeutic, a favorable change in non-dietary or dietary conditions has sharp limitations as the sole remedial measure. Under the strict and rigid requirements, removal of adverse non-dietary conditions does not bring about complete recession of a deficiency process. It may contribute to but not solely accomplish complete discharge of the nutrient deficit. Similarly, even a satisfactory diet is an auxiliary. Because of the narrow limits to the levels of nutrients which it can supply, its power to bring recession is restricted. Within bounds the lower the nutrient level, the longer the time needed for recession. But under the most favorable levels of nutrients, the time necessary for recession is long. The excess of nutrients in the currently satisfactory diet is so slight in comparison with the accumulated deficit presented by advanced chronic manifestations that recession, slow under the most effective conditions, is much slower under improved diet alone and would require an extremely long period for completion. Practically, therefore, diet alone with its limited plane of provision is not likely to bring about more than slight recession in a reasonable stretch of time. However, these therapeutic limitations of non-dietary and dietary conditions give no basis to underrate their contributory effects and to fail to include them in the corrective regimen. In particular, recommendations for improvement in diet should always be a part of the therapeutic program for the additional reason of instilling proper dietary habits against the day when, recession complete, therapy is withdrawn and maintenance with prevention of new deficiencies rests entirely upon diet.

Administration of nutrients in pure form can provide them

at more potent levels, the so-called therapeutic levels which are above those for maintenance, and can therefore, barring unsurmountably adverse conditions, bring about a more effective and complete clinical response. Usually this procedure is employed by intention as therapy rather than by chance. It can reverse a chronic process and if continued for a sufficient period can lead to complete recession of the tissue lesion. It is an important measure in moderating an acute process; it is indispensable for reversing a chronic process to extinction. Unfortunately under present practice it is stopped when the first of these benefits is achieved; its continuation would reverse an underlying chronic process which otherwise is left untouched. Here it is imposed, not inherent, limitations that restrict its effects. In treatment of a chronic process, the fewer the adverse conditions to be overcome, the more effectual is the administration of pure nutrients in reversing it. Under certain adverse conditions, such as infection, pure nutrients administered at therapeutic levels apparently or actually are partially dissipated.

For most effective results in recession of the chronic, all three types of change in conditions may be combined as therapeutic measures. An adequate diet especially is a favorable condition to be recommended together with provision of pure nutrients.

Because the chronic manifestations recede so slowly under therapy and are so susceptible to exacerbation, they may undergo temporary acute or subacute outbursts during the early period of therapy. Here especially adverse conditions have not been removed and the effect of therapy has not progressed to the point that the tissue has improved sufficiently to withstand them. But as therapy is continued any recurrence of exacerbation is at longer intervals and less severe until a point is reached where it no longer appears.

After arrest of the chronic process at any point in its recession, or after restoration of satisfactory nutrition, favorable conditions may disappear or give way to adverse and tissue status relapse, taking any of the courses already described.

Lag between Action of Conditions and Ensuing Manifestations in Tissue. In presenting the course of events in deficiency processes it is seen that through the ratio, conditions influence the status of tissue morphology. It has been noted further that a change in conditions does not immediately complete its alteration of the tissue; rather that continued application of the new status of conditions is necessary for a time. Indeed a change in conditions and an ensuing change in tissue manifestations are not synchronous. Alteration of conditions does not at once produce its effects in perceptible, much less in expected magnitude. Rather, with a change in the conditions, there is usually a lag before a change in the character of the tissue manifestations is discernible. The length of this interval varies according to circumstances.

In the absence of preexisting pathology, an adverse change in conditions, even a downward shift in the ratio expressing a deficiency, does not at once create initial visible, to say nothing of full-blown, manifestations in tissue. If the body is in a satisfactory nutritional status, adverse conditions ultimately capable of inducing a deficiency process must be in operation some time before tissue manifestations reflect their influence. Nor will a set of adverse conditions common to a group produce a tissue manifestation of identical or similar intensity and velocity in all persons at the same time. In contrast to persons in good nutritional status and free from deficiency pathology, those in an inferior status with existing chronic pathology break down and show signs of an acute process very much sooner under an otherwise equivalent set of adverse conditions. Nevertheless, during this exacerbation of preexisting pathology, there is still an interval, though much shorter, between the advent of an exciting or precipitating condition and the incidence of acute manifestations in the tissue.

A similar lack of concurrence is noted between a favorable change in conditions and the onset, aside from completion, of subsidence in an acute process or particularly reversal of chronic pathology. When a highly favorable condition is intro-

duced, for example, therapeutic levels of pure nutrients, the period before demonstrable response of extremely acute manifestations may be very short, but there is an interval. Under a similar change in conditions, signs of improvement in the pathology of a chronic deficiency are not at once perceptible. Indeed, in contrast to subsidence of an acute process, the interval is very much longer before beginning reversal of the chronic manifestations is detected.

The explanation for this lag lies in the nature and quantities of conditions and counter-conditions undergoing change. A condition requires time for operation through its channels. Then, it or its effect is opposed, minimized, and retarded by counter-conditions until they are overcome. These actions likewise consume time. Outstanding among the counter-conditions is the existing status of the tissue: whether pathology is present or absent; if it is present, its type, intensity, and stage. Time is necessary for the development as well as the recession or abatement of pathology. And the amount of time depends on the type of pathology with its particular rate, its intensity and stage.

ON LOCALIZATION OF DEFICIENCY MANIFESTATIONS IN TISSUE

Action of Conditions: General or Specific. In the exposition of the etiological complex it has been stated that the conditions exert their influence upon a nutrient. Does one condition act upon a particular nutrient and only that one; or may it act upon most, if not all, known nutrients? Is there general or particular, selective and specific action? Whether its effects are general or specific depends upon the nature of the condition and scope of its application. In its nature, it may be general or particular. Its scope of application is its sphere of action; as its point of impact is broad or restricted so correspondingly its effect is general or particular.

1. A condition may be general in nature and scope; its action then is general, not selective and specific. Obviously, it affects

all nutrients. It has been shown that the same condition may produce different deficiency states in different people (14). Intestinal disorder, for example, may lead to beriberi and pellagra. The particular deficiency sign or signs that become manifest depends upon the patient's absolute and relative status in respect to the nutrients and not upon any selective action of the enteric condition.

2. But a condition may be selective in its action because it is both particular by its nature and by restriction. Malocclusion has an adverse effect on the ascorbic acid status of gums. Here malocclusion is a particular item in the larger category under the general term, trauma. Furthermore, its operation is restricted to a particular site and perforce largely to the particular nutrient intimately associated with the nutrition of the tissue in that area.

3. A condition may be particular in nature and unrestricted in scope. Its action will be particular. A narrow band of light within certain definite wave lengths is by nature a particular part of the more general condition, light. Though several nutrients may be exposed, yet only one will be affected by that particular band of light.

4. Still further, a condition that is general in nature but restricted in its application to a particular bodily area will be selective in its action. For example, light is reported to affect the tissue sites of avitaminosis A, ariboflavinosis, and aniacinosis. Light may affect only one nutrient, or at least affect it to a greater extent, if only a particular part of the body is exposed, the particular nutrient being the most susceptible in that tissue. Here the scope of light depends on the exposed surface, its location and extent.

Because of these several categories, it may be seen that depending on its nature and scope, one condition may act on only one nutrient, whereas another may act on many nutrients. The latter is the more frequent. But conditions are in action as a group, and their aggregate includes many that are general as well as some that are particular in their effect on nutrients. All categories of conditions assume significance because of their pathological consequences in tissues; but the distinction be-

tween those with general and those with specific effect on nutrients is especially important in relation to localization.

Typical Localization. Conditions affect not only the character but also the localization of the lesions. Here discussion will at first be limited to the typical distribution of manifestations in a deficiency disease which reflects the influence of commonly or more frequently occurring adverse conditions. This localization of lesions displays three characteristics: the manifestations appear in particular sites in sequence; this order is uniformly regular forming a definite pattern; it is distinctive and typical of the nutrient deficiency. From deficiency in a particular nutrient, lesions usually occur in a sequence of sites characteristic of it. For the most part, deficiencies in different nutrients lead to changes in different organs, systems, and sites. Each nutrient deficiency differs from others in the initial site of localization of its manifestations; therefore presents its early signs in a distinctive site. As the deficiency progresses it affects particular tissues in definite sequence with its own unvarying pattern of selectivity.

In the infrequent instances that some manifestations of two completely developed deficiency diseases are located in the same organ, system, or site, it will be noted that different types of tissue are affected. Or in the still less frequent instances when the same type of tissue is also affected, the lesions occur in different components and at different stages in the sequences; and have a different pathology and appearance. Thus, the scorbutic and rachitic "rosaries" are readily distinguishable. If some manifestations of two deficiencies occur in the same type of tissue, usually they are located in different organs, systems, or sites; and occur at different stages in the sequences. Added to all this, the association of signs in the ensemble of manifestations is so dissimilar for each deficiency that differentiation is obvious. All in all, distribution of manifestations for each deficiency disease is orderly, uniform, and distinctive.

In considering the production of local manifestations through the mechanism of conditions, it is desirable to point out the

distinction between the original appearance of these lesions and what is often mistakenly identified for them, their exacerbation to an acute form. The appearance of scurvy presenting acute signs or of its less complete development in acute gingivitis does not mark the beginning of that deficiency state and its local manifestations, nor does its subsidence denote its end. This distinction takes on significance because the reaction of a tissue to a change in conditions differs depending upon its nutritional status. When adverse conditions predominate, acute manifestations occur more readily as an exacerbation of a preexisting lesion than de novo from tissue of previously satisfactory status. On the other hand, under a favorable change in conditions, the exacerbation responds not only with very much more readiness than does its underlying chronic process but also to a different set of conditions. Temporary confinement to a dark room of a person with acute ocular manifestations of ariboflavinosis will mitigate the symptoms and may abate the acute pathology but it will not substantially reverse the underlying chronic process. Because an exacerbation does not mark the origination of a lesion and responds differently from the chronic form to a change in conditions, it is not sound to cite evidence on just exacerbation, as is so often done, in considering the mechanism of production of local manifestations. Unfortunately much of the recorded evidence on man has come from observations on exacerbation. In contrast in the many experiments in which deficiency states have been produced in young animals, local lesions were induced de novo. Yet, because diet was purposely overweighted and some non-dietary conditions common to man were minimized in this procedure, the actual settings in human life which lead to local manifestations were not exactly mirrored. Nevertheless, by compensation the two sources provide ample valuable evidence.

Three types of conditions bring about this localization of manifestations: (1) conditions conducive to a bodily or systemic deficiency; (2) selective sensitivity of tissues to nutrient

deficiencies; and (3) conditions with topical action on tissues. Under scope of conditions, it has already been explained that some contribute to general bodily deficiency; others have more localized effects; and still others contribute to both ends. Bodily deficiency is not the blood level of a dietary nutrient or even its biologically active form. Rather it is the insufficient amount or deficient performance of the active nutrient in the various tissues in which it customarily functions. Those selectively sensitive to this inadequacy show local effects in sequence. Its clearest demonstration arises during a conspicuous dietary deficiency. But its development is not restricted to that condition; nor are the two terms synonymous. Indeed it has already been indicated that a bodily deficiency arises from multiple adverse conditions influencing the ratio. Later nutrient intake may improve or some condition interfering with supply or increasing requirement may be removed and gross balance in body may appear to be positive as judged by fluid levels or saturation tests. But local tissue change requiring much more time to recede is still pathological. That tissue is still in deficient status and has increased requirements.

Several lines of evidence indicate that bodily deficiency is a localizing influence. When animals are subjected to a deficient diet, a series of local tissue manifestations appear in regular sequence in the evolution of the ensuing deficiency disease. By restoration of an adequate diet, the local manifestations improve. Odom and McEachern (27) found that a traumatically induced lesion in the brain of an animal remained asymptomatic until thiamin deficiency was induced by dietary restriction. Most important is the fact that among persons exposed to the same environmental conditions to the same degree, for example, to cold and glare, some may show acute ocular lesions while others show widely different degrees and stages of chronic manifestations in their tissues most plausibly indicative of their different bodily nutritional statuses in respect to the nutrient riboflavin (28). By administration of appropriate therapy, the symptoms disappear and the local lesion recedes

even though environmental conditions imposing stress on them continue unabated.

As the second condition, the selective sensitivity of tissues to deficiencies contributes to the localization of manifestations. In a body deficient in one nutrient, not all tissues show effects; hence they are presumed not to be equally sensitive to inadequacy of it. Moreover, as the deficiency in this nutrient progresses, its manifestations appear in distinctive sites in definite sequence, a pattern indicating a preferential sensitivity of these tissues. Thus in deficiency of a nutrient, there is selectivity of tissues and sites affected and a preferential order of sensitivity of these tissues reflected in localization of lesions.

Furthermore, evidence may be added from the distinctive manifestations of deficiency in each of various nutrients. For the most part, deficiencies in different nutrients lead to pathological expressions in different organs, systems, and sites. In niacin deficiency characteristic manifestations occur early in the tongue; whereas in vitamin A, thiamin, or ascorbic acid deficiency, no gross changes appear in it. Thus the various organs, systems, tissues and sites in them are not equally sensitive to deficiencies in various nutrients. As a corollary, a tissue requiring several essential nutrients for maintenance of satisfactory nutritional status will exhibit need for one most sensitively. It should be remembered that essential nutrient may mean an enzyme rather than its several components. An order of priority in tissue needs of specific nutrients and a corresponding preferential order of sensitivity to deficiency in them may therefore be visualized. This selective sensitivity of tissues to deficiency in particular nutrients conduces to the localization of manifestations. This selective sensitivity is, of course, a condition.

In addition to bodily deficiency and the preferential sensitivity of tissues, conditions acting topically to raise requirements or interfere with supply to these sensitive tissues also contribute to localization of manifestations. A condition particular in nature, or a general condition of restricted scope will be

selective in action. Is it a coincidence that sites of early external lesions occur at points which are exposed to more or less constant stress under such conditions? Among these conditions are: mechanical movement with friction or trauma, e.g., the tongue, dental occlusive action on gums, joints, sites of muscle insertion, and angle of the mouth; sunlight and glare on the eyes and skin; wind on the skin. Thus stress applied to or concentrated upon a particular site where the tissue is selectively sensitive is contributory to pathological localization (18, 29).

Because of its implications, it is important to look into the role of these conditions in the production of localization. One point to be examined is whether each of the three sets of conditions can alone bring about localization. Bodily deficiency without selective sensitivity of the tissues would not exhibit a consistent pattern of signs for each nutrient. On the other hand, selective sensitivity is a potentiality that requires a bodily or local deficiency for expression. Then too, consideration of selective sensitivity alone is a theoretical point, for it is difficult to exclude conditions with topical action.

As to conditions with topical action, we shall first consider a deficiency state that has not progressed beyond its initial or early site of localization. This distinction has become important because so much of the current deficiency states are in that stage. Then too, the conditions with topical action most commonly under discussion and therefore best serving as examples do not otherwise form a homogeneous group. Although all of them affect the ratio adversely, some are natural, necessary conditions, such as tongue movement, dental occlusion; some are natural but obviously deleterious, such as wind, dust, infection; and some are unnatural, such as soap in the conjunctival sac. They also differ in the usualness of their occurrence and in intensity. Accordingly the several types must be considered separately.

Movement of the tongue may act as a condition in glossitis from niacin deficiency. Yet with the same amount of move-

ment in thiamin deficiency, the tongue is not affected. The same argument holds for the effect of dental occlusion on the gums in relation to ascorbic acid deficiency. It is evident that usual mechanical stress of usual intensity as a condition with topical action is not alone responsible for localization.

Wind and dust are regarded as natural deleterious agents to which has been ascribed causation of conjunctival and limbic changes. But persons exposed to the same degree of them for the same length of time may show the widest possible range of conjunctival and limbic status, from severe to very slight change. Furthermore, when the persons are left under the same exposure, the conjunctival and limbic lesions respond respectively to vitamin A and riboflavin.

Historically, the best known example of local infection was in xerophthalmia. Since this lesion could be induced by dietary deficiency, yet the cornea invariably showed signs of infection, it was long debated whether it was a deficiency disease or infection. After much experimentation it was found that deficiency preceded the infection (23). Furthermore, the lesion with its infection receded under vitamin A therapy. It was generally accepted that tissue deficiency was basically at fault with almost invariable supervention of infection.

By 1920 this argument appeared to have been settled; but in the last few years it has recurred over another lesion, gingivitis. It is clear from the description in Lind's original treatise on scurvy (29a) that the gums of his patients were heavily infected. More recently it has been demonstrated that in persons showing chronic gum changes in a moderately advanced stage as the only externally perceptible sign of avitaminosis C, infection almost invariably supervened, usually to produce a subacute or acute gingival process (24). Again has arisen this question: Is this lesion the sign of an infection or a deficiency state? It is a fallacious question. It insists upon setting forth deficiency state and infection as alternatives to the exclusion of their possible relationship. Actually, infection may become, indeed as the deficiency lesion reaches advancing

stages ordinarily does become, a part of the pathological process. Even when infection in the gums is largely eradicated by chemotherapy exposing and leaving the underlying chronic deficiency process, the infection usually recurs. But its recurrence can be prevented or minimized over a given period by little more than maintenance levels of ascorbic acid (25). Furthermore, gums showing marked infection lose it without administration of germicidal chemotherapy under intensive and prolonged therapy of ascorbic acid alone (24).

It is obvious that these two common examples do not represent de novo local lesions and infection alone is not responsible for them. In both there is a preexisting local manifestation of a deficiency process. Nutritional deficiency predisposes to the local infection which in turn as a condition aggravates and accentuates the already impaired nutritional status. Essentially what happens is that infection produces an exacerbation of a preexisting deficiency process.

To prove that conditions with topical action are alone responsible for the local manifestations of deficiency states is indeed difficult, for it would be necessary to demonstrate that prior to the operation of these conditions the tissue was in perfect nutritional status. But actually the possibility that prior to the operation of topical conditions the tissue at the local site was in perfect nutritional status is a situation less frequently encountered than might be surmised. It is usually possible to demonstrate that a low-grade chronic process, indicative of a bodily deficiency, preexisted there. It is obvious that the poorer the tissue state becomes along with general bodily deficiency, the less intense must be the localizing tissue factors to further impair it and the more intense will be the resultant manifestations. On the other hand, the more nutritionally satisfactory the tissue state, the more intense must be the topical conditions to impair it. If it be assumed that topical conditions may overcome tissue in perfect nutritional status and alone produce local manifestations de novo, so overwhelming must be its force that there is no guarantee that it

is only topical in action. Its effects may not be limited to that site. Bearing on this point is the observation that sunlight aggravated not only the exposed skin but also the unexposed tongue of pellagrins (18). On the basis of rationalization it is to be concluded that a definite combination of highly potent conditions with topical action would be necessary in proper sequence to produce the consistent pattern so characteristic of a deficiency disease if they alone were responsible for the ensemble of signs. But such a situation is unlikely. Then too, never are conditions with topical action alone in operation: those conducive to general bodily deficiency are ever in action. It must be rare indeed that topical conditions alone are responsible for local lesions de novo in a fully-developed deficiency disease.

All in all, it does not appear that any of the three sets of conditions conducive to localization can alone reproduce consistently the pattern distinctive for each nutrient deficiency. They are truly conditions, not causes.

In considering further the production of localization, the essentiality of each of the three sets of conditions may be tested by its omission. It is conceivable that without bodily deficiency the regular sequence of local manifestations, in whole or in part, so typical of a deficiency disease could arise from a combination of selectivity and some conditions with topical effect. These topical conditions would be acting upon susceptible sites. However, much evidence indicates that without a bodily nutrient deficiency, there is no local lesion. Intense or scattered light has an adverse effect on the eyes that becomes manifest in ariboflavinosis. But among persons equally exposed to intense light or glare, many do not show ocular symptoms (28). The most credible explanation is that they do not have a bodily deficiency sufficiently severe to be aggravated by even stringent conditions with topical action. Furthermore, one and the same condition with topical effect may aggravate one or several deficiencies depending on the number and nature of the existing bodily deficiencies. For example, light is

inimical to not only the eyes in ariboflavinosis (22) but also the skin in pellagra (18, 29, 30).

Similar results have been obtained from a therapeutic approach. When bodily deficiency is counteracted by nutrient therapy, exacerbations become less frequent or do not occur. It has been found that chemotherapy largely overcomes the local infection in gingivitis and brings temporary subsidence of the exacerbation, but ascorbic acid prevents the recurrence which otherwise is the rule (25). It has further been shown that exacerbations become less frequent and finally no longer appear under prolonged ascorbic acid therapy alone (24). The chronic infection is overcome. That full-blown deficiency diseases, actually exacerbations, abate under the usual short period of therapy is a familiar observation.

For present consideration, even more weighty is the evidence, not on exacerbation, but on the underlying chronic lesion which is more truly indicative of the course and stage of the original localization. Among persons equally exposed to the same glare for approximately the same protracted period, all do not exhibit the same stage or intensity in their chronic ocular lesions. This disparity in pathology is most convincingly explained as a reflection of the differences in bodily deficiency. If bodily deficiency be remedied by nutrient therapy, local lesions recede and associated symptoms disappear even under the stress of topical conditions. For example, upon administration of ascorbic acid for sufficient time to persons with gingivitis, the bodily deficiency fades, any local infection disappears and can no longer gain a new foothold, the chronic pathology recedes, and the gums can withstand the stress of occlusion. Results of animal experiments are in accord with these several lines of evidence. All indicate that bodily deficiency is an indispensable element of localization.

Selective sensitivity of tissue is also a necessary component in the localization of nutrient deficiency manifestations. It is perhaps an academic assertion since by its nature selective sensitivity is an inherent tissue property that cannot be ex-

cluded. Nevertheless, without it bodily deficiency and conditions with topical action could not produce designed localization. Their chance co-activity would not bring about the regular and invariable pattern of localization distinctive for each deficiency disease; rather it would produce such a variable and variegated distribution of lesions that there would be no consistent pattern. Deficiency in one nutrient would show no difference from another. Only if pertinent topical conditions obeyed a complicated system in which particular ones were active while others were inactive would there be a selective effect distinctive for a deficiency in each nutrient; but that postulation is contrary to their natural operation. In either event the outcome would not conform to recorded evidence.

Quite different is the relation of conditions with topical action to localization. In exacerbations removal of these conditions leads to subsidence of symptoms and the acute or subacute process in the local lesion. For example, chemotherapy dislodges most of the local infection in gingivitis; confinement to a dark room brings abatement of the acute process in the limbus and symptomatic ocular relief in ariboflavinosis. It should be particularly noted, however, that in each instance, temporary abolition of the condition with topical action brings mitigation of the acute but not recession of the chronic process. Unless the bodily status is improved through nutrient therapy, the likelihood of recurrent exacerbation is extremely high. Again, it should be observed that in arguments on localization, conclusions from exacerbations alone may be misleading; they are subject to modification from observations on the underlying process.

Upon subjecting guinea pigs to a scorbutogenic diet for ten to twenty days, it was found that typical bony lesions of scurvy developed in legs allowed freedom of movement, but not in an immobilized hind leg (20). From this study it might be argued that without the topical condition, mechanical action in this instance, deficiency pathology does not occur. But two points are to be noted: (1) the criterion adopted was the pathology

of scurvy, which as the marked acute is only one form of avitaminosis C; (2) pathological changes, perhaps of chronic avitaminosis C though certainly not of scurvy, were seen in the immobilized leg. Similarly, it should not be forgotten that in each of the avitaminoses A and C, pathology without infection precedes the intervention of infection. These results indicate that bodily deficiency and selective sensitivity together are able to produce localization. But in reality under natural circumstances, many topical conditions are always in operation to a greater or less extent; hence they may play an added part in localization. Thus conditions with topical action may not be necessary for localization, though they may contribute to it. Upon existing lesions they also exert considerable influence. For they share in the accentuation of the local manifestations through production of a more intense and rapid change that at its height characterizes the traditional florid violent form of deficiency.

All in all, it is seen that in the usual pattern of a deficiency state at least two sets of conditions are necessary for localization: bodily deficiency and selective sensitivity of the tissues. The third set, conditions with topical action applying their stress locally, contribute to the initiation or accentuation of the local pathology. Through application of the ratio $\frac{\text{supply}}{\text{requirements}}$ to sensitive tissues, it may be noted that conditions contributing to bodily deficiency affect the sensitive tissue adversely, while conditions with local affect depreciate its ratio the more. Thus conditions not only affect the occurrence and character of a deficiency state but also elicit or accentuate its localized manifestations.

Specificity. Through their influence on the localization of lesions conditions impart distinguishing signs to deficiency states. As has already been stated, one characteristic of localization of deficiency lesions is that their sequence of appearance and their fully-developed pattern in each deficiency disease are distinctive and typical. Indeed, localization takes

on significance for diagnosis because of this distinctive histopathological distribution of lesions in each deficiency disease. The selective sensitivity of tissues to particular nutrient deficiencies primarily explains the distinguishing differences in the localization of lesions between the several deficiency diseases. It is implicit in these conclusions that an established set of signs in a deficiency disease is specific in three respects: for a nutritional deficiency; a bodily, not a local, deficiency; and a particular nutrient deficiency.

Historically, before xerophthalmia, beriberi, scurvy, and rickets were recognized as separate entities and their relation to nutrient deficiency was demonstrated, what was later shown to be in reality a combination of two or more of them, e.g., beriberi and scurvy was regarded as one disease. Through animal experimentation, deficiency in a particular nutrient was found to be associated with a specific and distinctive set of symptoms, signs and histopathology which had its naturally occurring analogue in man. These demonstrations were substantiated in man by studies with specific therapy. Thus the respective deficiency diseases were separated, each with its appropriate relationship to a particular nutrient. Differential diagnosis between beriberi and scurvy, or rickets and scurvy became possible. Each affected different sites and tissues from the others; in short, each had specific nutrient etiology, signs, and therapy. Indeed, they were called specific deficiency diseases, a designation based on the relationship between a particular nutrient deficiency and the distinctively selective localization of its pathological manifestations. No one today would think of prescribing thiamin for scurvy or ascorbic acid for rickets. No one raises any question about the nutritional, bodily deficiency and nutrient specificity of severe, acute, fully-developed deficiency diseases, with the exception of a current trend toward a reservation that an amino acid as well as niacin deficiency may be associated with pellagra.

But desirability of appraisal of nutritional status including recognition and diagnosis of deficiencies in their mild, early,

and chronic forms has led to observations on a site affected early in each of them. It is over this erroneously so-called monosymptomatic system that difference of opinion arises. These single local lesions have raised three questions: (1) Do they reflect nutritional change and therefore relation to nutrition? (2) If so, do they reflect bodily deficiency? (3) Do they exhibit nutrient specificity? In short are they specific for nutrition, bodily deficiency, and a particular nutrient deficiency. These points are important in diagnosis from an early sign.

Nutritional Specificity. It is sometimes asserted that the single early signs associated with deficiency diseases may be or are the consequences solely of nondietary causes acting locally; e.g., wind, dust, light, infection, or mechanical stress such as malocclusion or ill-fitting dentures. This argument carries either of two implications: (1) the consequences of nondietary causes are non-nutritional; and (2) if the sign has any nutritional significance, it is indicative purely of a local, not a bodily, deficiency.

In support of the premise it would be maintained that producing a single local lesion is decidedly simpler than reproducing the distinctive pattern of a fully-developed deficiency disease; and that a "cause" acting locally, such as those cited, may alone or with the selectivity of the tissue bring about the former even though it cannot accomplish the latter. But to prove the point, the preexisting nutritional status of the tissue at the site of the impact would have to be satisfactory and all other circumstances conducive to the production of a lesion would have to be absent or inactive. Then it would have to be shown that the "cause" acting topically could alone bring about the local lesion.

Of the first desideratum it may be said that absolute freedom from existing signs of pathological change, however minimal, is relatively uncommon; and absence or inactivity of other concurrent circumstances conducive to production of the lesion is contrary to fact. But even if it be assumed that the tissue site of impact was free from a deficiency and all other cir-

cumstances conducive to pathological change were at a minimum, the agent with topical action that could overcome it would have to be potent. Only certain of the listed "causes" would qualify. This restriction would narrow the potentially effective adverse influences to one in the deleterious pathogenic group, such as virulent local infection, or to the unnatural type such as a local irritant or trauma. Wind, dust, smoke, light, and malocclusion would be excluded; for when they are within ordinary limits, the nutritionally sound tissue can withstand them.

Thus it is seen that such phenomena as wind, dust, light, infection, ill-fitting dentures, and malocclusion are not causes of but conditions conducive to production of local lesions. They are topical conditions. On occasion a particular few may be a major condition. But, because one of them is a conspicuous condition associated with an early, isolated sign, it does not follow that unsatisfactory diet and existing poor nutritional status as well as other adverse conditions are not also operative. Indeed, what is more important, it has already been demonstrated that no one condition, either dietary or nondietary, is solely responsible but acts in concert with other conditions upon the nutritional ratio.

Unsubstantial as the premise has been shown to be, its fallacy is much less consequential than the erroneous conclusion drawn from it that the effects of non-dietary "causes" are non-nutritional. Even if the premise were generally true and widely applicable, it does not necessarily follow that the local effect of a topical condition is not nutritional. Indeed, evidence shows that it is nutritional.

Sites subject to the influence of nondietary conditions with topical action are the same as those undergoing change in fully-developed deficiency diseases. In the experimental production of deficiency diseases in animals, lesions develop at these loci when the dietary condition is prominent and the nondietary conditions with local action figure in a lesser capacity; and they recede under appropriate nutrient therapy. The same

lesions appear in naturally-occurring deficiency diseases in man where a number of conditions, often but not necessarily including a diet debased to some degree, are in effect. Then too, it has already been established by evidence and argument that, even if the diet is satisfactory, a combination of nondietary conditions can conduce to these signs. Removal of conditions with topical action brings only temporary abatement of an aggravated local lesion; but the underlying chronic process recedes under nutrient therapy. Sites already in or restored to satisfactory nutritional status can withstand the topical stress of the nondietary conditions. From these lines of evidence it may be asserted that nondietary conditions affect nutrition and the resulting changes are nutritional in character. The local lesions are indicative of, even specific for, nutrition.

Specificity for Bodily Deficiency. A variant conclusion from the belief that the early signs are the consequences solely of nondietary causes acting locally is that, if these manifestations have any nutritional connotation, they are indicative only of a local deficiency. To accept this view would necessitate the assumptions that one or more conditions operating topically were, alone of all, active or not counteracted by supply; that their force was sufficient to produce the lesion; that conditions usually operating systemically or more generally in the body were inactive or their demands were being successfully met; that supply equalled or exceeded requirements; and that nutritional status elsewhere in the body was satisfactory. These are very exacting and sweeping assumptions.

The fallacy of the premise to this argument and negation of the first two assumptions has already been demonstrated. Against the remaining assumptions are weighty observations and reasons. In the evolution of a deficiency disease, in due time a series of local tissue changes appear in regular sequence, at which juncture it is generally agreed that a bodily deficiency is in existence. The fact that a single lesion occurs in the same site as the early lesion of a fully-developed deficiency disease and may be similar to it is suggestive that it is likewise in-

dicative of a bodily deficiency. But admittedly it is not conclusive. Other grounds are more convincing.

One and the same condition with topical effect may aggravate one or several deficiencies depending on the number and nature of the existing bodily deficiencies. For example, light has an adverse effect on the eyes in ariboflavinosis and skin in pellagra. Actually it is an exacerbation of one or more existing deficiencies. And these existing bodily deficiencies are a prerequisite to the exacerbation. Conditions with topical action did not cause these signs; rather they accentuated an existing chronic deficiency. Not only was bodily deficiency present, but conditions conducive to it were inherently at work. If in the exacerbation, the conditions with topical action are inactivated or removed without remedying the bodily deficiency the exacerbation subsides as shown by the response of gingivitis with infection to chemotherapy; but it is subject to recurrence upon reexposure. Protection, however, comes with lessening or eradication of bodily deficiency.

From attempts at what is tantamount to development of original or fresh lesions in previously satisfactory or improved tissue, the evidence is even more striking. This situation is best studied after therapy has improved or restored the tissue. The tissue can then withstand stress of conditions with topical effect without deterioration in its status. It may therefore be concluded that bodily deficiency is an indispensable element of localization. Conditions with topical action are an added insult with aggravating effects.

It is evident that local manifestations are associated with and indicative of a bodily nutritional deficiency. Usually the local lesions do not occur without it. As a corollary it may be stated that localization of the lesion does not predicate that only a local deficiency exists. The local lesion indicates a bodily deficiency.

Nutrient Specificity. For deficiency in each nutrient, there is a definite regular sequential order in localization of lesions to form a pattern typical and distinctive of it. The difference

in sites and sequence of localization for each nutrient deficiency imparts this specificity to its local manifestations. Upon the selective sensitivity of a tissue to a particular nutrient deficiency is based the specificity of its manifestations.

It should be noted that in the concept presented here a localized lesion is specific for the biologically active form of the nutrient, not necessarily the dietary form. In most instances, however, it has thus far proved to be also specific for the nutrient as ingested. Indeed, the nutrient specificity of severe, acute, fully-developed deficiency diseases is generally accepted; e.g., ascorbic acid not thiamin is the recognized therapy for scurvy. Likewise, the nutrient specificity of their solitary early signs, particularly in chronic form, rests upon a scientific foundation. Each of these single lesions used in the appraisal of nutritional status and diagnosis has been established to be an early sign of a particular specific deficiency disease: e.g., changes in the conjunctiva in avitaminosis A; the ocular limbus in ariboflavinosis; the gums in avitaminosis C; and the tongue in aniacinosis. Their experimental production in animals under a specific nutrient deficiency and their disappearance upon provision of the specific nutrient; their natural occurrence in man as part of a specific deficiency disease and their response to specific nutrient therapy argue for this specific relation.

Nevertheless, one full-fledged deficiency disease, pellagra, and the solitary early signs, particularly the limbic changes in ariboflavinosis (31), have had their specificity questioned on the basis that deficiency in any of two or more nutrients may give rise to them. Rats on diets containing corn as a source of protein or certain purified proteins underwent retardation in weight increase, an outcome that could be corrected by addition of either tryptophane or niacin (32). Implicit in some of the conclusions drawn from these results is the view that pellagra and inferentially its tissue lesions are not specifically the consequence of niacin deficiency. Then too, besides their better known occurrence in ariboflavinosis, limbic changes have

been reported as the results of a series of nutrient deficiencies, especially amino acids.

These observations have given rise to the view that the same deficiency disease or lesion may be induced by inadequacy of any of several nutrients. One theory constructed to explain these observations points out that the enzymes of which vitamins form prosthetic groups likewise contain amino acids. Hence theoretically impairment of the enzyme system could ensue from deficiency in a critical amino acid as well as in the prosthetic vitamin.

Although this may ultimately prove to be true, other evidence and explanations must be given consideration. For one thing, it has been suggested that corn may contain an antivitamin against which both tryptophane and niacin are active (33). But the tryptophane-niacin relationship prevails when corn is not contained in the diet. From biochemical data it has been concluded, as another explanation, that tryptophane functions as a metabolic precursor of niacin both in the rat (34) and man(35). Thus it has by no means been demonstrated that niacin deficiency is not specific for pellagra. In species capable of synthesizing niacin, a deficiency of it might be conditioned by an inadequacy of its precursor. In all species, whether synthesizing niacin or requiring it preformed, an antivitamin would by another mechanism produce a conditioned deficiency. Both of these conditions, included in the present concept, are consonant with, not counter to, the view of nutrient specificity.

Furthermore, neither in animal nor man has an amino acid deficiency been demonstrated to lead to a complete syndrome comparable to or identical with ariboflavinosis or pellagra. In addition, the early lesions of amino acid deficiency produced in animals have not been similarly produced in man; nor have such lesions occurring naturally in man been shown as yet to respond to amino acids.

In two other ways conditions may operate in the pathogenesis of a deficiency disease to the possible confusion of

views on nutrient specificity. First, one deficiency state may condition another. For example, where two adjacent sites are, respectively, subject to pathological change from deficiency of a different nutrient, a pathological process in one may impair the other by extension (22). As another instance, with a different channel, pellagra with pronounced gastrointestinal disturbance interfering with absorption may conduce to other deficiency states (14). Secondly, in a different category are the therapeutic studies on man in which the spontaneous operation of conditions makes the results so susceptible to erroneous interpretation. Under a spontaneous change in conditions an acute process may abate; but the obvious circumstances lay the event open to misinterpretation. Whatever therapy is being administered at the moment is credited with the effect and therefore with etiological significance. The history of the treatment of frank deficiency diseases attests to the frequency of this pitfall in inference. It is to be noted that this source of error applies only to acute deficiencies. On these grounds it is essential to scrutinize rigorously such types of evidence from which are drawn conclusions casting doubt on nutrient specificity.

According to the new concept, a local lesion is specific for a deficiency in the biologically active form of a particular nutrient. Historically, the local lesions of a full-blown acute deficiency disease were held to be specific for a particular nutrient in its dietary form. As yet there is not sufficient concrete evidence on man to reject this latter or to allow for exceptions. If incontrovertible evidence against it in man does come, specificity for the biologically active form would still hold. But until it is demonstrated otherwise, it is proper and justifiable to maintain that the local lesion is likewise specific for a nutrient as ingested.

The two critical tests for validity of a typical localized lesion as a specific sign of a nutritional, bodily, and particular nutrient deficiency are its experimental induction and response to therapy. Its acceptability in these respects is not demonstrated

without fulfilment of the first three of the following stipulations, preferably all four:

1. In an appropriate species of animal the sign is experimentally induced under conditions in which a specific dietary deficiency is a major influence.
2. In animals the experimentally induced sign recedes and disappears with provision of the missing nutrient.
3. In man the naturally occurring sign recedes and disappears with provision of the appropriate nutrient at a therapeutic level for a sufficient time. For the acute form the first positive response should be followed alternately by induced relapses and positive responses to therapy.
4. In man the sign is experimentally induced under conditions in which a specific dietary deficiency is a major influence.

Until a typical sign under these stipulations is shown to be related to more than one dietary essential it may be presumed to be specific for one.

Atypical Distribution of Lesions. It should be noted that in the fully-developed acute deficiency disease the so-called typical sequence in the procession of signs simply reflects the influence of combinations of conditions most frequently prevailing. In contrast, less common combinations of conditions occasion what is called atypical localization. That term is perhaps unfortunate because it tends to carry a prejudicial connotation. The very name atypical has consigned the lesions unwarrantedly to a position of relative unimportance. Two classes of atypical localization may be considered.

In a strict sense, the first is actually more often atypical accentuation than distribution. The usual sites are affected giving the regular stereotyped pattern, but it displays atypical points of emphasis. To take one example, with lesions already established in typical sites, there may be exacerbation and accentuation of a later sign out of all proportion to an earlier. Intensification of a topical condition influencing a site of late change or of a general condition with protection of an early site is responsible for this effect in which a late becomes more

prominent than an earlier manifestation. Exposure to sun may heighten the skin lesions in pellagra without necessarily bringing corresponding accentuation of the lingual lesion (18). A chronic deficiency state and a supervening impairment of cerebral circulation, perhaps on a basis of arteriosclerosis, together with contributory conditions may be conducive to an encephalopathy, without acute signs of pellagra elsewhere, yet with response to niacin (36). Sun (37) or an ill-fitting denture (21) may aggravate the angular stomatitis in ariboflavinosis without commensurate exacerbation of the earlier corneal lesion. In the past it has been called actinic cheilitis (38). Sometimes accentuation of the later sign is so striking that inspection for earlier signs of the underlying chronic process is neglected or they are overlooked; and erroneous conclusions are drawn. A new process may seem to be developing and in its evolution to be violating the rule of regular sequence in signs. Actually it is an instance of atypical emphasis.

Another example of this class is the absence of balanced symmetry (39). Usually deficiency diseases exhibit a bilateral symmetry. Occasionally unilateral alteration or exacerbation will be seen. One member is exposed to, whereas its counterpart is protected from, an adverse topical condition.

A second class of atypical change is the true atypical lesion in the sense that an unusual or infrequent site is affected (40). It represents an actual departure from the typical pattern. Here a less frequent condition with topical action may aggravate an unusual site producing an atypical sign. For example, an existing chronic deficiency state and an added endocrine disorder, together with other adverse conditions, may bring about an ocular or abdominal hemorrhage actually on the basis of a vitamin C deficiency (41). A highly instructive instance on an experimental basis was Odom and McEachern's observation that a traumatically inflicted cerebral lesion at a site not usually associated with manifestation of a deficiency process became symptomatic when thiamine deficiency was induced (27). Conditions, then, may conduce to atypical as well as

typical localization of deficiency manifestations in tissue. When lesions are atypical the tendency erroneously is to regard them as unrelated to nutrition and to fail to recognize in them signs of a deficiency state.

ON RESPONSE TO THERAPY

Because of the effect of conditions, the response of deficiency manifestations to therapy may be of several kinds leading to erroneous and confusing interpretations unless their influence is taken into account. Among these conditions particularly is the character of the deficiency process, whether acute or chronic, which affects the kind of response.

1. *Positive Response to a Variety of Substances Given as Therapy but Which Actually Have no Corrective Action for Deficiency Process.* This type of reaction has been seen almost exclusively in severe, acute deficiencies, which respond rapidly and for which the period of therapy is traditionally short. Historically the literature is filled with reports of cures of beriberi, pellagra, scurvy, and rickets with a long list of substances. During the years before the chemical natures of the specific etiological nutrients were definitely identified, the number of substances to which therapeutic effectiveness was attributed but later unsubstantiated ran into the hundreds. Indeed the number of spontaneous "cures" with distilled water or without therapy recorded in the literature is lengthy. A beneficial change in other conditions, not the substance being taken, is really responsible for the improvement in these cases. It has already been explained that an acute deficiency disease shows ebb and flow in accord with change in conditions. Its ebb brings about the spontaneous improvement. Any substance administered as therapy at the time of ebbing is mistakenly given credit for the cure. This pitfall is a serious concern in studies and observations to discover whether a disease of unknown etiology is nutritional, to ascertain the nutrient specificity of tissue manifestations, and to test a substance for its therapeutic action.

It is sometimes argued that the long-term therapy of pure nutrients in studies on chronic deficiency states leads to uncertain results because diet or other conditions may become more favorable over a prolonged period and may bring about beneficial effects mistakenly ascribed to the specific nutrient therapy; therefore only short term therapy studies upon acute processes are trustworthy. The truth is quite to the contrary. Although improvement in diet may bring about reversal of the chronic process to some extent, it is even more effective in abating acute manifestations. Of equal, if not greater, moment, an erroneous interpretation from a spontaneous change in non-dietary conditions is very much more apt to arise in treatment of the acute than of the chronic process. In reality, the acute process is a temporary episode subject to spontaneous remission from a change in such conditions. In contrast, spontaneous reversal with an appreciable recession in the chronic is uncommon. Mitigation of adverse non-dietary conditions which is responsible in many instances for the spontaneous subsidence of the acute process is not likely to reverse a chronic deficiency. From their different natures, the acute process is more readily abated than is the chronic reversed by an equally favorable change in conditions. On the score of a chance beneficial change in conditions leading to erroneous conclusions about the therapeutic activity of a substance simultaneously under test, the acute deficiency is more open to misdirection than is the chronic. The shorter opportunity for an acute manifestation to be influenced by fortuitously improved conditions is outweighed by its inherent tendency to spontaneous subsidence and its greater susceptibility and readiness to respond to a favorable occasion. For these reasons, the response of a chronic deficiency to therapeutic test is much less liable to be misleading than is that of an acute process. The long history of numerous substances with therapeutic powers for acute deficiency diseases attributed to them, only to be found subsequently without effect, is eloquent testimony to the high degree of fallibility in studies on the acute form.

The usual safeguard against chance change in uncontrolled conditions is the established procedure of including a "control" group. It is applicable to studies on both acute and chronic deficiencies. Since an acute deficiency is more susceptible to stray or unplanned changes in conditions that yield a positive response, for which an ineffective substance simultaneously administered may receive credit, further precautions may be taken when that form is under observation. After a positive response with a therapeutic agent, a relapse should be induced by withdrawal of therapy with continuation of an appropriately deficient diet; then therapy should again be given and a positive response obtained; and preferably an alternate relapse and therapeutic response should again be obtained. Such a procedure increases the dependability of the results and offers greater protection against unwitting misinterpretation.

2. *Exacerbation Under Therapy With Proper Nutrient.* Depending on a change in conditions, an untreated chronic deficiency may undergo recurrent exacerbations to a subacute process with subsequent subsidence. During the first year of therapy with the appropriate nutrient, a chronic process may exhibit one or several episodes of exacerbation with later abatement. Or a subacute exacerbation may be present at the time therapy is instituted, then after subsiding may reappear later. In either instance a premature pronouncement on the inefficacy of the therapy would be unwarranted. Usually as time passes and the chronic lesion slowly recedes under therapy, the exacerbations become milder and farther apart until finally none occurs except under some extreme condition. Such episodes may be seen in the chronic gingivitis of avitaminosis C under the stress of secondary infection, and in the chronic superficial keratitis, angular stomatitis, and cheilosis of ariboflavinosis under exposure to light. One patient, occupied constantly indoors, with a pronounced underlying chronic ariboflavinosis as manifested in the cornea, lips and angles of mouth, upon exposing himself over week-ends to sunbaths on the deck of a boat with little protection except dark glasses invariably de-

veloped an exacerbation of the lesion in the angles of the mouth (37). The character of the lesion and the conditions under which it was elicited was typical of so-called actinic cheilitis. When riboflavin was administered only slight protection from exacerbation upon solar exposure was at first afforded; then gradually protection increased until exposure could be tolerated without exacerbation, all this concomitant with gradual recession of the original lesion. This course of events is explained by the underlying chronic process and the long period of therapy necessary for its recession. Tissue resistance at first was slight; but as the chronic process in the tissue receded, resistance increased. If this situation were not recognized and therapy were prematurely terminated observations would indicate that the lesion had worsened or not improved under therapy; erroneous conclusions would then be drawn that the therapy was ineffective and that the lesion was not indicative of a deficiency in the particular nutrient administered.

3. *Negative Response of Chronic Process to Short-Term Therapy.* If a chronic process is treated for only a short period, say a few weeks or months, even with therapy of the proper nutrient, no perceptible improvement may be noted in that time. The concomitant operation of a potent adverse condition with its retarding influence further slackens the already slow recession of the lesion. Similarly, a subacute process superimposed on a chronic lesion with secondary infection as the precipitating condition may for some time show little or no perceptible improvement under administration of the appropriate nutrient. If therapy is prematurely terminated no improvement would, of course, be noted. The erroneous conclusion would be drawn that the lesion is unrelated to the deficiency process for which the therapy is appropriate or that the lesion is a pseudo-type; or if the therapy is under test as to kind, route of administration, or potency, it would be mistakenly regarded as inappropriate. Obviously the real fault is that the period of therapy is too short. Recession of a chronic lesion with or without a subacute is a protracted affair; and

discernible improvement may be noted only after a prolonged period of therapy, the length of time depending on the stage of the lesion.

4. *Positive Results from Change in Therapy.* Occasionally there are reports of negative response to therapy of the appropriate nutrient with seemingly beneficial results upon change to other therapy. If a subacute process is ebbing and flowing upon a chronic deficiency under the influence of a potent adverse condition, even proper therapy may not immediately moderate the exacerbation. If therapy is changed at a point coincident with a beginning ebb of the subacute process due to an uncontrolled change in other conditions or to the effects of the first therapy then about to become manifest, the new therapy though ineffective and inappropriate, would erroneously be credited wth potency. An outstanding pitfall in experimental studies is an uncontrolled change in procedure, in this case therapy, during the study.

Thus through their presence, absence, or change, conditions other than therapy with pure nutrients may profoundly influence response to it. Since one approach to the determination of the validity of lesions as signs of nutritional disturbance and of a particular deficiency state, to the assignment of deficiency in a particular nutrient as the etiology, and to the recommendation of proper therapy hinges upon changes in tissue in response to therapy, it is essential to understand the effects of other conditions else incorrect interpretation will create confusion and error. Their influence on the results and conclusions about signs and etiology will in turn affect the evidence and views on the prevalence of deficiency states.

On Experimental Induction of Deficiency States

Attempts to induce the various deficiency diseases in persons have been numerous, but for the most part unsuccessful. In these, mindfully or unmindfully, the objective has been to induce the acute form. In some the goal has apparently been its development to a severe, complete syndrome. Efforts to this

end, however, have fallen far short of achievement. In other attempts the goal has been production of one or more of the earlier signs. A few studies have succeeded in inducing these in subacute form and mild degree. Yet some of these results could not be reproduced by other investigators elsewhere.

Despite this disappointing record, there is no reason to doubt that acute deficiency states—or chronic for that matter—can be induced in man. The few successful instances of producing early mild signs bear evidence. The reason for success or failure in the enterprise may be sought in the conditions. For they influence not only the occurrence of natural but also the induction of experimental deficiency states. Analysis of the conditions under which deficiency diseases are produced experimentally in animals and occur naturally in epidemics in man is instructive. Although they may not present the same set of conditions, they reveal patterns in principle.

In production of an acute deficiency disease in the rat, the animal is restricted to an exceedingly unbalanced diet almost totally deficient in a nutrient. But this dietary condition alone is not sufficient to bring about the desired result. Only in the period of rapid growth is the acute deficiency readily induced. It is difficult to obtain it in mature older animals. With its extraordinary demands growth is a potent condition. Under these and other conditions the deficiency slowly builds up velocity and intensity. It does not at once attain the velocity and degree of a severe acute process but gradually takes on acceleration and intensity before it bursts forth in flagrant form. Thus it takes time to induce a deficiency and to produce histopathology in tissues. Indeed if the deficiency be exceedingly rapid and severe and the tissue previously free from pathology, the animal may die before there has been sufficient time to develop histological alteration.

In the natural occurrence of an acute deficiency in man his diet is ordinarily not so devoid of the nutrient as that in the animal studies. But usually he has a preexisting pathology of a chronic deficiency; therefore his tissue status is already un-

satisfactory prior to the outburst of acute manifestations. It is easier for the acute process to occur as an exacerbation of an existing chronic deficiency with its pathology than afresh on previously satisfactory tissue as a culmination or climax of unfavorable conditions. Other conditions than these also exercise considerable influence on the natural occurrence of an acute deficiency disease in man. Physical exertion, disease, pregnancy, and exposure to environmental stress may be cited. Then too, while an acute deficiency may sometimes seemingly flare up over night in man, actually it is but an episode in a chronic deficiency that has been a long time in the making. From the viewpoint of the entire passage of time for development of the chronic base from which it emerges the acute process requires considerable period before its occurrence.

Among the sets of conditions conducive to the experimental induction of the acute state in animals and its natural epidemic occurrence in man, some are seen to be common to both but with a different degree of intensity and influence. Other conditions appear only in one or the other. Nevertheless, the net result is the same in both sets. Chief among the conditions in one, or the other, or both, are: inadequate diet, growth, preexisting chronic deficiency with pathology, diverse major and precipitating conditions, and time.

Most of the unsuccessful attempts to induce signs of an acute deficiency in man have lacked a sufficient number of the prerequisite conditions. Although in all a deficient diet was used, in some it was made progressively deficient by steps so that its accelerating and intensifying influence on the deficiency was greatly curbed. Usually adults past the period of growth with its rigorous requirements were selected as subjects. Although their tissue status was not recorded, they were said to be "normal." It may be presumed, however, that most were not entirely free from chronic pathology but that their status was not already decidedly inferior. In contrast, among the recorded successes in inducing one or two signs, it is more than probable that the subjects already had a considerable degree of es-

tablished chronic pathology. When growth is not operative and preexisting nutritional status is only slightly at fault other conditions must be the more adverse. But in the unsuccessful studies adverse environmental conditions, major or precipitating, were also at a minimum. Physical exertion was not severe; infection and other disease were purposely excluded. Those subjects under institutional management with their regulated life may especially be protected on this score.

The length of these experimental attempts has varied but usually it has been only from a few weeks to a few months. As a rule, under the rigorous set of conditions imposed, an acute deficiency with clinically recognizable manifestations is not produced in animals under three or four weeks, which is equivalent to two years in man. In experimental attempts on a human subject, the approximate period necessary to bring on the acute signs will depend on the conditions prevailing, especially his preexisting tissue status. But it is obvious that a few weeks or months is ordinarily not sufficient to achieve the objective.

With attention to these various conditions, it should be possible to induce experimentally signs of an acute or subacute deficiency. Actually, when it is produced in man, it is likely that it will be as an exacerbation. Its production is, however, of more than academic interest. For, like response to therapy, the experimental induction of signs of an acute or subacute deficiency in man furnishes one of the lines of evidence for views on the etiology of deficiency diseases, the validity of clinical signs attributed to them, and their prevalence. Thus far, few attempts have been directed toward the equally, if not more, important end of inducing or worsening chronic manifestations in man. But there too, consideration of conditions would be just as applicable.

ON DIETARY REQUIREMENTS

Here nutrient requirements created by conditions in the ordinary vicissitudes of life and meetable by supply from food are under consideration. Bodily requirements, it may be reiterated,

represent amounts of nutrients that should be supplied to the tissue; food is the usual source of supply. Since conditions alter the supply of nutrients to tissue, supply by food and supply to tissue are not synonymous; and dietary requirements are not necessarily identical with tissue requirements. Rather dietary requirements are expressed in amounts of nutrients as supplied in food, or in terms of food, that will satisfy bodily requirements. It is to be noted that dietary requirements must cover the influence of conditions not only on the supply of nutrients to tissue but also on its requirements.

By common consent, dietary requirements embrace an area with definite bounds. As has been indicated, they represent requirements arising from conditions in every-day life that can be satisfied by supply from food. Certain criteria are specified in recognition of the conditions and their effects. Some of these criteria are made applicable to all persons because the conditions hold for all. Among these are the states of health and nutrition.

By convention, dietary requirements apply to normal, healthy persons already in good nutritional status. Thereby are excluded requirements in states of disease or poor nutritional status, which cannot be or are not most effectively met by ordinary means, namely, diet alone. For admittedly these two conditions set up greater requirements; indeed, they constitute a specialized therapeutic problem. As the principal common qualifications associated with dietary requirements, the terms normal, healthy, and satisfactory nutritional status need definition.

In usage normal may mean conformable to a particular standard usually implying a satisfactory state; or it may mean the usual, ordinary, or typical state. Whichever the meaning, it may be asked: normal in what respects? Although this point is usually unspecified, presumably it may be in any or all respects. At most it may mean that structure, function, behavior, nutrition, and health are in a normal state; or it may refer to only some of these attributes. According to one usage,

its application includes health and nutritional status; to another, it refers to health alone.

As commonly used in connection with requirements, health has often meant absence of disease; therefore, any state short of disease is health. Here they are two arbitrary absolute opposite terms. But they are open to another interpretation. Health and disease together may be visualized as representing a range, each with gradations. In this view health is a relative term with degrees of impairment short of disease. Such adjectives as excellent, good, fine, fair, poor, underpar, commonly applied to health, are an attempt to grade it. For what passes for health is not abundant, unadulterated health. Besides its degrees, the term health is popularly extended to include states which might properly be questioned as representing it. Health merges imperceptibly into disease and the allocation and assignment of states in the intermediate zone is a difficult and at times a necessarily arbitrary matter. This area is exemplified by the frequent complaint: "not sick, but not healthy." Ill-health with nondisabling, undiagnosable symptoms; the prodromal stage of disease with its vague, ill-defined complaints; morbid processes in silent areas; these are often not considered as disease, at least at the time, and by exclusion are placed under health. Unless the state presents well-defined symptoms or signs, or a diagnosable entity, it is apt to be excluded from disease. Moreover, the health of a person free from all symptoms varies from day to day; and extended periods or transient episodes of borderline ill-health may punctuate the course. It is obvious that a definition of health is difficult. The intent is clear: to ascertain and set forth requirements of healthy persons; but the expression of it may be obscure. In common use many impairments short of outright disease may be embraced in health. Some, if not most, of these are conditions affecting nutrition. When the term "healthy" includes ill-health as well as degrees of health, the requirements are higher than when it is used in a stricter sense.

As for the other common qualification on the terms of dietary

requirements, namely, satisfactory nutritional status, sometimes it is implicit in normal and healthy; at other times it is explicitly added. Regardless, the designation "satisfactory" for nutritional status must likewise be defined and a corresponding standard erected just as for health. Nutritional status is at once an effect for which conditions are responsible, and itself a condition. It is obvious that poor status will have higher requirements than does good status. By arbitrary definition, requirements are not gauged for and do not apply to persons in unsatisfactory status. But at what point nutritional status ceases to be satisfactory is a question that must be decided. If some degree of impaired nutritional status is to be allowed under the term satisfactory, the standard "normal" requirements will be different from those under a definition which excludes such a tolerance.

Health and good nutritional status are the only characters supposedly common to the entire class and are therefore its definitive bounds. But within it groups and individuals are subject to other widely different conditions regarded as normal. These various sets of conditions create different dietary needs. Hence, depending on conditions, individuals, and groups, each have different dietary requirements. The question, requirements for whom, is the same as requirements for persons under what conditions?

Several of these conditions, e.g., growth, work, pregnancy, and lactation, are recognized in most tables of requirements with increased allowances for them (19). For some conditions, however, provision is not made. An example of one type is occupational exposure to toxic or noxious substances. Only recently has the adverse effect of these conditions upon nutrition been appreciated. It is evident that these conditions raise the level of requirements for at least some nutrients, the kind depending perhaps in part upon the nature of the toxic principle. Another type of requirement-raising condition which goes unreckoned is an adverse environmental or occupational condition. For example glare arising from reflection of intense

sunlight on snow affects inhabitants of the North country (28), just as that from haze affects aviators. It must certainly raise requirements for riboflavin, since it is capable of precipitating severe acute episodes of a deficiency state of that nutrient. Thus occupation, geographical region, and climatic phenomena present particular conditions of stress or trauma which mightily influence requirements. What is enough under more moderate is not under these more rigorous conditions. Requirements are heightened under their influence.

Under normal health and satisfactory nutrition are included various states setting up different requirements. On these scores alone, persons may differ in their requirements. Furthermore, they differ in respect to the other conditions to which they are exposed or subject. Then too, they differ in the extent to which they come under the same condition. In the influence of conditions on dietary requirements it is to be noted that not only the number and kinds of conditions but also the quantitative level of each bear upon the level of need. For all these reasons, persons classified in the same category differ in their requirements. It is clear that conditions make requirements a highly individual, personalized matter.

ON METHODS OF DETERMINING DIETARY REQUIREMENTS

Conditions are intimately associated not only with dietary requirements but also with determination of the levels. They influence the manner in which evidence is obtained and therefore its nature. In the conduct of studies on dietary requirements, the necessity of conforming to certain criteria is commonly recognized. The subjects must be comparable to the class of persons for whom the standards are to erected. In addition, the studies must be conducted under conditions comparable to those prevailing in the everyday life of the standard class. Ordinarily the adequacy of the dietary level under test is judged by success or failure in protecting against signs of nutritional deterioration.

Despite accord in principle, there is wide divergence in prac-

tice in meeting these criteria. First, the measurement and appraisal of health is by no means a matter of common agreement. Secondly the evaluation of satisfactory nutritional status has not achieved uniformity. Both of these situations are reflected in the selection of subjects. The definition and standards of health and satisfactory nutritional status adopted will influence the character of the sample of human subjects in these two respects. Thirdly, the presence or absence of various conditions during the study which distinguish it from everyday life or from the situation specified in the standard may unfortunately receive little or no attention. In consequence, the conditions of the study and those implicit in the standard may bear little resemblance. Fourthly, while time is always an important element in nutrition studies, it is of much significance in the prophylactic type. There it is doubly necessary to be sure that enough time is allowed for any inadequacy in the dietary level to manifest itself. Since in man it has been found to be difficult and to require a long period to induce signs of a deficiency even under conditions of a severe inadequacy in diet, it may be imagined how much longer time would be required for development of perceptible lesions under conditions of milder degree and slower impetus inherent in prophylactic studies. Lastly, there is no uniformity in the adoption of indices of nutritional deterioration. If an insensitive or inadequate index be taken, it may in the more critical zone of intake reveal no deterioration, when in fact a more reliable and valid index points to impairment. It should be noted that these variances and shortcomings in practice are over conditions. Thus, the plan and conduct of studies on dietary requirements, the evidence adduced, the conclusions and generalizations drawn from it, and the standards set will depend on the extent to which the influence of conditions is recognized and taken into account.

That statement is illustrated by the reaction designated as adaptation (42, 43) which has been advanced as an argument for the adequacy of low levels of intake. When conditions become adverse or rigorous, the changes which the body under-

goes in response may be viewed as an attempt to fit itself to them, to maintain its usual activities and even to protect life. Whether the response may be regarded as successful depends upon the criteria selected. Accordingly there are degrees of success. Contrastingly, there are limits beyond which it is generally agreed that adjustment has been exceeded; at the extreme, even life is threatened. The term adaptation, according to one definition, is usually reserved for situations in which the net result is regarded as ostensibly successful in preserving activities and in protecting and sparing the body from detrimental effects. In short, it connotes a high degree of adjustment. It is a general term covering many examples with various mechanisms. In nutrition the process has come under consideration through the relation of the efficiency of utilization to the level of intake. This relationship may be visualized as extending over a range of levels of intake but in the present instance it is restricted to the response to reduced intake of a nutrient or to underfeeding.

Two examples may be cited. In one, evidence is adduced that it is possible to obtain equilibrium on low levels of calcium intake without perceptible ill-effects, especially clinical signs of a deficiency state. From these observations it is reasoned that within limits low intake induces reduced expenditure without detectably unfavorable consequences; that it elicits a more economical use of a nutrient and thereby reduced requirements with no adverse effects on the body and its tissues. It is then concluded that the dietary requirement for this nutrient may be safely lowered from its present level.

Unless otherwise stated, it is usually agreed that dietary requirements are set to maintain existing satisfactory nutrition. In the argument for the adequacy of low intake because of adaptation it is assumed that metabolic equilibrium and absence or appearance of deficiency signs are valid indices for judging maintenance versus deterioration of nutrition. For calcium in this critical zone of intake, that assumption is questionable. It has been shown that is is indeed possible to obtain equilib-

rium on low levels of calcium intake; but as the level is increased to higher points, there is an increase in retention (44) in the calcium content of the bones and body, in growth, and in the life span (45, 46, 47). These evidences of effects to be gained at levels above equilibrium cast doubt upon the suitability of lesser amounts for maintenance of satisfactory nutrition. It is likewise questionable that the nonappearance of localized clinical signs of calcium deficiency is an adequate indication that satisfactory nutrition has been maintained. Balance studies are ordinarily of short duration; so short as not to allow sufficient time for pathological manifestations of a deficiency to develop. But more decisive, it is difficult to diagnose early, slight, or chronic pathological manifestations attributable solely to calcium deficiency in the child and adult.

The second example is based on reports that in populations with admittedly low intake of food, acute deficiency states may seldom be seen. From this observation is raised the question: Cannot caloric and nutrient intake be safely lowered? The most striking instances of lowered intake are in prolonged marked underfeeding, starvation, or fasting. But extremes of these may exceed adaptation inasmuch as survival is imperiled. Adaptation is applied to lesser degrees of underfeeding within limits that supposedly have a satisfactory outcome as judged by one or another criterion including non-appearance of clinical signs of deficiency states, whether acute or chronic.

It is true that in starving or grossly underfed populations, acute deficiency states may not be prevalent. For that there is a rational explanation. In total undernutrition, loss in weight, lowered metabolism, retarded growth, and restricted activity do lower requirements. To the extent that this effect from these counter-conditions balances the diminution in supply, the severity of the deficiency is mitigated and its tempo is slackened or held in check. Hence, in the absence of potent, exciting conditions, any acute process is likewise prevented or allayed. It has long been known that barring the intervention of powerful exciting conditions, acute deficiency diseases do not develop

during fasting or marked underfeeding; rather they are moderated by it. Underfeeding is a deterrent, not a producer, of acute deficiency states.

But it does not necessarily follow that non-appearance of acute means absence of chronic and subacute deficiency states or presence of satisfactory nutrition. The fact that clinicians surveying populations of moderate or low intake may not have reported on chronic deficiency states is no evidence that this form was absent. To a nutrition world trained in the tradition of acute deficiency states by both animal experiments and clinical reports, the criterion of observation would naturally be the acute form. Moreover, most of the reports antedated the concept of the chronic state and the means of recognizing it. Under these circumstances the observer would be apt to overlook or disregard any chronic lesions; therefore, it would not be expected that chronic deficiencies would be reported. Actually, more recent evidence does show that chronic lesions, many severe, are highly prevalent among a moderately underfed population (28, 48). In induced underfeeding, assuming perhaps academically that the subjects were initially free from chronic lesions, it should be noted that the study might not be conducted for sufficient time to allow development of chronic pathological manifestations, especially if the restriction on intake was slight or moderate.

ON CORRELATION OF SIGNS WITH DIET INTAKE OR CHEMICAL LEVELS

It is argued that if data show a high prevalence of a deficiency of a nutrient in the diet or body fluids, there should be a corresponding frequency of clinical signs; or vice versa. Such a correlation appears to be always expected; it is regarded almost as an inviolable premise. But it is seldom achieved. The fault is in expecting an invariable positive correlation. As a general rule, such a correlation is more apt to be obtained when diet or nutrient levels in the blood and clinical deficiency status are both exceedingly bad. In lesser degrees of inferiority it is more difficultly and much less frequently found. In reality there are

understandable reasons why correlation should not necessarily be expected.

Absence of positive correlation appears in two forms. In the one, data indicative of prevalence of unsatisfactory dietary intake or nutrient level in a body fluid are not associated with a corresponding degree of frequency of signs of unsatisfactory status referable to that nutrient. This negation may be due to several reasons: (1) The diet standards used in the particular instance for a particular group may be too high. As has been shown, non-dietary conditions influence these dietary requirements and standards. (2) It has been pointed out that a generally lowered intake, such as in underfeeding, mollifies signs of deficiency diseases, though not obliterating them. (3) The signs of malnutrition selected are not sensitive or are not used sensitively. Use of late, or severe, or acute signs only would exclude early, or mild, or all chronic deficiencies. (4) The expectation of positive correlation is built upon an assumption of a simple relationship in which diet as a sole cause produces malnutrition. It should be recalled that diet intake is a condition and not the only conditon influencing nutrition. What is attempted is to correlate one condition, admittedly an important one, with effects brought about under the influence of a complex of conditions. Hence, non-dietary conditions are partial determinants whether correlation is obtained. (5) In persons previously free from deficiency disease, adverse conditions would have to be in force some time before signs appeared. It takes time to produce pathology.

In the second type of negative correlation, dietary data or nutrient levels in body fluids are not in accord with clinical evidences of unsatisfactory nutrition. Several reasons are likewise responsible: (1) Diet standards are too low for the particular subjects surveyed under their conditions. (2) Diet is only one condition in the complex influencing the etiology of deficiency states. Dietary inadequacy may be slight and of relatively minor influence while other conditions predominate. As diet approaches a satisfactory level, correlation becomes

increasingly difficult. Diet as a single condition then has less influence relatively as well as absolutely, and other conditions more. (3) If chronic signs constitute the clinical evidence, they represent cumulative effects over the lifetime. Whereas, the dietary data and nutrient level of body fluid are of the moment with no necessary reflection beyond the present or immediate past. Diet and body fluid values may have improved before the survey while the effects on tissue of previously adverse conditions will have prevailed. If correlation is to be found between diet or the body fluid levels of a nutrient and clinical signs, usually it will be when the latter indicate the more acute or the more severe deficiency. But most often even this is disappointing; for acute signs are not necessarily or absolutely synchronous with dietary levels and nutrient concentration in body fluids.

From these considerations it is clear that the assumption of the necessity of invariable positive correlation between unsatisfactory diet or nutrient levels in body fluids and clinical signs of deficiency states is unsupportable. Indeed it clarifies why such a correlation is usually not obtained.

Unfortunately such attempted correlations have been used to test the validity of clinical signs (31). Because so many conditions influence the data that correlation is not necessarily to be expected, this approach is not designed to be a reliable test of signs and to yield a true and accurate answer.

RECIPROCITY

From studies with animals it is known that deficiencies have effects besides specific localized lesions. These additional effects are on inherent bodily properties and primary biological functions. Among them are: retardation or cessation of growth; loss in weight; impairment of reproduction especially gestation and parturition in the female; increased susceptibility and lowered resistance to infection. Some of these consequences, at least, may be designated as constitutional. And some, if viewed broadly, are non-specific for the nutrient.

These functions affected by nutrition may be recognized also as conditions affecting nutrition. Because of this interaction, it is clear that evidence from animals points to a reciprocity in nature.

That these functions, as conditions, affect nutrition in man is well substantiated. But whether the converse is true, whether nutrition influences these functions and thus completes the circle so that the interrelationship holds for him, has been a transcendent question. Though admittedly the studies on man on this point have been too few, they have thus far for the most part yielded results in agreement with those from animals. The effect of inferior nutrition on the growth of children has been abundantly demonstrated. And evidence from several sources indicates that nutrition influences the course of pregnancy. Because of its significance and scope it is of exceeding interest to contemplate the possibilities arising from such an interplay between conditions and nutrition.

Conclusion

In sum, the concept presented here sets forth the etiology of deficiency states and brings out the relationship of the many environmental conditions, both external and internal, to nutrition. It also explains the character and course of deficiency processes and their prevalence. It bears directly upon the assignment of causality in diagnosis. With it comes the realization that the possibility that a disease of unknown cause may be nutritional in nature is not to be forthwith dismissed because it apparently is not the effect of dietary deficiency alone; rather, this contingency can be examined on broader etiological grounds. Beyond these relations, the influence of conditions is seen to extend into almost every aspect of nutrition.

References

1. Kruse, H. D.: A Concept of Deficiency States. The Milbank Memorial Fund *Quarterly,* July, 1942, 20, No. 3, pp. 245–261.

2. Kruse, H. D.: The Place of Nutrition in the Relationship between Environment and Health. The Milbank Memorial Fund *Quarterly,* January, 1948, 26, No. 1, pp. 41–57.

3. Roussel, Théophile: TRAITÉ DE LA PELLAGRE ET DES PSEUDO-PELLAGRES. J. B. Baillière et Fils, Paris, 1866, p. 517.

4. McCarrison, Robert: STUDIES IN DEFICIENCY DISEASE. Henry Frowde and Hodder & Stoughton, London, 1921, Chapter iv.

5. Jackson, C. M.: THE EFFECTS OF INANITION AND MALNUTRITION UPON GROWTH AND STRUCTURE. P. Blakiston's Son & Company, Phliadelphia, 1925, pp. xi and xii.

6. Bender, W. L.: Pellagra Secondary to Lesions of the Stomach Interfering with Nutrition. *Journal of the American Medical Association,* April 25, 1925, 84, pp. 1250–1253.

7. O'Leary, P. A.: Secondary Types of Pellagra. *Medical Clinics of North America,* November, 1926, 10, pp. 647–658.

8. Ellis, R. W. B.: Pellagra Secondary to Gastro-Intestinal Disease. *American Journal of the Diseases of Children,* May, 1930, 39, pp. 1036–1044.

9. Strauss, M. B.: The Role of the Gastro-Intestinal Tract in Conditioning Deficiency Diseases. *Journal of the American Medical Association,* July 7, 1934, 103, pp. 1–4.

10. Strauss, M. B.: The Therapeutic Use of Vitamin B_1 in Polyneuritis and Cardiovascular Conditions. Clinical Indications. THE VITAMINS, Chapter x, American Medical Association, Chicago, 1939.

11. Wilbur, D. L.: The Role of Gastro-Intestinal Tract in Conditioning Deficiency Diseases. *Medical Clinics of North America,* March, 1943, 27, pp. 519–535.

12. McIntosh, Rustin: Disorders of the Digestive System Leading to Vitamin Deficiency States in Infants and Children. *Bulletin of The New York Academy of Medicine,* January, 1944, 20, pp. 25–33.

13. Platt, B. S.: Aspects of Nutritional Research. *British Medical Bulletin,* 1944, 2, pp. 204–207.

14. Jolliffe, Norman: Conditioned Malnutrition. *Journal of the American Medical Association,* May 29, 1943, 122, pp. 299–306.

15. Ershoff, B. H.: Conditioning Factors in Nutritional Disease. *Physiological Reviews,* January, 1948, 28, pp. 107–137.

16. Cowgill, G. R.; Rosenberg, H. A., and Rogoff, J.: Studies in the Physiology of Vitamins: XVI. The Effect of Exercise on the Time Required for the Development of the Anorexia Characteristic of Lack of Undifferentiated Vitamin B. *American Journal of Physiology.* Nov., 1931, pp, 589–594.

16a. Johnson, R. E.; Darling, R. C.; Forbes, W. H.; Brouha, L.; Egaña, E., and Graybiel, A.: The Effects of a Diet Deficient in Part of the Vitamin B Complex upon Men Doing Manual Labor. *Journal of Nutrition,* Dec., 1942, 24, pp. 585–596.

17. Spies, T. D.: Pellagra: Improvement While Taking So-Called "Pellagra-Producing" Diet. *American Journal of the Medical Sciences,* December, 1932, 184, pp. 837–845.

18. Ruffin, J. M., and Smith, D. T.: Studies on Pellagra at the Duke University School of Medicine. Chapter xv in CLINICAL PELLAGRA by Seale Harris. The C. V. Mosby Company, St. Louis, 1941.

19. National Research Council: Recommended Dietary Allowances. Reprint and Circular Series No. 129, Washington, D. C., October, 1948.

20. Follis, R. H., Jr.: Effect of Mechanical Force on the Skeletal Lesions in Acute Scurvy in Guinea Pigs. *Archives of Pathology,* April, 1943, 35, pp. 579–582.

21. Ellenberg, Max, and Pollack, Herbert: Pseudoariboflavinosis. *Journal of the American Medical Association,* July 4, 1942, 119, pp. 790–792.

22. Kruse, H. D.: Sydenstricker, V. P.; Sebrell, W. H.; and Cleckey, H. M.: Ocular Manifestations of Ariboflavinosis. *Public Health Reports,* January 26, 1940, 55, pp. 157–169.

23. Mori, S.: Primary Changes in Eyes of Rats Which Result from Deficiency of Fat-Soluble A in Diet. *Journal of the American Medical Association,* July 15, 1922, 79, pp. 197–200.

24. Kruse, H. D.: The Gingival Manifestations of Avitaminosis C, with Especial Consideration of the Detection of Early Changes by Biomicroscopy. The Milbank Memorial Fund *Quarterly,* July, 1942, 20, No. 3, pp. 290–323.

25. Linghorne, W. J.; McIntosh, W. G.; Tice, J. W.; Tisdall, F. F.; McCreary, J. F.; Drake, T. G. H.; Greaves, A. V.; and Johnston, W. M.: The Relation of Ascorbic Acid Intake to Gingivitis. *The Canadian Medical Association Journal,* February, 1946, 54, pp. 106–119.

26. Jackson, D., and Park, E. A.: Congenital Scurvy. *Journal of Pediatrics,* 1935, 7, pp. 741–753.

27. Odom, Guy, and McEachern, Donald: Subarachnoid Injection of Thiamine in Cats: Unmasking of Brain Lesions By Induced Thiamine Deficiency. *Proceedings of the Society for Experimental Biology and Medicine,* May, 1942, 50, pp. 28–31.

28. Moore, P. E.; Kruse, H. D.; Tisdall, F. F.; and Corrigan, R. S. C.: Medical Survey of Nutrition Among the Northern Manitoba Indians. *The Canadian Medical Association Journal,* March, 1946, 54, pp. 223–233.

29. Bass, C. C.: Pellagra. *Medical Clinics of North America,* January, 1926, 9, pp. 869–874.

29a. Lind, James: A TREATISE ON THE SCURVY. Third Edition. S. Crowder, London 1772, 560 pp.

30. Gherardini, Michele: DELLA PELLAGRA DESCRIZIONE DI MICHELE GHERARDINI. Gio. Batista Bianchi, Milan, 1780, 104 pp.

31. Dann, W. J., and Darby, W. J.: The Appraisal of Nutritional Status (Nutriture) in Humans with Especial Reference to Vitamin Deficiency Diseases. *Physiological Reviews,* April, 1945, 25, pp. 326–346.

32. Krehl, W. A.; Sarma, P. S.; Teply, L. J.; and Elvehjem, C. A.: Factors Affecting the Dietary Niacin and Tryptophane Requirement of the Growing Rat. *Journal of Nutrition,* January, 1946, 31, pp. 85–106.

33. Woolley, D. W.: Reversal by Tryptophane of the Biological Effects of 3-Acetylpyridine. *Journal of Biological Chemistry,* January, 1946, 162, pp. 179–180.

34. Rosen, F.; Huff, J. W.; and Perlsweig, W. A.: The Effect of Tryptophane on the Synthesis of Nicotinic Acid in the Rat. *Journal of Biological Chemistry,* April, 1946, 163, pp. 343–344.

35. Sarett, H. P., and Goldsmith, G. A.: The Effect of Tryptophane on the Excretion of Nicotinic Acid Derivatives in Humans. *Journal of Biological Chemistry,* January, 1947, 167, pp. 293–294.

36. Cleckley, H. M.; Sydenstricker, V. P.; and Geeslin, L. E.: Nicotinic Acid in

the Treatment of Atypical Psychotic States Associated with Malnutrition. *Journal of the American Medical Association*, May 27, 1939, 112, pp. 2107–2110.

37. Kruse, H. D.: Unreported Observation.

38. Sutton, R. L., and Sutton, R. L., Jr.: DISEASES OF THE SKIN. Tenth Edition. The C. V. Mosby Company, St. Louis, 1939, p. 1479.

39. Bean, W. B.; Spies, T. D.; and Vilter, R. W.: Asymmetric Cutaneous Lesions in Pellagra. *Archives of Dermatology and Syphilology*, May, 1944, 49, pp. 335–345.

40. Spies, T. D.; Cogswell, R. C.; and Vilter, Carl: Detection and Treatment of Severe Atypical Deficiency Disease. *Journal of the American Medical Association*, November 18, 1944. 126. 752–758.

41. Kruse, H. D.: Unreported Observation.

42. Meyers, F. M.: Possible Adaptation to a Low Vitamin B_1 Intake. *The American Journal of the Medical Sciences*. June, 1941, 201, pp. 785–789.

43. Mitchell, H. H.: Adaptation to Undernutrition. *Journal of the American Dietetic Association*, September, 1944, 20, pp. 511–515.

44. Sherman, H. C., and Hawley, E.: Calcium and Phosphorus Metabolism in Childhood. *Journal of Biological Chemistry*, August, 1922, 53, pp. 375–399.

45. Sherman, H. C., and Campbell, H. L.: Effects of Increasing the Calcium Content of a Diet in Which Calcium is One of the Limiting Factors. *Journal of Nutrition*, 1935, 10, pp. 363–371.

46. Lanford, C. S., and Sherman, H. C.: Further Studies on the Calcium Content of the Body as Influenced by That of the Food. *Journal of Biological Chemistry*, 1938, 126, pp. 381–387.

47. VanDuyne, F. O.; Lanford, C. S.; Toepfer, E. W.; and Sherman, H. C.: Life-Time Experiments Upon the Problem of Optimal Calcium Intake. *Journal of Nutrition*, March, 1941, 21, pp. 221–224.

48. Adamson, J. D.; Jolliffe, N.; Kruse, H. D.; Lowry, O. H.; Moore, P. E.; Platt, B. S.; Sebrell, W. H.; Tice, J. W.; Tisdall, F. F.; Wilder, R. M.; and Zamecnik, P. C.: Medical Survey of Nutrition in Newfoundland. *The Canadian Medical Association Journal*, 1945, 52, pp. 227-250.