

A CONCEPT OF THE DEFICIENCY STATES^{1,2}

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ALTHOUGH nation-wide dietary inadequacies have been revealed by surveys, the occurrence of deficiency diseases has not been generally noted except in city hospitals or endemic regions. Clinicians have asserted that they do not see deficiency diseases. This apparent discrepancy, despite much discussion, has remained baffling.

According to one explanation, many manifest cases are unrecognized. But even if these were detected, the figures on the prevalence of deficiency diseases would not match the data on the frequency of dietary inadequacies. Another explanation has been that deficiency diseases in an early or mild state are undetectable by ordinary clinical methods. This state was recognized in pellagra by Roussel who designated it incipient in preference to prodromal, latent, or larval (1). Recently it has been called subclinical.

This explanation raised two new questions. One was: By what means may deficiency diseases in this state be detected or recognized? Over the answer to this question there has been considerable division of opinion. The other was: What is the nature of deficiency diseases in this state? The views on this have been varied and vague. Yet it is a fundamental question, for its answer expresses a concept. Obviously, the prevalence of deficiency diseases that will be revealed depends on the methods of detection which are inseparably linked with the concept.

Study of the pathogenesis of deficiency diseases makes the existence of an early or mild state thoroughly understandable. A deficiency disease on a dietary basis develops in the following sequence: lowered concentration of the essential factor in the blood; depleted storage in the body's reservoirs; diminished excretion in

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the urine; microscopic change in tissue; gross morphological and functional change. It is not to be inferred, however, that each step is completed before the next begins. The alteration in transport and storage and the microscopic change in tissue show that the disease does exist in a state which is undetectable by ordinary clinical methods. For most deficiency diseases these changes have been demonstrated by appropriate sensitive methods.

One line of evidence comes from biochemical methods in analyses of blood and urine. In avitaminosis C, for instance, low blood values for ascorbic acid have been found in a definite proportion of population samples (2, 3). True, some investigators have argued that such values for ascorbic acid in the absence of other signs do not constitute scurvy. Judged by clinical criteria, the condition is not scurvy. Not until it has advanced to macroscopic tissue changes and developed signs is it designated scurvy. But that view draws a purely arbitrary distinction. Its only justification is that it differentiates two states of severity in the process. One is the beginning or mild state; the other the fully-developed disease. But whatever the former is called, it is a step in the process. As a practical matter, it may call for therapy.

The other line of evidence on the existence of the early or mild state in deficiency diseases has been the demonstration of morphological changes. The early changes revealed by x-ray in scurvy have been described (4). Biomicroscopy has disclosed still more about the early and mild state of several deficiency diseases. Just as the microscope was highly useful to the pathologist in extending his range of vision to lesser changes in postmortem tissue, it has now proved highly informative to apply it in deficiency diseases to changes in living tissues. It is particularly revealing if the site showing very early changes is selected for observation. Kruse has found specific biomicroscopic changes for four deficiency diseases: avitaminosis A (5), ariboflavinosis (6, 7), aniacinosis (8), and avitaminosis C (9).

In this morphological study of these deficiency diseases, with biomicroscopic in conjunction with macroscopic examination, it was possible to see all gradations and to reconstruct the sequence of changes. These observations, combined with the results from administration of specific therapy, have clearly shown that the early or mild state has a deeper meaning than was previously recognized. While each of these four deficiency diseases was a separate and distinct entity and had its specific individuality in details, all showed a similarity in their general biological behavior. They seemed to reflect certain principles. Accordingly, they have formed the basis for a new concept of deficiency diseases, their evolution, the state in which they exist, how they may be recognized, and their response to specific therapy.

First, it should be stated, each avitaminosis shows a specificity and invariability of the particular tissue sites in which characteristic lesions appear. This point has been demonstrated over and over in animals and humans. For studying the evolution of each condition, a tissue site affected early and undergoing changes throughout the entire course yields most information. It is found that the pathological process manifests a definite sequence of changes in this tissue.

Whether developing or receding, a deficiency disease possesses certain properties. First, the pathological process in the tissue has velocity. In the beginning this is not a constant, but an increasing velocity, an acceleration. How rate behaves next cannot be definitely stated. Probably the process, having achieved its potential maximum velocity, moves ahead for a time with little change in it. Naturally, this rate would not be absolutely constant. These velocities are determined by the causal force³ which in turn is a function of causal degree and rate. The causal force increases or decreases

³To many persons the term "deficiency disease" connotes a disorder arising solely from a deficiency in the diet. But a deficiency disease may occur without any inadequacy in the diet. True, dietary inadequacy is the most common cause; but there are many others.

according to these two factors. As counteracting forces go into action, the velocity of the process is slowed. Or with therapy, the pathological process undergoes deceleration, arrest, and reversal. But the maximum rate at which the curative force can act is governed by the rate at which the tissue process developed. The possible time schedules on which the process may evolve will be arbitrarily classified here into two main kinds, which are subdivided.

In the one, the pathological process in tissue is rapid in onset, in running its course, and in responding to therapy. For the process to have marked acceleration the immediate causal force must be considerable. Its magnitude depends on the degree and rate of the cause. For maximum effect this may be brought about by a sudden change from an optimum diet to one markedly deficient in an essential. Such a deficient diet, applied abruptly, causes the body to draw steadily on its reserves to compensate for deficit in intake. As the reserves increasingly fail to meet the demands, there is rapidly increasing deficiency in the body. Thus, there is increase in its intensity and its rate, an acceleration, which is reflected in its force. At the start, the tissue to be affected had a pathological rate of zero, or perhaps a negative value. Markedly increasing the force of the deficiency accelerates greatly and imparts a rapid velocity to the pathological process. It appears and progresses at a rapid rate. It

More properly, the term "deficiency disease" should connote a deficiency in the bodily tissues rather than in the diet. Indeed, its meaning should be even broader; it should include not only a deficiency but also any metabolic disturbance of the essential in the tissues. The causes of such a deficiency or disturbance are numerous and may be complex. They may be conveniently classified as external and internal. Dietary deficiency is the most common external cause. Any bodily condition interfering with digestion, transport or utilization, promoting destruction or excessive excretion, or raising the requirements of the dietary essential is an example of an internal cause. Almost every non-nutritional disease affects nutrition. A cause comes about through a combination of circumstances. For example, assuming a satisfactory internal mechanism, a deficiency disease may arise from insufficient intake relative to age, activity, exposure to light, storage, state of tissue, and probably other factors.

The innumerable chemical reactions and complex relationships in which the vitamins participate are just beginning to be appreciated. In full cognizance of their biological importance, it would nevertheless be inappropriate to attempt to bring into the present discussion these intermediate details. Rather, the broad aspects are sufficient for the present purpose, a consideration of the development of the deficiency states as manifested in tissue.

has characteristic manifestations reflecting this swift velocity. This is an acute process, an acute deficiency disease. With application of therapy in sufficient amount, the velocity changes similarly but in the reverse direction. The pathological process is decelerated and stopped; then the restorative process is accelerated. Pathological changes which have developed rapidly recede quickly. This acute process is rapid in development, progress, and recession.

There is another form in this acute category. Here the bodily deficiency occurs rapidly but becomes only slight or moderate in degree. Thus, it acquires a marked increase in rate but only slight intensity. This resultant is reflected in its force which is somewhat less than in the acute form. The pathological process is rapid but less rapid than in the acute form. It might be called subacute. Or, since it is mild in intensity, it might be designated mild acute.

The second main form of the process is slow in onset, progress, and response to therapy. Its development might be conceived as follows: For the process to have only slight acceleration the immediate causal force must be slight. This state may be brought about by a very slow change from an optimum to a moderately or markedly deficient diet. Such a deficient diet, applied very slowly, causes the body to draw very slowly on its reserves to compensate for the deficit in intake. As the reserves steadily fail to meet the demands, there is a slowly increasing deficiency in the body. Thus, there is an increase in its intensity, but at such a slow rate, over such a long period, that its force never becomes marked. Slightly increasing the force of the deficiency slowly accelerates and imparts only a slow velocity to the pathological process. It develops and advances at a slow rate. It has characteristic manifestations reflecting this slow velocity. This is a chronic process, a chronic deficiency disease. With application of therapy in sufficient amount and for a sufficient period, it gradually but completely recedes. The chronic form is slow in development, progress, and recession. The acute and chronic processes differ fundamentally in velocity.

Another form belongs in the chronic category. In this the bodily deficiency occurs very slowly and becomes only slight or moderate in degree. Its slight increase in rate and intensity is reflected in its force which is very slight and somewhat less than in the chronic form. The pathological process, more gradual than in the chronic form, is very slow. We have designated it mild chronic.

Time, a much neglected factor in malnutrition, operates in another way, namely duration. Here again the acute and chronic processes differ. Just as the acute process is rapid in rate, it is relatively short in duration. A few weeks out of a lifetime is almost infinitesimal. In these instances, time is almost zero. If uninterrupted, the acute process runs through a definite sequence of manifestations in a rather short time. It may, therefore, be divided into stages. Naturally, it may be interrupted at any stage and reversed to normal if the therapy is complete.

The chronic process, if uninterrupted, will run at its slow rate for a long period, in fact probably for life. During this time it progresses in a definite sequence. Therefore, it too may be divided into stages. In the past it may have been thought that a slight dietary deficiency prevailing even for years produced no tissue change. On the contrary, with persistence of a slightly deficient diet over years, the chronic process progresses with mild intensity in a definite course. This chronic process may be interrupted at any stage by therapy; but only adequate dosage and time bring complete reversal.

Besides its rate and duration, the pathological process also has intensity. The intensity of the cause leads to a corresponding intensity of the lesion. Just as there may be all degrees of intensity in causation—for example, all degrees of a deficiency in the diet—so there are all degrees of resulting lesions. Actually, the number of degrees which would be expressed would depend on the units and scale arbitrarily adopted. For present purposes, it is sufficient to divide the gradient levels into two groups: (1) severe, which is suf-

ficiently marked to produce gross lesions, from the just perceptible to the most pronounced; (2) mild, which is of so low intensity as to produce changes perceptible only by microscopy.⁴ These two categories, mild and severe, it will be noted, refer to actual tissue change, not to symptoms. They apply to both the acute and chronic processes.

In considering the deficiency diseases in relation to intensity and time, it is evident that the acute and chronic states may be either mild or severe. Therefore, the simplest classification provides the categories: mild acute, mild chronic, severe acute, and severe chronic, with each divided into stages. The action of intensity, rate, and duration in determining the tissue state may be visualized from Figure 1. Divisions representing stages have not been indicated. Under this classification such a term as latent or subclinical state is no longer necessary. It is seen to be a broad state comprising the mild acute and mild chronic conditions. It is preferable to use the more specific designation corresponding to the actual condition.

Thus far we have presented the evolution and recession of the acute and chronic states in their simplest course: as if they arose in normal tissue and with therapy their cure was always complete.

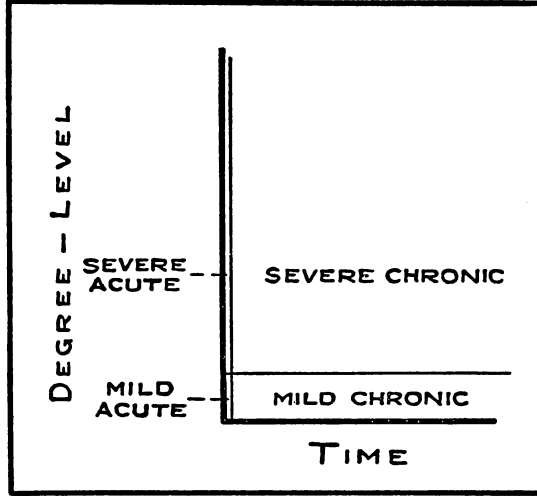


Fig. 1. States of a deficiency disease according to form, intensity, and stage. Divisions representing stages have not been indicated. From this chart the action of degree, rate, and duration of the cause in determining the tissue state may be visualized.

⁴ Actually, our system of rating now in use provides for four degrees of intensity for each stage in both the chronic and acute process.

But actually, in life, events are somewhat more complex. In the acute form there are several eventualities. It may run its acute course. With an untreated severe process, the patient either succumbs, or becomes inactive and has a poor appetite, both being protective mechanisms. In the latter event the process then advances at a slower rate. Or this first acute episode may be relieved by improvement in diet. But complete recovery, based on tissue restoration rather than symptomatic relief, would at best be slow because of the limited potency of food. If therapy is terminated upon relief of distressing symptoms or disappearance of late signs, response would be rapid but recovery incomplete. It is clear that as a result of any of these procedures, cure of the acute process would not always be finished. The recession in intensity, stage, and rate would not be complete. Consequently, the process would be brought to a new state with subsequent developments depending on circumstances.

With lapse from an optimum to a moderately deficient diet before recession was complete, the pathological process would resume at a slow rate. With a good diet following incomplete therapy, the process would remain stationary; with a slightly or moderately deficient diet, the pathological process would renew its advance at a slow rate. Also, an untreated mild acute process, running its course, would continue at a slower rate. As the result of any of these circumstances, the pathological lesion does not return to normal but persists on a lower level in the chronic state. Here it may be in equilibrium or progressing as a chronic process at a slow rate. In addition to arising from normal tissue, a chronic process may be seen to arise from an acute. Circumstances would again determine further developments.

By appropriate intervention this chronic process may be interrupted at any stage. But only by adequate therapy for sufficient time is its recession complete. In the event that a previously unsatisfactory diet is corrected, the chronic process becomes static or recedes very little and extremely slowly. Or with therapy for an in-

sufficient period, the process will recede incompletely. Thereafter, if the diet is slightly deficient, the slowly receding process may turn to a progressing chronic process. Or with a deficient diet and no therapy, the chronic process will continue its advance. Under these various unfavorable circumstances the chronic process, once contracted, may recede slightly, become stationary, or progress, depending on the diet.

The person with an arrested or chronic process may shift his diet from bad to worse and vice versa, but seldom to good. It is common knowledge that moderate or marked dietary deficiencies are apt to occur seasonally. They set up a mild or severe acute process, emerging usually in the spring. Other causes may act more infrequently but similarly from time to time. The arrested or chronic process constitutes a base on which this acute change is superimposed. To attain the same velocity, it takes less force to speed up an existing arrested or slowly moving process than to establish and then accelerate a process. Or, expressed in another way, a degree of dietary deficiency that would not produce an acute process in a well-nourished body would produce it in an already deficient body with a chronic process. Thus, an acute process may arise more easily from a chronic base. Under incomplete treatment the acute process disappears and leaves the chronic base, which may again undergo exacerbation. Repeated every year, this cycle is known as seasonal recurrence.

These do not represent all the possible changes in rate, stage, and intensity which a process may undergo. The diagram presenting the field suggests many more possible movements. The result is much more complex than was originally presented. But in sum, a mild or severe acute process in any stage may be seen on a mild or severe chronic form in any stage. These combined states add to the number of categories which must be borne in mind. It cannot be overemphasized that these combined states are very prevalent, perhaps the most prevalent.

The severe acute state is the form on which almost all clinical attention to deficiency diseases has hitherto been focused. Historically, this form, presenting a grave problem, was the first to be recognized; consequently, the recorded knowledge on the symptoms, signs, and pathology of this form predominate in the literature. Similarly, in experimental work, where the objective was to demonstrate the existence of new vitamins or to assay foods, animals were suddenly shifted from an optimum natural to a deficient "purified" diet in which every trace of an essential had been as far as possible removed. Naturally, the severe acute form of deficiency ensued.

In the past the mild and chronic states have received only sporadic and scant notice. By nature they have not been likely to attract attention. The mild are not conspicuous; indeed, they are below the level of unaided perception. Their associated symptoms, though often troublesome, are not so intense as to be unbearable or to necessitate medical consultation. Often the patient is unaware of symptoms until therapy has brought relief. The grossly perceptible chronic process comes on so gradually and insidiously as not for a long time to be obtrusive. Only in the advanced stages is it likely to draw complaint. Though noted often, little significance has been attached to it. Its relation to nutrition has been unrecognized.

Since the chronic state of deficiency diseases has not been commonly recognized, it is worth while to mention some of its characteristics. Its essence is time. For persons this is age. The longer persons live, the more chance they have to incur changes and to have them develop to an advanced state. Consequently, chronic changes are seen with greater frequency and in the latest stages with increasing age. This I have noted for avitaminosis A, ariboflavinosis, aniacinosis, and avitaminosis C.

In the past these chronic alterations have been called senile changes with the implication that senility causes them. But senility *per se* is not responsible for them. That has never been a satisfactory

explanation. Not all elderly persons show the changes. On the other hand, they occur in children. Time, not senility, is the essential point. And time does not start the changes, it simply is a dimension over which they progress. They are specific avitaminoses in a state of chronicity, due usually to respective dietary deficiencies running over a period of years. Their prevalence and severity vary with the number and degree of deficient diets and therefore with economic level. Most important of all, they are reversible, yielding slowly but completely to appropriate therapy.

This rate of response is another characteristic peculiar to chronic changes. Whereas acute changes respond with considerable promptness, chronic changes recede very slowly. In acute changes we are accustomed to expect improvement with dramatic rapidity. Actually, some of the rapidity is more apparent than real. For one thing, it is a relative matter; the more pronounced the acute, the more spectacular is a given degree of improvement. Often, removal of late signs constitutes supposedly rapid cure of an acute deficiency. Obviously, this is far from complete cure. But it is mainly because the relief of symptoms, the first event, is so prompt as to be striking. If judged solely by freedom from symptoms, the therapeutic response of acute is rapid. But when judged by complete restoration of all tissue changes, as seen by the biomicroscope, response in the acute condition is not quite so spectacularly quick as it is reputed. Nevertheless, response is very much more rapid in the acute than in the chronic state. The reason lies in the differential nature of their pathology. The tissue changes in the acute form of a deficiency disease are of a kind that appears rather rapidly and disappears just as readily. Those in the chronic form, with time allowing progression, are of a kind that progresses slowly and insidiously and recedes just as gradually.

Scattered observations in the literature on deficiency diseases are in accord with the concept presented here. The states are designated in terms identical with or similar to our nomenclature. In describ-

ing various forms of rickets, Eliot and Park mentioned: early mild, florid, and mild chronic (10). Their description of the course of these respective states may be interpreted in terms of intensity and time.

Furthermore, the literature records the characteristic difference between the acute and chronic forms in response to treatment. Eliot and Park remark that in one form of rickets the complete cure is slow (10). It has also been noted that in treatment of polyneuritis in animals, the acute fulminating type disappeared very speedily in a few days, the chronic type very slowly, in fact only after many months (11).

Even more significant has been the experimental production of scurvy in four states, depending on varying degrees of deficiency in vitamin C and the length of the experimental period (12). Tozer differentiated the chronic from the acute state on a time basis. She stated that the chronic form varies in severity according to the degree of deprivation of vitamin C. Indeed, using a different nomenclature to express intensity, she described mild and severe degrees for both the acute and chronic forms. Similar results have been reported on experimental vitamin B₁ deficiency (13, 14, 15).

Some broad generalizations can be drawn about these states in relation to factors affecting them. Like prevalence, the status of a deficiency disease is influenced by economic level, geographical region, and age, as well as by lesser environmental factors. Of these three it may be seen that the first two are indices of the number, nature, and degree of dietary deficiencies. Age is again the time factor. In the lower economic groups, deficiency diseases tend to be more numerous, more severe, and more advanced than in the higher economic groups. In geographical regions where a particular deficiency disease is endemic, the severe acute form is common; in other regions, it is rarely seen. If the disease is present in the latter, it is mostly in the chronic form. At younger ages, deficiency diseases are likely to be less prevalent and mostly in the mild acute or begin-

ning chronic state; at older ages they are apt to be more frequent and largely in the chronic form.

These influences are not invariable, absolute or completely decisive. Economic level and geographic region are far from perfect correlates of deficient diets; age does not initiate a deficiency disease. Nor are these influences of equal weight. Perhaps the most influential is economic level. But many persons in the higher economic groups do have severe deficiencies; while some in the lower miraculously escape. Only a small proportion of persons in an endemic region come down with an acute deficiency disease; almost all of these are in the low-income group. As for the influence of age, adults may be normal; whereas children, particularly if they are from low-income families, may exhibit a chronic process. We have seen numerous children from 8 to 11 years old with chronic changes similar to those most frequent in the middle-age group. But all these children were in the low economic group.

Obviously, the recorded prevalence of malnutrition depends on the concept, criteria, and means of recognizing it. In the recent past it has been judged by physical measurements or by presence of signs, including those of the acute severe type of deficiency disease. Neither method has revealed any considerable prevalence of malnutrition. It is very misleading to rely solely on them and to accept data only from them as evidence of malnutrition. Simple inspection is not sufficiently sensitive to detect very mild changes, whether acute or chronic. Most of the chronic changes, even when severe, have not been recognized as specific characteristics of deficiency diseases. These mild acute and mild or severe chronic conditions constitute the largest part of malnutrition.

As a means of appraising nutritional status, various new methods have been proposed for recognizing deficiency diseases. It is now plain that a method should detect and grade such a disease, whatever its state. The method should apply to both the acute and chronic forms, in all their stages and degrees. At once it should be stated

that the various new methods pertain to different aspects of a deficiency disease, yield dissimilar kinds of information, and are unequal in meeting the requisites.

For the appraisal of nutritional status, the biochemical determination of the concentration of a vitamin in the blood or urine, with or without a test dose, has very definite and narrow limitations beyond which it is misleading. In the evolution or recession of a deficiency disease, the blood and tissue changes are not synchronous. They are on different time schedules; they do not start simultaneously, nor do they proceed at the same rate. A shift in the blood value constitutes the first bodily change. The concentration of the vitamin in the blood changes much more rapidly than does the tissue process.

Values on the concentration of a vitamin in the blood reflect very sensitively the recent dietary habit (16) as well as other conditioning factors. They may change not only with season (17) but also within shorter periods; they may fluctuate. Hence, the blood values may temporarily be moderate or high without demonstrable improvement in an existing chronic tissue lesion (9). Indeed, there is much to indicate that sustained satisfactory blood levels resulting from conversion and adherence to a satisfactory diet are not accompanied by an appreciable recession in the tissue pathology.

Potent therapy will produce maximum blood levels and entirely restore bodily saturation in several weeks but will completely repair the slightest chronic tissue lesion only in months (9). Hence, the blood value may be high while the tissue pathology has yet shown little recession; the high blood level will be maintained over the many months while the tissue lesion is receding but is, of course, still abnormal.

In any of these events, the blood value would indicate a satisfactory nutritional status while the tissue would be pathological, a rather common occurrence. Manifestly, an assessment based on blood data alone would be erroneous.

It should be clear that there is no necessarily high correlation be-

tween data derived by different methods on the same deficiency disease. They provide information on different aspects and states of the disorder. Unfortunately, this fact has not been appreciated. Rather, it has been thought that various methods applied to the same deficiency disease should yield similar data. On this basis it has become the practice to test the validity of a method by comparing its results with blood values. This procedure is entirely unsound. When it is remembered that blood values shift rapidly and may fluctuate intermittently, while tissue changes very slowly, there should be no expectation of identical results.

The limitations of the blood methods for the evaluation of nutritional status cast no discredit. Used appropriately, they have their value. For following of dietary habits in the body, for secondary screening of persons without avitaminotic tissue changes, for specific metabolic studies, the blood technics are the methods of election.

The methods which embody gross and biomicroscopic examination of specific tissues for characteristic morphological changes—the eyes for avitaminosis A and ariboflavinosis, the gums for avitaminosis C, and the tongue for aniacinosis—meet most requirements for appraising nutritional status. Particularly, they permit both the acute and chronic forms in any stage and degree of tissue change to be detected. True, if the tissue is normal, it is possible that the blood values may be low. This situation, however, is the least frequent in the general population. Such a circumstance would be most frequently encountered in infants and preschool children. But tissue change is so prevalent over all age groups, and the biomicroscopic system as a primary screen is so sensitive in detecting its very early or mild form, that practically blood values as a secondary screen would add information in only a comparatively small number of instances.

Already the gross and biomicroscopic methods of examining tissue have yielded results indicating a high prevalence of malnutrition. Even in high economic groups, there are few people in abso-

lutely perfect nutrition. Yet these results are not surprising. Very few persons have consistently followed throughout life a diet satisfactory in all essentials, escaped the many other causes of malnutrition, or had complete recovery from any impairment of their nutrition. The older the person, the more opportunity he has had for some dietary lapse or adverse influence. Then too, the standard of perfection in the tissue is very exacting. And the biomicroscopic method is so sensitive that it is capable of detecting slight abnormalities. From all these considerations, the high prevalence of deficiency diseases is not unexpected.

Taken by and large, most of the malnutrition is chronic, with or without mild acute; some of it is mild, but much is rather severe. This condition too is understandable. Much malnutrition, with incomplete or no treatment, passes into the chronic form either as an arrested or slowly progressive process. The latter is not uncommon. Often faulty diets persist for long periods, even years.

This concept of the deficiency states has further applications. In all treatment of deficiency diseases, it shows the need to recognize the chronic state and to carry on therapy for a sufficiently long time. Otherwise, seemingly disappointing results may lead to erroneous and misleading conclusions.

Finally, it furnishes a plausible basis for the interpretation of any relation that may be found between nutrition and health and resistance to disease.

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