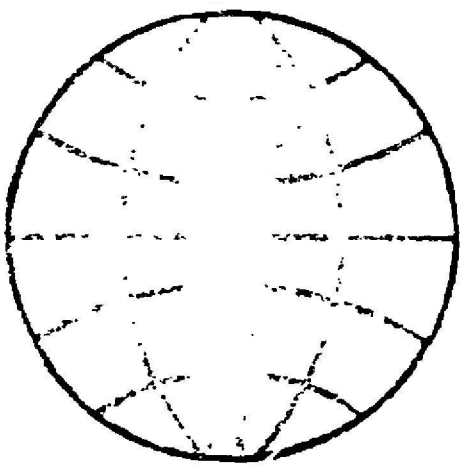
THE MEDICAL CLINICS OF NORTH AMERICA



CURRENT CONCEPTS IN CLINICAL NUTRITION

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Infectious Disease in the Malnourished

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Medicine has long recognized that a host deficiency in nutritional state enhances the risk of an acquired infection; and when infectious disease follows, both course and severity often are heightened. A less appreciated circumstance is that infection, in turn, commonly intensifies the existing nutritional state so prominent in its origin. The two processes interact with one another.

An impressive mass of evidence from animal experiments demonstrates a varied response to combinations of the two diseases. The usual consequence is an increased clinical reaction as judged by death, complications, and duration, an effect beyond the summed result expected from either disease acting alone. This is synergism; the infectious process is exaggerated and a moderate nutritional disorder, such as weight loss due to protein-calorie malnutrition, is precipitated into manifest kwashiorkor. In some severe specific deficiencies in experimental animals the observed result is antagonism, the dietary effect being on the infectious agent rather than on the host. The resulting pathologic process is then less severe than usual. This has never been demonstrated in man since naturally occurring deficiencies are not ordinarily of the type required, and since it is unethical to induce them experimentally.

Investigations of the recent past have evaluated the significance of these experimental interactions in their relation to clinical medicine. More importantly, they have permitted recognition of a set of principles governing the behavior of individual nutritional disorders and the more common infectious diseases, as they occur together.[9]

In most industrialized nations the clinical and public health possibilities of an interacting malnutrition and acute infection are underrated, for the principal reason that the nutritional state of the general community is at a high level and infections occur far less frequently

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than formerly. Regions are identifiable, however, where the incidence of both conditions rivals that of earlier times, even matching situations presently characterizing most developing countries. Patchy distributions, small numbers in relation to total population, and a restriction to persons of lower economic status require the epidemiologic measurements of time, place, and person for detection. There is now a resurging national concern that such areas are more common and more extensive than previously appreciated. Yet they must be searched for. They are not the all-pervading circumstance so distinctive in developing countries.

In countries of the western world, an accompanying and striking decline during the past two decades in the incidence of most communicable diseases, and in deaths from that cause, has resulted in minimal opportunity for combined action of the two disease entities. The pronounced nutritional deficiencies so often employed to demonstrate synergism or antagonism under laboratory conditions, furthermore, are not those ordinarily seen in clinical practice. What is too little recognized is that nutritional deficiency disease in less developed parts of the world is of another order—far more frequent and more severe. Infectious diseases prevail there as they did 50 years ago in presently more privileged regions. That the practical problem of an interacting nutrition and infection is so far distant makes it no less tangible; and importantly, it involves three-fourths of the world population.

PATTERNS OF INTERACTION

The practical gain to clinical medicine and the public health extends beyond a clearer demonstration of interaction between malnutrition and infectious disease. That was established by multiple historical events of associated famine and pestilence. The situation was clearly evident in the early history of presently industrialized countries where the two conditions presented with equal intensity for so many years. Death rates were beyond present comprehension.

General biologic laws govern these interactions. In experimental animals some infectious agents regularly result in synergism with some nutrient deficiencies; others more commonly evidence antagonism, if any effect is observed. Still other experimental combinations show variable results: sometimes synergism, occasionally antagonism, but invariably dependent on recognizable and specific ecologic circumstances.

The broad generalization is that free-living infectious agents acting extracellularly lead with most nutritional deficiencies to synergism, while those confined to an intracellular existence frequently result in antagonism.

Whatever the infectious agent, the ultimate determinant is whether obligate dependence for successful invasion is on the enzyme system and metabolites of host cells or on the dietary requirements of the infectious agent. From this it follows that synergism is almost always the expected result when invasion by bacteria, rickettsiae, and intestinal

helminths or protozoa combines with malnutrition. Viral agents in similar combination, and systemic helminthic and protozoal invaders result variously in synergism or antagonism.

The effect of individual nutrient deficiencies on intercurrent infection can also be predicted to a considerable degree. General inanition is regularly synergistic, although occasionally antagonistic when the infection is systemic by a virus, protozoan or helminth. With few exceptions, protein lack is synergistic and usually strongly so. Avitaminosis A is regularly synergistic, with important after-effects occurring in many parts of the world. Vitamin D deficiency, by contrast, seldom has a determinable effect on infections, although with a few the result is synergism. The vitamin B complex and some individual B vitamins behave variably, being sometimes synergistic and in other circumstances antagonistic. Vitamin C deficiency is usually synergistic although antagonism has been observed. Mineral deficiencies take either course, largely according to the kind of infectious disease, and the extent of the underlying nutrient deficit.

MECHANISMS OF INTERACTION

A concept of synergism between a nutritional and an infectious disease requires a mutual contribution by each element to the resultant enlarged effect. The evidence is thus from two viewpoints: first, the means by which malnutrition favors infection; and conversely, the mechanisms by which infection magnifies an existing malnutrition.

The following summaries are drawn from the monograph *Interactions of Nutrition and Infection*,[9] in which a variety of observations from laboratory, clinic, and field fully document the frequency with which severity and outcome of infection are worsened by malnutrition. Prevalence also is increased for such common conditions as acute enteritis, upper and lower respiratory tract infections, and a wide range of others. Furthermore, in developing countries the high infant and preschool morbidity attributed to infectious disease is not characteristic of well nourished children of those areas.

Effect of Malnutrition on Infection

The relative importance of various potentially protective mechanisms whereby nutritional deficiencies influence resistance to infectious disease under natural conditions is indeterminate. They include the following.

ANTIBODY FORMATION. Although other mechanisms may be equally important in defense against infection, the formation of specific antibodies for infectious agents or their toxins has received the most attention, perhaps because excellent techniques exist for detecting antibodies.

Severe deficiencies of protein, vitamin A, ascorbic acid, riboflavin, thiamine, pantothenic acid, biotin, and niacin-tryptophan are known to interfere with antibody production in experimental animals. A number of studies confirm that protein deficiency in man can limit the formation

of antibodies in response to an antigenic stimulus. Several reports show false-negative tuberculin reactions in malnourished patients with clinical tuberculosis. In human volunteers, antibody formation has been suppressed by inducing metabolic deficiencies of pantothenic acid or pyridoxine by feeding the corresponding antimetabolites, desoxypyridoxine and omega methyl pyridoxine. A similar effect has been observed in severe pellagra and with a moderately severe deficiency of several of the B vitamins.

PHAGOCYTIC ACTIVITY. The microphages, and the macrophages of the reticuloendothelial system, have an important part in protection against infectious diseases particularly those caused by bacteria. Nutritional deficiency can reduce both the number and the phagocytic capacity of these cells. Children with kwashiorkor have little or no leukocyte response to superimposed infections. Macrophage activity is decreased in the presence of deficiencies of vitamin A, ascorbic acid, thiamine, and riboflavin in experimental animals. Both animal studies and clinical observations of folic acid deficiency have shown production of phagocytes in mammalian bone marrow to be depressed to the extent of nullifying the effect of protective antibodies.

TISSUE INTEGRITY. Except as an aftermath of protective immunization, antibody formation takes place only after the infectious agent has entered the host. Its action then is to minimize possible pathological consequences of infection rather than to act as a preventive. The same is true of phagocytosis. The integrity of the skin, mucous membranes, and other epithelial tissues does serve a protective capacity through preventing entry of an infectious agent. The various pathological changes which occur in tissues depend on the type and severity of the nutritional deficiency. Mucus secretions may be reduced or absent, mucosal surfaces become easily permeable, and changes take place in intercellular substance; there may be epithelial metaplasia, edema in underlying tissues, and accumulation of cellular debris to form a favorable culture medium for the infectious agent. Deficiencies in vitamin A, ascorbic acid, niacin, and protein are especially likely to cause tissue changes that lower resistance.

WOUND HEALING AND COLLAGEN FORMATION. How long an infection will be disabling depends on how rapidly it can be localized and contained. Nutritional deficiencies affect not only tissue integrity but also wound healing, fibroblastic response to trauma, walling off of abscesses and collagen formation. In protein-deficient rats, the walls of induced sterile subcutaneous abcesses were much thinner than those of spontaneous or induced abscesses in well nourished animals. The fibroblastic response in deficient rats is markedly reduced, and as a result fatal septicemia frequently follows:

Protein deficiency, especially with an inadequate intake of methionine, interferes with conversion of procollagen to collagen and weakens the tensile strength of collagen fibers. Ascorbic acid must be adequate for synthesis of the amino acids from which collagen is formed, particularly hydroxyproline and hydrolysine, which are almost unique to collagen. The skin at the edges of wounds in scorbutic guinea pigs shows

almost no hydroxyproline. Restoration of ascorbic acid to the diet induces rapid production of hydroxyproline, and wound healing.

NONSPECIFIC RESISTANCE FACTORS. The importance of various nonspecific mechanisms of resistance is difficult to assess. The effect of nutritional deficiencies on most of them is not clearly understood. The so-called lysozymes, which help to destroy pathogenic microorganisms, are found in tears, sweat, saliva, and other body fluids. Their activity apparently is reduced by generalized malnutrition, particularly by vitamin A deficiency.

Properdin is a euglobulin present in the serum of all normal animals thus far tested; it is associated with natural resistance to many diseases of bacterial, viral, and even protozoal origin. The properdin system is vulnerable to nutritional deficiency in formation of the compound itself, as well as in the presence of an appropriate complement of magnesium. The only published evidence, however, is a report of marked reduction of properdin in the serum of pantothenic acid-deficient rats.

Interferon is a natural product of animal cells that supplements other mechanisms of resistance to viral and some other infections. It appears to act by uncoupling oxidation from phosphorylation, so that the production of adenosine triphosphate is inadequate for replication of the infectious agent. Since interferon is a protein molecule, it seems likely that its formation is depressed in deficiency states in which protein synthesis is impaired.

Most of the destruction of bacterial toxins or resistance to them in animal hosts occurs as the result of combination with specific antibodies. There is some evidence of other mechanisms also. For example, rats suffering from deficiencies of B vitamins or vitamin A are more susceptible than controls to diphtheria toxin, despite similar antitoxin titers and rates of disappearance of injected toxin in the two groups. There are no clinical observations in man.

Changes in the intestinal microbiota (particularly the bacterial flora) induced by diet can influence susceptibility to some intestinal pathogens. In kwashiorkor, bacteria of the lower intestinal tract tend to appear at higher levels. In milder degrees of protein malnutrition, it seems likely that intestinal organisms not normally pathogenic to the well nourished host may cause diarrheal disease. The frequency and severity of such episodes are decreased by dietary supplements. Changes in gastrointestinal mobility secondary to malnutrition may also affect the severity of protozoal and helminthic infections.

Endocrine factors are intimately involved in a number of the mechanisms of resistance already mentioned. Examples include the loss of resistance to infection in adrenalectomized animals and patients with Addison's disease, and the serious problem of secondary infections in poorly controlled diabetic patients. Prolonged adrenocorticotrophic hormone (ACTH) or cortisone therapy, however, increases the spread of many infections, presumably because these hormones inhibit local inflammatory reactions at the site of bacterial proliferation. These observations bear on the question of how malnutrition influences resistance to infection, since protein deficiency, caloric deprivation, and a number of other nutritional deficiencies influence endocrine balance.

Effect of Infection on Nutritional Status

One of the earliest and most constant consequences of infection is loss of appetite and a decreased tolerance for ingested food. Another is the almost universal tendency to change the diet of patients to one more liquid and higher in carbohydrates, at the expense of foods that are good sources of protein and other essential nutrients. The practice is especially common in the feeding of young children in less developed areas. Often when a child has diarrheal disease or other acute infection, milk and solid foods are eliminated in favor of starchy gruels and cooking water from cereal grains or plant leaves. Therapeutic agents such as purgatives may reduce intestinal absorption, or in the case of sulfonamides and antibiotics, interfere with intestinal synthesis of some nutrients. The direct influence of fever in increasing both basal metabolism and loss of nutrients in sweat must also be taken into account.

PROTEIN. Acute infections cause a response qualitatively the same as that observed in states of pain, anxiety, fear, and other psychological stress. Mediated by cortisone and insulin, the stress reaction mobilizes amino acids from skeletal muscle and other tissues from which they can be spared, for gluconeogenesis in the liver. This necessarily depletes body protein because the amino acids thus mobilized are deaminated to provide the carbons of glucose, and the nitrogen is excreted in the urine largely as urea.

Nitrogen losses during severe infectious diseases of bacterial origin—typhoid fever, tuberculosis, and many others—have long been recognized and can be equivalent during the acute phase of the illness to the nitrogen of 2 to 3 kg. of muscle. Rickettsial and viral diseases have the same capacity. Respiratory infections, tonsillitis, otitis media, staphylococcal abscesses, and even immunization against smallpox and yellow fever induce the stress reaction with consequent increased urinary nitrogen loss.

A stress of short duration may be balanced by an increase in nitrogen retention during the same or succeeding 24 hours. However, the catabolic period associated with an infectious disease episode is likely to last for several days, and the anabolic period of increased nitrogen retention is generally twice as long. After the acute stress is over, dietary amino acids are returned to the depleted tissues, and hence protein intakes above maintenance levels are required. In individuals already depleted by low levels of protein intake, the urinary loss of nitrogen during stress is less than that observed in well nourished persons. Nevertheless, increases in urinary nitrogen loss during minor infections have been found even in experimental subjects receiving a nitrogen-free diet.

With so many factors adversely affecting protein nutritional status during infectious disease, it is not surprising that in underdeveloped countries the protein deficiency disease, kwashiorkor, is commonly precipitated by acute diarrheal disease, measles, and other childhood infections in persons whose nutritional state is already precarious. Similarly, infections are responsible for much of the protein deficiency seen in adults, especially attacks of chronic nature.

VITAMINS. Blood levels of vitamin A are reduced in acute infections, sufficiently that xerophthalmia and keratomalacia frequently follow in children receiving diets deficient in that nutrient. Giardiasis is known to interfere with vitamin A absorption, and any intestinal infection producing malabsorption will have the same effect.

Pneumonia and malaria have been recognized as significant factors in the occurrence of beri beri in civilian populations; dysentery was a common precipitant of that disease among Japanese prisoners of the Second World War.

Clinical manifestations of thiamine, folic acid, vitamin B_{12} and ascorbic acid deficiency have all been related to a preceding infection of a vulnerable host.

MINERALS. Hookworm infection, if sufficiently severe, is well recognized as responsible for enough loss of blood to induce microcytic-hypochromic anemia even when dietary intakes of iron appear adequate.

Increased losses of calcium and phosphorus have been reported in tuberculosis of both man and guinea pigs. Losses of sodium, chloride, potassium, and phosphorus are of particular moment in diarrheal diseases of infectious origin, and an important cause of death.

LIPIDS. A marked increase in concentrations of total serum lipids has been observed in patients with gram-negative bacillary infections. Infectious or serum hepatitis causes heightened levels of serum triglycerides and cholesterol. Absorption of fat is decreased in infections that provoke diarrhea. Increases in liver fat and some degree of steatorrhea have been reported in patients with influenza and pneumonia, and are probably associated with other infections.

ANEMIA OF INFECTION. Chronic infections of almost any type are likely to produce the so-called anemia of infection by shortening the life span of erythrocytes and interfering with red cell production in bone marrow.

WEANLING DIARRHEA

Experimental studies are useful but there is no substitute for clinical examples. Two of the commonest infectious diseases of man, weanling diarrhea and measles, illustrate the way in which nutritional deficiency and infection combine synergistically. Acute intestinal infection of infants and young children, with diarrhea the main presenting sign, is a minor occurrence in highly developed regions. This was not always so. Acute diarrheal disease has lost the significance it had no longer than 50 years ago, a time when frequency and mortality matched that now present in the remaining bulk of the world today. Many factors account for the change, including a more favorable economy, improved environmental sanitation, as well as gains in human nutrition, the control of communicable diseases, and the evolution of modern pediatrics.

Acute diarrheal disease is an outstanding feature of life in less developed regions—from the arctic to the tropics. Repeated attacks occur during and immediately after weaning. Malnutrition is especially

common at that time. The two conditions are so interrelated that the illness is appropriately termed weanling diarrhea.[2] Not only is the condition worldwide, it is unsurpassed as an illustration of synergistic interaction between malnutrition and infection: costly in the disability it causes, in the deaths that follow, and in immediate and long-term after-effects.

Infants in developing regions are almost universally breast-fed, the necessity being so great that "nurse or die" is a common axiom. They do well in growth and development during the first 3 or 4 months; gain in weight keeps pace with that of well nourished children in more favored parts of the world. The nutritional demands of rapid weight increment in those early months soon surpass the food supply provided by breast milk.

The infant's need for more food becomes serious usually by the fifth or sixth month. The ordinary food supplement does not provide nutritional requirements; by custom or economic necessity it consists of gruels or starchy foods that lack the required animal protein. Weight gain is depressed, depletion sometimes reaching extreme limits, with the result that departure from the weight curve characteristic of well nourished infants becomes clearly evident in the latter half of the infant year, more forcefully so in the second year, and often continuing through the third year as breast feeding and supplementation remain insufficient. With completed weaning, the ordinary family diet with some restrictions takes its place.

The frequency of diarrheal disease runs a parallel course. Attack rates are at low levels during the wholly breast-fed stage. Episodes become more frequent as supplementation follows; a greater incidence occurs with milk alone added; diarrhea is more frequent when solid foods are included; and the greatest frequency is in late weaning, with almost equivalent rates in the immediate three months thereafter.[4]

At this peak, rates average four attacks per year, with sometimes as many as eight or ten. The disease contrasts with the milder indisposition of the well nourished child of the western world. Onset is acute and rapidly progressive, with multiple daily stools varying from three to as many as 20. A variable proportion of patients, commonly a third, have blood or mucus in the stools, and frequently pus. Fever may be absent, but a low grade temperature rise is usual, along with malaise, toxemia, intestinal cramps, and tenesmus. The usual clinical course lasts four to five days. In malnourished children, a low grade indisposition often continues for a month or more, sometimes as long as 3 months, with irregularly recurring loose stools, short of true diarrhea, and a progressively depleted nutritional state. In some 15 per cent of cases, this takes an exaggerated form, with recurrent episodes of acute diarrhea interspersed with periods of freedom, and recognized as chronic recurrent diarrheal disease. Dehydration and electrolyte imbalance are common and difficult to control.

The above usually coincides with an increasing degree of malnutrition. Weight gain turns upward after weaning, so that in the years immediately thereafter it parallels that of well nourished children,

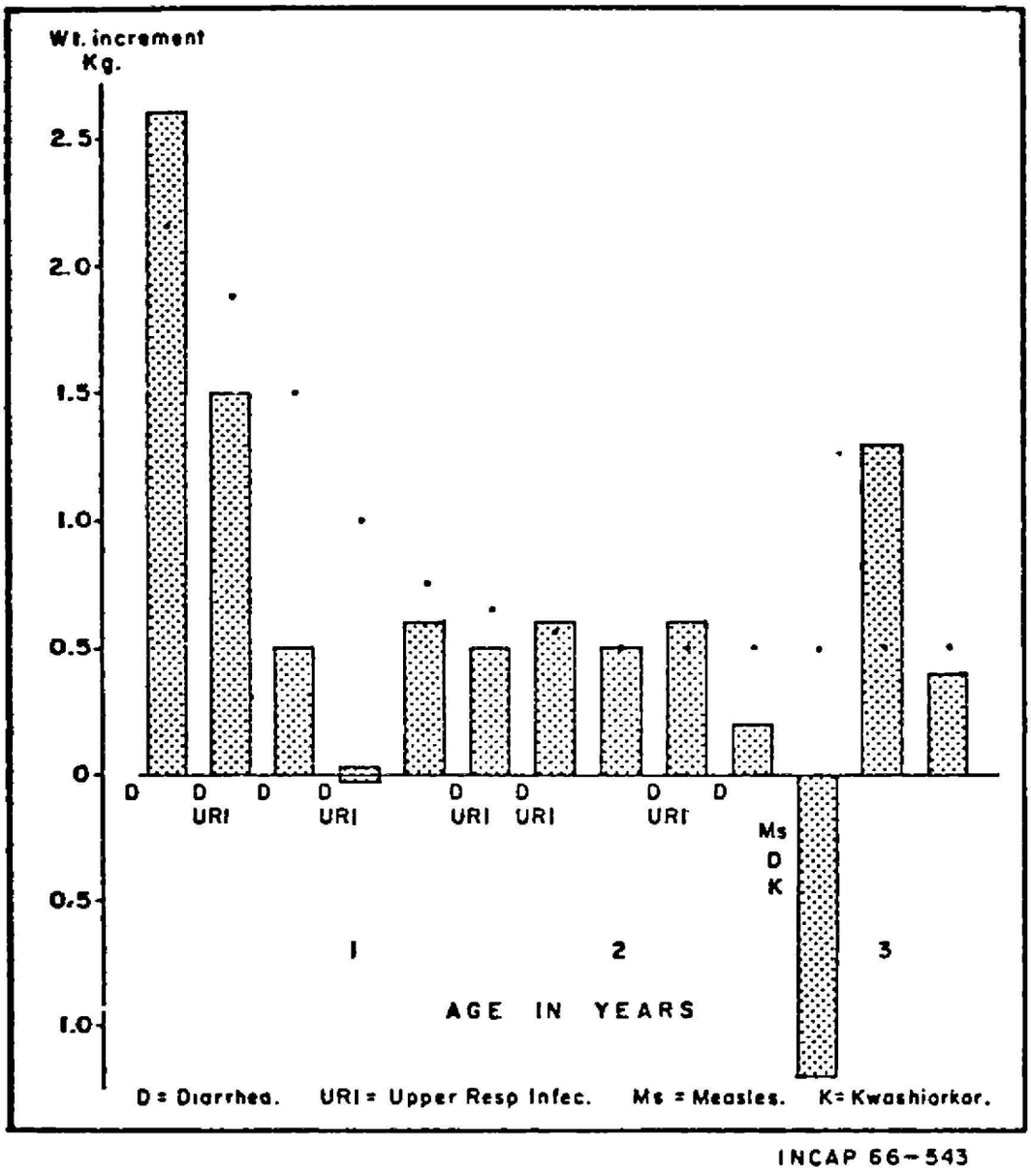

Figure 1. Quarterly increments of body weight in kilograms and preceding illnesses of a Guatemalan boy who at age 33 months contracted measles, a complicating diarrhea, and subsequent kwashiorkor. Dotted line denotes mean weight increments of well nourished children.[6]

A more virulent strain of measles virus is not the answer, because children of middle and upper class families of the same region have a wholly ordinary disease. The high fatality occurred at those ages when malnutrition prevails, during the weaning period. The following case history is from a Guatemalan village epidemic.[6]

A boy aged two years and nine months, the third child in an Indian family, had breast milk as the sole food during the first three months. Weaning started then with the addition of food supplements from the family table. Breast feeding ended in the 22nd month, the child subsisting thereafter on selected foods served by the family, predominantly corn (tortillas), vegetables and sometimes the broth of a meat and vegetable soup.

During the first year the child had the usual medical history of infants born in that environment: four attacks of acute diarrheal disease, totaling 37 days, and 23 days of upper respiratory disease in two episodes; in all, he had 60 days of illness, or the equivalent of 17 per cent of his first year, distributed by quarterly periods as shown in Figure 1.

The first and fourth quarters of the second year were free of illness, but 26 days of diarrheal disease and 25 days of respiratory infection were accumulated

during the second and third quarters, again 15 per cent of the second year, in four separate illnesses. The third year had provided a similar experience when measles developed at 33 months. The disease was associated with a severe diarrhea of 9 days' duration first evident in the prodomal period preceding the rash of measles. Kwashiorkor developed three weeks later.

The effect of this succession of illnesses on growth and development and the ultimate nutritional collapse precipitated by measles is illustrated by the quarterly variations in weight. Weight increments are taken as more expressive of weight change at a particular time than actual accrued weight.

The rate of growth in the first three months was better than the standard. Subsequently, in the face of ensuing infections, rates of growth decreased progressively until at the end of the first year there was no demonstrable increment. With no illness during the first 3 months of the second year, a normal growth pattern resumed and despite minor illnesses was maintained until the second quarter of the third year. A 12-day attack of diarrheal disease at that time decreased the weight increment by half. Shortly thereafter, the patient had measles and a second episode of diarrhea.[8] The result was an inversion of the growth pattern, a marked loss of weight and ultimately kwashiorkor. With hospitalization and a high protein diet, the weight rebound was gratifying.

Measles and a complicating diarrhea were clearly the precipitating cause of kwashiorkor. The real origin was more remote, primarily in the long series of acute infectious illnesses, to give a moderate protein-calorie malnutrition. Measles decided the issue.

Measles is no isolated instance among childhood infections. Whooping cough and chicken pox have an almost equal effect. That train of events is associated with all of the common communicable diseases of early childhood.

NUTRITIONAL ECOLOGY

That nutritional deficiency diseases tend to be chronic, and that most infectious diseases are acute, greatly simplifies questions of synergism and antagonism when these two conditions occur together. The nutritional disorder almost invariably precedes the infection. When two acute processes are so associated, for example diphtheria and scarlet fever, the order in which they appear influences the subsequent result importantly.

The regularity of an infection superimposed on a nutritional disorder leaves most of the significant variables to be found within the environment, to a lesser extent in the affected host. Nutritional ecology thus becomes the dominant consideration in their interaction. The time that association occurs and how long it lasts are key determinants of the end result.

Timing

Nutrient demands are greatest and malnutrition thus more likely during periods of rapid growth. The risk of infection is continuous, and

greater in less developed countries than elsewhere. The opportunity for synergistic interaction of nutrition and infection is therefore pronounced at recognized times of life.

Growth is greater in the first 3 months of life than in the remainder of the first year; greater in the second year than in other years of the preschool period, as the child takes on an independent existence with increased risk of disease and injury. It is greater in preschool years than during school ages. The curve extends back into fetal life, when rates of growth are highest.

By animal experiment and by observation of children dying accidentally, Winick[12] has advanced a concept that growth is in three stages. The early period is mainly through cell proliferation, but with proportional increase in organ weight and protein content. There is a second phase in which cell proliferation continues but at a slower rate than cell enlargement, usually from late fetal life and variously for different organs and tissues after birth. A third phase follows, wholly postnatal, in which growth is due entirely to increase in cell size. This separation of growth phases has important connotations. Inhibited cell proliferation appears irreversible, that of cell size remediable by proper feeding.

That infection can occur in fetal life when cell proliferation is most active is well demonstrated by maternal rubella during early pregnancy. That it occurs more generally is supported by recent studies of IgM in fetal serum. The significance of maternal infections during pregnancy and of the infant in the early years of life in the face of a coexistent malnutrition is manifest.[5] Weanling diarrhea and the other common infections of early childhood are thus of greater significance than when they occur later in life.

Timing of an interacting nutrition and infection again comes into play as nutritional state deteriorates under physiological stress, notably at puberty, in pregnancy, and during lactation. The increasing frequency of teenage pregnancies in the United States, and their common occurrence in populations of less developed regions, adds significance to this part of the problem. The prospective mother is called upon to sustain her own genetic potential for growth as well as meet the demands of a developing pregnancy. The difficulty is intimately connected with the fetal malnutrition already mentioned.

Risks of a synergistic interaction of nutrition and infection are further related to a variety of social influences, largely dependent on custom, habit and culture. They include elderly persons living alone, food faddists, persons on imbalanced reducing diets, teenagers with aberrant food habits, patients with chronic degenerative and metabolic diseases, and residents of institutions.

Duration of the Synergism

Duration of the antecedent nutritional deficiency, the length of time it is associated with an infection, and the extent of after-effects all enter into determining the significance of the interaction.[11] The closely spaced postnatal episodes illustrated in Figures 1 and 2 constitute an essentially chronic disease process, because of the brief interval between attacks

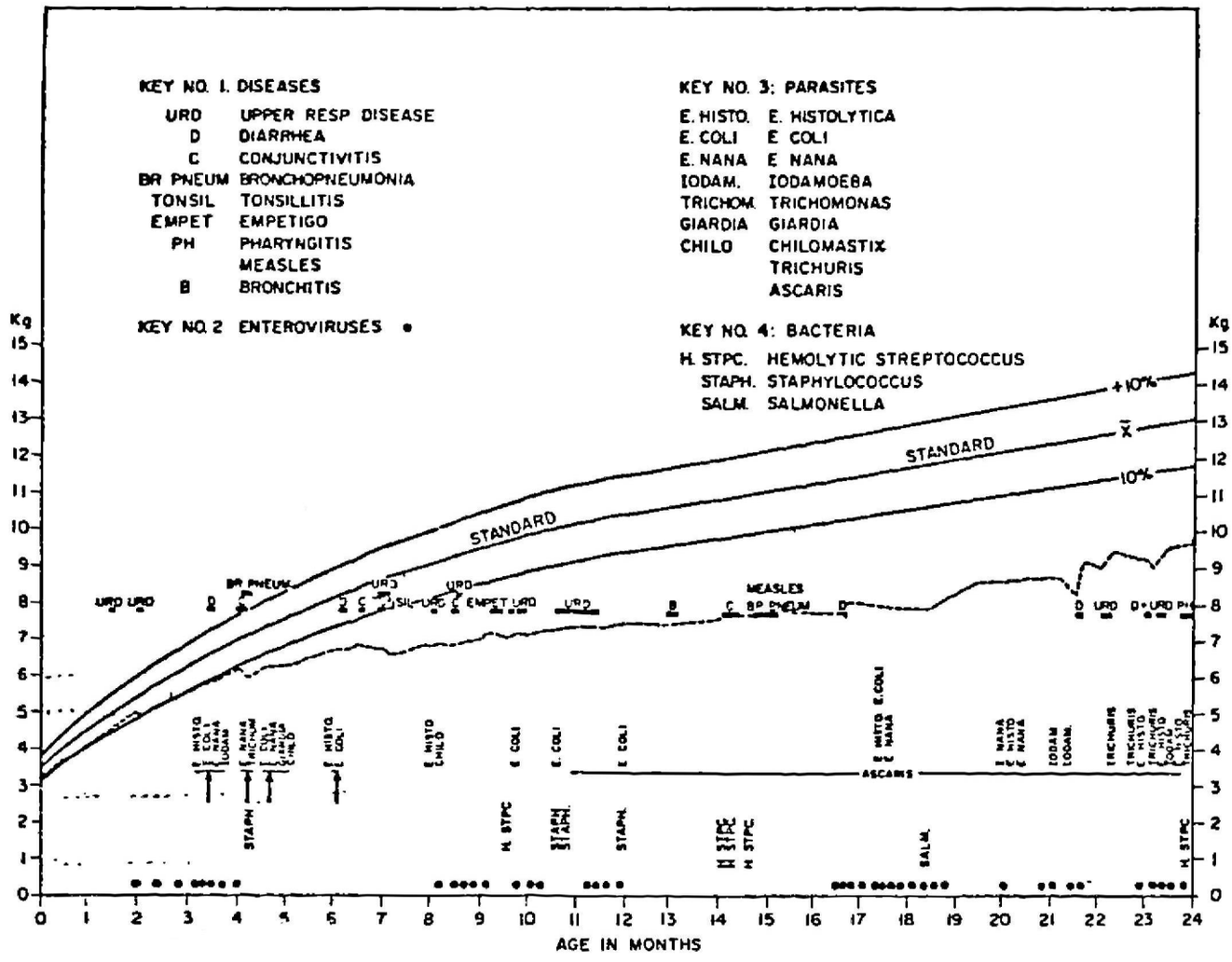

Figure 2. Recurring illnesses, invasion by bacteria, parasites, and enteroviruses, and ensuing malnutrition in a 2 year old Mayan village child, Guatemala. Adapted from Mata et al.[4]

and their great number.[7] The chronic recurrent diarrheal disease earlier mentioned is indeed such a continuing process. When the burden of infection is heavy during the critical phase of growth by cell proliferation, the effects are particularly serious.

Place

In less developed regions, it is reasonable to devote attention to a general population on a place basis, because malnutrition is so generally prevalent and infectious disease so universally existent. Assessment of the problem involves practically all children, and prevention and control are universally applicable.

To follow the same approach in developed countries is wasteful and minimally productive. To be sure, there are areas in which an associated malnutrition and infection is more significant and the need for control greater than in others. More benefit is promised by attention less to places than to kinds of people. In good and poor districts there are fractions of the population more affected than others. The groups most involved are those listed earlier. The indicated approach is more social than geographical, and should deal with the vulnerable segments of the population.

SIGNIFICANCE

In developing countries the synergism of malnutrition and infection is responsible for most of the excess mortality seen in young children. It contributes to greater mortality of older persons. It adds importantly to the morbidity that interferes with the schooling of children and the productivity of adults. Its occurrence in the young can contribute to subsequent impaired learning and behavior.

For these reasons a synergism of nutrition and infection has public health significance in industrialized countries in those pockets of poverty and underprivilege where poor nutrition and high grade environmental exposure to infection persist.

For the clinician, the possibility of synergism is always present wherever and whenever the two conditions coexist. The patient whose nutritional state is impaired by chronic disease, unwise dieting, food fads or any other cause has a greater probability of acquiring an infection. Clinical management of either nutritional deficiency or infectious disease thus necessarily takes into account the possibility of both and their potential interaction.

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