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INTERACTIONS OF NUTRITION AND INFECTION

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Editor's Note: *Perhaps the best definition of a classic in science is a publication that redefines or initiates a field of scientific inquiry. Rarely is that contribution made by a review article, but such was the case with the article excerpted below, which was expanded into a World Health Organization monograph (WHO Monograph Series no. 57, Geneva, 1968). The many hundreds of articles reviewed and cited in these seminal publications by Scrimshaw, Taylor, and Gordon are exceeded only by the many more that they have stimulated.*

The idea that nutritional deficiencies and infections have something to do with each other follows from the historical association between famine and pestilence. Numerous field and clinical observations and many experimental studies support this view. The extensive literature also includes many conflicting and inconclusive observations, to such extent as to obscure good evidence that many of the important infections of human populations are rendered more serious in their consequences by the presence of malnutrition; that a few infections are indeed less severe when associated with nutritional deficiency; and that many infections themselves precipitate nutritional disturbances.

Definite patterns of interaction between nutrition and infection can be identified. This information is useful in planning health programs for underprivileged areas; it also has value as a stimulus and aid to research. . . .

Soon after World War I the separate currents of investigation in infectious disease and in nutrition began to meet, a circumstance largely accounting for the time distribution reports of their interaction. Microbiological research continued to identify new infectious agents, but with growing appreciation that constitutional factors determining host resistance had to be studied along with antibodies in measuring the reaction of the host to invasion. Concurrently, increasing numbers of specific nutrients were recognized and the scientific basis of nutrition was established by biochemical and field studies. These nutrients proved so beneficial that it was natural to associate them with the long standing notion that nutrition and infection are interrelated, and to imply that their presence was protective. The oversimplification implicit in such terms as the "anti-infective vitamin" for vitamin A, diligently fostered by vitamin salesmen, carried medical practice far beyond scientific evidence.

During and after the second World War excessive claims of the value of vitamins in preventing and treating infections, abuses in vitamin administration, and the lack of result

when these elements were added to an already adequate diet led to a sharp reaction against vitamins and against nutrition in general, as factors in resistance to infection. Moreover, a number of experimental nutritional deficiencies were found to retard the development of viral and protozoal infections through adverse effect on the metabolism of the infectious agent. . . .

Patterns of Interaction

An imposing number of publications deal with the association of nutritional deficiency and infection in the human or animal host. Each study has been classed arbitrarily as evidencing synergism, antagonism or no demonstrable effect. . . .

Bacterial infections. Interactions between dietary deficiencies and bacterial infections are regularly, indeed almost uniformly synergistic. . . .

Tuberculosis illustrates better than any other disease the dominant synergistic effect of associated bacterial infection and dietary deficiency. The general increase in tuberculosis during wartime is difficult to ascribe to any single nutritional factor. Faber reported that mortality from tuberculosis in Denmark declined sharply during the final years of World War I after reaching a maximum in 1917, while rates in other European countries continued to rise until the war ended. Although general living conditions deteriorated in Denmark, nutrition improved because export of meat and dairy products ceased with blockade of ports by German submarines. Corroboration comes from prisoner-of-war camps in Germany during World War II. Prevalence of tuberculosis among Russian prisoners was 19%, among the British 1.2%, with marked differences in diet a distinguishing feature. That deficiency of vitamin A and C may lower resistance to tuberculosis is suggested by field studies by Downes in New York and Getz *et al.* in Philadelphia. . . .

Viral infections. Antagonism is the common and well defined reaction in virus infections associated with nutritional disorders. . . .

Most instances of antagonism to viral infections are with members of the vitamin B group. The action of thiamine deficiency in increasing resistance of mice to the viruses of poliomyelitis and western equine encephalitis, and of avian encephalomyelitis in chicks seems well established. Lichstein *et al.* found that acute folic acid deficiency had no effect on poliomyelitis infection in monkeys but that chronic deficiency resulted in high grade resistance. On the other hand increased resistance to pneumonia virus of mice has been demonstrated with acute pyridoxine deficiency which changed to synergistic reduction of resistance in chronic deficiency of more than 8 days.

Viruses show considerable specificity in their interactions with vitamin deficiencies. Riboflavin deficiency was antagonistic to poliomyelitis infection in mice but had no effect on Theiler virus, while pantothenic acid deficiency was antagonistic to Theilen virus and had no effect on poliomyelitis. The evidence is unconvincing that vitamin C has any therapeutic effect on viral infections despite frequent firmly held clinical opinion. . . .

Rickettsiae. All studies of the interaction of malnutrition with rickettsial infections showed synergism. . . .

Protozoa. Synergism and antagonism are observed with almost equal frequency in protozoan infections. . . . Intestinal protozoa, especially amebae, are almost uniformly synergistic with deficiencies, while protozoa of the blood, especially malaria parasites, are more frequently antagonistic. . . .

Influence of Infection on Nutritional Status

Discussion thus far has been confined to the influence of nutrition on the course of infection. Conversely, most infections have a deleterious effect on nutritional status, a fact insufficiently recognized. . . .

Infection and protein metabolism. Kwashiorkor is a major factor in the high mortality among preschool children characteristic of at least 50 technically underdeveloped countries. The symptoms are commonly precipitated by an acute infection. Either diarrhea or measles is most often responsible, but any infection may be involved. Seasonal increase in hospital admissions and deaths attributable to diarrhea often precedes a similar rise in kwashiorkor by 4 to 8 weeks. Kwashiorkor can originate in dietary deficiency alone, but most cases are the result of synergism between infection and protein malnutrition.

In many cultures solid foods, especially those of animal origin, are traditionally withdrawn from children with intestinal and other infections; thin cereal or starch gruels become the diet. Furthermore, a child with infectious diarrhea is likely to be given strong purgatives for worms, mistakenly blamed for diarrhea. These practices hasten the appearance of frank protein deficiency.

Infections have long been known to exert a strongly unfavorable effect on nitrogen balance. In 1910 MacCallum cited a German case in which the nitrogen equivalent of 2.5 kg of muscle was lost in 8 days of fever. Increased urinary nitrogen excretion has been demonstrated in malaria, pneumonia and streptococcal infections, erysipelas, pyelonephritis and paratyphoid, typhoid, tuberculosis, and meningitis. Loss of urinary nitrogen is partly from greater energy requirements imposed by higher body temperature, but mainly from toxic destruction of protein. Nitrogen loss may continue long after fever has subsided or may begin during the prodromal period before fever and clinical signs appear. Similar nitrogen loss occurs in dogs with sterile abscesses and minimal febrile reaction.

Chronic infections also have an adverse influence on protein metabolism; hypoproteinemia may develop despite normal protein intakes and dietary protein supplements are less effective.

Nitrogen loss in infections has particular significance in young children because of high requirements for protein per kilogram of body weight. Negative nitrogen balance in infectious diarrhea may occur despite intake of 2 or more grams of protein per kilogram per day. Close described a child with kwashiorkor whose serum albumin increased in 7 weeks from 1.05 to 3.58 gm. per 100 ml.; the patient then contracted typhoid fever and the level fell promptly to 1.59 gm.

Decreased absorption of nutrients from the gastrointestinal tract probably plays a minor role even in infectious disorders. In scarlet fever control of pancreatic enzyme was reduced, presumably a common occurrence in other infections. Nevertheless where fecal nitrogen has been measured, the increase is small. . . .

Infection and vitamin deficiencies. Infection may precipitate frank clinical signs in individuals with subclinical vitamin deficiencies. It has long been known that infections can cause florid scurvy in persons on a diet low in vitamin C. Either experimental trypanosomiasis or tuberculosis may hasten the appearance of scurvy in guinea pigs.

Diarrheal and other infections may decrease serum vitamin A levels and more importantly precipitate xerophthalmia, keratomalacia, and even blindness. Giardiasis sometimes interferes with vitamin A absorption in children. In Japanese prison camps beriberi developed in more than half of persons with dysentery. There can be no doubt that infections contribute to the production of frank vitamin deficiencies in poorly nourished populations .

Infection, growth and development. Children recovering from kwashiorkor fail to gain weight when intercurrent infection is present and may lose weight despite high intake of calories and protein; once the infection ends the weight curve resumes an upward trend. Children on a low protein diet had pronounced and protracted depression of growth after respiratory infections; well-nourished children had only transient weight loss. Conversely, an effective control program for malaria and filariasis resulted in a spurt in growth by West African village children. Rates of growth and maturation are relatively sensitive indicators of adverse metabolic influence from infection. . . .

A Concluding Thought

A basic biologic fact has inadequate recognition. The interaction between nutrition and infection is dynamic, frequently characterized by synergism and less commonly by antagonism. The mistaken impression that this interrelation is of secondary importance does little harm in countries where malnutrition is rare. Where both malnutrition and infection are serious, as they are in most tropical and technically underdeveloped countries, success in control of either condition commonly depends on the other. Problems of nutrition and infectious disease are interdependent in laboratory experiments, in clinical management of patients and in public health programs.

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