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INTERACTIONS OF NUTRITION AND INFECTION

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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.

The bibliography of this review is necessarily and desirably selective. Publications with no direct reference to interaction of nutrition and infection are omitted except where the data bear on some essential feature of one or the other. On some aspects of the problem the number of publications is so great that only representative papers or review articles are cited. Many contributions in the older literature have been disregarded as failing to meet modern scientific criteria; few areas of investigation are more replete with unsupported statements of opinion, impression and speculation.

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 of 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 oversimplication 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. In this context, the review of Aycock and Lutman[17] rejected vitamin prophylaxis of infection as a general epidemiological principle.

The reports of conferences in 1949[65], and in 1955[230] seemed to indicate that the relationship of each nutrient to each infectious agent in each host would need to be worked out individually, an approach supported by the recent reviews of Geiman[114], Smith[307] and others[55,295c]. However, even in 1949, Howie[149] recognized a greater uniformity among results of different workers than a casual familiarity with the literature would suggest. McClung[207] stressed the frequency with which nutritional deficiency lowers resistance to bacterial infections in experimental animals, and Cannon[50e] insisted that at least minimal dietary protein is necessary for immunological defense against infection. Schneider[295a, 295e] helped maintain perspective in stating that his negative results with identified virulent or avirulent strains of an infectious agent, tested in genetically homogenous mice having a specific nutritional deficiency, were of less practical significance than his positive results with strains of ordinary virulence in randomly bred mouse populations.

Two useful reviews summarize the older literature. Clausen[67a] suggested that although diet does not as a rule influence frequency of infections, severity may be greatly enhanced by an inadequate diet, a generalization still valid. In reviewing over 300 reports concerned only with the effects of vitamins, Robertson[271] stressed the frequency with which experimental deficiencies of vitamins A and C lowered resistance to bacterial infection.

Terms and Interpretations. In the interests of clarity we have spoken only of an increase or decrease in resistance to infection, avoiding the term susceptibility. These are reciprocal functions; as one increases the other decreases. Schneider[295f] distinguished "susceptibility factors" which decrease the extent or effect of infections when withheld, from "resistance factors" which lead to their increase when not supplied. We find it more convenient to express this difference by the term

"antagonism" for that situation where a nutritional deficiency results in decreased frequency or severity of an infection, and to use "synergism" where deficiency results in an increase. These terms imply an interaction of host and infectious agent in determining the outcome of infection[307,329]; in general, synergism is the usual result when the dominant action of the nutritional deficiency is on the host, and antagonism when the main impact is on the infectious agent.

A difference also is to be recognized between two broad forms of malnutrition. A reduction in intake of all essential nutrients leads to a state of undernutrition or inanition called marasmus in children. The other situation is that of a relative or absolute deficiency of one or more specific nutrients. The distinction is important because the former may not be associated with detectable physiological or biochemical changes, while signs of specific nutritional deficiencies develop as a result of disproportion among nutrients. The many biochemical changes in kwashiorkor and their absence in infantile marasmus[29,153], or the development of beriberi only when the intake of calories is relatively greater than of thiamine, are examples.

In some experiments the low palatability of the diet or complications of induced specific deficiences such as anorexia, vomiting or diarrhea have led to material differences in food intake between control and experimental animals. Interpretation is then hazardous, since positive results may be due to food restriction alone. Such experiments do not measure the specific deficiency intended.

Further confusion results from failure to recognize that nutrition influences infection in at least four ways, and that negative evidence about one mechanism does not apply to all. Nutritional deficiencies conceivably determine the progress of infection either through action on the host to facilitate initial invasion of the infectious agent; through an effect on the agent once established in tissues; through favoring secondary infection, of especial importance under field conditions; or by retarding convalescence after infection.

Many of the better controlled experimental studies have measured resistance almost exclusively by ability of the host to produce antibodies. Antibody response to experimental or natural infection is not synonymous with resistance, a term defined in the American Public Health Association Handbook, Control of Communicable Diseases in Man as "the sum total of body mechanisms which interpose barriers to the progress of invasion of infectious agents"; this includes both specific antibodies and nonspecific (autarcetic) mechanisms.

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. This information, along with the particular host, the infectious agent concerned and the nature of the nutritional deficiency, is presented in a series of tables arranged according to major divisions of infectious agents.

From the assembled data, a number of patterns of behavior become evident; they are identified and briefly described. The responsible mechanisms are the major concern in subsequent discussion, along with practical implications for prevention and control.

Bacterial Infections. Interactions between dietary deficiencies and bacterial infections are regularly, indeed almost uniformly synergistic, Table 1.

TABLE 1.—EFFECT OF NUTRITIONAL DEFICIENCIES ON BACTERIAL INFECTIONS

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Guinea pig	Multiple (green food)	Pneumonia	Synergistic	Smith, 1913[313]
Human	General	Tuberculosis	Synergistic	Faber, 1938[95] Leitch, 1945[183] Leyton, 1946[184]
Mouse	Acute starvation 75% undernutrition	Tuberculosis	Synergistic No effect	Dubos 1947, 1948[87a,b]
Rat	50% caloric undernutrition Vitamin A	Tuberculosis	No effect	Sriramachari and Gopalan, 1958[317]
Mouse	Multiple	Salmonella and 4 other bacteria	Synergistic	Webster, 1930[356]
Mouse	Multiple (? Protein)	Salmonella	Synergistic	Watson, Wilson and Topley, 1938[353]
Pigeon	Starvation (4 days)	Anthrax	Synergistic	Corda, 1923[73]
Mouse	Fasting	*Shigella flexneri III*	Synergistic	McGuire *et al.* 1958[214]
Human	Multiple	Respiratory infections Tuberculosis	Synergistic	Orr and Gilkes, 1931[240]
Rat	Vegetarian diet	cholera	Synergistic	Chen and Li, 1930[58]
Rat	Vegetarian diet	Pneumococci	No effect	Chen and Li, 1930[58]
Mouse	Multiple diet	Tuberculosis	Synergistic	Dubos and Pierce, 1947, 1948[88a,b]
Human	Vitamins A and C	Tuberculosis	Synergistic	Getz *et al.*, 1951[117]
Monkey	Vitamins A,C,B and Protein	Bacillary Dysentery	Synergistic	Rao, 1942[259]
Guinea pig	Multiple (green foods)	*Pasturella pseudotuberculosis*	Synergistic	Zachorowski, 1952[374]
Mouse and Rat	Unknown factor in wheat	Pneumococci	Antagonistic	Hitchings and Falco, 1946;[145a,b] Dworetsky, 1949[92]
Mouse	Unknown factor in wheat	Salmonella	Synergistic	Schneider and Webster, 1945[296] Schneider, 1949, 1951[295b,295e]
Rat	Vitamin A	Spontaneous infections (Pneumonia, mastoiditis, sinusitis, ophthalmia, nephritis, pancarditis, cystitis, enteritis, etc.)	Synergistic	McCollum, 1917[209] Drummond, 1919[86] Daniels *et al.*, 1923[78] McCarrison, 1931[206d] Green and Mellanby, 1930[123b]
Infant	Vitamin A	Severe infections	Synergistic	Clausen, 1935[67b] Bloch, 1924, 1928[39a,b]
Infant	Vitamin A	Severe infections	Synergistic	Blackfan and Wolbach, 1933[37]
Rat	Vitamin A	Salmonella	Synergistic	Webster and Pritchett, 1924[357] Pritchett, 1927[251] Lassen, 1930, 1931[178a,b] McClung and Winters, 1932[208b] Seidmon and Arnold, 1932[301] Kligler *et al.*, 1945[165] Robertson and Tisdall, 1989[274]

TABLE 1 (cont'd)

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Mouse	Vitamin A	Tuberculosis	Synergistic	Finkelstein, 1931–32[100]
Dog	Vitamin A	Spirochetes (black-tongue of Underhill's syndrome)	Synergistic	Smith *et al.*, 1937[309]
Guinea pig	Vitamin A	Diphtheria toxin Tetanus toxin	No effect	Torrance, 1936[338]
Rat	Vitamins A and D	Tetanus toxin Dead Typhoid Bacilli	Synergistic	Blackberg, 1928[36]
Sheep	Vitamins A and D and minerals	Toxin of lamb dysentery	Synergistic	Mackie *et al.*, 1932[197]
Rat	Vitamin A	Saprophytic bacteria	Synergistic	Boynton and Bradford, 1931[43] Turner *et al.*, 1930[341]
Rat	Vitamin D	Saprophytic bacteria I-P	No effect	Boynton and Bradford, 1931[43]
Mouse	Vitamin D	Pasturella	No effect	Hill, Greenwood and Topley, 1930[143]
Rat	Vitamin D	Pyogenic bacteria	No effect	Green and Mellanby, 1928[123a]
Rat	Vitamin D (subclinical)	Salmonella	Synergistic	McClung and Winters, 1932[203b]
Rat	Vitamin D	Salmonella	Synergistic	Robertson and Ross, 1930[273]
Monkey	Vitamins A and B	Septicemia	Synergistic	McCarrison, 1919[206c]
Bird	Vitamin B	Salmonella	Synergistic	McCarrison, 1918[206a]
Monkey	Chronic folic acid	Dysentery (? Shigella)	Synergistic	Waisman and Elvehjem, 1943[349]
Mouse	Thiamine	Shigella	Synergistic	Sporn *et al*, 1950[315]
Mouse	Riboflavin Pyridoxine Niacin Biotin Folic acid	Shigella	No effect	Sporn *et al.*, 1950[315]
Mouse	Riboflavin Biotin	Salmonella	Synergistic	Kligler *et al.*, 1944, 1946[164,166]
Rat and mouse	Thiamine			Guggenheim and Buechler, 1946[127a]
Rat	Thiamine	Borrelia	Synergistic	Guggenheim and Halevi, 1952[129]
Mouse	Thiamine Riboflavin	Pneumococcus	Synergistic	Wooley and Sebrell, 1942[371]
Rat	Pantothenate	Corynebacterium	Synergistic	Seronde *et al.*, 1956[304]
Rat	Pantothenate Riboflavin	Pneumococcus	No effect	Robinson and Siegel, 1944[275]
Rat	Thiamine Pyridoxine	Pneumococcus	Slightly synergistic	Robinson and Siegel, 1944[275]
Rat and Mouse	Pantothenate	Pneumococcus	No effect	Day and McClung, 1945[80]
Monkey	B Complex	Streptococcus Group C	Synergistic	Saslaw *et al.*, 1943[292]

TABLE 1 (cont'd)

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Dog	B Complex	*Clostridium welchii*	Synergistic	Rose, 1928[280]
Dog	B Complex	*S. aureus*	Synergistic	Rose and Rose, 1936[281]
Pigeon	B Complex	Pneumococcus Meningococcus *E. coli* Salmonella	Synergistic (only with low body temp.)	Findlay, 1923[98a]
Pig	B Complex	Salmonella	Synergistic	Luecke, 1955[192]
Rat	B Complex Thiamine	Rat leprosy	Synergistic	Lamb, 1935[173] Badger *et al.*, 1940[19]
Dog	B Complex	Spirochetes (Goldberger Syndrome)	Synergistic	Smith *et al.*, 1937[309]
Human	Riboflavin	Secondary infections of mouth	Synergistic	Riddle *et al.*, 1940[267]
Guinea pig	Vitamin C	Pneumococci Streptococci	Synergistic if advanced scurvy	Schmidt-Weyland and Koltzsch, 1928[294] Jackson and Moody, 1916[151]
Monkey	Vitamin C	*Spirillum sputigenum*	Synergistic	Kelly, 1944[160]
Guinea pig	Vitamin C	Diphtheria bacilli	Synergistic	Wamoscher, 1927[350]
Human	Vitamin C	Pneumococci	Synergistic	Hess, 1932[141b]
Guinea pig	Vitamin C	Diphtheria toxin	Synergistic	King and Menten, 1935[162] Bieling, 1925[34]
Chicken	Vitamin C or other antioxidant	Salmonella	Synergistic	Hill and Garren, 1955[142]
Guinea pig	Vitamin C	Tuberculosis	Synergistic	McConkey and Smith, 1933[210] Birkhaug, 1939[35] Gangadharam and Sirsi, 1953[112]
Mouse	Protein	Salmonella	Synergistic	Watson, 1937[352] Watson *et al.*, 1938[353] Guggenheim and Buechler, 1947, 1948[127c,d]
Mouse	Casein	Salmonella	Synergistic	Miles, 1951[227] Robertson and Doyle, 1936[272]
Rat	Protein	Salmonella (light infection) Tuberculosis (light infection)	No effect on antibodies or blood cells	Metcoff *et al.*, 1948[222] Metcoff *et al.*, 1949[223]
Mouse	Protein	Pneumococcus	Synergistic	Sako, 1942[289]
Rat and Rabbit	Protein	Pneumococcus	Synergistic	Wissler, 1947[366a,b]
Rat	Protein	Spirochetes of relapsing fever	Synergistic	Guggenheim *et al.*, 1951[128]
Mouse	Protein	Staphylococcus *Mycobacterium fortuitum* *M. tuberculosis*	Synergistic	Schaedler and Dubos, 1956[293] Dubos and Schaedler, 1956[89]

TABLE 1 (cont'd)

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Chicken	Protein	Pneumococcus	Synergistic	Steffee, 1950[319]
Chicken	Excess fish meal Low fish meal	Salmonella Salmonella	Synergistic Antagonistic	Smith and Chubb, 1957[311] Smith and Chubb, 1957[311]
Rat and Hamster	Vitamin E	Human leprosy	Synergistic	Mason and Bergel, 1955[203]
Rat	Protein	Tuberculosis	Synergistic	Koerner *et al.*, 1949[169]
Rat	Protein	Tuberculosis	No effect	Lange and Simmonds, 1923[175]
Rat	Protein (casein)	Inhalation tuberculosis	Antagonistic	Ratcliffe, 1951[263a]
Hamster	Protein (casein)	Inhalation tuberculosis	Synergistic	Ratcliffe and Merrick, 1957[264]
Guinea pig	Protein (casein)	Inhalation tuberculosis	Synergistic	Ratcliffe, 1954[263b]
Human	Animal protein	Tuberculosis	Synergistic	Marche and Gounelle, 1950[201]
Mouse	Animal protein	Tuberculosis	Synergistic	Sengupta and Howie, 1948–49[303]
Mouse	Fatty acids plus protein	Tuberculosis	Synergistic	Hedgecock, 1955, 1958[137a,b]
Mouse	Starvation	Staphylococcus	Synergistic	Smith and Dubos, 1956[312]

Food restriction leading to starvation or inanition lowers resistance to some bacterial infections. Suggestive early reports[34,271] are confirmed by such well controlled experiments as those of Dubos and coworkers[87a,87b,89,90] who showed that 24 to 48 hours of complete fasting decreased the resistance of mice to staphylococcus, Friedlander bacillus and the tubercle bacillus. With adequate refeeding, normal resistance returned in 1 to 3 days. Substitution of an inadequate diet temporarily aggravated the condition, but eventually these animals also regained normal resistance.

Multiple deficiencies are more common in humans than deficiencies of a single nutrient and therefore are of greater public health significance. Monkeys on a basic rice diet deficient in vitamins A, B, C and animal protein, as observed by Rao[259], had chronic diarrhea typical of bacillary dysentery. McKenzie[217] reported similar findings in East African laborers.

Children and experimental animals on vitamin A deficient diets frequently develop spontaneous infections[67b,123b]. Synergism between salmonella infections and vitamin A deficiency in mice and rats is reported repeatedly, with resistance lowered before clinical signs of deficiency disease. Clausen[67a] and Watson[352] concluded that in most studies vitamin D deficiency was incidental to more important vitamin A deficiencies. Robertson and Ross[273], however, showed significant improvement in resistance by nothing more than ultraviolet irradiation of a deficient diet.

Deficiency of various B vitamins is reported to lower resistance to a variety of infections, particularly intestinal pathogens[166], pneumococci[371], other

Gram-positive cocci[292], spirochetes[309], clostridia[280], and the bacillus of rat leprosy[19]. The frequent and extravagant claims[211a,211b] of a therapeutic effect of vitamin C overshadow all research on this vitamin. Reasonably well controlled studies indicate, however, that severe scurvy reduces the resistance of guinea pigs to Gram-positive cocci[294] and the diphtheria toxin[162].

Difficulty in producing single nutrient deficiencies often confuses judgment as to which of several missing elements is responsible for an observed clinical condition. Guggenheim and Buechler[127c,127d] showed by paired feeding experiments that synergistic effects with salmonella infections and diets intended to be vitamin A deficient were actually better explained by coexistent lowered food intake and probable protein deficiency. The report of Webster and Pritchett[357] that fats containing vitamin A restored resistance to salmonella in colonies of mice on deficient diets was discounted by Watson's[352] demonstration of even more dramatic reaction in mice on similar diets when casein was given. Of particular value methodologically was the application of techniques of experimental epidemiology by Watson, Wilson and Topley[353]. It is usually stated that Metcoff *et al.* failed to confirm a relationship between protein deficiency and resistance to salmonellosis[222] and tuberculosis[223] in rats. Unwarranted extrapolations have been made from the limited objectives of these two carefully designed and executed studies in which the immunologic and hematologic response of animals with minimal, nonfatal infections remained unmodified by deficiencies of short duration. All other studies indicate a more or less proportional loss of resistance with severe protein depletion.

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[95] 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[184] 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[85] in New York and Getz *et al.*[117] in Philadelphia.

A complex dietary interaction of proteins and fats is suggested in tuberculosis by the well controlled laboratory studies of Hedgecock[137a,137b]. When lard was the only source of fat in diets of mice, no protein deficiency effect on resistance could be demonstrated. With a special mixture of five fatty acids from coconut oil, however, addition of protein gave statistically significant protection.

Viral Infections. Antagonism is the common and well defined reaction in virus infections associated with nutritional disorders. Synergism is less frequent. Experiments on virus infections, being generally of more recent date than those with bacteria, have the advantage of modern standards of experimental design and statistical appraisal. Those listed in Table 2 have more reliability.

TABLE 2.—EFFECT OF NUTRITIONAL DEFICIENCIES ON VIRAL INFECTIONS

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Chicken	Multiple	Rous sarcoma virus	Antagonistic	Rous, 1911[282]
Mouse	Multiple	Rous sarcoma virus	Antagonistic	Tannenbaum, 1940[327]
Guinea pig	Multiple	Foot and mouth disease	Antagonistic	Olitsky *et al.*, 1928[238]
Rabbit	Multiple	Vaccinia	Antagonistic	Rivers, 1939[269] Sprunt, 1942[316]
Bird	Multiple	Psittacosis	Synergistic	Meyer, 1942[226]
African negro	Multiple	Hepatitis	Synergistic	Findlay, 1948[98b] Hahn and Bugher, 1954[131]
Monkey, Mouse	Multiple	Yellow fever	Synergistic	Kuczynski, 1937[172]
Monkey	Multiple Vitamin B complex	Influenza	Synergistic	Saslow *et al.*, 1942[292]
Monkey	Folic acid	Influenza	Synergistic	Wilson *et al.*, 1947[384]
Cotton rat	Partial inanition Vitamin B	Poliomyelitis	No effect	Weaver, 1945[355a]
Cotton rat	Vitamin A	Poliomyelitis	Synergistic	Weaver, 1946[355b]
Rat	Vitamin D	Coryza	Synergistic	György *et al.*, 1926[130]
Monkey	Thiamine	Poliomyelitis	No effect	Clark *et al.*, 1945[66]
Mouse	Thiamine	Poliomyelitis Theiler	Antagonistic	Rassmussen *et al.*, 1944[261] Toomey *et al.*, 1944[337] Foster *et al.*, 1942, 1944[106a,b,c]
Mouse	Thiamine	Western equine encephalitis	Antagonistic	Kearney *et al.*, 1948[159a]
Chick 1-day old	Thiamine	Avian encephalomyelitis	Synergistic	Cooperman *et al.*, 1946[72]
Chick 2-wk. old	Thiamine	Avian encephalomyelitis	Antagonistic	Cooperman *et al.*, 1946[72]
Pigeon	Thiamine	Psittacosis	Synergistic	Pinkerton and Swank, 1940[248]
Mouse	Pyridoxine (acute)	Pneumonia	Antagonistic	Leftwich and Mirick, 1949[182]
Mouse	Pyridoxine	Pneumonia	Synergistic	Mirick and Leftwich, 1949[231]
Monkey	Pyridoxine analogue (deoxypyridoxine)	Poliomyelitis	Synergistic	Bodian, 1948[41]
Chick embryo	Thiamine analogue (oxythiamine)	Mumps Influenza	Antagonistic	Cushing *et al.*, 1952[76]
Tissue cultures	Pyridoxine analogue (deoxypyridoxine)			
Mouse	Riboflavin	Poliomyelitis	Antagonistic	Rassmussen *et al.*, 1944[262]
Mouse	Riboflavin	Theiler	No effect	Rassmussen, *et al.*, 1944[262]

TABLE 2 (cont'd)

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Mouse	Pantothenic acid	Poliomyelitis	No effect	Lichstein *et al.*, 1944[187]
Mouse	Pantothenic acid	Theiler	Antagonistic	Lichstein *et al.*, 1944[187]
Monkey	Folic acid (acute)	Poliomyelitis	No effect	Lichstein *et al.*, 1946[185]
Monkey	Folic acid (chronic)	Poliomyelitis	Antagonistic	Lichstein *et al.*, 1946[185]
Chicken	Folic acid	Rous sarcoma virus	Antagonistic	Little *et al.*, 1948[188]
Mouse	B-complex	Vesicular stomatitis	Synergistic	Sabin and Olitsky, 1938[286]
	Thiamine		(delayed maturation resistance)	Sabin and Duffy, 1940[285]
	Vitamin E			Sabin, 1941[284]
Mouse	Protein deficiency also high protein Low fat	Theiler	No effect	Kearney *et al.*, 1948[159a,b]
Mouse	Choline	Hepatitis(MHV3)	No effect	Ruebner *et al.*, 1958[283]
Mouse, mature	Protein (acute)	Swine influenza	Antagonistic	Sprunt, 1949[316]
	Protein (more than two weeks)	Swine influenza	No effect	Sprunt, 1949[316]
Mouse, immature	Protein	Swine influenza	No effect	Sprunt, 1949[316]
Mouse	Tryptophan	Theiler	Antagonistic	Kearney *et al.*, 1948[159b]
Mouse	Lysine	Poliomyelitis	No effect	Jones *et al.*, 1947[154]
Rat	Protein defic.	Hepatitis (? human)	Synergistic	MacCallum and Miles, 1946[195]
Mouse	Potassium Phosphorus	Theiler	Antagonistic	Lichstein *et al.*, 1946[186]
Mouse	Calcium Sodium Magnesium	Theiler	No effect	Lichstein *et al.*, 1946[186]
Mouse	Potassium	Poliomyelitis	No effect	Jones *et al.*, 1947[154]
Mouse	Phosphorus Calcium	Poliomyelitis	Synergistic	Foster, 1949[105]

Chance laboratory observations indicate that general malnutrition is antagonistic to the viruses of foot and mouth disease[238], Rous sarcoma[282], vaccinia[269, 316] and psittacosis[226]. Clinical studies in Africa[98b,131] on enhanced fatality of infectious hepatitis in malnourished West Africans are supported by clinical observations[345] that adequate protein nutrition limits sequelae of chronic cirrhosis. Only two experimental studies with vitamin A[355b] and D[130] deficiency were encountered, both suggesting synergism.

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[106b,261,262] and western equine encephalitis[159a], and of avian encephalomyelitis[72] in chicks seems well established. Lichstein *et al.*[185] found that acute folic acid deficiency had no ef-

fect on poliomyelitis infection in monkeys but that chronic deficiency resulted in high grade resistance. On the other hand increased resistance to pneumonia virus (P.V.M.) of mice has been demonstrated with acute pyridoxine deficiency[182] which changed to synergistic reduction of resistance in chronic deficiency of more than 8 days[231].

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[262], while pantothenic acid deficiency was antagonistic to Theiler virus and had no effect on poliomyelitis[187]. The evidence is unconvincing that vitamin C has any therapeutic effect on viral infections despite frequent firmly held clinical opinion.

Protein deficiencies ordinarily have little or no effect on viral infections. A striking exception is the report by Kearney *et al.*[159b] that tryptophan deficiency gives almost complete protection of mice from the paralytic effects of Theiler virus, with nearly all control animals paralyzed. Despite lack of paralysis, virus titers in brains of deficient mice were as high as in normally fed controls, and histological evidence of infection equally marked.

The results of deficiency of specific minerals range from synergism to antagonism. For example, phosphorus deficiency was synergistic with poliomyelitis infection in mice[105], but antagonistic to Theiler virus[186]; potassium deficiency had no effect on poliomyelitis[154] and was antagonistic to Theiler virus[186], while calcium deficiency was synergistic with poliomyelitis[105] and without effect on Theiler virus[186].

TABLE 3.—EFFECT OF NUTRITIONAL DEFICIENCIES ON RICKETTSIAL INFECTIONS

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Rat	Vitamin A	Typhus	Synergistic	Zinsser *et al.*, 1931[377] Wertman *et al.*, 1952[361]
Rat	Thiamine Pantothenic acid Pyridoxine Riboflavin Folic acid B_{12}	Murine typhus	Synergistic	Wertman and Sarandria, 1951, 1952[362a,b,c] Pinkerton, 1949[246b] Pinkerton and Bessey, 1939[247] Fitzpatrick, 1948[101]
Rat	Vitamin C	Murine typhus	Synergistic	Pinkerton, 1949[246b]
Guinea pig	Vitamin C	Epidemic typhus	Synergistic	Pinkerton, 1949[246b] Zinsser *et al.*, 1931[377]
Rat	Protein	Murine typhus	Synergistic	Fitzpatrick, 1948[101]
Rat	Pyridoxine Nicotinic acid Choline	Murine typhus	No effect	Fitzpatrick, 1948[101]

Rickettsiae. All studies of the interaction of malnutrition with rickettsial infections showed synergism, Table 3. In laboratory studies by Wertman and coworkers[361,362a,362b,362c] almost all members of the vitamin B group except niacin brought about decreased antibody production against murine typhus in rats. Pinkerton[246a,246b] and Pinkerton and Bessey[247] showed that deficiency of ascorbic acid, riboflavin, pantothenic acid, thiamine, vitamin A

and protein is synergistic with murine typhus in rats, and starvation with epidemic typhus in guinea pigs. Epidemics of typhus have been linked with famine more consistently than almost any other disease. Aycock and Lutman[17] and Sigerist[306] developed historically the idea that this relationship is probably secondary and incidental, since war brings both famines and typhus epidemics.

Helminths. With few exceptions the consequences of parasitic infection[150, 339b] are generally more serious in malnourished hosts[114,307], a synergistic reaction, Table 4.

TABLE 4.—EFFECT OF NUTRITIONAL DEFICIENCIES ON HELMINTH INFECTIONS

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Dog	Multiple	*Ancylostoma caninum*	Synergistic	Foster and Cort, 1931, 1932, 1935[104a,b,c,d]
Rat	Multiple	*Nippostrongylus muris*	Synergistic	Chandler, 1932[54a]
Lamb	Multiple	*Trichostrongylus axei*	Synergistic	Gibson, 1954[118]
Lamb	Multiple (ewes as well as lambs)	*Trichostrongylus* sp. *Ostertagia* sp. *Haemonilius* sp. *Aesophagostonum* sp. *Cooperia* sp.	Synergistic	White and Cushnie, 1952[363]
Lamb	Multiple	*Haemonchus contortus* sp. *Esophagostonum* sp. *Columbianum* 7 additional species		Laurence *et al.*, 1951[179] Taylor, 1934[331]
Mouse	Partial fasting or alcohol	*Hymenolepis nana*	Synergistic	Larsh, 1947[176a]
Chicken	Vitamin A	*Ascaris galli* *A. lineata*	Synergistic	Ackert *et al.*, 1927[2] Ackert and McIlvaine, 1931[3]
Chicken	Vitamin D	*A. lineata*	No effect	Ackert and Spindler, 1929[5]
Dog	Vitamin A	*Toxicara canis* *Toxoscaris leoninia*	Synergistic	Wright, 1935[372]
Pig	Vitamin A	*A. lumbricoides*	No effect	Clapham, 1934[62c]
Chicken	Vitamin A	*Syngamus trachea*	Synergistic	Clapham, 1934[62d]
Rat	Vitamin A	*Parascaris equorum*	Synergistic	Clapham, 1933[62a]
Chicken	Vitamin A	*Heterakis gallinae*	No effect	Clapham, 1934[62b]
Rat	Vitamins A,D,E and protein	*Hymenolepis dimunata*	No effect	Chandler, 1943[54b]
Rat	Vitamin A	*Strongyloides ratti*	Synergistic	Lawler, 1941[180]
Rat	Vitamin A	*Schistosoma mansoni*	Synergistic	Krakower, 1940[170a]
Rat	Vitamin A	*Trichinella spiralis*	Synergistic	McCoy, 1934[212]
Rat	Vitamin C	*S. mansoni*	No effect	Krakower *et al.*, 1944[170b]
Mouse	Vitamin E, selenium and cystine	*S. mansoni*	Synergistic	DeWitt, 1957[82]

TABLE 4 (cont'd)

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Duck	Vitamin B Comp.	*A. galli*	Synergistic (more worms but smaller)	Ackert and Nolf, 1931[4]
Chick	Pteroylglutamic acid	*A. lineata* *A. perspicillum*	Synergistic	Sadun *et al.*, 1949[288] Zimmerman *et al.*, 1926[375]
Rat	Thiamine Riboflavin	*N. muris*	Synergistic	Watt, 1944[354]
Chick	Protein (Arginine, glycine, leucine, lysine)	*A. galli*	Synergistic	Riedel and Ackert, 1951[268b]
Chicken	Protein	*A. lineata*	Synergistic	Ackert and Beach, 1933[1]
Rat	Protein	Trichinella	Synergistic	Rogers, 1942[278d]
Dog	Diet of whole milk only	*A. caninum*	Synergistic	Foster, 1936[103]
Rat	Protein	*N. muris* *H. nana*	Synergistic	Donaldson and Otto, 1946[84] Larsh, 1950[176b]
Rat	Iron (whole milk)	*N. muris*	Synergistic	Porter, 1935[250]
Chicken	Calcium	*H. gallinae*	Synergistic	Clapham, 1934[62b]
Chick	Manganese	Tapeworm	Synergistic	Harwood and Luttermoser, 1938[13]
Chicken	Phosphorus Calcium	*A. galli*	Antagonistic	Gaafar and Ackert, 1953[111]
Chicken	Manganese	*A. galli*	No effect	Gaafar and Ackert, 1953[111]

Nutritional deprivation has long been known to aggravate hookworm infection in human populations. Laboratory confirmation was provided[104a, 104b,104c,104d] through dogs infected with *Ancylostoma caninum;* heavy infections of malnourished dogs were followed by prompt loss of worms and reduction in egg production when the animals were placed on an adequate diet. Well nourished dogs are infected with difficulty by the cat strain. and likewise the normally fed cat with the dog strain. On poor diets this "specific resistance" is lost.

Hymenolepis infections of rats and mice were rendered more serious by generalized dietary inadequacy[54a]. When both vitamins A and D were deficient, infection of young rats with adult Trichinella was heavy, large numbers of larvae were deposited in muscle, and active immunity to reinfection was absent[212].

In vitamin B-complex and pteroylglutamic deficient fowl, ascarids[4,288] appear in greater numbers than in controls. Both thiamine and riboflavin deficiencies proved synergistic with infections of Nippostrongylus in rats[354], an effect even more pronounced in superinfection.

Deficiency of protein permits greater development of Ascaris[268b], Trichinella[278d], Nippostrongylus[84] and Hymenolepis[176b] in various animal hosts. In ascaris infection of chickens the quality as well as the quantity of protein is important[268a].

An associated iron deficiency in Nippostrongylus infection in rats[250] and hookworm in man[75] results in increased parasitism, and conversely iron therapy reduces the number of worms; the

iron deficiency produced by hookworms thus leads to still heavier infections. Deficiencies in phosphorus and calcium[111] proved antagonistic to ascaris infection of chickens, suggesting specific dependence on these metabolites; the worms were reduced in number and in size.

Protozoa. Synergism and antagonism are observed with almost equal frequency in protozoan infections, Table 5. Intestinal protozoa, especially amebae, are almost uniformly synergistic with deficiencies, while protozoa of the blood, especially malaria parasites, are more frequently antagonistic.

TABLE 5.—EFFECT OF NUTRITIONAL DEFICIENCIES ON PROTOZOAL INFECTIONS

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Human	Multiple	*E. histolytica*	Synergistic	Blumenthal *et al.*, 1947[40] Alexander and Meleney, 1935[7] Elsdon-Dew, 1949[93] Martin *et al.*, 1953[202]
Monkey	Multiple	*E. histolytica*	Synergistic	McCarrison, 1919[206b]
Guinea pig	Synthetic diet	Amebiasis	Synergistic	Lynch, 1957[194]
Human	General famine	Malaria	Antagonistic	Ramakrishnan, 1954[254b]
Rat	Starvation	*P. berghei*	Antagonistic	Ramakrishnan, 1953[254a]
Monkey	Multiple	*P. cynomologi* *P. knowlesi*	Antagonistic	Passmore and Sommerville, 1940[244]
Chicken	Vitamins A and B protein	Coccidiosis	Synergistic	Allen, 1932[8]
Guinea pig	Vitamin C	Amebic infections	Synergistic	Sadun *et al.*, 1951[287]
Monkey	Vitamin C	*P. knowlesi*	Antagonistic	McKee and Geiman, 1946[216] Geiman and McKee, 1948[115]
Mouse	Biotin	*P. berghei*	Synergistic (fatality) Antagonistic (parasitemia)	Ramakrishnan, 1954[254e]
Mouse	Pyridoxine PABA	*P. berghei*	Antagonistic	Ramakrishnan, 1954[254d]
Monkey	PABA	*P. knowlesi*	Antagonistic	Anfinsen *et al.*, 1946[11]
Duck	Niacin	*P. lophuræ*	Synergistic	Roos *et al.*, 1946[279]
Chicken	Pantothenic acid	*P. gallinaceum* (blood induced)	Antagonistic	Brackett *et al.*, 1946[44]
Chicken	Pantothenic acid	*P. gallinaceum* (sporozoite induced)	No effect	Brackett *et al.*, 1954[44]
Chicken	Riboflavin	*P. lophuræ*	Antagonistic	Seeler and Ott, 1944[300a]
Chicken	Thiamin Biotin Folic acid	*P. lophuræ*	Synergistic	Seeler, Ott and Gundel, 1944[300e] Seeler and Ott. 1945, 1946[300b,d] Trager, 1943[339a]
In vitro duck cells	Folinic acid	*P. lophuræ*	Synergistic	Trager, 1949, 1958[339b 339d]

TABLE 5 (cont'd)

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Pigeon	B complex	*T. brucei*	Synergistic	Salazzo, 1929[290]
Rat	B complex	*T. equiperdem*	Antagonistic	Reiner and Paton, 1932[265]
Rat	Pantothenic acid	*T. lewisi*	Synergistic	Becker and Smith, 1941–42[24] Becker *et al.*, 1946 1947[25]
Rat	Biotin	*T. lewisi*	Synergistic	Caldwell and György, 1943, 1947[49a,b]
Rat	Thiamine	*Eimeria nieschulze*	Synergistic	Becker and Dilworth, 1941[23]
Rat	Pyridoxine Pantothenate	*Eimeria nieschulze*	Antagonistic	Becker and Smith, 1941–42[24]
Mosquito	Vitamin C	*P. gallinaceum*	Synergistic	Terzian, 1950[333] Terzian *et al.*, 1952, 1953[334 335]
Mosquito	Thiamine Niacin Pantothenic acid Biotin	*P. gallinaceum*	Antagonistic	Terzian *et al.*, 1953[334]
Suckling mouse	PABA (restriction in mothers)	*P. berghei*	Antagonistic	Hawking, 1953, 1954[136a,b]
Bird	Protein	*P. lophuræ*	Synergistic	Seeler and Ott, 1945[300c]
Mouse	Methionine	*P. berghei*	Antagonistic	Ramakrishnan, 1954[254e] Taylor, 1956[328]
Rat	Protein	*T. lewisi*	No effect	Caldwell and György, 1947[49b]
Mouse or rat	Milk diet plus vitamins	*P. berghei*	Antagonistic	Maegraith *et al.*, 1952[200] Hawking, 1954[136b] Ramakrishnan, *et al.*, 1953[256]
Monkey	Milk diet plus vitamins	*P. cynomologi* *P. knowlesi*	Antagonistic	Maegraith, 1953[199] Bray and Garnham, 1953[45]
Pup	Milk diet	*T. rhodesiense* *Babesia carus*	No effect	Maegraith, 1953[199]
Human	Milk diet plus vitamins	*P. vivax* *P. falciparum* *P. malariæ*	No effect	Chaudhuri and Dutta, 1955[57] Miller, 1954[229]
Chicken	Milk diet	*P. gallinaceum*	Synergistic	Ramakrishnan *et al.*, 1953[255]

The clinical observation that inadequate diets precipitate amebiasis has support from several sources. Prisoners of war are especially prone to develop amebic dysentery; with improved feeding dramatic improvement is usual[40,202] In South Africa[93] fulminating amebic dysentery was common among maize-eating Bantus, rare among Indians on a rice and curry diet but with liver abscess relatively frequent; while Europeans on a balanced diet rarely

had either condition. Almost half of wild caught monkeys[206b] placed on milled rice diets developed amebic dysentery and died.

Malaria parasites *in vitro* have rather precise nutritional requirements[11,215, 339c,339d]. Specific dependence on nutrients is indicated also by the pattern of antagonistic and synergistic response observed with various deficiencies. judged by levels of parasitemia, the specific deficiencies antagonistic to bird, monkey and mouse malaria are vitamin A, vitamin C, riboflavin, pantothenic acid, and para-aminobenzoic acid[254e,300d]. Deficiencies synergistic with experimental infections of malaria include thiamine, niacin, biotin, folic acid and protein[114,279]; fatality is excessive and rapid in experimental malaria associated with either riboflavin or thiamine deficiencies[300a].

With one exception[265], trypanosome infections are reported as synergistic[49a, 49b,290] with deficiencies of the vitamin B group. Biotin deficiency[25] had such an effect on rats infected with *T. lewisi* that hyperimmune serum gave no protection. Excess biotin administered after infection of biotin deficient rats had no therapeutic effect; indeed, the intensity of parasitemia sharply increased.

A further series of observations on protozoal infections are contrary to the general dictum that only deficiencies are of consequence in relation to infection. Both synergistic and antagonis-

TABLE 6.—EFFECT OF DIETARY EXCESS OF CERTAIN NUTRIENTS ON PROTOZOAL INFECTIONS

Host	*Diet*	*Agent*	*Action*	*Reference*
Dog	Liver (raw) or liver extract supplement	*E. histolytica*	Antagonistic	Kagy and Faust, 1930[156]
Dog	Ventriculin Solid residue of heated liver Canned salmon	*E. histolytica*	Synergistic	Faust and Kagy, 1934[96] Faust *et al.*, 1934[97]
Dog	Intracecal injection of salmon	*E. histolytica*	Antagonistic	Faust *et al.*, 1934[97]
Dog	Intracecal injection of tryptic and peptic digests of salmon	*E. histolytica*	Synergistic	Faust *et al.*, 1934[97]
Guinea pig	High protein (50% casein)	Amebiasis	Synergistic	Taylor *et al.*, 1952[330]
Rat	Animal protein excess	Trichomonas	Antagonistic	Hegner and Eskridge, 1935[139a]
Rat	High carbohydrate diet	Trichomonas	Synergistic	Hegner and Eskridge, 1937[139b]
Human	Vitamin C excess	Malaria	Antagonistic	Mohr, 1943[232]
Chicken	Thiamine excess	*P. gallinaceum*	Synergistic	Seeler and Ott, 1946[300d] Rama Rao and Sirsi, 1956[253]
Mouse	Meat protein excess	*P. berghei*	Synergistic	Ramakrishnan, 1954[254c]
Mouse	Protein (10%, 20%, 30% casein)	*T. congoleuse*	Antagonistic	Keppie, 1953[161]

tic effects have been observed with an excess of nutrients, Table 6. Administration of an excess of either thiamine or riboflavin to animals with experimental malaria and deficient in these vitamins resulted in a sharp increase in parasitemia[300a,300d]. An extremely active research has developed from the observation that a milk diet suppresses rat[136b,200] and monkey malaria[199].

Mechanisms in Synergism. Distinctive patterns of interaction in respect to main classes of microbiologic agents of disease and kinds of malnutrition have been identified and listed in the preceding section. Possible mechanisms accounting for those groupings are now considered.

Genetic Constitution of Host. Synergistic and antagonistic interactions are best seen in populations of heterogeneous genetic origin[295d,296,356]. The less homogeneous a population the broader is the range within which nutritional factors influence infection. The possibilities may be listed as follows: (1) Natural or constitutional resistance is so high relative to agent potential that disease will not result from infection, no matter how nutrition is varied. (2) Natural or constitutional resistance is so low in relation to potential virulence of the agent that severe infectious disease will ensue regardless of nutritional factors. (3) Natural or constitutional resistance is in such balance with agent potential that nutritional factors may influence the course of infectious disease to a greater or less extent. Successful attempts to measure the effect of nutritional factors are limited to the last situation; since people and microorganisms vary, it is more common among natural populations than the other two.

Specific Host Factors. An association of deficiency and infection often produces an opposite response with different hosts. Ratcliffe[263a,263b,264] developed a method of standardizing tuberculous infections through inhalation of as few as five tubercle bacilli. Guinea pigs and hamsters on 5 to 6% casein showed more rapid progression of infection than those receiving 25% casein, while the disease in rats progressed most rapidly in animals given 25 to 40% casein.

Age of the host also influences the pattern of interaction. The usual increased resistance to avian encephalomyelitis infection[72] of thiamine deficient 2-week old chicks was reversed by using day-old chicks. Sabin and coworkers[284,285,286] reported an opposite influence in 2- to 4-week old mice exposed to the virus of vesicular stomatitis. Mice of this age normally develop "maturation resistance" to infection presumably localized at the peripheral nerve endings since animals continue susceptible to intraneural or intracerebral inoculation. By placing either mothers or weanling mice on diets deficient in B-complex, thiamine, vitamin E or restricted total calories, marked retardation was noted in appearance of this normal resistance. A similar mechanism may account for the established observation that only infant mice are susceptible to Coxsackie virus.

Vitamin Deficiencies and Antibody Response. Because of ease and exactness in measurement, antibodies have had major attention in efforts to evaluate end results of coincident infection and malnutrition. Most specific vitamin deficiencies interfere with antibody production in the experimental animal. Although antedated by a number of investigations[67a,271], that of Blackberg[36] in 1928 is one of the first having controls. Killed typhoid bacilli or small doses of live bacilli injected into rats deficient in vitamins A and D resulted in measurably lower titers of agglutinin and bacteriolysin than in control ani-

mals. Similarly[241], bacteriolytic and agglutinating response of sheep to *E. coli* and *S. choleraesuis* was lower in animals fed on poor pasture or denied access to grass.

Pyridoxine deficiency[321,322] decreased the response of rats to sheep erythrocytes. Hemagglutinin response in rats inoculated with human erythrocytes was impaired by dietary deficiencies of biotin, thiamine[14a], riboflavin and especially of pantothenic acid and pyridoxine[15]. Paired feeding trials proved the result was due to specific vitamin deficiencies and not to decreased food intake[191]. Further studies[190] showed that deficiencies of vitamin A, niacin and tryptophan also had a depressing effect on antibody response, pteroylglutamic acid deficiency still more so, and vitamin D deficiency not at all.

Wertman *et al.*[361,362a,362b,362c] investigated vitamin deficiency states in development of complement-fixing antibodies in the rat against rickettsiae of murine typhus. Single deficiencies of pantothenic acid, thiamine, pyridoxine, riboflavin, folic acid and vitamin B_{12} each resulted in reduced antibody response to small doses of rickettsiae; with large immunizing doses the effect was evident only with pyridoxine. Niacin deficiency and food restriction in pair-fed controls had no effect. Rabbits on a diet deficient in pantothenic acid were injected with typhoid-paratyphoid vaccine with and without pantothenic acid[225] and tested 10 and 45 days later by Widal reaction. Gamma globulin values[225] and agglutinin titers[224] were higher in vitamin fed groups; the number of animals used was not mentioned.

In a recent summary of his studies, Axelrod[14c] makes clear that adequate nutrition is required for both primary and secondary response to an antigen. By administering deoxypyridoxine shortly before secondary immunization of rats with diphtheria toxoid, the induced pyridoxine deficiency interfered with the secondary response of antibodies even after a normal primary response.

Most if not all of the effect of vitamin deficiency on antibody formation presumably is due to interference with protein synthesis[14a,14b] and indeed specific roles in protein synthesis are known for many of the vitamins. Similar effects have been obtained by experimental use of amino-acid analogues[318b].

Protein or Amino-acid Deficiencies and Antibody Response. Madden and Whipple[198] reported that dogs depleted of protein by repeated plasmapheresis had reduced ability to elaborate specific antibodies; the animals were more susceptible to infection[228], a change that could be reversed by protein feeding. By similar methods Cannon *et al.*[51] observed a lesser capacity of rabbits to produce agglutinins to *S. typhosa* and *S. paratyphi,* and explained it on the basis of insufficient protein for synthesis of gamma globulin. Subsequent work[31,32,116,367] led to firm conclusions that protein deficiency not only interferes with antibody production but also affects phagocytosis, qualitatively and quantitatively.

Attempts by a number of investigators to demonstrate a similar effect in man have ended in failure[33,135,177], probably because the protein deficiencies were not sufficient to induce a significant fall in serum protein fractions. Inability to demonstrate diminished antibody response in patients with chronic wasting diseases[20], mainly carcinomas, could have been due to inanition rather than protein deficiency as claimed. A greatly slowed antibody response to typhoid vaccine was observed by Wohl *et al.*[368] in 88 patients with serum albumin values below 4

gm. per 100 ml., compared with 14 similar patients given special supplements of protein or protein hydrolysate. No observations have yet been made on antibody response in kwashiorkor, a severe and widely prevalent protein malnutrition of children.

Antibodies formerly were assumed to originate from preformed serum protein components. Recent use of radioactively labeled amino-acids[122,125,326] indicates that antibodies may be synthesized directly from amino-acids. The initial lag between injection of antigen and immunologic response may well be the interval required for synthesis of antibody-forming enzymes, rather than for elaboration of template protein as initially suggested by Cannon[50a,50c,50d].

Antibody response is not the sole factor in resistance to infection[16,98c]; in a number of infectious diseases, reduction in ability to form antibodies is not associated with greater severity. For example, Zucker *et al.*[378] found no relationship between the decreased ability of rats to form agglutinins to a vaccine prepared from killed cultures of *C. kuscheri,* and resistance to infection with this organism. Similarly, Miles[227] saw no significant difference in agglutinin response of rats in protein deficiency states, despite the more severe disease in deficient animals. As Schneider[295g] has pointed out, if the effect of nutritional deficiencies is merely to slow rather than block formation of antibodies, the ultimate effect on resistance may not be great.

For observations in experimental animals to have practical application to clinical medicine, deficiencies must match those present in ordinary human diets. Opportunity for proof at a high level of deficiency is to be found in many parts of the world in kwashiorkor, xerophthalmia and infantile beriberi. The malnutrition of children studied by Kahn *et al.*[157], while stated to be severe, was not sufficient to warrant the generalization that "in man, unlike laboratory animals, malnutrition does not impair immune-body production."

Evidence supports a view that a number of severe nutritional deficiencies can interfere adversely with antibody response; in some diseases and in some hosts this may result in demonstrable synergism with the infectious agent. The deficiency necessary for such an effect is not commonly encountered in man in technically developed countries but is common in regions where food supply is inadequate. However, the adverse effect on antibody response is only one of several mechanisms active in observed synergistic effects of malnutrition and infection.

Reduced Phagocytic Activity. Some evidence[189,233] exists that a number of nutritional deficiencies[6,14c,318a] depress reticuloendothelial activity thus affecting both antibody production and phagocytic activity.

No characteristic alteration in number or distribution of leukocytes[140,342] occurs in vitamin A deficiency, but phagocytic activity is depressed in both rats[74] and humans[134]. Rats, rabbits and pigeons[359,360] fed on diets deficient in vitamin A and B-complex had a normal opsonic index but the rate of phagocytosis of bacteria injected into the peritoneal cavity was definitely lowered[242]; the inoculated paratyphoid bacilli were removed and destroyed in liver, spleen and peripheral lymph nodes. Animals receiving a heavy infecting dose or having vitamin A deficiency[178a,178b] developed secondary bacteremia with subsequent severe and often fatal disease.

Scurvy in guinea pigs has been associated with decreased numbers of granulocytes and lesser phagocytic power[181, 237]. In scorbutic animals, intraperitoneal

injections of irritating substances failed to produce the exudate clouded by pus cells characteristic of normal animals.

From experimental and clinical studies Doan[83] concluded that folic acid deficiency produces cellular inadequacy in mammalian bone marrow, interfering with production of phagocytes to such extent as to nullify the effect of protective antibodies. Others have had difficulty[185] in maintaining folic acid deficiency in macacus monkeys because of frequent leukopenia, severe dysentery and death. When fed a deficient diet[292] these animals develop a striking granulopenia, accompanied by markedly lowered resistance to spontaneous infection, and to experimental infection with Group C hemolytic streptococci or influenza virus, in all instances with high fatality.

Because severe protein depletion leads eventually to marked atrophy of liver, spleen and bone marrow[26,52,340] where most phagocytic cells are presumed to originate, normal production of phagocytes should be inhibited. Supporting evidence comes from the work of Guggenheim and Buechler[127b,127c] that protein deficient diets "invariably" impair leukocyte regeneration in rats; dietary protein reversed this effect, the result depending on what was fed as well as amount. Leukocyte replacement was related to growth promoting characters of the diet, except that peanut protein promoted blood regeneration more than growth[127e]. Optimal amino-acid patterns for growth and for maintenance of resistance may not be identical[9].

Most infections superimposed on kwashiorkor give rise to no more than a feeble leukocytosis; children with this disease are notoriously susceptible to intermittent infection[340].

Severe undernutrition produces no uniform effect on phagocytes[155]. Balch and Spencer[21] found normal numbers of circulating neutrophils in the last stages of prolonged wasting disease, while Livieratos *et al.*[189] report functional impairment of the reticuloendothelial system.

Altered Tissue Integrity. Dietary deficiencies have long been assumed to decrease resistance to infection through adverse effects on the integrity of epithelial tissues. If sufficiently severe, gross lesions of epithelial surfaces appear, such as angular stomatitis, cheilitis, dermatitis and enteritis in deficiencies of vitamins of the B-complex, the gum changes in scurvy, and the pellagroid skin lesions and atrophy of intestinal mucosa in kwashiorkor.

Pathological changes incident to nutritional deficiency conceivably influence resistance through a variety of mechanisms[148], with no present means to judge relative significance. The main possibilities are (a) increased permeability of intestinal and other mucosal surfaces, (b) reduction or absence of mucous secretions, (c) accumulating cellular debris and mucus[237] to give a more favorable culture medium, (d) alterations in intercellular substance by deficiencies such as scurvy[221], (e) interference with normal tissue replacement and repair, (f) loss of ciliated epithelium in the respiratory tract or (g) nutritional edema with increased fluid in the tissues[332].

Mellanby and Green[218] demonstrated metaplasia and keratinization of respiratory epithelium in rats as a result of vitamin A deficiency, a condition conceivably favoring penetration of the mucosal barrier by infectious agents. Wolbach and Howe[369] arrived at a similar conclusion, and Mellanby[219] reported comparable changes in dogs deficient in vitamins A and D. Recently Weaver[355b] demonstrated that the mucosa of parts of the gastrointestinal tract of cotton rats is more readily penetrated by poliomyelitis virus when the

diet is deficient in vitamin A. Salmonella penetration to the viscera of rats was shown to be enhanced in deficiencies of vitamin A, riboflavin, biotin and protein[127d,166]. By contrast absorption of botulinus toxin was not increased by vitamin A deficiency[323].

Frye[110] believes that resistance to most intestinal parasites is a property of the local intestinal mucosa. Lynch[194] produced fulminating amebiasis in guinea pigs by a special synthetic diet which altered bacterial flora. Since this result could not be reproduced by feeding massive doses of bacteria derived from the lesions, attention was directed to local causes; a thinning and vacuolation of the mucosa was thought accountable. Grant[121] also produced alterations in the permeability of the intestinal wall of guinea pigs to a human strain of tubercle bacillus by manipulating calcium, vitamin C and vitamin D in the ration.

Interference with Nonspecific Protective Substances. In many instances, an observed variation in "bacteriocidal power" is impossible to relate to a specific mechanism, either antibodies or nonspecific substances. Blood serum of rachitic rats had considerably lower bacteriocidal effect on *S. typhosa*[243,310] and staphylococci[99] than serum from normal rats. Swartz, Alicata and Lucker[325] described specific growth-inhibiting substances in horses and rats that retarded development of intestinal nematodes; nutritional deficiencies interfered with this process. In the extensive studies by Guggenheim and Buechler[127b] the peritoneal fluid of rats deficient in thiamine, riboflavin or vitamin A had decreased capacity to destroy inoculated *S. typhimurium.*

Anderson[10] reported greatly reduced lysozyme in tears of 2 children with xeropthalmia which "increased remarkably with 5 to 7 days of cod liver oil therapy." Increased lysozyme has been reported[324] in human vitamin A deficiency. Dawson and Blagg[79] tested saliva from patients with cholera, others with severe malnutrition, and from healthy controls against a variety of infectious agents. Saliva from cholera patients and the malnourished group had little or no antibacterial action compared with controls.

The significance of these sparse observations is difficult to assess. No agreement exists on the importance of lysozymes. Less is known of other nonspecific antimicrobial substances. The possible effect of nutrition on properdin levels[144,351] warrants investigation.

Nonspecific Destruction of Bacterial Toxins. Resistance to bacterial toxins ordinarily is considered a function of antibodies. Additional ways are possible. In the experience of Werkman *et al.*[360] rats suffering from deficiencies of B-complex vitamins or vitamin A were more susceptible than controls to diphtheria toxin, although antitoxin production was equal and rate of disappearance of injected toxin was normal.

Skin reactivity of scorbutic guinea pigs to diphtheria toxin was increased[12] and survival time following parenteral injection reduced[34,162]. Rats[36] deficient in vitamins A and D and also vitamin B-complex were 40 to 100 times more susceptible to tetanus toxin than controls. Sheep on diets low in minerals and in vitamins A and D reacted more strongly than controls to intradermal injection of toxin of the bacillus of lamb dysentery[197]. Torrance[338], however, could not confirm previous results, including his own, that vitamin A content of the liver was in any way correlated with survival of guinea pigs following injection of either diphtheria or tetanus toxin.

Brief fasting[87a] as well as feeding deficient diets had an influence on the susceptibility of mice to endotoxin of

Klebsiella pneumoniae; lesser doses were required for a fatal result, which occurred a few hours after injection and long before an immune response would be expected. Conditions were reversed after 48 hours on a good diet.

Alterations in Intestinal Flora. Intestinal synthesis of some essential nutrients depends upon the bacterial flora of the intestine[64]. The action of diet on symbiotic bacteria can have an independent influence on growth and development of experimental animals. By intubating patients with sprue, Frazer[109] proved that the bacterial flora of the colon moves high into the small intestine in large numbers and presumably competes with the host for B-complex vitamins before they can be absorbed.

Changes in bacterial flora caused by diet sometimes have a favorable and sometimes an unfavorable influence on symbiotic and pathogenic parasites. In guinea pigs[194] a synthetic diet drastically altered the bacterial flora and intestinal mucosa; presumably this contributed to the fulminating amebic dysentery that followed. Hegner[138] was impressed by the rarity of intestinal protozoa in many carnivores; he found that rats fed high animal protein diets were less favorable hosts for *Giardia muris, Trichomonas muris* and *Hexamitus muris* than animals subsisting mainly on vegetable proteins and carbohydrate. Diets of herbivores are stated to lead at times to alimentary stasis, thereby favoring production of toxin by *Clostridium welchii*[270].

Altered Endocrine Balance of Host. Altered endocrine function is probably involved in some of the mechanisms previously presented. Endocrine involvement in nutritional synergism and antagonism with infections is almost wholly unexplored. On the effect of protein and choline deficiency in lowered adrenal function, as well as the less direct relationship of ascorbic acid deficiency, Kinsell[163] states that "it has been well established that the resistance of the Addisonian patient or the adrenalectomized animal to infection in particular and to stress in general, is markedly diminished." Despite evidence that cortical hormones may have a direct inhibiting effect on certain bacterial endotoxins[42,113], the general mechanism of corticoid action in infection is not clear. Selye[302] states that low carbohydrate diets "augment the efficacy of both corticotropin and of corticoid steroids;" this may be responsible for the depressed resistance commonly observed.

Infection is a common and severe complication in diabetes, although notably less with long-acting insulin preparations. Huge nitrogen loss once was common during the short period of ketosis associated with regular insulin. Pollack[249] believes that maintenance of positive nitrogen balance with protamine-zinc insulin, even with glucosuria, is the key to the better resistance to infection characteristic of diabetics under modern management.

Nutrient in Excess of Host Requirements. Therapeutic use of nutrients to control infection has led to much uncritical enthusiasm. Only a few studies meet even elementary scientific criteria and merit mention. An *in vitro* antibacterial action of vitamin C has been repeatedly demonstrated[234,236]. Hill and Garren[142] in well controlled experiments on 40 groups of 40 chicks infected with salmonella showed that resistance was increased by large doses of all the known vitamins if an anti-oxidant was present. The fact that either ascorbic acid, which is not known to be a dietary requirement of chickens, or diphenylene diamine could be used to provide the anti-oxidant effect suggested a nonspecific action.

Excess biotin given to deficient rats

infected with *T. lewisi* produced a sharp increase in numbers of parasites[25]. Wooley and Sebrell[371] having demonstrated the synergism of deficiencies of riboflavin and thiamine in either *ad-libitum* or paired-fed mice with Type I pneumococci then showed that doses of either of these vitamins ten times greater than in the control diet increased mortality. It is possible that the high doses caused an imbalance of some other nutrient to produce a relative deficiency. In detailed investigations on the interaction of specific deficiencies with avian malaria, a phenomenon of interest was the abrupt rise in parasitemia observed when therapeutic doses of either riboflavin or thiamine were given to deficient birds[300d].

Suppression of malaria by diets of milk supplemented only with vitamins was reported by Maegraith *et al.*[200] in *P. berghei* infections of mice. This finding has been confirmed in malaria of monkeys but reports in humans are conflicting[46,57,229]. Infections relapsed when the mice were placed on a normal diet; subinoculation during suppression showed that a few parasites were present. Hawking[136a] attributed the suppressive action to the relative absence of para-aminobenzoic acid in milk at certain seasons and claimed that its addition abolished the suppressive action. The suggestion is that this nutrient is essential to the malarial parasite but not to the host. Ramakrishnan[254d] found that methionine and pyridoxine also caused the parasitemia to return to high levels. Ramakrishnan *et al.*[257] have now reported the isolation of a milk-resistant strain of *P. berghei.*

Mechanisms of Antagonism. Evidence already introduced establishes the generalization that antagonism is a common manifestation of nutritional deficiency when associated with viral and protozoan infections; it is relatively uncommon in rickettsial, bacterial and helminth infections. These effects seemingly result from dependence of certain infectious agents on the biosynthetic processes of host cells, which in turn require specific metabolites. The many studies on nutrient requirements of viruses are beyond the scope of this review[94,147].

Viruses are among the more resistant infectious agents to chemotherapeutic attack[107]. They are known to divert certain enzyme systems of host cells to the synthesis of viral precursors. Recent studies by tissue culture show with increasing precision specific enzyme and metabolite requirements, with RNA (ribonucleic acid) occupying a key role[56]. For growth of the virus of psittacosis in tissue culture[18] only the following amino-acids are essential: tyrosine, threonine, methionine, isoleucine, phenylalanine, tryptophan, leucine, valine and cystine; of these cystine and tyrosine are not required in human nutrition if adequate methionine and phenylalanine are present. Such observations have obvious potential in indicating future methods of treatment[64,98c, 285,286]. The more complex host frequently can compensate for altered metabolic systems by alternative enzymes or nutrients.

Research directed toward retarding enzyme systems essential to the parasite but not necessary for the life of the host is closely linked with the growing attention paid to metabolic antagonists. The detailed studies on metabolites, antimetabolites and enzyme inhibitors in relation to growth of vaccinia virus[330] are in good illustration. Metabolic antagonists of vitamins have been used to demonstrate both synergistic and antagonistic effects. Bodian[41] showed that pyridoxine deficiency in monkeys induced by deoxypyridoxine decreased resistance to poliomyelitis. Although paralysis almost never follows

oral infection of normal monkeys with poliomyelitis, 3 out of 12 pyridoxine deficient monkeys developed severe paralysis when given virus by mouth. Using chick embryos Cushing *et al.*[76] have demonstrated that the thiamine analogue, oxythiamine, caused complete suppression of mumps virus and partial suppression of influenza virus; deoxypyridoxine caused complete inhibition of both viruses.

Wooley and Murphy[370] have reported *in vitro* studies in which pyridoxine deficiency induced by deoxypyridine inhibited the development of *E. coli* bacteriophage but had no effect on growth of the bacteria. Since this effect was reversed by pyridoxine and by such compounds as acetic acid, propionic acid, glycine and butyric acid, the authors suggest that pyridoxine deficiency blocks the utilization of glucose by the bacteriophage.

Rickettsiae multiply[376] best in host cells which have little metabolic activity in contrast with viruses which grow best in rapidly metabolizing cells. It seems probable that the rickettsiostatic effect of para-aminobenzoic (PABA) acid[124,246b] is due to the ability of this compound to increase metabolism of host cells. Folic acid, although it has PABA as part of its molecule does not have an equivalent effect in inhibiting the rickettsia of typhus fever.

Much work on the biochemistry and physiology of protozoa[44,193] indicates that many of the assumptions stated above in reference to viruses apply also to highly parasitic protozoa. The important criterion again appears to be the degree of dependence of the organism on the metabolic systems and nutrition of the host.

Nutritional requirements often vary according to the developmental stage of the parasite. For example, pantothenic acid is adequate for survival of intracellular forms of *Plasmodium falciparum*[339c] but culture of extracellular forms requires formed coenzyme A; folic acid permits growth of intracellular forms but folinic acid is required in extracellular cultures. Both para-aminobenzoic acid and folic acid enhance parasitemia in infected ducks[339d]; infected erythrocytes actually contain more folic acid.

Antagonism between malnutrition and infection is rare among bacteria and helminths; examples of interference with the metabolism of the agent are correspondingly scarce. The similarity of enzyme systems in *Schistosoma mansoni* and in the mammalian host implies[47a,47b,47c] that factors interfering with the metabolism of host cells also may be expected to interfere with worm development, but other effects of malnutrition on resistance may overweigh this.

A striking example of natural antagonism is the discovery that virulent strains of *S. typhosa* require cystine and tryptophan while avirulent mutants also need a purine[102]. Mouse peritoneal fluid normally is lacking in purine. An avirulent strain became virulent when a purine, xanthine, was injected intraperitoneally or when the organism reverted to purine independence.

Although failure to meet the nutritional needs of the infectious agent provides a ready explanation for antagonism, the practical importance of this mechanism has been overestimated. Melnick[220] pointed out that nutritional deficiencies usually result in antagonism only when the animal is in such deficient state as to be almost moribund; he believes that in most mild deficiencies virus and host cell compete for a nutrient, with the virus seemingly having priority. Under these circumstances, any advantage to the host in combating the virus is offset by the adverse effects of malnutrition, including synergism with secondary

infections and interference with convalescence.

The mechanisms involved seem to preclude the use of dietary deficiencies as control measures in most situations where antagonism is known to occur. Some specific metabolic antagonists, however, block reactions of vital importance to the agent and of lesser importance to the host. Information as to the enzymatic and metabolic influences of diet on specific enzyme systems in animals of the kind recently summarized by Knox *et al.*[167], needs to be correlated with knowledge of the specific biochemistry and physiology of microorganisms.

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. At a recent three-day conference on Nutrition in Infections[230] no principal speaker mentioned this feature of the problem.

Infection and Protein Metabolism. Kwashiorkor is a major factor in the high mortality among preschool children characteristic of at least 50 technically underdeveloped countries[28,297]. The symptoms are commonly precipitated by an acute infection[13,81,153,299]. Either diarrhea[26,340] or measles[252] 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[27,119]. 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 the diarrhea[153,299]. 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[196] 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[22], pneumonia and streptococcal infections[91], erysipelas[69], pyelonephritis and paratyphoid[168], typhoid[70,171], tuberculosis[205,258], and meningitis[126]. Loss of urinary nitrogen is partly from greater energy requirements imposed by higher body temperature, but mainly from toxic destruction of protein[245]. Nitrogen loss may continue long after fever has subsided[126,276] or may begin during the prodromal period before fever and clinical signs appear[30]. Similar nitrogen loss occurs in dogs with sterile abscesses and minimal febrile reaction[71,77,373].

Chronic infections also have an adverse influence on protein metabolism; hypoproteinemia may develop despite normal protein intakes[50b] and dietary protein supplements are less effective[348].

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[61,260,276]. Close[68] 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[343b] control of pancreatic enzyme was reduced, presumably a common occurrence in other infections. Nevertheless where fecal nitrogen has been measured, the increase is small.

Intestinal helminths can interfere with protein digestion by competing with the host for nitrogen, producing antiproteolytic enzymes and damaging the intestinal mucosa[47a,146,291]. For example, significant increases in nitrogen have been demonstrated in Indian children after treatment for ascariasis[344]. Both *Ascaris lumbricoides* and *Strongyloides edentatus* have enzymes not only for utilization of carbohydrate[278a], but for the digestion of protein[278c] and fat[278b]. *Trichinella spiralis* in rats[278d], *Trichostrongylus colubriformis* and mixed nematode infections in lambs inhibited protein digestion[108]. Eleven nematode species have been shown to decrease protein absorption in sheep[320].

Infections with intestinal protozoa occasionally reduce nutrient absorption. Véghelyi[343a] has shown that increased fat in stools of children with *G. lamblia* is due to impaired absorption. He related this to his observation in rabbits of as many as 1,000,000 giardia per square centimeter of mucosa. Under such circumstances absorption of nitrogen could be affected.

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[141a]. Either experimental trypanasomiasis[235] or tuberculosis[34] may hasten the appearance of scurvy in guinea pigs.

Diarrheal and other infections may decrease serum vitamin A levels[152,305] and more importantly precipitate xerophthalmia, keratomalacia and even blindness[38,239,314]. Giardiasis sometimes interferes with vitamin A absorption in children[59,158]. In Japanese prison camps beriberi developed in more than half of persons with dysentery[308]. 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[298]. Children on a low protein diet had pronounced and protracted depression of growth after respiratory infections[358]; 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[213]. Rates of growth and maturation are relatively sensitive indicators of adverse metabolic influence from infection.

Infection and Anemia. Infections significantly reduce hemoglobin levels even with an adequate diet[63,132]. In Uganda, Trowell *et al.*[340] found that severe bacterial infections including pneumonia, meningitis, septicemia and tuberculosis caused anemia, sometimes suddenly. Mildly anemic[48] patients with tuberculosis, chronic lymphangitis, or pneumonia had marked inhibition of bone marrow with shortened erythrocyte life span, as demonstrated by radioactive isotypes of iron.

Chiriboga *et al.*[60] reported macrocytic anemia to be common among poorly nourished patients with malaria, and microcytic anemia in those with hookworm. With associated malaria and hookworm, the two types of anemia were equally frequent. Low

serum iron levels are stated to be the most constant feature of anemias associated with infections in man[53a].

Extensive information is available on anemias of experimental infections. In pigs either staphylococcal infection or sterile turpentine abscesses[53b,365] resulted in a pronounced hypoferremia and anemia. In fasting dogs either endometritis or sterile abscess interfered with hemoglobin production[277]. Spontaneous infection in monkeys or sterile turpentine abscesses resulted in folic acid deficiency and megaloblastic anemia[204], suggesting that additional vitamin B_{12} or folic acid was required during severe or prolonged infection.

That hookworm infection reduces weight, strength, stamina and performance of adults and contributes to retardation of both physical and mental growth of children is well established[174]. The study of Rhoads *et al.*[266a, 266b] in Puerto Rico, supported by many others, shows that addition of iron even without antihelminthic treatment gives marked improvement in anemia. By competing with the human host for vitamin B_{12}, the cestode, *Diphyllobothrium latum*, has been shown to cause a form of macrocytic anemia[346a,346b,347].

Areas for Research. Certain lines of investigation appear especially promising in furthering knowledge of interaction between nutrition and infection.

Field Studies on Human Populations. Community programs for improved nutrition should include measurement of the impact of diet on extent, course and frequency of infectious disease[120], as well as the more conventional appraisal of physical development and nutritional status. This applies especially to the many studies now in progress on kwashiorkor. The strong association between infection and the subsequent appearance of frank malnutrition in infants and young children needs systematic exploration, particularly during the difficult period of transition from breast feeding to an adult diet.

Dependable information on morbidity and mortality is regularly lacking in countries where infant mortality is great. Field studies provide the only practical means of acquiring this essential information for some time to come. The feasible procedure is to incorporate such effort in activities of the health demonstration centers now developing in many countries.

Even in technically developed countries, individual cases of malnutrition will be encountered in clinical practice, by reason of environmental or genetic factors. The influence on staphylococcal and common respiratory infections merits study.

Experimental Studies on Laboratory Animals. The value of laboratory investigation is in testing hypotheses and exploring individual clues derived from clinical and epidemiological observations. Specific deficiencies from single nutrients can be produced and their effect evaluated; in the field most deficiencies are multiple and mixed. Interaction of induced deficiencies with infection by strains of an infectious agent of known virulence can be identified in host animals of pedigreed genetic background. Such specificity is important in defining mechanisms and determining possible control measures. The results should not be extrapolated to human populations without proper field investigation.

Many laboratory studies of the past suffer from poor experimental design and analysis; the present is not exempt. Some 10 years ago an outstanding conference[65] of workers in the field codified ground rules for the conduct of such investigations. For the particular purpose of determining interaction between infection and nutrition, they may

be enlarged and modified as follows: (1) The fundamental importance of the genetic constitution of both host and parasite has been repeatedly demonstrated. (2) Infections of a type occurring spontaneously in the animal host, or with a clinical reaction in laboratory animals paralleling that in humans, are generally preferred as subjects for study. (3) If a natural portal of entry is possible, the practical value of the results commonly is greater than for infectious agents introduced artificially, especially where local trauma is involved. (4) Dose and virulence of the infectious agent requires careful control. Since nutrition studies commonly extend over long periods, the agent should be suitably stored to provide a stable preparation for continuing experiments. (5) There is need for precise definition of nutritional deficiencies, distinguishing particularly those due to specific nutrients and those incident to inanition or dehydration, through lesser palatability, decreased appetite, or inability to assimilate food and water. Severe and highly specific deficiencies can be produced by antimetabolites, a technique of proven usefulness in pyridoxine, thiamine and other deficiencies. Greater use can be made of paired feeding, but not to exclusion of ordinary controls which provide conditions more nearly comparable with natural situations. (6) The level of the deficiency should be controlled and recorded. Interaction is possible within limited ranges and at low levels of deficiency. The competition for nutrient between host and agent needs to be evaluated. (7) Virus studies show that duration of deficiency is sometimes important; reversals between antagonism and synergism have occurred as deficiencies pass from acute to chronic stages. (8) Criteria for measuring resistance should be specified; more than one measure of resistance is desirable, such as survival, production of antibodies, phagocytic activity or localization of pathogenic organisms. (9) Attention to factors such as age, weight, sex, segregation of litter mates, physical condition of cages, likelihood of coprophagy, variation in intestinal flora, temperature and humidity of the laboratory are basic elements in good experimental design. (10) The numbers of experimental animals should be sufficiently large to permit satisfactory statistical appraisal of results, with consideration of the advantages of factorial methods of design and analysis. (11) Appropriate controls include uninfected animals on the deficient diet, normal animals receiving the infectious agent, and normal animals given the medium or normal tissue without the agent, the latter because of possible nutrients in this material.

Biochemistry and Metabolism of Infectious Agents. Investigation of specific nutritional requirements of such readily cultured infectious agents as the bacteria is now extended by modern techniques to those requiring living cells for multiplication or having a direct parasitic relationship to host metabolism. The possibility of new means for biochemical control of infectious agents by interfering with their metabolism has progressed beyond the speculative stage; the usefulness of the sulfonamides rests in their ability to act as metabolic antagonists to para-aminobenzoic acid. Ways of reaching intracellular agents by acting on their metabolic processes through the enzyme systems of host cells are under study. The dependence of viruses on the enzyme systems of host cells has been well demonstrated[107]. A possible attack is that host cells may have alternate metabolic systems permitting substitution of nutrients, while viruses and other agents presumably are more limited in the biosynthetic processes

used. If specific nutrients are found essential to a microorganism but not required by host cells, experimental efforts to produce these deficiencies by metabolic analogues become logical.

Mechanisms of Synergism and Antagonism. Although agent metabolism probably will continue as the primary interest in studies of antagonism, other mechanisms of interaction are possible. Research in synergism should escape its present major restriction to measurement of antibodies. Properdin[144] and other nonspecific factors in resistance, such as rate of cellular metabolism, edema versus dehydration of tissues, the balance of electrolytes and endocrines, and types of inflammatory response all merit consideration. More information is needed on optimum diets for convalescence.

Some Common Misconceptions. A frequent inclination to dismiss the association of nutrition and infection as of little practical importance is based on the following erroneous interpretations of existing data. (1) Examples of antagonism are such spectacular departures from previous concepts that they are sometimes overemphasized and considered the prevailing type of relation. Comment: The preceding tables and text demonstrate the greater frequency of synergism over antagonism. (2) Much published information claiming synergism fails to meet modern standards of scientific evidence, with the result that the basic concept is put in doubt. Comment: Many well designed and executed studies leave no doubt of the frequent occurrence of synergism. (3) Since antagonism does occur, a poor diet might be advantageous to an infected host. Comment: Poor diet is neither an accepted nor an effective therapeutic measure; even where antagonism exists, such a diet under natural conditions will delay convalescence and lead to synergistic appearance of secondary infections, increasing the threat to survival. (4) The degree of malnutrition necessary to produce synergism and antagonism in experimental animals does not occur in populations of man or domestic animals. Comment: This comes from incomplete knowledge of the seriousness of malnutrition in technically underdeveloped areas of the world; extreme degrees of deficiency exist today in both human and animal populations due to grossly inadequate intakes of protein and other specific nutrients. (5) Experimental studies demonstrate genetic characteristics to be more important than nutritional factors. Comment: This is based on erroneous generalizations from work on inbred laboratory strains of animals having fairly uniform resistance and exposed to controlled infection. It does not usually apply to natural populations of diverse genetic background exposed to multiple infections. (6) Improving the diet or prescribing vitamins is ineffective in improving resistance to infection. Comment: This applies to diets already adequate and is irrelevant to understanding of the consequences of a deficient diet.

Working Generalizations. The following generalizations are proposed as a guide to continuing investigations in clinical and community medicine: (1) In human populations interaction between nutrition and infection is probably more important than the results of laboratory investigation would indicate. Greater response to nutritional influences occurs in host and agent populations of heterogenous genetic origin than in homogenous populations. (2) Synergism is the dominant interaction. No competent observer can witness the deaths from seemingly trivial infections of malnourished persons in technically underdeveloped areas or scan the list of causes of death

in such regions without realizing that large numbers of people are dying from infections ordinarily not fatal. Multiple infections with parasites and bacteria, larger infecting doses because of poor sanitation, genetic susceptibility, and environmental conditions are explanations commonly advanced for this high fatality. Wartime experiences and clinical evidence from wards of hospitals receiving large numbers of poorly nourished patients support many laboratory studies that synergism is of particular importance. Worldwide research on kwashiorkor demonstrates that protein deficient children are at high risk of fatal infection and with refeeding this risk steadily decreases. (3) That type of synergism in which infections contribute to malnutrition needs far more emphasis than it has received. With malnutrition so frequent in many parts of the world, infection often sets off a train of events resulting in death from malnutrition or a related terminal infection. Children might well survive one or the other but not both. (4) Adding nutrients to an already adequate diet usually has no effect on infections. The major exceptions are infections with certain intestinal parasites where secondary action on bacterial flora and other factors come into play, and less pertinently the highly questionable evidence on vitamin C. (5) The demonstrated antagonism between nutritional deficiencies and viral and protozoal infections has no recognized practical usefulness. (6) A gradient is evident, from a state of synergism characteristic of more or less free-living extracellular microorganisms, to antagonism with intracellular agents. While synergism occurs across the gradient, antagonistic phenomena appear only where organisms have obligate dependence on the enzyme systems of host cells. Based on type of microorganism the following patterns of interaction have been defined: a) Bacteria, rickettsiae and helminths are regularly synergistic with nutritional deficiencies; b) protozoa are as often antagonistic as synergistic; c) viruses are more often antagonistic than synergistic. (7) Patterns of interaction according to deficiencies in nutrients have the following characteristics: a) General inanition is regularly synergistic with most infections, but antagonism has been found with viruses and protozoa; b) protein deficiencies produce synergistic effects; rare instances of antagonism result from need of an infectious agent for a specific amino-acid; c) vitamin A deficiency is regularly synergistic; d) vitamin D deficiency commonly fails to interact with infections, but synergism has been demonstrated; e) vitamin B deficiencies result in synergism or antagonism depending upon agent and host; they are responsible for most known instances of antagonism; f) vitamin C deficiencies are usually synergistic, but antagonism has been demonstrated; g) specific minerals are either synergistic or antagonistic.

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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