

EFFECT OF INFECTION ON NUTRITIONAL STATUS

Introduction

The ways in which infectious disease influences the nutritional state of the poorly nourished received much attention in the early decades of the present century. Communicable diseases were then highly prevalent; knowledge of nutritional deficiencies was advancing rapidly; and connection between the two was increasingly evident. Eventually interest declined and was superseded by a concern for the reverse relation, that of malnutrition to resistance. A three-day conference on "Nutrition in Infections", held in New York in 1955, dealt solely with the effect of nutrition on infection, and made essentially no reference to the effect of infection on nutritional status (Miner, 1955). This may be partly explained by the fact that populations of North America and Europe are now so well nourished that the stress of acute infection on nutrition is rarely of practical significance.

Interest in this relationship has recently revived, largely because of recognition that kwashiorkor is an important disease in many less developed areas and of the demonstration that infection precipitates this syndrome in children suffering from subclinical, chronic, protein malnutrition.

Infections have a deleterious effect on the nutritional status of the host through physiologic and anatomic changes. These changes become evident in such systemic reactions as fever, leukocytosis, and stimulation of adrenal cortical activity. Local reactions include diarrhea, tissue inflammation and necrosis, increased mucus secretion, fatty liver, and changes in skin and hair. The investigations of earlier years, together with recent studies, provide conclusive evidence that almost all infections produce changes capable of influencing nutritional status.

The main research effort in this field has utilized laboratory animals because they can be subjected to rigidly controlled diets, induced infections,

and complete examination of tissues. For ethical or practical reasons, some studies can be done only with laboratory animals. Others can be conducted more profitably in man. Metabolic effects are best measured in hospitalized patients. The deleterious nutritional results of reduced food intake due to loss of appetite, of "therapeutic" diets less adequate in protein than normal diets, and of purgatives and other medicines are best observed in patients under clinic or field conditions. Information on mortality, morbidity, and general community health can be obtained only by investigating whole populations. The numerous clinical studies dealing with biochemical or metabolic consequences of infection are valuable in helping to understand the sequence of events, but they do not take the place of epidemiologic investigations in assessing the public health significance of a situation.

The observed effect of infection on nutritional status varies with time, place, and person. Less developed areas of the world are today experiencing many of the problems that confronted physicians and public health workers in Europe and the USA fifty years ago. The age or the physiologic state of the host often determines whether nutritional deficiency will be manifest or clinically inapparent under a given circumstance. For example, growing children and pregnant and lactating women are particularly vulnerable. An added stress such as infection, often relatively innocuous of itself, may be sufficient to precipitate acute malnutrition.

Many physicians and public health workers from economically favored countries are now called upon to advise or actually work in less privileged areas. What is still more important, many of the eventual health leaders of the latter countries are being trained under conditions far different from those in which they will practice. Both groups of workers need to be familiar with the seriousness of the synergism between infection and malnutrition when both conditions are present simultaneously in appreciable numbers of the population.

This chapter provides a summary of present knowledge and suggests further research. The number of studies dealing with the effect of bacterial and helminthic infections on nutrition is relatively large. Fewer reports are available on viral and rickettsial diseases, principally because techniques for studying these infectious agents have developed more recently. Little information is at hand on fungus infections or on the injuries and infections arising from arthropods, although in tropical areas these agents are responsible for a significant amount of disability.

Evaluation of the effect of infectious disease on nutritional status was a direct objective of most of the reports now to be discussed. Sufficient investigations are cited to document the important impact of infection on nutrition, particularly when a borderline deficiency already exists. Systematic review of all articles on the various infectious diseases would yield many additional pertinent references, but is deemed unnecessary.

Infection and Protein Nutritional Status

Intestinal infection of bacterial origin

Bacterial infections of the intestinal tract have an adverse influence on protein nutrition that is of major public health importance. In less developed countries this is most evident among young children during the weaning period, when inadequate diets lead to malnutrition. Some of the earliest observations were on the effects of typhoid fever and other enteric infections on nitrogen excretion because these diseases were prevalent in the more developed countries at the time when human requirements for protein were first being recognized. Furthermore, their relation to the intake, digestion, and absorption of food was obvious.

In his Harvey lecture of 1908, MacCallum (1910) drew attention to the findings of Vogel (1854) and Traube (1855) that typhoid fever causes a striking increase in urinary output of nitrogen. He referred to a patient described by Leyden & Klemperer (1841) who experienced a loss of 100 g of nitrogen, equivalent to 3.2 kg of muscle tissue, in only 12 days. A patient described by Müller (1884) lost nitrogen corresponding to 2.5 kg of muscle in eight days. Two important papers by Coleman & Gephart and by Coleman & DuBois in 1915 similarly reported large nitrogen losses due to typhoid fever, even when adequate calories were fed. As a result, therapeutic diets for patients with typhoid fever were changed from a low to a high protein content.

In typhoid fever, Krauss (1926) found a two- to three-fold increase in nitrogen excretion together with a decrease in urinary creatinine due to loss of muscle mass. Shaffer & Coleman (1909) were unable to maintain nitrogen balance in typhoid fever patients even with 90 calories and 1.6 g of protein per kilogram of body-weight. One patient with paratyphoid fever excreted 14.5 to 16.0 g of urinary nitrogen daily at a time when the intake was 2.2 g of nitrogen and 56 calories per kilogram of body-weight. All of the nitrogen loss was through the urine; fecal nitrogen was within normal limits. Although diarrhea was a regular feature, nitrogen absorption was little affected. Modern chloramphenicol treatment of typhoid fever has reduced the duration of the febrile period, but a strongly negative nitrogen balance is still a prominent feature of the disease (Woodward & Smadel, 1964).

Close (1953) described a child recovering from kwashiorkor whose serum albumin rose within seven weeks of therapy from 1.05 to 3.58 g per 100 ml, only to fall to 1.59 g per 100 ml five days after the onset of typhoid fever. A decrease in serum albumin is characteristic of acute infections. In an authoritative review of the characteristic pattern of plasma proteins in acute infectious disease, Belfrage (1963) described a more or less regular alteration for the various clinical types. Acute bacterial infections such as

pneumonia produce marked changes in all blood serum components, especially a decrease in albumin and an increase in alpha and beta globulins. An increase in the gamma globulin fraction is associated with lymphoid activity and prolonged antigenic influence. Experimental fevers induced by bacterial endotoxins produced essentially the same changes as bacterial infections of short duration. Most recently, Crawley and co-workers (1966) have described an early increase in blood urea nitrogen and a slow decrease in serum proteins as a result of the intravenous administration of a purified enterotoxin, type B.

Blood amino acid changes may prove to be one of the earliest detectable metabolic responses to infection. An early increase in whole blood amino acids was observed in young men with experimentally induced typhoid fever who subsequently developed symptoms, but not in those who had no clinical illness (Feigin et al., 1968). A significant decrease in blood amino acid concentration followed the development of the disease in subjects who became ill. In experimental tularemia in man, the amino acid decrease occurred 12 to 60 hours after exposure and prior to clinical symptomatology (Feigin & Dangerfield, 1967). In Venezuelan equine encephalomyelitis, blood amino acid response tended to occur at least a day earlier in subjects inoculated at 8 a.m. than in those infected at 8 p.m. (Feigin et al., 1967).

An outstanding epidemiologic feature of kwashiorkor is the frequency with which it is precipitated by an attack of acute diarrheal disease. Many observers have emphasized this sequence, among them Brock & Autret (1952), in Africa; Autret & Béhar (1954), in Central America; Waterlow & Vergara (1956), in Brazil; Jelliffe and co-workers (1954), in Jamaica; Van Der Sar (1951), in Curaçao; Gerbasi (1956, 1957), in Sicily; Pretorius and associates (1956), in South Africa; Cravioto (1958), in Mexico; Gupta (1958), Rao and co-workers (1959), and Bhattacharyya (1961), in India; and Ryan & Murrell (1964), in New Guinea. Gopalan (1955), in India, and Jelliffe and associates (1960), in Trinidad, noted that infectious diarrhea reached its peak at the beginning of the dry season, when flies were prevalent, and was, in turn, followed by outbreaks of kwashiorkor three to four weeks later. A survey of severely dehydrated children with gastroenteritis showed that over 60% had severe hypoalbuminemia (Truswell et al., 1963).

Smythe (1958), in Cape Town, observed a regular overlapping of the seasonal prevalence of gastroenteritis and kwashiorkor, which he believed to be due to metabolic effects of the infection along with a marked disturbance of the intestinal flora. In studying the absorption of amino acids from an isolated Thiry loop in an adult man, Orten and co-workers (1962) found that spontaneous infection in the loop retarded total absorption of an 18-amino-acid mixture by 14%. Administration of neomycin markedly altered the intestinal flora and decreased absorption by 30%. In general, the rapidly absorbed amino acids in the mixture were less inhibited than those more slowly absorbed.

In acute gastroenteritis, as in typhoid fever, only a small part of the adverse nitrogen balance is apparently attributable to decreased absorption of nitrogen. As early as 1915, Holt and associates noted that even with severe diarrhea nitrogen absorption rarely fell below 75%. Chung (1948) and Chung & Višćorová (1948) found that the loss of nitrogen in diarrhea was much less than that of fat, and that the feeding of protein consistently increased the net absorption of nitrogen. In diarrhea, however, nitrogen absorption was reduced from 90% to approximately 75% and, in one instance, to as low as 27%.

It is relevant that the administration of antibiotics to patients on restricted vegetarian diets resulted in reduction of fecal nitrogen, along with an increase in urinary nitrogen, urea, and ammonia comparable to levels seen in patients on an iso-nitrogenous diet supplying protein of animal origin (Deosthale et al., 1964). The effects of the antibiotic and the animal protein diet given together were not additive. Obviously, the type of intestinal flora associated with the vegetable protein diet was less favorable for nitrogen absorption than that present when animal protein was in the diet.

Chickens infected with *Salmonella pullorum* (Ross et al., 1956) showed a seven- to ten-fold increase in blood urea, even though the formation of blood urea through the ornithine-citrulline cycle is normally insignificant in chicks and other animals that excrete nitrogen as uric acid. Administration of arginine apparently prolonged survival by activating this cycle. Measurements of urinary nitrogen were not made, but a significant amount of urea nitrogen in the urine was the probable reason for the nitrogen imbalance. A similar nitrogen loss occurred in dogs with sterile abscesses and minimal febrile reaction (Cook & Whipple, 1918; Daft et al., 1937; Yuile et al., 1953).

The general deduction is that, although intestinal infections of bacterial origin may cause some decrease in absorption of nitrogen from the gastrointestinal tract, the more important and constant effect is increased urinary nitrogen and a secondary anorexia. In a poorly nourished child, diarrhea may begin as an acute infection and end as chronic diarrhea, perpetuated by protein deficiency.

Tuberculosis

The nutritional effects induced by tuberculosis were among the first to be studied. The interest still continues because tuberculosis is an important cause of death everywhere, and especially in less developed regions.

As early as 1922, McCann showed that urinary nitrogen excretion was markedly increased in patients with tuberculosis. Krauss (1926) described a two- to three-fold increase in febrile tuberculosis and a change in urinary ratio of sulfur to nitrogen from 1:7 to 10:7. In afebrile patients the effect was small. More recently, Johnston (1953), Co Tui and co-workers (1954),

and Rao & Gopalan (1958) have confirmed these results in active, febrile tuberculosis.

Getz and associates (1951) have emphasized the relatively low levels of serum albumin in patients with tuberculosis, compared with other illnesses. Excessive sputum conceivably has nutritional significance, since normal loss of nitrogen in sputum averages 0.68 g per day, and may be as high as 1.7 g even for healthy persons (Kocher, 1914).

Reports from West and Central Africa (Morley, 1959; De Maeyer, 1957), from South Africa (Pretorius et al., 1956), and from India (Jayalakshmi & Gopalan, 1958; Bhattacharyya, 1961) all suggest that tuberculosis can precipitate kwashiorkor in children already suffering from chronic malnutrition. This would be expected in view of the strongly negative effect on nitrogen balance.

Guinea-pigs with tuberculosis showed a negative nitrogen balance except when fed a high-protein diet (Rao & Gopalan, 1958). Tuberculosis produced low serum albumin levels in chicks (Wogan et al., 1961), although increases were observed in alpha-3, beta, and gamma globulin fractions. The amounts of protein and of lysine in the liver were also depressed (Squibb et al., 1965).

In summary, the increased excretion of nitrogen and the decreased intake of food associated with active tuberculosis not only complicate clinical management, but may be of considerable public health importance in regions where protein malnutrition is common.

Other acute bacterial infections

Other infections also affect nitrogen balance and, as recently demonstrated, bring changes in concentrations of amino acids in blood and urine. In calves infected with *Bacillus abortus*, there is an increase in serum globulin and a tendency for a decrease in albumin fractions (Howe & Sanderson, 1924).

Rats injected with *Pasteurella tularensis* showed a disappearance of serum cystine, arginine, and phenylalanine within 72 hours, as measured by paper chromatography, along with a marked lowering of other free amino acids in the blood (Woodward et al., 1954). These changes did not occur with either killed or avirulent bacilli. After the rats recovered, plasma amino acid levels returned to normal. Excretion of free amino acids in the urine was unchanged.

In extensive and well-controlled studies in man (Beisel, 1966; Beisel et al., 1967), healthy young adults experimentally inoculated with *P. tularensis* experienced a marked increase in urinary nitrogen excretion coincident with onset of fever.

Kocher reported in 1914 that 2.5 to 3 g of protein per kilogram of body-weight were required daily for nitrogen equilibrium in patients with erysipelas,

pneumonia, and pyelonephritis. In erysipelas (Coleman et al., 1922) and in arthritis (Cecil et al., 1922), nitrogen equilibrium, even with adequate calories, may require up to 15 g of nitrogen daily.

Johnston & Maroney (1938) demonstrated that even chronically infected tonsils exert a marked catabolic effect. Isonitrogenous diets were fed, urine samples collected daily, and feces pooled for three-day periods in a group of children. In nine children with enlarged tonsils, a history of recurrent attacks, but no acute infection at the time, the average nitrogen balance was -0.06 g of nitrogen per kilogram of body-weight per day. After tonsillectomy the balance rose in all patients to an average of $+1.52$ g.

Nitrogen balance studies at the Institute of Nutrition of Central America and Panama (INCAP), originally designed to determine the quality of dietary protein, were complicated by a variety of intercurrent infections, including asthmatic bronchitis, bronchopneumonia, tonsillitis, sinusitis, and staphylococcal abscesses (Scrimshaw et al., 1960). Such infections were regularly followed by a decided drop in nitrogen retention, which persisted for one to two weeks after recovery.

Almost all bacterial infections produce an increased urinary excretion of nitrogen. Generally they also result in some decrease in protein intake. Both effects depend on the severity of the disease and, with respect to urinary nitrogen, on the nutritional state of the host as well. The return to a normal nitrogen balance is frequently delayed beyond clinical recovery from the acute episode.

Viral infections

Specific studies of viral infections and the nutritional status of the host are relatively few, and most of them are recent.

Field observations suggest that measles, of all the common communicable diseases of childhood, imposes an unusually severe nutritional stress. Morley believes that measles precipitates kwashiorkor in malnourished children of West Africa more frequently than any other infectious disease (Morley & MacWilliam, 1961; Morley, 1962; Morley et al., 1963; Morley, 1967). Purcell (1939) and Sai (1965), in Ghana; De Maeyer (1957), in the Congo; Gans (1961), in Lagos; Avery (1963), in Sierra Leone; Bezon (1959), in Algeria; Restrepo Molina (1955), in El Salvador; and Netrasiri & Netrasiri (1955), in Thailand all emphasize the importance of this disease as a contributory cause of kwashiorkor. A fall in serum albumin in measles has been observed by Mansharamani (1961) and Giuliani (1963). Diarrhea is a frequent accompaniment of measles in malnourished children (Morley, 1962; Scrimshaw et al., 1966*a,b*) and must impair intestinal absorption to some degree. Patients studied by INCAP showed a negative nitrogen balance during the febrile stage, due primarily to increased urinary excretion of

nitrogen. Salomón and associates (1968) have cited examples of kwashiorkor precipitated by measles, German measles, chickenpox, and whooping cough.

Kearney and associates (1948a) showed that Theiler virus encephalomyelitis in mice precipitated a tryptophan deficiency in animals on a diet low in that nutrient. Symptoms were identical with those caused by tryptophan deficiency alone, but death occurred at about 18 days instead of 34. These investigators mentioned similar results with diets deficient in either methionine or valine, but gave no details. One possible mechanism is suggested by the finding that cellular protein synthesis has been found to be markedly depressed after infection of mouse L cells in tissue culture with Venezuelan encephalomyelitis virus (Lust, 1966).

Sanslone & Squibb demonstrated that nitrogen retention in chicks infected with Newcastle virus increased during the incubation period and decreased during the active stage of the disease. The increase seemed to be due to the infection *per se*, whereas paired-feeding studies indicated that the decrease was due to a reduction in food intake. The loss in body-weight and increase in liver size in chicks with this disease were accompanied by a lower level of free amino acids in the blood, similar to that in starved birds (Squibb, 1964a).

Whedon & Shorr (1957) attributed the negative nitrogen balance in children with paralytic poliomyelitis to atrophy of muscle, because of a parallel decrease in body-weight and a drop in creatinine excretion in the urine. Studies of chickenpox by Wilson and co-workers (1961) suggest, however, that viral infections not associated with muscular paralysis also have a significant depressing effect on nitrogen balance. A markedly increased nitrogen retention for at least two weeks after recovery from the acute disease was evident in young children fed a daily ration of 1.5 to 2.0 g of protein (unpublished INCAP data, 1966). Chickenpox is also known to precipitate kwashiorkor in poorly nourished children (Salomón et al., 1968). Even as mild a viral infection as that induced by 17-D yellow fever vaccine (Gandra & Scrimshaw, 1961) or smallpox vaccine (unpublished INCAP data) produced a detectable effect. Increased nitrogen losses in children with influenza have been demonstrated by Górnicki and co-workers (1967). Beisel et al. (1967) have reported that the onset of negative nitrogen balance in sandfly fever coincided with the onset of clinical symptoms in six subjects.

The apparent effect of stress on nitrogen balance is less marked in laboratory animals already severely depleted of protein (Cuthbertson, 1954, 1961). This is consistent with the findings of Davies and associates (1959) in a patient with chronic hepatitis and an initial serum albumin level of 1.4 g per 100 ml. The disappearance rate of intravenously administered ^{131}I -labeled serum albumin and the total excretion of nitrogen in the urine were only about half the normal amounts. Unfortunately, details of dietary intake were not given, and protein intake may have been reduced.

Thus, all viral diseases, even the mildest, exert a detectable adverse effect on nitrogen balance. Epidemiologic evidence indicates that viral diseases precipitate kwashiorkor in a substantial number of underprivileged children.

Rickettsial infections

The nutritional consequences of rickettsial infections have not had much study. The frequency of edema and low serum protein levels in Rocky Mountain spotted fever led Harrell and associates (1946) to carry out nitrogen balance studies in a group of adult patients. Over 4.0 g of protein per kilogram of body-weight were required to maintain balance while fever was present. Beisel et al. (1967) have shown that Q fever also markedly increases urinary excretion of nitrogen in young men, even in one asymptomatic case displaying only rickettsemia.

Rickettsial diseases do not seem to differ from other infections in producing deleterious effects on the protein nutritional status of poorly nourished persons.

Protozoal infections

Many investigations, in man and in animals, have been concerned with the nutritional consequences of acute and chronic malaria. Except for two studies of trypanosomiasis in monkeys, no systemic protozoal disease other than malaria seems to have been investigated for its effect on nitrogen metabolism.

The protein metabolism of rats infected with *Plasmodium berghei* malaria is particularly instructive (Dema et al., 1959). Infected animals have been shown to be less able to absorb protein nitrogen, partly because of reduced intestinal proteolytic activity. Increased nitrogen excretion in the urine and a lower ratio of urea to total urinary nitrogen in the infected animals were even more important. Other statistically significant changes included increased liver fat, more total body water, and lower values for hematocrit, hemoglobin, and serum protein. Uninfected pair-fed controls showed no significant change in protein metabolism.

MacDonald (1960) has shown that the combination of experimental malnutrition and *P. berghei* infection in mice resulted in more hepatic fibrosis than in similarly infected well-fed animals. These results confirmed the hypothesis of Walters & Waterlow (1954) that malaria and malnutrition are jointly responsible for the frequent hepatic fibrosis of children in Gambia. Zuckerman & MacDonald (1964) have subsequently shown that hepatic fibrinogenesis in mice infected with *Schistosoma mansoni* is increased in animals consuming a high-carbohydrate, low-protein diet compared with control animals with the same infective dose.

A steady increase in concentration of all amino acids in erythrocytes was observed as parasitemia progressed in chicks infected with *P. gallinaceum* (Rama Rao & Sirsi, 1958). Aspartic acid, valine, glycine, threonine, and phenylalanine reached three to six times their original values. However, the plasma concentration of most amino acids fell during parasitemia, after a slight initial increase during the incubation period. Liver and brain tissues showed a steady decrease of almost all amino acids. Because of a probable close relation to plasmodial metabolism, the investigators making this study directed particular attention to the observed increase of amino acids in the erythrocytes.

In 1918, Barr & DuBois observed that, without exception, a negative nitrogen balance occurred during the acute, febrile period of malaria. In a study of 12 young men with experimentally induced *P. vivax* malaria, Taylor and co-workers (1949) found that levels of serum albumin were 14.5% lower when patients were experiencing five to eight paroxysms and an average of 193 hours of fever at 101 °F (38.3 °C) or more than during control periods. Oomen (1957) noted that Indonesian children between one and 12 years of age who were suffering from both malnutrition and chronic malaria had larger livers than those suffering from one of these conditions alone. Malaria prevalence was estimated by splenic enlargement.

Chicks with acute coccidiosis produced by injection of *Eimeria acervulina* or *Eimeria necatrix* in the fourth week of life gained only 63 g during the fifth week, as compared with 247 g for controls (Panda, 1963). During the sixth week, however, both groups had the same rate of gain, and during the seventh to fourteenth weeks the rate was slightly greater in the previously infected birds (Panda et al., 1962a). Nitrogen retention during the fourteenth week was also slightly greater in the infected chicks (Panda et al., 1964). The adrenal cortex was larger and cells of the islets of Langerhans were hypertrophied and more numerous (Panda & Combs, 1964). These late findings were presumably compensatory.

Acute trypanosomiasis produces a greatly decreased serum albumin and increased serum gamma globulin levels in monkeys (Woodruff, 1959; Smithers & Terry, 1959). Mice injected with a "non-pathogenic" strain of *Trypanosoma duttoni* and then starved, died significantly earlier than controls (Sheppe & Adams, 1957).

Janz & Pinto (1963) were unable to establish that rats infected with *T. rhodesiense* experienced any significant change in nitrogen metabolism directly attributable to the infection. With lower food intake and a continuing fever, changes in nitrogen metabolism were demonstrable.

Giardia lamblia may attach itself to the intestinal mucosa in man in sufficient numbers to impair nutrient absorption (Cortner, 1959). Undoubtedly, nitrogen absorption is affected, although no direct studies have been made.

Both trypanosomiasis and malaria tend to produce, in their febrile stages, a negative nitrogen balance, but only when the concentration of

parasites is relatively great. Severe infections with pathogenic intestinal protozoa also influence nitrogen balance adversely, although few have been studied.

Helminthic infections

Most of the infections thus far discussed cause an increased excretion of nitrogen in the urine, with little or no interference with nitrogen absorption from the gastrointestinal tract. Investigators of the nutrition of domestic animals have long recognized that helminthic infections interfere directly with protein utilization. Many years ago, the University of Cambridge Institute of Animal Pathology carried out nitrogen balance studies in sheep infected with a variety of nematodes. Fluctuations in protein absorption paralleled changes in the worm burden (Stewart, 1932-33). Even when many worms were present, the digestion of other components of the ration was unaffected, with the possible exception of crude fiber.

It is conceivable that in some helminthic infections anti-enzymes directly inhibit pepsin and trypsin in the intestinal lumen. For example, Sang (1938) assigned the name "ascarase" to an enzyme isolated from *Ascaris lumbricoides* that *in vitro* has an inhibitory effect on pepsin and trypsin and *in vivo* a significant capacity to decrease food absorption. Since absorption of nutrients other than proteins may be affected at the same time, mechanical damage to the mucosa may also be a factor.

Franklin and associates (1946) found that *Trichostrongylus colubriformis* infection in sheep depressed not only protein digestibility, but also calcium and phosphorus utilization. Sheep on a hay diet lost weight and died when infected with *Trichostrongylus axei* whereas control animals kept worm-free remained unaffected (Gibson, 1954).

Working with rats experimentally infected with *Trichinella spiralis*, Rogers (1942) observed a marked lowering of protein digestion in the immediate 4 to 12 days after infection. A second and less marked response occurred after 30 days, presumably due to the departure of adult female worms from the intestinal wall. A decrease in nitrogen excretion in the urine also suggested that the acute infection affected protein absorption. By the twenty-fourth day, urinary nitrogen had increased to three times the normal amount. Rogers attributed this to tissue inflammation and destruction.

Heavy infection of rats with the hookworm *Nippostrongylus muris* markedly reduced net protein utilization, mostly by decreasing the amount of absorbed dietary nitrogen (Platt et al., 1961). This was also true of puppies infected with *Toxocara canis* (Platt & Heard, 1965).

Human adults with heavy hookworm infection had an average nitrogen absorption of 62.5%, compared with 73.3% in worm-free subjects on the

same diet (Darke, 1959). Holmes & Darke (1959) emphasized the greater importance of hookworm disease when food supplies were limited. Puerto Rican army recruits with severe hookworm disease had decreased intestinal absorption of nutrients (Sheehy et al., 1962). In severe infections more albumin was lost into the gut than would be expected from loss of red cells alone, since the hookworms appeared to ingest tissue fluid as well as capillary blood (Gilles et al., 1964).

In careful studies of nine children with heavy *Ascaris lumbricoides* infection, Venkatachalam & Patwardhan (1953) observed a decrease in fecal nitrogen per 24 hours from 1.3 to 0.7 g after de-worming. They attributed the original loss to an antiproteolytic substance secreted by the parasite. Darke's (1959) findings in nine patients in Buganda, Africa, were similar.

Schistosomiasis due to *Schistosoma haematobium* may produce a loss of albumin in the urine sufficient to result in lowered serum albumin and severe edema. Losses of 8 to 9 g of albumin within 24 hours were observed in two patients with severe disease (Farid, personal communication, 1965).

Loughlin & Mullin (1955) suggest that infectious diseases due to intestinal parasites and a variety of other causes have the capacity to shorten the time that food remains in the gastrointestinal tract of children ("intestinal hurry"). The result is a diminished opportunity for digestion and absorption. The anorexia, indigestion, colitis, and bloody stools in severe cases of trichuriasis fall into this category (Jung & Beaver, 1951). Venkatachalam & Patwardhan (1953) list "intestinal hurry", mechanical blockage, and mucosal damage as factors in the effect of ascariasis on the nutritional status of children.

Many investigators mention the frequent association of intestinal helminths and kwashiorkor. Among those expressing a belief that helminths are often a factor in precipitating the nutritional disorder are Peña Chavarría and co-workers (1948), in Costa Rica; Gillman & Gillman (1951), in South Africa; Jelliffe (1953a), in Western Nigeria; Williams (1953), in Ghana; Thomson (1954), in Malaya; De Silva (1954), in Ceylon; Netrasiri & Netrasiri (1955), in Thailand; Stransky & Reyes (1955), in the Philippines; Platt (1958b), in Africa; Pohowalla & Singh (1959), in India; and Fraga (1965), in Brazil. In a child with prior growth failure, there was a gain in body-weight with no change in diet following treatment of a heavy ascaris infection (Jelliffe, 1953a).

It should be noted, however, that Bray (1953) found no difference in fecal nitrogen in West African children before and after treatment for ascariasis and hookworm disease. On the basis of measurements of fecal fat and the urinary excretion of a test oral dose of D-xylose, Kotcher and co-workers (1966) found no evidence of intestinal malabsorption in children with strongyloidiasis or hookworm infection, but they did not measure nitrogen absorption. On the other hand, De Lima et al. (1966) reported D-xylose almost uniformly lower in 20 children with various combinations of

hookworm, *Trichuris*, *Strongyloides*, *Ascaris*, and *Giardia* than in 12 children without intestinal parasites. However, primary differences in nutritional status as well as the presence or absence of parasitism may have contributed to the results. Unpublished INCAP observations indicate that these diseases produce a detectable effect on nitrogen balance, as determined by examination of children on a constant intake of protein before and after treatment, only when they occur in a severe form. In India, the frequency with which intestinal parasites and ova were found in the intestines of children admitted to the Pediatric Hospital was essentially the same, whether or not they were suffering from kwashiorkor. (India, Council of Medical Research, Nutrition Research Laboratories, 1965).

By interfering with intake, absorption, and retention of protein nitrogen, almost any unusually heavy infection by an intestinal helminth can probably induce protein malnutrition in persons whose diet is otherwise adequate. Severe intestinal helminthic infections are common in many populations. The mere presence of a helminth does not, however, justify an assumption that it has clinical or metabolic significance. The relative importance of these infections in contributing to protein malnutrition is often over-emphasized, for the simple reason that intestinal helminths are visible or are readily demonstrated microscopically, whereas other infectious agents or the action of nutrients can be recognized only by complicated technical procedures. Unfortunately, few specific epidemiologic data are available regarding schistosomiasis, filariasis, onchocerciasis, and other helminthic infections that might well be expected to exert a systemic nutritional effect.

Excess of protein or amino acids

Increasing attention is at present being given to possible imbalances of nutrients, particularly the amino acids. Proof has accumulated that excess consumption of some nutrients markedly alters the requirements for certain others (Harper, 1957-58; Hsu, 1963). For example, excess methionine increases the requirement for tryptophan to the point of creating a relative deficiency. An instance of such antagonism was reported by Gershoff and associates (1952), who found that excess methionine interfered with type 2 poliovirus in mice; as they had previously demonstrated an antagonism between the virus and tryptophan deficiency, they concluded that the methionine acted by creating a relative deficiency of tryptophan. This methionine-induced tryptophan deficiency was further accentuated by giving the analogue 6-methyltryptophan.

A second instance, reported by Squibb (1964b), is that Newcastle disease, a viral infection of chicks, is made worse by either a deficiency or a surfeit of protein. The surfeit was induced by a diet containing 41% of casein. Two possible explanations were offered: first, that the raised energy requirements resulting from the infection caused an increase in the metabolic

use of protein, thus producing an amino acid imbalance; second, that the extra protein caused an increased multiplication of the virus.

Infection and recovery

If the increased urinary nitrogen excretion associated with trauma and acute infection arises from so-called "toxic destruction" of protein, as was formerly believed (DuBois, 1927; Peters & Van Slyke, 1946), it then becomes necessary to explain why the "destruction" is much less in malnourished persons than in those with adequate protein stores (Fleck & Munro, 1963). Increased loss of urinary nitrogen with no apparent tissue destruction also occurs through stress of psychological origin (Scrimshaw, 1963; Ohlson, 1958).

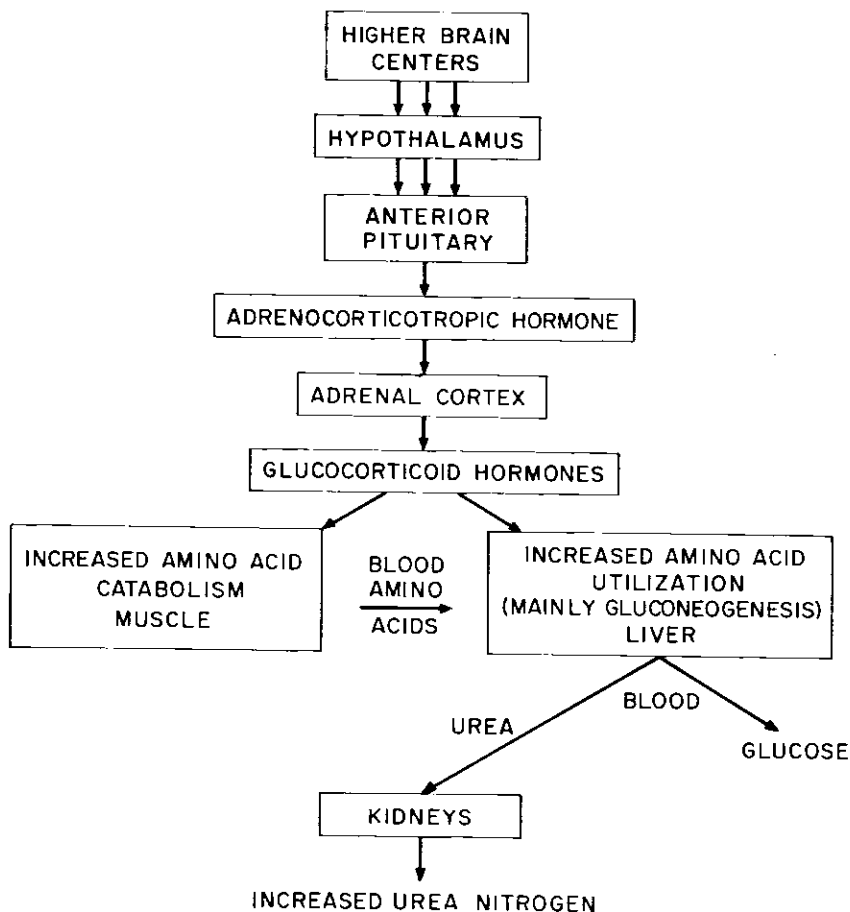
Much of the excess nitrogen in the urine of individuals with infectious disease probably comes from skeletal muscle, mobilized as a result of the adrenal cortical response to additional adrenocorticotrophic hormone (ACTH) produced by the anterior pituitary during stress from infection. The increased 17-hydroxysteroid hormones exert a catabolic influence on muscle, so that amino acids are released into the blood-stream. At the same time, these hormones are anabolic for the liver and stimulate gluconeogenesis from amino acids.

The endocrine relationships are shown schematically in Fig. 1. It cannot be assumed, however, that they comprise the whole mechanism. Adrenalectomized animals on a maintenance dose of cortisone are capable of the stress response, although it has been postulated that this arises from adrenal tissue outside the adrenal glands.

During recovery from stress of infectious origin, additional nitrogen must be retained to replenish that lost from muscle and other tissues. The so-called "anabolic phase" of recovery from infection or trauma was measured quantitatively in patients with typhoid fever and pneumonia as early as 1875 (Svenson, 1901), and is now so well known as to require no further documentation.

Waife and associates (1950) studied 12 patients with protein depletion and a complicating infection. Six patients given relatively large protein supplements in addition to an already adequate diet retained an amount of nitrogen directly proportional to that provided in the supplement. Four patients retained little or no additional nitrogen. Another patient, receiving a somewhat smaller protein supplement of about 4 g daily, utilized this nitrogen with increasing efficiency so that, toward the end of 38 days, she was storing more and more of the total protein intake. The twelfth patient, whose diet was unsupplemented and regarded as the control, apparently began to reach nitrogen equilibrium after 50 days of a mildly positive balance; a nitrogen balance of +3.54 g in the first ten days dropped to +0.51 g for the last five days. These investigators, in an effort to interpret

FIG. 1. SIMPLIFIED SCHEME SHOWING EFFECT OF STRESS OF INFECTIOUS, TRAUMATIC, OR PSYCHOLOGICAL ORIGIN ON PROTEIN METABOLISM

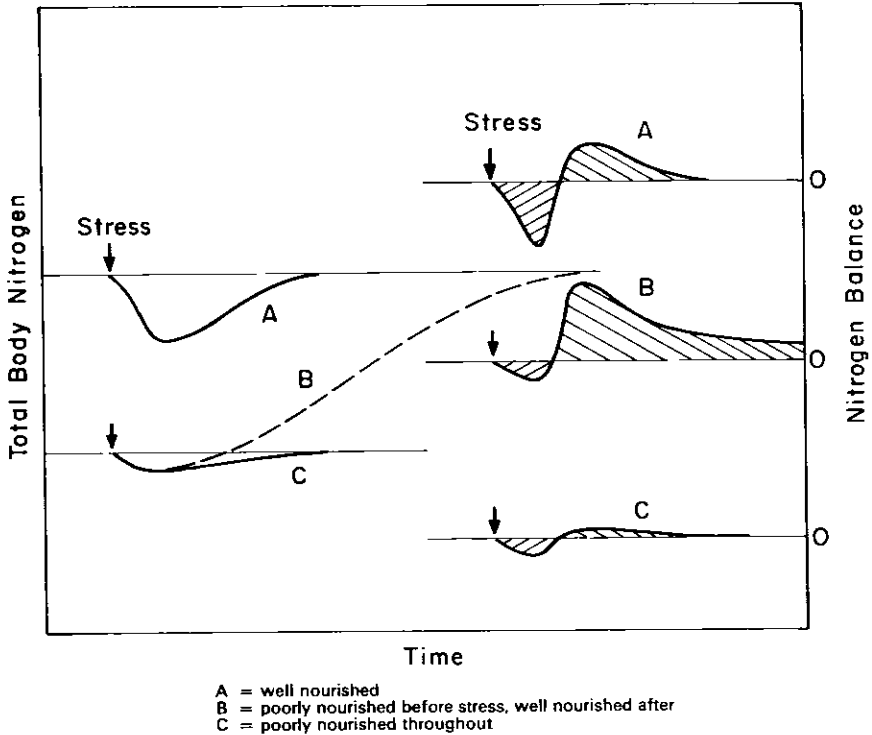


the variable results, proposed the scheme from which Fig. 2 has been derived.

The magnitude of the initial catabolic response to stress, as measured by the nitrogen balance technique, appears experimentally to be inversely proportional to the degree of nitrogen depletion in the animal. The magnitude of the stress itself may or may not be reflected in the nitrogen balance, depending upon the initial state of nutrition of the host. Fig. 2 shows diagrammatically the expected changes in nitrogen balance under various conditions.

Whatever the initial response, an anabolic phase of nitrogen balance would be expected after the catabolic phase if the dietary protein intake were sufficient. In a repleted animal subjected to a short period of acute

FIG. 2. EXPECTED CHANGES IN NITROGEN BALANCE UNDER VARIOUS CONDITIONS



stress, equilibrium might be regained quickly, whereas a depleted animal would require a long time regardless of the smaller initial response.

The previously described effects of infection on nitrogen metabolism are consistent with the interpretation just given. Since psychological stress is also followed by an increase in urinary nitrogen, the action of the endocrine mechanism is probably much more important in stress from infection than is the direct "toxic" destruction of protein by the infectious agent. This conclusion receives support from a recent report by Rapoport et al. (1968) describing endocrine and liver enzymes in the course of experimental pneumococcal infection in mice.

Another way in which infectious disease may increase nitrogen loss is through the sweating associated with fever. Under minimum sweating conditions (27-28°C, 43-45% humidity), the nitrogen loss in perspiration has been assessed at 0.36 g per day for an adult male. Exposure to moist heat (37-39°C, 64-73% humidity) can result in nitrogen losses equivalent to 20 g or more of protein (Mitchell & Hamilton, 1949).

These observations were recently confirmed by Consolazio and associates (1963) by intermittently exposing human volunteers to different temperatures

and humidities for periods of 8 to 24 hours over several days. A compensatory reduction in urinary nitrogen output was not observed. Clearly, the increased loss of amino acids and other nitrogenous compounds during fever deserves more attention than it has thus far had.

Infection and Nutritional Status, Other Nutrients

Vitamin A

Because low intakes of vitamin A are common in human diets, the direct effect of infection on vitamin A metabolism is of practical importance.

Chicks infected with *Eimeria tenella* had decreased liver stores of vitamin A, even when large amounts of the vitamin were fed to them (Erasmus et al., 1960). Although the enhanced vitamin A in the diet did not alter the severity of the coccidiosis, it resulted in better appetites and faster growth in the surviving chicks. Coryza of chickens also lowered vitamin A levels in the tissues, but paired-feeding studies indicated this was due to a drastic decrease in food intake (Squibb et al., 1955). Newcastle disease had no effect on vitamin A reserves of chicks nor on absorption of this nutrient from the gut. Furthermore, vitamin A therapy of chicks with adequate nutritional reserves prior to infection was without benefit (Squibb, 1961a).

Because turpentine-induced abscesses lower vitamin A concentrations in the blood of rats by as much as 50% and also decrease the concentration of vitamin A in the liver, it is often presumed that septic abscesses have the same effect. When excess vitamin A was supplied in the diet both to rats with turpentine-induced abscesses and to control rats, concentrations in the liver were almost identical, suggesting that absorption and storage proceeded normally despite the simulated infection (Kagan, 1955).

Soliman (1953) found low liver reserves of vitamin A in cattle with lungworms and in guinea-pigs with livers infected with the lungworms *Dictyocaulus viviparus* and *D. filaria*. The reserves averaged 2.5 IU per gram, compared with 23 IU in healthy animals.

Thirty days after administration of 100, 500, or 1000 *Ascaridia galli*, chickens maintained on a constant diet had vitamin A levels in the liver of 122, 104 and 88.5 μg per 100 g, respectively, compared with 177 μg in control birds (Šihobalova & Kustova, 1950; Šihobalova et al., 1951). The process of formation of antibodies to *Ascaridia* in the chicken not only lowered the vitamin A concentration in the liver but also increased vitamin A in the mitochondria (Leutskaya, 1963). The changes were more marked with purified antigen than with broth cultures (Leutskaya, 1964a,b).

Rats infected with scabies developed signs of vitamin A deficiency on a deficient diet much more rapidly than those free of infection (LeGallic, 1955).

In children, concentrations of vitamin A in the blood are appreciably reduced in pneumonia, rheumatoid arthritis, acute tonsillitis, and rheumatic fever (Shank et al., 1944; Jacobs et al., 1954). Intestinal absorption of vitamin A may also be impaired in the presence of *Giardia lamblia* (Chesney & McCoord, 1934; Katsampes et al., 1944). Normally, vitamin A is not excreted in the urine, but does appear in such pathologic states as obstructive jaundice, chronic nephritis, and pneumonia (Moore, 1957; Goldsmith, 1959).

As early as 1892, Spicer, in England, noted that children with meningitis, infantile diarrhea, chronic tuberculosis, measles, whooping cough, and severe chickenpox frequently developed xerophthalmia. Subsequently, a number of investigators noted that infection precipitates acute clinical avitaminosis A in persons with a latent deficiency (Oomen, 1958). This nutritional disease is still an important cause of blindness in Indonesia and other countries where vitamin A deficiency is endemic among young children (Oomen, 1959). Although no longer a problem in the USA and Western Europe, xerophthalmia and keratomalacia still occur sporadically, after infections, among malnourished infants in nearly all developing countries, even those in which vitamin A deficiency is not common among older children and adults.

In reviewing the frequency of night-blindness in the tropics, Rodger and associates (1960) have emphasized the lower serum carotene and vitamin A values in persons with hookworm disease compared with persons in the same communities without the infection. Steatorrhea and decreased absorption of vitamin A and xylose were found to be common in Puerto Rican army recruits with severe hookworm disease (Sheehy et al., 1962); and, in Colombia, malabsorption has been reported in patients with anemia and multiple intestinal parasites, including hookworms (Vélez & Orrego, 1963).

Onchocerciasis reportedly causes less blindness in endemic areas where agricultural development is good than it does where farming conditions are poor (Rodger, 1960, 1962). There is evidence that vitamin A is the important variable, but other factors may well be responsible. Rodger (1957) described high infection rates with the parasite in eastern Nigeria; but blindness was less frequent where red-palm oil, which is high in vitamin A, was used extensively. However, supporting data have not been published.

In summary, infections exert a sufficiently adverse effect on vitamin A nutrition to have practical significance in animal husbandry and in public health practice. This has been proved by both experimental studies in animals and clinical and field observations in man.

Thiamine

A variety of studies on laboratory animals and man support the conclusion that infection affects thiamine metabolism.

Although mice infected with Western equine encephalitis virus and fed a diet severely deficient in thiamine showed no clinical signs of infection, they developed thiamine deficiency earlier than did uninfected thiamine-deficient animals (Kearney et al., 1948b). In rats infected with the tapeworm *Hymenolepis diminuta* and injected with ³⁵S-labeled thiamine, Chandler and co-workers (1950) found that the worms obtained thiamine from the blood and tissues rather than directly from the gastrointestinal contents of the animal host. Rama Rao & Sirsi (1956) demonstrated that three- to four-week-old chicks infected with *Plasmodium gallinaceum* had a markedly lower level of thiamine in the blood during the acute infection.

Although quantitative data are few, many qualified observers, themselves interned in Japanese prisoner-of-war camps in the Second World War, remain convinced that bacillary dysentery precipitates acute beriberi in persons on thiamine-deficient diets for long periods (Smith & Woodruff, 1951). Suzman (1955) cites examples of beriberi following pneumonia and malaria. In persons with borderline thiamine deficiency, even bed-bugs have been listed among stress factors capable of producing acute beriberi (Platt, 1958b).

Najjar & Holt (1943) demonstrated that man utilizes thiamine and other B-complex vitamins that are the result of synthesis by intestinal bacteria. When the intestinal flora of nine adolescents on diets marginally deficient in thiamine was suppressed by succinylsulfathiazole, thiamine promptly disappeared from the urine, but reappeared when the sulfonamide was discontinued. Obviously, any pathologic process interfering with the normal distribution and function of intestinal bacteria can affect thiamine nutrition adversely in the presence of insufficient vitamins in the diet (Ellinger et al., 1947).

In summary, infectious disease can precipitate clinical beriberi in persons maintained on a diet inadequate in thiamine. In some regions, many people consume such diets; and the number is often greatly augmented in times of natural disaster or civil disturbance. Under such circumstances the action of infection on thiamine nutrition has major public health importance.

Other B-complex vitamins

Experimental studies in man have proved that infections have an effect on other B-complex vitamins such as niacin, pyridoxine, folic acid, and vitamin B₁₂.

Naturally occurring respiratory infections have precipitated megaloblastic anemia in monkeys maintained on a diet low in folic acid, as have subcutaneous abscesses induced by turpentine (May et al., 1952). Luby (1959) concluded that 9 of 27 children with megaloblastic anemia would not have developed that condition from diet alone; a superimposed infection was the deciding factor.

Campbell & Pruitt (1952) claimed that, in patients with acute infectious hepatitis, supplementary vitamin B₁₂ brought about an earlier return of appetite and normal liver size than did a high-protein, high-carbohydrate diet, even when this was supplemented with brewers' yeast as a source of B-complex vitamins. Although the study included 100 patients, the implication that viral hepatitis puts a special stress on vitamin B₁₂ metabolism cannot be accepted without better evidence, because the chronic nature of the disease and the tendency toward remissions make therapeutic measures difficult to evaluate.

The classic studies of Von Bonsdorff in Finland (1948, 1952, 1956, 1964) have demonstrated that the fish tapeworm *Diphyllobothrium latum* has such a voracious appetite for vitamin B₁₂ that it often causes megaloblastic anemia in affected persons, a finding substantiated by the use of ⁶⁰Co-labeled vitamin B₁₂ (Scudamore et al., 1961) and the determination of vitamin B₁₂ blood serum levels (Nyberg et al., 1961). Recovery from the anemia follows expulsion of the worms (Palva, 1962). This subject has been reviewed by Nyberg and co-workers (1961). Even optic atrophy has been attributed to vitamin B₁₂ deficiency in fish tapeworm carriers (Björkenheim, 1966).

In the experience of Layrisse and associates (1959), patients with anemia due to hookworm infection had a low absorption of folic acid and low levels of serum vitamin B₁₂.

Khalil (1924) reported that pellagra in Egypt was six times more frequent in persons with hookworm disease than in those without that infection.

The observations of Jiménez Díaz and co-workers (1952) that the feces of children suffering from acute enteritis were unusually low in thiamine and pyridoxine but unchanged in riboflavin content are significant. Had this been a non-specific effect from reduced food intake, the riboflavin content of the feces would also have been affected. As Frazer (1949) has suggested for sprue, the effect may be due partly to interference with bacterial synthesis in the small intestine, after replacement of the normal duodenal flora by a microbiota characteristic of the lower intestinal tract.

Ellinger & Abdel-Kader (1947) showed that the intestinal flora contains niacinamide-synthesizing *Escherichia coli* as well as niacinamide-consuming bacteria such as *Shigella sonnei*, *Shigella dysenteriae*, *Shigella flexneri*, *Streptococcus faecalis*, and *Proteus vulgaris*. A predominance of one group over the other may affect the niacinamide nutritional state. The ingestion of *p*-aminomethylbenzene sulfonamide increased the niacinamide content of the fecal flora and urinary output of *N*-methylnicotinamide by stimulating the niacinamide-synthesizing coliform bacteria and inhibiting the growth of non-coliform micro-organisms. The predominance of dysentery bacilli in the intestine would conceivably lead to consumption of niacinamide and might aggravate a deficiency in the pellagra-preventive factor.

Trager (1947b, 1954) has found that *Plasmodium lophurae* malaria in chickens lowered by half the levels of biotin and co-enzyme A in the liver

after only five days. He believes the pathology of the infection to be influenced by this action.

Although infection often causes a deficiency of an essential nutrient, micro-organisms occasionally increase the supply. Levels of niacinamide tend to be high in the tissues of tuberculous patients (Abdel-Kader et al., 1951; El-Ridi et al., 1958), which may explain the rarity of coexistent pellagra and pulmonary tuberculosis. *Mycobacterium tuberculosis* is a niacin-synthesizing micro-organism (Bird, 1947). Tryptophan, a precursor of niacin elaborated by coliform bacilli (Ellinger et al., 1947; Ellinger & Abdel-Kader, 1949), has been shown to have an inhibitory action on human strains of *Mycobacterium tuberculosis*, both *in vitro* and *in vivo*, in the guinea-pig (Abdel-Kader & Zaki, 1958), the indole ring of tryptophan being mainly responsible for the tuberculostatic effect (Abdel-Kader & Zaki, 1958, 1960a,b). In this instance, the body apparently utilizes a metabolic product as a defense against an invading pathogenic micro-organism. From tissue culture studies it is known that the filterable agent of psittacosis is capable of synthesizing folic acid (Bader & Morgan, 1961).

The important role of the intestinal flora in synthesizing vitamins has long been recognized (Nightingale et al., 1947; Elvehjem, 1948; Johansson & Sarles, 1949). The synthesis of the B vitamins (Barnes et al., 1960; Wostmann et al., 1962) and of vitamin K (Gustafsson, 1959; Wostmann et al., 1963) is particularly important. Some of these vitamins are absorbed directly from the gut; others are available only to animals that practice coprophagy (Levenson & Tennant, 1963a; Barnes et al., 1963; Daft et al., 1963).

In summary, systemic infections are able to induce anemia when folic acid is deficient. Fish tapeworm may cause anemia because of its high requirement for vitamin B₁₂. Although pellagra is sometimes associated with infection in persons deficient in niacin, proof is lacking that infection is a major factor. There is no reason to believe that the demonstrated effect of infection on pyridoxine metabolism has clinical significance. Various mechanisms are involved in the deleterious effect of infections on the various other B vitamins, but more work is required to establish their clinical role.

Ascorbic acid

Interest in infection and ascorbic acid dates back to the early years of the present century, when scurvy was a common disease among children of North America and Europe.

In 1924, Nassau & Scherzer reported an earlier onset of scurvy in guinea-pigs on a deficient diet when an experimental trypanosomiasis was also present. Guinea-pigs on scorbutic diets died of scurvy much sooner in the presence of chronic "healed" tuberculosis (Bieling, 1927). Rinehart and

co-workers (1934) reported that scorbutic guinea-pigs developed mild lesions suggestive of rheumatic fever, which were considerably worsened by superimposed infection with beta hemolytic streptococcus. Well-nourished animals exposed to the infection did not develop appreciable lesions.

Even in the rat, which does not normally require dietary ascorbic acid, Nyden (1948) was able to demonstrate interference with the reduction of ascorbic acid in the spleen and adrenals of animals infected with *Trypanosoma hippicum*. The reduced form of ascorbic acid was present in a lower concentration, despite a normal level of the oxidized vitamin. The effect was less noticeable in skeletal muscle and was absent in liver and blood plasma. Similarly, McKee & Geiman (1946) described significantly low ascorbic acid levels in the plasma and whole blood of monkeys with *Plasmodium knowlesi* parasitemia.

According to Kroshman (1940), children infected with malaria showed a marked decrease in blood concentrations of vitamin C and increased excretion in the urine when compared with non-infected children living under comparable conditions. Lotze (1938) and Mohr (1941) described similar findings in adults. Typhoid fever markedly decreased blood serum levels of ascorbic acid, and dehydro-ascorbic acid accumulated in the blood (Banerjee & Belavady, 1953). Vaishwanar and associates (1959) reported low levels of blood ascorbic acid among schoolchildren in India after an outbreak of influenza. Wirth (1952) believed that, in two cases of hemorrhagic measles in patients whose diets were deficient in vitamin C, the added stress of the viral infection was sufficient to precipitate the clinical picture of vitamin C deficiency.

As early as 1917, Hess called attention to the frequency with which children from low-income families in New York City developed florid scurvy after contracting a febrile illness such as otitis media, pneumonia, or nephritis. Although Hess was not aware that scurvy was a vitamin-deficiency disease, he concluded that it was "precipitated in infants with 'latent' scurvy when an infectious disease such as 'grippe' was superadded". Even vaccination against smallpox has been reported to have had this effect in malnourished German children (Stern, 1923).

Sweany and associates (1941) noted that ascorbic acid saturation decreased with an increasing severity of tuberculosis. In 32 fatal cases the vitamin-C content of the tissues was low relative to the intake of the vitamin. From these data, they estimated that extra amounts of vitamin C up to 150 mg per day disappeared from the body of patients with severe tuberculosis. Getz and co-workers (1951) also found serum ascorbic acid values especially low in tuberculous patients.

Recent INCAP studies have demonstrated an increased loss of vitamin C in the urine during the height of the primary reaction to vaccination against smallpox and to vaccination with attenuated measles virus, as well as during

the acute clinical stages of measles and chickenpox (INCAP unpublished data, 1962).

Clinical manifestations of ascorbic acid deficiency and low urinary excretion of this vitamin were reported for schoolchildren of Madagascar Island having severe ascariasis or other intestinal parasitic disease (Dodin, 1955). No proof of a causative relationship was given.

Among some less privileged populations, the ability of infectious disease to worsen the ascorbic acid nutritional status of man continues to have public health significance.

Vitamin D

In early pneumonia superimposed on rickets, Perevoščikova and co-workers (1956) noted a pronounced decrease in levels of phosphorus and, occasionally, of calcium in the blood, the reaction being in direct proportion to the severity of the infection. Even large doses of vitamin D were unable to bring calcium and phosphorus levels to normal in the blood. The conclusion is that pneumonia may aggravate rickets. Rickets has also been shown to be more severe in chicks suffering from coccidiosis (Stafseth, 1931).

Vitamin K

Increased prothrombin times, indicative of a greater requirement for vitamin K, were observed by Squibb (1964c) in chicks with Newcastle disease. This happened only in the early stages of disease in chicks fed on diets causing low vitamin K reserves. A commercial diet or a single massive dose of menadione sodium bisulfite, injected 24 hours prior to blood sampling on the fifth day after inoculation, provided sufficient vitamin K to maintain normal prothrombin times.

Iron

The effects of acute infection on iron metabolism in man are well documented, although some of the mechanisms are only partly understood. These effects have considerable clinical and public health importance.

Infections influence iron metabolism most directly through loss of blood and a resulting anemia. The figure of 0.67 ml of blood lost per day per hookworm, frequently cited in the older literature (Faust & Russell, 1957), is now known to be an overestimate. By measuring the excretion of ⁵¹Cr-labeled hemoglobin, Roche and co-workers (1957a,b) showed that each *Necator americanus* causes daily losses of 0.031 ± 0.017 ml of blood or 2.74 ± 1.50 ml per million eggs. Gilles and associates (1964) obtained a figure of 0.05 ml of blood lost per worm per day for this species. Using the same techniques, Farid and co-workers (1965a) found that the blood

loss for *Ancylostoma duodenale* was five to ten times greater than that cited for *Necator*. They reported a loss per worm per day of 0.26 ± 0.045 ml. In heavily infected patients, the loss ranged from 14 to 45 ml of blood per day, with a daily iron loss of 3.56 to 9.94 mg. Mean values were 26.4 ml of blood and 6.06 mg of iron. These investigators concluded that the mean blood loss per 1000 ova per gram of feces was 4.47 ± 1.6 ml.

^{51}Cr escapes from the blood only through the worm, and is not absorbed from the gastrointestinal tract. By studying hemoglobin labeled simultaneously with ^{51}Cr and with ^{59}Fe , Roche & Pérez-Giménez (1959) demonstrated that an average of 44.1% of the iron lost through hookworms was reabsorbed; individual figures ranged from 13.1% to 76.4%. Two patients studied by Gilles and associates (1964) reabsorbed 47% and 60%, respectively, of the iron from hemoglobin entering the gut. No alteration in red cell survival was found.

In patients with hemoglobin values less than 6.5 g per 100 ml as a result of *Ancylostoma duodenale* infection, Farid and co-workers (1965b) found, by ^{51}Cr determination, a shortened red cell half-life; this returned to normal when the anemia was corrected. They believed that iron-depleted red cells were sequestered by an enlarged spleen. Layrisse and associates (1961, 1964, 1965) reported similar findings, although they attributed the reduced red blood cell survival to lack of an intrinsic factor within the cell.

An adequate dietary intake of iron often compensates for a mild to moderate hookworm infection, so that iron-deficiency anemia does not develop (Walker, 1955). Even with light infections (fewer than 100 worms), the loss may be 1 to 1.5 mg per day (Tasker, 1961). The data of Vinke & Jansen (1962) from Curaçao suggest that hookworms lower hemoglobin only when the infection is heavy and the diet deficient. In mildly endemic hookworm areas, the prevalence of iron-deficiency anemia may not correlate with the frequency of hookworm infection (Scrimshaw et al., 1953; Mayet & Powell, 1966).

In hyperendemic areas, however, 10% to 20% of hookworm patients may have more than 2000 eggs per gram of feces (Roche et al., 1957a), equivalent to infection with at least 100 worms; uncommonly, a single human host may have 500 worms or more (Faust & Russell, 1957). Anemia is usual with such severe infections.

In Georgia, USA, Hill & Andrews (1942) observed a progressive decline in hemoglobin with hookworm infection only when counts were in excess of 2500 ova per gram of feces. Dealing with infections in most instances in excess of 2000 ova per gram of feces and several with more than 10 000, White and co-workers (1957), in Peru, found a reasonably good inverse correlation between numbers of *Necator americanus* eggs and hemoglobin values, as did Farid & Miale (1962) for *Ancylostoma duodenale* in Egypt. Among Nigerians, iron-deficiency anemia was found only in persons with more than 20 000 ova per gram of stool, or about 800 worms (Gilles et al.,

1964). Obviously, a synergistic combination of a diet low in iron and a heavy hookworm infection has major health significance for some populations.

Studies by Cruz (1934), in Cuba, and by Rhoads and associates (1934a) and Payne & Payne (1940), in Puerto Rico, indicate that anemia resulting from hookworm disease responds promptly to the addition of iron to the diet, or more slowly to anthelmintic treatment. White and co-workers (1957) demonstrated good hemoglobin response to as little as 15 mg of iron daily. Needless to say, the most rapid and lasting improvement occurs when the two procedures are combined (Rhoads et al., 1934a,b; Cruz & de Mello, 1948).

Pérez & Comparini (1960), in Guatemala, found hookworm infection in 61% of general hospital patients with hemoglobin levels below 6 g and in only 5.5% with normal levels. Chiriboga and associates (1950) reported a frequency of 42% microcytic and 9.5% macrocytic anemia among 21 patients having more than 500 hookworms, as judged by fecal egg counts. With lighter infections, anemia was much less frequent. As suggested by Foy & Kondi (1960, 1961), a direct relationship almost certainly exists between number of bleeding points, extent of mucosal damage due to hookworms, and nutritional status.

An outstanding feature of chronic malaria is the anemia it produces. This is apparently due to the fact that the malaria parasites meet their high protein requirements by splitting hemoglobin, leaving large amounts of unused heme as malaria pigment (Ball et al., 1948; Deegan & Maegraith, 1958). The pigment is picked up by the reticuloendothelial system and only slowly reoxidized to hemosiderin to be re-used (Rigdon, 1945). Iron may also be lost in malaria through hemoglobinuria (especially in "black-water fever") and, to a small extent, through the gastrointestinal tract (Deegan & Maegraith, 1958).

In a study by Chiriboga and associates (1950), 20 patients with malaria who also had more than 500 hookworms each were found to have an average of 23% macrocytic and only 15% microcytic anemia, whereas 9 of 19 patients with malaria alone had macrocytic anemia but no instance of the microcytic anemia classically associated with iron deficiency.

From studies in East Africa in areas where malaria was uncontrolled and in others where control measures were successful, Draper (1960) cited evidence that the rise and fall of hemoglobin levels directly paralleled the prevalence of malaria. Unfortunately, types of anemia and of malaria were not specified.

In well-fed mice with experimental hepatosplenic schistosomiasis, DeWitt & Warren (1959) observed development of a severe anemia (hemoglobin 4-6 g per 100 ml) in some of the animals in the tenth week of infection. Although the type of anemia was not recorded, it was probably the anemia of chronic infection.

Some evidence exists that *Schistosoma mansoni* causes iron-deficiency anemia (Jamra et al., 1964), although blood loss is irregular and may be negligible (Walters & Waterlow, 1954). Serum bilirubin, fecal urobilinogen, reticulocyte counts, and red cell half-life (determined by labeling with ^{51}Cr) were normal in patients investigated by Farid and co-workers (1964). Such anemias as occurred were apparently due to inadequate iron intake and responded readily to ferrous sulfate. In *Schistosoma haematobium* infection, the blood loss, estimated through uptake of ^{59}Fe , averaged 4 to 10 ml of blood per day (Farid, personal communication, 1965). Ten patients had an average hemoglobin of 4.3 g per 100 ml.

Even extensive bedbug bites have been suggested as a factor in the development of iron deficiency in children, through direct loss of hemoglobin (Venkatachalam & Belavady, 1962). *Trichuris* infection has been reported to produce a fecal blood loss of about 0.005 ml per worm per day, sufficient to cause anemia in children with heavy infections of over 800 parasites (Layrisse et al., 1967).

The hypochromic, microcytic anemia characteristic of iron deficiency also occurs in populations in which neither hookworm nor malaria is endemic. Of 91 English women in the thirty-second to thirty-fourth week of pregnancy and having a urinary infection, 56 were described as having iron-deficiency anemia; in 30, the hemoglobin rose significantly when the infection was treated (Giles & Brown, 1962).

The anemia associated with chronic infectious disease varies greatly with the nature and severity of the infection. "Anemia of infection" was first explored systematically in a series of papers from the University of Utah. Cartwright and co-workers (1946) showed that both staphylococcal and sterile turpentine abscesses produced hypoferremia and anemia in dogs. Wintrobe and associates (1947) obtained the same results with pigs and also showed that the hemopoietic response of iron- or pyridoxine-deficient animals to the missing nutrient was markedly impaired in the presence of infection.

The anemia of infection is not the result of blood loss, overt hemolysis, or iron deficiency, and does not respond to administration of folic acid or vitamin B_{12} . The bone marrow has a decreased proportion of red cell precursors, some increase in proportion of immature cells, and poor hemoglobin production in normoblasts (Harris, 1963). Administration of radioactive iron revealed reduced iron-binding capacity and thereby decreased iron retention (Bush et al., 1956; Princiotto et al., 1964). Cartwright and associates (1946) state that the effect can be simulated in dogs by injection of ACTH.

The life span of erythrocytes is shortened by a variety of chronic infectious diseases (Ebaugh et al., 1954; Freireich et al., 1954; Bush et al., 1956) and by acute rheumatic fever (Reinhold, 1954). The bone marrow in these situations is unable to increase red cell production by the 50% needed to

compensate for a shortened life cycle, although normal bone marrow can increase erythrocyte output six- to eight-fold (Brown, 1950). Apparently, patients with chronic infection exhibit marked inhibition of erythropoiesis. A defect in the release of iron from the reticuloendothelial cells to transferrin for hemoglobin synthesis has been interpreted as at least one responsible factor (Gubler et al., 1950; Freireich et al., 1957a,b). This, together with an elevated erythrocyte protoporphyrin concentration, has been viewed as a quantitative defect in the rate of conversion of protoporphyrin to hemoglobin (Vaughan, 1948; Cartwright & Wintrobe, 1952).

Among 28 patients with a chronic infection accompanied by weight loss, Clark and co-workers (1947) found total hemoglobin reduced, on an average, to 58% of values calculated according to normal weight. Comparing 15 patients with infectious and "toxic" diseases with 17 controls, Jarnum & Lassen (1961) found a lower serum concentration of transferrin that closely paralleled a fall in albumin. They attributed both findings to a temporary decrease in the rates of synthesis to values less than those of breakdown.

Hemolytic anemia may develop in association with some acute infections to such an extent as to dominate the clinical findings. Jandl and co-workers (1961) pointed out that the following conditions may also cause anemia: an acute, often lethal, intravascular hemolysis during invasion of the bloodstream by such organisms as *Clostridium perfringens*; a direct infection of red cells by *Bartonella bacilliformis*, causing splenic trapping and hemolysis; the acute or chronic hemolysis associated with cold agglutinins or hemolysins; and increased splenic sequestration.

Dogs with experimentally induced staphylococcal abscesses developed anemia within two weeks (Matsumoto et al., 1962). Another group of dogs whose reticuloendothelial system was blocked by intravenous injection of India ink also developed anemia. With both infection and blockage of the reticuloendothelial system, the severity of anemia increased. A frequent association of anemia with amebic abscess of the liver has been noted by Mayet & Powell (1964).

To summarize the studies cited, hookworm disease is apparently responsible for much iron-deficiency anemia, due to blood passing through the worms into the intestine. Malaria, especially chronic malaria, often results in significant iron loss. Chronic infections of bacterial or viral origin produce the so-called "anemia of infection" by interfering with iron-binding capacity and erythrocyte life span. Some acute infections induce hemolytic anemia.

Other minerals

Numerous systemic infectious diseases, as well as local enteric infectious processes, cause diarrhea and, with it, a frequent profound disturbance of electrolyte balance. There is limited evidence that infections also cause

significant alterations of calcium and phosphorus metabolism in domestic and laboratory animals.

Nematode infections of sheep contribute to less-effective utilization of both calcium and phosphorus (Shearer & Stewart, 1932-33; Franklin et al., 1946), but the metabolism of sodium and potassium does not appear to be affected. In studies of lambs experimentally infected with *Cooperia curticei* or *Trichostrongylus clubriformis*, Andrews (1938) found no effect on absorption of calcium and phosphorus, although weight gain per unit of food consumed was less.

It has been observed that *Trichinella spiralis* in rats interferes more with assimilation of calcium than with that of protein (Rogers, 1942). In the same study, urinary phosphorus excretion fell notably during the acute infection, indicating that absorption of this mineral from the gastrointestinal tract was reduced. Rao & Gopalan (1958) found a marked calcium and phosphorus loss in tuberculous guinea-pigs compared with non-infected animals on a comparable diet.

In an extended study of nearly 1000 adolescent girls (Johnston, 1953), 39 with active tuberculosis had a negative calcium balance that was corrected only by increasing the calcium intake during several months.

Large increases in serum copper values have been reported for patients with tuberculosis (Panvalkar et al., 1961), but the significance of this finding is unknown.

Any infection causing diarrhea results regularly in a disturbed mineral balance, since the loss in feces is usually sufficiently large to deplete the body of sodium chloride, potassium, and phosphorus, as well as other nutrients (Rapoport et al., 1947; Achor & Smith, 1955). The potassium loss occasioned by kwashiorkor is particularly significant (Hansen & Jenkinson, 1956). Diarrhea often appears early in kwashiorkor as the result of an accompanying infection. It then continues after the infection has run its course because of the changes in intestinal physiology induced by the protein deficiency. By the time kwashiorkor has fully developed, a profound hypokalemia is usually present (Hansen & Jenkinson, 1956; Kahn, 1959; Smith & Waterlow, 1960), as well as serious serum and tissue changes relating to other electrolytes.

One of the most dramatic metabolic effects in any infection is the fulminating electrolyte imbalance in cholera, so commonly followed by circulatory collapse. Although the end results have long been known, recent studies with modern biochemical methods have greatly clarified understanding of this sequence of events. Years ago, O'Shaughnessy (1832) pointed out that, in addition to the obvious dehydration, there occurred a massive salt and bicarbonate loss from the blood, these elements being "present in large quantities in the peculiar white ejected matters". Studies in Bangkok, Dacca, and Calcutta (Phillips, 1963) have shown that the electrolyte loss is primarily in potassium, bicarbonate, and, to a lesser degree, sodium and chloride. The potassium loss can result in a 15% to 30%

deficit of body stores. It appears to be responsible for the kidney damage that so commonly results in uremia. Other evidence suggests that a toxin paralyzes the "sodium pump" in the intestinal mucosa, preventing reabsorption of electrolytes from the upper bowel, where they are normally present during digestion (Huber & Phillips, 1960; Phillips, 1963). Major therapeutic advances from this work have reached the point where prompt treatment should make cholera a far less terrifying disease.

In young men with acute tularemia, Beisel & Sawyer (1964) observed an increased excretion of potassium. A sudden renal retention of chloride was characteristic of recovery. Negative calcium balance followed the peak of fever (Joy et al., 1964; Beisel et al., 1964, 1967).

The extensive literature on malaria and electrolyte balance has been reviewed by McKee (1951). Much discussion has centered on the suggestion that the typical paroxysms of chills and fever are due to the massive release of potassium from erythrocytes at the completion of the sporulation cycle (Zwemer et al., 1940). Although this explanation suffices with respect to laboratory animals, the process appears somewhat more complicated in humans (Flosi, 1944; Overman et al., 1949a). A part of the electrolyte effect has been attributed to exhaustion of the adrenal cortex (Overman et al., 1949b). By contrast, sodium and phosphorus values of plasma are decreased. It is believed that the sodium effect is due to such factors as altered cell permeability and excessive sweating (Overman et al., 1949a). The phosphorus decrease may be due to the demonstrated high requirement of the malaria parasite for this electrolyte as part of its dependence on phosphorylative glycolysis for energy requirements (Speck & Evans, 1945a,b; Speck et al., 1946; McKee, 1951).

Eimeria necatrix infection in chicks has been shown to interfere with the absorption of orally administered zinc-65 (Turk & Stephens, 1966), a finding consistent with the interference of this organism with absorption of vitamin A (Erasmus et al., 1960), previously referred to.

Infectious disease thus appears to interfere with calcium and phosphorus metabolism in both animals and man. Furthermore, diarrhea, a symptom of most enteric and some systemic infections, causes a potassium and chloride loss that requires prompt corrective measures. For these reasons, a major part of the public health effort to reduce infant and child mortality from diarrheal disease is directed toward early rehydration and restoration of electrolyte balance.

Lipids

Surprisingly little is known about the action of infection on fat metabolism. Infections such as influenza and pneumonia commonly result in increased liver and fecal fat (Boyd, 1961). This also occurs after infection with *Giardia lamblia* (Cortner, 1959) and perhaps other intestinal parasites.

Von Brand & Mercado (1958) infected rats with *Plasmodium berghei* and found that liver lipids were increased in direct proportion to the parasitemia.

Some intestinal infections clearly decrease absorption of fat, with the result that steatorrhea follows, provided the diet has a continuing normal fat content. Steatorrhea, however, is not harmful; and absorption of fat remains relatively high. Since the anorexia of infection makes the maintenance of an adequate caloric intake difficult, fat should be continued in the usual amounts as a much-needed source of calories (Holt et al., 1915; Chung & Viščorová, 1948; Chung, 1948).

The conclusion follows that, although infection often increases the amount of fat in the liver, any clinical significance is doubtful. The appearance of steatorrhea during enteric infection indicates a somewhat less efficient utilization of this important source of energy, but is no reason to reduce dietary intake of fat. Unless intestinal helminthic infections are very severe, fat absorption is not impaired (Abdalla et al., 1963; Kotcher et al., 1966; Layrisse et al., 1964). The same appears to be true for giardiasis (Palumbo et al., 1962).

Carbohydrates

Markedly low levels of blood glucose are common in infectious disease, probably secondary to reduced caloric intake. The action of systemic protozoa on glucose and glycogen metabolism has special interest. A decrease in blood glucose levels in experimental trypanosomiasis has been shown by Schern (1925), Regendanz & Tropp (1927), von Brand (1961), and others. Regendanz (1929) described the same phenomenon for *Haemobartonella muris* in the duck.

During parasitemia of rats infected with *Plasmodium berghei*, Mercado (1952) found that whole-blood glucose levels fell to 68 mg per 100 ml from the normal level of 96 mg per 100 ml and that serum levels showed a similar decrease from 115 mg per 100 ml in normal serum to 55 mg in parasitized animals. Subsequently, Mercado & von Brand (1954) showed that liver glycogen decreased by about 90% in rats heavily infected with *P. berghei*, and that carcass glycogen was only 40% less. Simultaneous administration of fructose and meticcortelone stimulated glycogenesis (Mercado & von Brand, 1957).

Malaria also causes a drop in whole-blood glucose levels in ducks (Marvin & Rigdon, 1945) and monkeys (Christophers & Fulton, 1938). Devakul & Maegraith (1958) reported well-maintained blood-sugar levels in rhesus monkeys until the terminal stages of *P. knowlesi* infection. Devakul (1959) has reported a blood sugar level of 4 mg per 100 ml in a patient with *P. falciparum* malaria. The liver glycogen of animals dying from malaria is low, but glyconeogenesis is possible even in terminal stages of the disease, as indicated by increased glycogen in liver and skeletal muscle after intra-

venous administration of glucose or adrenal cortical hormones. The investigators believe that direct competition for glucose between parasite and host is exaggerated when glucose supplies are limited.

Malaria parasites of several species satisfy their energy requirements *in vitro* by oxidizing glucose, mannose, fructose, or glycerol (Maier & Coggeshall, 1941). *In vivo*, however, they depend almost wholly on glucose. The parasitized erythrocyte utilizes about 25 to 100 times the amount of glucose consumed by a normal red cell. Under anaerobic conditions most of this glucose is converted to lactic acid, demonstrated in monkey malaria to cause a distinct fall in pH of the blood (McKee, 1951). *P. vivax* uses *in vitro* three or more times the glucose consumed by other malarial species (Geiman, 1948). The phosphorylative anaerobic glycolysis from which the malaria parasite derives its energy utilizes only 10% of the total energy available from the complete oxidation of glucose (McKee, 1951). Whatever the mechanism, malaria is characterized by low levels of blood glucose and liver glycogen.

Staphylococcal enterotoxin poisoning in monkeys has also been shown to produce early changes in glucose metabolism, possibly related initially to catecholamine release and, later, to increased utilization of glucose and to metabolic acidosis (Crawley et al., 1966). Such changes were seen during clinical illness from tularemia in seven human subjects (Shambaugh & Beisel, 1967), and probably occur with most other infections.

Enzymes

The general opinion derived from an extensive literature is that infections commonly alter the activity of essential enzymes. For example, *Pasteurella tularensis* reduces aconitase and fumarase activity in liver tissue of rats by more than a third (Woodward & Miraglia, 1961). Recent studies with bacteriophage-infected *Escherichia coli* (Flaks et al., 1959) make it clear that introduction of viral deoxyribonucleic acid (DNA) in the host cell alters the pattern of enzyme activity. A possible relation to the nutritional status of higher organisms has not been explored.

In the late stages of *Plasmodium knowlesi* infection in monkeys and *P. berghei* infection in mice (Riley & Maegraith, 1961), blood serum contains a factor that inhibits the normal oxidative phosphorylation of liver mitochondria *in vitro*. Although not specific, since it occurs with any prolonged anemia or with starvation, this may be an important factor in pathogenesis. Other enzyme systems of monkeys (Maegraith et al., 1962) and mice (Riley & Maegraith, 1962) also depressed under these conditions include succinic, glutamic, and beta-hydroxybutyric dehydrogenases, and dinitrophenol-stimulated adenosine triphosphate (ATP) activity. Both latent and magnesium-stimulated ATP activity are increased.

In observations on 32 children with scarlet fever (Véghelyi, 1949), all except 5 had a marked decline in duodenal amylase, trypsin, and lipase activity, and all had lowered values for blood amylase. Presumably, the effect was primary, not secondary to protein or other nutritional deficiency, since the children appeared well nourished. There is evidence, from the USSR, of decreased duodenal activity in opisthorchiasis (Sokolova, 1948); and Plotnikov (1953) has reported the same effect in pancreatitis associated with *Schistosoma japonicum*. Decreased activity of intestinal enzymes in infectious disease could conceivably lead to poorer digestion and absorption of nutrients, as it does in kwashiorkor, thus exacerbating the nutritional difficulties of children already suffering from protein deficiency.

The ability of various infections to increase alkaline phosphatase and other blood and tissue enzymes is outside the scope of this presentation. The marked effect of infections on neutrophil alkaline phosphatase of man has been reviewed by Beisel (1967).

Unknown factors

A number of studies suggest a probable nutritional disturbance after an infection, without giving any indication which nutrients were involved. An example is the report of Gibson (1954) on sheep infected with *Trichostrongylus axei* and fed a diet of hay. Infected animals developed severe loss of weight, severe oligocythemia, and a tendency toward neutrophilia just preceding death. Control animals fed the same diet had no symptoms.

Effect of Infection on Growth and Development

In addition to altering absorption, metabolism, and the excretion of specific nutrients, as this chapter has described, infections reduce food intake by an action on appetite. Also, as a part of therapy, a frequent custom is to withdraw solid food or otherwise change the diet during an illness, thereby reducing nutrient intake. Purgatives and other medicines likewise interfere with absorption and utilization of nutrients. Consequently it is not surprising that severe or prolonged illness has an adverse effect on growth and maturation, especially when a child is already malnourished.

Several investigators have failed to find any deleterious effect of the usual infectious diseases on the growth of well-nourished children (Martens & Meredith, 1942; Sontag & Lipford, 1943; Cahn & Roche, 1961). Other long-term studies of well-nourished children have identified instances in which growth appears to have been depressed (Maresh & Washburn, 1940; Valadian et al., 1959). The Oxford Child Health Survey of 650 children observed from birth to five years of age (Hewett et al., 1955) ended with the demonstration that children escaping all illness would be one inch taller than those who had experienced "severe" illness, and 0.4 inches taller than those

suffering an "average" amount of sickness. No corresponding effect on bone maturation was observed.

Most investigators in developing countries have been content to recognize a retardation of growth and development in malnourished children who experience a heavy and continued burden of infection. Usually no attempt has been made to distinguish the relative importance of infectious disease and malnutrition. Worse still, some observers have arbitrarily assigned major importance to one or the other according to personal bias, with no facts to support their contention.

Bruce-Chwatt (1952), in Southern Nigeria, described exaggerated flattening of growth curves for children who acquired malaria after five months of age. The eradication programs against malaria in some hyper-endemic areas offer a rare opportunity to compare nutritional status before and after a prevailing high incidence of the disease. However, Draper & Draper (1960) failed to find an increased growth in children following area elimination of malaria.

The experience at INCAP indicates that most infectious diseases inhibit growth and development in poorly nourished children, although the relative importance of infection and other factors is often difficult to determine. During an acute disease such as measles, malnourished children lose considerable weight (Morley et al., 1963, 1968; Scrimshaw et al., 1966). Salomón et al. (1968) have reported significant loss of weight in such children after whooping cough, mumps, rubella, and chickenpox, as well as measles. Growth is generally inhibited during both illness and convalescence.

Among children participating in a comparative study of diets of animal and vegetable protein-based mixtures, Truswell and co-workers (1959) noted a sharp drop in weight in those who contracted chickenpox; nitrogen balance was not measured.

Experimental feeding programs among pre-school children in rural Guatemala improved growth and development, but the children were still markedly retarded for their age, compared with well-nourished Guatemalan children (Scrimshaw et al., 1965). The depressing effect of chronic diarrheal disease on the growth and development of children in Chile has been emphasized by Martinez & Weidenslaufer (1963).

Crowley and associates (1956) found that loss of weight in Puerto Rican army recruits was directly related to hookworm infection and was lessened by appropriate therapy. Further investigations are badly needed.

Studies with rats make it clear that pneumococcal septicemia and chronic otitis media have the same effect as acute starvation, in that they cause immediate slowing of chondroplasia followed by a reduction of osteoblastic activity (Acheson & MacIntyre, 1958; Acheson, 1959). Lines of arrested growth appear, similar to those often visible in the roentgenograms of the metaphyses of young children subject to malnutrition. It is clear that

relatively short, acute infectious diseases are able to cause permanent stunting of the skeleton in the rat.

Depression of body-weight of cockerel chicks by Newcastle disease was found to be directly proportional to severity of infection (Squibb, 1961a,b). In subsequent work, alterations in the amino acid pool of infected animals were demonstrated, and it was suggested that this was the mechanism responsible for growth depression (Squibb, 1966). In the experience of Lev & Forbes (1959), germ-free chicks grew faster than animals reared under natural circumstances and having the usual intestinal flora. A main inhibitory effect was from a strain of *Clostridium perfringens* normally present in the conventional chick intestine; it could be reduced to inconsequential levels by an appropriate antibiotic.

The known ability of partially germ-free NCS mice to grow well on a deficient diet has been related to their simple intestinal flora. These mice, however, develop more exacting nutritional requirements when treated with endotoxin. Dubos and associates (1965), in studying the influence of infection on nutritional requirements of germ-free mice, reported an increased need for some essential amino acids, apparently because of an infectious process. Their work confirmed an effect of the indigenous bacterial flora on nutritional state.

The widespread use of antibiotics in commercial feeds for poultry and swine is based on extensive experimental evidence of their ability to increase rates of gain in weight of growing animals (Schendel & Johnson, 1954). Antibiotics presumably act by suppressing unfavorable intestinal micro-organisms (François, 1959; François & Michel, 1964; Jukes, 1955). Holtzman & Visek (1966) present evidence that the mechanism of improved growth in rats fed chlortetracycline may be the reduction in the number of micro-organisms releasing ammonia in the intestinal tract (indicated by a slower turnover in urea hydrolysis in animals given the antibiotic). They suggest that the ammonia released by bacteria in the intestinal tract may cause a thickening reaction in the mucosal wall that might impose a greater demand for nutrients or perhaps cause a loss of necessary substances in the feces.

Daily administration of antibiotics to malnourished children living in an insanitary environment has given equivocal results. Scrimshaw and co-workers (1954) demonstrated a significant increase in height and weight of Guatemalan schoolchildren fed 50 mg of aureomycin daily for six months, compared with those given placebos. At the end of 12, 18, and 24 months, however, there was no difference between experimental and control groups. Penicillin under similar circumstances had no effect at all on growth. MacDougall (1957) found a highly significant increase in the average weekly weight gain of severely undernourished hospitalized African children given aureomycin over periods of two to seven weeks; no increase was observed in a control group given a placebo.

In spite of their effectiveness in the treatment of acute infectious disease, there is no evidence that the prolonged administration of antibiotics to children under natural conditions, even in developing countries, is of any value in increasing their growth and development or in decreasing the frequency of diarrheal disease.

An increased rate of growth in mice infected with *Trypanosoma duttoni* (Lincicome & Shepperson, 1963) is an exception to the usual depressant effect of infection on growth. Mice were observed for a month in two experiments, and for 58 days in a third. Enhancement of growth was apparent at the close of all three studies, despite a three-week period of parasitemia.

Although *Schistosoma mansoni* infection in rats had only a slight effect on food intake and growth, a reduction in maze learning was observed by Kershaw and associates (1959). The results were shown not to be due to decreased food intake *per se*.

Work with animals shows that factors interfering with early growth also influence motor development (McCance, 1962; Lát et al., 1960), the number of neurons in the brain (Lowry et al., 1962; Heard et al., 1961), and behavior (Cowley & Griesel, 1963; McCance, 1962; Nováková, 1966). There is some evidence that malnourished children with arrested somatic growth and biochemical maturation have a coincident retardation of mental development (Stoch & Smythe, 1963; Geber & Dean, 1957; Robles et al., 1959; Wug et al., 1964; Ramos-Galván et al., 1960, 1965; Coursin, 1965).

Summary

The effect of many specific infectious diseases on the nutritional state of the invaded host needs further study. Some nutrients have had little or no attention. Nevertheless, the available facts are sufficient to establish conclusively that most infections have some adverse effect on nutritional status. This has public health significance wherever substantial numbers of persons have nutritionally inadequate diets.

Even trivial infections result in increased loss of nitrogen in the urine. Infections also contribute to protein and other nutrient deficiencies by decreasing appetite and diminishing tolerance to food. In areas where diets are already quantitatively or qualitatively inadequate in protein, the diet given to persons with an infectious disease is usually even more deficient in protein. Treatment of infection often includes administration of purgatives and other medicines with adverse effects on nitrogen absorption or nitrogen retention. Finally, the acute diarrhea so characteristic of most intestinal and some systemic infections has the particular characteristic of decreasing nitrogen absorption. Severe helminthic disease also reduces nitrogen absorption, even in the absence of diarrhea.

It is generally accepted that kwashiorkor is precipitated by acute diarrheal disease, measles, or some other infection superimposed on a diet already dangerously low in usable protein or calories. Evidence also exists that keratomalacia, scurvy, and beriberi are frequent aftermaths of an infectious process in persons subsisting, respectively, on diets deficient in vitamin A, ascorbic acid, and thiamine. Experimental studies in laboratory and domestic animals and in man confirm the adverse effect of infection on the metabolism of these vitamins. Although the evidence is less convincing, infection may precipitate pellagra in niacin-deficient persons.

Infections interfere with the metabolism of calcium and phosphorus. The electrolyte imbalance commonly associated with diarrhea is of major clinical and public health significance in many regions. Chronic infections alter iron metabolism and erythrocyte production to such an extent that the so-called "anemia of infection" develops. Microcytic anemia also results from intestinal bleeding occasioned by severe hookworm disease, and occasionally from urinary blood loss, as with *Schistosoma haematobium*. Infection with the fish tapeworm *Diphyllobothrium latum* frequently leads to macrocytic anemia through avidity of the parasite for vitamin B₁₂.

Frequently, infection leads to an accumulation of fat in the liver and some degree of steatorrhea, although usually neither finding is of clinical importance. Many infections lower blood glucose and limit deposition of glycogen in the liver. Specific infectious diseases also influence various types of enzyme activity.

To an important extent, infectious disease, in conjunction with reduced food intake and an altered metabolism of protein and other specific nutrients, is associated with retardation of growth and maturation of young children. Endocrine factors are directly involved. The need for more protein during convalescence from an infectious disease is a further limiting factor in the growth of those children whose usual diet is of borderline protein adequacy.

Infections so consistently worsen nutritional status that they must be taken into account in all clinical problems and public health programs that involve persons whose diet is inadequate or whose nutritional status is suboptimal.
