Effect of Infection on Nutritional Status

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ABSTRACT

All infections no matter how mild decrease nutrient intakes and increase nutrient losses even when subclinical. The losses include decreased intestinal absorption, direct loss of nutrients in the gut, internal diversion for metabolic responses to infection and increased BMR when fever is present. Infection influences in this way not only protein and energy status but also that of most other nutrients. The clinical importance of these consequences of infection depends on the prior state of the individual, the nature and duration of the infection and the diet of the individual during the infection, particularly dietary intake during the convalescent period and whether full recovery takes place before another infection occurs. In industrialized countries particular attention must be paid to the nutrition of hospitalized patients since they are frequently debilitated by their primary disease, morbidity, and their nutritional status. Morbidity and mortality are increased by nosocomial infections to which the poorly nourished individual is more susceptible.

Key words: nutrition; infection; parasitic disease; nutritional status; diarrhea; respiratory disease; immune status; physical performance; cognitive performance.

The WHO Monograph "Interactions of Nutrition and Infection" (Scrimshaw et al., 1968) presented extensive evidence that all infections, no matter how mild, affect energy intakes and requirements through a number of mechanisms. Moreover, the presence of an infection is more likely to be responsible for nutritional disease than a shortage of food. During the recovery phase, however, the quantity and quality of food available is usually the limiting factor. For rapid recovery, protein and calorie intake during this period must be greater than for the uninfected individual.

Failure to recover adequate nutritional status may be due either to low food availability or to a new infection following closely. As the 1968 Monograph also pointed out, the probability of additional infections is increased for individuals in poor nutritional status by two factors. One is that the same social and environmental circumstances that lead to malnutrition are likely also to increase the probability of frequent exposure to infection. The other reason is the reduced resistance to infection in the malnourished.

While this chapter focuses only on the effects of infection on nutritional status, the relationship between malnutrition and infection in human populations is synergistic. Each worsens the other, and the result is generally more serious than could be predicted from the effects of either alone.

Variation in Morbidity from Infectious Disease

Under circumstances that vary with time and place, infections are frequent in some populations and rare in others. Regardless of the prevalence rates under any specific set of circumstances there is always great individual variability. Nevertheless, the morbidity due to infectious diseases among infants and young children of the poor in developing countries is generally very high (Chen and Scrimshaw, 1983; James, 1972). For diarrhea alone, rates in Pactuba, Brazil averaged 6.0 episodes per child per year (Guerrant et al., 1983), 6.1 in Matlab, Bangladesh.
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(Black et al., 1984), and 7.9 in Santa Maria Cauque, Guatemala (Mata, 1978). Since some children have few or no episodes, the burden of this disease on many of the children is much greater than these rates suggest.

Examples are shown in Figs. 1 and 2 taken from the long-term studies of Mata (1978) in a Guatemalan highland village. Fig. 3 taken from Chavez and Martinez (1982) illustrates the frequency of illness for 17 children during their first three years of life in a Mexican village. These high infectious disease rates apply to most other underprivileged populations in Africa, Latin America, and Asia.

In both developing and industrialized countries nosocomial infections are responsible for worsening the nutritional status of hospitalized patients and thereby increasing overall morbidity and case fatality rates (Gorse et al., 1989; Scrimshaw, 1989). Not enough attention is paid to the significance of the high frequency of intercurrent infections among hospital patients who are already frequently debilitated and vulnerable. The first INCAP studies of kwashiorkor were conducted under conditions of several children to a bed in a crowded open pediatric ward. We observed in every case a stationary period with no weight gain for many weeks after initial recovery and disappearance of edema (Scrimshaw et al., 1958). After changing our studies to a small private hospital with individual cubicles to minimize cross infections, we never again observed this stationary period.

Even under relatively favorable institutional conditions morbidity rates can be very high. Table 1 lists 108 infections in 90 days among 32 well-fed
Table 1. 108 Acute Infections Among 32 Children Age 2 to 9 Years Observed in a "Model" Convalescent Home in Guatemala City for 90 Days

<table>
<thead>
<tr>
<th>Disease</th>
<th>Total No Diseases</th>
<th>Disease</th>
<th>Total No Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious hepatitis</td>
<td>2</td>
<td>Gonococcal vaginitis</td>
<td>11</td>
</tr>
<tr>
<td>Measles</td>
<td>2</td>
<td>Purulent otitis media</td>
<td>4</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td>3</td>
<td>Acute tonsillitis</td>
<td>7</td>
</tr>
<tr>
<td>Bronchial asthma and</td>
<td>15</td>
<td>Upper respiratory</td>
<td>15</td>
</tr>
<tr>
<td>asthmatic bronchitis</td>
<td></td>
<td>infection</td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>5</td>
<td>Fever of unknown origin</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>9</td>
<td>Urinary infection</td>
<td>1</td>
</tr>
<tr>
<td>Parotitis</td>
<td>4</td>
<td>Impetigo and cellulitis</td>
<td>13</td>
</tr>
<tr>
<td>Chicken pox</td>
<td>3</td>
<td>Skin allergy</td>
<td>5</td>
</tr>
</tbody>
</table>

(Unpublished INCAP data)

Table 2. Illnesses Among 60 Children 2-5 Years Old in a 6-Month Orphanage Feeding Study (Vellore, South India)

<table>
<thead>
<tr>
<th>Illness</th>
<th>No.</th>
<th>Jaundice</th>
<th>Fever</th>
<th>Conjunctivitis</th>
<th>Diarrhea/dysentery</th>
<th>Gingivitis</th>
<th>Skin infection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infections</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>136</td>
</tr>
<tr>
<td>Fever</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea/dysentery</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin infection</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Pereira unpublished data)

children 2 to 9 years old recovering from severe malnutrition in a model convalescent home in Guatemala City (Unpublished INCAP data). Table 2 identifies 136 infections among 60 children 2 to 5 years old in a six months supplementary feeding study in an orphanage near Vellore, India (E. Pereira, unpublished data). The burden of infections under less favorable institutional circumstances is even greater.

Infection and Growth

In children whose nutritional status is poor, episodes of any of the common communicable diseases of childhood can be devastating. The child represented in Fig. 4 required twenty-two weeks after the onset of whooping cough to regain the weight lost (Mata, 1978). Table 3 reveals the frequency with which this disease retarded growth for many weeks in children in the same village.

Measles also impacts strongly on nutritional status causing a sharp drop in serum albumin (Dossetor and Whittle, 1975) and lean body mass (F. Viteri, unpublished INCAP data) as well as growth (Mata, 1978). In children whose nutritional status is marginal, measles will reduce growth in ensuing weeks (e.g. in India, Kiellman et al., 1978; Reddy et al., 1986; in Kenya, Duggan and Milner, 1986).

A reciprocal relationship between morbidity from diarrheal and other infectious diseases and growth has been reported from many countries including India (Kielmann et al., 1978), Guatemala (Martorell et al., 1975; Mata, 1990), Colombia (Lutter et al., 1989), Gambia (Rowland et al., 1977), Uganda (Cole and Parkin, 1977), Mexico (Condon-Palomino et al., 1977; Mama, 1990), Bangladesh (Black et al., 1984), Sudan (Zumwally et al., 1987). In the Guatemalan, Colombian and Mexican studies, the negative effect of diarrhea on growth was prevented by a nutritious supplement.
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Thus when the diet is adequate, the effect of acute infections on growth is usually transient and they are usually sufficiently widely spaced to permit full recovery in between.

Nevertheless, when nutritional status is marginal even seemingly minor infections can influence growth. In a longitudinal study in India, young children grew significantly less well in the three-months period during which they received multiple immunizations (Kielmann, 1977; Kielmann et al., 1978).

Precipitation of Nutritional Diseases by Infections

Because of the multiple effects on nutritional status, infections are likely to precipitate frank nutritional disease in individuals whose nutritional status is borderline. Kwashiorkor may follow measles, chickenpox, (Scrimshaw et al., 1966; Scrimshaw and Wilson, 1960) German measles, and whooping cough. Diarrhea is reported from many countries to be the most common contributory cause of kwashiorkor (Scrimshaw et al., 1968; Whitehead, 1977). This is the case even when not necessarily severe, because it may be only the latest in a long series of diarrheal, respiratory and other infections which progressively deplete the young child, when there is neither sufficient food or time for complete recovery between episodes.

Among prisoners of war of the Japanese during World War II whose diet was deficient in thiamine, it was well known that once a prisoner developed diarrhea or other infection, acute beriberi was likely to follow (Smith and Woodruff, 1951). It was noted by Spicer in 1982 and strongly reaffirmed by Oomen (1958) that xerophthalmia and keratomalacia can be precipitated in children by a wide variety of common communicable diseases when their vitamin A status is already borderline.

How Infections Worsen Nutritional Status

Anorexia

Experience with nitrogen balance studies that have been disrupted by intercurrent infections reveals a consistent decrease in food intake. This is true even when efforts are made to maintain a constant food intake in metabolic studies, including infections as asymptomatic as immunization against yellow fever (Gandra and Scrimshaw, 1961). Moreover, this is a consistent effect of infection that affects not only protein and energy intakes but also that of most other nutrients. It will be a factor in precipitating clinically evident deficiencies of any nutrient that is already borderline or deficient.

Cultural and therapeutic practices

Withdrawal of food from individuals with fever, diarrhea or other symptoms of infection is an almost universal practice that exacerbates the effect of anorexia. In the case of young children with diarrhea or febrile infection there is a strong tendency of the mother to withdraw solid food and substitute thin starch or sugary gruels that are low in protein and caloric density or to offer herbal decoctions of various sorts (Khan and Ahmad, 1986; Hoyle et al., 1980). In Guatemala, for example, children with measles are frequently given “agua de tisana” made from various local wild herbs.

In field studies it is not possible to separate the effects of anorexia from those of deliberate withdrawal of food for cultural reasons (Martorell et al., 1980; Brisco, 1979). Table 4 from Martorell and Yarbrough (1983) indicates the average reduction in caloric intake associated with the presence of specific symptoms of infection in Guatemalan children. The overall reduction was 19%. Martorell et al. (1990) and Martorell and Yarbrough (1983) report consistently less dietary energy intakes of Guatemalan children with diarrhea than those without at all periods from 15 to 60 weeks. Mata et al. (1977) found a strong inverse correlation between infections and energy intake in the second year of life in Santa Maria Cauque, Guatemala.

Table 4. Average Reduction in Intake Associated with the Presence of Specific Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Energy (kcal/day)</th>
<th>Protein (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>effect</td>
<td>p</td>
</tr>
<tr>
<td>SC</td>
<td>-175</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Respiratory illness</td>
<td>-67</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-160</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Apathy</td>
<td>-175</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

*Significance testing refers to an analysis of variance where the independent variables were age (11 groups) and presence or absence of the symptoms. The dependent variable was either energy or protein. Degrees of freedom were 1/3438. The findings remained unchanged when dummy variables for either sex or village were added as independent variables.

(Martorell and Yarbrough 1983)
In Matlab, Bangladesh (Hoyle et al., 1980) caloric intakes in children under five years of age during the acute stage of diarrhea were more than 40% below those after recovery. The differences were greater with diarrhea caused by rotavirus and E. coli than with cholera and Shigella (Molla et al., 1981a, b). In Peru, low caloric intakes decreased from 10% to 86% among breast-fed children with diarrhea (Bentley et al., 1991).

Many years ago Chung (1948) in New York City and Chung and Viscorova (1948) in Poland showed that, despite a decrease in both intake and absorption due to the infection, the loss in young children was very much less than when food was given. Many similar studies have followed (Molla et al., 1983; Mahalanabis et al., 1979), and it is now recognized and recommended that normal food intake should continue to be encouraged during diarrheal and other infections. The acute stage can be compensated for by providing a higher intake during the convalescent period (Molla et al., 1983).

**Malabsorption**

The significant decrease in absorption of nutrients with diarrhea is referred to above. Chung demonstrated this in New York City in 1948. Concurrently, Chung and Viscorova reported that when adequate food was provided the absorption of nitrogen in four children with diarrhea varied from 40% to 74% and that of fat from 39% to 67%. For two similar cases in which food was withheld absorption percentages were mildly negative for both nitrogen and fat. In the metabolic studies of INCAP, protein absorption was generally reduced 10% to 30% and rarely as much as 40%. In Bangladesh, absorption during diarrhea due to rotavirus averaged 43% for nitrogen, 42% for fat, 74% for carbohydrate and 55% for total calories. Corresponding absorption figures for diarrhea due to enteropathogenic E. coli and Shigella were slightly higher (Molla et al., 1981a; Molla et al., 1982). Despite the reduced absorption it is important to maintain food intake to the extent possible during bouts of diarrhea. The frequency of diarrheal disease in young children makes it an important contributor to the frequent periods of protein and energy losses in young children due to infections.

The range of infections that are associated with malabsorption is wide. They include the bacterial, viral and protozoan enteritides, intestinal parasites such as hookworm, fish tapeworm, ascaris, strongyloloides, and systemic disorders such as measles, tuberculosis, malaria, and streptococcal infections. These infections act by shortening intestinal transit time, physically blocking mucosal surfaces, or reducing mesenteric blood flow.

A certain proportion of children with acute diarrheal disease of nonspecific causes have persistent carbohydrate intolerance and undergo a much more severe and prolonged nutritional deficit (Rosenberg and Scrimshaw, 1972). In addition, between 30% and 50% of individuals living in an unsanitary environment experience chronic changes in the intestinal epithelium that includes flattening of the villi and loss of microvilli given the name tropical jejunitis (Brunser et al., 1970; Bayless et al., 1971; Lindenbaum et al., 1972). The resulting malabsorption attracted considerable attention when it was identified in returning U.S. Peace Corps volunteers, missionaries and other expatriates who had lived in unsanitary environments and required up to a year for full recovery (Klipstein and Falaiye, 1969).

Malabsorption of xylose and lactose was later found in American military and Peace Corps personnel in Thailand (Keusch et al., 1970). Xylose malabsorption has been reported for local populations in Haiti (Klipstein et al., 1968; Cook, 1972), India (Baker, 1972; Gorbach et al., 1970), Thailand (Sprinz et al., 1962; Keusch, 1972), Bangladesh (Lindenbaum et al., 1971), Colombia (Mayoral et al., 1967; Ghitis et al., 1967), Puerto Rico (Lugo-de-Rivera et al., 1972) and undoubtedly occurs in most developing countries. While only xylose absorption was studied, other nutrients are undoubtedly also affected. Rosenberg et al. (1977) showed that most rural Guatemalans had reduced absorption of protein and carbohydrate.

**Catabolic losses**

A catabolic response occurs with all infections even when they are subclinical and not accompanied by fever (Beisel, 1972, 1975, 1977; Beisel and Wannemacher, 1980; Keusch and Farthing, 1986). Since carbohydrate stores are inadequate to meet the increased energy requirement resulting from fever and the metabolic response to infection (Cahill, 1970), and since lipid stores are not effective, another source of energy is required. This is mainly gluconeogenesis.

Under the stimulus of the release of interleukin-1 by leukocytes, endocrine changes are initiated that lead to the mobilization of amino acids from the periphery, primarily from skeletal muscle (Dinarello, 1984). Amino acids such as those of the branched-chain group are utilized as energy sources for the synthesis of alanine or glutamine. The latter are rapidly taken up by the liver and utilized for gluconeogenesis. Amino acids, such as phenylalanine and tryptophan, which cannot be metabolized in
skeletal muscle are released in elevated amounts (Wannemacher, 1977).

Fig. 5 shows that in a young man with Tularemia more than two thirds of the negative nitrogen balance was due to this metabolic response and the remainder to a spontaneous decrease in food intake (Beisel et al., 1967). Fig. 6 shows that even an individual with completely asymptomatic Q-fever can be cumulatively increasing nitrogen balance for as long as 21 days (Beisel, 1977).

In INCAP experience with metabolic studies in children, infections are always associated with a period of negative nitrogen balance, even in the case of immunization with yellow fever vaccine which provoked no symptoms or immune response (Gandra and Scrimshaw, 1961). Beisel et al. (1967) found the nitrogen balance responses of immunized adults with only mild tularemia to be qualitatively similar to those with the typical clinical disease.

Anabolic losses

A marked increase in nitrogen retention may occur following an infection despite only a modest decrease in retention during the acute period (Wilson et al., 1961). During an infection, amino acids are diverted from normal pathways for the synthesis of immunoglobulins, lymphokines, C-reactive proteins and a variety of other proteins including key liver enzymes (Wannemacher, 1977). This would explain the common finding that the extra nitrogen retained during the recovery period in metabolic balances studies exceeds that accounted for by the magnitude of the negative balance during the acute phase of an infection.

Fever

Whatever its benefits in resisting infection, fever has a metabolic cost. The regulation of normal body temperature within a narrow range is a complex phenomenon that is modified by the endogenous pyrogenic activity of interleukin-1 released by mononuclear leukocytes in response to infection and acting on the hypothalamus. The resulting fever increases BMR 13% for each 1 degree C (Dubois, 1937). In some extended infections such as pneumonia and typhoid fever, the elevated temperature is maintained at a higher level with daily variations similar to those in the normal range. Conversely in malaria there are sudden rises and falls in temperature. During the period of maximum fever, metabolism may increase by nearly one-third.

Fig. 7 from the 1936 Third edition of the classic book of Eugene du Bois on Basal Metabolism in Health and Disease shows the relationship of basal metabolic rate to the degree of fever in various infections. Van't Hoff's law that the coefficients for the increase in the velocity of various chemical reactions with temperature lies between 2 and 3 implies an increase of 30% to 60% for a 3 degree rise from 37 to 40 degrees C. In addition, food intake is reduced during fever, the fever causes an additional depletion that needs to be made up during recovery.
Additional intestinal losses

Malnutrition is difficult to measure separately from malabsorption but a significant additional cause of further malnutrition is the direct loss of nutrients into the gut. Protein losing enteropathy has been described for measles (Axton, 1975; Dossetor and Whittle, 1975; Sarker et al., 1986) and diarrhea (Waldman, 1970; WHO, 1980; Mujibur Rahaman and Wahed, 1983) especially when due to Shigellosis (Rahaman et al., 1974). Alpha 1-antitrypsin is a simple and useful quantitative marker for estimating the loss of protein into the gut in diarrheal disease (Mujibur Rahaman and Wahed, 1983). It should be used for this purpose with other kinds of infections.

In ICDDRBR studies, nearly two-thirds of patients with enterotoxigenic E. coli (ETEC) and 40% of those with rotavirus diarrhea were also associated with excessive loss of protein in the feces. They reported that due to protein-losing enteropathy between 100 and 500 ml of serum were lost with feces each day in patients with shigellosis.

Bleeding into the intestine from Schistosoma mansoni, or hookworm also represents a loss of calories. Brisco (1979) has concluded that each adult hookworm causes the loss of about 1 kcal/day. Using an estimate of an average hookworm load of 100 hookworms ICDDRBR studies show that this would amount to an energy loss equivalent to 5% to 10% of the caloric intake of young children.

Reduced growth and weight loss

Figs. 1, 2 and 4 illustrate the impaired growth that characterizes children subjected to frequent infections and borderline diets. The net result is to decrease nutrient requirements although the effect is less significant for energy than it is for protein. This is because the requirement for average daily growth of a two year old child is about 12 percent of the total protein requirement and for energy about 2% of the total (3% of BMR).

The relatively small protein and energy savings from stopping growth is generally not sufficient to avoid actual weight loss. Nevertheless, the weight loss that is associated with a single episode is easily made up if the diet is adequate to permit this. However, recurrent episodes without sufficient food or time for recovery accounts for most of the poor growth of young children in developing countries.

Effects of Specific Infectious Diseases on Nutrient Requirements

Bacterial and viral

As already emphasized intracellular infections of any kind will set off the train of metabolic responses outlined earlier. Previous figures illustrate the impact of a rickettsial infection, Q-fever and a viral infection, and chicken pox on nitrogen balance. Fig. 8 from Beisel (1977) shows the cumulative negative nitrogen balance in a viral infection, sandfly fever, a Bedsonian infection, tularemia, and malaria, due to an intracellular protozoan. Thus the metabolic consequences of systemic infections are not dependent on the specific causative organism but to the sequence of metabolic events already described. Diarrheal disease caused by a variety of bacterial and viral agents is the most common cause of morbidity and mortality in most
developing country populations (Chen and Scrimshaw, 1983).

**Parasitic infections**

As an acute febrile illness, malaria has the same consequences as acute infections of bacterial, viral or rickettsial origin (Barr and Dubois, 1918; McGregor, 1982; Tomkies et al., 1983). This is also true for febrile episodes associated with toxoplasmosis, onchocerciasis, leishmaniasis and trypanosomiasis. However, there may be additional local effects.

Reduced intestinal absorption of nitrogen can occur in malaria as a consequence of reduced mesenteric blood flow (Migasena and MaeGraith, 1969). In endemic areas there is an association between malaria and low birth weight and malaria is associated with failure to gain weight (Bruce-Chwatt, 1952; McGregor and Smith, 1952; Cannon, 1958; Spitz, 1959; Giles et al., 1969; Rowland et al., 1977). Anemia is a common sequel to *Plasmodium falciparum* infection and to a lesser extent in the other types of malaria (McGregor et al., 1966; Giles et al., 1969). This is due in part to increased iron loss due to hemolysis, but immunological destruction of unparasitized erythrocytes may also occur (Zuckerman, 1966). Malaria infection of the placenta can inhibit fetal growth or even cause a miscarriage (MacGregor and Avery, 1974).

*Giardia lamblia* is a common cause of chronic malabsorption including wasting, hypoalbuminemia, and diarrhea (ChauJuri, 1943; Amini, 1963; Solomons, 1982), and malabsorption of fat and carbohydrate has been well documented (Veghelyi, 1938; Palumbo et al., 1962; Khosla et al., 1978; Riis, 1975; Kluska, 1972). Poor absorption of vitamin A with this protozoan infection was first described by Chesney and McCord (1934) and Katsampes et al. (1944) and more recently by Mahalanabis et al. (1979). Several investigators have reported evidence of ileal malabsorption of vitamin B12 (Peterson, 1957; Antia et al., 1966; Notis, 1972) and low serum folate levels in patients with *Giardia* infection have been described. It may also contribute to poor nutritional status in children (Loewenson and Mason, 1986).

Intestinal helminths such as *Ascaris lumbricoides* (Gupta et al., 1977; Brown et al., 1980; Taren et al., 1987; Venkatachalam and Patwardhan, 1953; Tripathy et al., 1972), hookworm (Drake, 1959; Layrisse et al., 1964), *Strongyloides* (Milner et al., 1965; O’Brien, 1975; Carvalho Filho, 1978), *Trichuris* (Layrisse et al., 1967; Jung and Beaver, 1951), and *Trichocephalus* (Crompton, 1986), may also reduce intestinal absorption of protein and other nutrients. Malabsorption of vitamin A has been described with *Ascaris* (Sivakumar and Reddy, 1972). The impact of various helminth infections on human nutrition has been comprehensively reviewed by Stephenson (1987). Careful metabolic balance studies generally fail to detect a significant effect of mild to moderate worm burdens on intestinal absorption although appetite may be reduced (Bray, 1953; Kotcher et al., 1966; El-Mawla et al., 1966; Tripathy et al., 1972; Schneider et al., 1981). *Ascaris* and *Clonorchis sinensis* can also cause biliary and pancreatic obstruction (Rosenberg and Bowman, 1982).

Hookworm is a common cause of iron deficiency anemia (Giles, 1964). The iron losses are associated with hookworm and *Schistosoma hematobium*. Individuals with *S. hematobium* lose blood in the urine and are also at increased risk of iron deficiency. *Necator americanus* causes daily loss of about 0.3 ml of blood per day (Roche et al., 1957a, 1957b; Roche and Perez-Gimenez, 1959), and *Ankylostoma duodenal* results in a loss per worm five to ten times higher (Farid et al., 1965; Farid and Miale, 1962). Although more or less half of the iron is reabsorbed, the loss in heavily infected patients ranged from 14 to 45 ml of blood per day (Roche and Perez-Gimenez, 1959; Giles et al., 1964) or 6 g of iron per day (Blackman et al., 1965). Most of the protein in the blood entering the gut due to intestinal bleeding in hookworm infection is reabsorbed, but in heavily infected patients increased fecal protein loss may occur (Gupta et al., 1974).

Surprisingly, even with severe hookworm anemia, adequate dietary iron can fully compensate for these losses without removal of the worms (White et al., 1957; Giles et al., 1964; Basta et al., 1979). Stephenson et al. (1980) described growth impairment with *Ascaris* infection and later (1989) showed that active antihelminth treatment improved the growth of Kenyan school children with combined hookworm, *Tricuris* and *Ascaris* infection (see also Gupta and Urrutia, 1982).

Because of their bulk, some parasites require sizeable quantities of nutrients, which must be obtained from the same sources available to host cells. Physicians practicing in northern Michigan, Wisconsin, and Minnesota where the Scandinavian custom of consuming marinated raw fresh water fish persists, found that massive infection of the fish tapeworm, *Diphyllobothrium latum* is associated with megaloblastic anemia. This is due to competition of the parasite for vitamin B12 (Scudamore et al., 1961; Nyberg, 1961; Von Bonsdorff, 1948, 1956, 1964). Some of this effect and that of *Giardia lamblia* may also be due to hypochlorhydria or achlorhydria in the stomach (Hoskins et al., 1967), which would interfere with vitamin B12 absorption.
Gastric acidity is common in intestinal parasitic infection and produce a severe swallowing disorder. Loss of T. cruzi can destroy the neural plexuses in the esophagus (Layrisse et al., 1964; El-Mawla et al., 1966; Stephenson, 1987).

**Effects of Infections on Specific Nutrients**

Physicians called upon to determine an appropriate nutritional regimen for patients with acute or chronic infection should be aware that any past dietary deficiencies have been worsened and that current intake and absorption of essential nutrients is likely to be impaired. Correction of these deficiencies by diet alone while the infection persists is likely to be difficult. Therefore, careful consideration should be given the use of enriched formulas for oral feeding. Where parenteral alimentation is judged necessary, nutritional status should be appraised and the formula adjusted as required. Some of the specific nutritional effects of infection to be taken into consideration under these circumstances include the following:

**Protein**

Powanda (1977) has summarized data from a wide variety of acute infectious diseases by adding the total nitrogen losses and dividing them by the number of days over which these losses occurred. For all infections the average loss of 0.6 g of protein lost per kg per day, is equal to the mean estimated total protein requirement for adults. Diseases associated with diarrhea or dysentery produced an average loss of 0.9 g of protein/kg per day. Higher losses were observed with typhoid fever and other severe infections, reaching 1.2 g or protein/kg per day.

Another approach to the magnitude of the catabolic response in infection is to measure urinary 3-methylhistidine as a measure of muscle protein catabolism in the septic patient. Long et al. (1977) have reported an increase from 12 mg/day to 30 mg during the peak fever response. By this measure, the average additional loss in the urine during sepsis was the equivalent to 1.14g of protein/kg per day.

Such calculations are underestimates because they do not include energy expended for the multiple anabolic responses. As emphasized earlier, balance studies during recovery indicate these to be substantial.

While the absolute loss of N with infection is less in the malnourished, the relative significance of the loss is greater. Both metabolic and field observations suggest that, even with an optimum diet, it may take two to three times longer to replete than to deplete an individual. In this case any figure for daily additional dietary protein during recovery needs only to be from one-half to one-third of the daily loss during the acute phase of an infection. If the diet is not sufficient for a maximum rate of recovery, daily improvement is correspondingly reduced and the time required for complete recovery increased. Under developing country conditions there is a high risk that another episode of infection will occur before recovery has taken place (Wilson et al., 1961; Scrimshaw et al., 1968). The more severe and closely spaced the episodes of infection, the more likely that full recovery will not occur and that the adverse effects will become cumulative.

**Lipids**

Infections affect plasma lipids, but the changes are highly variable and depend upon the duration and severity of infection, the degree of fever, and age (Beisel and Fisher, 1970). They include changes in triglycerides, free fatty acids, ketone bodies, and the partially oxidized products of fatty acids by the liver (Gallin et al., 1969; Blackburn, 1977; Masoro, 1977).

**Carbohydrates**

The catabolic responses described above have as one principle function the provision of amino acid substrate for gluconeogenesis. Thus a continual conversion of alanine carbon to glucose carbon occurs with acute infection, even when exogenous carbohydrate is adequate. It appears to be the rate of release of glycogenic amino acid substrates from peripheral tissues that determines the rate of hepatic gluconeogenesis (Long, 1977).

All of the hormones that regulate carbohydrate metabolism participate in host responses to infection (Beisel, 1977). A number of groups have documented an increased fasting concentration of both glucagon and insulin in serum (Shambaugh and Beisel, 1967; Rocha et al., 1973; Rayfield et al., 1973). Despite the initial stimulation of gluconeogenesis, the body may eventually become severely hypoglycemic. Lethal hypoglycemia may result in septic neonates (Yeung, 1970) and in severe viral infections of the liver such as fulminating hepatitis (Felig et al., 1970) or as shown in monkeys, yellow fever (Wakemen and Morrell, 1931).

**Energy**

The energy costs of communicable diseases in infancy and childhood have been recently reviewed...
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(Scrimshaw, 1990a). The energy cost of depositing a gram of protein has been estimated to be 24 kcal or about 6 kcal of total weight gain (UNU 1979). If this figure is applied to the observed protein losses summarized above, calculated average caloric losses from this source alone would be between 4 and 5 kcals per kg per day. This seems small, but it represents from 14 to 29% of the requirements of a one year old child. Increased protein loss during infections estimated from increased urinary 3-methylhistidine excretion alone is the energy equivalent of about 7 kcal/kg/day.

Jackson et al. (1977) in Jamaica measured the energy cost of growth of children recovering from protein-energy malnutrition and reported a range of 4 to 5 kcal/g weight gain with 40% of this considered to be fat tissue and 60% protein tissue. They estimate the energy cost of synthesizing a gram of lost protein to be 7.5 kcal g and 11.6 kcal for replacing a gram of fat. There are "savings" of dietary energy during the acute phase of an infection that are due to anorexia and reduced physical activity. During the recovery period, however, this must be made up together with the losses due to the deficits arising from the malabsorption, increased catabolism, and internal synthesis associated with infections. Thus with each infectious episode there is a small decrease in de facto dietary requirement at the time of the infection and an increase during the convalescent period that is difficult to quantitate because it is so variable.

Obviously, the severity of the caloric deficit is related to the duration and magnitude of the morbidity in each individual situation, and rarely poses a major threat to nutrition unless the infection is chronic or recurrent. For most respiratory disease the energy cost would be trivial, but for diarrheal disease and the common communicable diseases of childhood it could add significantly to either a chronic energy deficit or to increased dietary energy need depending on dietary adequacy during the infection.

If the proof of the pudding can be said to lie in the eating, food intake is observed to drop during acute infection and to increase above normal levels if the diet is sufficient to allow this. Fig. 9 shows the large increase in caloric intake during convalescence from diarrhea in Bangladesh when a good diet is available ad libitum (Sarker et al., 1982).

Vitamin A

Vitamin A blood levels are appreciably reduced in pneumonia, rheumatoid arthritis, acute tonsillitis, infectious hepatitis (May et al., 1940; Shank et al., 1944; Harris and Moore, 1947; Jacobs et al., 1954). Vitamin A is not normally found in the urine but it does appear with at least some infectious diseases (Moore, 1957; Goldsmith, 1959). Lower serum carotene and vitamin A levels have been reported with hookworm disease (Rodger et al., 1960).

The capacity of infections to precipitate xerophthalmia and keratomalacia in individuals already marginally deficient is well established (Oomen, 1958, 1959; McLaren, 1963, 1986; Sommer, 1982; Sommer et al., 1984; Tielsch et al., 1986; Stanton et al., 1986; De Sole et al., 1987) and the effect is particularly severe with measles (Sommer et al., 1984) and also noted for chicken pox (Campos et al., 1987). A significant drop in serum vitamin A levels has been observed in children with acute respiratory infection, gastroenteritis, and measles with levels returning to normal after recovery (National Institute of Nutrition, 1980).

The adverse effect of intestinal parasitic infections on vitamin A absorption has already been described. Enteric infections of bacterial and viral origin also have this effect (Nalin et al., 1980; West and Sommer, 1985). In addition, vitamin A malabsorption occurs during systemic febrile illnesses (Heymann, 1936; Lala and Reddy, 1970; Shank et al., 1944; Sivakumar and Reddy, 1975). Sivakumar and Reddy (1972) reported that in children with acute diarrhea and respiratory infections only 30% to 70% of ingested vitamin A is absorbed. While infection clearly impairs dietary carotene and vitamin A absorption (West et al., 1989), sufficient amounts of supplementary vitamin A can still be absorbed orally for effective treatment of corneal xerophthalmia.

Ascorbic acid

As already noted ascorbic acid levels decrease in plasma and increase in the urine in infected individuals compared to non-infected persons living under comparable conditions. This is even seen with vaccination against small pox and measles (Scrimshaw et al., 1968) and the common cold (Hume and Weyers,
than historical interest since alcoholics often consume diets low in these vitamins and infections increase the likelihood of clinically significant deficiencies of them. Given the frequency with which infections occur in indigent alcoholics, physicians treating them should be aware of this.

The diets of indigent alcoholics are likely to be low in riboflavin a nutrient that is also adversely affected by infection. Beisel et al. (1972) has shown a marked increase in riboflavin excretion with sandfly fever in individuals already on a borderline diet.

B-vitamins

The classical nutritional diseases of beriberi and pellagra were known to be precipitated in vulnerable individuals by a variety of infections. This is of more than historical interest since alcoholics often consume 

Minerals

Iron

As already mentioned, one metabolic consequence of infection is a decrease in serum iron due to its sequestering in the reticuloendothelial system (Beisel et al., 1974). In addition, lactoferrin with a higher iron binding capacity than bacterial siderophores, is released by phagocytes. The net effect is to deprive the infectious agent of iron for its replication and inhibit the spread of the infection. If anemia is present at the time of the infection, or even moderate iron deficiency without anemia, a number of normal resistance mechanisms are compromised. These include impaired phagocytic killing power, delayed cutaneous hypersensitivity, T-cell proliferation and T-killer cell activity, and if sufficiently severe, impaired antibody formation (Chandra and Saraya, 1975; Keusch, 1990).

When individuals, compromised in this way, are given parenteral iron or large doses of oral iron, a disastrous exacerbation of the infection and death may occur (Murray et al., 1975, 1978a, 1978b; Barry and Reeve, 1977; Becroft et al., 1977; Weinberg, 1978, 1984). This occurs because iron is supplied with iron before the host immune system has had time to recover. However, in field studies, supplementation of poorly nourished adults with up to 100 mg of iron daily and proportionately less for children, has always resulted in decreased morbidity from infectious disease (Scrimshaw, 1990b).

Copper and Zinc

Infections decrease both serum copper and zinc (Beisel et al., 1974; Srinivas et al., 1988; Wannemacher et al., 1972). Careful metabolic studies by Castillo-Duran et al. (1988) have documented the impact of diarrhea on zinc and copper status. Metabolic balances of these minerals were strongly negative during the period of acute diarrhea compared with strongly positive balances in the control subjects. During the recovery period zinc balances became positive (405.3 ± 60.8 mcg/kg/day) but copper balance remained negative, although less so (−21.5 ± 46.7 mcg/kg/day).

The mechanism for the loss is wastage from the gastrointestinal tract from both malabsorption and excessive endogenous losses. Since the normal state for the growing infant is net retention of these minerals, the true magnitude of these losses is somewhat greater. The inevitable combination of reduced oral intake and increased fecal losses of minerals should clearly be taken into account in the management of prolonged diarrhea.

These losses cannot be predicted from serum levels since copper levels often increase during infections as a result of stimulation of the hepatic production of ceruloplasmin (Kampschmidt et al., 1973). It is noteworthy that in this study serum copper levels were significantly lower in the diarrhea than in the control cases. Conversely, plasma zinc levels often decline during acute infections because of an internal redistribution of the metal to the liver (ibid). The reduced retention of zinc during diarrhea thus interacts with the redistributitional influence of the infection. On the basis of this study it is reasonable to suggest that treatment regimens for diarrhea should contain supplemental amounts of copper and zinc, but whether this would make a detectable difference in therapeutic results remains to be demonstrated.

Nutrient Allowances for Infectious Disease Morbidity

While it is important to provide a nutritious diet and encourage adequate nutrient intakes during an acute infection, some decrease is almost inevitable due to anorexia. It is generally useless to attempt to increase food intake during illness. Nevertheless, for the multiple reasons discussed in this chapter persons are depleted to a greater or lesser degree during an infection. However, during the recovery period, there is a metabolic window in which appetite is increased and the rate of retention, as least for protein, may be as much as 9 times the average daily requirement.

A 1979 UNU report calculated that a malnourished one year old child depleted by an infectious episode of 7 days duration would need approximately 136 kcals/kg/day and 2.56 g protein/kg/day for
repletion in 30 days. It should be noted that the same weight deficit without infection would have required less than one-third the amount of protein per kg/day but approximately the same number of calories.

Despite the clear evidence of the heavy burden of infection on developing country populations, and the increased nutrient needs above normal requirement levels during convalescence from episodes of infectious disease, this issue is not dealt with quantitatively in national and international recommended nutrient allowances. The comment of the FAO/WHO/UNU Consultation on Energy and Protein Requirements (1985) is illustrative: "... the increased average requirement of a population of school children would not be large." The report goes on to emphasize the need for preventing infections rather than simply meeting increased requirements for recovery resulting from them. This is true but not helpful to the hundreds of thousands of developing country children whose diets are already deficient or borderline and who are experiencing frequent infections.

Whitehead (1977b) recommended a 30% increase in calories and a 100% increase in protein to optimize nutritional repletion of young children depleted by infection. This is consistent with data summarized by Powanda (1977) and Scrimshaw (1977). Moyer and Powanda (1983) discuss the basis for significantly increased nutrient requirements during convalescence without arriving at quantitative recommendations. However, a task force report (Rhode et al., 1983) utilizing this and other information concluded that a child should be offered 50% more than their usual diet for two to four times the duration of the illness or fed extra food daily until pre-illness weight is regained or exceeded.

In a recent INCAP study, supplementation before and during diarrheal disease completely offset the negative effect on length observed in unsupplemented children, attesting to the importance of an adequate diet during the recovery period (Lutter et al., 1989). Adults also need extra food available to them during convalescence. Unfortunately, the diet of most infants and young children and some adults in developing countries is commonly too marginal to permit repletion before another episode of infection depletes the child further.

Other Effects of Malnutrition and Infection

There are other consequences of the synergistic interaction of nutrition and infection that are beyond the scope of this paper, but that should be taken into account. For example a UNESCO monograph (Pollitt, 1990) explores malnutrition and infection in the classroom. It documents the adverse consequences of nutritional deficiencies that are exacerbated by infection in the ways described in this paper. The effects of iron deficiency anemia (Pollitt and Leibel, 1982; Scrimshaw, 1990b) and protein-energy malnutrition (Brozek and Schurich, 1984; Pollitt, 1988) are particularly well documented. In addition, the increased frequency of infections in the malnourished contributes to absenteeism that affects the learning process as well as reducing agricultural and industrial productivity.

An example of the latter is the observation on an Indonesia rubber plantation of a higher frequency of absenteeism due to infection in workers with hookworm anemia compared with those who were not anemic that was due largely to diarrheal and respiratory infections (Basta et al., 1979). The difference was eliminated after 60 days of iron supplementation. There is also extensive evidence for the direct effect of iron deficiency on work capacity and productivity summarized by Scrimshaw (1984) and Spurr (1990). Much of this deficiency is due more to the effect of infections than to diet alone. Most of the impact of the interaction of infection and nutrition on productivity in developing countries goes undocumented and unrecognized.

Summary

This paper can be summarized by emphasizing a number of generalizations:

1. All systemic infections, even when not sufficiently severe to cause overt disease, have adverse effects on the status of protein and other essential nutrients.
2. The practical significance of this effect depends on the prior nutritional status of the individual, the diet during the infection and the adequacy of the diet for prompt recovery.
3. Optimum recovery from infections requires about one-third more protein than normal maintenance, more or less depending on the nature of the infection.
4. Intestinal parasitic infections interfere with absorption of nutrients when sufficiently severe and have a variety of additional adverse effects that depend on their specific nature.
5. Individuals who live in an unsanitary environment with frequent enteric infections develop chronic intestinal mucosal changes that impair nutrient absorption.
6. The interaction between nutrition and infection is synergistic in the sense that not only does infection worsen nutritional status but also the more malnourished an individual becomes the more resistance to infection is reduced and the likelihood of new infections or complications of existing ones increases.

7. Food intake should be maintained to the extent possible during an infection despite the anorexia and during the convalescent period should be significantly greater for at least two to four times longer than the acute period or in the case of children until pre-illness weight is attained or exceeded.

8. The synergistic interaction of malnutrition and infection in developing countries reduces educational effectiveness, increases health burdens, reduces agricultural and industrial productivity, and hinders social and economic development.

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