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Research in Translation

Malnutrition and Infection: Complex Mechanisms and Global Impacts

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"I am not interested in the bloody system! Why has he no food? Why is he starving to death?"
Bob Geldof in The Observer, *1985*

Activation and sustenance of immune responses during infection requires increased energy consumption. Protein energy malnutrition (PEM) is a critical, yet underestimated factor in susceptibility to infection, including the "big three" infectious diseases: HIV/AIDS, tuberculosis, and malaria. In this article, we discuss current concepts and controversies surrounding the complex influences of malnutrition on infection and immunity, and point to practical consequences of countermeasures in acute malnutrition. We call for new strategies to overcome worldwide morbidity and mortality caused by chronic malnutrition in impoverished countries and by the newly emerging public health threat of overnutrition in industrialized societies.

Background

In response to infection, the immune system first executes innate and then subsequently acquired host defense functions of high diversity. Both processes involve activation and propagation of immune cells and synthesis of an array of molecules requiring DNA replication, RNA expression, and protein synthesis and secretion, and therefore consume additional anabolic energy. Mediators of inflammation further increase the catabolic response. Studies in a simple system, involving measurement of the survival of malnourished bumblebee workers, showed that the energy cost of immunity further impairs fitness [1]. Consequently, the nutritive status of the host critically determines the outcome of infection.

Apart from deficiencies in single nutrients, such as vitamins, fatty acids, amino acids, iron, and trace elements, undernourishment based on PEM greatly increases susceptibility to major human infectious diseases in low-income countries, particularly in children [2–4]. Malnutrition is responsible, directly or indirectly, for 54% of the 10.8 million deaths per year in children under five and contributes to every second death (53%) associated with infectious diseases among children under five years of age in developing countries [5]. Infection causes energy loss on the part of the individual, which reduces productivity on the community level and perpetuates the alarming spiral of malnutrition, infection, disease, and poverty (Figure 1).

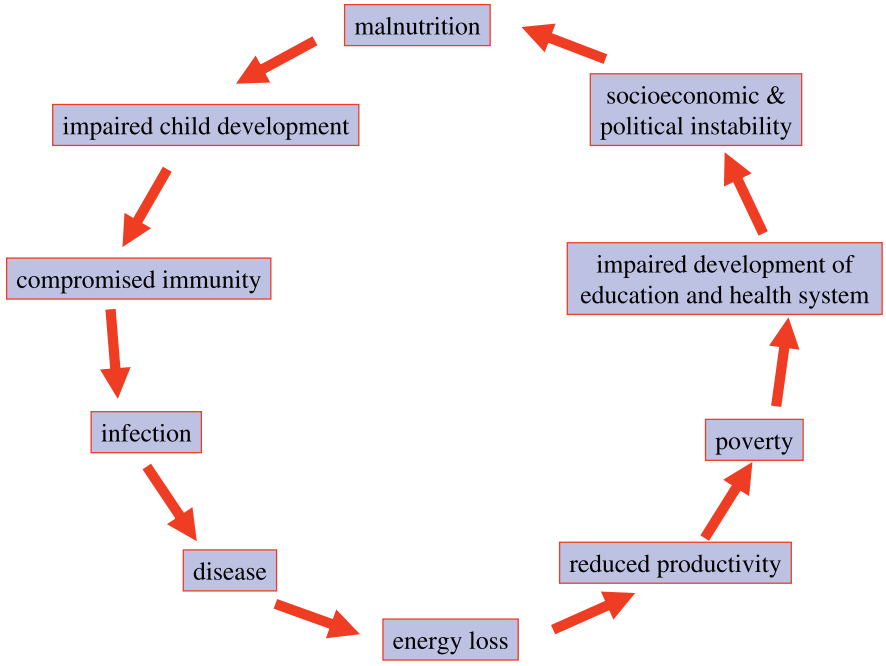

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Figure 1. Protein Energy Malnutrition Increases Prevalence of Infection, Leading to Energy Loss for the Individual

On the community level, this burden reduces productivity, including food production, and perpetuates the relentless spiral of further malnutrition, infection, disease, poverty, and socioeconomic and political instability.

Malnutrition and Infection

Malnutrition increases risk of infection. PEM is a common cause of secondary immune deficiency and susceptibility to infection in humans (Table 1). This

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Abbreviations: BMI, body mass index; Ig, immunoglobulin; PEM, protein energy malnutrition; RNI, reactive nitrogen intermediate; ROI, reactive oxygen intermediate; TH1, type 1 T helper cell; TH2, type 2 T helper cell

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Table 1. Conditions of Under- and Overnutrition and Their Influence on Host Defense Functions

Deficiency	Response Mechanisms Affected/Promoted	Infections
Acute PEM	Phagocytosis, RNIs, ROIs, antigen presentation, leukocyte extravasation, inflammation, T cell activation, T cell memory, antibody titres (IgG, IgA), cytokine secretion, leptin levels, macrophage activation	Opportunistic, respiratory, and intestinal infections, helminths, tuberculosis, measles, influenza, *P. carinii*
Chronic PEM	Thymic development, T cell differentiation, T cell expansion, T cell memory, IgA, IgG, complement and leptin levels decreased, macrophage activation	Respiratory and intestinal infections, helminths, BCG, malaria, AIDS, measles, influenza, skin infections, noma
	Vaccine efficacy	BCG, encapsulated bacteria, measles
Overnutrition	Permanent preactivation of leukocytes, IFN-γ/TNF-α increased, suppressed NK and T cell activation, reduced phagocytosis, increased leptin concentrations often paired with leptin resistance	Opportunistic and fungal infections
Diabetes	Neutrophil, macrophage functions (i.e., phagocytosis, chemotaxis, extravasation), ROIs due to NADPH consumption by polyol pathway	Tuberculosis, diseases due to opportunistic, multibacterial, and fungal infections, osteomyelitis, diabetic foot *(P. aeruginosa, Staphylococcus aureus, S. pneumoniae, Enterococcus)*

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causal relationship is further supported by animal studies.

Severe PEM in children is clinically defined as less than 70% weight-to-height and/or the appearance of pitting edema on both feet, described as either marasmus, a chronic wasting condition, or kwashiorkor, characterized by edema and anemia. Children with kwashiorkor often suffer from marked skin infections. Severe malnutrition during childhood affects thymic development, which compromises immunity in children by a long-term reduction of peripheral lymphocyte counts [6]. This immunodeficiency represents a key factor in susceptibility to infections and has therefore been termed nutritionally acquired immunodeficiency syndrome [7]. In severely malnourished patients, both acquired immunity—i.e., lymphocyte functions—as well as innate host defense mechanisms—i.e., macrophages and granulocytes—are affected. Diminished immune functions render undernourished patients more susceptible to infections, notably those by opportunistic pathogens commonly prevalent in patients with HIV/AIDS [2–4,8,9]. The opportunistic fungus *Pneumocystis carinii,* frequently diagnosed in patients with AIDS, was repeatedly identified in malnourished children after the Second World War [9]. Noma is an opportunistic infection in children between one and four years with PEM, which occurs worldwide, but is most common in sub-Saharan Africa. The infection evolves from gingival inflammation to orofacial gangrene and is commonly preceded by other infections such as measles, malaria, severe diarrhea, and necrotising ulcerative gingivitis. Noma coincides with the period of linear growth retardation in malnourished children [10].

In addition to promoting acute and chronic infections, PEM impairs the linear growth of children, leading to a further reduction in food intake, nutrient absorption, direct or catabolic nutrient losses, and increased metabolic requirements. It has been suggested that acute phase response and proinflammatory cytokines directly affect the bone remodelling required for longitudinal growth [11].

Correlation of malnutrition and growth retardation allows assessment of the individual nutritional state, which is usually measured as mid-upper arm circumference or body mass index (BMI). BMIs are given either as weight-for-height to indicate acute PEM (wasting), or as weight-for-age (underweight) or height-for-age (stunting), correlations for chronic PEM. A study in Kenya found a significant association between HIV infection and lower mid-upper arm circumferences and serum albumin concentration, another measure of malnutrition, but found no such association with BMI [12]. Independent of HIV, socioeconomic factors and severity of tuberculosis are important correlates of acute PEM or wasting [12].

Infection itself contributes to malnutrition. The relationship of malnutrition on immune suppression and infection is complicated by the profound effects of a number of infections on nutrition itself. Examples of how infections can contribute to malnutrition are: (1) gastrointestinal infection can lead to diarrhea; (2) HIV/AIDS, tuberculosis, and other chronic infections can cause cachexia and anemia; and (3) intestinal parasites can cause anemia and nutrient deprivation [13].

Stimulation of an immune response by infection increases the demand for metabolically derived anabolic energy and associated substrates, leading to a synergistic vicious cycle of adverse nutritional status and increased susceptibility to infection. Under inflammatory conditions such as sepsis, mediators increase the catabolic disease state characterised by enhanced arginine use. Furthermore, arginase is induced during infection and uses up arginine as substrate. It has been suggested that depletion of this amino acid impairs T cell responses [14], and exceeding the body's arginine production leads to a negative nitrogen balance [15].

A study in Nigeria found that the severe metabolic demands made during acute measles infection further deteriorated the condition of malnourished children, leading to further weight loss, wasting, and reduced serum levels of essential amino acids [16]. Increased energy consumption due to immune responses may also affect the efficacy of live attenuated vaccines in populations ridden with PEM.

Arginine treatment has been shown to improve nitrogen balance and lymphocyte function and stimulate arginine transport in the liver. These benefits have made arginine an essential constituent of immunonutritive formulas currently in use for critically ill patients.

PEM is an important health determinant for critically ill patients and increases susceptibility to infections in malnourished elderly patients and

patients with anorexia. A large and strictly controlled inpatient study in France pinpoints malnutrition as an independent risk factor for nosocomial infections, which account for 6%–10% of all in-hospital deaths worldwide [17]. Accordingly, nutritive management has to become an elementary part of intensive health care. In summary, nutritional quality and composition are pivotal for anti-infectious immunity.

Malnutrition Affects Immunity

Severe protein malnutrition in newborns and small children causes atrophy of the thymus with reduced cell numbers and subsequently ill-developed peripheral lymphoid organs, i.e., lymph nodes and spleen [6]. This causal chain leads to long-lasting immune defects characterized by leucopenia, decreased CD4 to CD8 ratio and increased numbers of CD4/CD8 double-negative T cells, and, therefore, the appearance of immature T cells in the periphery. Malnourished children suffer in greater proportion from respiratory infections, infectious diarrhea, measles, and malaria, characterized by a protracted course and exacerbated disease. These malnourished children present with diminished functional T cell counts, increased undifferentiated lymphocyte numbers, and depressed serum complement activity (Table 1).

Reduced antibody responses to polysaccharide antigens of encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* exacerbate susceptibility to these pathogens [2,4,18]. Moreover, immune defense at the epithelial barrier of the undernourished host is compromised due to altered architecture of the gut mucosa, such as flattened hypotrophic microvilli, reduced lymphocyte counts in Peyer's patches, and reduced immunoglobulin A (IgA) secretion [7]. Availability of complement components is restricted by malnutrition, thereby affecting the capacity of professional phagocytes to engulf and eliminate pathogens. In mice with experimental PEM, phagocytosis and production of reactive oxygen intermediates (ROIs) and reactive nitrogen intermediates (RNIs) by macrophages is diminished, as is antigen presentation to T cells by dendritic cells [19]. Temporary PEM in mice challenged by experimental peritonitis resulted in impaired immune cell migration and extravasation, as indicated by reduced numbers of CD11b/CD18-positive cells at the site of infection, probably involving lower concentrations of the chemokine MIP-2.

Peripheral T lymphocytes from infected children with PEM had lower expression of the activation marker CD69, and predominantly showed an intermediate ($CD45RA^{low}/CD45RO^{low}$) rather than a memory phenotype ($CD45RO^{high}$) when compared to healthy donors [20,21]. These T cells were biased towards type 2 T helper cell (Th2) responses, represented by decreased IFN-γ/IL-2 (type 1 T helper cell [Th1]) and increased IL-4/IL-10 (Th2) production [22]. Experimentally undernourished weanling mice had predominantly T cells of the naïve quiescent phenotype ($CD45RA^{+}/CD62L^{+}$) [23,24]. In these mice, IFN-γ responses were depressed and IL-10 and the Th2-associated antibody, IgE, were increased, while IL-4 production remained normal [25].

These findings, however, should not be taken to suggest that PEM generally biases towards Th2 responses. Rather, PEM appears to alter immune responses, thus hampering protective immunity of any type. Protective T cell responses against helminth infections are predominantly of the Th2 type comprising IL-4 production, expansion of eosinophils, and IgE secretion. However, malnourished children are deficient for protective IgE antibodies against *Ascaris lumbricoides* [26,27]. By suppressing such responses in mice, PEM increases susceptibility to infection with the intestinal parasite, *Heligmosomoides polygyrus* [28]. Malnourished children suffering from helminth infections have high concentrations of total IgE. Yet these antibodies are neither worm-specific nor protective, and their memory T cells do not recognize helminth antigens [27,28].

Malnutrition and Tuberculosis: Yesterday and Today

Malnutrition is generally appreciated as a major risk factor in the onset of active tuberculosis [9]. This notion is largely based on historical reports but also on more recent experimental animal studies.

One of the major disease burdens globally, tuberculosis is a well-documented example of the way in which malnutrition leads to worse disease outcomes. During the First World War, Denmark was affected by a tuberculosis epidemic similar to that prevailing in countries at war. The Danish tuberculosis epidemic could be explained by widespread malnourishment, since the export of meat, fish, poultry, and dairy products meant that food was scarce inside the country. This tuberculosis epidemic plummeted once the German blockade of Denmark was established and food became available to the Danish population again, but the epidemic continued in other countries [9].

A comparative radiographic survey of prisoners of war held in German camps during the Second World War under similar living conditions found a tuberculosis prevalence of 1.2% versus up to 19.0% among the British and Russians, respectively, with more severe outcomes in the latter. This difference in prevalence and severity is probably a direct consequence of the fact that only the British prisoners received—in addition to

Five Key Papers on the Link Between Malnutrition, Immunity, and Infection

Ing et al., 2000 [28] Employing an animal model for helminth infection, this study shows that malnutrition interferes with protective immunity.

Cegielski et al., 2004 [9] This paper summarizes, for the first time, clear evidence of the link between malnutrition and tuberculosis.

Zarkesh-Esfahani et al., 2004 [60] The authors show the link between leptin-induced TNF- and neutrophil activation.

Turnbaugh et al., 2006 [66] This paper puts a new component on to the map of research on overnutrition: the gut flora's influence on energy uptake.

Tectonidis, 2006 [76] This paper points out a quick and practical approach to remediate acute malnutrition.

Unexplored Research Topics on the Link Between Malnutrition and Infection

1. Control of energy uptake by the host through microbial communities in the gut.
2. Changes of gut flora in malnutrition and influence of probiotics.
3. Regulation of energy requirement and food uptake during immune responses.
4. Role of cytokines in regulating nutrient uptake.
5. Crosstalk between immune (cytokines) and nutrition-related "hormones" (e.g., leptin).
6. Tissue-specific loss of nutrients during infection, inflammation, and immunity.
7. Efficacy of vaccines and drugs given under acute and chronic PEM conditions.
8. Identification of essential immunonutrients and development of food supplements easily accessible for societies with chronic PEM.
9. Schedules for sustainable local food production and safe water supplies by societies suffering from PEM.
10. Efficacy of additives to drinking water and food to prevent infection.
11. Engineering nutritionally enhanced food to prevent infections (e.g., rice, sorghum)
12. Bringing it to the people: Improved infrastructures for food distribution in developing countries.

the regular prison diet—a Red Cross supplement of 30 grams of protein and 1,000 kilocalories per day. This causal relationship is in line with the positive correlation of below average BMI with increased risk of pulmonary tuberculosis [9].

More contemporary reports provide further support that malnutrition has an impact on the clinical outcome of tuberculosis [29]. A statistically significant number of patients with tuberculosis were malnourished in a recent study in Sri Lanka and skin test reactions for tuberculosis were negatively affected by malnutrition [30,31]. Hence, in poor settings, nutritional measures should be considered as an adjunct to anti-tuberculosis drug treatment.

Animal experiments, mainly in the guinea pig tuberculosis model, document detrimental consequences of chronic PEM on immunity to *Mycobacterium tuberculosis*. In these experiments, lymphocyte stimulation as well as secretion of the Th1 cytokines IL-2, IFN-γ, and TNF-α, involved in control of *M. tuberculosis*, were significantly reduced in animals with PEM [9]. Moreover, macrophages from such animals produced more transforming growth factor β (TGFβ), which further suppresses T cells and inflammation [32,33]. A study in murine tuberculosis reached similar conclusions and additionally found that malnourished mice showed hampered production of RNIs, which act as critical effectors against tuberculosis in mice. Consequently, malnourished mice suffered from higher bacterial burdens and died earlier of infection [34]. Finally, efficacy of BCG vaccination against tuberculosis was profoundly reduced in malnourished guinea pigs as compared to normally fed animals, due to impaired T cell priming and function [9,35].

Malnutrition, Leptin, and Immunity

Leptin is a central mediator connecting nutrition and immunity. Levels of the pleiotropic hormone leptin, which regulates satiety, are reduced in patients with PEM. Leptin concentrations correlate with body fat mass and are quickly reduced by fasting [36]. Leptin is a 16 kDa α-helix type protein similar to the cytokines IL-6 and IL-12, and is mainly secreted by adipose tissue. At least six receptors representing different splice forms encoded by one gene are broadly distributed on different cell types. The full-length ObR_b isoform is not only expressed in the hypothalamus, but is also prevalent on lymphocytes and macrophages [36,37]. Leptin binding to ObR_b activates immune cells via the JAK-2/STAT-3 and the MAPK pathway and induces TNF-α, IL-6, and IL-12 secretion in macrophages. Leptin stimulates naïve T cells ($CD45RA^+$) but blocks proliferation of memory T cells ($CD45RO^+$). Concomitantly, leptin promotes IFN-γ secretion by memory T cells, inhibits Th2 responses [38,39], and induces activation markers (CD69, CD25, and CD71) [40]. Apart from inducing lymphopoiesis, leptin seems to deliver survival signals to T cells by upregulating anti-apoptotic proteins T-bet and $Bcl\text{-}x_L$ [36].

Active tuberculosis is associated with cachexia, weight loss, and low serum concentrations of leptin [41–44]. Moreover, leptin-deficient mice are more susceptible to *M. tuberculosis* than wild-type mice, and T cell numbers, including those producing IFN-γ, are reduced in infected lungs, suggesting that leptin contributes to protection against tuberculosis [45]. However, a causative correlation between severity of tuberculosis and leptin is not fully established, and leptin concentrations do not predict wasting in human tuberculosis [44].

Malnutrition causes immunosuppression through a variety of mechanisms, including the involvement of leptin and the hypothalamic-pituitary-adrenal axis. PEM reduces leptin concentrations and increases serum levels of stress hormones, i.e., glucocorticoids [2,4,46–48]. Thus, it is likely that the hypothalamic-pituitary-adrenal axis plays a critical role in malnutrition-associated immune deficiency.

In well-nourished people, infection and inflammation increase leptin levels in an IL-1-dependent manner and increase glucocorticoid concentrations, which subsequently can control inflammation [40,49,50]. Under conditions of PEM and low leptin concentrations, glucocorticoids impair macrophage functions by decreasing NF-kB translocation into the nucleus [49]. Macrophages from mice with experimental PEM are less sensitive to activation with lipopolysaccharides, partly due to decreased NF-kB translocation. Their ability to engulf pathogens and to produce cytokines and ROIs is impaired [51–54]. However, the suggestion that malnutrition suppresses macrophage functions due to elevated glucocorticoid levels was not supported by a recent study [55]. Further experiments are required to identify the mechanisms connecting PEM and immunosuppression.

Overnutrition and Immunity

The hormonal connection between immunity and nutrition becomes equally evident in nutritional dysregulatory eating disorders such as obesity, which is becoming alarmingly common in high-income countries, notably in the United States and United Kingdom, and is also spreading to transitional societies at an unexpectedly high speed.

Obesity in humans is correlated with high concentrations of leptin, often associated with leptin resistance [36]. Patients with obesity present with increased TNF-α production, altered T cell subset ratios, repressed T cell responses, and higher incidence of infectious diseases, all of which can be reversed by weight loss (Table 1) [56–58]. Diet-induced or inherited obesity in rodents causes NK and T cell suppression and increased TNF-α secretion [56,57,59]. Leptin-induced production of proinflammatory cytokines by macrophages causes neutrophil activation and TH1-derived IFN-γ secretion [60–62]. The obese phenotype in leptin-deficient *ob/ob* mice is also associated with diminished circulating T cells, reduced T cell responses, and lymphoid atrophy [40]. Although seemingly in a committed stage, macrophages from *ob/ob* mice have reduced phagocytic activity [40]. Furthermore, the natural ligand of the secretagogue receptor of the pituitary gland, ghrelin, which regulates fat storage and consumption, is directly linked to immune functions by its counteraction of leptin-induced activation of monocytes and T cells [63,64].

Recently, the cytokine IL-18, which usually drives TH1 responses in synergy with IL-12, has been linked to obesity. IL-18 knockout mice became obese through overeating and resistant to insulin through increased gluconeogenesis in the liver [65]. Consequently, intracerebrally administered IL-18 inhibited food intake. Another study demonstrated that a differential gut flora with distinct metabolic requirements was found in obese versus lean humans as well as mice. Even more intriguingly, when transferred to germ-free mice, the "obese" but not the "lean" gut flora caused an increase of total body fat [66]. These reports add two more components to the already complex relationship of nutrition, inflammation, immunity, and infection: cytokine patterns and gut flora compositions.

Thus, regulation of food uptake and storage is closely intermingled with immune functions. However, a higher nutrient uptake may also be beneficial for the host response, likely due to higher energy requirements, as illustrated by a recent study showing that a cholesterol-rich diet accelerates clearance of bacilli during the treatment of tuberculosis [67,68].

Diabetes mellitus is a hormonally regulated metabolic disease which affects immunity to infection (Table 1). Neutrophils and macrophages from patients with diabetes have suppressed functions, including phagocytosis, generation of ROIs, chemotaxis, and extravasation. T cell activation is also affected, as evidenced by reduced delayed-type hypersensitivity reactions [69]. Generation of ROIs requires NADPH, which is consumed by the polyol pathway for glucose metabolism. Patients with diabetes are more prone to diseases caused by *Staphylococcus aureus* and *M. tuberculosis*, and show higher mortality and morbidity from infections with *S. pneumoniae* and influenza virus [69]. In patients with diabetes, diseases due to urogenital tract and opportunistic infections by *Enterococcus*, *Mucor mucedo*, and *Candida albicans* are common. *Pseudomonas aeruginosa* is a frequent cause of abscesses in patients with diabetes, as are polybacterial infections causing skin ulcers (diabetic foot), and severe osteomyelitis [69,70]. There is clear evidence that proper control of hyperglycemia improves immune functions and resistance to infection.

Outlook

Extrapolating the studies discussed, malnutrition can be considered a major risk factor for morbidity and mortality worldwide due to infections with bacterial, viral, and protozoal agents [2,8,9]. This causal relationship was suggested in the US Surgeon General's Report in 1988 [71]. With more than 842 million chronically malnourished people worldwide [72], we agree with the notion that "…malnutrition may account for a greater population-attributable risk of tuberculosis than HIV infection, and certainly a much more correctable one" [9].

In the context of what is known as the 10/90 gap (10% of global health research funding is being targeted to health problems that account for 90% of the global disease burden) [73,74], research on infection and malnutrition are highly warranted for scientific, economic, and ethical reasons [75].

To conquer malnutrition, cost-efficient and practical approaches need to be established. Measures to counteract acute malnutrition are now available and were successfully applied in 2005 when Niger was affected by a famine. The crisis did not come as a surprise to the consortium of stakeholders, i.e., the government of Niger, its international partners, and the Famine Early Warning Systems Network of the US Agency for International Development. To avoid disturbance of the market and long-term development goals, food was sold to starving people for too high a price instead of being freely distributed. The catastrophe became apparent as vast numbers of malnourished children were brought to medical stations. Ready-to-use therapeutic food was delivered by doctors from Médecins Sans Frontières as an outpatient measure (community therapeutic care) with enormous success [76].

Usually children are hospitalized under such circumstances and given milk products as therapeutic food. Outpatient treatment during emergencies, however, decreases (1) duration of maternal absence from the family, thereby limiting children's risk of malnourishment, (2) time needed to establish treatment centers, and (3) risk of spreading nosocomial infections among hospitalized children in a limited number of overcrowded places. New therapeutic food formulations with balanced contents of macro- and micronutrients, which are ready to use and do not need a clean water supply for their preparation, are important prerequisites for such rapid aid measures. In the past, life-threatening respiratory infections, diarrhea, and malaria were frequent complications requiring short-term inpatient anti-infectious treatment. Under the emergency conditions of the Niger famine in 2005, the measures employed by Médecins Sans Frontières kept child mortality at the rate of non-famine periods. Thus, there is a precedent of effective interventions for acute malnutrition in an emergency to avoid subsequent infections.

This measure, however, is unlikely to minimize mortality and morbidity due to *chronic* malnutrition worldwide. Further research and development in diverse areas ranging from biomedicine to public health are required to stop the downward spiral of chronic malnutrition, infection, disease, and reduced economic productivity in impoverished societies with the consequences of migration and economical and political instability or war (Figure 1). Diseases resulting from overnutrition in industrial societies are of equal concern and similar conditions are already spreading to developing countries. Under- and overnutrition and diet-related chronic diseases represent a critical risk factor for more than half of the world's diseases and incur hundreds of millions of dollars in public expenditure [5], requiring the immediate attention of biomedical science and public health agencies alike. ■

Supporting Information

Alternative Language Abstract S1.
Translation of article summary into Russian

Found at doi:10.1371/journal.pmed.0040115.sd001 (21 KB DOC).

Alternative Language Abstract S2.
Translation of article summary into Spanish

Found at doi:10.1371/journal.pmed.0040115.sd002 (20 KB DOC).

Alternative Language Abstract S3.
Translation of article summary into French

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References

1. Moret Y, Schmid-Hempel P (2000) Survival for immunity: The price of immune system activation for bumblebee workers. Science 290: 1166–1168.
2. Scrimshaw NS, SanGiovanni JP (1997) Synergism of nutrition, infection, and immunity: An overview. Am J Clin Nutr 66: 464S–477S.
3. Ambrus JL Sr, Ambrus JL Jr (2004) Nutrition and infectious diseases in developing countries and problems of acquired immunodeficiency syndrome. Exp Biol Med (Maywood) 229: 464–472.
4. Woodward B (1998) Protein, calories, and immune defenses. Nutr Rev 56: S84–S92.
5. World Health Organization (2005) Nutrition: Challenges. Available: http://www.who.int/nutrition/challenges. Accessed 29 March 2007.
6. Savino W (2002) The thymus gland is a target in malnutrition. Eur J Clin Nutr 56 (Suppl 3): S46–S49.
7. Beisel WR (1996) Nutrition in pediatric HIV infection: Setting the research agenda. Nutrition and immune function: Overview. J Nutr 126: 2611S–2615S.
8. Field CJ, Johnson IR, Schley PD (2002) Nutrients and their role in host resistance to infection. J Leukoc Biol 71: 16–32.
9. Cegielski JP, McMurray DN (2004) The relationship between malnutrition and tuberculosis: Evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis 8: 286–298.
10. Enwonwu CO, Falkler WA Jr, Phillips RS (2006) Noma (cancrum oris). Lancet 368: 147–156.
11. Stephensen CB (1999) Burden of infection on growth failure. J Nutr 129: 534S–538S.
12. Villamor E, Saathoff E, Mugusi F, Bosch RJ, Urassa W, et al. (2006) Wasting and body composition of adults with pulmonary tuberculosis in relation to HIV-1 coinfection, socioeconomic status, and severity of tuberculosis. Eur J Clin Nutr 60: 163–171.
13. Scrimshaw NS, Taylor CE, Gordon JE (1968) Interactions of nutrition and infection. Monogr Ser World Health Organ 57: 3–329.
14. Bronte V, Zanovello P (2005) Regulation of immune responses by L-arginine metabolism. Nat Rev Immunol 5: 641–654.
15. Kurpad AV (2006) The requirements of protein & amino acid during acute & chronic infections. Indian J Med Res 124: 129–148.
16. Phillips RS, Enwonwu CO, Okolo S, Hassan A (2004) Metabolic effects of acute measles in chronically malnourished Nigerian children. J Nutr Biochem 15: 281–288.
17. Schneider SM, Veyres P, Pivot X, Soummer AM, Jambou P, et al. (2004) Malnutrition is an independent factor associated with nosocomial infections. Br J Nutr 92: 105–111.
18. Caulfield LE, de Onis M, Blossner M, Black RE (2004) Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles. Am J Clin Nutr 80: 193–198.
19. Abe M, Akbar F, Matsuura B, Horiike N, Onji M (2003) Defective antigen-presenting capacity of murine dendritic cells during starvation. Nutrition 19: 265–269.
20. Najera O, Gonzalez C, Toledo G, Lopez L, Cortes E, et al. (2001) CD45RA and CD45RO isoforms in infected malnourished and infected well-nourished children. Clin Exp Immunol 126: 461–465.
21. Najera O, Gonzalez C, Toledo G, Lopez L, Ortiz R (2004) Flow cytometry study of lymphocyte subsets in malnourished and well-nourished children with bacterial infections. Clin Diagn Lab Immunol 11: 577–580.
22. Rodriguez L, Gonzalez C, Flores L, Jimenez-Zamudio L, Graniel J, et al. (2005) Assessment by flow cytometry of cytokine production in malnourished children. Clin Diagn Lab Immunol 12: 502–507.
23. Woodward B, Hillyer L, Hunt K (1999) T cells with a quiescent phenotype (CD45RA+) are overabundant in the blood and involuted lymphoid tissues in wasting protein and energy deficiencies. Immunology 96: 246–253.
24. ten Bruggencate SJ, Hillyer LM, Woodward BD (2001) The proportion of CD45RA(+)CD62L(+) (quiescent-phenotype) T cells within the CD8(+) subset increases in advanced weight loss in the protein- or energy-deficient weanling mouse. J Nutr 131: 3266–3269.
25. Neyestani TR, Woodward B (2005) Blood concentrations of Th2-type immunoglobulins are selectively increased in weanling mice subjected to acute malnutrition. Exp Biol Med (Maywood) 230: 128–134.
26. Hagel I, Lynch NR, Di Prisco MC, Sanchez J, Perez M (1995) Nutritional status and the IgE response against Ascaris lumbricoides in children from a tropical slum. Trans R Soc Trop Med Hyg 89: 562–565.
27. Hagel I, Lynch NR, Puccio F, Rodriguez O, Luzondo R, et al. (2003) Defective regulation of the protective IgE response against intestinal helminth Ascaris lumbricoides in malnourished children. J Trop Pediatr 49: 136–142.
28. Ing R, Su Z, Scott ME, Koski KG (2000) Suppressed T helper 2 immunity and prolonged survival of a nematode parasite in protein-malnourished mice. Proc Natl Acad Sci U S A 97: 7078–7083.
29. Singal A, Pandhi D, Agrawal SK (2005) Multifocal scrofuloderma with disseminated tuberculosis in a severely malnourished child. Pediatr Dermatol 22: 440–443.
30. Liebeschuetz S, Bamber S, Ewer K, Deeks J, Pathan AA, et al. (2004) Diagnosis of tuberculosis in South African children with a T-cell-based assay: a prospective cohort study. Lancet 364: 2196–2203.
31. Metcalfe N (2005) A study of tuberculosis, malnutrition and gender in Sri Lanka. Trans R Soc Trop Med Hyg 99: 115–119.
32. Dai G, McMurray DN (1999) Effects of modulating TGF-beta 1 on immune responses to mycobacterial infection in guinea pigs. Tuber Lung Dis 79: 207–214.
33. Dai G, McMurray DN (1998) Altered cytokine production and impaired antimycobacterial immunity in protein-malnourished guinea pigs. Infect Immun 66: 3562–3568.
34. Chan J, Tian Y, Tanaka KE, Tsang MS, Yu K, et al. (1996) Effects of protein calorie malnutrition on tuberculosis in mice. Proc Natl Acad Sci U S A 93: 14857–14861.
35. McMurray DN, Dai G, Phalen S (1999) Mechanisms of vaccine-induced resistance in a guinea pig model of pulmonary tuberculosis. Tuber Lung Dis 79: 261–266.
36. Matarese G, Moschos S, Mantzoros CS (2005) Leptin in immunology. J Immunol 174: 3137–3142.
37. Matarese G, La Cava A, Sanna V, Lord GM, Lechler RI, et al. (2002) Balancing susceptibility to infection and autoimmunity: A role for leptin? Trends Immunol 23: 182–187.
38. Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, et al. (1998) Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature 394: 897–901.
39. Lord GM, Matarese G, Howard JK, Bloom SR, Lechler RI (2002) Leptin inhibits the anti-CD3-driven proliferation of peripheral blood T cells but enhances the production of proinflammatory cytokines. J Leukoc Biol 72: 330–338.
40. Faggioni R, Feingold KR, Grunfeld C (2001) Leptin regulation of the immune response and the immunodeficiency of malnutrition. Faseb J 15: 2565–2571.
41. Cakir B, Yonem A, Guler S, Odabasi E, Demirbas B, et al. (1999) Relation of leptin and tumor necrosis factor alpha to body weight changes in patients with pulmonary tuberculosis. Horm Res 52: 279–283.
42. Schwenk A, Hodgson L, Rayner CF, Griffin GE, Macallan DC (2003) Leptin and energy metabolism in pulmonary tuberculosis. Am J Clin Nutr 77: 392–398.
43. van Crevel R, Karyadi E, Netea MG, Verhoef H, Nelwan RH, et al. (2002) Decreased plasma leptin concentrations in tuberculosis patients are associated with wasting and inflammation. J Clin Endocrinol Metab 87: 758–763.
44. van Lettow M, van der Meer JW, West CE, van Crevel R, Semba RD (2005) Interleukin-6 and human immunodeficiency virus load, but not plasma leptin concentration, predict anorexia and wasting in adults with pulmonary tuberculosis in Malawi. J Clin Endocrinol Metab 90: 4771–4776.

45. Wieland CW, Florquin S, Chan ED, Leemans JC, Weijer S, et al. (2005) Pulmonary *Mycobacterium tuberculosis* infection in leptin-deficient ob/ob mice. Int Immunol 17: 1399–1408.
46. Monk JM, Makinen K, Shrum B, Woodward B (2006) Blood corticosterone concentration reaches critical illness levels early during acute malnutrition in the weanling mouse. Exp Biol Med (Maywood) 231: 264–268.
47. Jacobson L (2005) Hypothalamic-pituitary-adrenocortical axis regulation. Endocrinol Metab Clin North Am 34: 271–292.
48. Alleyne GA, Young VH (1967) Adrenocortical function in children with severe protein-calorie malnutrition. Clin Sci 33: 189–200.
49. Auphan N, Didonato JA, Helmberg A, Rosette C, Karin M (1997) Immunoregulatory genes and immunosuppression by glucocorticoids. Arch Toxicol Suppl 19: 87–95.
50. Van Molle W, Libert C (2005) How glucocorticoids control their own strength and the balance between pro- and anti-inflammatory mediators. Eur J Immunol 35: 3396–3399.
51. McCarter MD, Naama HA, Shou J, Kwi LX, Evoy DA, et al. (1998) Altered macrophage intracellular signaling induced by protein-calorie malnutrition. Cell Immunol 183: 131–136.
52. Redmond HP, Gallagher HJ, Shou J, Daly JM (1995) Antigen presentation in protein-energy malnutrition. Cell Immunol 163: 80–87.
53. Redmond HP, Leon P, Lieberman MD, Hofmann K, Shou J, et al. (1991) Impaired macrophage function in severe protein-energy malnutrition. Arch Surg 126: 192–196.
54. Redmond HP, Shou J, Kelly CJ, Leon P, Daly JM (1991) Protein-calorie malnutrition impairs host defense against Candida albicans. J Surg Res 50: 552–559.
55. Stapleton PP, Barden CB, McCarter MD, Mackrell PJ, Freeman TA, et al. (2003) Serum leptin levels in acute protein deprivation. JPEN J Parenter Enteral Nutr 27: 132–136.
56. Tanaka S, Isoda F, Ishihara Y, Kimura M, Yamakawa T (2001) T lymphopaenia in relation to body mass index and TNF-alpha in human obesity: Adequate weight reduction can be corrective. Clin Endocrinol (Oxf) 54: 347–354.
57. Tanaka S, Isoda F, Kiuchi Y, Ikeda H, Mobbs CV, et al. (2000) T lymphopenia in genetically obese-diabetic Wistar fatty rats: Effects of body weight reduction on T cells. Metabolism 49: 1261–1266.
58. Nieman DC, Henson DA, Nehlsen-Cannarella SL, Ekkens M, Utter AC, et al. (1999) Influence of obesity on immune function. J Am Diet Assoc 99: 294–299.
59. Yamakawa T, Tanaka S, Yamakawa Y, Kiuchi Y, Isoda F, et al. (1995) Augmented production of tumor necrosis factor-alpha in obese mice. Clin Immunol Immunopathol 75: 51–56.
60. Zarkesh-Esfahani H, Pockley AG, Wu Z, Hellewell PG, Weetman AP, et al. (2004) Leptin indirectly activates human neutrophils via induction of TNF-alpha. J Immunol 172: 1809–1814.
61. Zarkesh-Esfahani H, Pockley G, Metcalfe RA, Bidlingmaier M, Wu Z, et al. (2001) High-dose leptin activates human leukocytes via receptor expression on monocytes. J Immunol 167: 4593–4599.
62. Sanchez-Margalet V, Martin-Romero C, Santos-Alvarez J, Goberna R, Najib S, et al. (2003) Role of leptin as an immunomodulator of blood mononuclear cells: Mechanisms of action. Clin Exp Immunol 133: 11–19.
63. Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, et al. (2004) Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. J Clin Invest 114: 57–66.
64. Xia Q, Pang W, Pan H, Zheng Y, Kang JS, et al. (2004) Effects of ghrelin on the proliferation and secretion of splenic T lymphocytes in mice. Regul Pept 122: 173–178.
65. Netea MG, Joosten LA, Lewis E, Jensen DR, Voshol PJ, et al. (2006) Deficiency of interleukin-18 in mice leads to hyperphagia, obesity and insulin resistance. Nat Med 12: 650–656.
66. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, et al. (2006) An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 444: 1027–1131.
67. Perez-Guzman C, Vargas MH (2006) Hypocholesterolemia: A major risk factor for developing pulmonary tuberculosis? Med Hypotheses 66: 1227–1230.
68. Perez-Guzman C, Vargas MH, Quinonez F, Bazavilvazo N, Aguilar A (2005) A cholesterol-rich diet accelerates bacteriologic sterilization in pulmonary tuberculosis. Chest 127: 643–651.
69. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW (1999) Infections in patients with diabetes mellitus. N Engl J Med 341: 1906–1912.
70. Guptan A, Shah A (2000) Tuberculosis and diabetes: An appraisal. Ind J Tub 47: 2–8.
71. United States Department of Health and Human Services (1988) The Surgeon General's report on nutrition and health. Washington (D. C.): DHHS Publishing. pp. 427–463.
72. World Food Programme (2004) Hunger facts. Available: http://www.wfp.org/aboutwfp/facts/hunger_facts.asp. Accessed 29 March 2007.
73. Blackburn GL (2001) Pasteur's Quadrant and malnutrition. Nature 409: 397–401.
74. World Health Organization (2003) Investing in health: A summary of the findings of the Commission on Macroeconomics and Health. Available: 29 March 2007.
75. The World Bank (2006) Repositioning nutrition as central to development: A strategy for large-scale action. Available: http://siteresources.worldbank.org/NUTRITION/Resources/281846-1131636806329/NutritionStrategy.pdf. Accessed 29 March 2007.
76. Tectonidis M (2006) Crisis in Niger—Outpatient care for severe acute malnutrition. N Engl J Med 354: 224–227.