3. INFECTIONS, IMMUNITY AND NUTRITION

The connections between nutrition, infections, and immunity are not immediately obvious to doctors working in the northern hemisphere. In contrast, they are flagrant in the tropics. Overseas, one must be blind not to notice the impact of nutrient deficiencies on the course of infections and those of all kinds of infections on the patient's nutritional status. The appalling mortality of measles amongst the malnourished is a classic example of the relation between infections and nutrition. What is more, the relation amongst these factors are governed by the socio-economic conditions that prevail in developing countries.

Malnutrition undermines resistance, as has always been known. The impact of weaning, which is associated with multiple onslaughts of fever, and diarrhoea, is a striking example of this connection. On the other hand, foetal malnutrition in utero *– which is so frequent – has an unknown influence on the infant's future. Each unbalanced diet, whether due to a global or to specific deficiencies in trace elements or minerals, for example, inclines the organism to infections. The theoretical calorie and energy requirements to be fulfilled are well known, but their completion is seldom satisfactory.*

Moreover, the body's resistance, based to a large extent on immunity, is constantly challenged to oppose infectious agents. Considerable progress has been made in our understanding of humoral mechanisms, especially through analysis of the immunoglobulins' functions. Cell-mediated immunity is not so well known. This concerns not only the various T and B lymphocytes, but also the role of thymus atrophy in the functional deficiencies of apparently competent immune cells. Thorough knowledge of each of the combined actions of immune competent cells and thymus is required to determine the type of vaccine to be developed. Certain antigens, for example those of poliomyelitis and measles antigens, are known to produce everlasting humoral antibodies better than other antigens. To optimize the vaccination schedule deeper knowledge of the most favourable immunogenic conditions is required. Moreover specific nutritional conditions have probably to be fulfilled, particularly concerning trace elements and minerals.

Another question concerns the synergism and antagonism of multiple intestinal parasites, especially their impact on nutrition and on the host's immune defences. Mass worming campaigns are fully justified when the pilot trials include, in addition to the parasite properties, the assessment of their consequences at critical periods of their development but also the appraisal of the carrier's nutritional status and resistance.

All these aspects require more than a simple awareness. Close collaboration of field personnel, epidemiologists, nutritionists, and immunologists is required. WHO has already cleared the ground. A great step forward has been taken. All studies and research on the connections between infections, immunity, and nutrition would certainly help the medical care and social services to be more efficient.

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The relation between nutrition and infections is complex and acts in two directions: infections can provoke or worsen malnutrition and malnutrition can increase the risk of infection, as well as its duration, its severity and the importance of its after-effects.

This relation is not easy to prove, in part for semantic reasons. Is a child malnourished if it grows more slowly than apparently healthy children in the same population, or have we to compare it with the ideal standards of industrialized countries? Have we to consider infectious diseases as acute illnesses threatening health in a severe but temporary way, and have we also to look for subclinical parasitic infections, persisting throughout childhood or even throughout the entire life?

Two aspects will be briefly reviewed: the impact of malnutrition on the immune system of the host and the effect of malnutrition on the parasites themselves.

1. The impact of acute infections on the nutritional status

Some time after birth, the growth curve of children in developing countries deviate more and more from the ideal one. This occurs shortly after weaning at a moment when the passive defence mechanisms inherited from the mother are disappearing. Every episode of fever or diarrhoea, so common at this age, makes the situation worse (DeMaeyer and Vanderborght, 1954; Vis, 1975).

The underlying mechanisms are multiple:

- physiological ones such as anorexia and the increase of metabolic needs in case of fever,
- pathological losses through damaged mucosal surfaces,
- cultural reasons such as refusing food and beverages to diarrhoeic children for fear of aggravating their condition.

The feeding balance of these children is very unstable after weaning. They have to ingest a very large quantity of hypo-caloric food to cover their needs. There is also a strict partition of food within the family, which does not allow for supplements to the child on the road to recovery. For these reasons it is difficult for the children to catch up with their growth curve after an infectious episode.

The onset of malnutrition as a result of an infection has been emphasized by DeMaeyer *et al.* (1954).

2. The impact of nutrition on infections

It is obvious that children from developing countries suffer more frequently from infections than children from industrialized countries. Malnutrition is however linked together with other characteristics of poverty: promiscuity, poor hygienic conditions, lack of clean water, etc. These populations live under conditions which favour both malnutrition and infections, see table I (WHO, 1992). The severity of measles for example, is said to be related more to housing conditions than to the nutritional condition.

Table I

Deaths from major infectious diseases in the world (1990)	
Acute respiratory infections:	6,900,000 per year
measles	220,000
whooping cough	100,000
Diarrhoeal diseases	4,200,000
Tuberculosis	3,300,000
Malaria	1,500,000 (approx.)
Hepatitis	1,500,000 (approx.)
Bacterial meningitis	200,000
Schistosomiasis	200,000

(WHO estimate, 1992)

Overcrowding is supposed to be responsible for the extension of infections which also result in severe diseases (Tomkins, 1986).

Malnutrition nevertheless remains a major factor in the severity and mortality due to infectious diseases, through its impact on immune defence mechanisms.

3. Malnutrition and the immune system; Morphological and functional deficiencies

The standard of living in developing countries favours chronic or recurrent infections, challenging continously the immune system. Malnutrition decreases the defence mechanisms, sometimes resulting in a fatal vicious circle. This situation resembles curiously infection by HIV, leading to the acquired immune deficiency syndrome (table II on p. 420). Therefore opportunistic infections such as *Pneumocystis carinii*, characteristic of severe immune deficiency, are also seen in cases of extreme malnutrition (Purtilo *et al.*, 1975).

Mainly young children will suffer from this interaction between infection and malnutrition. Their immune system is relatively immature, their nutritional needs are high and they are frequently exposed

to multiple infectious agents. Theoretically one could differentiate global deficiencies from those in oligo-elements, vitamins, proteins, calories, etc. Actually, malnutrition is mostly global in protein and energy (PEM), apparent in classical growth failure (Chandra, 1983a).

3.1. *Deficiencies of specific cellular T-dependent immunity*

3.1.1. *Morphological and clinical aspects*

The lymphoid organs become atrophic. Cells in the thymo-dependent regions of thymus, spleen, lymph nodes and Peyer patches decrease in number (Chandra, 1983a).

Clinical manifestations include tonsillar atrophy and skin anergy to antigens calling for cellular immune response, such as BCG, candida or trichophyton.

In practice, cutaneous delayed hypersensitivity reactions can be tested with the *Multitest®* (Mérieux). Results are, however, not reliable before the age of three months. A deficiency in the cellular immunity becomes evident through a decrease or an absence of tuberculin-like reaction to memory eliciting antigens such as tetanus toxoid, candidin, streptokinase-streptodornase (Chandra, 1991).

3.1.2. *Immunological aspects*

In the course of protein-energy malnutrition three elements are observed:

- A visible global lymphopenia. Proportionally the T cells are decreased, whereas the percentage of B cells remains normal or increases slightly. In contrast, the percentage of non-B, non-T lymphocytes (null cells) is higher. In addition, lymphocytes expressing terminal de-oxy-nucleotidyl transferase (TDT) increase, which is a sign of immaturity of T lymphocytes. The null cells could be precursor cells unable to differentiate into mature T cells as a consequence of thymic atrophy and of decreasing levels of serum thymic factor (Chandra, 1983b).
- Typing of T cells sub-populations indicates a pronounced deficiency of T4 helper-inducer cells, a relatively stable proportion of T8 cytotoxic suppressor cells and consequently a reduction of the ratio T4/T8. This situation is similar to HIV infection which is also accompanied by malnutrition and recurrent infections. Nevertheless, the immune deficiency related to malnutrition is fully reversible which of course is not the case in HIV infection (Cuisinier-Raynal *et al.*, 1985).
- A functional deficiency of T lymphocytes is evidenced by a subnormal production of lymphokines, notably interferon and interleukin-2. This deficiency could explain the cutaneous anergy and the increased susceptibility of malnourished children to tuberculosis, to viral infections and to those parasitic infections which are characterized by a largely T-cell dependent immune response.

3.2. *Deficiency of specific B-cell dependent humoral immunity*

Clinical and experimental data are apparently conflicting:

- Laboratory animals, malnourished in terms of proteins, calories or other nutrients, produce fewer specific antibodies after administration of an antigen and generally present *hypo*-gammaglobulinaemia.
- Malnourished infants in contrast, frequently present high levels of serum immunoglobulins, even when their lymphocytes produce subnormal levels of immunoglobulins *in vitro*. This global *hyper*-gammaglobulinaemia of malnourished infants is in fact polyclonal; and is not a direct consequence of malnutrition but is a non-specific reaction seen in many diseases, including AIDS.

Nevertheless in severe malnutrition, such as marasmus, the polyclonal reaction disappears and *hypo*-gammaglobulinaemia appears. In addition, *Zoppi* (1983) found *hypo*-gammaglobulinaemia and an increased incidence of infections in normally growing Italian infants, who had been fed during the first year of their life with milk poor in proteins.

In developing countries malnourished infants present slight deficiencies in the production of specific antibodies, even when their total level of immunoglobulins is normal or elevated. After vaccination, specific antibodies appear later and have a reduced affinity for their antigen. In addition, serum and secretory IgA is frequently low in spite of global *hyper*-gammaglobulinaemia, which is in accordance with the tendency to develop intestinal and respiratory infections.

The cellular basis has been analyzed by *Chandra* (1983b). He demonstrated experimentally by culturing together B lymphocytes from malnourished infants and T lymphocytes from normal infants, and *vice versa*, that the B cell function remained normal but the T-helper function was deficient in malnourished children. Therefore a normal or elevated level of immunoglobulins in malnourished infants does not ensure an adequate immune response. In practice the humoral deficiency does not prevent an adequate response to vaccination, even if the antibody titres are low and if the acquisition of protective antibodies is delayed.

Similarly, malnutrition does not increase the side-reactions to vaccination. But BCG vaccination, which relies on cellular immunity, could become less efficient (Zoppi *et al.*,1983; Chandra *et al.*,1984; Ajjan *et al.*, 1987).

For these reasons, vaccination should be applied as soon as possible and certainly before weaning. A simplified schedule from an immunological point of view is:

- *at birth*: BCG
- *3-5 months*: the first DTC + inactivated polio
- *9 months*: second DTC + inactivated polio + measles

(see the chapter Immunizations pp. 737 and 745)

The extension of the AIDS epidemic may give an impetus to review these schedules in the future especially by being careful to apply living vaccines such as BCG.

3.3. *Malnutrition and non-specific immune mechanisms*

The disturbed complement activity in malnourished infants is evidenced by the reduction in total haemolytic capacity. The activity of C3 is significantly lowered. Congenital or acquired deficiencies of C3 are associated with frequent bacterial infections.

The chimiotactic, phagocytic and bactericidal activities of polynuclear and mononuclear cells are decreased in malnutrition.

Malnutrition is often associated with shortages in oligo-elements and minerals. All these factors are relevant for immunity mechanisms and their insufficiency plays an additional role in the immune depression observed in malnutrition.

Immunity at the level of gastro-intestinal and bronchial mucosal surfaces is especially weak:

- the regional lymph nodes are atrophied and produce insufficient secretory IgA,
- the jejunal mucosa shows a severe atrophy of villi especially in kwashiorkor but milder in marasmus. Their height is reduced and they are separated by intervillar spaces. Such alterations result in absorption problems, which reduce the defence against infection.

3.4. *Epidemiological consequences of immunity and malnutrition*

A close correlation has been demonstrated between the level of *mortality* and the deterioration of the nutritional status as expressed by the weight for height ratio (Kielman *et al.*, 1978).

As far as *morbidity* is concerned, however, it becomes difficult to assess the role of malnutrition in the natural evolution of a disease.

Three series of contradictory data follow:

3.4.1. *Diarrhoea and respiratory infections*

- A study carried out in Nigeria indicated a sharp increase in the frequency and duration of episodes of diarrhoea in malnourished infants.
- A more recent study carried out in Bangladesh (Koster *et al.*, 1987) is more cautious, the authors confirming the negative influence of malnutrition on the duration of diarrhoea but not on respiratory infections or on the frequency of fever upsurges without diarrhoea. Cutaneous anergy, the main indication of cellular immune deficiency, appeared to correlate with the increased vulnerability to diarrhoeal disease.
- In a third study carried out in Brazil, on more than 6,000 infants admitted for diarrhoea or pneumonia, malnutrition was shown to be a more important risk factor for pneumonia than for diarrhoea (Victora *et al.*, 1990).

3.4.2. *Measles*

In developing countries, measles frequently runs an unfavourable course. Malnutrition has traditionally been considered as one of the most important determinants of a severe evolution. An analysis of studies on measles confirms a close relationship between the weight-for-age ratio and the deaths in hospital from measles. By contrast, field studies in the general population indicate that other risk factors such as the number of sick children within a family, overcrowding, conditions of hygiene, etc., are more important than malnutrition itself (Aaby, 1988).

3.4.3. *Post-operative septicaemia*

Compared to people with normal weight, malnourished adults have a five times higher risk of developing a moderately severe septicaemia after surgical intervention (Chandra, 1991). The same observation holds true for AIDS.

3.5. *Malnutrition and immune deficiency relations in clinical situations*

3.5.1. *Immuno-competence as a parameter of nutritional status*

Signs of immune deficiency can appear before clinical signs of malnutrition and infection (Chandra, 1990). Quantification of T lymphocytes in the peripheral blood or delayed hypersensitivity tests to antigens could therefore be considered as tests to predict and prevent infectious complications, and to evaluate the response to dietary supplements (Fahkir *et al.*, 1989; Black *et al.*, 1989).

Table II: Nutritional and HIV-induced immune deficiency

	Malnutrition	HIV Infection
I. T LYMPHOCYTES:		
a) Number: total	↓ / ↓ ↓	↓ / ↓ ↓
CD4(+) = T helper	↓	↓ ↓ / 0
CD8(+) = T cytotoxic suppressor	=	↑ / = / ↓
b) Function: delayed type hypersensitivity	↓ / ↓ ↓	↓ / ↓ ↓
proliferative response *in vitro*	↓ / ↓ ↓	↓ / ↓ ↓
II. B LYMPHOCYTES		
a) Number	=	= / ↓
b) Function: polyclonal hyper-gammaglobulinaemia	↑	↑
specific antibody response	↓	↓
secretory antibodies	↓	?
III. PHAGOCYTOSIS: function of neutrophils and monocytes	↓	= / ↓
IV. ANTI-HIV ANTIBODIES	–	+
V. IMPROVEMENT AFTER NUTRITIONAL INTERVENTION	++	–

3.5.2. *Viral or nutritional immuno-deficiency*

The immunological and clinical picture of AIDS is very similar to immune deficiency as seen in malnutrition particularly in the decrease of the T4/T8 ratio (see Table II).

The prevalence of immune deficiency and malnutrition increasing in the same populations (Corman, 1985), which results in diagnostic problems, arise when serological HIV detection is not available. Even more important are the problems of treatment and of health education which need to be specific for each of these different diseases. People might become distrustful towards infant nutrition programmes, because childhood AIDS cases are not responding to nutritional supplementation.

3.5.3. *Importance of breast-feeding*

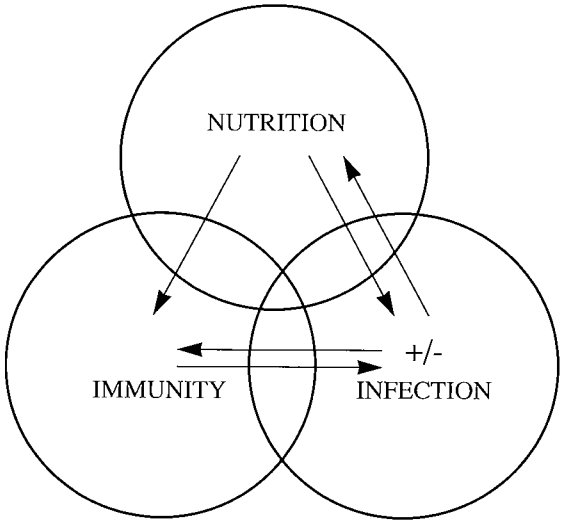
Breast-fed newborn babies will not – except in extreme cases – present signs of immune deficiency even when the mother is moderately malnourished. In fact several protective factors are abundantly present in breast milk including lysozyme, lactoferrin, secretory immunoglobulins and maternal T lymphocytes (Fisher, 1987). The newborn takes advantage of the immunological memory of his mother. Infectious agents stimulate the production of antibodies in the mother and are transferred to the newborn. The advantages of breast-feeding remain in any case more important than the limited risk of infection, even when the mother is HIV positive (Halsey *et al.*, 1990; Van de Perre *et al.*, 1991).

4. Parasitic infections and malnutrition

Parasitic infections are caused by very diverse organisms, protozoans and helminths, which belong to at least eight zoological classes. Nevertheless parasites have as common features their relatively large size and their more complex morphology as compared to other pathogens. Their frequency is increased in developing countries for direct reasons such as the presence of vectors, or indirect reasons such as the precarious living conditions. From birth and throughout their lives, inhabitants of these regions are exposed to multiple parasites. Parasitism is frequently subclinical and remains undetected. It contributes nevertheless to an increased infant mortality. Also the productivity of infected adults is reduced, as is their quality of life. Those living in poor conditions are more or less continuously carriers of two to six types of parasites, as a consequence of the extended lifespan of some species and of the frequency of successive re-infections.

The relationship between parasites and nutrition was explored in 1966 by Scrimshaw. His views are summarized in figure 1:

Interactions between nutrition, immunity and infection



(from Scrimshaw, 1966)

Our knowledge of these interactions has not significantly advanced since then (Beisel, 1982; Stephenson, 1987). As a rule, one has not sufficiently taken into account the specific biology of each species, the importance of parasitic loads, the occurrence of polyparasitism (the simultaneous presence of multiple parasites which can interfere with each other) and the influence parasites have on the intestinal flora.

The impact of malnutrition on parasites is mediated mainly through immunity, as has been relatively well studied and is described above. Malnutrition has a deleterious effect on immunity and consequently favours parasitism.

Since these organisms are large in size and have a high level of organization, one guesses that malnutrition of the host could also have negative effects on the parasites he carries. This ambiguity is the basis of the notions *synergy* and *antagonism* introduced by Scrimshaw, which are more than just academic.

4.1. *Intestinal helminthiasis*

Since the sixties effective anthelminthic drugs are available against intestinal helminthiasis; they are easy to use, well-tolerated, present a large spectrum of activity and can be used for mass treatments. Previous studies in the Cameroon (Gateff, 1972), in Zaire (Gatti *et al.*, 1972) and in Kenya (Stephenson, 1987) seemed to show that mass treatment of school children resulted in weight gain when compared to placebo treated controls. Anthelminthic treatment was said to be more cost-effective than alimentary supplementation (table III). However, the figures from Zaire and the Cameroon became less impressive when the gain was compared to the initial weight and was found to be less than 5%, which is clearly negligible (Nesheim, 1989).

Table III: Increase in weight one year after treatment by an anthelmintic drug as compared to a placebo

Children (8-16 y.o.)	After placebo	After ant-helminthics	Difference	% of difference
Zaire *	1.700 g	2.000 g	300 g	17,5
Cameroon **	1.870 g	2.220 g	350 g	18,5

* Gatti *et al.*, 1972
** Gateff *et al.*, 1972

The question was asked whether periodical anthelminthic mass treatments should not have an economically worthwile effect to control malnutrition. On the other hand the alternative could be to provide alimentary supplements whereby the prevalence of parasitic infections could be reduced to inoffensive levels. Such nutritional improvement could however also favour the parasites according to the principles of Scrimshaw. In the latter case, the control of parasites should be linked up with a strategy of nutritional improvement.

In the end the question can be asked if all this is realistic, while improved nutrition is related to an improvement on the socio-economical level as a whole and is therefore also associated with a better standard of hygiene which would automatically decrease the transmission and the prevalence of parasitic infections. Decision-makers should take into account these complex interactions, before defining priorities.

4.2. *Complex relation between nutrition and parasites*

The following examples aim to illustrate the complexity of the relation of nutrition to parasitosis (Diamond, 1982).

a) Clinically evident *amoebiasis* is relatively infrequent in pastoral populations of eastern Africa. Their

milk diet is poor in iron. When the diet changes or when iron supplements are given, amoebiasis becomes clinically evident. Such increased incidence of amoebic disease is also observed in South Africa in Bantu populations and this has been ascribed to acculturation processes. These are good examples of antagonism since iron deficiency also appears deleterious to the parasites (Murray *et al.*, 1980).

b) *Malaria,* the most important parasitic disease of manhood, presents another example of antagonism (McGregor, 1988). Potentially lethal cerebral malaria is more frequently observed in well-nourished rather than in malnourished infants. Newborn babies are passively protected during the first months through transplacental acquisition of maternal antibodies and probably also through the relative lack of para-aminobenzoic acid (PAB) in breast milk. PAB is known as a growth factor for *Plasmodium* at least under experimental conditions. In western African refugee camps, situated in non-endemic areas, malaria attacks were relatively rare in malnourished people. Acute malaria became more frequent after re-alimentation.

c) A quarter of the total world's population is infected by *Ascaris*. Several dozens of large nematodes, up to 40 cm long, can be found in the intestine of infected infants and their weight can attain up to 10% of the weight of the host in massive infections. The relationship between ascaridiosis and malnutrition has been insufficiently studied and a real advantage of mass treatment has not yet been demonstrated (Nesheim, 1989).

d) *Hookworms* are as frequent as ascaris but smaller. They attach themselves to the mucosa surfaces by impressive hooks. Both this method of attachment and the metabolic needs of the hookworm itself, result in important blood losses. The blood does not, however, run into the environment but into the intestine, where its constituents, iron and proteins, are largely reabsorbed after digestion. The interaction between iron and hookworms is remarkable (Crompton and Stephenson, 1990). In regions of the world where nutrition is iron-poor, a small worm load can already provoke anaemia whereas the same load has no immediate impact on the red blood cell count, when the alimentary iron is sufficient. In the latter case, the turnover of red blood cells is accelerated and perfectly caught up by the iron supply. There is also, however, an antagonic aspect since the degree of anaemia is a limiting factor for the egg load in the stools, a reflection of the worm load in the host.

5. Conclusions

Taken all together, our knowledge on the interaction between infection, nutrition and immunity remains rather limited. This is due, in part, to the diversity of parasitism and its clinical manifestations. An episode of acute diarrhoea or of malarial fever in an infant with a labile nutritional equilibrium can not be compared to the persistent but generally asymptomatic impact of infections by a limited number of hookworms. In the evaluation of the nutritional status, less attention is usually given to deficiencies of oligo-elements that can have positive or negative effects on different species of parasites.

Interactions between several parasitic infections have not been studied and it would anyway be difficult to find a statistically significant sample.

Before considering approaches to these problems, more insight should be gained into the reciprocal relations between immunity, nutrition and infections. Parasitic infections result in a decreased quality of life regardless of their impact on the nutritional status. The issues discussed above illustrate once again the necessity of an integrated multi-disciplinary approach. Improvement of nutrition and prevention of infections are but part of the solution to nutrition issues besides population control, improvement of housing, provision of drinking water, environmental sanitation, access to integrated health care for all, in short, global improvement of living conditions of the populations of the Third World.

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