This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES
No. 314

NUTRITION AND INFECTION

Report of a WHO Expert Committee

WORLD HEALTH ORGANIZATION
GENEVA
1965

WHO EXPERT COMMITTEE ON NUTRITION AND INFECTION

Geneva, 23-29 March 1965

Members * :

Dr A. Delaunay, Chef du Service de Pathologie expérimentale, Institut Pasteur, Annexe de Garches (Seine-et-Oise), France

Dr Z. Farid, Director, Clinical Research Division, Medical Department, US Naval Medical Research Unit No. 3, Cairo, United Arab Republic

Dr B. G. Maegraith, Professor of Tropical Medicine, School of Tropical Medicine, Liverpool, England (*Vice-Chairman*)

Dr N. N. Plotnikov, The E. I. Marcinovskij Institute of Medical Parasitology and Tropical Medicine, Moscow, USSR

Dr N. S. Scrimshaw, Professor of Nutrition, Head of the Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Mass., USA (*Chairman*)

Dr B. Vahlquist, Professor of Paediatrics, Paediatric Clinic, University Hospital, Uppsala, Sweden

Secretariat :

Dr V. N. Patwardhan, Chief, Nutrition, WHO (*Secretary*)

---

* Unable to attend :

Dr J. C. Edozien, Professor and Head of the Department of Chemical Pathology, University of Ibadan, Nigeria

Dr P. S. Venkatachalam, Assistant Director, Nutrition Research Laboratories, Indian Council of Medical Research, Hyderabad, India

---

© World Health Organization 1965

Publications of the World Health Organization enjoy copyright protection in accordance with the provision of Protocol 2 of the Universal Copyright Convention. Nevertheless governmental agencies or learned and professional societies may reproduce data or excerpts or illustrations from them without requesting an authorization from the World Health Organization.

For rights of reproduction or translation of WHO publications *in toto*, application should be made to the Division of Editorial and Reference Services, World Health Organization, Geneva, Switzerland. The World Health Organization welcomes such applications.

PRINTED IN SWITZERLAND

CONTENTS

Wld Hlth Org. techn. Rep. Ser., 1965, **314**

NUTRITION AND INFECTION

Report of a WHO Expert Committee

The WHO Expert Committee on Nutrition and Infection met in Geneva from 23 to 29 March 1965. The meeting was opened by Dr M. Candau, Director-General of WHO. Dr N. S. Scrimshaw was elected Chairman and Dr B. G. Maegraith Vice-Chairman.

1. INTRODUCTION

The concept that malnutrition could make man more susceptible to infectious disease and also alter the course and outcome of the resulting illness has long been current in the history of medicine and public health. Circumstantial evidence is plentiful, principally based on clinical experience. Well-controlled observations have been few, and hence clear proof in support of the concept has been slow to accumulate. It has been much easier to demonstrate that infection is often directly responsible for lowering the state of nutrition. The fact that infectious diseases were widespread in the same regions of the world as those in which malnutrition also prevailed led gradually to a realization that the two phenomena might be interrelated.

The public health significance of this interrelationship was recognized early in WHO's history, especially in the context of chronic malnutrition. The report on the first session of the Joint FAO/WHO Expert Committee on Nutrition [1] recommended that WHO promote studies on the relation of the state of nutrition to resistance to parasitic diseases. This was at a time when the significance of the wide prevalence of protein-calorie malnutrition (kwashiorkor and marasmus) in infants and young children as the most important malnutrition problem in developing countries was not yet fully appreciated, for careful epidemiological investigations were still to be done. Within the next few years, however, it became reasonably clear that parasitic infections were important contributory factors in the prevalence of protein-calorie malnutrition in developing countries. Thus, the Joint FAO/WHO Expert Committee on Nutrition [2, 3] was led specifically to recom-

---

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1950, **16**, 9.

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1951, **44**.

[3] *Wld Hlth Org. techn. Rep. Ser.*, 1953, **72**.

mend studies on the influence of tropical parasitism in determining kwashiorkor. It recognized that infections interfered with the intake, digestion, absorption, and metabolism of food, thus accentuating malnutrition.

Partly as a result of these recommendations, WHO assisted the Government of Northern Rhodesia in a study of the " relationship between parasitic diseases and malnutrition ... and the stress of each one of the parasitic diseases as a precipitory cause of malnutrition ".[1] A few years later, WHO supported an investigation by the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala on the association between nutrition and diarrhoeal diseases. It also organized diarrhoeal diseases teams to collect information on the epidemiology of these diseases as they occur in different countries, in order to identify the major factors involved in their etiology with a view to advising governments on their prevention.

These activities, although important in themselves, were of limited significance in the context of the fundamental question of an interrelation between nutrition and infection. Although it was true that interest still centred around the problem of elucidating the relationship between infection and kwashiorkor, the time was ripe to examine the broader question of malnutrition as a whole in relation to diseases due to a variety of infectious agents, including bacteria, rickettsiae, viruses, protozoa, and helminths. This was no simple task, for it involved investigation of various aspects of a complex problem, such as examination and interpretation of morbidity and mortality data, consideration of the effects of infection on the state of nutrition and of nutritional status on the clinical behaviour of infectious disease, elucidation of the mechanisms of interaction, and analysis of a vast amount of epidemiological, clinical, and experimental evidence.

That an examination on such a broad base was necessary became apparent from experience gained in the WHO-assisted programmes for the control and prevention of communicable disease. To cite only two examples, a WHO Study Group on Diarrhoeal Diseases that met in 1958 and a WHO Expert Committee on Enteric Infections [2] took note of malnutrition as one of the contributory causes of the diarrhoeal diseases and recommended among other things that this aspect should be appropriately investigated. Similarly, a WHO Expert Committee on Helminthiases [3] recommended study of the nutritional factors involved in host resistance to helminth infection. The Joint FAO/WHO Expert Committee on Nutrition in its fifth [4] and sixth [5] reports had reiterated the need for continued

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1958, **149**, 36.
[2] *Wld Hlth Org. techn. Rep. Ser.*, 1964, **288**.
[3] *Wld Hlth Org. techn. Rep. Ser.*, 1964, **277**.
[4] *Wld Hlth Org. techn. Rep. Ser.*, 1958, **149**.
[5] *Wld Hlth Org. techn. Rep. Ser.*, 1962, **245**.

attention to the subject. WHO accordingly decided to convene the present committee to examine the whole problem in detail.

2. TERMINOLOGY

The combined effects of malnutrition and infection cannot be predicted from the presence and characteristics of either alone. Infectious disease nearly always worsens co-existing malnutrition. Furthermore, the consequences of infection are likely to be more serious in a malnourished host than in a well-nourished one. When infection aggravates malnutrition or when malnutrition weakens resistance to infection, the relationship between the two can be termed *synergistic*. The simultaneous presence of malnutrition and infectious disease may result in an interaction that is more serious for the host than the additive effects of the two working independently. Furthermore, by precipitating clinical malnutrition, infection can, in turn, give rise to a more severe disease in the malnourished host.

In some special circumstances malnutrition adversely affects the infectious agent more than it does the resistance mechanisms of the host. In this event, the interaction between malnutrition and infection can be identified as *antagonistic*.

The Committee felt that there should be general agreement on the meaning and interpretation of several other terms, and it agreed to use —though not necessarily endorse—the definitions employed in the tenth edition of the American Public Health Association's *Control of communicable diseases in man*.[1]

3. EFFECTS OF MALNUTRITION ON MORBIDITY AND MORTALITY FROM INFECTIOUS DISEASE

3.1 General

The interaction between infectious disease and the nutritional status of the host has never been clearly defined in man, partly because of the fact that in the developing countries, where this problem is of special importance, vital statistics are often incomplete and unreliable, with resultant difficulties in interpretation. Available data usually reflect the situation with regard to communicable disease better than to nutritional status, since the latter is seldom adequately assessed by the physician and is often hard to define clinically. Another problem is to distinguish

[1] American Public Health Association (1965) *Control of communicable diseases in man*, New York, 10th edition, page 13.

cause and effect when both infectious disease and malnutrition co-exist in the same individual. These problems have commonly been dealt with independently by specialists in either nutrition or infectious disease. The Committee believes that an attempt should be made to bring together the points of view of these and other specialists.

A striking feature of the generally higher mortality rates in developing countries is that they are far higher for children aged less than five years than for the same age group in the developed countries. Investigations suggest that much of infant mortality and, even more, of mortality among children 1-4 years of age can be attributed to the synergism between malnutrition and infectious disease. [1]

Well-controlled field studies conducted by INCAP in Guatemala have shown that, if supplementary feeding is insufficient, the synergistic effect of malnutrition and infection is particularly serious in the latter half of the first year of life and throughout the second year, since breast milk is inadequate as a source of dietary protein and other nutrients. The Committee believes that these findings have wide applicability in other areas, and urges that comparable investigations be undertaken in other parts of the world.

In addition to nutritional deprivation, depletion of water and electrolytes in tropical regions resulting from high ambient temperatures may influence the response to disease. It should be borne in mind that short periods of inadequate food intake, which may not be detrimental to the adult, may have a far-reaching effect on the young rapidly growing child. This may account for the greater frequency of severe infections in children during relatively short periods of famine or food restriction.

The Committee recognized the necessity for considering, in addition to nutritional factors, other multiple environmental and host factors, such as age, climatic conditions, customs and habits of life, and traditional methods of treatment. Such factors may influence the susceptibility to infection and the course and outcome of disease.

3.2 Systemic infections

There is considerable epidemiological, clinical, and experimental evidence of the importance of nutritional factors in tuberculosis. Although some reported results are based on observations and experiments with poor controls, the evidence favours the view that malnutrition may be an important factor in the high morbidity and mortality from tuberculosis in populations subjected to food shortage.

Mortality rates from measles in less developed parts of the world are often several hundred times those of the USA and Western Europe which,

---

[1] Béhar, M., Ascoli, W. & Scrimshaw, N. S. (1958). *Bol. Ofic. sanit. panamer.*, **45**, 412.

in 1962, ranged between 0.1 and 0.5 per 100 000 population. For instance, deaths from measles in Mexico in 1962 were 85 times greater than in the USA, 268 times greater in Guatemala, and 274 times in Ecuador. Compared with the more industrialized countries, measles in India, Chile, Nigeria, and most other developing countries appears to be a disease of younger pre-school children, as far as can be judged by the selected populations of clinic and hospital patients. That these observations really reflect the over-all situation in developing countries is indicated by occasional studies of whole populations, as in three Guatemalan villages in which, during a five-year period, the commonest age of attack by the disease was in the second year of life.[1]

The low age of attack is one of several factors responsible for the high fatality; that the nutritional state is probably a more important factor has been shown by recent studies in Guatemala, India and Senegal.

Much of the interest in the effect of nutrition on infection has been focused on a few diseases, such as tuberculosis, measles, and acute diarrhoeal disease. There is every reason to believe, however, that the unfavourable interaction between malnutrition and infectious disease plays a large role in many other diseases, particularly in the young child. For example, clinical experience and mortality data indicate that whooping-cough is still, as it was before immunization programmes were widely adopted, a more serious disease among malnourished children than among those who are better nourished.

Primary herpes simplex is another infectious disease in which children have been reported to be more seriously affected when they are concurrently malnourished. Both tuberculosis and typhus fever have been reported to be more severe under war-time conditions in poorly nourished individuals. It is important to keep in mind, however, that war-time data may be unreliable; their interpretation must take into account the multiple factors involved.

3.3 Diarrhoeal diseases

It is well known that children in the lower-income groups of developing countries begin to be malnourished in the second half of the first year of life, when breast milk is no longer available in adequate amounts for the size of the child. The child may continue to be seriously malnourished until weaning is completed and he can make full use of the family diet. During this period, diarrhoeal disease is exceedingly common and is a major cause of death. The term "weanling diarrhoea" has been adopted for the diarrhoea seen as an almost universal epidemiological entity among

---

[1] Gordon, J. E., Jansen, A. A. J. & Ascoli, W. (1965). *J. Pediat.* **66**, 779.

infants and young children in less developed areas.[1] It seems to arise from the synergistic effect of malnutrition and a great variety of infectious agents. These include known pathogens, such as *Shigella*, *Salmonella*, *Escherichia coli*, *Entamoeba histolytica*, and the enteropathogenic viruses, but in the majority of cases a pathogen cannot be identified. The hypothesis has been advanced that in malnourished individuals organisms not normally pathogenic may, especially when present in unusually high numbers—which is often the case where environmental sanitation is poor—, cause diarrhoeal disease or contribute to its development.

Except among infants in rare nursery outbreaks, the acute gastroenteritis of children in economically advanced communities is more a matter of discomfort than of serious morbidity. The clinical picture of diarrhoea is quite different in young children whose growth and development are retarded by an inadequate diet. Among malnourished children, acute diarrhoeal disease does not usually occur as an isolated episode with prompt recovery as in well-nourished children. Symptoms often continue for longer periods and new attacks result in a progressively depleted nutritional state.

In developing areas, several episodes—often as many as six or eight—usually occur during each year in infants and young children. In malnourished children, severe dehydration and electrolyte imbalance are more frequent and the treatment more difficult. A bloody or mucopurulent faecal exudate may be present. Deaths often account for a fourth of all fatalities at these ages, diarrhoeal disease being the most commonly recognized cause of death.

The concept of weanling diarrhoea as a true synergism between malnutrition and infection is supported by the available evidence. Well-controlled trials of feeding programmes for pre-school children have shown results in the shape of reduced morbidity and mortality from weanling diarrhoea, even without the introduction of other significant health and environmental measures. The incidence of diarrhoeal disease was sharply reduced following the distribution of supplementary food to children under five years of age in both Guatemala and Colombia. The only additional public health measure introduced in either study was oral instruction on personal hygiene in the Colombian programme. In some other developing countries, health education specifically aimed at the instruction of mothers in the proper preparation and use of locally available foods for infants and young children has given good results. It should be stressed, however, that the health hazards of contaminated food, poor environmental sanitation, and inadequate personal hygiene must also be eliminated in any balanced and effective programme for the prevention of weanling diarrhoea as well as of other types of diarrhoeal disease.

---

[1] Gordon, J. E., Chitkara, J. D. & Wyon, J. B. (1963) *Amer. J. med. Sci.*, **245**, 345.

3.4 Helminthic infections

Evidence is accumulating that a better response to treatment occurs in patients with bilharziasis whose nutritional deficiencies are corrected. Further work, however, is necessary to confirm this and also to evaluate the results of treating other helminthic infections such as ancylostomiasis and ascariasis following correction of malnourishment.

Studies have not been carried out to determine whether malnutrition affects the susceptibility of the human host to infection with hookworm or is related to the number of adult worms in the gut. On the other hand, there is clear evidence that the development of hookworm disease after infection takes place is influenced by the state of the host's iron reserves, and probably also by depletion of the exchangeable albumin pool. Similarly, differences in the tissue reserves of vitamin B_{12} may account for the fact that individuals infected with *Diphyllobothrium latum* do not necessarily develop megaloblastic anaemia.

Ascaris infection is widespread and often occurs in malnourished individuals. There is little conclusive evidence, however, that malnutrition *per se* influences the number and development of the worms. On the other hand, ascariasis may be of such intensity that the heavy worm burden helps to deplete the host of important nutrients.

Some observations indicate that in infected subjects prolonged or periodic starvation may cause increased migration of the worms from the gut to aberrant sites. This may explain the greater frequency of complications requiring surgery and other complications in some regions.

3.5 Research opportunities

In developing countries, where for many reasons vital and health statistical data are incomplete, valuable information can be obtained by long-term longitudinal studies in selected representative population groups. An example of such studies and their potentialities can be seen in the work carried out by INCAP in Guatemala. It is the opinion of the Committee that similar studies using a common methodological approach should be stimulated by WHO in other parts of the world.

More information is needed on the effect of fasting practices on nutritional status and resistance to disease. In large population groups that already have difficulty in meeting their minimal nutritional needs, superimposed fasting may exert a significant added stress. In some religious groups fasting means only a rearrangement of the times of meals, but in others it eliminates essential nutrients from the diet, sometimes for long periods.

Seasonal variations in food production and in labour patterns with their consequent effects on food consumption should also be examined for their possible effects on resistance to infectious disease.

4. EXPERIMENTAL STUDIES ON THE EFFECT OF MALNUTRITION ON INFECTIOUS DISEASE

4.1 Information available

Certain generalizations can be made from the published studies of many different experimentally induced nutritional deficiencies employing a wide range of infectious agents and a variety of hosts. Malnutrition is almost always synergistic with infections due to bacteria, rickettsiae, intestinal helminths, and intestinal protozoa ; it is sometimes antagonistic with viruses and systemic helminthic or protozoal infections.

Patterns of interaction grouped according to types of deficiencies have the following broad characteristics : (1) general calorie deficiency is synergistic with most infectious diseases, but antagonism has been found with those due to viruses and protozoa ; (2) protein deficiencies produce synergistic effects ; rare instances of antagonism result from the need of an infectious agent for a specific amino acid ; (3) vitamin A deficiency is almost always synergistic ; (4) vitamin D deficiency commonly fails to interact with infections ; (5) deficiencies of the vitamin B complex result in synergism or antagonism depending upon agent and host ; they are responsible for most known instances of antagonism in viral infections ; (6) vitamin C deficiencies are usually synergistic, but antagonism has been demonstrated ; and (7) deficiency of specific minerals may be either synergistic or antagonistic.

There is a clear range from a state of synergism characteristic of extracellular infectious agents to antagonism with intracellular agents, such as viruses, which are highly dependent on the metabolism of host cells.

The following conclusions of public health application may be drawn from this large number of experimental studies :

1. The experimental work confirms the clinical and epidemiological impression that severe protein deficiency and generalized malnutrition increase the susceptibility of the host to many infectious diseases. There is also some evidence indicating that overnutrition may be synergistic with infection. For example, a recent study has shown distemper to be more rapidly fatal in over-fed than in moderately nourished or under-fed dogs. [1]

2. Among the specific vitamin deficiencies, those of vitamins A and C are synergistic with most infections. So are other vitamin deficiencies under some circumstances. When vitamins are present in the diet in adequate

---

[1] Miller, J., Hall, A., Newberne, P. M. & Scrimshaw, N. S. (1965) *Fed. Proc.*, **24**, 2, Part 1.

amounts, however, no benefit has been convincingly demonstrated to accrue from supplementing the diet with additional vitamins.

Antagonism has not been described with the type of deficiencies naturally occurring or safely produced in man. It is desirable, however, to investigate the epidemiology of viral diseases in people suffering from deficiency of one or more of the B complex vitamins, in an area, for example, where either beriberi or pellagra is endemic.

In clinical studies of the effects of malnutrition produced by antimetabolites such as desoxypyridoxin, omega-methylpantothenic acid, and neopyrithiamine, the susceptibility of the subjects to spontaneous respiratory and other viral infections should be recorded.

4.2 Indications for research

In studying the influence of malnutrition on infection, two types of resistance in the host can be differentiated : (*a*) the " natural " or inherent resistance of the host to a specific infection which exists before exposure, (*b*) the acquired resistance of the host after the infection has taken place. The failure of either " natural " or acquired resistance in the host which manifests itself in clinical disease is significant from the standpoint of public health practice.

In all investigations, it is of great importance to realize that nutrition is only one among many other environmental and host factors that determine the development and outcome of an infectious disease. Age, sex, genetic background, and climate all play a role and should, therefore, be kept as constant as possible in all experimental work. In view of the importance of malnutrition and infectious diseases in the young children of developing countries, it is particularly important to conduct experimental studies of the various aspects of the problem in the young growing animal.

The possibilities of *in vitro* studies employing infectious agents in cells from malnourished and well-nourished animals should be explored. Furthermore, the opportunity of varying the nutrition of infected cells in tissue culture by appropriate modifications of the nutrient medium should not be overlooked. *In vitro* studies are not, however, a substitute for experiments using intact animals, since the systemic effects of infection are frequently more important than the local manifestations. The influence of nutrition on the carrier state for various pathogens is another useful line of investigation that has been neglected.

Many of the experiments, especially those reported in older studies, lack some of the features deemed essential. In order to differentiate the effects due to a specific deficiency in an experimental animal from those resulting from a reduced food intake, dehydration, or other factors, pair-feeding becomes a necessary part of experiments involving deficient diets.

Such experiments should deal with well-defined deficiencies of essential nutrients and should consider the effect of these deficiencies on the metabolism of the agent as well as of the host, particularly of zoal parasites. The differences between acute and chronic deficiencies need exploration, since the consequences may be wholly different.

It is important to establish clearly defined criteria for measuring the resistance of the experimental animal, such as survival rate, degree of multiplication and normal or abnormal localization of the infectious agent, and other related factors. The modes of entry chosen to establish the infection should ordinarily be those occurring in nature, but unnatural methods of infection will sometimes prove useful or even necessary. Similarly, the organism used to produce the infection in the experimental animal should generally be one that is pathogenic to the animal under natural conditions, but a number of valuable studies have demonstrated the susceptibility of malnourished animals to infectious agents they normally resist.

5. MECHANISMS OF SYNERGISM

5.1 Antibody formation

In experimental animals, severe protein deficiency generally reduces antibody formation [1]. The same result has been obtained with deficiencies of those essential amino acids investigated; phenylalanine, tryptophan, lysine, and methionine. Experimental vitamin deficiencies may also reduce antibody formation, as has been demonstrated for riboflavin, thiamin, pantothenic acid, pyridoxin, folic acid, and vitamins A and B_{12}. [2]

Despite their scientific value, these results are not necessarily directly applicable to the public health problem of the malnourished man. Seldom does a patient suffer as specific and as pronounced a deficiency as those experimentally produced; furthermore, multiple deficiencies are the general rule. Also, the antibodies most conveniently studied in animal experiments are not necessarily those with anti-infectious potentiality. The situation in delayed hypersensitivity (which is possibly due to cell-bound antibodies) should be clarified, since the effects of malnutrition on this type of immune response may differ from the effects on the circulating antibodies usually studied. In patients with kwashiorkor, immunization with TAB vaccines and administration of diphtheria toxoid generate little antibody; this situation corrects itself as treatment improves the nutritional state of the subject. It has been reported that persons having less than 3.4 g/100 ml

---

[1] Klimentova, A. A. & Frjazinova, I. B. (1963). In : Zdrodovskij, P.R., ed., *Voprosy infekcionnoj patologii i immunologii*, Moscow, page 45.

[2] Delaunay, A. (1964) *Ann. Nutr.* (Paris), **18**, No. 2.

of serum albumin [1] also have a diminished antibody response to immunization with TAB vaccine [2]; human adults receiving 0.3 g of egg-protein per kg body weight for 10 weeks as the sole source of protein were found to have a similar impairment. [3]

Further clinical research is desirable in this field. For example, the antibody response following smallpox, yellow fever, measles, or pertussis immunization campaigns should permit comparison of the responses elicited in malnourished and normally nourished populations. The effect of the amount of antigen per unit of body weight on antibody response should be considered. The therapeutic value of measles convalescent sera could also be examined in connexion with the nutritional status of the donors.

5.2 Phagocytic activity

Phagocytic activity is generally reduced in nutritionally deficient animals; this has been shown both by *in vitro* experiments and by *in vivo* experiments measuring the rate at which the reticulo-endothelial system removes an infecting agent from the bloodstream.

A reduction in phagocytic activity may be a factor contributing to the severity of intercurrent infections in kwashiorkor, but a distinction should be made between the absence of leucocytosis in the infected kwashiorkor patient and the phagocytic activity itself, a feature not sufficiently studied.

Future studies on the leucocytic reactions of patients with an infectious disease and in different states of malnutrition may benefit from the latest methods of assessing leucopoiesis quantitatively. It must be recognized, for example, that total and differential white cell counts in blood may reflect the redistribution of leucocytes between pre-existing compartments (the circulating pool, the marginal pool and the bone marrow reserves) and not necessarily be indicative of true changes in leucopoietic and leucolytic rates.

The information available at present on phagocytic activity in man is scarce and usually less precise than that gathered on antibodies. Since *in vitro* methods evaluating phagocytic activity have been much improved in the last few years, more research should be carried out on it, as well as on the phagocytes themselves (using biochemical, histochemical and electron-microscopic methods).

Research of this kind could also give information on the opsonic activity of the sera of malnourished subjects before and after immunization, and

---

[1] Using the Kingsley-Howe method, in which the normal values are 4.5 ± 0.5 g/100 ml because α-globulins are measured together with the albumin fraction.

[2] Wohl, M. C., Reinhold, J. C. & Rose, S. B. (1949) *Arch. intern. Med.*, **83**, 402.

[3] Hodges, R. E., Bean, W. B., Ohlson, M. A. & Bleiler, R. E. (1962). *Amer. J. clin. Nutr.*, **10**, 500.

clarify the action of the γG immunoglobulin that was shown to have therapeutic activity against *Plasmodium falciparum*.

5.3 Non-specific factors

More research is needed to determine whether nutritional deficiencies have significant effects on the presence and activities of such non-specific resistance factors as lysozymes, properdin, and interferon.

Lysozyme levels are reduced in the tears of children with xerophthalmia, but a corresponding increase in conjunctival susceptibility to infection has not been shown. Reduced lysozyme activity has been noted in the saliva of generally malnourished subjects.

Lysozyme does not appear to have an important function in the protection of the host against infection, although it is normally present in phagocytes and may have some role in their activity. Other intracellular enzymes have recently been extracted and isolated from leucocytes: lysosome enzymes (hydrolases), leukin, phagocytin, and leukozymes, which are regarded as the agents responsible for the destruction of bacteria.

Properdin is a plasma component analogous to antibodies, but active against several types of infectious agents. It would be anticipated that protein deficiencies would diminish properdin levels, but so far this effect has only been demonstrated in pantothenic acid deficiency.

Interferon is a substance produced by virus-infected cells; it protects the infected cell against further viral invasion by decreasing the availability of cellular adenosine triphosphate (ATP). No connexion has yet been shown between nutritional status and interferon activity.

5.4 Tissue integrity

Dietary inadequacies have long been assumed to decrease resistance to infection by reducing the integrity of the tissues. Nutrient deficiencies frequently result in gross tissue lesions such as the metaplastic hyperkeratosis due to lack of vitamin A; the dermatitis, cheilosis, and angular stomatitis resulting from deficiencies of riboflavin or pyridoxin; the characteristic dermatosis and mucosal atrophy of pellagra; the spongy gums of scurvy; the mucosal changes of iron deficiency; and the atrophy of skin and gastro-intestinal mucosa of severe protein deficiency.

When cultures were made 30-60 minutes after parenteral inoculation of *Salmonella typhimurium* into rats deficient in vitamin A or the vitamin B complex, a significant increase in these micro-organisms was observed in the liver. This did not occur in similar studies in which *Salmonella enteritidis* was introduced into the rats by stomach tube.

The broad range of pathological tissue changes that occur in states of nutritional deficiency conceivably influences resistance to infection through one or more of the following mechanisms:

(*a*) increased permeability of intestinal and other mucosal surfaces;

(*b*) reduction or absence of mucus and other secretions;

(*c*) accumulations of cellular debris and mucus providing a favourable culture medium;

(*d*) alteration of intercellular substances;

(*e*) interference with normal replacement and repair;

(*f*) increased fluid in the tissues.

It is not possible at present to judge the relative significance of each of these changes in relation to resistance to infection, but scattered observations indicate that several are of practical importance. It can be added that the delayed healing of wounds in malnourished persons must favour the entry of infection. The decrease in collagen formation in protein and ascorbic acid deficiency may also be significant in this regard.

5.5 Endocrine balance

It is well known that certain endocrine disorders increase susceptibility to infection. Notable examples are uncontrolled diabetes and Addison's disease. It is also common clinical experience that prolonged cortisone administration decreases resistance to infection by diminishing the protective inflammatory response. The breakdown of tuberculous lesions, the spread of staphylococcal infections, and the greater severity of chickenpox are recognized hazards of such therapy.

Another example of an endocrine effect on infection is the almost invariable association of systemic mucormycosis with metabolic disorders, most frequently diabetes mellitus. This has also been demonstrated experimentally in alloxan diabetes of rabbits infected with *Rhizopus oryzae*, even when exposure to the fungus precedes the diabetes by several days. Similarly, clinical hypoparathyroidism favours fungal infection, especially of the skin and nails.

There is no doubt that the endocrine balance is altered by some types of malnutrition, and panhypopituitarism has been described in severely malnourished individuals. Nevertheless, information is lacking on the significance of endocrine factors in the decreased resistance to infection occurring in most types of malnutrition. The possibility of endocrine factors being involved in the apparent increased susceptibility to infection of physically and mentally retarded children, such as mongoloids, should be explored.

5.6 Gastro-intestinal flora

The bacterial content of the normal large intestine requires clearer definition. The composition of the intestinal flora varies according to age and diet. *Lactobacillus bifidus* predominates in the intestine of the wholly breast-fed infant. On the other hand, the flora of the gut of the artificially fed infant resembles that found in the gastro-intestinal tract of adults, in which *Lactobacillus bifidus* is present in varying but relatively small proportion. It has been demonstrated that the intestinal flora can be altered through dietary means or by administration of therapeutic drugs, the effects being mediated through alterations in the physico-chemical environment within the intestinal lumen. Factors influencing intestinal secretion or the composition of the bile excreted in the intestine may also affect the gastro-intestinal flora.

The significance of the intestinal flora in relation to the invasion of the intestinal tract by pathogens has yet to be fully elucidated. The suggestion that *Lactobacillus bifidus* may inhibit the multiplication of intestinal pathogens has not been substantiated. However, the possibility that changes in the kind, number, and location of intestinal micro-organisms might influence the growth of certain pathogenic infectious agents, such as *Shigella*, or be responsible for intestinal disorders has been indicated by some observations in man and in animals. In certain circumstances, bacteria ordinarily indigenous to the colon may occupy the small intestine and it has been suggested that this situation may give rise to the malabsorption of sprue and kwashiorkor. A careful study of these phenomena is needed.

Observations on the gastro-intestinal flora in health and in infectious disease are not numerous. Most of the available information is from work done in developed countries, and almost none from developing countries in which malnutrition and infectious diseases commonly occur together. This gap needs to be filled by carefully controlled observations in well-nourished and malnourished communities, with a view to elucidating the role of the gastro-intestinal flora and fauna in the interaction of nutrition and infection.

6. MECHANISMS OF ANTAGONISM

Antagonistic effects in the sense described on page 7 have been observed only in animals, never convincingly in man. Antagonism, as found in experimental animals, involves mainly viral and systemic zoal parasitic infections. In the case of viruses, antagonism is understood as a condition in which the infectious agent is no longer able to obtain the specific metabolites it requires ; this occurs when the metabolism of the host cell has been altered by the deficiency involved, or when the diet fails to supply a nutrient essential to the agent but less critically so for the host.

In current research on the metabolism of parasites attempts are being made to identify specific pathways where appropriate manipulation could set in motion an analogous inhibitory mechanism.

7. EFFECT OF INFECTION ON NUTRITIONAL STATUS

7.1 General factors

A number of social and cultural factors determine the ways in which infection can influence nutritional status. Infection may also have a direct effect on the metabolism of the host. The clinical consequences depend on the state of nutritional inadequacy at the time the infection is acquired. An infection may have no serious consequences in a well-nourished individual, but in persons already in a precarious nutritional state it can set off a fatal chain of events. For example, kwashiorkor is usually brought on in an already malnourished child by an acute systemic infection or a diarrhoea of infectious origin. Seasonal increases in hospital admissions and deaths attributable to diarrhoea are often followed several weeks later by a rise in kwashiorkor.

From the public health aspect, special attention should be given to the influence of infection on food intake. Even a relatively mild infectious disease may cause a decrease in appetite or intolerance to food. Moreover, the diet taken by the patient is commonly changed, usually becoming more liquid and containing more carbohydrate and less protein and other essential nutrients. This kind of diet may be part of the traditional treatment. The situation may be further complicated by the indiscriminate giving of medicines, in particular strong purgatives and indigenous vermifuges, which interfere with absorption from the gut and so may worsen the nutritional status even more.

In the nursing infant, the anorexia associated with an acute infectious disease not only decreases the child's food intake but may also lead to an added and more lasting disturbance. If the mother does not empty her breasts when the infant fails to do so, the secretion of milk may decrease or even stop completely. Renewal of lactation can then be difficult to achieve.

Special attention should be given to the group of children with a low birth weight. In many developing countries, the number of children with a birth weight of less than 2500 g amounts to 20% or more of all live births. Many of these infants succumb shortly after birth. Those surviving will in many ways represent a highly vulnerable group because of their reduced iron stores and protein reserves.

The extent to which infection may influence the nutritional status also depends on the genetic constitution of the infant. Some children show a proneness to excessive stress reactions (e.g., high fever, intense tachycardia, profuse sweating, and undue peristalsis). There is reason to believe that the instability of the autonomic nervous system thus expressed may prove particularly unfavourable under the combined influence of infection and nutrition.

7.2 Protein metabolism

Infections are known to exert a strongly adverse effect on the nitrogen balance. Increased urinary excretion of nitrogen has been demonstrated in many bacterial and in viral, rickettsial, generalized protozoal, and systemic helminthic infections. There is almost no specific information on fungal infections or on the injuries, intoxications, and infections resulting from arthropods.

In febrile infectious diseases, nitrogen loss may begin during the prodromal period before the appearance of fever and clinical signs and may continue long after the fever has subsided. Increased nitrogen loss occurs even in diseases with little or no febrile response, as well as in immunization with live virus vaccines against measles, smallpox, or yellow fever.

Chronic infectious diseases also have an adverse influence on protein metabolism. Hypoproteinaemia may develop despite a normal intake of protein and the use of protein supplements. The loss of nitrogen during the acute phase of an infectious disease has received the most attention, but the prolonged period of increased nitrogen retention during convalescence is equally important. Interference with nitrogen absorption seems to be of minor importance unless the diarrhoea or the intestinal parasitism is clinically severe.

In severe diarrhoea, the passage of food and fluid through the gut may be rapid (" gastro-intestinal hurry "). In spite of this, the absorption of nutrients may be affected to only a moderate extent. Nitrogen absorption rarely falls much below 75 %, even with severe diarrhoea.

7.3 Carbohydrate metabolism

Infections may have adverse metabolic consequences other than those, so far the most studied, on the nitrogen balance. They may influence carbohydrate metabolism in several ways. One is through decreased activity of intestinal enzymes (duodenal amylase, and probably also the mucosal disaccharidases), which may be unfavourable in situations where carbohydrates constitute a major part of the diet.

The blood glucose level is markedly lowered in many infectious diseases; this is often secondary to a reduced calorie intake. Hypoglycaemia has been consistently reported in the late stages of severe malaria in both man and animals. The liver glycogen stores are markedly reduced and sometimes wholly depleted when examined at autopsy. There is also some evidence that in severe malaria active competition for the available glucose exists between parasite and host.

7.4 Vitamin deficiencies

It has been known for some time that children with meningococcal meningitis, diarrhoea, febrile tuberculosis, measles, whooping-cough, severe chickenpox, and other acute infections often develop keratomalacia, commonly ending in blindness.

Blood levels of vitamin A have been shown to be considerably reduced in children during pneumonia, rheumatoid arthritis, acute tonsillitis, and rheumatic fever. A consistent effect of the primary smallpox vaccination studies conducted in Guatemala was a decrease in the blood serum levels of vitamin A. Although vitamin A is not normally excreted in the urine, it may be in certain pathological states, including pneumonia, obstructive jaundice, and chronic nephritis. Giardial infections in children have been shown to interfere with vitamin A absorption.

Overt scurvy used frequently to appear in children from low-income families after they had contracted a febrile illness such as otitis media, pneumonia, or nephritis. Vaccination against smallpox has been reported to have this effect in malnourished German children, and recent INCAP studies have demonstrated a decrease in the ascorbic acid in the blood and an increase in the urine at the peak of a primary reaction to smallpox vaccination.

During the Second World War, among prisoners in the Far East receiving thiamine-deficient diets but showing no clinical manifestations of thiamine deficiency, infectious diarrhoea very frequently precipitated severe and often fatal beriberi.

A deficiency of vitamin B_{12} can result from *Diphyllobothrium latum* infections. This leads in man to the development of megaloblastic anaemia.

7.5 Mineral deficiencies

Chronic infectious diseases may alter iron metabolism and erythrocyte production to produce the so-called anaemia of infection. Acute infections interfere with the metabolism of calcium and phosphorus. The sodium, potassium, and chloride imbalance commonly associated with acute diarrhoeal disease is often of major clinical and public health significance.

Iron deficiency anaemia is known to result from the blood loss caused by *Ancylostoma duodenale* and *Necator americanus*. Recent evidence from Egypt suggests that the blood loss in *Ancylostoma* infections may be as much as ten times greater per worm per day than the figure of 0.02-0.03 ml for *Necator* infections. Haematuria in *Schistosoma haematobium* infections may also deplete the body's iron stores and lead to iron deficiency anaemia.

7.6 Gastro-intestinal function

Malnutrition and failure to gain body weight and height have commonly been reported in children heavily infected with *Ascaris lumbricoides*. It is possible that the growth, development, and metabolic activity of large numbers of ascarids in the small intestine could lead to this adverse effect on the host. Massive infections may also interfere with digestion by the production of anti-enzymes. Heavy infections with *Trichuris trichiura* can result in anorexia, indigestion, colitis, and the passage of bloody stools, which eventually lead to malnutrition and anaemia.

In chlonorchiasis and opisthorchiasis involving the pancreas and the liver, the enzyme content and activity of duodenal secretion are reduced.[1] Lowered enzyme concentration in the small intestine may also result from invasion of the pancreatic ducts by ascarids.

8. EDUCATION AND TRAINING

The Committee noted that the importance of the interaction of nutrition and infection receives little emphasis in the training of physicians and public health workers.

In general, neither health workers concerned with nutrition nor those engaged in the control of communicable disease show enough awareness of the value of co-ordinated measures to reduce the burden of infection and improve the nutritional status. In some diseases, particularly in weanling diarrhoea, nutritional improvement may be the most practical means in certain areas of reducing morbidity and mortality. This may also be so in the reduction of mortality from measles and other infectious diseases.

It is important that the interaction between nutrition and infection be taught to medical and public health workers at all levels. Furthermore, this concept should be embodied in the content of health education of the public.

9. GENERAL OBSERVATIONS

The amount of evidence that has accumulated on the occurrence of synergism between nutrition and infection is impressive. The Committee believes that it deserves more widespread recognition, particularly in relation to the effects of malnutrition on the morbidity and mortality attributed to infectious diseases in populations of developing countries and the frequency with which these diseases are a major contributory cause of clinical malnutrition in such populations.

It also noted that the various anaemias which interfere with the vitality and working capacity of children and adults in less developed areas are to an appreciable extent the result of infection acting in individuals whose diets are inadequate. Impressive evidence has also accumulated on the extent to which a synergistic interaction between poor infant-feeding practices during and after weaning and exposure to a wide variety of

---

[1] Plotnikov, N. N. (1953) [*Opisthorchosis of the liver and gall bladder*], Moscow.

infectious agents is responsible for weanling diarrhoea, which is a major cause of morbidity and mortality in less developed areas. The public health significance of this interaction in formulating control programmes is apparent.

The Committee is aware of the antagonistic effects of some nutrient deficiencies induced in animal experiments on the development of certain types of infections. It emphasizes strongly, however, that the antagonism to infection sometimes observed experimentally is not a justification for believing naturally occurring malnutrition to be useful in inhibiting infectious disease in man. The types of deficiencies occurring naturally in human populations reduce resistance to bacterial and other infections and have never been conclusively shown to inhibit any infection. This does not mean that the character of the diet will not influence the bacterial flora and intestinal parasites but only that nutritionally deficient diets should not be employed for this purpose.

The Committee discussed the need for a broad epidemiological approach to the problems of nutrition and infection. Disease results from the interaction of agent, host, and environment. Preoccupation with a single factor, whether infectious or nutritional, has often resulted in failure to note significant interactions. The development of effective control measures requires recognition of the multifactorial causation of disease, particularly in developing areas, and the initiation of public health activities that attack simultaneously as many vulnerable points as possible in the chain of causation.

With regard to the multiple effects of infection on nutritional status, the Committee noted the extent to which a Joint FAO/WHO Expert Committee on Nutrition has emphasized the effects of intestinal parasites. The evidence now available indicates that systemic and enteric infections are of major significance in precipitating acute nutritional diseases, such as kwashiorkor and keratomalacia. In most areas, infectious diarrhoea makes a far greater contribution to morbidity and mortality than the intestinal helminthic infections, both as a primary cause of death in malnourished children and in precipitating kwashiorkor and other fatal malnutrition states. Not enough attention, however, has been paid to the frequency of respiratory disease and its nutritional repercussions in less developed areas. This is not in any way to deprecate the importance of reducing intestinal parasites or minimize the net adverse effect of their presence in individuals living on inadequate diets. It is merely to emphasize that a wide variety of infections are serious hazards for the malnourished populations of developing areas.

Attention was called to the extent to which the synergism of malnutrition and infection is involved in the retarded growth and development of children in less developed areas. The effects of infectious disease are apparent in field studies and extend well into the post-convalescent period.

A major reduction of the burden of infection is needed as well as dietary improvement to enable children to reach their full growth potential. It appears from recent studies that the retarded growth of the young child, due to the combination of malnutrition and infection, affects mental development as well and thus has an even greater public health importance than has hitherto been appreciated.[1]

The Committee also noted the importance of appropriate diets in the treatment of infectious disease as well as in the nutritional rehabilitation of malnourished convalescents. Rehydration as treatment for children with severe diarrhoea, for example, must be followed up with an appropriate feeding programme.

Much more information is needed on the quantities of milk actually supplied during the later stages of prolonged breast-feeding. The milk production at different stages of lactation should be measured in selected groups of mothers in developing countries in order to determine the amount of supplementary feeding required to avoid serious malnutrition and its synergistic effect with infections.

In many developing countries there is an urgent need for official health agencies to assemble more complete and reliable vital and health statistical information on births, deaths, and the occurrence of diseases. Data are particularly required for the correct evaluation of the synergistic effects of malnutrition and infectious diseases, especially in the youngest age groups. It is hoped that the increasing number of deaths recorded by medical certificate in some developing countries will give better opportunities in the future for the evaluation of both the primary and the contributory causes of death.

In the proposed new edition of the *International statistical classification of diseases, injuries, and causes of death*, some progress has been made with respect to the classification of malnutrition. Furthermore, a proposal has been made by the WHO Expert Committee on Enteric Infections to include under the heading 031 (" diarrhoeal diseases ") two subgroups 031.0 (" with mention of malnutrition ") and 031.1 (" without mention of malnutrition "). These improvements in classification should be adopted since they have much potential value in elucidating the ill effects of the combined action of malnutrition and infectious disease.

In reporting vital and health statistics at present, separate data are given for the first year of life but the following four years are grouped together. Since in the developing countries mortality is still exceptionally high in the second year of life and the number of deaths in the second year of life alone may be as high as in the three following years taken together, the introduction of separate recording of mortality for the second year of life strongly urged in all countries.

---

[1] Cravioto, J. (1963) *Amer. J. publ. Hlth*, **531**, 1803.

10. RECOMMENDATIONS

1. The interaction between nutrition and infection is of such importance to the health of the populations of developing countries that WHO should take steps to bring it to the attention of Member Governments in the various ways at its disposal and to encourage joint consultation and programme planning by the technical personnel concerned with nutrition and with communicable disease in WHO and in Member countries.

2. The interaction between malnutrition and infection should be regularly taught in schools of medicine and public health or hygiene, in schools for nurses and auxiliary health workers, and in short-term and refresher courses for public health personnel. It should also form part of the content of health education for the public. WHO should promote such education and training activities.

3. Understanding of the problems of nutrition and infection has been seriously handicapped by inadequate statistics. WHO should encourage countries to furnish data on mortality rates by cause in the second year of life (since, in many countries, this is the age of greatest synergism between malnutrition and infection), and make available such data as it can obtain. More accurate classification of nutritional and enteric diseases is needed, as proposed by the Joint FAO/WHO Expert Committee on Nutrition and the WHO Expert Committee on Enteric Infections.

4. One reason for the adverse effects of infection on nutritional status is the variety of harmful dietary and therapeutic measures applied to the sick person. WHO should encourage the study of current practices and assist countries in developing and applying measures for their correction when necessary. As the WHO Expert Committee on Enteric Infections has also indicated, knowledge of local beliefs and customs must be actively sought and applied in preventive medicine programmes.

5. The Committee agrees strongly with the conclusion of the WHO Expert Committee on Enteric Infections " that particular attention should be given to the nutritional adequacy of diets for children after weaning in view of the increase in the number of deaths from acute diarrhoeal disease during this period ".[1] More attention should also be paid to the consequences of the inadequate quantity of breast milk that many children in developing countries receive without recognition on the part of the mother and without adequate supplementation. Weanling diarrhoea as a synergistic interaction of malnutrition and infection should receive the

---

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1964, **288**, 23.

same attention in health programmes as is accorded to other major nutritional and communicable diseases of less developed areas.

6. The special vulnerability of the growing child to the combined effects of malnutrition and infection deserves specific consideration in programmes of research and in public health practice. WHO should strive to integrate programmes for the control of communicable disease in children with measures to improve their nutritional status. It should also actively promote research on these and other aspects of the synergism of malnutrition and infection in young children. Most needed are well-controlled field studies of young children in populations in developing countries. Maternal and child health services are logical sources of administrative and technical support for such programmes.

7. It was obvious to the Committee that many of the most fundamental relationships between nutrition and various infections have never been explored in human subjects despite evidence of their importance from experiments with animals. What are most needed are well-controlled field studies in which the nutritional and infectious disease components are explored with equal skill and care. In view of the absence of information on many problems that urgently require research, the Committee recommends that WHO help in organizing and co-ordinating such research, especially that listed in the following section.

11. RESEARCH SUGGESTIONS

11.1 General

Properly controlled research is needed on all aspects of the interrelation of nutritional status and infection, covering both elements and involving both human and animal studies. The Committee emphasized the importance of the results of veterinary studies on malnutrition and infection and the desirability of collaboration between workers in human and veterinary medicine in research of this type.

Priority in research should be given to problems of synergism and antagonism of public health importance. As far as possible, clinical and field studies should have priority over animal experiments, since it is often difficult and sometimes impossible to extrapolate the findings in the latter to human beings. In studying these problems, valid statistics and a consideration of age factors are of the maximum importance in the assessment of synergistic responses, especially in relation to long-term effects on the physical and mental development of young children. The cultural aspects of child feeding and rearing practices must be included in investigations of the interaction of malnutrition and infection among pre-school children.

11.2 Specific

11.2.1 *Effects of infection on nutritional status*

The metabolic consequences of infection are still incompletely understood. More work is needed on, for example, the effects of various degrees of malnutrition on the extent of the alterations in protein metabolism caused by systemic infections.

Changes in the metabolism of vitamins in infections have been inadequately studied. There is evidence that the blood levels of some vitamins may be lowered in various infections, including clonorchiasis and opisthorchiasis. The relation between infection and these effects and other recorded disturbances of vitamin balance requires further investigation. In evaluating the metabolic response to helminthic diseases, the factor of allergic tissue response should be considered.

There is need for much more study of the effects of infection and nutrition on the movement of water and electrolytes within the body compartments of the host. The net movements across the gut membrane are particularly important in diarrhoea.

Studies are also needed on the absorption and excretion of other substances in the gastro-intestinal tract, including protein and fat, especially in enteric, bacterial, and helminthic infections. The occurrence of malabsorption in the small intestine in some diseases is a factor that might well influence the malnourished host; in this respect the physiological consequences of giardiasis need consideration.

The direct effects of gastro-intestinal helminthic infection, in the form of protein and blood loss from the host, needs more careful assessment in individual cases. The effect of these infections and of bilharziasis on the protein balance should be examined, particularly in regard to the mobile protein pool and the re-synthesis of protein, since it could affect the over-all nutritional status of the patient.

The mechanisms involved in the production of anaemia in hookworm disease and in bilharziasis are still not entirely clear. The high rate of blood loss from *Ancylostoma duodenale* infection recorded recently from Egypt should be confirmed in other areas, and the loss of blood from the intestine other than that caused by the worm should be further investigated. The relation between iron-deficiency anaemia and the state of the iron reserves of the host and the possibility of toxic or other interference with the absorption, transport, and utilization of iron in the infected host urgently require study.

In *Schistosoma haematobium* infections, a major factor in the production of anaemia is the loss of blood from the genito-urinary tract, but there appears to be an element of hypersplenism as well. This should be further studied in the other forms of bilharziasis.

The mechanism involved in the production of megaloblastic anaemia in infections, including that with *Diphyllobothrium latum*, should be more closely studied, especially in reference to nutrition and to the flora and biochemistry of the intestinal contents. The explanation for the occasional elements of megaloblastic anaemia due to folic acid deficiency seen in hookworm disease and in certain haemolytic states, including sickle-cell disease, should be sought.

In the dwarfism and anaemia associated with bilharziasis that some workers have recently reported, the plasma zinc concentrations were reduced. The role of trace elements in this syndrome and in other megaloblastic anaemias should receive further consideration, especially where parasitic disease may be a contributing factor.

In some patients, in particular those with helminthic infections, organs such as the liver undergo degeneration and changes that cannot always be directly related to the presence of the infecting agent. An example is the extensive pipe-stem fibrosis of the liver in bilharziasis. The role of malnutrition and its synergistic effect on the infectious process in the pathogenesis of these conditions have not been adequately determined.

11.2.2 *Effects of malnutrition on resistance to infection*

Epidemiological and clinical studies are needed, particularly in young age groups, on the effect of malnutrition on acute gastro-intestinal infections, especially weanling diarrhoea and cholera, occurring under endemic or epidemic circumstances in communities.

There is some evidence, from Africa in particular, of a greater severity of amoebic dysentery in malnourished individuals, but more is needed. The problem of the pathogenesis of amoebic infection and the factors, including diet and state of nutrition, that may modify its effects on the host demand further investigation. An important area of study is the differentiation of simple infection of the gastro-intestinal tract from tissue invasion and disease. The significance of the various strains of parasites, of the four-nucleated amoeba, and of cyst carriers is another unsolved problem. Factors responsible for the carrier state also need study in other infections, including hookworm disease and typhoid fever.

Information is lacking concerning the effect of the intensity of parasitic infections on the nutritional status of the host. Even less is known of the effect of the level of nutrition on the number and development of zoal parasites.

Research is needed into such problems as the role played by malnutrition in determining the effect on the host of helminthic invasion. Bilharziasis, ascariasis, and other gastro-intestinal helminthic diseases, and human trematode infections should be investigated from this point of view. More information is needed on products of these worms that may adversely influence the nutritional status, for example by disturbing digestion, absorption, and intestinal motility.

11.2.3 *Mechanisms of interaction between nutrition and infection*

In view of recent advances in the knowledge of phagocytic mechanisms and activity and in the techniques for studying them, more experiments should be instituted in man and animals to study the significance of phagocytosis and related tissue cell phenomena in the interaction of infection and nutrition.

A very important field for investigation is the production and turnover of antibodies, as well as of other serological factors important in resistance to infection, in malnourished human subjects. In addition to the specialized clinical and laboratory research necessary for these investigations, some useful data may be obtained during the immunization of communities against infectious diseases. More intensive research using modern serological techniques should be carried out in animals on the effect of diet and specific dietary deficiencies on antibody production. In such experiments, greater attention should be paid to the amount of antigen employed per unit of body weight of the host.

More consideration should be given to the possibility that in some instances malnutrition may lead to changes in the infectious agent itself, thus altering its behaviour in the malnourished host. Similar factors may be involved in the behaviour and synergistic effect of drug-resistant strains of organisms such as malaria parasites, in which the metabolic pathways may be different from those of normal parasites.

Comparative studies of the intestinal bacterial flora in malnourished and well-nourished children during acute and chronic infectious disease are particularly needed in developing countries. Changes in the flora often parallel alterations of the physico-chemical environment of the bowel, which could become highly significant in amoebiasis. Alterations in the bacterial flora of the large intestine might also influence the growth and adaptability of certain bacterial pathogens. In certain circumstances, it has been suggested, the flora of the colon might spread to the small intestine and give rise to malabsorption and ultimately to nutritional disturbances, as in sprue. These points all need further study.

Comparative studies should be made of the effect of the various widely used drugs, including antibiotics, sulfonamides, and certain anthelminthics, in the reaction of malnourished and well-nourished children to infectious agents other than the specific one under treatment. Features of helminthic and protozoal infections that require further study are the nutritional and synergistic effects of mass chemotherapy, for example in the control of malaria and bilharziasis.

A fruitful field of research would be the factors influencing intestinal secretions of the excretion of bile, which conceivably also affect the flora of the intestinal tract. Factors that might affect the selection of hosts for infections, for instance with certain helminths, should also be studied; in this respect, the importance of the quantity and relative proportions of the bile salts and acids in the intestinal juices should be further examined.

ACKNOWLEDGMENT

The Committee acknowledges the special contributions made during its discussions by the following members of the WHO Secretariat: Dr J. M. Bengoa, Nutrition; Dr B. Cvjetanović, Chief, Bacterial Diseases; Dr J.-P. Dustin, Nutrition; Dr F. W. Lowenstein, Nutrition; and Dr C. W. Schwabe, Parasitic Diseases.