Proc. Indian natn. Sci. Acad. B **44**, pp. 59-64 (1978)

Immunology

J. C. BOSE MEMORIAL MEDAL LECTURE*

THE INTERFACE BETWEEN MALNUTRITION AND IMMUNOLOGICAL REACTIVITY

by V. RAMALINGASWAMI, *All-India Institute of Medical Sciences, New Delhi* 110 016

(Delivered on 1 *January,* 1978*)*

May I, at the outset, express my sincere thanks to the Indian National Science Academy for the high honour they have done me in asking me to deliver this prestigeous lecture — the First J. C. Bose Memorial Medal lecture. I would like to pay my tribute to Professor M. G. Deo and Dr V. N. Bhuyan whose work I am quoting here and with whom it has been a privilege for me to collaborate over the years.

PROTEIN ENERGY MALNUTRITION

There are four major nutritional diseases that constitute important hazards to public health in the world today. These are protein-energy malnutrition, nutritional anaemia, keratomalacia due to Vitamin A deficiency and endemic goitre. Of these, protein-energy malnutrition affecting young growing infants and children is by far the most widespread and the most serious. It occurs endemically in the greater part of the developing world and represents the end product of under-development and mass poverty. In its most severe form it manifests as kwashiorkor, marasmus or marasmic kwashiorkor. However, these most severe forms together constitute only the tip of the iceberg, the moderate and milder forms being far more common. The World Health Organization estimates that there are, at any point of time, approximately 10 million children under the age of five who are afflicted with the most severe forms of protein-energy malnutrition and another 90 million who show moderate degrees of it. The inter-American study of the Pan American Health Organization has indicated that malnutrition, directly or indirectly, is responsible for 56 % of the mortality of children between 0 and 4 years of age. The situation is a great deal worse in Africa and Asia. The fact of the matter is that malnutrition and infectious diseases are affecting human development on a vast scale throughout the developing world.

* This is a record of the lecture as it was delivered and as such it carries no references. The author will be glad to supply on request a list of references on which the lecture was based.

The Dilemma of Communicable Diseases

Major parasitic diseases together with malnutrition form much of the substratum of tropical pathology. Communicable diseases are widespread and multiple infections are common. Each parasitic diseases is, in fact, a group of diseases. For example, there are four species of malarial parasites that attack man, four of schistosomiasis, there are eight different filarial parasites including onchocerciasis, there are three forms of trypanosomiasis and at least three types of leiashmaniasis. Some infections kill rapidly as in falciparum malaria (malaria is killing one million children every year in Africa alone) ; some kill in weeks or months as in African Trypanosomiasis. Yet others take longer time to produce serious effects but nevertheless can be eventually fatal. According to WHO 1975 statistics, more than a billion people in 66 developing countries live in areas where malaria is endemic. 180 to 200 million persons are believed to have been infected with schistosomiasis; many of them are children. About 290 million people live in areas endemic for filariasis. We are not on the winning front with respect to many of the currently prevalent tropical communicable diseases. Vector resistance to insecticides and microbial resistance to chemotherapeutic agents together with managerial failures are largely responsible for the losing battle against communicable diseases. Known technology is becoming increasingly ineffective and increasingly more uneconomical. New tools are needed and the new biology compounded of immunology, genetics and molecular biology offers fresh approaches.

The Interface

In this presentation, I would like to examine the interface between malnutrition and immune response. It is a well known observation that amongst malnourished people, the frequency and severity of infectious diseases are enhanced. Measles is attended by much higher mortality in malnourished children than in well-nourished children. Common childhood infections which are often passing events in the life of a child pose a considerable threat to life in children with malnutrition. Malnutrition and infection are generally regarded as synergestic in their effects. They operate in the form of a vicious cycle. Malnutrition tends to lead to frequent infections. Some infections in their turn tend to impair immunological capability of the host and also tend to precipitate the onset of acute malnutrition. The scene is characterized by a high infant and child loss compensated by a high birth-rate, by a disease pattern reflecting the synergestic interaction between malnutrition and infectious disease and by pervading poverty. There is a cluster of causes and a multiplicity of effects. A high proportion of illnesses and deaths in malnourished societies occur in infants and pre-school children and their mothers. They relate to the environment and the community more than to the individual.

Experimental Findings

Human disease often has a multifactorial etiology. In human malnutrition there are often multiple deficiencies. In such a situation it is difficult to understand the

precise relationship between the nutritional status of an individual, the immune response and disease manifestation. Experimental studies in which the nutritional and infectious variables can be controlled offer an opportunity to understand the true relationship between the nutritional status and infectious disease.

General tissue reaction to protein energy malnutrition

Protein and energy deficiencies affect every cell and tissue in the body although they are not affected at the same time or to the same extent. There is a pattern in the reaction to these deficiencies. Organs with a high protein turnover show more rapid and extensive metabolic and structural alterations. Among these are organs with stable cell populations but with high cytoplasmic protein turnover such as the liver and the pancreas. There are those with a high rate of cellular renewal either as continuous cell renewal systems such as gastro-intestinal tract, bone marrow, skin, etc., or as conditional renewal systems, such as the immune apparatus brought on as a reaction to injury. In organs with stable cell populations but with high cytoplasmic protein turnover, the changes affect the synthesis of enzymes and the synthesis and secretion of other proteins. In organs with a continuous cell renewal system, a slowing down of cell generation and consequent shrinkage of the pool size and atrophy of the cellular elements are observed.

The thymus plays a key role in the immune response and it shows consistent and conspicuous atrophy in protein and energy deficiencies. The atrophy is due to depletion of cortical lymphocytes. The lymphnodes, the spleen and the gut-associated lymphoid tissue also undergo extensive and generalized atrophy. In these organs, the lymphoid depletion is pronounced in the thymus-dependent paracortical areas of lymphnodes and the periarteriolar lymphatic sheath of the spleen. There is also a spectacular reduction in the number and size of germinal centres.

Dynamics of Lymphopoiesis in Protein Depletion

The mesenteric lymphonodes which drain the intestine and receive constant antigenic stimulation exhibit normally a great deal of lympho-proliferative activity. My colleague, Dr Bhuyan, studied the lympho-proliferative activity in the mesenteric lymphnodes of guinea pigs in protein deficiency. Germinal centres are reduced in number and size, new formation of germinal centres in the medulla is rare, the mitotic index, mitotic duration and the turnover of cells are markedly reduced and also the labelling of cells is reduced in protein depletion. There is, however, no reduction in plasma cells and gamma globulin levels are raised, lymphopenia and neutropenia, lymphopenia being more pronounced than neutropenia.

Macrophage Function

In another experiment Dr Bhuyan found that in protein depletion in guinea pigs, there is a delayed and defective mobilization of macrophages. Studies with the protein deficient guinea pigs have shown that the BCG nodule induced by

intradermal injection of BCG is poorly formed on account of delayed and deficient mobilisation of macrophages. Low circulating pool of mononuclear cells, impaired proliferation of these cells, diminished mobilization of macrophages and retarded transformation of macrophages into epitheloid cells and tubercles are the hallmarks of protein deficiency. The draining lymphnodes also show poor lymphoid cell proliferation in the paracortical areas, with the result that disseminated infection and bacilli persisting in the tissues are characteristic and tuberculin sensitivity is greatly impaired. Rapid mobilization of macrophages, their organization and maturation into epitheloid cells, tubercle and granuloma formation are attempts at the containment of mycobacteria. These attempts are severely restricted in protein depletion.

In another experiment, in which accelerated granulomatous response by macrophage mobilization, was studied in rabbits immunized with BCG and subsequently challenged with intravenous BCG, Dr Bhuyan found that in protein-depleted rabbits there was a marked reduction of macrophage mobilization and granuloma formation in various organs. The granulomas formed were few, small, aberrant and ill-formed.

Non-specific Natural Immunity

My colleague, Professor Deo, has shown that the mobilizable pool of neutrophils in the bone-marrow is reduced in protein deficient monkeys. Their numbers are reduced in the circulating blood in a number of animal species. Dr Bhuyan has demonstrated spreading necrotizing lesions and impaired localization of staphylococcal infections in protein depletion.

There is a great deal of uncertainty in the literature on the phagocytic activity of neutrophils and their bactericidal capacity in protein depletion. Our own studies have shown that individual neutrophils appear to be capable of adequate bactericidal activity but their quantitative reduction may be playing an important part in the impairment of host defences.

In other experiments in monkeys and rats, Professor Deo and Dr Bhuyan had independently demonstrated that the phagocytic activity of the reticulo-endothelial system is markedly impaired in protein depletion. In these studies, the rate of clearance of colloidal carbon of staphylococci and of P^{32}-labelled *E. Coli* from the circulation in rats, monkeys and rabbits has been found to be impaired in protein depletion.

Human Studies

Recent studies among malnourished children in different parts of the world show an enlarging picture of multiple defects in the defence mechanism of children with protein energy malnutrition. There is well marked thymolymphatic atrophy; as Professor Smythe has observed, perhaps to the child with kwashiorkor, extreme thymic atrophy is more important than the fatty liver. The child with kwashiorkor and the rhesus monkey with severe protein depletion can be described as having a 'nutritional thymectomy'. The thymus may be described as the most critical barometer of protein energy malnutrition.

Depression of cell mediated immunity has been demonstrated in protein-energy malnutrition in many human studies but the humoral responses to specific antigenic stimuli, have been rather variable. Low levels of serum complement proteins have also been described. Depression of polymorpho-nuclear neutrophilic defences, largely as a result of diminished numbers and possibly also as a result of some reduction in phagocytic and bactericidal activity has been described. Poor mobilization of macrophages and granuloma formation have been found. The possible effects of protein-energy malnutrition on mucosal barrier immunity have been indicated through studies on secretory IGA.

This is the immunological background against which the manifestations of disease in malnourished children are often observed. Thus disseminated infection with varicella and herpes simplex viruses is common in malnourished children. There is a tendency for spreading gangrene in pyogenic infections rather than localized abscesses, gram negative septicemia is common, anergic disseminated tuberculosis is often seen. In the fatal forms of measles, giant cell pneumonia as predicted by McFarlane Burnett is observed. Professor Robert Good had observed that the lungs of children who died of measles and who had protein-energy malnutrition, had overwhelming Hecht pneumonia. They were filled with fusion giant cells, teaming with inclusion bodies but showed very little or no lymphocytic infiltration or plasma cell reaction. The lymphnodes were astonishingly small and hypo-cellular and the thymus although clearly involutional, was so depleted in some children that it was remindful of the underdeveloped thymuses of those who died with Severe Combined Immuno-deficiency Disease.

Concluding Thoughts

These reflections of multiple immunological deficits on the clinical horizon in malnutrition constitute today the nutrition-immunity inter-action. Cellular proliferation, cellular growth and differentiation, cellular migration and death are the basic components of the reaction to injury. I use the term injury here in its widest sense, be it microbiol, toxic, chemical or any other. These are also the basic components of the ontogeny of growth and development. Immunological competence, for example, involves the primary proliferation and differentiation of lymphocytes in the central organs such as the bone marrow and the thymus, and the proliferation and differentiation of antigen reactive lymphocytes necessary for effecting immunity in the peripheral lymphoid tissues such as lymphnodes and the spleen. Here we are dealing with cell numbers, cell movement and cell differentiation under an intricate regulatory apparatus involving growth and development of cells in a heterogeneous and continually changing manner.

We have seen that protein and energy deficiencies affect the ability of the organism to make new cells and to synthesise and secrete certain classes of proteins. Consequently, the reactive capacity of the organism to injury is significantly affected.

Even if we are unable to fully comprehend the nutrition-immunity interaction in the present state of our knowledge, the encouraging feature is that both the

humoral and cell mediated immune responses show remarkable recovery following adequate protein and energy nutrition. This suggests an essentially intact but relatively ineffective immune apparatus in protein-energy malnutrition.

There are, however, still some unanswered questions with regard to the reversibility of impaired immune competence observed during foetal growth retardation. The crucial biological questions of our times are what are the effects of intra-uterine and early post-natal malnutrition on the growth and development of the brain on the one hand and on the immune competence on the other. The small for gestation age infants have depressed thymus dependent lymphoid system and are born with diminished defences. The question of reversibility of this form of immuno-suppression still remains undecided. The crucial questions are how long do these deficits last, what kind of biological remembrance is carried into adult life of these early life impairments and deficiencies? What are their possible long-term effects in terms of quality of life and more specifically in terms of susceptibility to infections, to autoimmune disease, to neoplasia and to ageing, are matters of great importance to the infants' future. These are clearly the most challenging problems of our times for which clear-cut answers are needed. As Dr Norman Kretchner said the other day, we should not let our present ignorance jeopardize the future of children yet unborn.