NUTRITION, IMMUNITY, AND INFECTION

Mechanisms of Interactions

R. K. CHANDRA
Memorial University of Newfoundland
St. John's, Newfoundland, Canada

P. M. NEWBERNE
Massachusetts Institute of Technology
Cambridge, Massachusetts

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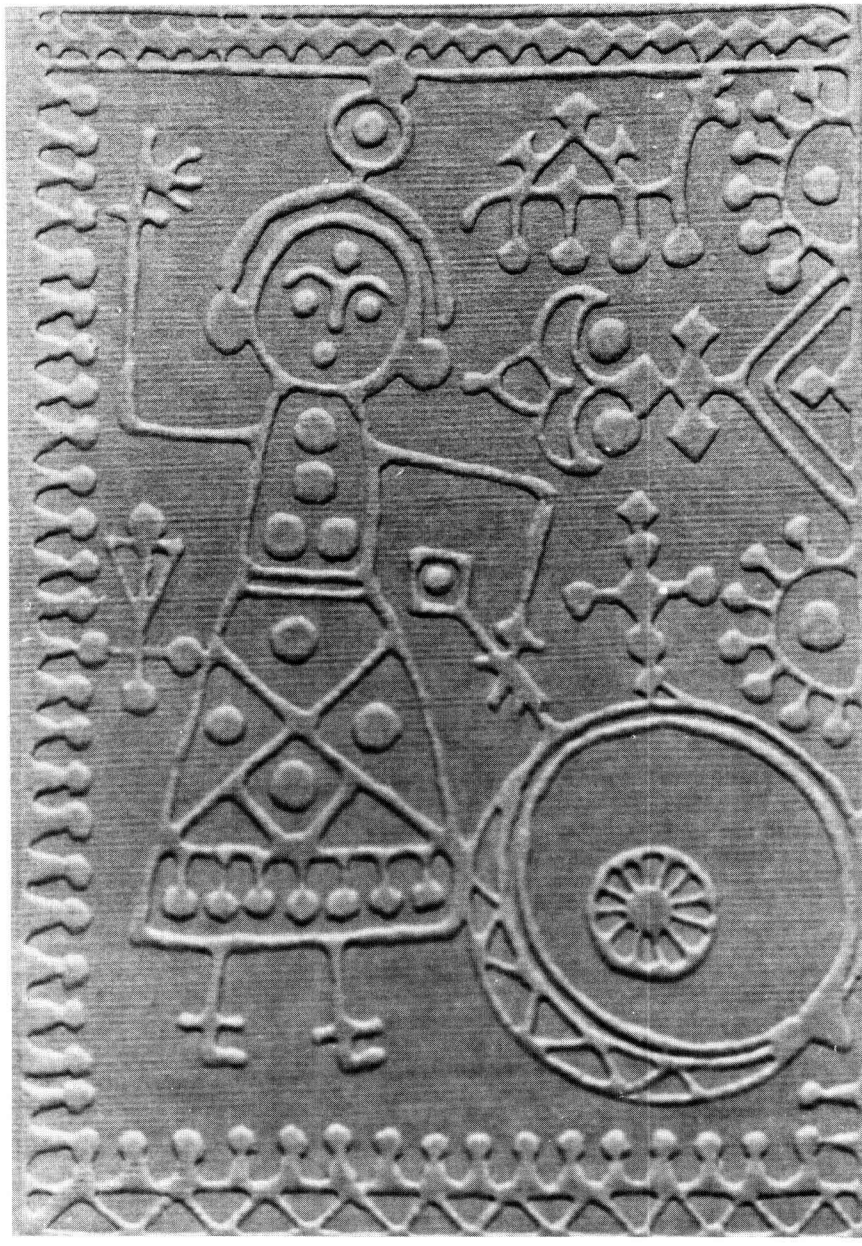

Annapurna, the goddess of food and plenty specially revered in the villages of India. From a mud mural. The importance of dietary intake and physical and mental health is discussed in ancient Indian scriptures written several centuries B.C. (Courtesy of India Tourism Development Corporation.)

To our families

FOREWORD

I welcome the privilege of writing some words of introduction to this important book. Its authors have been courageous in bringing together in one text a triad of topics that cover such large tracts of biomedical sciences as epidemiology, biochemistry, immunology, and clinical medicine. Malnutrition and infection are known to be closely linked, the one promoting the other. The adaptive immune system forms a part of the link since it is responsible for a good deal of defense against infection, and it may be affected adversely by malnutrition and indeed by infection itself. Knowledge in this complex field is of great potential importance because malnutrition and infection are such dominant features of the ill-health of many of the world's underprivileged people.

As this book shows, there is no lack of technical facets for study. There are now so many components of the immune response which can be measured or assessed and so many aspects of nutritional biochemistry which can be studied that the problem is to select what to study and where to begin. Moreover, the great number of variables in the nature of nutritional deficiencies, in types of infections or multiple infections and in the genetic, environmental, and social background of the affected people, all combine to make interpretation and application of findings a speculative business. Descriptions of cause and effect must usually be provisional rather than definitive. There are, quite rightly, so many occasions in this book when a conditional verb must be used that research workers could be tempted to ask whether these topics can indeed be integrated in a systematic and useful way.

That is no reason for not trying. The biomedical scientist trying to apply his knowledge and skills to the improvement of health in the community cannot expect to find controlled condi-

tions comparable to those that can be achieved in the test tube or the inbred mouse. Some consistency has already emerged in this complex field. In malnourished children, the T cell system—thymus, T lymphocyte, and cell-mediated response—are regularly impaired, although amounts of immunoglobulin are not reduced and may even be raised. Antibody formation is normal or reduced, perhaps (note the conditional clause) due to defective T cell function. Such findings imply, for example, a relationship between nutritional status and the effectiveness of vaccines. No doubt all nutritional problems could be solved by food, but unless we are so sanguine as to imagine that an optimal diet will in the near future be available for all, it would be well to consider possible strategies to minimize the adverse effects of malnutrition.

Immunization with present vaccines, and the new ones to come, might be more effective if carried out under nutritionally favorable circumstances as, for example, during a season when food was more plentiful or after a period of dietary supplementation. Alternatively, it may be possible to design the vaccine, and, in particular, its adjuvant, to stimulate an effective T cell response even in malnourished subjects.

Much of the research described in this book concerns the essential laboratory base upon which further advances can be made. But even the most elegant triumphs in this field will ring hollow if their relevance to the control of human disease cannot be assessed or realized. There is now, more than ever, a need to link the more fundamental laboratory and clinical studies with observations on man. Longitudinal epidemiological studies on infectious diseases that seek to assess the significance of nutrition and immunological changes alongside other factors such as genetics and social and economic circumstances are one powerful approach that has already been exploited in some areas. This book will be a valuable source of knowledge and ideas for such studies.

DAVID S. ROWE

Special Programme for Research and Training in Tropical Diseases
World Health Organization
Geneva, Switzerland

PREFACE

The intimate and complex relationship between diet and health finds mention in the ancient scriptures of India, in the treatises of Chinese and Roman medicine, and in the Corpus Hippocratum. It is sad that in spite of phenomenal advances in agricultural techniques and medical sciences, we still see in 1977 the struggle between diminishing food supply and increasing population growth in its starkest form. Undernutrition, often combined with the intertwined problem of infection, continues to threaten the health and survival of the majority of the world's population, particularly infants and children. If nutritional deficiency and susceptibility to infectious illness are a conjugate pair, it is important to understand the pathogenetic processes involved.

Recent advances in immunological concepts and techniques have stimulated many studies in the general field of nutrition–immunocompetence–infection interactions. Several noncellular factors and the number, morphology, and function of many cell types have been found to be altered in nutritional deficiency states. The studies have provided an insight into the intricacies of Nature's methods of preferential synthesis of cells, proteins, and enzymes required for host defense, at the expense of expendable elements. Nutritional modulation of immunity may be an important determinant of morbidity and mortality associated with a variety of disease processes. Interestingly, undernutrition as well as overnutrition can alter immune responsiveness. Thus "optimum nutrition" is the key phrase for dietary influences to keep immune response within normal limits. Questions arising from observations in man have led to controlled experimentation in

laboratory animals. It is unlikely that the results of animal experiments can be directly extrapolated to the human situation. However, such fundamental observations point the way to the interesting possibility of dietary manipulation of immune response, which may determine susceptibility or resistance to many diseases.

The data generated have to be interpreted with caution. Many aspects of the immune response have been studied, often in isolation from other parameters and seemingly out of context with other critical environmental variables which influence the occurrence of infectious illness. In the feverish excitement of research, it is easily forgotten that in complex biological systems the total effect of a series of components is not necessarily the sum of their individual effects. Differences in the nutritional status of the subjects evaluated, variations in the techniques used, the presence or absence of complicating infections and stress hormonal and metabolic processes, make it difficult to compare and collate observations.

In this interpretative monograph, we have attempted to summarize and analyze critically the reported information, to bring out the controversies, and to point out the lacunae where further data are required. We have drawn upon the work of others and of our own, and have included some previously unpublished observations. We have asked many questions which cannot at present be answered. The inevitability of increase in scientific knowledge cannot be denied. It is our fervent hope that the efforts of many research workers and health professionals will lead to solutions with the ultimate objective of preventing or alleviating suffering generated by malnutrition and infection.

We wish to acknowledge the excellent assistance of Rose Marie Puddicombe, Louise Kittridge, Rosemary Burklin, Clifford George, Gordon King, and Jim Thistle, in the preparation of the manuscript.

R. K. CHANDRA
P. M. NEWBERNE

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1

INTRODUCTION

The important role of nutritional deficiency as a contributor to childhood mortality particularly from infectious disease, as a conditioning factor in the complex mosaic of many diseases, and as a hurdle to socioeconomic advancement, is widely recognized. Improvements in nutrition, together with better hygiene and immunization, can take most of the credit for decreasing death rate from infectious disease and for the longer expectation of life in industrialized countries. This change in the mortality pattern came before the development of antibiotics and modern medical techniques. In developing countries, gross life-threatening malnutrition in the shape of marasmus and kwashiorkor continues to be rampant. These dramatic syndromes represent the clinical end points of nutritional pathology, and form the tip of the massive iceberg of undernutrition. More than 100 million preschool infants and children suffer from moderate-severe malnutrition in the world. And for one case of kwashiorkor or marasmus, there are at least 100 with mild to moderate deficiencies of one or more nutrients. Recent studies in the Americas have revealed a surprisingly high incidence of nutritional problems. The Pan American Health Organization survey of mortality patterns carried out in Central and South America showed malnutrition and infections to be the most serious health problems in children, as primary or more often as secondary factors in deaths (Puffer and Serrano, 1973). Fifty-seven percent of the children who died under 5 years of age revealed signs of undernutrition, intrauterine and/or after birth, as either the underlying or an associated cause of mortality. The death rate from infectious diseases, mainly diarrhea and

measles, was found to be 23%. Random population surveys in the United States (Department of Health, Education and Welfare, 1972) and in Canada (Nutrition Canada, 1973) have revealed a high prevalence of nutritional problems particularly among the impoverished segments of society. An examination of 300 randomly picked preschool children of poor black families in Memphis showed that about one-sixth were below the third percentile of standards of weight and height, one-fourth were anemic, 27% had retarded skeletal development, and 44% had low levels of vitamin A (Zee *et al.*, 1970).

Clinicians have long observed that undernutrition predisposes the host to the risk of acquired infection and that the course, frequency of complications, severity, and mortality of the infectious illness are augmented. It is likely that this is the result, in part, of impaired immunocompetence secondary to nutritional deficiency. Infection in turn frequently worsens the nutritional status, often precipitating overt symptoms and signs, and causes immunosuppression. A variety of complex pathogenetic mechanisms probably underlie these multicornered interactions (Fig. 1.1).

There is an intimate relationship between nutritional status, immune response, and infection (Fig. 1.2). The common concurrent existence of malnutrition and infection may symbolize a pathophysiologic interaction between the two, to produce effects including immunosuppression that are more than the summed result expected from the two diseases acting singly, the phenomenon of synergism (Scrimshaw *et al.*, 1968). Or an antagonism may exist. Alternatively, the frequent coexistence of malnutrition and infection may simply indicate the occurrence of common causative factor(s) in the same ecosystem. In most industrialized countries, economic affluence, availability of food in sufficient amounts, immunizations, and improvement in sanitation have led to the decline of malnutrition as well as infectious illnesses. In the economically less privileged nations, however, the opportunities for combined mutually aggravating effects of undernutrition and infection continue to prevail and to pose a threat to the health of the majority of their populations, most particularly young children under 5 years of age.

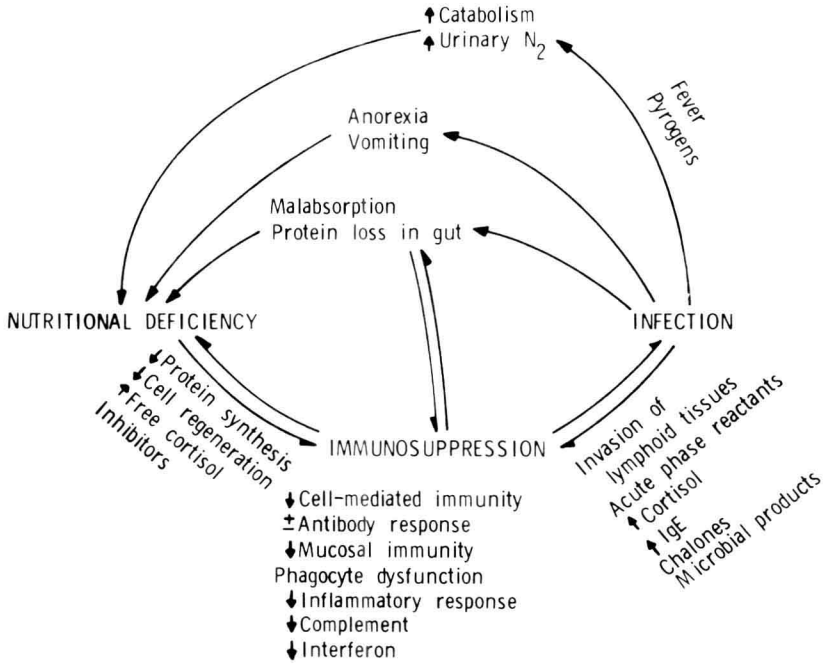

Figure 1.1. Mechanisms of interactions between infection, nutritional deficiency, and immunosuppression.

In the continuous struggle between the host and the pathogen, resistance ability of the former and virulence of the latter are the key determinants (Fig. 1.3). If the organism is highly pathogenic, for example measles virus, disease is the invariable result in the nonimmunized person. In the case of the relatively avirulent organism, for example *Candida albicans*, generally no disease ensues, and "immunity" develops. In the vast majority of instances, however, both these forces are of variable intermediate strength, and in such a situation factors modifying one or the other may tip the balance to morbidity and mortality, or to symptomatic infection with complete recovery. Nutrition is one of the critical determinants in this balance (Chandra, 1976b).

When nutritional deficiency and infection coexist, the former is often chronic and precedes the latter acute process. Infectious illness is likely to cause the greatest havoc during periods of rapid