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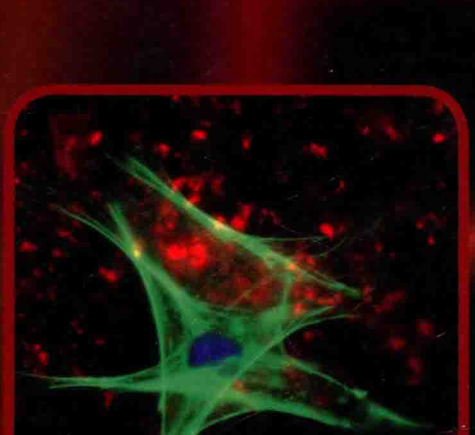

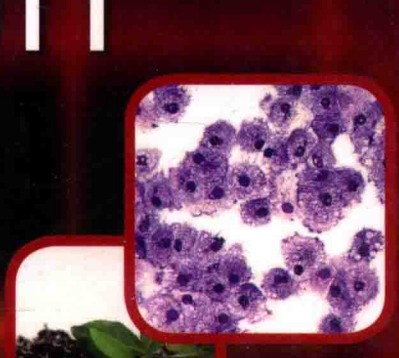

Prakash Shetty

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Nutrition, Immunity and Infection

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Nutrition, Immunity and Infection

For Nandini
No need to say anything. She knows.

Preface

This modular textbook *Nutrition, Immunity and Infection* has had a long gestation! For someone who has barely made any significant contribution to this specific field, accepting the invitation to develop a module on 'Nutrition and Infection' for the new Masters Course in Infectious Diseases at the London School of Hygiene & Tropical Medicine for London University's Distance Learning Programme, required some considerable arm twisting. Once I started working on the module it was apparent that an understanding of the interactions of nutrition and infection could not be accomplished without integration with immunity and immune function. For someone who was not overwhelmed by intimate association and deep involvement with any one of the aspects of the three corners of this interesting and interacting triad, it was apparent that there was a lacuna in the form of a book that could cater to the needs of the student from any one of the disciplines contributing to this triad without overburdening them with too much technical and scientific information related to the other disciplines involved. Interest expressed by CABI to publish a book on this topic meant I had to get clearance from London University's Distance Learning Programme and I am grateful to Professor Bo Drasar who not only encouraged me in this venture but also facilitated my receiving the required clearance.

My subsequent move to work for the United Nations in Rome soon thereafter meant I had to put this on the backburner for several years. It was my earlier intent to produce a small textbook which would be a beefed up version of the distance learning module and which I was particularly keen to be made available as an inexpensive paperback catering to the demands of students from developing countries. However, the passage of time meant that CABI, who had re-activated their interest in my book on my return to the UK, had decided that it would be one of a series of modular textbooks they would be producing. This has meant the current book is much bigger and more technical than was originally conceived. I hope it has the necessary balance and the right amount of information, and addresses the needs of a wide range of students. Graduate or post-graduate programmes cater to a wide range of students from diverse backgrounds, and a fair proportion of them are exposed to these disciplines for the first time. There are epidemiologists, statisticians and public health workers who have a barely passable knowledge of nutritional sciences or of the biology of human immune function. They need to obtain enough knowledge and information to appreciate the close interactions in the three legs of the triad of nutrition, immune function and infection.

I would like to express my gratitude to Professor Nevin Scrimshaw whom I have had the privilege to know for nearly three decades, and I am indeed honoured that he wrote a Foreword to this book. He is a pioneer in this field of interactions such as synergism and antagonism between nutrition and infection and published the first, most exhaustive review on the subject in 1959 (*American Journal of Medical Sciences* 237, 367), which then culminated in the World Health Organization's monograph of 1968 (*Interactions of Nutrition and Infection*). We need to salute Scrimshaw and his colleagues, who in their 1959 review made several important observations which are true to this day, 50 years hence. I quote from their review:

> Many of the important infections of human populations are rendered more serious in their consequences by the presence of malnutrition; that few infections are indeed less severe when associated with nutritional deficiency; and that many infections themselves precipitate nutritional disturbances.

It was written at a time when microbiological research continued to identify new infectious agents and when nutritional scientists identified increasing numbers of specific nutrients and the scientific basis of nutrition was being established. This was also a period when our understanding of immunology was nascent and the discipline was not exalted by terms so familiar to us now such as cell-mediated immunity and cytokines. The only measure of 'resistance' to infection in laboratory experimental studies was 'almost exclusively by the ability of the host to

produce antibodies'. However, it was also recognized that resistance to infection was 'the sum total of body mechanisms which impose barriers to the progress of invasion by infectious agents' – at a time when nutritional immunology was not even a speck on the horizon. According to these authors, reports in the literature as early as 1949 indicated that 'the relationship of each nutrient to each infectious agent in each host would need to be worked out individually'. We are only beginning to appreciate and understand this, and I hope this book illustrates some of that new knowledge.

This important review by Scrimshaw and colleagues published 50 years ago provided a working generalization that 'in human populations interactions between nutrition and infection are probably more important than laboratory investigations would indicate'. They concluded so presciently, 'Where both malnutrition and infection are serious, as they are in most tropical and technically underdeveloped countries, success in control of either condition commonly depends on the other'. How true and how evident it is, in our current global public health strategies.

Events, progress and time change perspectives. One cannot discuss the topic of nutrition and immunity without recognizing and saluting the yeoman contribution of Ranjit Chandra in the then new and emerging field of nutritional immunology, which he strode like a colossus for decades since his early contribution in the 1970s. Chandra deserves much of the credit for the growth of this scientific area in the pre-AIDS era, during much of which he ploughed a lone furrow, with his singular contributions showing impaired immune response and immunocompetence in protein–energy malnutrition.

In more recent years several technical and scientific monographs have highlighted the importance of nutrition on immune function and I owe a debt of gratitude to several contributors to many of these excellent volumes, which I have depended on and draw heavily upon in putting together this modular student textbook. Writing a textbook is different from writing a scientific manuscript or review, and enabling easy readability means compromising the need to cite all statements and all the evidence. Only crucial ones are outlined for further reading while all others are listed under sources. To the numerous authors and editors from whom I have learnt so much and whose ideas, information and evidence I have adapted and used so freely, I express my gratitude. A few specific mentions of my colleagues in Southampton whose edited volumes and books have provided much help would not be out of place here and they include Penny Nestel, Philip Calder and Barrie Margetts.

It would not have been possible to write this book without access to the various libraries and their most helpful staff – these include the University of Southampton Medical School library and the excellent libraries in London at the Royal Society of Medicine (RSM), University College, London (UCL) and London School of Hygiene & Tropical Medicine (LSHTM). I would like to place on record my thanks to Alan Dangour of LSHTM for his prompt help on several occasions to obtain crucial publications and books, which has been invaluable.

I would be failing in my duty if I did not record my gratitude to Sarah Mellor at CABI, whose constant support and faith in my ability to deliver the manuscript more than compensated for the occasional reminder of the deadline! I would like to thank Nigel Farrar, Rachel Cutts and Shankari Wilford, the Publishing and Production team at CABI. To have a good copy editor is to be fortunate, and I have been well looked after by Gill Watling. Numerous other staff of CABI have been responsible for the illustrations and in producing this book. Thank you all very much.

Prakash Shetty

Foreword

It is difficult to believe that as recently as the 1950s the relationship between nutrition and infection was unrecognized except for limited references to tuberculosis. With only minor exceptions, the textbooks on nutrition made no reference to infection, and those on infectious disease were similarly lacking mention of nutrition. The relationship first received attention as a result of the recognition in the 1950s that kwashiorkor, then common in almost all developing countries, was precipitated by infections in young children whose diets were already inadequate.

Extensive studies at the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala plus research in Ghana, Chile, Brazil, South Africa and a few other developing countries confirmed that kwashiorkor in young children, characterized by a severe deficiency of protein relative to energy, rarely occurred without the adverse metabolic effects of diarrhoeal or respiratory infections or the common communicable diseases of childhood, particularly measles and whooping cough.

Field studies of the relationship between infection and malnutrition soon led to the recognition that the high mortality rates in poorly nourished young children could not be ascribed to either malnutrition or infection alone. A two-year INCAP study of all deaths in children below 5 years of age in four Guatemalan villages found that about 40% at that time were due to kwashiorkor. However, all of these cases were precipitated by a preceding infection and probably none of the deaths attributed to diarrhoeal or respiratory infections would have occurred if the children had been better nourished.

Sceptical of such sweeping conclusions, the Pan-American Health Organization sent an epidemiologist and a statistician to investigate the causes of child deaths in eight Public General Hospitals in Latin American cities. Despite the limitations of the hospital records they reported that at least half of the deaths were due to a combination of malnutrition and infectious disease. Evidence for nutrition and infection interactions began accumulating in the world literature. However, it was not until these were brought together in the 1968 World Health Organization (WHO) Monograph on *Interactions of Nutrition and Infection*, with nearly 900 supporting references, that both workers in nutrition and those concerned with infectious disease began to appreciate the synergistic interrelationship of the two types of disease: infections worsen nutritional status and poor nutrition weakens immunity to infections.

By the time the WHO monograph was published, the mechanisms by which even subclinical infections had an adverse effect on nutritional status had been well worked out and described. However, those by which the various types of undernutrition and malnutrition were associated with increases in the prevalence and severity of infections were not understood. The principal potential mechanism known at that time was humoral immunity, i.e. antibody formation. However, in field studies, poorly nourished children with high morbidity and mortality usually did not have impaired antibody response to common antigens.

Immunology was then in its infancy! Cell-mediated immunity, its complex control by cytokines and the contribution of immunoglobulins to resistance to infections were almost entirely unknown. The WHO monograph established beyond doubt that malnourished individuals were more susceptible to infection, but it was not until the virtual explosion of research in the field of immunology that the reason for this was fully explained. Soon delayed cutaneous hypersensitivity, T-cell numbers, immunoglobulins and secretory antibodies were being described as affected by even mild malnutrition.

The first nine chapters of this textbook cover comprehensively and in a well-organized manner the great amount of new knowledge on the synergistic interactions of nutrition, immunology and infectious disease that has been developing rapidly in recent decades. The last of these deals with specific diseases of global importance: HIV/AIDS, malaria, tuberculosis and systemic helminthic infections. However, knowledge of nutrition and immune functions in man now goes far beyond their relationship to infectious diseases. This textbook appropriately includes a chapter on immunity in chronic diseases. Micronutrients that affect the immune system can also

play a role in chronic inflammatory responses and in cancer. Mild immune impairment may even be a feature of human obesity. A chapter deals with the complex effects of ageing on immune function and another with the rapidly growing field of probiotics, prebiotics and synbiotics. These compounds reduce the incidence and duration of acute diarrhoeal episodes in infants and children by exploiting the normal role of the intestinal microflora in modulating immune function and reducing the risk of infection. The final chapter discusses the growing problem of food allergies.

This book is authoritatively and clearly written. The summary points at the beginning of each chapter are particularly helpful and the references have been carefully selected for the material to which they refer without being excessive. It is written to be equally useful for students and researchers in developing and industrialized countries. Students who use this textbook will acquire a good basic understanding of the relationships among nutrition, immunity, infectious diseases and chronic diseases. This book is a valuable contribution to the training of students and researchers in nutrition, immunology, infectious disease, paediatrics, general medicine and public health.

Nevin S. Scrimshaw PhD, MD, MPH
Institute Professor Emeritus, Massachusetts Institute of Technology
President Emeritus, International Nutrition Foundation
Visiting Professor, Tufts University

Glossary

Achlorhydria A condition where the acid production in the stomach is abnormally low.

Acquired immunity or adaptive immunity Antigen-specific immunity that increases during infection. It is composed of highly specialized mechanisms that eliminate pathogens and has the ability to recognize and remember them, to mount stronger attacks each time the pathogen is encountered.

Allergen A non-parasitic or common environmental antigen capable of inducing a hypersensitivity reaction in an atopic individual.

Allogenic From different individuals of the same species.

Amoebiasis Infection caused by the pathogenic amoeba *Entamoeba histolytica*.

Anergy Lack of reaction by the body's defence mechanisms to foreign substances.

Angioedema Recurring attacks of oedema of the skin and mucous membrane, which suddenly appears.

Anorexia Loss of appetite leading to a reduction in food intake.

Antibodies Proteins (i.e. immunoglobulins) produced on exposure to an antigen that neutralize the activity of the antigen.

Antigen A molecule that induces a specific antibody or cell-mediated immune response.

Atopy or atopic syndrome A condition characterized by allergic hypersensitivity affecting parts of the body not in direct contact with the allergen.

Attributable risk The difference in the rate of a condition or disease between an exposed population and an unexposed population.

Autoantibody An antibody produced by the immune system that is directed against one or more of the individual's own proteins or cells.

Autoimmune disease A disease caused by an overactive immune response of the body against substances and tissues normally present in the body and where the body actually attacks its own cells, mistaking them for pathogens.

Bactericide A substance that can kill bacteria.

Body mass index (BMI) An index for assessing the appropriateness of weight-for-height in adults and children. It is weight (in kilograms) divided by the height (in metres) squared.

Candidiasis Also known as 'thrush'. A fungal infection which may vary from a superficial infection like oral thrush to a systemic and potentially life-threatening infection.

Cell-mediated immunity A defence mechanism directly mediated by cells, i.e. T lymphocytes.

Cephalo-pelvic disproportion A condition that exists when the capacity of the pelvis is inadequate to allow the fetus to negotiate the birth canal and may lead to obstructed labour.

Cheilosis An inflammatory lesion at the corner of the mouth, and often occurs bilaterally. Also referred to as angular stomatitis.

Chelator An agent that detoxifies poisonous and heavy metals, like mercury and arsenic, by converting them to a chemically inert form that can be excreted without further interaction with the body.

Chemokine A protein secreted by cells, which induces directed chemotaxis or chemical attraction in responsive cells.

Chemotaxis A process which causes cells, to direct their movements due to the presence of certain chemicals in the environment.

Colostrum The first milk produced by the mammary gland in late pregnancy, which is rich in antibodies.

Commensal An organism that exhibits commensalism, i.e. a relationship between two organisms where one organism benefits but the other is unharmed. Unlike mutualism where both organisms benefit and parasitism where one benefits and the other is harmed.

Complement system A biochemical cascade that amplifies the effects that result in helping to clear a pathogen from the body.

Complementary feeding The provision of foods and liquids along with continued breastfeeding of infants.

Cytokine A chemical that mediates communication between cells of the immune system.

Delayed cutaneous hypersensitivity (DCH) test A direct functional measure of cell-mediated immune response.

Eclampsia An acute and life-threatening complication of pregnancy, characterized by the appearance of seizures.

Endocytosis A process by which cells absorb molecules and nutrients from outside the cell by engulfing with their cell membrane.

Endotoxin Unlike an exotoxin, an endotoxin is not secreted in soluble form by live pathogens but is a structural component of the pathogenic cell and is released mainly when a pathogenic cell is lysed.

Epitope or antigenic determinant Part of the macromolecule (antigen) recognized by the immune system, more specifically by antibodies or by T and B lymphocytes. The part of the antibody that recognizes the epitope is referred to as the paratope.

Exclusive breastfeeding The provision of nothing but breast milk to an infant for the first 6 months of life.

Exotoxin A substance excreted by a pathogen that can cause major damage to the host by destroying cells, disrupting normal cellular metabolism. Exotoxins may be secreted or released like endotoxins following the death and lysis of the pathogenic cell.

Exposure The contact over time and space between the individual and one or more biological, chemical or physical agents.

Food allergy An adverse immune response to a food protein.

Food intolerance or non-allergic food hypersensitivity A delayed, negative reaction to a food, beverage or food additive that may produce symptoms in one or more body organs and systems.

Furunculosis Commonly referred to as a 'boil'. A skin disease caused by the infection of hair follicles and localized accumulation of pus and dead tissue. Individual boils can cluster together and form an interconnected network, called a carbuncle. Infection of the hair follicle of the skin is also referred to as folliculitis.

Gluconeogenesis Metabolic pathway through which glucose is produced from non-carbohydrate sources such as amino acids.

Gut-associated lymphoid tissue (GALT) The immune system within the gastrointestinal tract located in the lymphoid tissue.

Haptens A small molecule that can elicit an immune response only when attached to a large carrier protein, while the carrier may be incapable of eliciting an immune response by itself.

Helminth A parasitic worm which lives and feeds off a living host and may cause disease in the host.

Humoral immunity Defence mechanisms mediated indirectly by the production of antibodies by B lymphocytes.

Hyperkeratosis Thickening and keratinization of the skin.

Idiotype A shared characteristic between a group of immunoglobulin or T-cell-receptor molecules based on the antigen-binding specificity and the structure of their variable region.

Immunoglobulins A group of proteins categorized as gamma globulins that act as antibodies and come in different varieties known as isotype classes.

Immunomodulator A substance that modulates the immune response.

Immunosurveillance Immune cells that act as sentinels in recognizing and eliminating continuously arising, nascent transformed or abnormal cells.

Incidence A measure of the risk of developing a disease within a specified period of time. Often expressed simply as the number of new cases during a specific time period.

Incidence proportion or cumulative incidence The number of cases within a specified time period divided by the size of the population at risk.

Infant mortality rate The number of infant deaths (1 year of age or younger) per 1000 live births.

Inflammation Local changes that characterize the tissue response to the entry of a foreign body or pathogenic agent. It is a protective response to remove the injurious stimulus as well as to initiate the healing process.

Innate immunity or natural immunity Provides defence against infective agents and comprises mechanisms that defend the host in a non-specific manner. It does not confer long-lasting or protective immunity to the host.

Interferon A protein released in response to the presence of a pathogen or tumour cell which allows for the communication between cells, to trigger the immune system to respond to eradicate the pathogen or tumour cell.

Intrauterine growth restriction or retardation (IUGR) A condition that may result in a low-birth-weight or small-for-gestational-age infant.

Kwashiorkor Severe undernutrition in young children, characterized by oedema.

Leishmaniasis A disease caused by a protozoan parasite that is transmitted by the bite of certain species of sand fly.

Low birth weight (LBW) A full-term infant with a birth weight below 2500 g.

Lymphopaenia Abnormally low level of lymphocytes in the blood.

Lysozome A spherical organelle in the cell that contains enzymes to digest worn-out cell components, food particles, and engulfed and phagocytosed pathogens.

Marasmus Severe undernutrition in young children, characterized by severe muscle wasting.

Meta-analysis A statistical analysis that combines the results of several studies that address a set of related research hypotheses.

Metalloprotein A generic term for a protein that contains a metal ion as a cofactor. A metalloprotein fulfils several functions; when it acts as an enzyme it is referred to as a metalloenzyme.

Mitogen A protein that encourages a cell to commence division by triggering mitosis.

Multigravida A woman who has been pregnant more than one time.

Odds ratio The ratio of the odds of an event occurring in one group compared with the odds of it occurring in another group.

Opportunistic infection An infection caused by a pathogen that usually does not cause disease in a healthy host with a healthy immune system. A compromised immune system, however, presents an 'opportunity' for the pathogen to infect the host.

Opsonin A molecule that acts as a binding enhancer to facilitate phagocytosis.

Outcome The occurrence of disease, event or health related state.

Parasitaemia The quantitative content of parasites in blood, used as a measurement of parasite load in the organism and an indication of the degree of an active infection.

Partial breastfeeding The provision to the infant of other liquids and solids in addition to breast milk.

Pathogen Any foreign agent (worm or helminth, fungus, protozoan, bacterium, virus, prion) that gets into the human body and does harm of some kind.

Perinatal mortality Refers to the death of a fetus or neontate. The definition by the World Health Organization for perinatal mortality is 'deaths occurring during late pregnancy (at 22 completed weeks gestation and over), during childbirth and up to seven completed days of life'. Perinatal mortality thus includes the sum of both fetal and neonatal mortality.

Pertussis Also known as whooping cough. A highly infectious disease caused by the bacterium *Bordetella pertussis*.

Phagocytosis A cellular process which involves the engulfing and ingestion of solid particles or bacteria.

Population attributable risk The reduction in incidence that may be observed if the population were entirely unexposed, compared with its current exposure pattern.

Prebiotic A food ingredient that stimulates the growth and activity of bacteria in the gut which are beneficial to the health of the body.

Predominant breastfeeding The provision to the infant only of liquids, like water, in addition to breast milk.

Prevalence The total number of cases of the disease in the population at a given time, or the total number of cases in the population, divided by the number of individuals in the population.

Primigravida A woman who is pregnant for the first time or has been pregnant one time.

Prion An infectious agent composed solely of protein.

Probiotic Live organisms which when administered in adequate amounts confer health benefits to the host.

Prostaglandin A lipid mediator that acts on platelets and mast cells and is derived from essential fatty acids.

Protozoa Unicellular organisms, some of which may cause human disease like *Entamoeba* and *Giardia*.

Pyrogen Any fever-producing compound or substance.

Relative risk The risk of a nutritionally deficient child getting infection compared with the risk of a healthy child getting infection.

Retrovirus An RNA virus that is replicated in a host cell to produce DNA from its RNA genome; the DNA is then incorporated into the host's genome and the virus replicates as part of the host cell's DNA.

Rhinitis Irritation and inflammation of the inner mucosal surface of the nose.

Saccharolytic A form of fermentation of carbohydrate precursors by bacterial flora that results in the production of short-chain fatty acids.

Sarcopaenia The degenerative loss of skeletal muscle mass and strength associated with ageing.

SGA infant A full-term infant that is small for its gestational age due to intrauterine growth restriction.

Short-chain fatty acids (SCFA) A subgroup of fatty acids produced in the large intestine following the digestion of fibre and other carbohydrates by the microbial flora of the colon.

Stunting Undernutrition in children, characterized by growth faltering, which leads to short stature and a diagnosis of 'below acceptable range of height-for-age'.

Supplementary feeding The provision of extra foods to infants and children over and above the normal ration of their daily diets.

Synbiotic Nutritional supplements combining both prebiotics and probiotics.

Thalassaemia An inherited blood disease, which results in reduced synthesis of one of the globin chains of haemoglobin and causes the formation of abnormal haemoglobin molecules, thus leading to anaemia.

Vertical transmission Also known as mother-to-child transmission. The transmission of an infection from mother to child immediately before and after birth during the perinatal period.

Xerophthalmia Also known as keratomalacia. The eye signs associated with and characteristic of mild vitamin A deficiency in children, which may show as clouding of the cornea. It is a condition with pathologic dryness of the conjunctiva and cornea which, if untreated, may lead to corneal ulceration and blindness.

Contents