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Prologue: Historical Introduction

Immunonutrition in health and disease

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Nutrition: Infection: Immunity: Historical introduction

Prior to the publication in 1959 of a comprehensive review article documenting the Interactions of Nutrition and Infection[1] and its expansion to a 1968 WHO Monograph[2] with the same title, there was almost no recognition of the nature of this relationship except in farm animals. These two publications provided conclusive evidence that in the human populations, in nearly all cases, the interrelationship between nutrition and infection is synergistic, i.e. the effects of a combination of the two are worse than could be predicted from either alone. They offered longitudinal community data showing that much of the higher mortality of underprivileged populations was due to the interaction of malnutrition and infection and would not have resulted from either alone[3]. This was later confirmed through an evaluation of child death records in 11 public hospitals in Latin America[4].

After the WHO Monograph provided extensive evidence for the relationship between nutrition and infection, recognition of the concept followed rapidly. Acceptance of the concept was helped by the fact that the monograph could identify in detail the mechanisms whereby infections worsen nutritional status. Decreased food intake due to anorexia plays a role, as do metabolic losses in the urine, internal diversion of protein and other nutrients for synthesis of immune proteins (antibodies, globulins, C-reactive protein, etc.), decreased absorption if infection affects the gastrointestinal tract, increased metabolic rate with fever and in some cases protein-losing enteropathy.

The situation was quite different when we attempted to identify the mechanisms through which nutritional deficiencies can increase the frequency and severity of infections. The known defence mechanisms at the time were essentially limited to epithelial integrity, phagocytosis and humoral antibodies. Neither the epithelial barrier nor the white blood cell response could explain resistance to most infections. However, there was good evidence from controlled studies in both animals and humans that protein and micronutrient deficiencies, if sufficiently severe, interfered with antibody formation in response to test antigens. But available field studies in poorly nourished populations with high mortality from infections failed to detect impairment in antibody response to test antigens. The degree of severity of malnutrition in human populations was apparently less than in the experimental studies and not enough to affect the humoral response to infections.

When the WHO Monograph was published in 1968, the field of nutritional immunology was in its beginnings and knowledge of the role of nutrition in cell mediated immunity, secretory immunoglobulins, multiple T-cell function, the complement cascade, delayed subcutaneous hypersensitivity and the complex role of cytokines was still to come. Since 1980 there have been at least six books, a dozen symposiums and conferences and hundreds of relevant published studies on nutrition and immunity or nutrition and infection. For the 1994 Symposium on "Nutrition, Immunity and Infection" in Madrid, I reviewed the evidence available at that time[5]. It was noteworthy that the immune system, although complex, has only a limited number of responses that we measure. One consequence of this is that almost any specific nutritional deficiency, if sufficiently severe, can interfere with most of the known immunological functions. Nevertheless, the impact of nutritional deficiencies on morbidity and mortality from infections is due to a mixture of nutrient and disease specific interactions that are only beginning to be identified. A symposium on "Nutrition and Infection" in New Orleans in 2002 reviewed progress stimulated by the 1968 WHO Monograph and emphasized the enormous progress in immunology that had occurred since its publication[6].

Historically, the death rate from infectious diseases fell precipitously in England and Wales in the 18th and 19th centuries, and continued in the early part of the 20th before any specific treatments or immunizations were available. Thomas McKeown concludes that before 1935 the continuing drop in mortality from infectious disease in the U.S. and Europe was due to a gradual improvement in resistance to infection as access to food improved[7]. This is relevant today because mortality rates from the 1918-19 influenza epidemic have been extrapolated as a worst case scenario for the potential lethality to be expected if the hyper virulent H5N1 influenza virus mutates to become transmissible from person to person as in the 1918 flu epidemic.

Such an analysis overlooks the fact that mortality rates for individuals who were poorly nourished were higher and that

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those for persons over 30 years of age were quite low suggesting that they had been previously exposed to a similar influenza strain in the past[8]. For H5N1 there may not be such large proportion of the population with some immunity. In this case, mortality from a pandemic of this strain could be expected to be much higher than in 1918-19, perhaps as high as 80 per cent in poorly nourished populations, the observed case fatality rate from this disease in Indonesia in 2006[9].

For these reasons the World Health Organization no longer regards the 1918–19 pandemic as a worst case scenario for contingency planning on how to meet a possible pandemic due to this strain. This is a challenge for immunologists studying the lethality of potentially dangerous respiratory viruses and the role of better nutrition as a way of improving adaptive immune response to them. The global spread of this strain of "bird flu" is still only a threat, although a plausible and dangerous one, but other global pandemics, with high mortality rates, are already raging, affecting low income populations the most. Globally the three most important are tuberculosis, malaria, and HIV/AIDS.

The older literature provides good evidence that malnutrition increases tuberculosis morbidity and mortality in individuals and populations[2]. When specific therapies became widely available in the 1960 s, nutritional status was no longer a concern. However I was surprised to learn from recent WHO data that five decades after effective treatments became available, tuberculosis remains the most common cause of infection related deaths worldwide. The resurgence of tuberculosis is due in part to weakened immunity in untreated populations with HIV infection as well as the emergence of virulent multiple-drug resistant strains of tuberculosis. Thus once again, the role of nutrition in resistance to tuberculosis becomes important. Nutritional status is also an important determinant of mortality from malaria, particularly in young children in endemic areas before they acquire some degree of immunity and is also proving a factor in the spread and severity of HIV/AIDS, particularly in vertical transmission from mother to infants. Among HIV-infected patients reduced CD4 counts[10] and more rapid disease progression are associated with deficiencies of vitamins A, B6, B12 and E[11].

It is not necessary to emphasize here that relationships between nutrition and immunity are not limited to their critical role in resistance to infections. They concern almost all physiological and pathological functions in the human body. It is now generally agreed that nutrition is a factor in 35 %[12] to half of all cancers[13] and that the immune system plays a key role is the bodies' defence against cancer cells. Dietary risk factors in atherosclerosis may impact inflammatory cells directly as well as be associated with plaque formation in coronary arteries. Vegetable oils promote synthesis of pro inflammatory cytokines, whereas fish oils are anti-inflammatory[14,15]. Probiotics can result in altered intestinal microbiota associated with greater resistance to gastro-intestinal infections[16].

It is the continuing task of nutritional immunologists to identify the specific mechanisms involved in the complex interrelationships between nutrition, immunity and all forms of acute and chronic disease. This will inevitably lead nutritional immunologists into genomics, metabolomics and proteomics as they seek to understand the complex interactions involved in the relationship between nutrient status and immune function. The impressively wide range of topics at this symposium is testimony to the breadth, depth and importance of nutritional immunology, a field that although past infancy, is only in early adolescence.

Conflict of interest statement

The author has no conflict of interest to report.

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