EFFECT OF NUTRITION ON IMMUNE SYSTEM

Essay

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By

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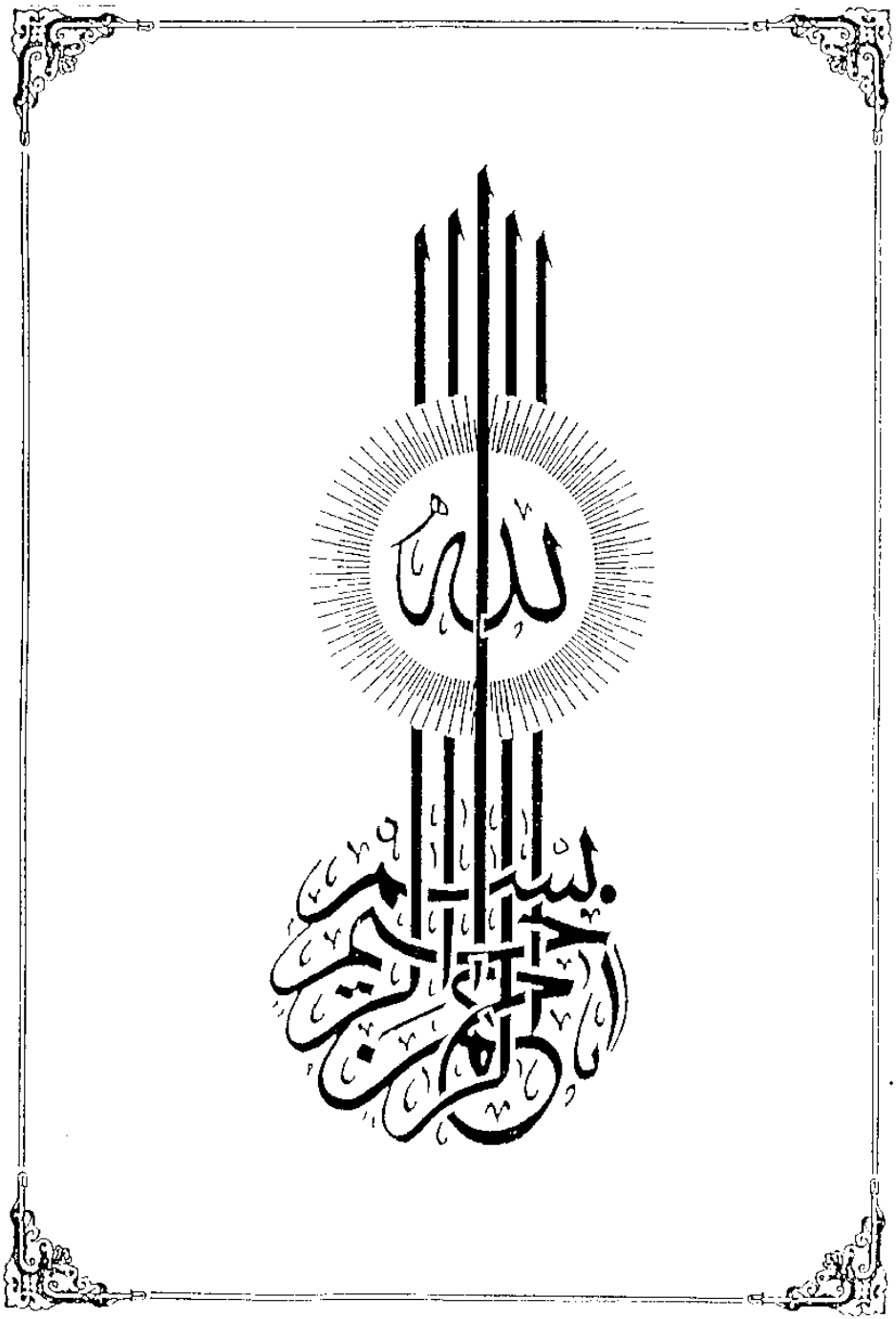
DEDICATION

To My Family.



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LIST OF ABBREVIATIONS

APC	Antigen presenting cell
BCG	Bacillus calmette guerin
Con A	Concanavalin A
C'_3	Complement number 3
DTH	Delayed type hypersensitivity
DDH	Delayed dermal hypersensitivity
HA	Haemagglutination
HMP	Hexosemonophosphate
IFN-gamma	Gamma interferon
IL-1	Interleukin 1
LPS	Lipopolysaccharide
MHC	Major histocompatibility complex
NK	Natural killer
PCM	Protein calorie malnutrition
PEM	Protein energy malnutrition
PFC	Plaque forming cells
PPD	Purified protein derivative
PHA	Phytohaemagglutinin
PWM	Pokeweed mitogen
PPA	Primary pernicious anaemia
PUFA	Polyunsaturated fatty acids
PGE_2	Prostaglandin E_2
RES	Reticuloendothelial system
TNF	Tumour necrosis factor

CONTENTS

INTRODUCTION

AND

AIM OF THE WORK

It is now established that nutritional deficiencies are associated with impaired immune responses. thus, the question no longer is whether malnutrition affects immune responses, but what aspects and to what extent. Malnutrition has been proved to be a common cause of immune deficiency with a significant effect on cell mediated immunity, phagocytosis and the complement system. Both malnutrition and excess food intake enhance the incidence of infections and possibly cancers. changes in cell mediated and humoral immunity are significantly modulated by nutrition.

Nutritional disorders, such as, protein calorie malnutrition, vitamins deficiencies, trace metal deficiencies and excess fatty acids, have profound effects on immune functions such as delayed type hypersensitivity. T-cell responses to mitogens, antibody production and natural killer cell activity. Some of these immune deficiencies are shown to be reversible with nutritional supplements.

In this essay, the above mentioned parameters and their effects on the immune system will be discussed and reviewed.

PROTEINS AND AMINO ACIDS

Proteins

The fact is well established that protein calorie malnutrition (PCM) predisposes to infection, particularly by intracellular pathogens, but the basis for this is unclear (Skerret *et al.*, 1990).

However, alterations in components of specific and nonspecific immunity have been identified in PCM. Specific cellular derangement include impaired T-cell mitogenesis, alloreactive cytotoxic T-lymphocytes and selective depletion of T-cell subsets (Hoffman *et al.*, 1985). Although the absolute number of ß-lymphocytes is normal or increased, functional analysis of humoral immune responses indicates relative impairment in both acute and chronic PCM (Nohr *et al.*, 1985). As regards nonspecific immunity, which is mediated by polymorphonuclear leukocytes and mononuclear phagocytes, it appears susceptible to protein caloric deprivation. Also, defects in chemotaxis, phagocytosis, and intracellular microbicidal mechanisms have been identified in PCM (Redmond *et al.*, 1992).

Effect of PCM on Phagocytosis

It is known that cell mediated immunity to mycobacteria and to other intracellular pathogens depends upon macrophage activation through T-cell co-operation (MacKaness,

1970). Activated macrophages exhibit the capacity to generate increased amounts of superoxide anion (O_2^-)[4] and hydrogen peroxide, which correlate with microbicidal capacity (Murray *et al.*, 1985).

Defective macrophage O_2^- generation in murine models of both short-term and long-term PCM has been reported. The severity of the nutritional insult may determine the specific pathophysiologic mechanisms responsible. Mild PCM appears to down regulate O_2^- through excess prostaglandin E_2 production, although alteration in critical membrane phospholipids with associated impaired receptor expression are associated with severe PCM (Redmond *et al.*, 1991).

Lipopolysaccharide (LPS) elicited macrophages from malnourished animals have less protein per cell, and exhibit less spreading and pseudopad development than PLS elicited macrophages from well nourished animals. There is also an impairment in induction of macrophages Ia antigen in response to IFN-gamma in protein deprived mice. Such impairment might relate to the blunted cellular immune responses in protein calorie malnutrition. Also, protein deprivation in mice significantly impaired production of IL-1 activity in response to LPS and this may explain the blunting of the febrile response to bacterial infection that

has been observed in malnourished patients (Reynolds *et al.*, 1992).

The biochemical basis for the decrease in macrophage activation is not understood, but plasma cortisol has been reported to be elevated in patients with PCM. Corticosteroids can inhibit the activity of the respiratory burst in human neutrophils and monocytes. Also, glucocorticoids render macrophages refractory to stimulation with lymphokines (Reynolds *et al.*, 1992).

As regards alveolar macrophages, Skerret *et al.* (1990), reported that many properties of alveolar macrophages, obtained from severely protein calorie malnourished rats, including adherence, phagocytosis, release of hydrogen peroxide and superoxide and production of IL-1 like activity and TNF were remarkably well preserved. But, these macrophages exhibited a marked shift in arachidonic acid metabolism when stimulated by Listeria, with diminished release of lipoxygenase products and increased release of cyclooxygenase products. alterations in arachidonic acid metabolism may interfere with the regulatory function of these macrophages.

Effect of PCM on Cellular Immunity

The number of lymphocytes and lymphocyte proliferation after stimulation by a mitogen *in vitro* are both

reduced in protein deprived animals (McMurray, 1983). T-cell proliferation in response to ovalbumin pulsed antigen presenting cells is also decreased in PCM (Rose *et al.*, 1982).

On the other hand Malavé *et al.* (1978), showed that *in vivo* chronic protein deficiency (CPD) allogenic T-cell responses were enhanced. This was confirmed by *in vitro* mixed lymphocyte reaction (Conzen and Janeway, 1988). The mechanism of this enhancement is unknown, but one might speculate that defective antigen presenting cell (APC) function present in CPD mice, results in a compensatory skewing of the class II-recognizing T-cell repertoire in favour of those cells with a lower threshold of activation which are thus hyperresponsive to ACP from normal mice (Conzen and Janeway, 1988).

However, Reynolds *et al.* (1990), showed that administration of a low-protein diet to mice did not significantly affect T-cell function in terms of mitogen activation, responsiveness to exogenous rIL-2, or induction of Ts as manifested both phenotypically and functionally.

As regards delayed type hypersensitivity (DTH) skin tests, protein deficiency is accompanied by the loss of tuberculin hypersensitivity to purified protein derivative (PPD) (McMurray, 1983). There is also increased numbers of

virulent mycobacteria in spleens and lungs of previously BCG-vaccinated malnourished animals challenged by the respiratory route with M. tuberculosis (McMurray, 1986).

In another study, protein deficient guinea pigs, vaccinated with mycobacterium bovis BCG vaccine and infected by the respiratory route with virulent mycobacterium tuberculosis, showed a significant loss of dermal tuberculin hypersensitivity, reduced purified protein derivative drive lymphoproliferation *in vitro*, and diminished interleukin-2 production (McMurray and Bartow, 1992). Also, the proportion of E-rosette receptor (CD_2) positive lymphocytes was significantly lower in the blood and thymus of low-protein guinea pigs. Thus the loss of antimycobacterial resistance which accompanies CPD may be due, in part, to alterations in the expression of CD_2 or the distribution of CD_2^+ T-cells.

A significant number of polymorphonuclear leukocytes in addition to T-lymphocytes and monocytes have been shown to enter the delayed type hypersensitivity skin test reaction to recall antigens (Razzaque and Blose, 1983).

Trying to explain the diminished DTH skin test response seen in protein deficiency, Tchervenkov *et al.* (1988), showed that malnutrition created by protein deprivation in rats, impaired the host's ability to deliver phagocytes to inflammatory lesions. Thus, part of the

diminished DTH skin test response in PCM may be due to the inability of effector cells to reach the site of antigen deposition and produce the local inflammatory changes that result in disposal of the antigen.

Also, malnutrition has been associated with decreased production of IL-1 (Tchervenkov *et al.*, 1988), and other lymphokines as well as alterations in prostaglandin synthesis (Alexander, 1986). These substances have been shown to be very chemotactic to neutrophils and are elaborated early in the inflammatory process by interstitial macrophages. It may be the lack of production of these substances in the early hours of an inflammatory reaction that is responsible for the decrease in the influx of phagocytic cells (Tchervenkov *et al.*, 1988).

In another study, impaired granuloma formation in protein-deficient mice, in response to BCG may be due to decreased response of macrophages to INF-gamma and this may affect other aspects of the granulomatous response such as the generation of giant cells (Johnston, 1988).

Effect of PCM on NK Activity

Natural killer cells (NK) represent a subpopulation of lymphocytes that mediate non MHC-restricted lysis of target cells, including certain tumour cell lines (Gorelik *et al.*, 1982). After both 2 and 3 weeks of protein deprivation

in mice, basal NK activity to YAC-1 was consistently reduced, but more marked effects were observed in the NK responses from mice pre-treated with poly (I:C). Impaired NK cell responses to poly (I:C) could result from reduced endogenous interferon production by macrophages or by decreased sensitivity of NK cells to interferon (Reynolds *et al.*, 1990). Also, Villa *et al.*, (1991), showed that PCM in cancer patients was associated with a marked decrease of their NK cell activity as compared to healthy controls. They showed that functional activity, but not the number of the NK cells was decreased.

Effect of PCM on Humoral Immunity

Activation of ß-cells by both cognate and non-cognate T-cell helps, as well as LPS-stimulated proliferation was found to be intact in CPD (Conzen and Janeway, 1988). In another study, intact TIB-cell proliferative and antibody producing responses in malnourished animals have been reported (Narayanan *et al.*, 1977).

Protein and protein energy malnutrition in children are commonly associated with an increased incidence of mucosal infections and diarrhoea, suggesting a malnutrition induced defect in the mechanism for protection of mucosal surfaces (McGee and McMurray, 1988).

McMurray *et al.* (1977), demonstrated a reduction in

the concentration of IgA in tears, saliva and nasal secretions of malnourished children. Another study reported a reduction in intestinal fluid IgA levels in malnourished mice (Reddy *et al.*, 1981). This decrease in intestinal fluid IgA found in the moderately malnourished animals may be not due to a reduction in the ability to generate immune cells but perhaps to alterations in the homing of these cells, their production of IgA, or even the transport of IgA across the mucosa (McGee and McMurray, 1988). However, increased levels if IgA in duodenal fluids of malnourished children was reported by Bell *et al.* (1976), who suggested that this may be due to an increased incidence of gastroinestinal infections in these children.

On the other hand IgA levels in the serum from protein malnourished mice are significantly higher than the well nourished control values (McMurray *et al.*, 1981). This excess serum IgA may represent an impairment of a mechanism for the removal of IgA from the serum which is extremely sensitive to protein deprivation (McGee and McMurray,1988).

Amino Acids

Besides the importance of adequate protein nutrition for maintaining immune system competence, several studies have shown that isolated deficits or excesses of a single