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NUTRITION AND IMMUNITY:The Influence of Diet on Autoimmunity and the Role of Zinc in the Immune Response

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INTRODUCTION

The effect of nutrition on immunity is manifold. Any single dietary category, be it protein, carbohydrate, fat, individual vitamins, or trace elements, taken in quantities either too large or too small, may cause metabolic abnormalities. These metabolic disturbances can, in turn, affect the well-being of the whole organism and/or a part of the whole, such as the immune system.

Many reviews have been published in the last two decades that amply document the adverse effect of either over- or undernutrition on all aspects of immune function (52, 53, 94, 140, 141, 199). In this chapter, we focus on the effect of diet on autoimmune diseases—including the major disease processes associated with aging—and on the role of a single nutrient, the trace element zinc, in the complex immune systems of man and animal.

It has been shown in experimental animals that diet influences the frequency and severity of several diseases associated with aging. For example, rats fed an unrestricted diet have been more susceptible to malignant, renal, myocardial, and prostatic disease (188) than have those fed a variety of fixed diets. Longevity of experimental animals of several species has also been

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influenced by many variables,including composition of the experimental diet, the quantity consumed, the time of life during which the experimental diet is imposed, duration of the experimental feeding period, and the sex and particular strain of the animal.

Dietary manipulation can, in fact, yield quite spectacular results. Ross, for example, reports that rats exposed to severe dietary restriction from the time of weaning to the time of death have lived to be more than 1800 days old (188), a life span equivalent to approximately 180 years in humans.

I. DIET AND AUTOIMMUNITY

Normal individuals, humans or animal, are immunologically tolerant to self and thus do not form antibodies to fight against native cells. When this aberration does occur, any of several autoimmune diseases may result. These range from the systemic lupus erythematosus to organ-specific diseases such as thyroiditis. It has been noted that autoantibodies occur more frequently in all people, both normal and diseased, as they grow older, an indication that self-tolerance tends to break down during the aging process. It is not surprising, then, that autoimmune disease should be found primarily among the middle-aged and elderly. The etiologies of autoimmune diseases are heterogenous, but the various autoimmune diseases do have many pathological changes in common, including glomerulonephritis, arthritis, and vasculitis. Pericarditis, pleuritis, dermatitis, and/or neuropathy can also be present. Less frequently seen is gonadal failure (211).

Two major factors have been identified in the pathogenesis of autoimmune disease: genetic (e.g. increased susceptibility to infection) and environemntal (e.g. exposure to potential pathogens), both of which can influence immune function (126, 160).

New Zealand Black (NZB) mice have provided investigators with a classic model for study of autoimmune disease (8, 22, 212). At an early age (3–4 months) these animals develop a Coombs positive hemolytic anemia, which in old age is accompanied by renal disease and failure similar to the type found in humans with lupus erythematosus. NZB mice are also prone to develop malignancies of the lymphoid system and other organs.

A related strain of mice, the (NZBxNZW)F_1 hybrid (B/W), is also unusually susceptible to autoimmune disease. Although hemolytic anemia is not a serious problem for them, they do develop a renal disease much like that seen in NZB mice and lupus patients. This lethal disease involves circulating free DNA, DNA-anti-DNA immune complexes and irregular deposits of DNA, complement, and immunoglobulin found in the glomeruli in the capillary basement membranes and on the epithelial side of the basement membranes.

Table 1 Comparison of spleen and thymus weights of NZB mice on normal and low-protein diets

Age (months)	No. of mice	Spleen[a] Mg ± S.E. Normal protein[c]	Spleen[a] Mg ± S.E. Low protein[d]	p[b] value	Thymus (mg) ± S.E. Normal protein[c]	Thymus (mg) ± S.E. Low protein[d]	p value
3–4	8	404 ± 35	397 ± 50	ns	174 ± 9	221 ± 27	ns
7–10	10	744 ± 132	425 ± 57	<.02	66 ± 10	136 ± 12	<.001

[a] Relative weights (100 gm. body weight).
[b] Student T-test.
[c] 22%
[d] 6%

A xenotrophic virus, originally described by Levy & Pincus (126) and later extensively studied by Levy (125), has been implicated in the autoimmune disease observed in both the NZB and B/W mice. Tables 1 and 2 show, in addition, early peaking (at three months of age) and decline (3–5 months) of immunologic function in both strains. By 8–12 months of age, at which time the autoimmune disease usually becomes apparent, many immune functions have all but disappeared.

Fernandes et al (62, 64) became interested in the effect of nutrition on autoimmune disease when they observed that two commercial diets, varying in relative fat and protein content (see Table 3), influenced the health and life span of NZB mice in quite different ways. The diet relatively high in fat and low in protein was associated with increased body weight and breeding capacity, more autoantibodies (largely IgG and IgA) on red cell surfaces, and anemia associated with reticulocytosis. The sera of these animals also contained more DNA antibodies. Compared to the mice on the

Table 2 Induction of GVH reaction by spleen cells of 9 month old mice with or without hemolytic anemia[a]

Protein (%)	Mean body wt. (g)	Mean spleen wt. (mg)	Mean thymus wt. (mg)	Mean hematocrit (%)	Coombs test	Mean spleen index	Positive tested
22	50.7	325	7	50.8	—	1.46	5/8
6	25.0	87	32	49.5	—	2.02	7/7
22	47.7	725	5	40.6	+[c]	0.97	1/7
6	25.7	210	25	38.4	+[c]	1.78	6/6

[a] Each (NZBxA)F_1 8 day-old litter was divided into five groups of 7–10 each and injected with spleen cells (10×10^6 I.P.) from individual mice with defined disease. Controls (Fifth Group) were not injected.
[b] Student T-Test indicates significance of <.01 level between animals on Diet I and Diet II.
[c] Highly positive.

Table 3 Effect of diets with varying amounts of fat and protein on autoimmune-prone NAB mice

Test	Sex	Age	High fat/low protein (g)[a]	Low fat/high protein (g)[b]	p = <
1. Average body weight	M	9 mos.	53.9	43.8	0.001
2. Total number young (mean)	F		241	171	
3. Hemolytic anemia	M	12 mos.	8/8[c]	13/15	0.02
4. Longevity/days SE	M		295 ± 21	456 ± 15	0.001
	F		305 ± 21	367 ± 18	0.05
5. Reticulocyte count % of 500 rbc	M	12 mos.	67.2 ± 9	22.8 ± 5	0.001
6. % Coombs positivity	M	6 mos.	93.7	62.5	0.01
	M	12 mos.	100	93.3	ns
7. Mean hematocrit % SE	M	12 mos.	31.2 ± 2	37.0 ± 1	0.02
8. Mean white blood cell count/mm^3	M/F	12 mos.	13,021 ± 2,869	6,950 ± 622	0.02
9. Hemagglutinating AB titers to SRBC (log 2)					
primary, day 10	M/F	9 mos.	10.5 ± 0.9	11.6 ± 0.2	ns
secondary, day 20			13.2 ± 0.5	12.4 ± 0.2	ns
10. GvH capacity (MSI SD)	M/F	11 mos.	1.10 0	1.67 ± 0	
	M/F	2 mos.		2.03 ± 0	
11. Target cell lysis—% Cr release					
C3H tumor cells	M/F	11 mos.	33	63	
A-strain sarcoma cells	M/F	11 mos.	0	15	
12. Autoantibodies at surface of red blood cells	M/F	11 mos.	greater number, greater variety	no IgA	

[a] 11 % fat, 17% protein
[b] 4.5% fat, 23% protein
[c] Number of animals affected/total number surviving animals

second diet, which was higher in protein and lower in fat, the first group had inferior tumor immunity, a lesser capacity to induce graft-vs-host reactions (GVHR), and a shorter life span.

In a later experiment, Fernandes et al (59) studied the effects of varying the amount of dietary protein, using again the NZB mouse for the experimental model. In this instance a low protein, normal caloric diet helped the animals maintain vigorous immune function longer than controls fed a normal protein, normal caloric diet. Immunoparameters tested included tumor immunity, ability to induce GVHR, the ability to produce antibodies to sheep red blood cells (SRBC), and the mitogenic response of splenic lymphocytes. Longevity was not significantly affected in this experiment.

When dietary protein and/or calorie intake was restricted for the B/W mouse, dissimilar results were obtained (60). It can be seen from Table 4 that protein restriction did not significantly prolong life, whereas calorie restriction did, and to a striking degree for both males and females. In this experiment, B/W hybrids fed a low calorie diet lived twice as long as controls fed a normal diet. Subsequent studies revealed that all of the immune functions that usually fade with age in the B/W mice were much more vigorous in the calorie-restricted animals (54). These included such basic immune functions as cell-mediated cytotoxicity to allogeneic tumor

cells, antibody response to sheep red blood cells, and the ability to initiate GVHR. Most recent reports have indicated, however, that for this strain of mouse, dietary fat is also a crucial variable (106). Animals fed a low caloric diet containing a relatively high proportion of fat have developed all the pathological signs—i.e. autoimmune disease, glomerular lesions, and early involution of immune function—regularly seen in mice fed more calories but a lower proportion of fat. Animals fed a low fat diet lived significantly longer than did controls (106). Diets low in the amino acids phenylalanine and tyrosine have also prevented the development of autoimmune kidney disease and doubled the life span of the B/W mouse, particularly the female (45). Similarly, Hurd et al (105a) interfered with development of this disease by restricting essential fatty acids, and Beach et al prevented and/or delayed the onset of these autoimmunities in autoimmune-prone mice by restricting dietary intake of Zn^{2+} (14a).

That diet is capable of influencing the health and longevity of B/W mice after the autoimmune process is underway has been demonstrated by Friend et al (70). They observed that protection from immune nephritis could be achieved either by moderately restricting protein consumption from the time of weaning or by implementing calorie restriction at a later time—i.e. at 4-5 months of age. In these animals, autoimmune activity can be detected in the form of antinuclear antibodies as early as 2 months of age, while evidence of the lupus-like renal disease syndrome becomes manifest by 4 months.

Table 4 The influence of low calorie intake on survival time of (NZB X NZW) F_1 mice

	Diet		Mean survival time/days	
	Protein %	Calories/day	Female	Male
1.	22 (normal)	20 (normal)	317	350
2.	22	10	550	770+
3.	6	20	306	487
4.	6	10	481	700+
5.	22[a]	20	331	488
6.	22[a]	10	547	700+
7.	22[b]	20	318	440
8.	22[b]	10	467	557

[a] Low unsaturated fat
[b] High unsaturated fat

It has been shown (191) that a low calorie diet that prolongs the life of the B/W mouse inhibits the formation of immune complexes and their deposition in vital organs. In this experiment three groups of mice were fed different diets (ordinary lab chow *ad lib,* special diet with 20 cal/day, or special diet with 10 cal/day). Circulating immune complexes (CIC) were measured by the Raji cell radioimmunoassay at 3, 9, 12 and 18 months. No significant differences were found at any age in CIC levels of animals fed regular lab chow and those fed 20 cal/day. At three months, CIC levels were normal for all three groups. At the nine month point an increase was noted in the CIC levels of both sexes in each dietary group. Highest CIC values were found in animals fed regular lab chow at 12 months. Most of these animals died soon thereafter. Mice on the low calorie diet, however, had, at 12 months, CIC values significantly lower than those of either other group. Male mice on the low calorie diet had, at 18 months, lower CIC values than at 12 months, while the control female mice died in the interim between 12–18 months. Those few female control mice still living at 18 months that had been fed the higher calorie diets maintained high levels of CIC.

Inhibition of Other Disease by Dietary Restriction

When dietary restrictions have been applied to other strains of mice not so susceptible to autoimmune disease, or to rats, varying results have been obtained. In 1939, McCay reported that growth-retarded rats subjected to a calorie-restricted diet for periods of 300, 500, 700, and 1000 days all lived longer than did controls fed a normal diet throughout. Other investigators have reported that varying levels of protein restriction had no effect on the longevity of female Sprague-Dawley rats (154). A low calorie diet has not significantly prolonged the life of DBA/2 (see Table 5) or C3H mice. DBA/2 mice, however, have responded favorably to protein restriction begun at the time of weaning. Such a diet has significantly prolonged their life (60).

Table 5 The influence of a low protein diet on longevity of the DBA/2 mouse

Diet		Mean survival time/days		20% survival (days)		Longest survival (days)	
Percentage of protein	Cal/day	Female	Male	Female	Male	Female	Male
22	20	434 ± 53	420 ± 33	650+	524	650+	560
22	10	414 ± 26	357 ± 40	512	444	560	498
6	20	525 ± 46	625 ± 46	650+	650+	650+	650+
6	10	429 ± 46	525 ± 29	550	650	600	650+

C3H female mice, which are prone to develop spontaneous mammary adenocarcinoma, do not do so when fed from weaning a diet restricted in calories (61, 214, 228). Spleen cells from C3H mice restricted to 10 cal/day responded more vigorously to T cell lectins PHA and Con A than did spleen cells from mice fed a conventional diet containing 16 cal/day. The primary PFC response of the calorie-restricted animals, however, was significantly reduced (2091 PFC/spleen vs 10,131 PFC/spleen) four days after immunization with SRBC. In contrast, the secondary PFC response was equivalent in both groups. When spleen cells from both groups were injected into lethally X-irradiated mice, a larger number of PFC/10^6 cells was generated from spleens of calorie-deprived donors. By measuring DNA synthesis in vivo, a suppressor effect was found in spleen cells of calorie-deprived mice. These experiments demonstrated that thymic-dependent cell function, as well as suppressor cell function, remains vigorous in spite of moderate calorie restriction. The interesting possibility that the increased suppressor cell activity observed in the calorie-restricted animals might also be suppressing directly the development of mammary cancer was raised. But, of course, enhancement of immunity by a low caloric diet might also result in an increased specific immunity to tumors (i.e. an antithesis of the "suppressor effect").

More recent studies, however, have shown that the primary effect of calorie restriction in this model comes from the reduction of the fat content of the diet. C3H animals fed low caloric diets with a high proportion of fat have had a high incidence of breast cancer, while those fed a low calorie, low fat diet were largely tumor-free (81).

Good et al (81) have shown that, in C3H mice, restriction of calories and fat inhibit the development and maturation of B type RNA virus particles in mammary cells. The dietary restrictions required to inhibit breast cancer in C3H mice, although perhaps delaying the onset of estrus, permit estrus cycling in an apparently normal fashion. Such diets also appear to permit conception and reproduction. Recently, following a lead from a group studying at the Lilly Laboratories (246) who showed that dihydroepidandrosterone (DHEA) inhibited weight gain at a certain level, Schwartz has employed DHEA to inhibit mammary tumor development in C3H mice (198). DHEA both inhibited weight gain in the mice and completely inhibited mammary adenocarcinoma development in female mice of this strain. Thus it seems likely that both tumor development and weight gain can be inhibited by intake of DHEA. What remains to be determined is whether the DHEA is operating to reduce breast cancer through influence on assimilation or metabolism of food, or through a more direct influence and change in the mammary tumor cells.

Dietary restriction has also exerted dramatic influences on the mice of the

very short-lived *kd/kd* mutant strain (128). Mice of the strain bearing this autosomal recessive trait live extremely short lives because they develop progressive nephronophthesis and renal failure. They usually die by 240 days of age. Such animals also develop autoimmune hemolytic anemia relatively early in life, which progresses as they grow older. Calorie restriction from the time of weaning prevents the development of interstitial nephritis, the progressive glomerular and tumular damage, and the autoimmunity that characterizes such mice (63). Whereas the great majority of putatively well-fed mice died of renal failure by 240 days of age, none of the group fed a restricted diet, reduced in total calories by approximately one third that given the controls, had died by 240 days. Changing half of the animals to the higher calorie intake at 240 days of age led to the rapid development of autoimmunity, interstitial nephritis, nephronophthesis, and death within 60 days. By contrast, all the mice that were continuously fed the low calorie intake survived beyond 300 days, and well over half of them lived to two years. For this strain also, total calories seemed a crucial variable. Protein, on the other hand, was not so important, since feeding diets of widely different protein compositions, ranging from 6% to 20% of the diet, did not alter the outcome of their genetically determined disease. Thus, for this strain, as for certain other autoimmune-prone strains studied, calories and fat especially and, to a much lesser extent, protein are crucial variables in determining length of life (63).

Another autoimmune-prone strain of mice, MRL/lpr, was similarly studied in our laboratories. In these mice, development of autoimmunity, apparent immunocomplex-based renal-vascular disease, a dramatic lymphoproliferative disorder, and early death are all strikingly delayed or inhibited entirely by restriction of dietary calorie intake from the time of weaning (55, 56). The vigor of immunity functions is also maintained by restricting the diet, and the animals' life spans are at least doubled.

Thus in several especially short-lived inbred strains of mice, autoimmune phenomena, diseases based on autoimmunity and immune dysfunction, vascular disease, renal disease, immunodeficiency occurring with aging, and even serveral forms of cancer in mice and rats can be very much inhibited by dietary restrictions imposed both early and later in life (70).

These findings indicate that nutritional factors can exert profound influences on immunity functions and immunoregulatory mechanisms, and can inhibit pathologic perturbations that occur with aging in mice and rats. Whether these leads can be exploited and applied to the prevention of diseases of aging that occur relatively early in life in certain humans depends, we believe, on thorough analysis of the cellular, endocrinological, and molecular bases of these most extraordinary influences of diet. We are optimistic that such leads can, indeed, be exploited to greatly prolong health

in humans who, like the short-lived autoimmune-prone mice, so regularly sicken and die with the same kinds of diseases of aging that plague these short-lived autoimmune-prone mice. The latter include cellular and humoral immunodeficiencies and consequent increased susceptibility to infection, autoimmunity and autoimmune diseases, hyalinizing renal disease, vascular diseases including arteriosclerosis and atherosclerosis, and amyloidosis. It is to be hoped that mechanisms like those found to underlie dietary prevention of the autoimmune diseases in experimental models may also permit manipulations that will make possible improved treatment or prevention of diseases associated with aging in humans.

T Cell Immunodeficiencies in Malnutrition—A Paradox

In parallel studies, which had been initiated by field observation in Egypt, Uganda, Thailand, and Austrialia, a paradox relating to nutrition and immunity was encountered. In most circumstances, protein or protein-calorie malnutrition (PCM) in the field was accompanied by profound immunodeficiency involving both T cell-mediated immunity and humoral immunity.

Paradoxically, although many antibody responses are deficient in PCM children, Ig levels were not always depressed. Indeed, in many circumstances Ig levels were elevated in children suffering from PCM (81). It is of special concern that in so-called protein calorie malnutrition in field studies, T cell-mediated immunity is usually severely depressed (81). Deficiencies of complement and defects of the effector cellular functions may also be observed in patients with PCM (81). By contrast and paradoxically, in all species studied, especially mice, guinea pigs, rats, and even monkeys, protein or protein-calorie restriction actually increased certain cell-mediated immunodeficiencies. Cell-mediated immunological functions that were actually enhanced by chronic protein or protein-calorie restriction in mice include proliferative responses to T-cell phytomitogens, delayed hypersensitivity, allograft rejection, tumor immunity, and MIF production. By contrast, these studies showed a depression of antibody production reflected by reduction in formation of antibody-producing cells in mice when protein, or protein and calories, were restricted. Whereas most cellular immunity functions were enhanced by dietary restriction in all species studied, antibody production was depressed in almost a linear diet dose-dependent fashion. The paradox to be resolved then was: Why, in contrast to these experimental findings, do protein and protein-calorie malnutrition in humans lead so regularly to profound cell-mediated immunodeficiency?

At least a partial resolution of this apparent paradox has come from the studies of the influence of zinc on immunity function (57, 197). Much of the cell-mediated immunodeficiency seen in the protein malnutrition and

PCM syndromes in humans appears to be attributable to concomitant deficiencies of intake of the element zinc (77, 79), under the circumstances that produce protein and protein-calorie malnutrition in the field. This deficiency does not exist when the circumstances of protein or protein-calorie deficiency are produced in the laboratory (58).

II. THE ROLE OF ZINC IN THE IMMUNE RESPONSE

Two "experiments of nature," one in animals, the other in humans, have provided evidence that adequate supplies of zinc are essential to the development and maintenance of a healthy immune system, particularly the cell-mediated arm of the system. A46 mutant cattle of the Dutch Friesian type inherit an inability to absorb zinc properly. Apparently healthy at birth, within the first few weeks of life they begin to show common signs of the disease, among them lethargy, a scruffy coat with patches of alopecia, tender skin lesions around body orfices and acral areas, bowed hind legs, joint pain, growth arrest, and extreme susceptibility to infection. Supplementary zinc treatment will bring complete and rapid remission, but in the absence of zinc therapy, the calves die at an early age, most of the deaths being due to infection (7, 24, 25, 152, 237).

Postmortem examination of these animals reveals a thymus that is strikingly small and involuted, as well as a generally hypoplastic lymphatic system. Immunological studies (24) have shown that affected calves had normal levels of IgA but significant elevation of IgG_1, IgG_2, and IgM. There was no lymphopenia but increased numbers of large immature lymphocytes. Early antibody response to tetanus toxoid was normal in the sick animals, but late phases of the primary response, measured on days 28 and 42, were diminished. Cell-mediated immune responses against DNCB and tuberculin tests were impaired. Thus, while the cell-mediated immune response is severely impaired in these animals, humoral immunity remains relatively intact. All of the above-mentioned immunological abnormalities in the A46 animals could be corrected, as were other signs of the disease, by adequate amounts of zinc given either orally or parenterally.

Clinical Studies

Acrodermatitis enteropathica (AE) is the human analog of the disease found in A46 cattle. First signs appear during infancy, often at the time of weaning, and include, in part, skin lesions on body extremities and around the orifices, diarrhea and anorexia, alopecia, severe growth retardation, mental disturbances that take the form of extreme irritability, withdrawal and/or lethargy, and easy susceptibility to infection (21, 40, 97–99). Supple-

mentary oral zinc, usually 150 mg given thrice daily in divided doses, can quickly correct all evidence of disease, but without treatment morbidity and mortality are high and death is most often due to infection.

Few precise immunological investigations of children with AE have been undertaken. When done, defective immune structure or function has been found. Autopsy exams have revealed thymuses that were undersized (112, 226), grossly absent (185), or depleted of lymphocytes (162). Lymphocytes obtained from a child dying from AE had decreased responses in vitro to stimulation with PHA (48). Several studies have demonstrated diminished or absent delayed hypersensitivity responses (12, 42, 87, 88, 156, 218). More than 50% of AE patients tested had normal levels of IgG, IgM and IgA, but some deficiencies have been reported (17, 107, 112, 162, 219). Depressed cellular chemotaxis of monocytes in vitro has been reported for three patients with AE (240), an abnormality subsequently corrected with zinc therapy.

Patients with AE suffer from a wide array of complaints, many of them similar to those found in children with severe PCM. And, indeed, there is much shared territory between the two groups (77, 146, 147, 153). Anorexia, a ubiquitous finding in AE patients, who almost always are severely underweight and sometimes described as marasmic, leads to some degree of PCM. PCM patients, in turn, are almost always found with low levels of zinc in their blood (26, 77–80, 120, 123, 194, 233, 247).

Several factors, in addition to low intake of dietary zinc, have been suggested as reasons for the presence of zinc deficiency in children with PCM. These include low levels of plasma proteins, among them albumin and transferrin, which are necessary for the transport of zinc; further intestinal loss of plasma protein or zinc due to diarrhea; metabolic changes caused by infection or stress that result in decreased levels of serum zinc (165, 194, 231); and/or a high dietary intake of zinc-binding fibers or phytate, which reduce the bioavailability of oral zinc (158, 183).

Golden & Golden have been first to study the relationship between zinc and immunoincompetence so regularly found in malnourished children. They found that the thymic atrophy associated with PCM could be reversed when treated with supplementary dietary zinc acetate (80). A subsequent study showed a significant negative correlation between plasma zinc levels in malnourished children and the efficacy of topical zinc sulfate in enhancing the delayed hypersensitivity response (79).

The extreme PCM seen in underdeveloped areas of the world or in chronically ill patients is only one of many examples of an acquired secondary zinc deficiency (see Table 6). Gastrointestinal disorders that cause malabsorption or excess excretion of zinc and/or intake of foods or drugs that chelate zinc and thus hinder its absorption, are other means by which

Table 6 Some means by which zinc deficiency is acquired

Cause or associated condition	References
1. Dietary/nutritional cause	
a. Excess phytate, fiber	150, 175, 183
b. Kwashiorkor[a] + other PCM states	77–80, 105, 123, 233, 247
c. "Marginal" undernutrition	91, 93, 192
d. Infants on formula with no added zinc	111, 230
e. Vegetarian diet	19, 69
2. Gastrointestinal problems	
a. Intestinal mucosal disease[a]	144, 206
b. Malabsorption syndrome	90, 132, 142, 229
c. Intestinal bypass	10, 75, 239
d. Cholecystectomy	216, 238
e. Crohn's disease	130, 204
f. Celiac sprue	205
g. Short bowel syndrome	203
3. Iatrogenic causes	
a. Drugs	
oral contraceptives	90
penicillamine	122
corticosteroids	65, 101
b. Total parenteral nutrition	16, 23, 104, 114–116, 159, 178, 196, 203, 207, 220, 235, 245
c. Major surgery or trauma	20, 75, 89, 127
4. Genetic or congenital defects	
a. Acrodermatitis enteropathica	13, 151
b. Down's syndrome	18, 90, 145
c. Cystic fibrosis	44, 90, 109
5. Infectious disease	50, 90, 127, 165, 202, 227
6. Hematological disease	
a. Hemolytic anemia	174, 200
b. Sickle cell anemia	176, 177
c. Pernicious anemia	187
d. Leukemia	42, 50
e. Hodgkin's disease	1, 11, 76
7. Renal problems	
a. Nephrotic syndrome	221
b. Renal failure	37, 90, 135–139, 186
c. Renal dialysis	9, 90
d. Renal transplants	48
8. Liver disease	
a. Cirrhosis	47, 187, 209, 210, 223–229, 236
b. Other	90

Table 6 *(Continued)*

Cause or associated condition	References
9. Miscellaneous	
a. Pregnancy and lactation	90, 102, 110, 187, 192
b. Alcohol abuse	100, 131, 133, 209, 217, 238, 242
c. Severe burns	28, 36, 39, 103, 124, 157, 173
d. Diabetes mellitus[a]	5, 168, 169, 215
e. Pancreatic defect	242
f. Neoplastic disease[a]	2, 41, 50, 74, 187, 196a, 242
g. Blood loss due to parasitic infection	175, 193
h. Anorexia nervosa	29, 49
i. Psoriasis[a]	82, 83, 171, 172, 244
j. Rheumatoid arthritis	84, 119, 170
k. Myocardial infarction and other heart problems	50, 90, 126
l. Thalassemia	174
m. Lupus erythematosus	129
n. Severe hypogammaglobulinemia	27, 38

[a] denotes inconsistent findings

one can become zinc-deficient. Metabolic conditions resulting from severe burns, surgery, infection, or chronic abuse of alcohol can create a zinc-deficient state. Zinc deficiency is also seen in liver disease, prolonged total parenteral feeding when inadequate amounts of zinc have been added to the solutions, some cancers, and blood loss due, for example, to parasitic infestation.

An acquired zinc deficiency may, in fact, be much more prevalent than commonly realized (3). Recent studies of zinc status in apparently normal Americans have shown that the zinc content of the average American diet may be borderline (91, 92, 230). Currently, the recommended daily allowance for zinc is 15 mg for adults (66), but this allowance is predicated on both normal bioavailability of the zinc ingested and on normal metabolism. Sandstead (192) reported that in the United States those most at risk of consuming too little zinc in their daily diet included some infants (particularly those on a formula unfortified with zinc), pregnant women, teenage and college women on self-selected diets, institutionalized people, and many living on low income diets.

Immunologic studies of patients suffering from iatrogenic zinc deficiency due to inadequate total parenteral nutrition are of special interest because these patients are not simultaneously deficient in either protein or calories. Different reports have found very low levels of IgG (207), impaired skin hypersensitivity (161, 164), decreased numbers of T cells (161), and a

depressed response in vitro to mitogenic stimulation (161, 164). All of these abnormalities returned to normal after zinc therapy.

Low levels of serum zinc have also been found in patients with severe hypogammaglobulinemia and one with idiopathic pulmonary fibrosis (38). Oral zinc therapy, in the absence of any other treatment, was associated with an improved lymphoproliferative response to antigens and mitogens in these patients. T and B cell number, including T cells bearing receptors for IgG and IgM, was normal both before and after zinc therapy. Zinc treatment did nothing to improve immunoglobulin levels, but thymopoietin levels, which were low initially, returned to normal in several instances.

In our laboratories, abnormal blood zinc levels have been found in cancer patients, most often when undernutrition was also present (74). Epitheliomas of the head and neck region, which interfere with food intake, were accompanied by low levels of zinc, but not cancer of the breast (73). Immunodeficiencies observed in patients with head or neck cancer were corrected by oral zinc therapy (74). Certain malignancies, however, such as Hodgkin's disease, are associated with low levels of serum zinc that cannot be explained by a dietary deficiency of the trace metal. In these instances abnormal zinc metabolism must be suspected.

The biochemical importance of zinc in the body environment began to be elucidated years ago when it was discovered that zinc was a necessary component of the carbonic anhydrase found in red blood cells (117, 118). Today we know that the proper structure and/or function of more than 90 metalloenzymes depends on the presence of zinc. Included among those metalloenzymes, in addition to carbonic anhydrase, are alkaline phosphatase and many involved in RNA and DNA synthesis, such as thymidine kinase, DNA polymerase and DNA-dependent RNA polymerase (184). With its active participation in protein synthesis and cell division, zinc may be especially important during life stages involving rapid growth and division of cells, such as pregnancy, infancy, and adolescence.

The immune system also depends on rapid proliferation of cells in order to be effective, and it is therefore not surprising to find that, in zinc-deficient men and animals, the function of the immune system is impaired. It has been shown that white blood cells are rich in zinc (222). While red blood cell zinc accounts for 75% of the zinc in whole blood, plasma zinc for 22%, and white blood cell zinc for only 3%, an individual leukocyte contains approximately 25 times the amount of zinc as does a single erythrocyte.

It has likewise been demonstrated that lymphoid cell surface receptors are sensitive to zinc. In vitro addition of small amounts of zinc chloride to lymphocytes derived from both healthy donors and cancer patients has enhanced spontaneous formation of rosettes with SRBC (134). Several studies have attested to the mitogenic effect of zinc when added to lym-

phocytes in vitro, either by itself or in addition to PHA (6, 15, 31, 72, 95, 96, 121, 166, 167, 182, 189, 190, 243). Zinc is, in fact, the only known naturally occurring lymphocyte mitogen to be found in the body. Recent experiments have demonstrated, however, that its success as a stimulant is dependent on the presence of monocytes (189). It is also apparently an age-dependent phenomenon. Rao et al (182) have reported that lymphocytes derived from young people had more of an enhanced mitogenic response to zinc than did cells derived from older subjects.

Animal Studies

Severe involution of the thymus and other lymphoid tissues have been found in many species of zinc-deficient animals (Table 7). Other aspects of the immune response, particularly those associated with cell-mediated immunity, have also been adversely affected. Circulating thymic hormone levels have been markedly low in A/J mice following three weeks of a zinc-deficient diet. By experimental week number 17, they had disappeared altogether (108). This was promptly corrected, however, when the animals were replenished with zinc. Progressive loss of relative and absolute number of Thy-1.2 cells, with a proportionate increase in the relative number of cells bearing Fc receptors, have been noted in the spleen of mice and rats experimentally deprived of zinc (30, 57).

Investigators have speculated that raised levels of plasma cortisol may contribute to the deterioration of the immune system, as adrenal glands are enlarged in zinc-deprived animals (179, 180), and it is known that the

Table 7 Studies of the thymus in zinc-deficient animals

Animal	Nutritional status	Thymic atrophy present	Reference
A46 cattle	Low weight	+	24, 25
Pigs	Low weight	+	201, 241
Piglets	Low weight	+	143
Rats	Low weight	+	30, 179, 180
S/D rats	Low weight	–[a]	51
Mice	Low weight	+	57
Mice	Not mentioned; presumed to be low	+	14
BALB/c mice	Low weight	+	71
A/J mice	Low weight	+	213
A/J mice, young adults	Low weight	+	68
Mice, adult	Low weight	+	67

[a] On zinc-supplemented diet, these animals had enlargement of thymus and spleen.

thymus and lymph nodes are adversely affected by hyperadrenocortical activity (45, 195, 234). Recent studies with adrenalectomized mice, however, have established that the depletion of thymic hormone seen in zinc-restricted animals is not due to pituitary adrenal hyperactivity (108a).

There are many additional reports of cell-mediated immune irregularities in zinc-deficient animals. Some of these observations include an abnormal migration of circulating lymphocytes (71), an increased number of immature T cells (155), and a diminished mitogenic response in vitro to PHA (85, 163) that could be restored, in one instance, by adding levamisole, an immunostimulatory agent, to the culture (86). Fernandes et al (57) have reported that zinc restriction in mice has a differential effect on T killer cell activity. They noted reduced natural killer cell activity, a normal antibody-dependent cell-mediated cytotoxic response to chicken erythrocytes, and a depressed allogenic cytotoxic T cell response to EL-4 tumor cells after in vivo immunization. Several studies have demonstrated defective T helper cell funtion as well (30, 57, 68, 213).

The humoral immune response of animals experimentally deprived of zinc from weaning has remained more normal than has the cell-mediated response. Activated B cells have proliferated and produced antibody despite exposure to extended periods of zinc restriction (68). In this particular experiment, cells of zinc-restricted mice produced normal numbers of IgM plaques in response to SRBC, but very low levels of IgG, or indirect (T dependent) plaques when compared to control values. Other mice, however, deprived of zinc since the first day of birth (most experiments have initiated zinc restriction at the time of weaning) had dramatically diminished direct splenic plaque-forming cell responses to SRBC. These animals also had highly irregular immunoglobulin levels, with no detectable IgM, IgG_{2a} and IgA, but greatly elevated serum levels of IgG_1 (14).

Individual complement component activity has been influenced, either inhibited or enhanced, by the addition of different levels of zinc chloride in vitro (148, 149). It was thought that zinc had to be present as a reactant during the activation and/or the binding step of each component in order to have an effect (148). Phagocytosis can also be affected by varying levels of cellular zinc in both animals (33–35, 113, 165) and humans (208, 232). It has been suggested that zinc regulates macrophage function through a direct effect on the plasma membrane (32–34) and through its influence on enzymes involved in phagocytic activity (248). Zinc is also able to stimulate macrophage spreading in vitro (181) and to inhibit lysosomal activity (4). Macrophages of rats and guinea pigs have migrated in vitro at a rate inversely proportional to the level of dietary zinc. That is, cells from animals on a low zinc diet migrated most, while those from animals on a high zinc diet migrated the least (248).

Table 8 The immune response in AE and other zinc-deficient states of man and animal

Immunoparameter	Acrodermatitis	Acquired zinc deficiency in humans		A 46 mutant in cattle	Experimental animals deprived of zinc
		PCM	Other		
I. HUMORAL IMMUNITY	Generally intact but may be low	Less affected than CMI		Less affected than CMI	Less affected than CMI
B cell number	Generally normal	Often N	Often N	Normal	Often normal
Immunoglobulins					
IgM	Variable; 55% N	N or ↑	Variable	↑	Highly irregular when Zn^{-} diet imposed at birth. By 4 wks, no IgM, IgG_{2a} or IgA; greatly elevated IgG_1 in outbred mice.
IgG	Variable; 62% N	N or ↑	Variable	↑ ($IgG_1 + 2$)	
IgA	Variable; 57% N	↑ or N		↑	
Secretory IgA		Low			
Antibody response					
T independent		Variable; often N		Early response N Late response ↓	Near normal
T dependent		Impaired	Impaired		Impaired
Autoimmune activity	Some				
II. CELLULAR IMMUNITY	Impaired	Impaired	Impaired	Impaired	Impaired
T cell number	Variable	Reduced	Variable, usu. impaired	Reduced; ↑ no. of large immature lymphocytes	Reduced
T cell function					
Suppressor cell	??	Impaired?	Impaired	▮	Impaired
Killer cell					Impaired in vivo; N in vitro with zinc
Helper		Impaired	Impaired		Impaired
Delayed hypersensitivity	Impaired	Impaired	Impaired	Impaired	Impaired
In vitro lymphocyte transformation					
PHA	Variable	Usu. low	Usu. impaired	Reduced; ↑ no. of large immature lymphocytes	Impaired, N or ↑
Con A			Impaired		Impaired
Specific antigens			Impaired		Impaired
Lymphokine production		Low			

SUMMARY

Nutrition exerts profound influence on immunological functions effecting both cell-mediated (humoral) and T cell-mediated (cellular) immune functions. Even the interaction of the immune systems can be profoundly influenced by restrictions or excesses of dietary constituents. In experimental systems where it is possible to control precisely the influence of specific nutriments, development and expression of autoimmune diseases and the associated immunodeficiencies of aging can be delayed by restrictions of dietary protein, protein and calories, fat, zinc, or even essential fatty acids. Tumor immunities likewise can be affected and sometimes even enhanced by restriction of protein, calories, or protein and calories, an influence associated with major delay in development of the experimental cancers—e.g. breast cancer. T cell-mediated immunodeficiencies associated with clinically apparent protein or protein calorie malnutrition are often attributable not to the major nutriment deficiencies per se but to accompanying zinc deficiency, a finding reflecting the vital role of zinc in many immunological functions. Dietary zinc deficiency appears to be responsible, at least in part, for the immunodeficiency that is so regularly associated with certain human cancers, such as epidermoid cancers of the head and neck region.

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