Interactions of Dietary Proteins with the Mucosal Immune System as a Component of Safety Evaluation

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Received January 24, 1984; revised February 6, 1984

Recent and historical data suggest that the interaction of antigenic materials, including food proteins, with the mucosal immune system is an important component of certain diseases, causative either of an important manifestation of or the disease itself. The adequacy of existing knowledge concerning digestion and absorption of dietary proteins, disposition of absorbed antigens, and potential adverse effects to meet requirements of a safety evaluation is addressed. Currently, the immunological consequences of introducing new food proteins (e.g., leaf and bean protein concentrates), new processing technologies (food irradiation, chemical sterilization), and changes in traditional foods through emerging technologies (genetic engineering) can be neither predicted nor routinely measured.

KEY WORDS: dietary proteins; immune complex disease; immunological deficiency syndromes; intestinal absorption.

1. INTRODUCTION

Conflicting reports exist concerning the potential for dietary proteins to contribute to certain systemic disorders, including vascular, renal, and gastrointestinal effects (Brenner et al., 1982; Kritchevsky and Czarnecki, 1983). Clinical and experimental factors frequently investigated are the level of protein in the diet, the nutritional qualities of the dietary protein judged by its ability to supply adequate amounts and an appropriate balance of essential amino acids as well as support synthesis of nitrogen-containing compounds, and the nonprotein constituents naturally associated with different sources, e.g., cholesterol, sterols, and phenolic substances. The potential for a specific protein to survive degradative digestive processes and contribute to systemic disorders as a long-term effect of dietary exposure is difficult to separate from the health aspects of other dietary factors and proteins (Rackis et al., 1979; Yavelow et al., 1983). Substantial evidence of antigen absorption, production of circulating specific antibodies, formation of antibody and antigen complexes, deposition of dietary antigens in tissues, and consequent pathology is lacking in most cases (Allison, 1982). The interactions of the mucosal immune system and dietary proteins influence each of these processes, although the mechanisms are incompletely understood (Bienenstock and Befus, 1980; Dobbins, 1983; Tomasi,

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1976). Available data and scientific opinion suggest that the interrelationship of dietary proteins with the mucosal immune system is an important consideration when evaluating the health aspects of specific proteins as food ingredients.

A body of circumstantial evidence has accumulated concerning the possibility that certain dietary proteins may be instrumental in inducing a primary vascular lesion, which subsequently develops into an atheromatous and finally an atherosclerotic plaque. However, no direct experimental evidence has ever been presented to support this possibility (Clifford et al., 1983; Davies, 1971; Deeth, 1983). That is, no studies have demonstrated conclusively suspect antigens, antibodies, or immune complexes in or underlying the atheromatous lesions.

2. MUCOSAL IMMUNE RESPONSES TO DIETARY PROTEINS

In the United States, dietary protein derives from meat, poultry, and fish (42.3%); dairy products (21.2%); flour and cereal products (18.6%); dry beans, peas, nuts, and soya products (5.4%); vegetables (6.2%); eggs (4.9%); and fruits and miscellaneous sources (1.4%) (United States Department of Agriculture, 1981, p. 36). Infants ingest proteins from few sources, usually breast milk or a commercial formula based on bovine milk or soybean proteins. The sources of proteins in the diets of older children and adults are more diverse and the relative proportions continually changing. For the majority of commercial food formulations, functional, sensory, nutritional, and economic factors play primary roles in the selection of protein ingredients (casein and whey from bovine milk, gelatin and collagen from animal hides and tendons, soy protein and isolates, and gluten from the flours of wheat, corn, and oats). Immunological considerations are of increased importance when formulating infant formulas, enteral nutrient mixtures, hypoallergenic foods, and other foods for special dietary purposes. For example, some pediatricians have questioned whether changes in nonprotein ingredients or processing procedures could inadvertently increase the antigenicity of infant formulas (Eastham and Walker, 1979). Theoretically, new sources of food proteins, wider distribution of current sources, new food processing procedures, and chemical modifications of proteins could initiate unpredicted immunological and other biological effects in persons consuming these new or chemically altered dietary proteins.

2.1. Oral Tolerance

In experimental animals, a phenomenon termed oral tolerance or hyporesponsiveness actively suppresses the development of systemic antibodies against soluble protein antigens that have been ingested as a single, large dose or repeated feedings of smaller doses (Tomasi, 1981). A similar phenomenon also occurs in humans. Ingestion of antigen can lead to stimulation of mucosal immune responses and production of suppressor T cells that suppress systemic responses to subsequent parenteral challenge (Hanson et al., 1979a,b; Richman et al., 1978, 1981). Suppression of humoral and cellular immunity is mediated by a variety of as yet poorly defined suppressor cells, probably T cells, and related soluble factors, which may be antibodies, modified antigens, anti-idiotypes, complexes, or various soluble cell-derived
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factors (Sy et al., 1980; Takaoaki et al., 1982). Investigations of the mechanisms of
 tolerance induction (oral and systemic) are of potential importance in understanding
 the immunological nature, e.g., determinants of antigenic structure (Hopp and
 Woods, 1981), and physiological responses of humans to food proteins (Rothberg,
 1969). For example, the importance of antigen configuration and distribution was
demonstrated by Rubin et al. (1981), who studied an animal model in which
susceptibility to proteolysis of one protein determined the type of immunological
response of the mucosal immune system to a second protein associated with a viral
coat complex. Observed responses depend on many variables, including experi-
mental animal species under study, dosage, and properties of ingested antigens.
Additional understanding of the processes by which ingested antigens affect gastroin-
testinal immune responses is required before ascribing a role to oral unresponsiveness
in normal protein digestion or in adaptation to food sources.

3. ABSORPTION OF PROTEINS

The scientific community holds diverse opinions on mechanisms and quantita-
tive aspects of the absorption of antigenically intact proteins (Walker, 1981). Several
methodologies are used to estimate the extent of protein absorption across the
intestinal epithelium and great care must be taken when interpreting and comparing
absorption data (Udall et al., 1981a). The quantities appear to be of possible
immunological significance, but of little importance in terms of protein nutrure
(Ho and Clifford, 1976; Udall et al., 1981b,c).

Age and dietary history alter immunological response to ingested antigens both
in experimental animals and humans (May et al., 1982). In infants, the presence of
circulating antibodies to specific food proteins indicates exposure rather than
existence of a food sensitivity that will correlate with clinical symptoms (May et al.,
1980). The occurrence of antibodies to bovine milk proteins is 100% in serum of
children ingesting bovine milk if their immune systems are functioning normally
(Bock, 1980). However, when carefully measured, elevated titers (above normal) of
antibodies to milk proteins suggest intestinal disturbance from either food sensitivity
or other disorders. The physiological significance of immune system reactions to
ingested antigens during maturation is an area of current investigation (Gruskay,
1982; May et al., 1982). Lactating women secrete antibodies in their breast milk
directed against food antigens they ingest (Cruz et al., 1981). It is possible that breast
milk secretory IgA ingested by infants reduces absorption and thus modulates
the type of immune responses to repeated ingestion of specific antigenic materials, e.g.,
favoring an IgA rather than an IgE response. If this immunological mechanism is
efficient and compensating, it could help explain why the incidence of "true allergy"
(IgE mediated) is low and considered unlikely to account for food intolerance in
most cases (Buckley and Metcalfe, 1982; Burr and Merrett, 1983).

3.1. Site of Absorption

Antigenic molecules are envisioned as potentially crossing the intact gut mucosal
barrier at two sites: (1) the more numerous columnar epithelial cells of the villi and
(2) specialized cells (M cells) of the epithelium overlying gut-associated lymphoid tissue (GALT), such as Peyer's patches.

Absorption via the columnar epithelial cells (Fig. 1) is greatly influenced by both species and age; this route appears to play no prominent role in humans, but is an important site of immunoglobulin absorption in lower animals (Walker and Isselbacher, 1974). After entering invaginations of the cell surface between microvilli, proteins or other materials that have been tested appear in vesicles or phagosomes via a tubular network in the apex of the cell (Owen, 1977). Lipid, horseradish peroxidase, ferritin, metal colloids, and adenoviruses are among the materials transported by this mechanism in experimental models. Lysosomes combine with

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**Fig. 1.** General mechanisms for the uptake and transport of macromolecules by the intestine. (1) Intracellular uptake. After adsorption and endocytosis by the microvillous membrane, macromolecules are transported in small vesicles and larger phagosomes. Intracellular digestion occurs when lysosomes combine to form phagolysosomes. Intact molecules that remain after digestion are deposited in the intercellular space by a reverse endocytosis (exocytosis). (2) Intercellular uptake. Alternatively, macromolecules may cross the "tight junction" barrier between cells and diffuse into the intercellular space. [From Walker and Isselbacher, (1974), with permission.]
these vesicles and hydrolyze their contents; however, unhydrolyzed materials may be extruded from vesicles into extracellular species if lysosomal capacity is exceeded. On the other hand, some evidence indicates that the membranes of columnar epithelial cells are more selective or bind fewer different ingested materials than the membranes of M cells (Wolf et al., 1981, 1982).

The M cells provide a specific site for antigens to pass from the lumen into the intestinal lymphoid system (Fig. 2). Owen (1977) documented with light and electron microscopy the presence of horseradish peroxidase (HRP) in lymphocytes of 2-month-old male, white Swiss mice after a specific absorption sequence: HRP adhered to the M-cell surface (also to the surface of columnar cells); adhesion extended into surface “pits” in M cells; HRP appeared in vesicles within the M cells (but not columnar cells); and HRP was released into the extracellular space between the lymphocytes and M Cells. Most available data support the hypothesis that M cells

HORSE-RADISH PEROXIDASE TRANSPORT ACROSS LYMPHOID FOLLICLE EPITHELIUM

1) ADHERENCE

2) PINOCYTOSIS BY M CELL

3) VESICULAR TRANSPORT

4) RELEASE INTO EXTRACELLULAR SPACE

5) UPTAKE BY LYMPHOCYTES

6) LYMPHOCYTE MIGRATION

Fig. 2. Diagram summarizing the stages observed in the transport of horseradish peroxidase (HRP) by the M cell from the intestinal lumen to the intraepithelial lymphocyte. C, Columnar cells; L, lymphocytes. [From Owen (1977), with permission.]
are important sites for limited absorption of protein antigens in human beings. Antigens do not necessarily enter the systemic circulation by this route. LeFevre et al. (1979) concluded that most transported antigens are taken up by local macrophages within the Peyer's patches. This "antigen sampling" may represent a source of stimulation necessary for effective proliferation of IgA-producing cells and of the mucosal immune system, but the role of the M cell in developmental sequelae requires further investigation. The route of entry through which ingested antigens may enter the systemic circulatory system remains to be demonstrated through experimental observations.

3.2. Conditions Increasing Absorption

A relative deficiency of intestinal secretory IgA, an affinity of antigenic materials and epithelial cells in the immature gut, enhanced pinocytosis of macromolecules, and decreased intraluminal proteolysis are among factors that could promote uptake (Ammann and Hong, 1971). Moroz and Yang (1980) suggested that the low molecular weight, resistance to proteolysis, and stability to acidic conditions of Kunitz soybean trypsin inhibitor may enhance its absorption. Increased passage of antigens through the gut into the systemic circulation is known to occur after jejunostomal bypass surgery and possibly with other gut permeability defects (Utsinger, 1980; Vanderhoof et al., 1980). Increased uptake of antigens by nonspecific diffusion rather than pinocytosis has been observed in animal models, for example, after ionizing irradiation treatment, administration of antimetabolites, and osmotic loading from tube-feeding mixtures, and, more commonly, feeding protein-deficient diets (Rothman et al., 1982; Worthington and Syrotuck, 1976).

Bloch and Walker (1981) observed that the association of intraluminal proteins with the wall of the duodenum and other parts of the small intestine was enhanced nonspecifically by local intestinal hypersensitivity, and postulated that such proteins might induce an IgE antibody response and thus increase the range of anaphylactic sensitivity. The IgE-mediated responses may exclude the specific antigen while enhancing nonspecific absorption of others. Roberts et al. (1981) demonstrated this phenomenon in hooded Lister rats that produced IgE antibodies against ovalbumin and absorbed more β-lactoglobulin from a mixture with OVA than when β-lactoglobulin was administered alone. Such observations provide evidence of a mechanism by which an IgE sensitivity to one food antigen might contribute to the development of sensitivities to other antigens by mediating change in gut permeability, increasing uptake of antigens from the lumen, induction of additional IgE reactions, and elaboration of local sensitivities.

3.3. Control of Absorption

The weight of evidence is compelling that physiological mechanisms severely restrict the absorption of antigenically intact dietary protein. Antigens combining with antibodies in the glycocalyx would be restricted from reaching the enterocyte membrane where they could be taken up by pinocytosis (Walker, 1976). The release of goblet-cell mucus in response to antigen-antibody complex formation within the
intestinal lumen may further lower or prevent interaction of antigens with the mucosal surface. Local antibody response to ingested antigens is thus an important component in limiting the amount of antigenic material absorbed from the lumen of the gastrointestinal tract; the relative importance of the various immunoglobulin types in preventing absorption of antigens is not clear.

Most experts agree that no definable hazard is presented by the low levels of protein antigen absorbed into the systemic circulation, because these antigens are cleared by normal processes such as IgA-mediated elimination of immune complexes by the hepatobiliary route (Russell et al., 1981). Definitive evidence is lacking, however, concerning potential adverse effects from chronic absorption of small amounts of dietary antigens by healthy persons (Parker, 1977).

4. INVOLVEMENT OF MUCOSAL IMMUNITY IN DISEASE

4.1. Immune Complexes

Investigation of cellular and tissue pathology in various disease states provides information on the mechanisms of immune complexes that may be critical to experimental approaches for studying normal responses to food antigens; however, a role for circulating immune complexes containing exogenous antigens in the examples that follow remains speculative. Immune complexes can play an important pathogenic role in certain diseases of vascular membranes, including the coronary arteries (McCluskey et al., 1960), glomerular capillaries (Dixon et al., 1961), and choroid plexus (McIntosh and Koss, 1974).

Physiological roles attributed to circulating immune complexes containing ingested antigens include clearance of absorbed antigens, involvement in tolerance mechanisms, and stimulation of development of the immune system. In most instances, these circulating immune complexes are in very low concentrations, approaching the lower limits of current immunological methodology used to detect them. The complexes or their constituent antigens are seldom studied by nonimmunologically based physical or chemical methods. A confounding factor in available methods of assay for immune complexes is their response to immunoglobulin aggregates (Solits et al., 1979). These aggregates may result from heating sera (a technique used to inactivate certain enzyme systems) or represent idiotype-antidiotype complexes. Thus, both the role of immune complexes in diseases and their very existence are open to question in some instances.

IgA-deficient patients provide the best example of the occurrence of food proteins in circulating complexes. Circulating immune complexes from IgA-deficient patients have been shown immunologically to contain bovine serum and milk proteins (Cunningham-Rundles, 1981).

4.2. Clearance and Disposition

Under normal conditions, the reticuloendothelial (RE) system presumably removes or clears immune complexes through the interaction of the immune complexes with specific cell surface receptors (Fe–IgG or C3) present on macrophages.
It has been hypothesized that defective RE system function may lead to prolonged circulation of immune complexes and thus contribute to tissue damage (Lawley, 1980). Increased levels of circulating immune complexes could overload homeostatic mechanisms and represent a health hazard in such instances (Finbloom and Plotz, 1979). Additionally, antigen structure itself is an important factor in the clearance of immune complexes under some circumstances. In C3H mice, blood clearances and hepatic uptake of orosomucoid-containing complexes with goat antibodies had a \( t_{1/2} \) in excess of 300 min, whereas the \( t_{1/2} \) for asialo-orosomucoid-containing complexes was 15 min (Finbloom et al., 1981).

Dimeric IgA (two IgA molecules connected by a “J-chain” polypeptide) scavenges absorbed macromolecules and eliminates them via a liver transport system that transfers the immunoglobulin and its complexed antigen to the bile (Russell et al., 1981). IgA is of prime importance in the local response to ingested antigens and has been implicated in dermatitis herpetiformis (Katz and Strober, 1978) and the recurrent nephritis described by Berger (McPhaul, 1977). It has been suggested that immune complexes containing IgA and ingested antigens may be important in these diseases (Tomasi, 1976). Gormly et al. (1981) described the association of IgA glomerular deposits and circulating immune complexes in a rat model of cirrhosis. The investigators reasoned that because the liver sequesters antigens derived from the gastrointestinal tract and a large fraction of circulating IgA is derived from the gut, the origin of the deposited complexes might be the gut.

An abnormality in IgA regulation is thought to contribute to renal pathology in Berger’s disease (IgA nephropathy) through an inhibitory effect on clearance of both deposited and circulating immune complexes (Stachura et al., 1981). A high proportion of patients with Berger’s disease have elevated numbers of IgA-positive lymphocytes, suppressor cell defects, selective IgA hypergammaglobulinemia, and the presence of cold-reacting factor in sera. The highly significant increase in the frequency of HLA-DRw4 (a specific histocompatibility antigen) in this form of glomerulonephritis may represent a genetic control of serum IgA levels.

On the other hand, Sakai et al. (1979) concluded that a decrease in IgA-specific suppressor T-cell activity may not be under genetic control in cases of IgA nephropathy. Recently, Hall et al. (1982) have identified the presence of IgA-containing circulating immune complexes in patients with IgA nephropathy. Van der Woude et al. (1983) suggested that multiple food antigens may be responsible for pathogenesis in patients with the combination of selected IgA deficiency and immune complex glomerulonephritis.

Patients with idiopathic glomerulonephritis exhibit impaired clearance of the circulating immune complexes after ingesting a meal, but do not demonstrate abnormal absorption of food antigens (Cairns et al., 1981). The primary defect may involve complement abnormalities or T-cell defects, and the persistence of circulating immune complexes may further modify the humoral and cellular immune function through interactions with cell receptors on immune cells. Defects of Fc-receptor function of macrophages may be responsible for the decreased clearance of circulating immune complexes in patients with systemic lupus erythematosus and dermatitis herpetiformis (Frank et al., 1979; Lawley et al., 1981). Carr et al. (1972) identified antibodies to bovine gamma globulin in sera of patients having systemic lupus.
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erythematous. Normal individuals without immune complexes who possess the HLA-B8 and DRw3 histocompatibility antigens have also been found to have an increased incidence of delayed Fc-mediated clearance. This is of particular interest because these histocompatibility antigens are associated with an increased incidence of a variety of autoimmune diseases. This Fc-receptor defect may play an important role in predisposing these individuals to autoimmune diseases.

4.3. Inflammatory Bowel Disease and Gluten-Sensitive Enteropathy

Within the scientific community, there is general acceptance that inflammatory bowel diseases have an immunological etiology. However, direct evidence to preclude nonimmunological processes is not available. Patients with celiac disease frequently have circulating antibodies to gluten, to gliadin, or to subfractions of these proteins. Adherence to a gluten-free diet eliminates or greatly reduces the titer of these antibodies (Unsworth et al., 1981). Rabin and Singh (1981) suggest that there are a minimum of three different etiologies or pathogeneses of inflammatory diseases of the colon such as ulcerative colitis and Crohn's disease. The mechanisms involve cell-mediated immune reactions against exogenous antigens localized in the colon, immune system reactions against autologous antigens of the colon, or deposition of immune complexes in the colon. Each of these mechanisms offers the hypothetical possibility of food antigen involvement (Falchuk et al., 1980; Fällström et al., 1978). For example, an inflammatory response may be initiated by an aberrant immune reaction to autologous colonic antigens, to one or more ingested antigens, or to a combination of ingested antigens with cell surface antigens.

In the case of gluten-sensitive enteropathy, gluten bound at the surface of certain histocompatibility antigens on the cell surface is the target of T- or B-cell-mediated mechanisms having adverse effects on gastrointestinal functions (Falchuk et al., 1980). The response might be to the histocompatibility antigen, to the gluten, or to the antigenic structure presented by the combination of the gluten and histocompatibility antigen. Gluten-sensitive enteropathy may in fact represent the result of a break in oral tolerance to dietary gluten (Strober, 1980).

Data are available on both sides of the question concerning the induction and pathogenesis of IgA-containing immune complexes in patients with gluten-sensitive enteropathy (Hall et al., 1981; Zone et al., 1982). An association of the level of IgA circulating immune complexes with morphological evidence of gastrointestinal changes suggests that circulating immune complexes containing IgA occur secondarily to the disease process.

4.4. Aspects of Immune Deficiencies and Autoimmunity

Buckley and Dees (1969) found a significant correlation between the deficiency of serum IgA and the presence of milk precipitins. An inability to respond appropriately to certain antigenic stimuli in IgA deficiency has the potential of initiating immunopathological reactions resulting in tissue damage, release of altered antigen, and resultant autoimmune reactions (Ammann and Hong, 1971). The incidence of selective IgA deficiency in various populations is reported between one in 500 to
one in 1000. Most individuals with selective IgA deficiency appear asymptomatic; however, clinically these patients may have repeated upper respiratory infections, allergic symptoms, and a variety of autoimmune disorders, including rheumatoid arthritis and systemic lupus erythematosus. Patients with selective IgA deficiency are a useful group for investigations directed at elucidating the effect of absorbed antigens on systemic diseases. IgA deficiency is associated with a higher incidence of autoimmune disease. This association is perhaps the best (but not incontrovertible) evidence that the normal gut immune system has mechanisms to prevent macromolecular absorption and any possible resulting autoimmune consequences. Cunningham-Rundles et al. (1978) suggested secretory IgA deficiency may be an insufficient reason for excessive gastrointestinal absorption of food proteins that may result from an unidentified immunological mucosal abnormality.

Many immunodeficiency states are not associated with abnormal absorption of food proteins. For example, IgA deficiency per se does not cause increased absorption, because absorption is not observed in X-linked hypogammaglobulinemia. Cunningham-Rundles et al. (1981) have suggested that the chronic excessive permeability of the gastrointestinal tract in patients with IgA deficiency permits the absorption of excessive food proteins that leads to the formation of antigen–antibody complexes and autoimmunity. Clinical autoimmune disorders are found in many types of immunodeficiencies besides selective IgA deficiency. Autoantibody formation in those instances may be favored by partial B-cell or T-cell dysfunction or phagocytic dysfunction.

Evidence from studies of bacterial and viral infections as well as of idiotypic–anti-idiotypic networks is consistent with an important role for the intestinal tract in the initiation of autoimmune processes (Johnson, 1981). For example, Van Snick (1981) described an age-related occurrence of serum anti-IgG autoantibody in normal 129/Sv mice, but not in germ-free animals of the same strain. The autoantibody was produced earliest in the lymph nodes draining the intestinal tract, and was detected at that site before its occurrence in the spleen or bone marrow.

The importance of the bacterial antigenic load from the gastrointestinal tract in the etiology of rheumatoid arthritis via chronic formation of immune complexes containing peptidoglycan remains an area of considerable interest to clinical investigators (Bennett, 1978). An underlying theme is the cross-reaction of antigenic determinants on infectious agents with those of the host components. In genetically susceptible individuals, such antigens might contribute to the mechanisms of chronic arthritis and other inflammatory processes; however, these antigenic determinants are unlikely to be present as dietary components.

Patients with systemic sicca syndrome (primary Sjögren's syndrome with systemic manifestations) have a general perturbation of IgA metabolism with a selective increase in the proportion of circulating polymeric IgA with rheumatoid factor activity. Noting that the source of human serum IgA is uncertain and that elevated levels of serum IgA or polymeric IgA occur in Henoch–Schönlein purpura, Berger's disease, and after oral immunization, Elkon et al. (1982) reasoned that mucosal events more than systemic diseases are responsible for altering serum IgA. Their data provide indirect evidence for a mucosal origin of the polymeric IgA rheumatoid factor in systemic sicca syndrome.
5. CONCLUSIONS

Evidence from experimental animal studies and patients with gluten-sensitive enteropathy, selective IgA deficiency, Berger's disease, various food sensitivities, and systemic sicca syndrome indicates that the interaction of antigenic materials with the mucosal immune system may be an important component of certain diseases, causative either of an important manifestation of or the disease itself. However, with the possible exception of gluten-sensitive enteropathy, these interactions have not been shown to involve a specific protein and may involve groups of proteins. Food antigens can be demonstrated in low concentrations in blood and they do elicit formation of immune complexes. The presence of antigen–antibody complexes even at elevated values is not in all cases associated with specific tissue injury. The immune system has a great capacity to compensate, and a genetic predisposition to certain diseases having an immunological etiology does not necessarily mean that an individual will develop clinically significant symptoms. Thus, a wide range of immune system modulations may represent normal rather than adverse responses. Therefore, such data should be interpreted cautiously if immunotoxicological assessment becomes an integral part of food ingredient safety evaluation.

ACKNOWLEDGMENT

This work was supported in part by the Food and Drug Administration under contract number FDA 223-79-2275.

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