A Single Blood Test for Detection of Food Allergy, Candidiasis, Microflora Imbalance, Intestinal Barrier Dysfunction, and Humoral Immunodeficiencies

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A. The "New" Lifestyle - A Threat to Health?

It is increasingly evident that human diseases are most often related to lifestyle, and should in theory be preventable. The stress of modern life, our reduced physical activity, and our consumption of manipulated and processed foods, and of chemicals including pharmaceuticals - all contribute to our decreasing resistance to disease. Much evidence supports the fact that our genes, adapted during millions of years to the lifestyle of our prehistoric ancestors, tolerate poorly the dramatic changes in lifestyle that have occurred, especially in food habits during the past 100 years.[1] Changes in food habits in Western countries that no doubt constitute stresses to the human body and that may predispose to inflammatory, infectious, ulcerative, degenerative, and neoplastic diseases include the following: the consumption of 100 lbs. refined sugar per individual per year; the 10-fold increase in sodium consumption; the fourfold increase in consumption of saturated fat; the doubled consumption of cholesterol; a much reduced consumption of vegetable fibers, and of minerals such as potassium, magnesium, calcium, and chromium; and a considerable reduction in consumption of omega-3 fats, membrane lipids, vitamins, and antioxidants. In severe disease, important food ingredients, such as arginine, glutamine, taurine, nucleic acids, vitamins, and antioxidants, such as glutathione are often not supplied in large enough quantities.[2,3]

Perhaps even more important than the decrease in these food ingredients is the fact that prehistoric food contained several thousand times more bacteria, mainly the so-called probiotic bacteria. Prehistoric methods of food preservation were either drying, or, more commonly, storing in holes dug into the ground, where the food became naturally fermented. This is how Stone Age man learned to produce most of our still common fermented foods, such as beer, wine, green olives, and sauerkraut. Our modern lifestyle has dramatically reduced the availability of foods produced by natural fermentation. After the early identification of microbes, bacteria were regarded mainly as a source of disease, and unwanted in commercially manufactured food. Furthermore, the desire of the food industry to prolong shelf life promoted alternative production methods such as the use of enzymes instead of live bacteria. Combined with extensive hygiene measures practiced during delivery and in childcare, children in Western societies may have difficulty developing a satisfactory protective indigenous gut flora. It is not known, but suspected, that this could be connected to the increasing incidence of allergy and infections seen among Western children.[2-4] A series of studies were published about an ethnic group in New Guinea with a dramatically different diet to that of people in the Western world. This diet contained no processed foods like butter, margarine, lard, oils, refined sugar, or alcohol. Instead, the group's diet was rich in fiber, water, vitamins, minerals, and omega-3 fats such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Despite the fact that about 80% of the population smokes and has a heavy consumption of saturated fat from coconut, cerebrocardiovascular diseases are virtually absent and the incidence of diabetes and cancer is very low.

B. The Gastrointestinal Tract - The Port of Infectious Diseases

The condition and function of the gastrointestinal (GI) tract are essential to our well being. After the respiratory tract, the GI tract constitutes the second largest body surface area, described to be somewhere between 25 and 40 m^2, comparable in size to a tennis court. During a normal lifetime 60 tons of food pass through this canal, which is important for well being, but also constitutes an enormous threat to the integrity of the digestive tract and the whole body. It is not surprising, therefore, that this organ is often affected by inflammatory diseases and cancer. The continuous challenges to the GI surfaces might be why most of the surface cells have a rapid turnover; most are replaced after three to four days in man and sometimes earlier in animals. Furthermore, the surface is protected by large quantities of important secretions, from saliva in the oral cavity to colonic secretion in the large bowel. These secretions contain factors of great importance for the lubrication of the mucosa and for functions of the GI tract, but also hundreds of ingredients of importance for intraluminal microbial defense. The secretory functions are extremely sensitive to foreign chemicals. About 50% of the 2000 pharmaceutical drugs registered in Sweden have reported GI side effects, for example, mouth dryness, nausea, vomiting, diarrhea, and constipation. It is hoped that future medicine will be more restrictive in the use of pharmaceuticals in general, and will use drugs with as few side effects as possible.[4]

Stress and Nutritional and Xenobiotic Influences of the GI Tract

Stress is known to affect the composition of the intestinal preventive flora. Infants fed on artificial infant formulas have, in contrast to breastfed ones, a very low degree of colonization with lactobacilli and bifidobacteria but high counts in enterococci, coliforms, and clostridia. This may relate to excessive hygiene measures during delivery in Western countries, which prevent transfer of anaerobic microflora from mother to infant. It is also known that cosmonauts on return to Earth have lost their lactobacillus flora, especially *L. planatarum*, which is partly replaced by a higher intestinal content of PPMs, changes attributed to stress and poor eating. Also,

xenobiotics in the diet can affect the contents of intestinal microflora.

In a recent observation it was proposed that ulcerative colitis is induced by xenobiotic metabolites, damaging the colonic epithelial barrier and exposing the mucosal immune system to luminal contents. It is possible to account for all of these observations by proposing that ulcerative colitis is caused by a toxic metabolite of a xenobiotic (an exogenous agent, such as an environmental chemical not usually present in the body) which is excreted in bile and activated during its passage through the colon (Figure 1). Intermittent exposure to the parent compound would be a feature of the environment, possibly part of the diet, in areas where the disease is more common.

The genetic influence could be explained by inherited differences in the capacity of the hepatic enzymes responsible for its metabolism, resulting in decreased elimination of the parent compound by its usual pathway and increased transformation into the reactive metabolite. The most likely candidate enzymes are members of the cytochrome P450 superfamily of mixed-function oxidases, although genetic polymorphisms of other enzymes involved in xenobiotic metabolism have been described. Induction by smoking or inhibition by estrogen of the P450 enzymes involved in alternative metabolic pathways would affect the proportion of the parent compound transformed into the toxic metabolite. Reactive metabolites produced by this system are commonly coupled to an endogenous conjugate such as glucuronic acid before excretion into bile.

Bacteria in the gut have enzymes, which can act on luminal substrates. In particular, bacterial β-glucuronidase and sulphatase are capable of hydrolyzing the products of hepatic conjugation. If the xenobiotic metabolite were to be slowly reactivated by intestinal bacteria, its luminal concentration would rise with passage down the colon. Once the concentration became toxic, the colonic epithelial barrier would be breached, allowing the mucosal immune system to react to luminal contents distal to that point. In susceptible individuals the biliary epithelium could also be damaged by the toxic metabolite, allowing presentation of biliary antigens to surrounding lymphocytes by cells carrying appropriate I-JLA molecules, thereby initiating an inflammatory response in the biliary tree.[5]

A xenobiotic prevalent in countries with a high incidence of ulcerative colitis is a substrate for a range of hepatic P450 enzymes (a to c). The majority is normally metabolized by enzyme c but individuals who inherit a defective enzyme c metabolize a greater proportion by alternative pathways a and b. Enzyme a produces a reactive metabolite which is conjugated before excretion into bile. Induction or inhibition of other enzymes influences the amount of these metabolites. Bacterial deconjugation in the colonic lumen releases the reactive metabolite and proinflammatory cytokines which may damage the colonic epithelial barrier and exposes the mucosal immune system to luminal contents.

C. Assessment of Intestinal Integrity

Imbalance of gut mucosa permeability is the origin of the intestinal integrity problem.

The development of the gastrointestinal tract in mammals is characterized by the integrated maturation of its many functions. Digestion and absorption of nutrients, the critical factor for survival, depends on the state of development of the gastrointestinal tract. As well as digesting, absorbing, and eliminating, the gut acts as a barrier between the internal and external environment.[6,7]

Control of macromolecular uptake is dependent on a number of factors present either within the intestinal lumen or on the intestinal mucosal surface.[8] These factors include both non-immunological and immunological processes. Nonimmuno-

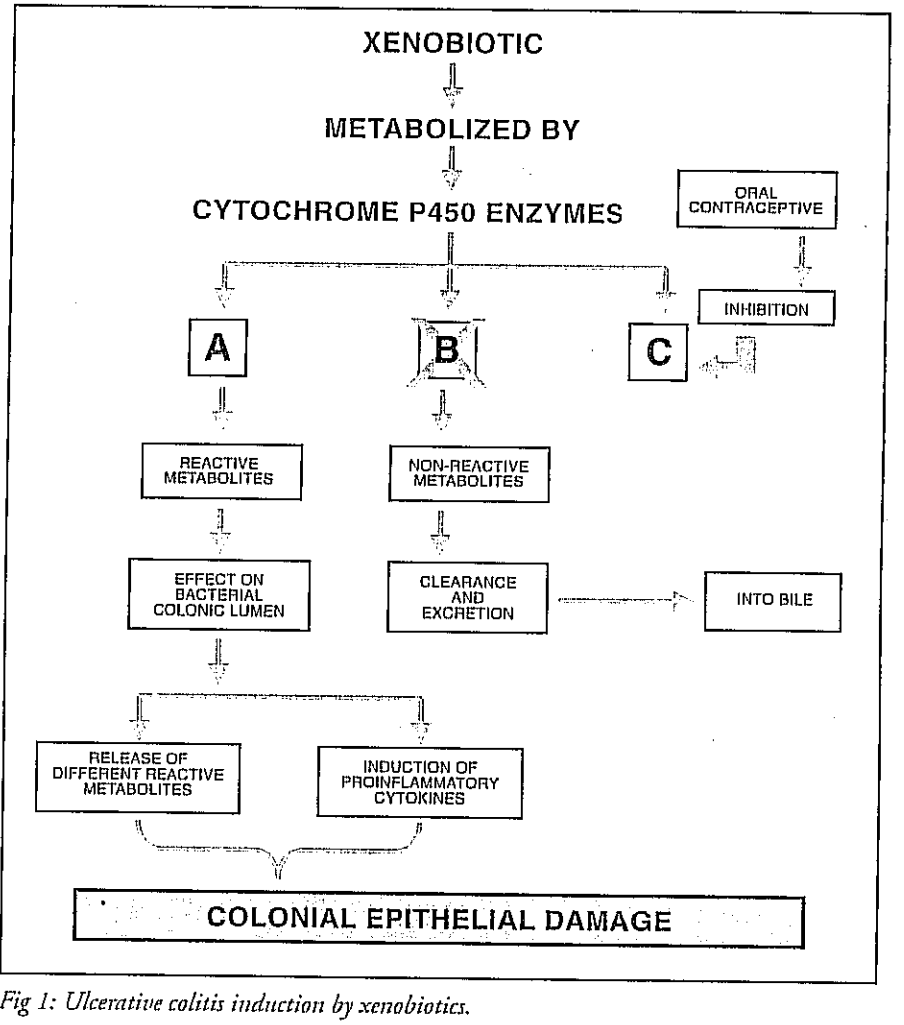

Fig 1: Ulcerative colitis induction by xenobiotics.

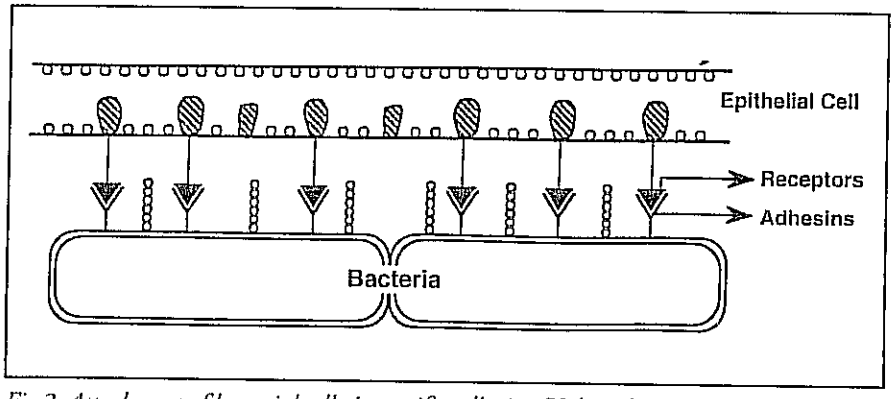

Fig 2: Attachment of bacterial cell via specific adhesins (Y-shaped structures) to complementary receptors (down arrows) on the host cell membrane.

logical factors (intestinal flora, secretion, gastric barrier, peristaltic movement, and live filtration) help control the proliferation of microorganisms present in the gastrointestinal tract, aid in decreasing adherence of organisms to the gut surface, and are important in limiting the available antigen mass that may otherwise overwhelm local immunological defense mechanisms and penetrate the mucosal barrier or enter the systemic circulation.[9-13]

Mucosal immunological factors (secretory IgA, cell meditated immunity, other immunoglobulins), and especially the common mucosal associated lymphoid tissue (MALT), are present at all epithelial surfaces that are in contact with the external environment. This is largely independent of the systemic immune response and is governed by antigenic stimuli at epithelial surfaces. A failure or abnormality in one of these mechanisms can result in symptoms such as anaphylaxis, rhinitis, and skin rashes which may be classified as food allergies.[7]

In normal conditions, factors within the intestinal lumen of the surface of epithelial cells and within the lamina propria combine to limit the access of antigens to systemic circulation. After macromolecular ingestion by the intestinal absorptive cells, most of the ingested material is broken down by lysosomal enzymes in digestive vacuoles.[14] That portion which escapes breakdown is transported out of the cell by an exocytic mechanism. Any interference with intracellular capacity to digest macromolecules could therefore result in an increased intestinal transport of molecules.[15] A number of factors can affect the stability and ability of lysosomes. For example, high concentration of vitamin A, radiation, bacterial and fungal endotoxins, and exotoxins can increase the ability of lysosomes, causing the rupture of lysosomal membranes in various cellular systems. On the other hand corticosteroids stabilize the lysosomal membrane and can interfere with the normal digestive function of these intracellular organelles. Thus, inhibition of lysosomal function could in turn result in enhanced transport of intestinal antigens, by decreasing intracellular organelles. Inhibition of lysosomal function could in turn result in enhanced transport of intestinal antigens by decreasing intracellular breakdown and increasing immune response against bacterial antigens.[16]

The basis for possible immune-mediated disease in these cases may be the increased uptake of intestinal pathogens or macromolecules, which can interact with the circulating antibody and complement a target organ to produce a characteristic autoimmune response.[17] Furthermore, patients with selective IgA deficiency have a greatly increased incidence of Celiac disease compared with the normal population. This is undoubtedly due to an increased uptake of gluten or its breakdown products.[18] In a similar manner, intestinal pathogens or their byproducts can penetrate the intestinal mucosa, resulting in a generalized malabsorption.[19] Therefore, increased or decreased intake of macromolecules may result in pathological conditions.[17-19]

D. Intestinal Barrier Function Test

Recently, there has been considerable interest in the concept of enhanced intestinal permeability and its possible role in the pathogenesis and pathophysiology of a variety of intestinal and extraintestinal disorders. Bacterial flora is greatly influenced by eating habits and by chemical contamination of the food which plays a significant role in the integrity of intestinal mucosa.

Mucosal surfaces in mammals provide an extensive area for adhesion of a wide variety of microorganisms. Soon after birth, the mucosal surfaces of the upper respiratory tract, the intestinal tract, and the lower genital tract become colonized by a variety of bacteria and other microorganisms.[20] Most of these organisms become established as the indigenous microflora or normal microflora by attachment of bacterial cells via specific adhesins to the complementary receptors on the host epithelial cell membrane (Figure 2).

During states of good health, all of the mucosal surfaces contain remarkable barriers against attachment of invading bacterial pathogens. But due to the typical western diet, (chemically contaminated food, increased dietary carbohydrates, usage of broad-spectrum antibiotics, corticosteroid hormones, and birth control pills), these barriers may break down and pathogenic bacteria may colonize large areas of the mucosal surfaces. From these colonized sites, pathogenic bacteria produce infectious diseases either by invading into deeper tissues or by excreting antigens and/or toxins that damage local and distant tissues.[9, 21] This systemic translocation of enteric bacteria and endotoxins plays a major role in the development of abnormal systemic immunity, which may end with multiple organ failure.

The pathogenesis of bacterial infectious diseases arising from mucosal surfaces involves a number of distinct interactions between the host and the bacterial pathogen. Virulence factors (for example, fimbriae) of the bacteria enable the microorganism to attach to and multiply on mucosal surfaces and to evade the defense mechanisms of the host. This observation could mean that the intestinal tract represents a potential site for the absorption of bacterial breakdown products, proteolytic and hydrolytic enzymes, as well as food antigens that normally exist in the intesti-

nal lumen.[8] Therefore, inhibition of microbial attachments to the epithelial cell receptors via competing molecules such as lectins, polysaccharides, and other nutritional factors is the best strategy for prevention of mucosal immune dysfunction. (Figure 3).

Mucosal immunodeficiency is an additional factor, which may contribute to an enhanced macromolecular absorption. Secretory IgA is the predominant immunoglobulin present in intestinal secretions. This class of immunoglobulin acts to protect the intestinal bacteria, fungi, and viruses, as well as the antigenic and toxic macromolecules. It is therefore possible that, in the absence of secretory IgA, and/or microflora imbalance, ingested proteins are absorbed from the gut in increased amounts.[17-25] See Figure 4.

Excessive uptake of bacterial, fungal, viral, and food antigens into the circulation may induce immune response first in the form of IgM and thereafter in the form of IgG and IgA antibodies (Figure 5) which results in clinical condition.

E. Increased Food Antigens Transfer in Atopic Eczema

Abnormal intestinal antigen handling is the root cause of atopic eczema.

Dietary antigens are macromolecules with a molecular weight in the range of 10,000 to 70,000 Dalton. They are absorbed across the epithelial layer by transcytosis along two functional pathways. The main degradative pathway entails lysosomal processing of the protein to smaller peptide fragments, and is important in host defense to diminish the antigen load. More than 90% of the protein internalized passes in this way. A minor pathway allows the transport of intact proteins, which results in antigen-specific immune responses. In health, paracellular leakage of macromolecules is not allowed because intact intercellular tight junctions maintain the macromolecular barrier. Consequently, in health, antigen transfer is well controlled, and aberrant antigen absorption does not occur.

Determination of both intact and degraded antigen absorption is important because they can be affected separately and their clinical and immunologic consequences may be different. Antigen handling in the gut is associated with the generation of oral tolerance. There is evidence that during the absorption process antigens are subtly altered into tolerogenic form. In the immature gut, because of immature absorptive functions, antigen exposure may result in priming for immune responses instead of oral tolerance. Increased uptake of intact food antigens in the immature gut has been explained by increased binding of antigens to the microvillus membrane. Aberrant and excessive antigen absorption increases the antigen load, which may be harmful to the host. In a like manner, incomplete degradation may result in the generation of new antigenic epitopes.[26]

It is not known whether altered antigen transfer is a primary or secondary phenomenon in atopic eczema. In food allergy, disturbances in intestinal permeability and antigen transfer occur when an allergen comes into contact with the intestinal mucosa. It has previously been shown that in active cows' milk allergy with predominantly gastrointestinal symptoms the absorption of both intact and degraded horseradish peroxidase (HRP) is increased in untreated cases, but after complete avoidance of cows' milk, HRP transport returns to normal.[27-29]

These results show that the intestinal mucosa is an important organ of defense, providing a barrier against the antigens encountered by the enteric route. The barrier functions may be incompletely developed in early infancy, which may explain the peak prevalence of food allergies in this age group. In attempts to correlate atopic eczema with impaired gut mucosal barrier functions, it is important to measure the intestinal permeability by a high molecular weight probe such as HRP rather than a low molecular weight probe such as the lactulose-mannitol test. This recommendation is based on findings that low molecular weight probes suffers from high degrees of false positivity.[30]

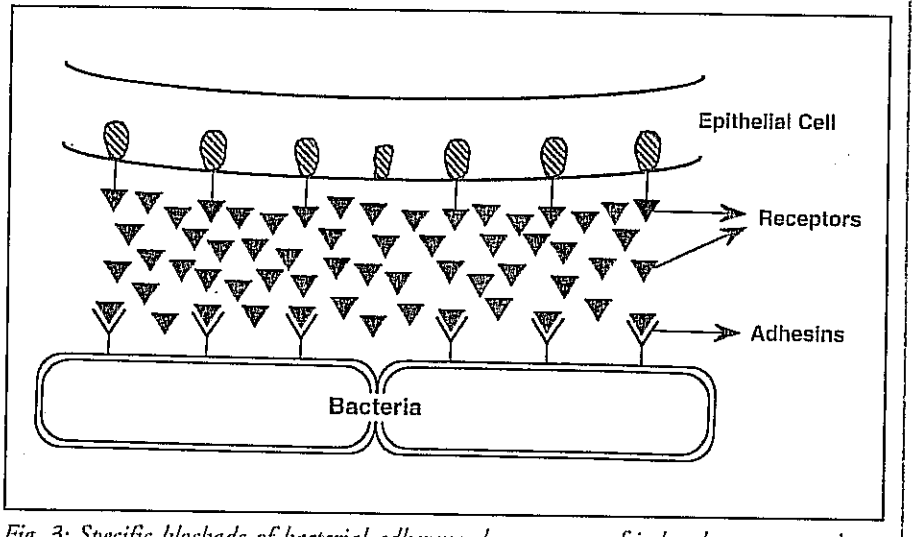

Fig. 3: Specific blockade of bacterial adherence by an excess of isolated receptor analogue material (down arrows).

F. Bacterial and Food Antigens may Induce Autoimmune Disease

The proposed mechanisms by which viruses or bacteria may initiate autoimmunity is through sharing of a common antigenic determinant between a virus or other microorganism and a host cell component. Such shared epitopes can be thought of as a three-dimensional conformation site or a stretch of amino acids forming a peptide. Thus, an antiviral or bacterial immune response would recognize both the microorganism determinant and the shared host self antigen. These cross-reacting antibodies and immune cells generated by molecular mimicry may in large part be responsible for the presence of autoreactive antibodies and cells found in many infections in humans.[31-32]

Similarly, epidemiological and ecological investigations suggest that early infant nutrition, particularly drinking cows' milk, may induce autoimmunity leading to insulin-dependent diabetes mellitus (IDDM). A supporting hypothesis is of immunological cross-reactivity between a fragment of bovine serum albumin and a β-cell protein of 69,000 M (p69) because both cellular and humoral immune responses to bovine serum albumin have been reported in patients with IDDM which cross-react with p69.

Human and bovine β-casein share approximately 70% homology and sequence differences could therefore be responsible for the generation of an immune response if milk proteins are introduced within the first weeks of life when the intestine is permeable to proteins. Based on results in NOD mice and evidence that patients with IDDM have autoantibodies to β-caseins at the time of diagnosis, T-cell reactivity to β-casein was measured.

The discovery of the proliferative response to β-casein reinforces the concept of this protein being involved in causing the disease as indicated by the recent report of autoantibodies to β-casein in these patients. This finding is specific for patients with IDDM because no lymphocyte proliferation to β-casein was observed with cells from patients affected by autoimmune thyroid disease. A proliferative response to β-casein in patients with IDDM diagnosed in childhood and as young adults suggests that this response has pathogenic relevance regardless of the age of onset of the disease. This data together with evidence derived from experimental studies in the NOD mice, and the observation that a high percentage of IDDM patients have antibody to β-casein, indicate that β-casein is a milk protein likely related to IDDM.[33]

It was concluded that the association between IDDM and early consumption of cows' milk may be explained by the generation of a specific immune response to β-casein. Exposure to cows' milk triggers a cellular and humoral anti-β-casein immune response which may cross-react with a β-cell antigen. It is of interest that sequence homologies exist between β-casein and several β-cell molecules.[33-35]

For this reason, measurement of circulating IgM antibodies against specific antigens of intestinal bacterial and fungal flora is of considerable importance in the pathogenesis of immunologically mediated diseases, including food allergies and autoimmunities.[36-39]

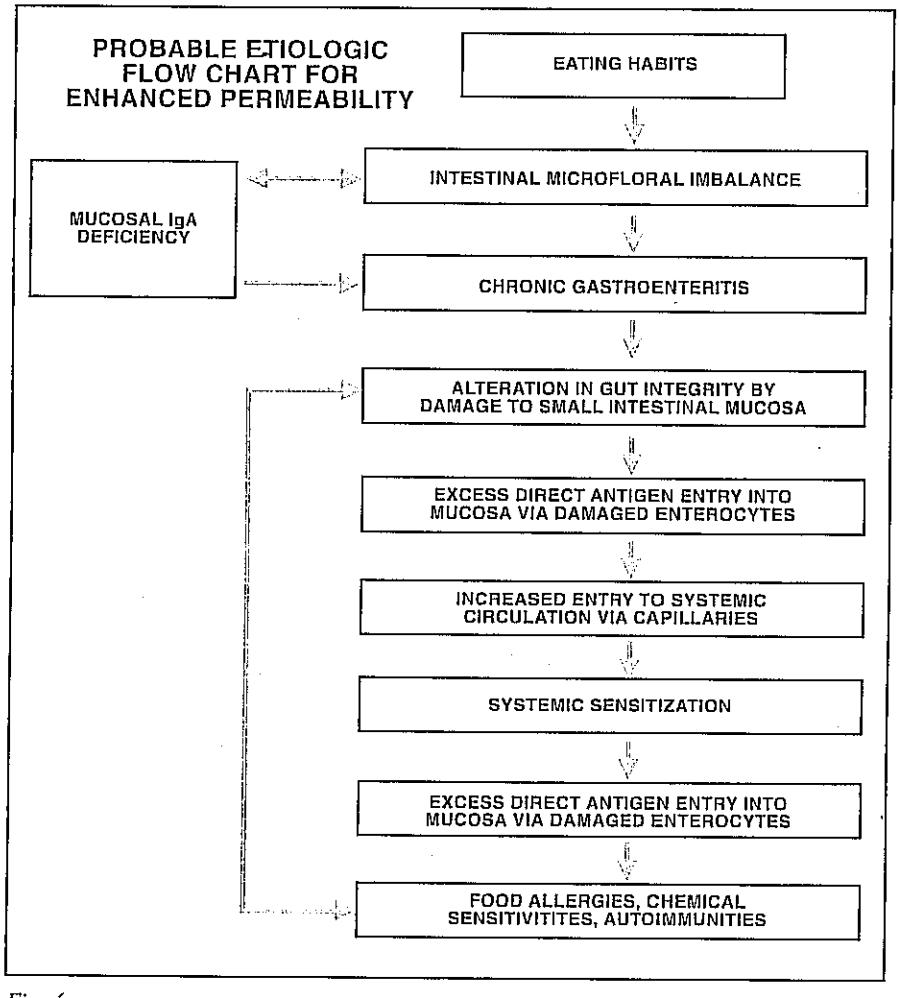

Fig. 4

This is the basis for a newly developed test called Intestinal Barrier Function (IBF). This test was developed because, in our experience, microbial flora imbalance cannot be fully understood in its diagnostic and therapeutic implications without coordination of all components of the intestinal flora, including the dietary proteins.[33, 40] IBF utilizes a highly sensitive and accurate ELISA test method that measures the serum IgG, IgM, and IgA specific antibody titers to the purified antigens from five different dietary proteins; three aerobic and two anaerobic microbes, including *Candida albicans*, *Candida tropicalis*, and *Candida cruzei*.[31-40]

Such quantitative and comparative test results may allow the determination of primary clinical conditions such as:

- Food Allergy
- Intestinal Imbalance
- Gut Barrier Dysfunction
- Bacterial Translocation
- Immunodeficiencies
- Candidiasis
- Autoimmunities

The Intestinal Barrier Function test is recommended for patients who:

- have candidiasis, which appears to be resistant to standard therapy

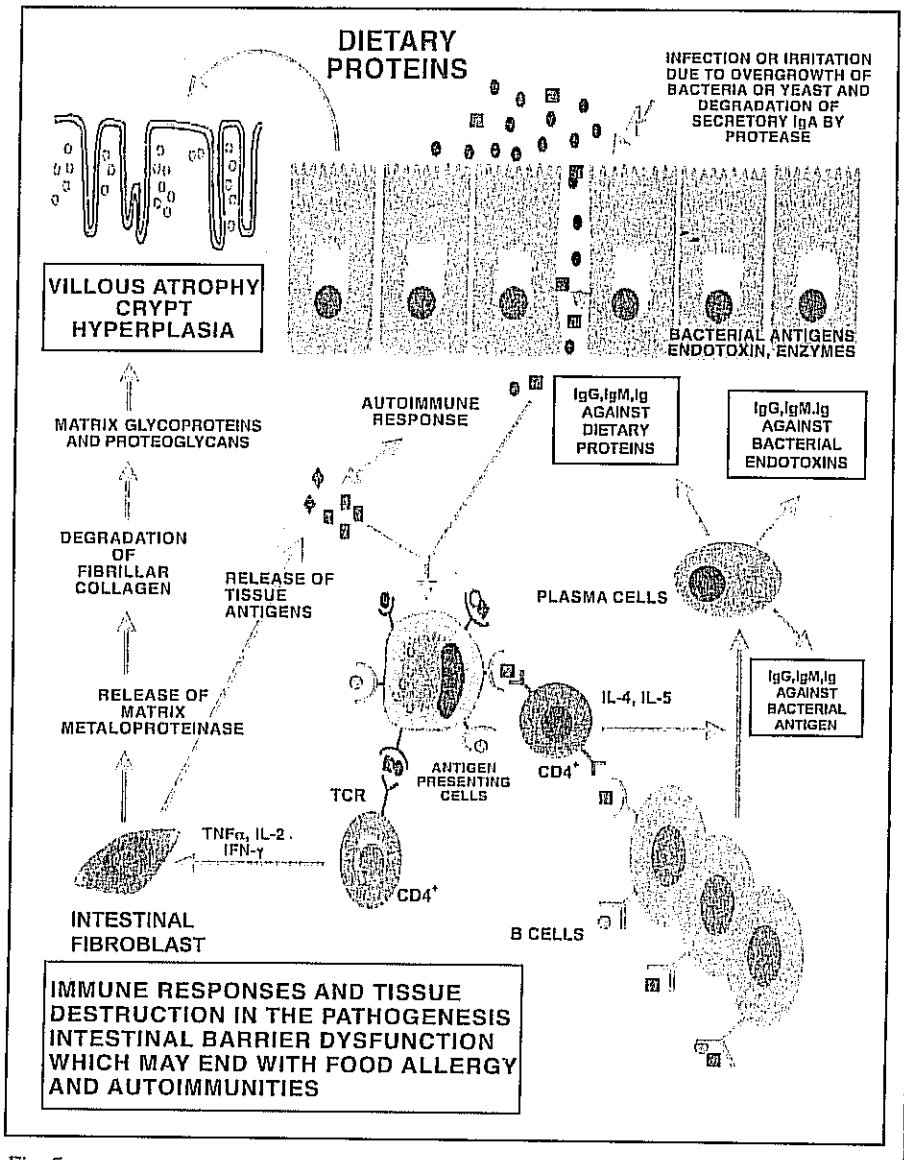

Fig. 5

- are suspected of suffering from disturbances of intestinal permeability and absorption
- complain of food intolerance (including 'food allergy')
- complain of chemical hypersensitivity
- present diagnostic problems with multiple symptom complaints (including Chronic Fatigue Syndrome)
- suffer from abnormal cell count and function (including auto-immune diseases)
- may develop post-operative sepsis due to bacterial translocation

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