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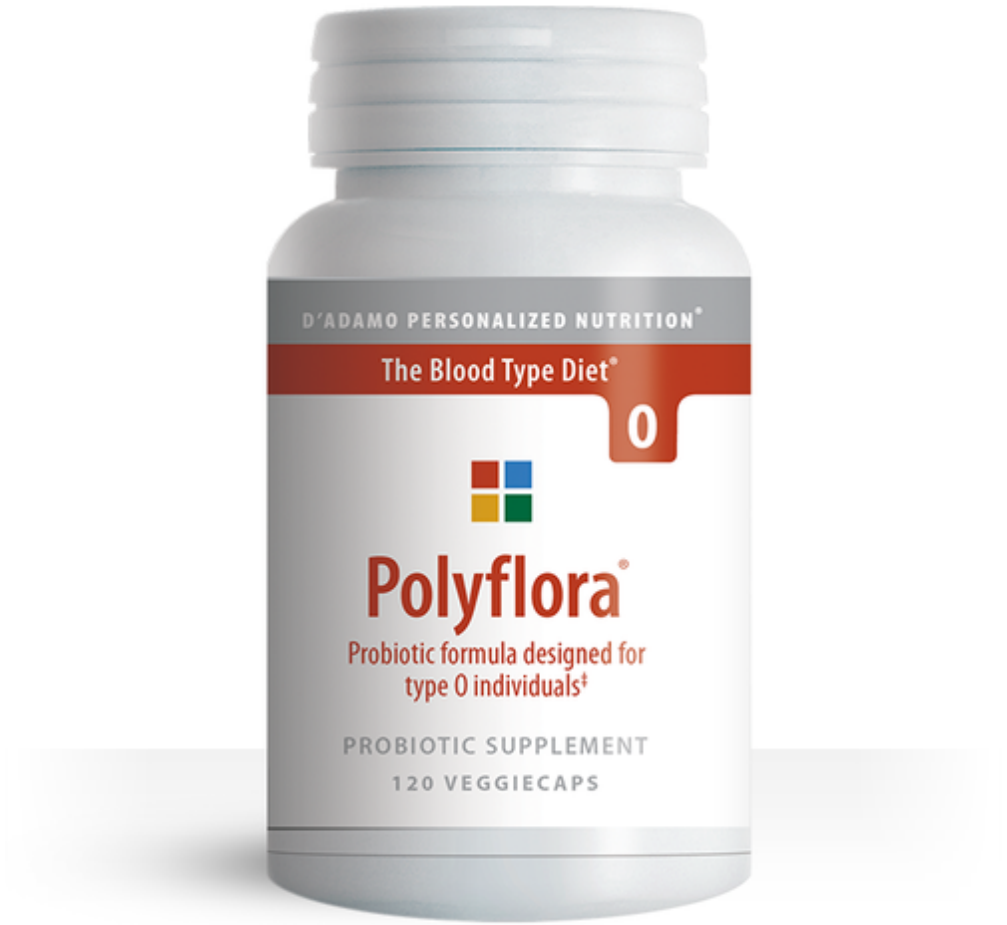

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ENDOTOXINS, ALLERGENS AND THE ALTERNATE COMPLEMENT CASCADE

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THE MUCOSAL IMMUNE RESPONSE

In 1919 Besredka showed that oral immunization of rabbits provided immunization against otherwise fatal Shiga bacillus infection regardless of the serum antibody level. Davis, in 1922, showed that fecal antibody was present in the stools of patients with bacillary dysentery before the antibody was found in serum. The discovery of the immunoglobulin classes in 1940, followed by the demonstration of a predominance of IgA at several local mucosal surfaces, renewed interest in mucosal immunity. Burnett first proposed the concept of an antiseptic paint consisting in part of antibodies lining the GI tract. Cysteine residues have recently been shown to predominate in mucus and it has been proposed that through this mechanism, antibodies, particularly IgA, maybe bound to the luminal surfaces of the epithelial cells of the digestive tract. Lymphoid tissue underlies all mucosal epithelium, and is found in the stroma of all external glands, the heaviest concentrations being in the gut, evidently the site of the greatest and most dangerous antigenic load.

IMMUNOGLOBULIN A (IGA)

The role of IgA is closely related to the potential for gut related health problems. Ig-A is most commonly used by the body to "soak up" allergic substances from the digestive tract. It is usually evenly distributed throughout the gut tissue except in specialized lymphoid areas where large amounts are manufactured and encapsulated. Lymphoid tissue is

found in those areas where immune activity is constantly required, such as the appendix, tonsils and Peyer's Patches of the intestines, areas which routinely become inflamed. IgA has two major functions. The first is to cause bacteria and allergic substances to stick to the mucus membranes. The second is to turn on the alternative complement pathway to destroy them. Improper function or secretion of IgA has been implicated in a variety of immune complex disorders including systemic lupus erythematosis and phlebitis.

IgA is often found with gut mucus, usually with one end of the immunoglobulin tailored to adhere to and anchor with the mucus lining and the other, "business end" of the molecule projecting out into the gut ready for immune reactions if necessary. Calculations suggest that up to 50g of IgA may be synthesized by the gut daily, a mass equivalent to the immunoglobulin producing tissue of the spleen. Most B lymphocytes at the external mucosa are dedicated to IgA synthesis and form a recirculating pool of cells that home preferentially back to mucosal sites. Antigens present in the small intestine are sampled by a special type of cell, called an M cell, located over each Peyer's patch and bordering on the intestinal lumen. The antigens are transferred to an environment of immune cells, accessory antigen presenting cells, and regulatory T cells within the patch.

After antigen stimulation, precursors of IgA plasma cells migrate via the lymphatics to the blood, the spleen and the liver; then they return to the gut or localize at distant

mucosal sites. Several factors have been postulated to explain the accumulation of potential IgA producing cells at these specialized sites. The mucosal environment, rich in microbial antigens and mitogens is known to influence the immune specificity of lymphocytes in mucosal tissue. T cells have been described that act on surface IgA positive B cells to increase or suppress IgA synthesis. When foreign material attempts to pass through the gut wall, IgA binds to it and forms an immune complex. Immune complexes are destroyed right at the site of attachment to IgA in the gut wall or transported to the liver and cleared by Kuppfer cells.

Insufficient IgA production is a common immunodeficiency (it is genetically produced in 1 of 600 individuals of European origin, and can result from dietary imbalance, tonsillectomy or appendectomy). If there is insufficient IgA in the tissues to bind with microbes or allergic particles, they will pass into the portal circulation and liver. If the liver is incapable of dealing with the immune complexes coming from intestinal absorption, they will pass into the systemic circulation and stimulate a general immune response. Allergic disorders and auto immunity occur with undue frequency in the milder forms of IgA deficiency. The former comprises reaginic IgE type) allergy in general and food sensitivity, especially gluten-sensitive malabsorption, in particular. The frequency of auto antibodies in IgA deficiency remains a riddle. Perhaps they appear as a result of excessive absorption of foreign material cross-reacting with self-substances, e.g. reticulin; alternatively they may be the hallmarks of slow virus infections made possible by the

failure of the gut barrier.

THE ALTERNATIVE COMPLEMENT PATHWAY

The complement system is made up of a series of 18 plasma proteins that are sequentially activated to mediate their biologic function. This function is to amplify specific and non-specific host defense, helping to mediate such functions as immune adherence, phagocytosis, chemotaxis and cytolysis. The classic activation pathway comprises the components C1, C4 and C2 and is dependent on the interaction of these complement proteins with antigen-antibody complexes to activate the initial cleavage of C3.

The alternative pathway activation occurs on mammalian cell surfaces in the absence of specific antigen-antibody c%) complexes. This non-specific activation is a major physiological advantage since host protection can be generated prior to the induction of humoral immune response. Factors capable of activating the alternate pathway include zymosan, inulin, bacterial polysaccharides and endotoxins, IgG4, IgA and IgE. Thus the alternative pathway probably represents an earlier, more generalized defense system which is now an auxiliary pathway to the activation of extremely potent complement enzymes within the blood, which come into contact with the outer membrane of the invader. This chemical reaction essentially "shoots holes" in the membrane of the invader, causing it to burst or lyze. When not in use the various chemicals of the alternate complement pathway lay in a sort of suspended animation inside the blood. Their activation is a chain of events of sorts

and is irreversible.

Stimulation of the alternate complement pathway also results in the production of several "intermediary" chemicals with special activity within the cardiovascular system such as serotonin, histamine and bradykinin. These chemicals cause an increase in the permeability of the capillary linings, allowing white blood cells to migrate from the tissues into the blood vessels. Chemotaxic hormones cause the white blood cells to be attracted and migrate towards the site of complement release. Serotonin can also act upon the brain and central nervous system while bradykinin is one of the most powerful inflammatory chemicals yet discovered and has been implicated in a wide variety of allergic reactions.

When the complement pathways are activated by existent infectious organisms, the system works quite well. But it is noteworthy that aggregated immunoglobulins to diverse elements -endotoxins, Candida, IgG4 mediated complexes (allergens and lectins) will summate and potentially augment C3b INA and C6 INA mediated ampliflication. Very often the highly destructive complement enzymes will turn upon the body itself, initiating autoimmune reactions which further elevate the immunoglobulin aggregate levels by increasing immune complex precipitation.

Thus the prognosis of any treatment rationale developed to combat inflammatory response to any single element in the bowel ecosystem will be in direct proportion to the degree of modulating the balance established between all correlating elements.

MUCIN

The digestive tract (mouth, throat, stomach, intestines etc.) can be thought of as being semi-permeable, that is, they selectively allow substances to pass through in both directions (digestion to blood, blood to digestion). The gut is both absorptive and secretory. Each section of the gut is tailored for special functions. Just as there are appropriate mechanisms for transferring substances through the gut membrane, there are many mechanisms designed to restrict entry. Perhaps the most important of these is mucus.

Mucus is a complex mixture of proteins and carbohydrates secreted by mucus cells located within the gut wall. There is tremendous variation in the types of mucus produced in each separate part of the body and even wider differences in mucus composition between the various species (sheep, dog, mouse, etc.). The physical properties of mucus include low solubility, high viscosity, elasticity and adhesiveness, making it ideal for protecting the delicate tissue structures of the gut.

High molecular weight glycoproteins, mucins, usually contain greater than 50% carbohydrate in the form of neutral and acidic oligosaccharide chains. These units may contain galactose, fucose, N-acetylgalactosamine, N-acetylglucosamine and sialic acids. What is especially interesting about the mucin glycoproteins is the correlation with the ABO antigen system. Additionally the MN antigens usually determine which particular sialic acid residues predominate.

SIALOGENS

One of the primary constituents of mucus are the sialic acids (neuraminic acids), compounds responsible for many of the characteristics of mucus. The sialic acid content of mucus determines how good a lubricant the mucus will be. Mucus with a high sialic acid content retains more water and "plumps," giving it the necessary three dimensional shape needed for its job. This occurs due to charge repulsion between negatively charged residues on adjacent oligosaccharide chains. Interestingly, in the presence of small amounts of calcium the viscosity of tracheal mucus has been shown to increase rapidly. Newborn mucin seems to contain more sialic acid and less fucose than that of adult. This seems to be an integral part of the defense mechanism of the newborn. Newborn mucus also was found to bind cholera toxin much more effectively than adult mucus, perhaps explaining the decreased susceptibility of newborns to cholera. Studies using neuramidase-treated blood group antigens showed that removal of the sialic acid residue from the blood group antigens was significant only for M or N antigens, which produced a loss of allergenicity. Other blood group antigens are probably oriented by membrane sialic acids, but their loss results in no significant loss of antigenicity.

Lining the surface of most human cells, sialic acid increases the affinity of complement enzyme C3 forits control factor ("substance H"). Thus cells which contain high amounts of sialic acid can quench the complement cascade, whereas cells without sialic acid promote it. Most bacteria and plant

cells lack sialic acid, which explains why the alternative complement pathway is so important for natural resistance: the body designed complement to be inactivated by a chemical common to all "self" tissue and uncommon to all "non-self" tissue.

Sialic acids exhibit profound antimicrobial effects: many naturally occurring glycoproteins, including ovomucoids, ovalbumins, and submaxilliary mucins, inhibit the replication of rotaviruses. The inhibition has been shown to be the result of direct virus-glycoprotein binding that is largely dependent upon the interactions with sialic acid oligosaccharides. It has also been recently reported that gay men who were double recessive for the gene producing a "long" form of membrane sialic acid showed a lower incidence of conversion to clinical AIDS.

The number of negatively charged terminal sialic acid residues attached to complementary groupings on the virus surface appears to determine primarily the inhibitory potency of the glycoproteins. This was extensively studied in influenza virus systems.

Thus:

virus + glycoprotein ---- virus-glycoprotein complex.

In which the equilibrium constant as to the reversibility of the adherence of the virus to the glycoprotein complex was directly relational to both the sialic acid concentration of the glycoprotein employed, and the complementarity of the glycoprotein to the viral receptor. Several glycoproteins, including N-acetyl-galactosamine can actually interfere with

the access of influenza virus to binding sites on the mucous glycoprotein.

It is interesting to speculate on the significance of increased sialotransferase activity in chronic myleogenous leukemia granulocytes (2.8 times higher in CML cells as compared to normal cells), which may account for the aberrant sialylation of o-linked oligosaccharides in CML cell lines. CML is characterized by the inappropriate early release of immature granulocyte precursors from the bone marrow, which may indeed result from aberrant sialylation and for the-prolonged circulation time.

Sialic acid may play a role in tumor metastasis: desialylated SKNMC neuroblastoma cells had significantly diminished platelet activating activity. Many human carcinomas contain elevated levels of membrane glycoproteins and glycosyltransferase. Sialic acid and the attaching enzyme sialyltransferase probably have direct roles in tumor cell growth. Several authors have found a correlation between the spontaneous metastatic behavior of murine tumor cell lines, their surface sialylation, and the platelet-aggregating activity of their cell surface extracts. This may in part explain some of the anti-tumor effects seen with anti-thrombogenic in tumor cell metabolism, particularly coumarin.

Sialic acid-rich glycoproteins have also been shown to be involved in the adherence of proteins from several strains of E. Coli. Furthermore, sialoglycoproteins on the RBC's seem to be receptors for Plasmodium falciparum merozoites.

ENDOTOXIN

Endotoxins are secreted exclusively by Coliform bacteria, so-called because they all morphologically resemble E. Coli, the most common species of the group. These bacteria should make up approximately 15% of the gut flora; however it is not uncommon for many people to have bowel populations of up to 85% or more coliform, bacteria. Gram positive bacteria do not secrete endotoxins on their surfaces. Gram negative coliforms are commonly coated with a mucus and fat slimy outer covering.

This coating is composed largely of lipopolysaccharides, fatty acids with long chains of simple sugars attached to them. The fatty portion is called Lipid A and it contains the toxic principal the polysaccharide portion (the 0 Antigen) however contains the reactive portion or antigen that stimulates the body's immune reaction, the production of antibodies. These lipopolysaccharides are extremely toxic to humans and animals. They are usually firmly bound to the bacteria outer membrane and are only released when the bacteria divides during reproduction or dies. Because they are bound in the bacteria membrane and not continually secreted, they are called endotoxins.

Although the cell walls of gram positive bacteria do not usually contain endotoxins, they contain other toxic chemicals on their surfaces which make them just as dangerous if you are infected with them. However these chemicals are: 1.) always found associated with the bacteria; 2.) they do not migrate independently through the bloodstream as endotoxins can and 3.) are only active during infection.

From birth the defenses of the body constantly encounter endotoxins in the bloodstream. Immune reactions, such as the development of antibodies to circulating endotoxins are constantly being produced to the many variations in their shape and size. Very often these antibodies can cross react and mark healthy tissue for destruction. This is seen with the Yersinia enterocolitica. There is some research showing that antibodies to these bacteria are capable of cross-reacting with and destroying thyroid tissue. People with Hashimoto's disease typically have high levels of circulating antibodies to this organism.

Figure I Overview of four-compartment complement system in Glynn and Steward's Immunochemistry: An Advanced Textbook, New York: Wiley 1988.

Endotoxins cause septic shock, a well recognized immune reaction found in post surgical patients and in other hospital patients with predisposing factors such as diabetes, cirrhosis, leukemia and cancer. The great majority of immunosuppressed hospital patients will also experience hospital related septic shock. Statistics show 16 out of 1000 hospital admissions will develop serious septic shock and the number has risen consistently every year since 1935. Most of the time the endotoxins are produced by the normal inhabitants of the digestive tract, although a disturbing increase is being noticed in the cases Of septic shock caused by bacteria which are unique to the hospital environment. Increased endotoxin loads can lead to hypotension, or paradoxically to constriction of the arteries and veins leading to decreased perfusion. This may be the

association noted between bowel endotoxemia and migraine headaches. The poor blood flow into the tissues also results in the accumulation of a wide variety of organic acids, leading to acidosis.

Endotoxins cause damage in relationship to the amount that can pass into the body. Small amounts, such as those found in bowel ecosystems with large coliform. Populations, have less outright manifestations than larger amounts, such as might result from infection or septic shock. However even moderate endotoxemia will influence the immunoglobulin aggregate.

Endotoxins can be extremely potent cancer promoters. The link between dietary nitrates, such found in smoked or preserved meats, is well known. Less well known is the fact that nitrate synthesis within the body is increased nine fold in the presence of E. coli endotoxin. It can be amply demonstrated that bacterial toxins do exist in the body and under specialized situations are capable of causing great harm.

CANDIDIASIS

Historically many earlier studies made clear the infectious potential of the Candida organism to invade a wide variety of human tissues and cause human disease. Unfortunately many physicians consider the role of Candida in chronic disease processes to be strictly limited to clearly definable instance of tissue invasion and infection. However, the organism has a much broader role in causing chronic illness by virtue of its ability to stimulate tissue sensitivity to the

organism and/or its byproducts.

Candida is a common inhabitant of the intestinal tract, the oral mucus membranes and the vaginal tract. Isolation from the mouth, vaginal secretions and feces is higher in hospitalized patients than normal subjects, although both can usually yield significant colonization rates. There are about 79 species of Candida and 6 have been implicated definitively in human disease. Candida albicans, the most common human pathogen, is found only in human and animal carriers so its acquisition from the environment is unlikely. There is clinical support for the sensitivization potential of Candida since protein antigens from the outer capsule have been shown to stimulate histamine release from rat cell tissue cultures. The organism has been known to be a pathogenic factor in selected cases of asthma, hives (urticaria), irritable bowel disease, and psoriasis.

Signs might include yeast overgrowth in the mouth, intestines, vaginal tract and esophagus. Women may suffer fatigue, premenstrual syndrome and loss of libido. In males fatigue and low grade depression and irritability are particularly common complaints. Children may complain of bowel disturbances, thrush, diaper rash and other signs. Common symptoms to all groups would include: abdominal bloating and gas and sugar cravings; impaired immunity; nutritional factors (lack of vitamin A, iron and folic acid); diabetes; medications (cimetidine or Tagamet, antibiotics, birth control pills, cortisone) and malignancies all predispose to candidiasis.

Research has shown cross reactions between antibodies to Candida. and healthy ovarian tissue. Thyroiditis is seen in candidiasis patients in a greater degree than in the general population. Mitral valve prolapse has also been seen in a close relationship with candidiasis and thyroiditis. Antibodies to T-helper lymphocytes have also been detected in candidiasis patients. It is this subpopulation of lymphocytes that becomes disturbed in AIDS and chronic Epstein-Barr viral infections. It has been suggested that the candidiasis seen in AIDS patients may not simply be another opportunistic infection, but rather a direct contributor to the development of the disease.

DIETARY ALLERGENS

The incidence of food allergies has increased in the last 15 years. This may have resulted from a variety of factors: increased stresses on the immune system (due to increased pollutants in the air, water and food); earlier weaning and introduction of solid foods to infants; genetic manipulation of plants resulting in foods which have a greater chance of cross reacting with normal tissue.

Food allergies have a well documented genetic predisposition. In households where both parents are allergic, 67%of the offspring are allergic. Where one parent is allergic, 33% are allergic. Food sensitive people have been observed to have unusually low levels of IgA. It has been suggested that a transient IgA deficiency may predispose to the development of food sensitivities in the first few months of life. It is interesting to also note the

correlation of stress levels to impaired IgA secretion. This may explain the relationship reported by many sources between food allergies and severe mental stress. Foods may produce allergic reactions by a variety of methods. Immunologically produced food reactions result from the reaction of the food substance with sensitized IgE antibodies located on circulating mast cells. This leads to immediate hypersensitivity, so called because most of the symptoms develop within 30 to 90 minutes of ingesting the offending food. These symptoms include the well known anaphylaxis symptoms of allergy; bronchiole congestion and asthma, hives and eczema, headaches, loss of memory and "spaciness."

The cytoxic or tissue destructive reaction results from the activation of complement. This reaction results in destruction of the cell in which the food allergen is bound. Up to 75% of all allergies are accompanied by a cytoxic reaction.

Immune complex related reactions result from further immune stimulation by the circulating immune complex of antibody and allergen. Normally taken up by the liver these can enter the general circulation and stimulate tissue injury by immune reaction or deposition of immune complexes in delicate tissues and organs. Improper digestion, a repetitive diet and a lack of integrity of the intestinal membranes all predispose to the development and maintenance of food allergies.

It has been well documented that partially digested dietary

protein can cross the intestinal barrier and be absorbed into the bloodstream. This causes allergic reactions at the site of transfer or at other distant sites, or systemically. Factors which influence intestinal absorption of macromolecules include immaturity of the GI system, abnormal intestinal flora, vitamin A deficiency, decreased gastric acid secretion, pancreatic insufficiency, mucosal ulceration or inflammation and diarrhea.

Symptoms and diseases commonly associated with food allergies would include such diverse problems as low back pain, bed wetting, chronic bladder infections, canker sores, middle ear infections, asthma, acne, headache and duodenal ulcers. Some of the common physical signs of allergy are dark circles under the eyes; puffiness under the eyes; horizontal creases in the lower eyelid; chronic swollen glands and chronic noncyclic fluid retention. Hyperactivity in children has been speculated to have its cause in food intolerance.

HEPATIC CLEARANCE

In many ways, the liver constitutes a "second line of defense" against substances which are able to pass the gut mucus membrane. In order for this to occur, nature has provided the liver with unique physical properties. For example, the liver possesses two blood supplies: the hepatic circulation which communicates with the regular veins and arteries of the body, and the portal circulation which is a separate circulation that exists between the gut and the liver. All blood return from the intestines is first sent to the liver via

the portal circulation. This was designed to allow the liver an opportunity to clear this blood of immune complexes and microorganisms before they can find entry into the general circulation.

Within the body of the liver are specialized white blood cells called Kupffer cells. These cells have evolved into highly specialized filters of the portal circulation. As microorganisms or immune complexes reach the liver from the intestines, Kupffer cells activate and take up these particles and destroy them. This "filtered" blood is then allowed to enter the general circulation. This process starts at birth and continues throughout the lifetime. Under normal circumstances the liver is more than able to cope with this continuous blood. clearance. However under certain circumstances such as physical stress and illness or specialized diseases of the liver such as cirrhosis and hepatitis, unwanted and dangerous material may be able to evade the liver and enter the general circulation where it can "go systemic." This can then lead to the activation of the alternative complement pathway. Many botanicals are capable of raising the aggressiveness level of the Kupffer cells ('opsonizing").

In addition to its vascular functions, the liver has two other major responsibilities. It is responsible for the synthesis and secretion of bile, which is used to emulsify fats in the lower digestive tract. The liver is also responsible for a multitude of metabolic functions. These include: carbohydrate, protein and fat metabolism; the storage of vitamins and minerals; the formation and storage of a variety of hormones and

chemical mediators; and the detoxification of internal and external toxins such as pesticides, drugs, and other hydrocarbons.

Endotoxins have been known to block their own absorption. This has been termed Schartzmann's phenomenon, a poorly understood mechanism by which the hepatic clearance is blocked by a small amount of endotoxin, allowing a larger amount entry into the circulation.

MYELOPEROXIDASE ACTIVITY

The neutrophils and monocytes of most patients with deseminated candidiasis have been found to lack detectable levels of the enzyme myeloperoxidase (MPO). This rarely affects phagocytosis of the organism, but markedly decreases intracellular destruction, resulting in the organism persisting as intracellular inclusion. This perhaps affords an explanation to the persistance of some health care practitioners in employing questionable superoxide therapies in candidiasis. MPO synthesis is dependent on adequate tissue levels of both iodine and ascorbate, the therapeutic employment of which offers a more sound and safe approach.