

# STONEBRIDGE ASSOCIATED COLLEGES

*Enzyme Deficit in the Human Body and its Role in Immune  
Dysfunction and Toxic Overload: A review*

by

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## INTRODUCTION

This scientific review is based on the argument that enzymes are the missing link for health. The lack of enzymes in modern human diets is the main cause of most degenerative diseases that are affecting a big portion of the civilized population. This idea was first introduced by Dr. Edward Howell and is described in its two books: "Enzymes for Health and Longevity" (Howell, 1980) and "Enzyme Nutrition" (Howell, 1985).

Dr. Howell argued that the act of cooking or processing food kills the enzymes present in raw food, thereby putting the entire digestive burden on the body. This leads to an imbalance in the production of metabolic enzymes according to the law of adaptive secretion. His research showed that humans in comparison to animals have a disproportionate amount of digestive enzymes. He believed that nature's plan call for food enzymes (enzymes in raw food) to help with digestion instead of forcing the body's digestive enzymes to carry the whole load.

Interestingly, Dr. Howell reported that all mammals do have a pre-digestive stomach. He called it a "Food Enzyme Stomach". In humans, it is the upper most portion of the stomach. Enzymes found in raw food pre-digest that food after it has been ingested. Enzymes secreted from saliva and other glands will likewise pre-digest some of the cooked food consumed. However, when cooked food is eaten, enzymes will be supplied from other organs to digest the cooked food. This produces a constant drain of enzymes from the immune system and other important organs. When this happens over a lifetime, organs begin to fail and eventually display symptoms of disease.

## THE FOOD ENZYME STOMACH

The concept of the human pre-digestive stomach seems bizarre at first sight; however, it can be deduced from the medical literature related to the physiology and function of the stomach:

Professors Hans Jorg Ehrlein and Michael Scheman (2006) from the Department of Human Biology at the Technical University in Munich, Germany explained that from a functional point of view, the stomach can be divided into the gastric reservoir and the gastric pump. Those sections are also called by others as proximal and distal stomach respectively. The gastric reservoir has functions to store and to evacuate digesta to the lower part of the stomach (gastric pump). In the gastric reservoir or proximal stomach the digesta is subjected to tonic contractions and peristaltic waves which send the digesta to the distal stomach, while mixing the digesta in the proximal section.

Collins *et al.* (1991) pointed that the proximal stomach plays an important role in the control of gastric emptying of solid foods while the distal stomach is important in the emptying of liquid nutrients. The solid component of the food initially resides wholly within the proximal stomach reservoir.

Doran *et al.* (1998) found that solid food can be stored in the proximal stomach up to three hours. In fact, 20 % of a solid meal can be found in the proximal stomach two hours after digestion.

Lorena *et al.* (2000) found that the time for emptying 50 % of the proximal stomach content after a solid meal is approximately 34 minutes. Additionally, 20 % of the meal still remains in the proximal stomach 100 minutes after digestion.

The Dr. Howell's "enzyme stomach" is surely what is actually called the "gastric reservoir" or the "proximal stomach". The only known function of this stomach section is to store the digested food and to mix it in a gentle way. It is in this stomach section, where the live enzymes within a raw food start pre-digestion of that food.

## FACTS ABOUT THE MODERN DIET

Cordain *et. al.* (2005) pointed that the introduction of agriculture and animal husbandry, some 10,000 years ago represents a very profound change in human diet and lifestyle conditions. The evolutionary collision of the human ancient genome with the nutritional qualities of recently introduced foods may underlie many of the chronic diseases of Western civilization. In developed countries, chronic illnesses and health problems either wholly or partially attributable to diet represent by far the most serious threat to public health. The authors cited obesity, hypertension, diabetes, high cholesterol, osteoporosis and cancer as major illnesses related to the diet.

Eaton & Cordain (1997) compared a pre-agricultural diet with a modern diet. Ancestral human nutrition was derived in 65 % by raw fruits, vegetables, nuts and honey (when available). The remainder 35 % was composed by lean game, wild fowl, eggs, fish and shellfish. In contrast, the modern diet is composed basically of prepared/processed foods including a 55% of highly processed cereals, pasteurized milk, milk products, sugar, sweeteners, separate fats and alcohol; a 25 % of cooked fatty meat, poultry, eggs, fish and shellfish; and only a 17 % of raw fruits, vegetables, legumes and nuts.

One of the most important changes in human nutrition has been the new methods of food processing. Cooking, boiling, heating, frying, etc... are all processes that destroy enzymes in raw foods. When highly processed foods are ingested, the proximal stomach loses its function of being a pre-digestive compartment.

Modern diseases associated to the diet can be considered from an evolutionary perspective; however, there is also the possibility that food processing can be the key issue in this discussion: from 1932 to 1942, Dr Francis Pottenger, Jr, of Monrovia, California (USA) (Pottenger, 1995) developed one of the most interesting clinical studies undertaken in the field of nutrition. He conducted a study involving over 900 different cats, including at least four generations. This study was not planned. Dr. Pottenger was using the cats to test adrenaline extract. He could not understand why the cats were such poor operative risks and their offspring were showing signs of nutritional deficiency. He was feeding what was then considered to be a high quality nutritionally complete diet consisting of two-thirds cooked meat scraps (muscle meat and organ meat) from a local sanatorium, one-third raw market grade milk and one third cod liver oil.

As neighbors kept donating an increasing number of cats to his laboratory, Pottenger exceeded his supply of cooked meat scraps so he placed an order at a meat packing plant for raw meat scraps. Again, including muscle meat, organ meat and bone. Perhaps the phobia of feeding raw meat was prevalent even then because he only fed a segregated group of cats the diet containing the raw meat scraps. Within a short period of time, however, the differences between the cats fed the raw meat scraps and those fed cooked meat scraps became evident.

Pottenger then conducted a controlled study to determine why the cats fed raw meat were apparently healthier than those fed cooked meat. This study was not conducted to benefit feline nutrition. The cats in Pottenger's study were laboratory cats being used to study the effects of heat processed food for the benefit of human nutrition.

The raw meat fed cats were uniform in size and skeletal development from generation to generation. Over their life spans, they were resistant to infections, to fleas and various other parasites and had no signs of allergies. In general, they were gregarious, friendly and predictable in their behavior patterns. They reproduced one homogeneous generation after another with a normal average weight at birth. Miscarriages were rare and litters averaged five kittens with the mother cat nursing her young without difficulty.

In the first generation of the cooked-food group, cats showed symptoms of chronic degenerative disease such as: allergies, asthma, arthritis (both rheumatic and osteo), cancers, heart disease, kidney, liver and thyroid disease, dental disease and osteoporosis. The second generation

manifested the same diseases, albeit even more severely. Most kittens were stillborn or born with disease, and died within six months in the third generation. By the fourth generation, the study ended because the cats were infertile and could not reproduce. These cats reproduced a heterogeneous strain of kittens, each kitten in a litter being different in size and skeletal pattern. They showed much more irritability. Some females were even dangerous to handle. The males, on the other hand, were more docile, often to the point of being unaggressive and their sex interest was slack or perverted.

Abortion in pregnant females was common, running to about 25% in the first deficient generation to about 70% in the second generation. Deliveries were generally difficult with many females dying in labor. The mortality rate of kittens was also high as the kittens were either born dead or are born too frail to nurse. Many cats showed increasing difficulties with their pregnancies and in many instances failed to become pregnant. The average weight of the kittens born of cooked meat fed mothers was 20 % less than the raw meat nurtured kittens.

Most of the deficient cats died from infections of the kidneys, lungs and bones. If these infections were eliminated as a cause of death by modern day antibiotics, it would have allowed the cats to reveal their ultimate degenerative fates.

Applying his results to human nutrition, Dr. Pottenger said, "While no attempt will be made to correlate the changes in the animals studied with malformations found in humans, the similarity is so obvious that parallel pictures will suggest themselves."

There is no similar experiment in medical literature. The findings were supervised by Dr. Pottenger along with Dr. Alvin Foord, professor of pathology at the University of Southern California and pathologist at the Huntington Memorial Hospital in Pasadena. These studies met the most rigorous scientific standards of their day. In drawing his conclusions, Dr Pottenger reported that an underlying nutritional factor had to be a "heat-labile substance". Unfortunately, he had not deduced them to be enzymes, because so little was known about them at the time.

## **WHAT ARE ENZYMES?**

Basically, enzymes are proteins which make life possible. They are needed for every chemical reaction that occurs in every living thing in this planet. Without enzymes, no activity at all would take place. Neither vitamins, minerals, nor hormones can do any work without enzymes. Enzymes are the "labor force" that builds the body just like construction workers are the labor force that builds a house. One may have all the necessary building materials, but to build a house workers are needed, which represent the vital life element. Similarly, one may have all the nutrients -- vitamins, proteins, minerals, etc., for the body metabolism, but one needs the enzymes -- the life element -- to keep the body alive and well.

In human body, for example, the enzyme carbonic anhydrase is found in red blood cells where it enables red blood cells to transport carbon dioxide from the tissues to the lungs. One molecule of carbonic anhydrase can process one million molecules of CO<sub>2</sub> each second. The enzyme acetylcholinesterase catalyzes the breakdown of the neurotransmitter acetylcholine at several types of synapses as well as at the neuromuscular junction — the specialized synapse that triggers the contraction of skeletal muscle. One molecule of acetylcholinesterase breaks down 25,000 molecules of acetylcholine each second. This speed makes possible the rapid "resetting" of the synapse for transmission of another nerve impulse.

In the immune system, the white blood cells rely on enzymes to perform its cleaning job. The leucocytes (white blood cells) contain lysosomes, which is an internal body containing digestive enzymes. More than a dozen of such enzymes acting on virtually all classes of organic substances have been identified in lysosomes. Some important enzymes in lysosomes are lipases,

carbohydrases, proteases, and nucleases (which digest nucleic acids). The lysosomes are used for the digestion of macromolecules from phagocytosis (ingestion of cells), from the cell's own recycling process (where old components such as worn out mitochondria are continuously destroyed and replaced by new ones, and receptor proteins are recycled), and for autophagic cell death, a form of programmed self-destruction, or autolysis of the cell, which means that the cell is digesting itself. Other functions include digesting foreign bacteria that invade a cell and helping repair damage to the plasma membrane by serving as a membrane patch, sealing the wound.

Toxic substances that enter to the human body are eliminated by a complex enzymatic process which transforms the toxins in two phases: functionalization, which uses oxygen to form a reactive site, and conjugation, which results in addition of a water-soluble group to the reactive site. These two steps, functionalization and conjugation, are termed Phase I and Phase II detoxification, respectively. The result is the biotransformation of a lipophilic compound, not able to be excreted in urine, to a water-soluble compound able to be removed in urine. Currently, over 10 families of Phase I enzymes are being described. Phase II reactions are equally complex, and involve multiple enzyme families as well (Liska, 1998).

The human body inherits a certain enzyme potential at birth which shall be preserved through the digestion of enzyme-rich foods. However, modern food processes such as heating, boiling, frying, baking, radiating, etc... destroy all enzymes in the food. Civilized people eat such large quantities of cooked foods that their enzyme systems are kept busy digesting food. This "stealing" of enzymes from other parts of the body to service the digestive tract sets up a competition for enzymes among the various organ systems and tissues of the body. As a result, the body lacks the enzymes needed to maintain the tissues in good health. If enzymes were in the food, they would do some or even a considerable part of the work of digestion by themselves. However, when one eat cooked, enzyme-free food, this forces the body itself to make the enzymes needed for digestion. This depletes the body's limited enzyme capacity. It is considered that this phenomenon is the underlying cause of almost all degenerative disease, as the resulting metabolic dislocations may be the direct cause of cancer, coronary heart disease, diabetes, and many other chronic incurable diseases. Also, this state of enzyme deficiency stress exists in the majority of persons on the modern, enzyme-free diet.

## **ENZYMES IN HUMAN METABOLISM**

From the point of view of nutrition, there are 45 known essential nutrients required in specific amounts in order for the body to function properly. In addition to carbohydrates, fats (lipids), complete proteins, and water, there are at least 13 kinds of vitamins and at least 20 kinds of minerals required for proper metabolic function. Once consumed, the food containing these nutrients must be digested, meaning that the food must be broken apart and reduced to a state that the nutrients can be absorbed into and transported by the blood stream to all parts of the body. Body cells are programmed to direct these nutrients which are used to build and repair the body's cells, bones, tissues, and organs. This process is called metabolism. Each metabolic reaction is started, controlled, and terminated by enzymes. Without enzymes there is no metabolic activity. A body that does not consistently and efficiently metabolize the essential food elements necessary for life will be unhealthy, out of balance, and this condition will result in a severe susceptibility to disease.

For the purpose of this document, enzymes related to human metabolism can be classified in three categories:

- 1) Digestive Enzymes
- 2) Food Enzymes
- 3) Metabolic enzymes

Digestive and food enzymes are active only within the digestive system. They have the important function of food digestion. Metabolic enzymes exist throughout the body in the organs, the bones, the blood, and inside the cells themselves. They are programmed to regenerate and maintain their host. These enzymes do their job carrying out their metabolizing mission as long as they are healthy and there are enough of them.

Digestive enzymes are secreted by the salivary glands, stomach, pancreas, and the small intestine. Technically, digestive enzymes are also considered to be metabolic enzymes whose metabolic role is to digest food. However, they deserve an especial category as they deal with digestion and they can be supplemented from an outside source. Digestive enzymes and food enzymes basically serve the same function.

The process of digestion begins in the mouth. The saliva contains an enzyme called ptyalin (amylase) which initiates the breakdown of carbohydrates by converting starches into simple sugars. The ptyalin is active in an alkaline, neutral or slightly acid medium and is inactivated by the highly acid gastric juices in the stomach. In the stomach, the physical action of peristalsis mixes and kneads solid food into a semi-solid amorphous mixture called chyme, this mixture undergoes chemical changes initiated by gastric juices secreted by the walls of the stomach. These juices include mucus for lubricating the stomach, hydrochloric acid and gastric enzymes. The enzyme in the gastric juice is pepsin. This enzyme in combination with hydrochloric acid starts the breakdown of proteins into absorbable amino acids called polypeptides. The gastric juice has no effect upon starches or fats.

The chyme leaves the stomach and enters the small intestine through the pylorus. Digestion is completed inside the small intestine by several excreted enzymes. From the liver comes the bile which converts fat globules into a smooth emulsion; however there are no enzymes in the bile. The pancreas contributes with various enzymes which continue the breakdown of proteins, help to divide starch into sugars and work with bile in digesting fats. The small intestine itself secretes enzymes from its inner wall to complete the reactions. When all the enzymes have done their work, the food is digested and rendered fit for absorption by the system.

As it has been pointed, enzymes that function in the digestion of foods can be either produced within the body or obtained through the consumption of raw foods. Raw, uncooked foods, especially fruits and vegetables, are a valuable source of enzymes. Unfortunately, the modern diet contains mainly cooked/processed foods. The application of heat to foods inactivates the enzymes contained in them.

Enzymes secreted from saliva and other glands will likewise pre-digest some of the cooked food consumed. However, when cooked food is eaten, enzymes will be supplied from other organs to digest the cooked food. This produces a constant drain of enzymes from the immune system and other important organs.

## **DEFICIT OF DIGESTIVE ENZYMES**

The deficit of digestive enzymes do not allow the appropriate hydrolysis of food molecules, thus leaving “big” food particles or molecules that can not be used as a nutrient by cells. Furthermore, the fate of those big particles or molecules fall between two alternatives, depending on their possibility to cross or not, the gut barrier (Loomis, 1999):

- 1) Inadequately hydrolyzed food molecules, not digested well enough to pass across the gut wall. Those particles pass down the alimentary canal, where they putrefy and form toxins that will be absorbed into the blood. Food putrefaction promotes bacterial dysbiosis and intestinal hyperpermeability syndrome; two pathologies that will be described in following pages.

- 2) Food particles digested enough to pass through the gut wall and into the blood but not reduced to particles small enough to be utilized by the cells for energy production. In this case, food particles act as antigens and promote an immune reaction. Food antigens lead to the formation of immune complexes, inflammation and related immune pathologies. The pathologies related to "food antigens" will be discussed next.

## **BACTERIAL DYSBIOSIS**

Recognition that intestinal flora have a major impact on human health first developed with the birth of microbiology in the late nineteenth century. It is generally accepted that human relationship with indigenous gut flora is "symbiotic," meaning a state of living together that is beneficial. Metchnikoff popularized the idea of "Dys-symbiosis, or Dysbiosis," a state of living with intestinal flora that has harmful effects. He postulated that toxic amines produced by bacterial putrefaction of food were the cause of degenerative diseases. The notion that dysbiotic relationships with gut microflora may influence the development of inflammatory diseases and cancer has received considerable experimental support over the past two decades. Intestinal dysbiosis should be considered as a mechanism promoting disease in all patients with chronic gastrointestinal, inflammatory or autoimmune disorders, food allergy and intolerance, breast and colon cancer, and unexplained fatigue, malnutrition or neuropsychiatric symptoms. (Galland & Barrie, 2006).

Most adverse effects of the indigenous gut flora are caused by the intense metabolic activity of luminal organisms. The following pathologies are associated with Putrefaction dysbiosis (Galland & Barrie, 2006; Catanzaro & Green, 1997):

1. The small intestine is the primary site of food absorption, and the metabolism of bacteria can interfere with this process. Bacteria can prevent the uptake of vitamin B12 in the distal ileum, causing B12 deficiency and megaloblastic anemia. The lost dietary B12 can be recovered bound to bacteria in the feces of patients with bacterial overgrowth.
2. The enzyme urease, found in some bacterial species, and induced in those organisms by a diet high in meat, hydrolyzes urea to ammonia, raising stool pH. A relatively high stool pH is associated with a higher prevalence of colon cancer.
3. Bacterial decarboxylation of amino acids yields vasoactive and neurotoxic amines, including histamine, octopamine, tyramine and tryptamine; these are absorbed through the portal circulation and deaminated in the liver. In severe cirrhosis they reach the systemic circulation and contribute to the encephalopathy and hypotension of hepatic failure.
4. Bacterial tryptophanase degrades tryptophan to carcinogenic phenols, and, like urease, is induced by a high meat diet. Urinary concentrations of indole and indican, which are degradation products of tryptophan, are increased in patients with small bowel bacterial overgrowth. This particular pathology is called Indicanuria and is considered to produce several diseases which are listed in the Table No. 1. Additionally, indoxyl sulfate, a sulfate conjugate of indoxyl (a derivative compound from hydrolysis of indican), is a known circulating uremic toxin promoting the progression of glomerular necrosis and renal failure.
5. Bacterial enzymes like beta-glucuronidase hydrolyze conjugated estrogens. Hepatic conjugation and biliary excretion is an important mechanism for regulating estrogen levels in the body. Bacterial deconjugation increases the enterohepatic recirculation of estrogen. A Western diet increases the level of deconjugating enzymes in stool, lowers estrogen levels in stool and raises estrogen levels in blood and urine, possibly contributing to the development of breast cancer.
6. Beta-glucuronidase and other hydrolytic bacterial enzymes also deconjugate bile acids. Deconjugated bile acids are toxic to the colonic epithelium and cause diarrhea. They or their metabolites appear to be carcinogenic and are thought to contribute to the development of colon cancer and to ulcerative colitis. Gut bacteria also reduce primary bile acids like cholate

**TABLE No. 1. SYMPTOMS OF INDICANURIA (INTESTINAL TOXEMIA)**

From Loomis, H. F. (1999) "Enzymes: The Key to Health: The Fundamentals". 21<sup>ST</sup> Century Nutrition Publishing, Madison, Wisconsin, USA.

<p><b>Skin-Hair-Nails</b></p> <p>Dermatosis</p> <p>Eczema</p> <p>Psoriasis</p>	<p><b>Eyes-Ear-Nose-Sinuses</b></p> <p>Diseases of nasal accessory sinuses</p> <p>Diseases of middle and internal ear</p> <p>Eye strain</p>	<p><b>Cardiovascular</b></p> <p>Tachycardia</p> <p>Cardiac arrhythmia</p> <p>Migraine</p>
<p><b>Genitourinary</b></p> <p>Foul odor to urine</p>	<p><b>Mouth-Throat</b></p> <p>Halitosis</p> <p>Body odor</p>	<p><b>Respiratory System</b></p> <p>Asthma</p>
<p><b>Gastrointestinal</b></p> <p>Gas and bloating</p> <p>Constipation/Diarrhea</p> <p>Crohn's disease</p> <p>Food allergies</p> <p>Foul stool odor</p> <p>Gastritis</p> <p>Heartburn</p> <p>Hiatal hernia</p> <p>Inflammatory bowel disease</p> <p>Ileocecal valve problems</p> <p>Malassimilation</p> <p>Weight loss</p>	<p><b>Musculoskeletal System</b></p> <p>Arthritis</p> <p>Low back pain and sciatica</p> <p>Fibromyalgia and myofascitis</p> <hr/> <p><b>Endocrine System</b></p> <p>Breast pathology</p> <p>Eclampsia</p> <p>Thyroid goiter</p>	<p><b>Nervous System</b></p> <p>Depression and melancholy</p> <p>Epilepsy/seizure disorders</p> <p>Excessive worry and anxiety</p> <p>Incoordination</p> <p>Irritability</p> <p>Lack of confidence</p> <p>Loss of concentration and memory</p> <p>Mental sluggishness or dullness</p> <p>Schizophrenia or senility</p> <p>Sensory polyneuritis</p>

and chenodeoxycholate to secondary bile acids like deoxycholate (DCA) and lithocholate. The secondary bile acids are absorbed less efficiently than primary bile acids and are more likely to contribute to colon carcinogenesis. The prevalence of colon cancer is proportional to stool concentration of DCA.

7. Amino acid absorption can be impaired while fecal nitrogen is increased and serum proteins lowered. These changes, associated with bacterial overgrowth, can contribute to the dysfunction of mucosal cells, impairing protein and carbohydrate absorption.
8. Degradation of digestive enzymes by bacterial proteases has been shown to occur by certain bacterial species. This may further contribute to enzyme insufficiency and maldigestion.

All the bacterial metabolites and toxins irritate the gut wall. When the functioning of any aspect of the gut mucosal barrier is sufficiently compromised, the integrity of the bowel itself becomes compromised, resulting in increased permeability to foreign or gut-derived antigens, allowing them to “leak” through the gut into the lymphatics and the systemic circulation. The “leaky gut syndrome” or intestinal hyperpermeability should be considered an integral part of any chronic pathological condition.

## **INTESTINAL HYPERPERMEABILITY**

The intestinal barrier function is considered to play an important role in protecting the penetration of luminal antigens, associated with the development of secondary infection and sepsis and the initiation of the multiple organ dysfunction syndrome (Sun, 1998). Leaky gut syndrome has been theoretically suspected as a major factor in a wide range of food and chemical sensitivities, arthritis, asthma, headaches, digestive problems of varying seriousness and chronic fatigue. It was quickly linked to many of the problems experienced in patients with severe *Candida albicans* overgrowths, since it was known that *Candida*, in its fungal form, can put down 'roots' into the gut wall, allowing comparatively large molecules to pass through into the bloodstream. Whether these are food molecules, bacteria or chemical toxins, the result would be the same: an immune response by the body, an attack by antibodies and the start of a cycle of immune response, inflammation and antibody-antigen reactions. Intestinal permeability is now respectable, thanks to the comparatively recent development of a urine-based diagnostic test (Martin, 1995).

Clinically, Intestinal Hyperpermeability Syndrome is associated with following diseases (Galland, 1998; Sun, 1998; Miller, 1997; Martin, 1995) :

Inflammatory bowel disease	Infectious enterocolitis
Spondyloarthropathies	Acne
Eczema	Psoriasis
Urticaria	AIDS, HIV infection
Cystic fibrosis	Pancreatic insufficiency
Multiple food and chemical sensitivities	Hepatic dysfunction
Irritable bowel syndrome with food intolerance	Chronic arthritis/pain treated with NSAIDs
Neoplasia treated with cytotoxic drugs	Celiac disease
Dermatitis herpetiformis	Autism & Childhood hyperactivity

Also, following symptoms are associated with the Intestinal Hyperpermeability Syndrome

Fatigue and malaise	Arthralgias
Myalgias	Fevers of unknown origin
Food intolerances	Abdominal pain
Abdominal distension	Diarrhea
Skin rashes	Toxic feelings

Cognitive and memory deficits  
Poor exercise tolerance

Shortness of breath  
Endo-toxemia

## ENZYME DEFICIT AND DISEASE

Enzyme deficit in the human body can be diagnosed in several diseases. For example, if allergies are analyzed from an enzyme point of view, it becomes apparent why so many of the medicines used to treat it work only temporarily. Allergies are the body's reaction to something entering via the blood, skin, nasal cavity or other source. When something enters the body in a healthy person, the immune system is called upon to investigate and clear the allergen (substance) from the body. This happens without any notice.

Because there are enough enzymes available in a healthy person, the allergen can be cleared unobtrusively. In someone with an allergic response to the same substance, the immune system is called to do the same work but finds it cannot handle the request. In a person who exhibits an allergic response, there are not enough enzymes available for the white blood cells to break down the allergen and rid the body of it. That person then experience the typical histamine response, including reddening of the eyes or local tissue, heat, runny nose and pain.

The Table No. 2 shows a review of papers from MedLine indicating major diseases associated to deficiency of pancreatic enzymes.

In this paragraph, it is important to describe some mechanism by which enzymes are exhausted in the human body. It shall be pointed that following papers evidenced that enzymes are not "indestructible" inside the human body. In fact, enzymes seem to have a relatively short span life and additionally are subjected to excretion.

Researches from Keller & Layer (2005), Holtmann *et. al.* (1997) and Layer *et. al.* (1986) show that there are significant losses of all digestive enzymes during the digestion process. The loss of enzyme activity is especially critical for the lipase, which is totally lost during its transit through the small bowel. Some proteases, mainly the chymotrypsin, play an important role in eliminating the lipase activity through the gut.

Additionally, the human body loses digestive enzymes through the feces as it is evidenced by Elphick & Kapur (2005); Walkowiak *et. al.*, (2003); Walkowiak *et. al.* (2002); Goldberg (2000); Lankisch *et. al.* (1998); Loser *et. al.* (1996); and Sziegoleit *et. al.* (1989). Digestive enzymes are also excreted through the urine as indicated by Elphick & Kapur, 2005; Hegewald *et. al.*, 2001; and Hedstrom *et. al.*, 1998.

## DIGESTIVE LEUCOCYTOSIS

In the past lines of this monograph, the impact of indigested food that remains in the intestinal lumen was described. In the following paragraphs, the fate of indigested material that is able to cross the intestinal barrier will be presented. As it has been pointed, those food molecules can not be absorbed by the cells for nutrition purposes, instead those molecules act as antigens thus activating the immune system.

Rudolph Virchow, the father of cellular pathology, described digestive leukocytosis in 1897 and considered it to be a normal condition because all its subjects demonstrated it after ingesting food. The leucocytes are rich in enzymes (lysosomes) and are called on to finish digestion not completed in the gut.

**TABLE No. 2. PATOLOGIES RELATED TO DEFICIENCY OF PANCREATIC ENZYMES**

<b>PATOLOGY</b>	<b>REFERENCE</b>
Geriatric patients & ageing	Nakae <i>et. al.</i> (1999) Laugier <i>et. al.</i> (1991) Ishibashi <i>et. al.</i> (1991) Vellas <i>et. al.</i> (1988a) Vellas <i>et. al.</i> (1988b) Howell (1985) Valenkevich (1976)
Diabetes mellitus	Keller & Layer (2005) Hardt <i>et. al.</i> (2003) Nunes <i>et. al.</i> (2003) Richter & Wagner (2001) Canaway <i>et. al.</i> (2000) Hardt <i>et. al.</i> (2000) Lankisch <i>et. al.</i> (1982) Domschke <i>et. al.</i> (1975)
Childhood protein energy malnutrition	El-Hodhod <i>et. al.</i> (2005)
Zinc malabsorption	Dutta <i>et. al.</i> (1998)
Secondary malabsorption syndrome	Walkowiak & Herzig, 2001
Celiac disease	Keller & Layer (2005) Morales (2001) Mercer <i>et. al.</i> (1990) Weizman (1987) Borulf & Linderg (1982) Regan & DiMagno (1980)
Functional Dyspepsia	Malfertheiner & Dominguez-Munoz (1993) Smith <i>et. al.</i> (1991) Andersen (1982)
Irritable Bowel Syndrome	Herrlinger & Stange (2000)
Patients HIV positive	Pride <i>et. al.</i> (2005) Carroccio <i>et. al.</i> (2001) Carroccio <i>et. al.</i> (1998)
Autism	White (2003) Kidd (2002) Horvath & Perman, (2002) Horvarth <i>et. al.</i> (1999)
Atherosclerosis (Pancreatic Lipase)	Hokanson <i>et. al.</i> (2002) Dugi <i>et. al.</i> (2001)

In 1930, a research was conducted to demonstrate the effect of food (cooked/processed vs. raw/natural) on the immune system. It was tested and documented at the Institute of Clinical Chemistry in Lausanne, Switzerland, under the direction of Dr. Paul Kouchakoff. Kautchakoff found that leukocytosis was not normal. In fact, the major cause of leukocytosis was discovered to be the eating of cooked food. An entire category of leukocytosis was classified as "digestive leukocytosis", that is, the elevation of the white blood cell level in response to the lack of enzymes in the cooked food in the intestine. It is pathological because the pancreas does not provide most of the digestive enzymes needed. Dr. Kautchakoff divided his findings into four classifications according to the severity of the pathological reaction in the blood:

- Raw food produced no increase in the white blood cell count.
- Commonly cooked food caused leukocytosis.
- Pressure cooked food caused even greater leukocytosis.
- Man-made, processed and refined foods, such as carbonated beverages, alcohol, vinegar, white sugar, flour, and other foods, caused severe leukocytosis. Cooked, smoked and salted animal flesh brought on violent leukocytosis consistent with ingesting poison.

Recent researches such as Husby (2000) consider that the appearance of small amounts of dietary antigens taken up into the circulation is a physiological event. B-cell responses to foods (antibodies and antibody-secreting cells) occur as a normal phenomenon locally and in the circulation in all three major immunoglobulin classes. A low level of IgE is also a normal condition. Previously Husby (1998) and Paganelli *et. al.* (1979) pointed that in humans the uptake of intact dietary antigen, free or in immune complexes, was reported in studies in healthy subjects and in patients with immune deficiency or atopy. Husby (1998) reported that some dietary antigens were measurable in serum up to 48 h after the meal, presumably as immune complexes. Dietary antigens have been detected in the mother's milk and may be important for the development of normal immunity to dietary antigens and in particular of cow's milk allergy in the infant. Antibodies to dietary antigens have previously been detected in a major proportion of healthy subjects. Interestingly, these antibodies were restricted to the IgG subclasses IgG1, IgG2 and IgG4.

Although, it can be considered that the presence of food antigens in serum is a normal condition, various researches show a clear correlation between various diseases non related to the gastrointestinal system and the specific presence of dietary antigens in serum, as for example in patients with:

- a) Multiple myeloma (Juranic *et. al.*, 2006),
- b) Multiple sclerosis (Reichelt & Jensen, 2004),
- c) Diabetes mellitus type 1 (Kohno *et. al.*, 2002; Ahmed *et. al.*, 1997),
- d) IgA nephropathy (Pierucci *et. al.*, 2002; Kovacs *et. al.*, 1996),
- e) Rheumatoid arthritis (Hafstrom *et. al.*, 2001),
- f) Atopic dermatitis (Caffarelli *et. al.*, 2001; Uchio *et. al.*, 1998, Duchon *et. al.*, 1997; Iida *et. al.*, 1995),
- g) Down Syndrome (Reichelt *et. al.*, 1994),
- h) Vasculitis (Lunardi *et. al.*, 1992),
- i) Chronic liver disease (Lerner *et. al.*, 1985)
- j) Migraines (Monro *et. al.*, 1980).

## **IMMUNE COMPLEXES FORMATION AND DEPOSITION**

Following the structure of this presentation, it was pointed that non-digested or inadequately hydrolyzed food molecules can cross the gut wall and will act as antigens activating the immune

system. The presence of food antigens is associated to various diseases. In this paragraph, one of the most important aspects of immune reaction to serum antigens will be described: the formation of immune complexes and its potential to tissue damage.

The concept that antigen-antibody complexes might be responsible in causing disease was first introduced by von Pirquet in the early 1900s. After studying serum sickness in humans, he proposed that the interaction of foreign serum antigens and host antibody in the circulation resulted in the formation of toxic factors, which were probably responsible for the characteristic lesions of this disorder.

The mechanism of immune complex mediated tissue injury is as follows (Espinoza, 1983): After exposure to foreign antigens, certain types of soluble antigen-antibody complexes that are formed in antigen excess freely circulate, and if not cleared from the circulation by the reticuloendothelial system, will be deposited in the wall of blood vessels or tissues throughout the body. Following immune complex deposition in vessel walls, the complement system is activated, resulting in the formation of chemotactic factors for polymorphonuclear leukocytes. These cells infiltrate the vessel walls and release their lysosomal enzymes. In addition to humoral factors, cellular factors also participate in immune complex-mediated tissue injury. The activation of neutrophils, platelets, basophils, lymphocytes and macrophages follows complement consumption.

The immunopathological and clinical consequences of the interaction of antigen-antibody complexes can vary depending upon the anatomic sites of union with antigen and antibody and upon the absolute and relative amounts of the two reactants. Multivalent antigens such as proteins and polysaccharides derived from food antigens when combined with their corresponding antibodies do form immune complexes of varying composition, depending of the molar ratio of the reactants.

In the presence of a large antigenic excess the resulting immune complexes are small, do not fix complement, and therefore cannot induce tissue damage. At the other side, immune complexes formed in great antibody excess, although capable of activating the complement system, are large and soluble, and thus rapidly removed from the circulation by the reticuloendothelial system. Pathogenic immune complexes capable of initiating inflammation are usually formed when antigen excess is modest. These complexes are usually intermediate in size, are soluble, and are capable of fixing complement, but are not rapidly eliminated from the circulation by the reticuloendothelial system.

The following disorders are associated with the presence of circulating immune complexes:

- Lupus erythematosus (Stokol, 2004; Walport, 2001; Davies *et. al.*, 1990; Alarcon, 1983)
- Rheumatoid arthritis (Stokol, 2004; Alarcon, 1983; Karsh, 1983)
- Vasculitides (Stokol, 2004; Beynon *et. al.*, 1994, Espinoza, 1983; Vasey, 1983)
- Glomerulonephritis (Stokol, 2004, Caulin-Glaser *et. al.*, 1983)
- Hematologic diseases (Yen *et. al.*, 1989, Carpentier *et. al.*, 1977))
- Malignant diseases (Golda *et. al.*, 2004; Vel'bri *et. al.*, 1986; Krapf, *et. al.*, 1983)
- Rheumatic fever (Castañeda, 1983)
- Diabetes mellitus (Espinoza, 1983; Bocanegra & Gomez-Sanchez, 1983)
- Multiple Sclerosis (Espinoza, 1983; Bocanegra, 1983)
- Optic Neuritis (Bocanegra, 1983)
- Guillain-Barre Syndrome (Espinoza, 1983; Bocanegra, 1983)
- Myasthenia Gravis (Alarcon, 1983; Espinoza, 1983; Bocanegra, 1983)
- Psoriasis (Espinoza, 1983)
- Cardiovascular diseases (Mustafa *et. al.*, 2001; Cristea *et. al.*, 1986)
- Atherosclerosis (Tarnacka *et. al.*, 2002; Kari Lefvert *et. al.*, 1995)
- Macular degeneration-related disorders (Hageman, 2005)

## CHRONIC INFLAMMATION DISORDERS

Circulating immune complexes (ICs) are produced continuously in response to infection, tissue injury, and immune reactions to foreign antigens. Most ICs are of little pathologic significance because they are rapidly cleared by hepatic and splenic phagocytes. However, excessive IC accumulation occurs in several immune-mediated diseases in human patients. Persistent IC accumulation and deposition give rise to chronic inflammation at site of ICs deposition.

The 'inflammatory process' includes a tissue based startle reaction to the IC deposition; go/no-go decisions based on integration of molecular clues for tissue penetration by antigens; the beckoning, instruction and dispatch of cells; the elimination of antigens and host cells they affect; liquefaction of surrounding tissue; and the healing of tissues damaged by the host's response. If at any step an order to proceed is issued but progress to the next step is blocked, the inflammatory process may detour into a holding pattern, such as infiltration of a tissue with aggregates of lymphocytes and leukocytes (granulomas) that are sometimes embedded in proliferating synovial fibroblasts (pannus), or distortion of a tissue with collagen bundles (fibrosis). Persistent inflammation can oxidize DNA badly enough to promote neoplastic transformation.

**TABLE No. 3 Disorders in which an important pathogenic role is assigned to Inflammation** (Based on Nathan, 2002)

Alzheimer's disease	Osteoarthritis
Anaphylaxis	Periodic fever syndromes
Ankylosing spondylitis	Psoriasis
Asthma	Rheumatoid arthritis
Atherosclerosis	Sarcoidosis
Atopic dermatitis	Systemic lupus erythematosus
Chronic obstructive pulmonary disease	Type I diabetes mellitus
Crohn's disease (regional disease)	Ulcerative colitis
Gout	Vasculitides
Myocardial infarction	Hashimoto's thyroiditis
Multiple sclerosis	Neoplasias

## INFLAMMATION AND CANCER

The link between inflammation and cancer was first suggested by Rudolph Virchow in 1863, when he demonstrated leucocytes in neoplastic tissue. Virchow's original hypothesis has been revisited by many research groups, and there are now ample data to corroborate inflammation-mediated oncogenesis. The epidemiological data available are very impressive and show a clear association between chronic inflammatory conditions and subsequent malignant transformation in the inflamed tissue (Balkwill & Coussens, 2004; Itzkowitz & Yio, 2004; Macarthur, M. *et. al.*, 2004; Coussens & Werb, 2002 )

In tumors, many of the cell types active in chronic inflammation can be found in the surrounding stroma and also within the neoplasm itself. In 1891, mast cells were reported as histological findings at the tumor periphery, and today, there is no doubt that many neoplasms, particularly those that are epithelial in origin, have a significant inflammatory cell component. This includes a diverse leukocyte infiltrate of macrophages, neutrophils, eosinophils, and mast cells often in association with lymphocytes. Tumor-associated macrophages are dispersed throughout many tumors, whereas the distribution of dendritic cells may vary according to their level of maturity. For example, in breast cancer, mature dendritic cells were found to be confined to the peritumoral area, whereas immature dendritic cells were interspersed in the tumor mass.

A cardinal feature of inflamed tissues is the generation of nitric oxide (NO) through inducible nitric oxide synthase. NO reacts with superoxide to form peroxynitrite and nitrosating species. NO and its products may exert oncogenic effects via several mechanisms including direct DNA and protein damage, inhibition of apoptosis, mutation of DNA, alterations of cellular repair functions and also via promotion of angiogenesis (Jaiswal *et. al.*, 2001).

## **CONCLUSIONS**

The evidence from scientific papers suggests that from a physiological point of view, the human stomach was developed to pre-digest the food by using the enzymes normally present in raw foods. Food processing eliminates all enzymes in foods rendering useless the stomach role of food pre-digestion.

The lack of stomach pre-digestion requires the body to dispose the entire enzymatic load to perform food digestion. In order to do this, the human body diverts enzymes needed for metabolic and defense purpose. This affects normal metabolic processes and body defense mechanisms.

The continuous demand of endogenous enzymes for digestion leads eventually to enzyme deficit affecting digestive and metabolic processes, immune defense and detoxification. Non hydrolyzed food can putrefy in the intestinal lumen, producing toxins, bacterial dysbiosis and intestinal hyperpermeability syndrome; or can cross the gut barrier and be absorbed into the bloodstream where it act as an antigen, activating an immune response, which leads to the formation of immune complexes, inflammation and related immune pathologies.

Toxins produced by putrefaction and bacterial dysbiosis overburden the detoxification system; while non-digested food particles in the blood stream are captured by leucocytes which end the food molecule hydrolysis. Under the phenomenon of enzyme deficit, the food is not just ineffective as a nutrient, but instead it produces toxic overload and the same symptomatology as a low grade chronic infection. The continuous drain of defense and detox resources in order to handle the enzyme-free foods, leads to the development of disease in the body.

Major diseases attributable to enzyme deficit are those related to bacterial dysbiosis, intestinal hyperpermeability syndrome, immune complexes pathologies and chronic inflammations, including the possibility of malignant diseases.

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