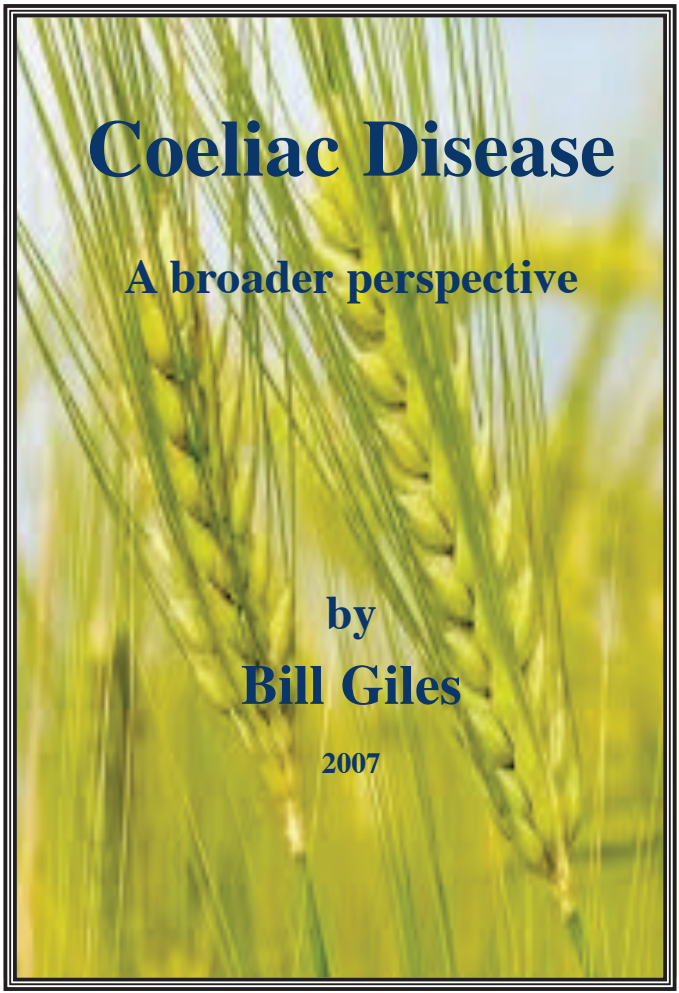

Coeliac Disease

A broader perspective

by

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Introduction

I am a biologist and have worked in a clinical practice for more than 20 years. My main focus has been immune related chronic health problems. I am not a paid research scientist nor a registered medical practitioner. However, I have used biological scientific principles to assist several thousand people regain normal health.

This booklet is about coeliac disease and its related immune driven ill-health symptoms based on my clinical experience. I have found that most information available to the public about this disease is conservative and reflects a real need for more broad ranging scientific inquiry into the causes of this and other autoimmune diseases as well as the necessary lifestyles to remove them.

Scientific studies of coeliac disease have comprehensively linked a grain defence protein known as gluten with a genetic aggressive predisposition of primary defence immune cells. The development of coeliac disease is now linked to the destruction of healthy intestinal villi cells by secondary defence immune cells—giving symptoms of malabsorption. Associated chronic ill-health symptoms often continue when the coeliac person is totally gluten free. I think the basis of many of these chronic symptoms is likely to be vegetable, grain or fruit defence proteins similar to gluten.

Hopefully in the near future, scientific studies will broaden in their scope and shed light on clinical observations such as mine. However in the meantime if you are coeliac or have another autoimmune disease, you can undertake your own investigations using some of the information presented in this booklet, and I think you will have an increased chance of acquiring better health.

What is gluten?

Gluten is a term for the sticky, glue-like protein in rye, wheat, oats and millet, that binds the starches and fibres in grain flours to make our delicious bakery products.

Prevention of malabsorption

To prevent a debilitating life and the increased possibility of a shortened life, the only successful treatment for coeliac disease known by science, is a change in lifestyle—the adoption of an eating lifestyle that incorporates the **total** removal of gluten food products for life! This allows the coeliac person to live an almost normal life. Bakery products made from rice, corn, soya, buck-wheat and other gluten-free flours greatly assist this. At the present time, if a person with coeliac disease experiences other types of immune related symptoms, even though they are off all gluten, the current treatment is strongly reliant on pharmaceutical drugs to lessen the symptoms and assist with better health.

Clinical observations

Having worked with thousands of people with coeliac disease, I have been continually dismayed to find that most continue to have some chronic symptoms, even when they have been gluten-free for years. While their intestinal symptoms would mostly abate and endoscopies would show normal structural ranges for the intestinal villi, they would still experience various chronic symptoms and invariably present with distended livers and chronic low-grade lymph node swelling—their health would be fragile.

I know that many people who are not coeliac, but have chronic immune symptoms, also benefit from the removal of gluten. Is there a broader connection between vegetable defence proteins and immune compromisation, which is not being recognised?

I have asked thousands of clients to undertake their own trials (comparing several weeks 'Without' grain foods to several weeks 'With' grain foods—balanced with a control) and not rely totally on their standard test results. In my experience, after they remove all grains from their diet, their symptoms can continue for several weeks before they change. Also following the reintroduction of grain foods, most people with chronic immune related diseases experience several days delay before their symptoms even show the smallest re-occurrence. Some symptoms also occur after eating even one mouthful of a grain food—the triggering dose appears to

be minuscule for some. These immense delays and durations are not yet recognised by the medical models of immune diseases!

Conclusions of Research

Medical authorities are required to follow the guidelines of their industry—its basis is scientific confirmation. The nature of scientific study is to find the most appropriate answer to a specific question, aiming to determine the highest degree of predictability for the broadest of situations that the study encompasses. Sometimes experiments are performed and sometimes observations are collated. Deductive and inductive logic are utilised and mathematical analysis are mostly used to support predictability and theories in an attempt to emulate the broadest of truths.

The results of a study are used to enhance the intended position of persuasion of the experimenter when presented to those who read the study. Science is never static for its very foundation of existence is dependent on further studies that either support or do not support earlier studies in the effort to get closer to the universal 'truths'. There is no end to scientific study of each and every question proposed. Science produces more questions than it answers.

The results of a scientific study greatly depend on the limits to which the study can go and the specific questions asked. Often opposing conclusions can be reached. We read this every day when

one study suggests a particular food like soya is good for health and another study which contradicts this. If the limits of a study are broader or are narrower or refer to a different context, the data evidence will vary. The results we often read in the newspapers are simply reflecting the limits imposed on a scientific study.

Many scientists are required to answer the 'bigger picture' questions and they have to reach for broader and broader generalisations and allow for more variables. The ideal study would have infinite variables! Sometimes having more variables tends to obscure relevance for the individual. For example, nutritionists conclude from evidence-based studies that wheat should be classified as an essential food for good health because of its ruffage, starch and nutrient content—a 'big picture' generalisation! However this conclusion does not apply to about 10% of the population who have coeliac disease. Immunologists, not having a major focus on nutrition, find through their evidence-based studies, that wheat should be classified as a lethal food for people with coeliac disease! So which group is correct in their assessments? Both are!

Scientific evidence at the population level has more relevance for decision making by governing bodies, but may not have much relevance for certain individuals. This is why sometimes it is essential for an individual to undertake their own studies and not totally rely on the evolution of scientific understanding.

Do you have unanswered questions about your health?

If you have poor health and you cannot improve it even with your medical practitioner's help, you may have to search outside the current guidelines of medical understanding. Undertaking your own research is fraught with difficulties and sometimes requires assistance from professionals. Here are some guidelines:

• Read widely and attempt to understand the current scientific thinking of your disease—and then ask questions.

• Do not presume that the current scientific thinking is comprehensive for your condition.

• If you have a nutrition problem, research the nutrition models. If you have an immune problem, research the immunology models—they are often completely opposite in their generalisations.

• Defence chemicals in plant foods most probably will have some connection with your autoimmune disease—treat all plant foods with suspicion and do 'With' and 'Without' trials for all types.

• Degrees of cooking of various plant foods has relevance to some autoimmune diseases—research this.

What is coeliac disease?

Coeliac disease is hereditary. It involves an inappropriate immune reaction to subunits of a grain protein (gluten), along with misdirected targeting of intestinal cells when they are associated with gluten. During the digestive process, gluten is broken down into fragments called peptides. More than 20,000 different gluten peptides exist in grains—only one of these (gliadin) is known to be linked to coeliac disease (a glutamine and proline rich 33-mer peptide). Becoming gluten reactive can begin at birth, but in most cases begins later in life after a period of immune weakening through stress, infections, toxicity or physical injury. Once kick-started, gluten reactivity is ongoing for life—three factors combine to initiate the immune response directed at gluten peptides.

These factors include a chronically weakened immune system, a genetic predisposition and the ingestion of a specific plant protein—gluten. The disease symptoms can be stopped by removing one or more of these factors—the easiest being the total avoidance of gluten from one's diet (Sollid and Thorsby 1993, Marsh 1992).

People with healthy immune systems (refer to Appendix 1.) can eat all types of grain foods, in any combination, any amount, at any time and not experience symptoms. Healthy people efficiently utilise the cereal sugars and fibre while eliminating the harmful

defence proteins. The triggering of coeliac disease undoubtedly involves a chronic weakening of immune health (Clevers 1986, Mothes 1995). This permanently reduces efficiency in communication between immune cells. It also increases the possibility of the immune cells mis-identifying harmless chemicals as a threat to the body. This mis-communication increases the possibility of the immune system attacking and destroying normally healthy cells in what is called an 'autoimmune response' (Appendix 2.).

Molecular mimicry

Molecular mimicry is a type of misdirected, first line of defence reaction that commonly is the trigger for the autoimmune response. Consider this: If the first line of immune defence is coded to stop specific chemicals or 'bugs' entering the body, it spontaneously initiates attacks on these and relays their actions to the second line of defence for assessment and sometimes help. In molecular mimicry, the genetically coded cells of the first line of defence mistake a harmless chemical or 'bug' for a lethal chemical or 'bug' and attack it, often causing inflammation—but they rarely kill healthy body cells. This is only the first stage—a pre-coeliac response. The second line of defence will not enter the fight if it determines that the first line has made a mistake. If the second line of defence has to enter the fight, it has the ability to destroy the body's own cells. When this occurs in coeliac disease, the cells of the intestine are destroyed and the condition of coeliac disease begins.

When an immune cell mis-identifies food chemicals or cells as infectious agents such as virus or bacteria, they initiate defence reactions (Oldstone 1987, von Herrath 1995).

In coeliac disease, cells known as macrophages, from the first line of immune defence (see Appendix 1.), cause inflammation and lymph swelling in the lymph nodes lining the small intestine as they engulf the gliadin peptides. Gliadin is an assembly of peptides (chemical compounds of more than two amino acids) which easily pass through the intestine wall into the submucosa. A person with coeliac disease has genetically different macrophages to the normal person in our populations. The macrophage cells of people who do not have coeliac disease disregard the gliadin chemical.

The reason why some people evolved macrophages that recognise gliadin as a threat could be explained this way: It is possible that the evolution of this genetic trait evolved in homosapiens living a million years ago or more in Africa. It is most likely that these people had to deal with a lethal gut 'bug' or lethal food chemical as their populations expanded. To survive, there would have been genetic selection for an efficient first line of defence against this 'bug' or chemical. Those that survived, inherited the genetically coded defence—macrophages—that could instantly recognise the particular 'bug' or lethal chemical. When homosapiens migrated from Africa, they left the 'bug' behind.

Ten thousand years ago, people came into contact with a new food source—grains. Since then, one of the many thousands of peptides in grains is now being mistaken by the genetically coded macrophages as being the lethal 'bug' or chemical!

The cells of the first line of defence communicate with cells of the second line of defence—as occurs in any army. The immune cells of this second line of defence known as T and B-cells (see Appendix 1.), exchange information about defence activity with these macrophages. If the T and B cells are strong and efficient, they are not influenced by the macrophage response to the gluten peptides, and will not become involved in any defence reaction. However if they are not strong and efficient, they are more likely to respond to the macrophage's 'request for help'.

A macrophage defence response is to engulf 'bugs' and chemicals. Immense numbers of macrophages doing this eventually form lymph pools. These are directed to the lymph nodes in the submucosa of the small intestine, which creates that heavy swelling in the lower abdomen that coeliacs experience. On the other hand, T-cells do not create inflammation nor lymph swelling—they inspect cells for health (see Figure 6, Page 37). If weakened T-cells are influenced by macrophages to join an attack, they inspect small intestine cells in the region of the macrophage assault.

Any cells with gliadin peptide association (mostly small intestine cells) are destroyed by these T-cells. Consequently the healthy small intestine structure is destroyed by the body's own immune system (Dalton 1992, Quaratino et al. 1995).

Intestinal Villi

In coeliac disease, these T-cells destroy large areas of the mucosal cells in the small intestine known as villi (Figures 1 - 4). Villi are finger-like extensions that increase the bowel surface area to increase nutrient uptake into the body. The destruction of villi primarily leads to malabsorption of food. This eventually results in many symptoms associated with chronic ill-health and eventually death. (Westerberg, et al., 2006).

There are 4 degrees of damage to villi:

1. **Infiltrated villi**—the villi are still upright and complete, but have higher associated immune activity (lymphocyte) than normal.

2. **Partially-shortened villi**—the villi are short and stubby—the bases of the villi (crypts) are broader with local inflammation.

3. **Flattened villi**—classic form of coeliac disease—the villi are destroyed (but can rebuild with long-term total gluten exclusion).

4. **Burned-out villi**—the villi are destroyed and cannot rebuild even on a gluten free diet (occurring in long-term coeliacs).

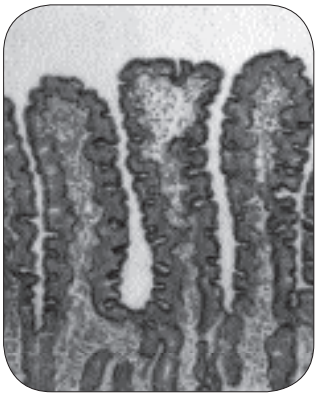


Figure 1—Normal intestine mucosa with tall finger-like villi. (Oxford Textbook of Med, Vol 1;2and 1987).

Figure 2—Coeliac disease mucosa. No villi and cells are inflamed. (Oxford Textbook of Med, Vol 1;2and 1987).

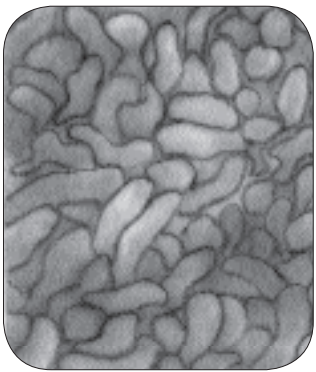


Figure 3—Normal mucosa—deep-pile carpet appearance. (Oxford Textbook of Med, Vol 1; 2and 1987).

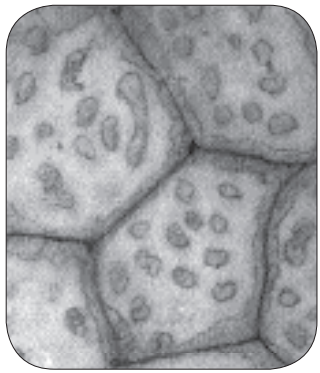


Figure 4—Coeliac disease mucosa with no deep-pile appearance. (Oxford Textbook of Med, Vol 1; 2and 1987).

Figure 5. shows an illustration of a section of the small intestine wall showing the positioning of a 'christmas tree' of lymph nodes in each of the villi, which swell due to macrophage activity (first line of defence) as they engulfing the gluten peptides and display a sign of this to the adaptive immune cells (the CD4 co-ordinator T-cells) regarding the occurrence of this potential pathogen. This activity relates to the genetic aspect of coeliac disease—mistaking the gliadin peptide as a pathogen.

The subversion of T-cells

All the different types of immune cells evolve from stem cells grown within the bone marrow. These mature into a first line of defence, such as macrophage cells, which possess genetically selected responses to chemicals and pathogens. Stem cells also mature into second line of defence cells, known as the T and B-cells, which are able to adapt to most types of chemicals and pathogens. Consider all these different types of immune cells to be like a combined police and military force (with the normal body cells being the citizens).

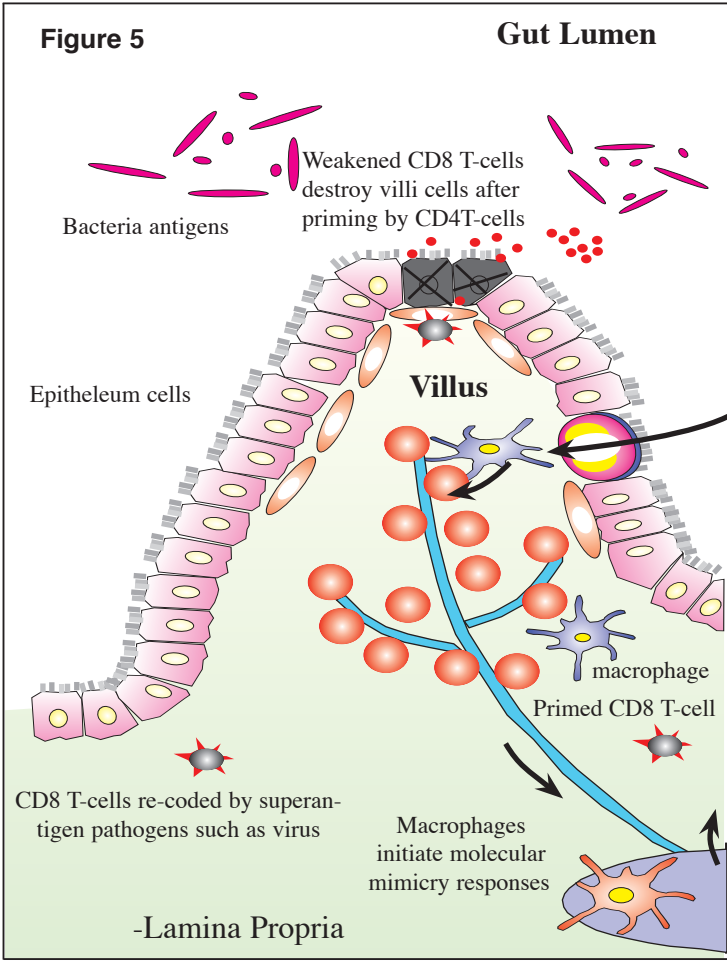
Microorganisms (pathogens) and unwanted chemicals are usually detected and destroyed buy the first line of defence before they can establish within the body. If an infectious organism breaches this first line of defence, then the second line of defence involving the variety of T and B-cells is activated.

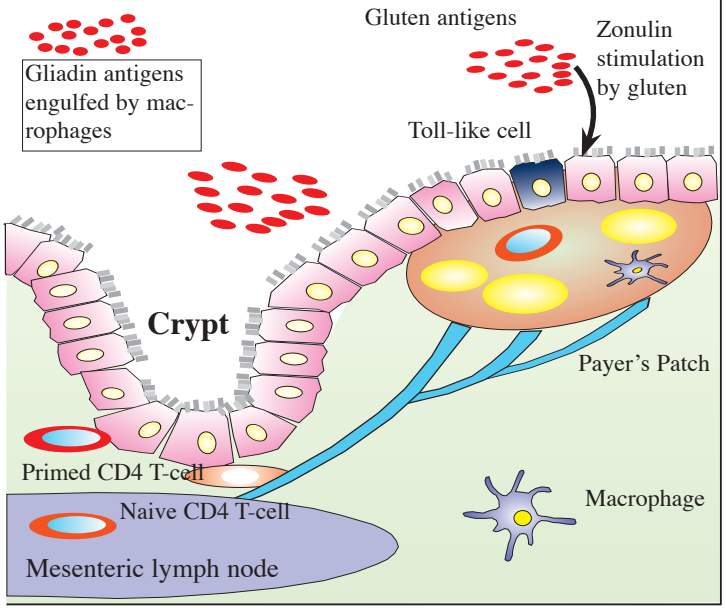
The T-cells have programmable receptors (like a computer) that recognise chemical peptide fragments as 'signatures' on the surface of all body cells. Through these, they can communicate with cells. One cell strongly linked to autoimmune diseases is known as a CD8 T-cell (a military cell). This cell identifies infected or unwanted cells through these signatures and destroys them. Another type of T-cell, known as a CD4 T-cell is considered the major coordinator of the immune system. These cells activate, direct and coordinate all the other types of immune defence cells.

People with the gene for coeliac disease (the genetically selected macrophages) experience variable lymph swelling in their abdomen throughout their lives—BUT this is not coeliac disease. The autoimmune response which is coeliac disease, involves mass targeting of healthy bowel cells by the CD8 T-cells (the military cells). But why do the T-cells even become involved with the macrophage attack on gliadin peptides in the first place?

Consider a criminal in our society who is being hassled by the police. To stop this, the criminal decides to subvert the police force. He creates a driver's license with a special code. When out driving, a policeman pulls him over. The criminal gives the police officer his driver's license. The police officer takes this to his car, inserts it in the police computer. It re-programs the computer at the head office. The police officer gives him back his license and he is free

Figure 5


Gut Lumen
Bacteria antigens
Weakened CD8 T-cells destroy villi cells after priming by CD4T-cells
Epitheleum cells
Villus
macrophage
Primed CD8 T-cell
CD8 T-cells re-coded by superantigen pathogens such as virus
Macrophages initiate molecular mimicry responses
-Lamina Propria


Gliadin antigens engulfed by macrophages
Gluten antigens
Zonulin stimulation by gluten
Toll-like cell
Crypt
Payer's Patch
Primed CD4 T-cell
Naive CD4 T-cell
Mesenteric lymph node
Macrophage

to go, now being registered as a citizen.

Later that day, you are driving along and are pulled over by a police officer. You give him your license. He inserts it into the computer which shows that you are listed as a criminal. The police officer arrests you and you protest your innocence without success.

This little story should give you an idea of how the T-cells become subverted. Human viruses and bacteria have the ability to re-code the 'computer' receptors of the CD8 T-cells. When told by the coordinator CD4 T-cells of the macrophage 'war' on gliadin chemicals (the bug), **healthy** T-cells will not become involved. However when the T-cells are re-coded, they become **unhealthy** and have difficulty determining whether to support the macrophages or not. If they join the ongoing 'war', coeliac disease occurs.

T-cells become vulnerable to subversion by human pathogens, after a severe bout of emotional stress, an intense infection such as glandular fever, a serious physical injury, or similar incidences.

Problems with plant defence chemicals

Although scientific studies have focused coeliac research mainly on one of the peptides of the gluten protein, I would not be surprised if future research identifies immune problems with other, similarly structured peptides that occur across the varieties of plants.

More and more defence proteins in plants are being discovered each year. There are at least 40 different protein components occurring in a single variety of wheat (Cordain 2004). Immune symptoms accompanying coeliac disease, like arthritis and other autoimmune diseases, are likely to be linked to types of molecular mimicry in combination with the inappropriate T-cell and/or B-cell destruction and re-coding of healthy body cells.

While rice, corn, fruit and vegetables do not have the gliadin peptides, they do have similar structured defence chemicals that could initiate similar chronic responses. If you have been diagnosed with coeliac disease and on total removal of gluten foods all your chronic symptoms disappear within a couple of months, then you should discipline yourself not to eat any gluten containing grain foods for life!

On the other hand, if you have removed all gluten from your diet, and you still have ongoing ill-health symptoms year in year out, then there is the possibility that peptides other than gliadin, but common to grains such as rice and corn (or even other vegetables and dairy) will be linked with your ongoing chronic symptoms. If you are unsure of your own health situation, you can set up your own trials and decide for yourself or contact the Canberra Medical Ecology Centre for advice (026 282 6800).

Symptoms of coeliac disease

Coeliac disease symptoms may start at anytime in life—as a child or as an adult. Chronic immune aggression that destroys the villi of the intestinal wall, decreases nutrient absorption. This eventually causes malabsorption symptoms such as: diarrhoea, weakness, weight loss, abdominal pain, abdominal distention, fatigue, oral ulceration, bleeding tendency, bone and joint pain, anaemia and others (Mayo Clinic, 2006).

According to Chinese medicine, when a person experiences organ disruption (such as coeliac disease), there are surface areas of the body that reflect this disruption. These are known as surface meridians. With chronic bowel disruption, arthritis or muscular symptoms commonly occur along the large intestine and small intestine meridians. Symptoms, including pain, commonly occur in the index fingers and thumbs first, extend to the other fingers, then to the dorsal areas of the wrists and even to the elbows. Further along the meridian, pain and weakness occurs in the acupuncture points of the lateral deltoids (shoulder pains) and eventually links to sinus disruption—chronic sinus infection, runny nose, blocked sinus. (See any recognised textbook on Chinese Medicine, eg. 'Essentials of Chinese Acupuncture', 1993).

People with chronic bowel symptoms such as irritable bowel syn-

drome and coeliac disease, also experience distention in the liver (due to chronic low-grade bowel inflammation)—often without any experienced pain until the liver is palpated (Carroccio, et al 1991, Robinson 1990, Trewby 1981, Bullen 1980, Brown, 1987). Most liver function tests of these people are within the normal range, however improving the function of the liver using specific herbal medicine removes the liver pain (even when palpated) and improves general health! However these herbs have to be taken on and off for life to keep the liver normal—or else the individual needs to further change their eating lifestyle to improve immune health in the bowel. Totally removing all gluten foods from the diet for a couple of weeks generally improves liver pain, although most need to remove corn and/or rice and test for dairy intolerance to improve overall liver health.

There are many ill-health symptoms connected to bowel dysfunction that are not recognised by scientific medicine. However other medical philosophies such as Chinese and Ayuverdic medicines recognise these. For example, people with chronic bowel pains often experience a variety of lower back symptoms. With coeliac disease, the lumbar-5/sacrum-1 joint (L5-S1) is often painful and inflamed. Provided the person does not have lesions or disc distention in this region, removal of all gluten food products for a couple of months often improves this type of back pain. From my clinical experience, individuals who continue to experience lower back

pain, have to remove other foods from their diet (sometimes dairy or even some fruit) in order to remove their lower-back pains!

People with coeliac disease who only have slight gastrointestinal symptoms, can also experience skin disruptions such as dermatitis herpetiformis—a skin disorder associated with papulo-vesicles on the knees, elbows, buttocks, mid to lower back etc. Around 25% of people with coeliac disease have dermatitis herpetiformis (Collin et al., 1997) while 90% of people with dermatitis herpetiformis also have coeliac disease (Hill et al., 2000).

Adults and teenagers with coeliac disease may also experience chronic depression and feel overtly emotionally stressed. At the same time they may experience a general feeling of chronic illness and tiredness (Green, 2006). Children with coeliac disease often present with behaviour similar to ADD and ADHD and present with delayed growth and development (Green, 2006). Epilepsy occurs twenty times more often in persons with coeliac disease than those in the general population. Calcium deposits form in the brain because of a deficiency of folic acid but tend to disappear after a few years on a gluten-free diet.

A decrease in bone density (osteoporosis and osteomalacia) is common with coeliacs. Adequate bone density is dependent upon adequate calcium. If calcium is not absorbed, due to small intestinal

damage, bones may lose their density more quickly than the average of the population and the 'fracture threshold' may be reached at a much younger age.

Coeliacs have a 78% greater occurrence of cancers and lymphomas of the mouth, bowel and esophagus, while the risk can be reduced after 5 years of strict adherence to a gluten free diet. (Celiac Disease Foundation. Winter 1992, Issue #5, p. 2.)

Common symptoms of coeliac disease

- Stomach pain, gas and bloating
- Chronic diarrhoea
- Pale, foul-smelling stools
- Weight loss
- Dermatitis herpetiformis, a painful rash of itchy blisters
- Osteoporosis/osteopenia (in 100 % of coeliacs)

Other associated symptoms

- Calcium, vitamin D and protein malabsorption
- Amenorrhea, infertility, impotence
- Acne
- Stunted growth (in children)
- Infertility
- Alopecia areata (especially alopecia universalis)
- Irritable bowel syndrome (IBS)
- Dental enamel defects
- Lactose intolerance
- Anaemia
- Anorexia and bulimia
- Irritable bowel syndrome
- Bone or joint pain (arms/shoulders)
- Chronic fatigue

Lactose Intolerance

About 50% of coeliac people are lactose intolerant at the time of diagnosis. Lactose is a large double sugar from cow's milk. The small intestine produces an enzyme called lactase which breaks lactose down into single sugars which your body can then absorb. From birth to an age of about three years, infants produce adequate lactase throughout the upper gastrointestinal tract. After infancy, this enzyme is available from fewer and fewer intestinal cells. Eventually in adults it is limited to cells at the tips of the villi. If the villi are damaged/eroded, the enzyme cannot be produced and the sugar cannot be split for assimilation. The lactose stays intact throughout the small intestine and passes into the larger intestine. If particular bacteria and parasites, such as round and thread worms, are resident in the large intestine they 'eat' the lactose and produce chemical toxins.

The intestinal response is to dilute these chemicals—the result is a watery, acid diarrhoea accompanied with bloating and the production of gas (O'Grady 1984). Following several months adhering to a gluten/dairy free diet, the villi in the small intestine will generally re-grow and be able to produce some lactase. Limited dairy products can then be eaten without causing bowel symptoms. If the villi do not regenerate, the consumption of dairy products will produce chronic low-grade ill-health symptoms. Improvement in lactose tolerance is generally a sign of intestinal healing.

When attempting to test the re-growth of bowel villi, the individual should start with a small amounts of skim milk first thing in the morning and note any symptoms. If symptoms occur throughout the day (bloating, gas, diarrhoea, back pains) then it is probable that the villi have not sufficiently re-generated. The dairy free diet should once again be reintroduced for a few more months and after this time re-tested. In general, most newly-diagnosed coeliacs should tolerate lactose after several months off gluten.

Dental abnormalities

Dental abnormalities, specifically permanent-tooth enamel defects, have been shown to be associated with coeliac disease in both adults and children (Aine 1986, Aine 1990, Maki 1991).

Gynaecological problems

Women with coeliac disease have a higher than normal incidence of obstetric and gynaecological problems when they continue to eat small amounts of gluten containing foods. Amenorrhea and spontaneous abortions are reported more often for women with coeliac disease than for controls. Infertility is more common among coeliac women than the norm of the population. Fertility and the ability to carry an infant to term, generally returns when women with coeliac disease strictly follow a gluten-free diet. (Molteni 1990).

Science and coeliac disease

In a lecture entitled "On the Coeliac Affection" given in London in 1887, Dr Samuel Gee first described the condition we refer to as coeliac disease (Gee, 1888, Dicke, 1953). Until 1950, the scene of people dying of coeliac disease in hospital, is one in which patients would be fed a bowel of soup and a piece of toast and they would not recover. In 1951 however, under the same circumstances they would be fed a bowel of soup only—and they would live. Coeliac disease was untreatable until the 1950s. For decades, the public had been suggesting that bread was connected with coeliac disease however it took a Dutch pediatrician, Willem Dicke, to link wheat flour with the symptoms of coeliac disease following a reduction in this disease when bread was not available during the latter stages of world war two. He advocated the removal of all wheat containing foods to remove the symptoms of coeliac disease.

The introduction of the small bowel biopsy in the late 1950s confirmed his theories that the small intestine was the organ involved with coeliac disease. Subsequent research isolated gluten as the protein compound linked to coeliac disease. Since the early 1960s, the advice given to coeliac patients, to remove their symptoms, has been to exclude all gluten food products from their diet for life. This still allows them to eat the non-gluten grains—rice and corn. Coeliac disease has been diagnosed in as many as 1 in 100 people

in southern Europe and the British Isles, but it is rarely diagnosed in Africa, Japan and China (Not et al., 1988). Recent studies in the United States indicate that there is a 1 in 80 chance that people with no family history of coeliac disease could develop it. However, a person's risk increases as high as 1 in 22 if they have a first-degree relative with coeliac disease and a 1 in 39 chance if they have a second-degree relative (Fasano, 2002). In Australia, coeliac disease has been diagnosed in less than one percent of the population—but probably is higher than this. Coeliac disease can occur at any age and females are more commonly affected than males in a ratio of almost 3 to 1 (Feighery et al., 1998). Coeliac disease is steadily increasing in prevalence in Western countries.

Genetic evolution and coeliac disease

Hereditary genetic factors are recognised as a major player in coeliac disease and other autoimmune diseases. However the genetic connection is also recognised as only one of the factors. For example, when coeliac disease is diagnosed in people who have an identical twin, in more than 40% of recorded cases only one of the twins suffers the disease while the other is free of it (Fasano, 1996). Also almost half of the world's population have genes linked to coeliac disease (the HLA DQ2 and DQ8 genes), but the majority do not develop coeliac disease (Fasano, 1996). However, a significant number of people without these genes also develop coeliac disease (Fasano, 1996)! Because of these and similar observations, it has

been concluded that other factors besides genetics are involved in the development of the disease. Infectious agents such as virus and bacteria are linked to the initiation phase of coeliac disease in both those with the coeliac genes and those without the genes. (Fasano, 1996). The link between infectious agents and coeliac disease involves chronic weakening of the adaptive part of the immune system (the CD8 T-cells), as was discussed earlier.

The incidence of coeliac disease across Europe has a geographical southeast to northwest gradient—extending from the Middle East towards northwestern Europe (Simoons, 1981). This gradient parallels the spread of agriculture and cereal grain consumption from the Middle East, starting about 10,000 years ago. The origin of farming probably occurred in the 'Fertile Crescent', including Southern Turkey, Palestine, Lebanon and Northern Iraq. A wide variety of wild cereals, Triticum dicoccoides (wheat) and Hordeum spontaneum (barley) were available when other traditional foods (such as the small mammals) became more scarce as continental drying progressed following the last ice age (Catassi, 1994).

Stable settlements were eventually founded and evolved into civilisations with large cities and armies to defend their land and food stores. Egypt is typical of a civilisation that developed in the 5th millennium and was based on farming wheat, barley and flax.

In the Middle East the progressive drought reduced dependency on hunting and favoured farming. In Europe the palaeolithic culture of hunting and gathering continued for another 5000 years or more and gradually transformed into the mesolithic age. The expansion of farming into Europe occurred throughout this time and by about 3000 B.C. had extended to Ireland, Denmark and Sweden (Cavalli-Sforza 1993). In these areas, the cultivation of wheat began 5000 years ago but was not a large part of the diet for another 2000 years. Today we see a very high occurrence of gluten intolerance in these countries compared to the Middle East countries.

A gradient for a gene known as HLA-B8 occurs from the Middle East to the northwestern European areas. This gene is not a direct marker for coeliac disease but is closely linked and implicated with the coeliac gene. Northwestern European populations have the least evolutionary exposure to cereal grain foods such as wheat and there is a high occurrence of this gene in the populations. Conversely, populations in the Middle East have low occurrence of this gene, yet have most evolutionary exposure to cereal foods, other than rice and corn (McNicholl et al 1981, Simoons, 1981).
It has been suggested that this gradient now occurs because people with the coeliac gene have been eliminated in the populations of the Middle East—due to increased mortality through natural selection related to coeliac disease and the continuous eating of gluten grains (McNicholl et al 1981, Simoons, 1981). The elimination of

individuals with the coeliac gene, is still occurring.

As a parallel observation: the incidence of Type-1. diabetes is 10 times higher in people with coeliac disease than in normal populations (Sategna-Guidetti, 1994; Stenhammar, 1993). The incidence of Type-1 diabetes, like coeliac disease, is found across Europe in a general NW/SE gradient similar to that for coeliac disease (Green, 1992; Scott, 1988). Grain foods appear to have a capacity to eliminate certain genetic profiles in the world's populations. This occurs if small amounts of grain foods are eaten every few days when a person has a chronic autoimmune disease such as coeliac disease or diabetes Type-1! Do the other grains such as rice and corn act in a similar but more disguised manner in eliminating genetically susceptible people to autoimmune diseases?

Grains and the increased risk of cancer

The occurrence of cancers are increasing worldwide. This is due in part to better diagnostic testing, however more deaths attributed to cancer are also being recorded. If you wish to read about the connection between coeliac disease and cancer, simply undertake a search on the internet: 'celiac-cancer'. There is growing scientific interest in a possible grain/cancer link.

People (coeliacs or non-coeliacs) wishing to increase their chances against contracting cancer would be well advised to totally remove

gluten from their diet. I would also suggest that people should trial the removal of corn and rice as well, in order to determine for themselves if there is any improvement to their immune efficiency, then make a decision Below are a few summaries of research conclusions regarding grains and cancer:

‘Celiac disease predisposes patients to the development of lymphoma. If this relationship is re-stated as "cereal grains cause cancer" the implication is more easily understood. There is evidence that strict adherence to a gluten-free diet long term will reduce the incidence of lymphoma. Anti-gliadin antibodies are most commonly found in the immune complexes, associated with major systemic disease.’ (Collin et al., 1996).

‘Dermatitis herpetiformis is a lifelong, gluten sensitive skin disease. Patients with dermatitis herpetiformis, similar to patients with coeliac disease not adhering to a gluten free diet, seem to have increased risk for lymphoma. Conclusion: The incidence of non-Hodgkin's lymphoma is significantly increased in patients with dermatitis herpetiformis. The results also confirm that the patients with dermatitis herpetiformis treated mainly with a gluten free diet have no increased general mortality.’ (Lewis et al., 1996)

‘Cancer of the small intestine is rare compared with other sites in the gastrointestinal tract. Of the major primary small-bowel

tumours (adenocarcinomas, lymphomas, carcinoid), adenocarcinomas and lymphomas are associated with diseases that seem to increase the risk of developing these malignancies.

In the case of immunoproliferative small intestinal disease and coeliac disease, both of which are thought to predispose patients to developing of primary lymphoma, treatment of the predisposing conditions seems to decrease the risk of developing subsequent malignancy. Recognition of the increased risk associated with other conditions, such as immunodeficiency syndromes, nodular lymphoid hyperplasia, Crohn's disease, the gastrointestinal polyposis syndromes, hereditary nonpolyposis colon cancer, neurofibromatosis, long-standing ileostomy, and urinary diversion procedures, may lead to early diagnosis and improved survival (Ryan, 1996).

'The Epstein-Barr virus has been implicated in the etiology of endemic Burkitt's lymphoma, post-transplant lymphoma, large-cell anaplastic CD30 (Ki-1)-positive lymphoma, and in many T-cell lymphomas. A recent report has found Epstein-Barr virus genome in association with 4 of 11 cases (36%) of enteropathy-associated T-cell lymphoma. In a retrospective study, we have characterised 22 consecutive cases of enteropathy-associated T-cell lymphoma from the West of Ireland where celiac disease is endemic. All cases were immunophenotyped with T—B-cell markers.' (Walsh, 1995).

THE FIRST PROBLEM—EATING GRAIN FOODS

Grains such as wheat are composed mostly of starches and fibre with a small amount of various proteins—including the defence protein (gluten). In the last several years, scientists have found that certain gluten proteins can alter the permeability of the intestinal wall. When this happens, unwanted chemicals and gut pathogens, that would normally be contained to the intestinal tract and eliminated from the body with bowel movements, are able to enter the body. This consumes valuable immune resources and exposes the individual to compromised health. This is a primary problem for many people including coeliacs and non-coeliacs.

The zonulin—gluten connection

Healthy intestinal operation is strongly dependent on the correct regulation of the intestinal wall permeability. This is the ability to allow digested foods to translocate from the intestinal tract through the intestinal wall and into the blood stream via the submucosa—while at the same time rejecting pathogens (fungi, bacteria, virus, parasites) and harmful chemicals (mostly the larger chemicals that have not been digested and broken down to smaller compounds). This permeability appears to be regulated by either allowing translocation to occur between the cells lining the intestine or to translocate through the cells lining the intestine. Permeability is now known to be regulated by the body's innate immune system

in association with cells named 'Toll-like receptor cells'. These cells act like gate-keepers opening and closing intestinal mucosal wall 'channels'. One of the chemicals that the Toll-like receptor cells use to achieve increase the permeability is a chemical called zonulin. Gliadin is known to stimulate the Toll-like receptor cells to produce more zonulin than is necessary and increase the permeability of the gut (this probably occurs in all people who ingest gluten) (Thomas, 2006).

This increased permeability allows unwanted larger proteins (such as gluten or even pathogens) into the intestinal submucosa where the macrophages intercept them and signal the T-cells for assistance. In people with unhealthy immune systems, the chances of T-cell aggression toward local intestinal cells as well as cells in other parts of the body (such as the pancreas, thyroid, joints, skin, nerve cells etc.) is thus heightened (Thomas, 2006).

Tissue transglutaminase and T-cell aggression

An enzyme in the submucosa known as tissue transglutaminase, probably also plays an important role in increasing the initiation of inappropriate immune responses. This enzyme changes gluten-derived peptides into glutamic acid. Glutamic acid has been shown to increase the binding ability of various peptides to HLA-DQ 2/8 genes within the 'signatures' of intestinal cells (Papadopoulos et al., 2001 Westerberg et al., 2006). This increases the probability

that weakened T-cells will initiate aggression towards intestinal cells which exhibit an extensive range of peptides. The discovery of this enhancement strongly suggests that other chemical interactions are probably also involved alongside coeliac immune responses. Possibly this is one reason why many coeliacs react to other vegetable foods.

Gene Signatures and coeliac disease

As suggested earlier, the glutamine and proline rich 33-mer peptide occurring in gluten has been linked to coeliac disease through molecular mimicry. This gluten peptide resembles human cell peptides associated with the identification 'signatures' on the surface of human body cells—and a weakened immune system can misread these chemicals as possible infectious agents.

In studies of the genetic relationship to the body's immune defence, the peptides of these 'signatures' are linked to DQ2 and DQ8 haplotypes (these are linked genes usually one from each parent) of the human leukocyte antigen (HLA). Human leukocyte antigens give antibody reactions to white blood cells that allow scientists to genetically type-map cellular immune communication in the body using the 'signature identification' system of human cells.

About 97% of people with coeliac disease have these haplotype genes, however most have the DQ2 gene rather than the DQ8 gene (Dalton, 1992). In the general population, while most people do

not have the symptoms of coeliac disease, it is estimated that 40% do have these genes (NIH, 2006). In theory, almost 40% of the Australian population could develop coeliac disease!

The association between these haplotype genes and coeliac disease is linked to the communication processes of immune cells. Healthy body cells have to prevent the CD8 T-cells from killing them and they do this by displaying on their surface, an identification 'signature' of their health and body status. These 'signatures' are specific glycoprotein molecules known as MHC molecules (see Appendix 1.) that evolve within cells and have an ability to bind within their structure many types of residual peptide fragments from inside the cell. For example, sometimes these peptide fragments emanate from the DNA structure—sometimes they are fragments of viruses that have penetrated into a cell. The MHC molecules collect these peptide fragments in a 'cleft' within their structure. They become stimulated to move through the cell wall and present the peptides on the surface of the cell as a 'signature' to the immune system to inspect. The presentation of these 'signatures' either secures the cell from attack by the immune system or these signatures initiate an immune attack. For example certain fragments indicate that a cell is either free of viral infection or that it is infected by viruses.

Thus when people with the human leukocyte antigen (HLA) genes DQ2 or DQ8 eat gluten foods, all healthy T-cells inspecting their

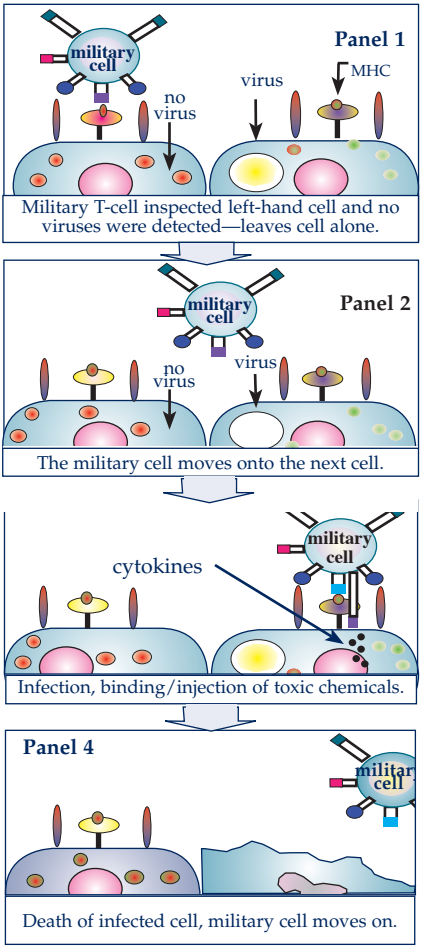
mucosal cells will have slightly greater difficulty correctly identifying the disease status of these cells. If, as was noted earlier, the T-cells become subverted by human pathogens such as viruses, their efficiency in correctly identifying the status of cell health is reduced even further. (Janeway, 2005, Shan, Lu et al, 2002, Kim et al., 2004).

Under circumstances where an immune system loses its communication efficiency, a localised attack in the submucosal region involving macrophages can expand to a full-scale war involving B-lymphocytes that inappropriately release chemicals within the blood and lymph systems. At the same time armies of T-cells begin to destroy large numbers of normal healthy body cells in various parts of the body—the autoimmune disease. A number of different autoimmune diseases can occur concurrently.

Figure 6. Next page: Panels 1 to 4 show CD8 T-cells inspecting body cells to determine whether they are normal or whether they are infected with viral pathogens. If the T-cell suspects viral infection, they adhere to the cell and kill it using chemicals called cytokines. Then they move on to the next cell to inspect. In this way they can detect tumour/cancer cells. If the T-cells are subverted, they may have difficulty detecting cancer cells. They may also mis-identify a healthy cells and kill them. This is the autoimmune response.

Figure 6.
T-cell (military cell) activity moving from cell to cell inspecting each cell for health and complience to the individual cellular organ community.

It does this by exchanging information between its surface receptors and those of the cell it inspects



THE SECOND PROBLEM— WEAKENING OF THE IMMUNE SYSTEM

When pathogens enter the body, they are met with a normal immune response but many can quickly evolve mechanisms to evade detection and elimination. Certain pathogens can stay in the body undetected for long periods of time, for life in many cases— for example the 'cold sore' virus or the 'chicken-pox' virus. The mechanisms these pathogens use to achieve this include:

(a) Gathering genes from cells to present as 'cell signatures' which stop T-cells identifying and killing them.

(b) They can also mimic cytokine receptor 'signatures' to inhibit attack by the immune system.

(c) They synthesise molecules to control the activation of 'complement' ('Complement' is a term used for a population of plasma proteins that are part of immune defence which can be activated by antibodies to bind and neutralise pathogens and/or prepare them for destruction by macrophages and other immune cells).

(d) Some human (superantigen type) viruses have the ability to alter the normal 'signature' of the MHC molecules. This alteration sets in process the re-coding of T-cells when they come into contact with MHC molecules. Once re-coded, the T-cells will search

for a ‘phantom’ pathogen that presents a ‘signature’ relating to this re-coding. Reading this ‘phantom’ signal on certain cells, the T-cells then kill these healthy cells—an autoimmune response. This occurs in coeliac disease and is responsible for the associated autoimmune diseases in other parts of the body.

The human herpes and pox viruses are well recognised subverters of immune cells (Janeway et al., 2005 10.3), initiating polyactivation of T or B-cells that cross-react with ‘self antigen signatures’ to cause molecular mimicry (Janeway et al., 2005, Fig 12.36).

People with coeliac disease have subverted T and/or B-cells. The beginning of the symptoms of coeliac disease can often be traced back to an intense infection (like glandular fever) by superantigen presenting viruses such as the herpes or coxsacci groups. Superantigens are types of molecules (like some peptides) that are able to stimulate cytotoxic T-cell attack towards ‘self antigen signatures’ presented by healthy body cells. They do this by binding to the MHC ‘signatures’.

Autoimmune diseases associated with coeliac disease

It is known that the majority of people with coeliac disease develop other types of autoimmune diseases as they age, Table 1. (Fasano, 1996). When people with coeliac disease totally remove gluten from their diet the symptoms of the other autoimmune diseases also reduce (Collin, 1994). For there to be progression and escalation to other autoimmune diseases, the individual more than likely would have to eat small amounts of gluten products on an occasional but regular basis. **This is a real trap for coeliacs.** It is really difficult to overcome on a day to day basis, unless well priced, and delicious gluten-free bakery products are readily available in our communities.

Table 1. Autoimmune diseases which occur with coeliac disease

Addison's disease	Aphthous ulceration
Asthma	Autoimmune thyroid diseases
Dental enamel defects	Dermatitis herpetiformis
IgA nephropathy	Epilepsy & cerebral calcifications
Primary biliary cirrhosis	Chronic active hepatitis
Selective liver diseases	Atopic diseases
Rheumatoid arthritis	Selective IgA deficiency
Sjo¨gren's syndrome	Systemic lupus erythematosus

Insulin-dependent diabetes mellitus

Primary sclerosing cholangitis

All autoimmune diseases appear to have similar triggering responses and evolution. Consider the following summaries of some of autoimmune diseases commonly associated with coeliac disease.

Dermatitis herpetiformis.

Dermatitis herpetiformis is characterised as an intensely itching papulo-vesicular skin disease, diagnosed by IgA deposits in the basement membranes (Fry, 1974). Dermatitis herpetiformis can be successfully treated by a gluten-free diet, although it may take years before the dermatitis is fully controlled by a gluten-free diet alone (Andersson, 1992). However, if the non-gluten grains, corn and rice, are simultaneously removed and toning herbs taken, the recovery is much, much quicker. Dermatitis herpetiformis and coeliac disease share a common genetic basis (HLA, DQ2). About 60% of people with dermatitis herpetiformis have moderate to severe small-bowel villous atrophy (Collin, 1994).

The precise tissue autoantigen in dermatitis herpetiformis is unclear, however, there are similar structural homologies between human elastic fibre tissue and glutenin—which have been shown to cause IgA cross-reactivity (molecular mimicry) between the two proteins in human serum (Bodvarsson, 1993).

Dermatitis herpetiformis is an extremely itchy skin rash. It effects the elbows, knees, buttocks, back of the head, and scalp. It comes on in waves. Crops of little bumps appear and soon turn into blisters that are extremely itchy. Dermatitis herpetiformis is not a skin allergy to gluten. In people with dermatitis herpetiformis there is an accumulation of antibodies under the lining of the skin, where they sit like 'land mines' for days, months, or years. In time they are triggered (sunlight, iodine in a cleanser, etc.) and little bursting blisters occur as the skin's immune system attacks these deposits.

Insulin-dependent diabetes mellitus IDDM

Insulin-dependent diabetes mellitus is an autoimmune disease in which the beta cells of the pancreatic islets of Langerhans are destroyed by T-cells, eventually reducing the production of insulin to zero. It is a complex disease involving several factors, however molecular mimicry between viral proteins and pancreatic beta-cell proteins (e.g. coxsackie virus protein and glutamate decarboxylase) is one mechanism for the disease (Atkinson, 1994). In addition to viral proteins cross-reacting with a beta-cell antigen, dietary proteins in cow's milk are suspected agents (Cavallo, 1996.) The feeding of wheat to animals with IDDM elicits a greater incidence of the disease than does straight milk (Schatz, 1996).

Numerous studies have demonstrated that feeding of wheat gluten to mice genetically predisposed to IDDM, increases the occur-

rence of the disease (Scott, 1988; Elliott, 1984; Hoorfar, 1993). The mechanism that allows wheat and other grain proteins to increase the occurrence of IDDM in genetically predisposed animals is unknown. However the same autoantibodies are found in (a) non-obese diabetic mice (Skarstein, 1993) and in (b) humans with IDDM (Fukazawa, 1994) and also in (c) humans with both IDDM and Sjogren's syndrome (Binder, 1989). This suggests a common environmental trigger such as grains, as the initiator for the disease. Removing all grains (including rice and corn) from the diet for two to three months improves the symptoms of IDDM in those individuals who still have beta cells in the pancreas!

Sjo¨gren's syndrome.

Sjo¨gren's syndrome is characterised by infiltration of CD4 T-cells into salivary and lachrymal glands. This leads to the continual symptoms of dry eyes and dry mouth (Sumida, 1995). Circulating antibody levels of gliadin and reticulin glycoproteins have been found to be higher in people with Sjo¨gren's syndrome than in controls (Teppo, 1984). Furthermore, Sjo¨gren's syndrome is about 10 times higher in people with coeliac disease than in people without the disease (Collin, 1994). Ro/SS-A autoantibodies are typically elevated in Sjo¨gren's syndrome (Binder, 1989 Sumida, 1995).

Because the four cytoplasmic RNA components of Ro/SS-A (hY RNA 1,3,4,5) exist together with a form of calreticulin (Lieu,

1997), molecular mimicry between gliadin and calreticulin may in part be responsible for this autoimmune response (Karska, 1995). Calreticulin is normally a cytolysolic protein, however viral infection has been shown to increase its cell-surface expression (Zhu, 1994). In a similar manner, grain lectins (including gliadin) are known to induce inappropriate expression of HLA class II molecules at nucleated cell surfaces (Mothes, 1995; Weetman, 1985).

In Sjo¨gren's syndrome an additional suspected autoantigen, termed BM180, has been isolated from basement membrane tissue in the lacrimal and parotid exocrine secretory glands. These are known to cross-react (molecular mimicry) with gliadin proteins (Laurie, 1995). Astonishingly, BM180 contains an amino acid sequence identical to that found in gliadin. Observed mono-clonal and polyclonal antibody reactions give the suggestion that BM180 is a mammalian form of gliadin (Laurie, 1995).

Autoimmune attacks by CD4 T-cells, primed by previous interaction with macrophages presenting gliadin, direct via molecular mimicry, destruction to lacrimal and parotid cells that present BM180. Despite the suggestive link between coeliac disease and Sjo¨gren's syndrome, as well as the molecular mimicry evidence, there are few clinical trials that have evaluated the effectiveness of gluten-free diets in Sjo¨gren's syndrome.

Rheumatoid arthritis

Rheumatoid arthritis is common inflammatory joint disease accompanied by the production of rheumatoid factor (an IgM anti-IgG antibody) that may also be produced in normal immune responses. This autoimmune disease is found more often in people having coeliac disease than any group of people with chronic illnesses (Collin, 1994; Lepore, 1996). While studies of people with arthritis have demonstrated elevated antibody levels for gliadin (O'Farrelly, 1988; Lepore, 1993) gluten-free diets have been shown to be reasonably effective in reducing arthritis symptoms in people with coeliac disease (Lepore, 1993; Charkravarty, 1992), while removing all types of grains including rice and corn greatly improves this response.

Although no clinical trials have been undertaken to specifically examine the effectiveness of gluten-free/grain-free diets in the treatment of arthritis, there are numerous case studies reporting the removal of arthritis symptoms through grain-free diets (Charkravarty, 1992; Shatin, 1964). It is noted that complete withdrawal of food during fasting also reduces the symptoms of the disease (Kjeldsen-Kragh, 1991).

Dietary antigens from three food sources (milk, grains and legumes) contain some peptides which mimic those found in joint tissue from people with arthritis. Grains and legumes also contain

lectins which induce inappropriate presentation of HLA class II molecules (Mothes 1995; Weetman 1985).

In people with arthritis, serum antibodies react to the antigen bovine serum albumin (from cow's milk). Bovine serum albumin contains similar amino acid sequences to human collagen Type 1. Molecular mimicry probably is the associated mechanism by which milk consumption triggers arthritis (Perez-Maceda, 1991). Glycine-rich cell-wall protein occurs throughout all grains and legumes. It has similar amino acid homology to human fibrous collagen and stimulates T-cell activity in people with rheumatoid arthritis (Ostenstad, 1995). A third dietary antigen which is linked to rheumatoid arthritis via molecular mimicry is the alpha-gliadin component of wheat, which shares significant amino acid sequences with calreticulin (Karska, 1995). Anti-calreticulin antibodies are found in people with rheumatoid arthritis (Routsias, 1993).

IgA nephropathy

This kidney disease is the most common form of primary glomerulo-nephritis worldwide. About one quarter of all people with the disease die from renal failure within the first decade of clinical diagnosis (Montinaro, 1992). IgA nephropathy is characterised by deposition of circulating IgA-containing immune complexes in the mesangium (part of the renal glomerulus where the afferent and efferent arterioles are closest). People with IgA nephropathy have

greatly increased intestinal permeability and elevated circulating antibodies to gliadin which are linked to the stimulation of interleukin-6 production (a nephritogenic cytokine) (Libetta, 1997). IgA nephropathy can be induced in mice through 100% grain diets. With this type of diet, both gliadin antibodies and IgA mesangial deposits increase (compared to gliadin-free controls) (Coppo, 1989). Observation shows that once the autoimmune response starts, introducing a gluten-free diet is not enough to alter the progression towards renal failure (Coppo, 1990). Amore et al. have suggested that the lectin activity of gliadin favours the binding of IgA to mesangial cells and this enhances destruction and dysfunction of the kidney cells (Amore, 1994). Other vegetable lectins must be considered as co-initiators of established IgA nephropathy.

Multiple Sclerosis MS

MS is a neurological disease characterised by focal de-myelination in the central nervous system, lymphocytic infiltration in the brain and a chronic progressive course. While there are observations that MS is positively correlated to latitude, there is good evidence showing that autoimmune activity is the real cause behind MS (Matthews, 1991; Wucherpfennig, 1995; Hartung, 1997).

In MS, several viral and bacterial proteins have been shown to cross-react with one of the suspected target antigens known as Nerve Myelin Basic Protein (Wucherpfennig, 1995). It is strongly

considered that plant antigens with similar amino acid composition to myelin and non-myelin target antigens initiate persistent T-cell activation. This continually initiates polyclonal expansion of T-cells in the peripheral immune system—similar to that occurring when there are bacterial and/or viral infections. Both grains and dairy have been identified as the likely food antigens, although no homologous amino acid sequences have yet been identified between these and the suspected autoantigens in people with MS (Shatin, 1994; Malosse, 1992).

There are a number of case reports showing remission of MS on gluten-free diets (Macdougall, 1973; Brady, 1978). A connection with the intestinal tract is noted in many people with multiple sclerosis who have altered intestinal mucosa (Pusztai, 1993; Doherty, 1981). It is suggested that an increase intestinal permeability to dietary antigens is linked with MS. However, people with MS generally do not show increased antibodies to gliadin (Husby, 1985). A number of case studies have not shown beneficial effects of gluten-free diets (Pusztai, 1989; Sjolander, 1984). On the other hand, case studies involving the total elimination of all grains (rice and corn included) have shown definite improvement in the disease within several months (personal observation).

THE DIAGNOSIS OF COELIAC DISEASE

Until recently, the only way to diagnose coeliac disease was through a biopsy of the small intestine—to look for villi atrophy. Pancreatic insufficiency, coeliac sprue, ulcerative colitis, coeliac disease and Crohn's disease are the five most common conditions that cause malabsorption. The development of less invasive antibody blood tests has made screening for these diseases easier, although biopsies are still used for confirmation. Coeliac disease tests measure the amount of autoantibody activity responsible for inflammation and damage to the intestinal wall. The autoantibodies (IgA found on the surface of the epithelium and IgG found in body fluid) are two of the five classes of antibodies the immune system creates to help defend the body. The IgA tests tend to be more specific, but the IgG tests are important as a follow-up test to avoid false negatives—because coeliac disease and IgA deficiency give a similar response (Mayo Clinic, 2006).

Autoantibody blood tests that are available include:

1. *Anti-tissue (blood) Transglutaminase Antibody IgA tests:* Tissue transglutaminase is an enzyme responsible for cross-linking certain proteins. Gliadin triggers the development of transglutaminase antibody autoantibodies.

2. *Anti-endomysial Antibodies IgA tests:* Endomysium is the thin connective tissue layer that covers individual muscle fibres. Anti-endomysial antibodies are developed in reaction to the ongoing damage to the intestinal lining. Almost one hundred percent of people with active coeliac disease and about seventy percent of people with dermatitis herpetiformis have Anti-EMA, IgA antibodies. Anti-transglutaminase antibody and Anti-endomysium antibodies measure the same tissue damage.

3. *Anti-Gliadin Antibodies IgG and IgA tests:* Anti-gliadin antibodies are autoantibodies against the gliadin protein created by those who are sensitive to this protein over a period of time.

4. *Anti-Reticulin Antibodies IgA tests:* Anti-reticulin antibody tests are not ordered as frequently as the others because they are not as specific or as sensitive as the other autoantibodies. These antibodies are found in about 60% of people with coeliac disease and about 25% of people with dermatitis herpetiformis. This test is ordered along with other coeliac disease tests to assist the confirmation of the diagnosis of coeliac disease.

THE PSEUDOCOELIAC RESPONSE

I have observed that people with chronic immune illnesses and accompanying symptoms of irritable bowel syndrome often do not test positive to coeliac disease—but improve their bowel function and other autoimmune symptoms when they totally remove all grain products from their diet (including rice and corn). I have called this the pseudocoeliac response.

People diagnosed with coeliac disease are advised to substitute corn and rice products for the gluten products. If the coeliac symptoms settle down but arthritis or other immune related symptoms persist, it is possible that an individual could be reacting to the defence chemicals in rice and corn and possibly other plant defence proteins.

Because individual immune systems weaken in an individual way, it is difficult to predict with any accuracy which food defence proteins may confuse an individual's compromised immune system—I advise undertaking an immuno-compromised protocol to determine which of all types of foods illicit molecular mimicry and promote subsequent autoimmune responses.

The treatment of coeliac disease

The recognised treatment for coeliac disease is a 100% gluten-free diet. Gluten is only found in wheats, barley, rye and oat food products. Gluten-containing grains are widely used in commercial and processed foods and as thickeners and binders in processed foods, eg. sausages, mince, vegetable and dairy products, fruit drinks, and beers (Farrell and Kelly, 2002). Dietary avoidance of gluten leads to symptom improvement in 60% of people with coeliac disease in 8 weeks and 80% within 12 weeks. About 20% of coeliacs always retain symptoms. Titers of transglutaminase, anti-endomysium antibodies and anti-gliadin antibodies are used to monitor compliance and response to therapy (since they decrease on a gluten-free diet). After 12 months, antibody levels usually become undetectable with strict gluten avoidance (Farrell and Kelly, 2002). Complete histological resolution of small bowel inflammation may take up to two years in some individuals (Greft et al., 1988).

To totally avoid gluten is difficult: when eating out, or travelling, with unlabelled food or the labels not being clear. When a coeliac accidentally ingests gluten it is possible for an acute coeliac attack to occur—diarrhoea, dehydration, acidosis, etc for many days (Lloyd-Still et al., 1972). Intravenous corticosteroid therapy and immosuppressant agents (Azathioprine and Cyclosporin-A) are used to reduce the acute responses (Rolny et al., 1999).

New methods to treat coeliac disease—a drug approach

New methods of treatment aimed at designing orally active drugs to allow people with coeliac disease to eat their favourite grain foods and not suffer the consequences, are in development. This approach is now possible because more understanding of the patho-physiology of coeliac disease is occurring. One area of current research is in peptidases (including bacterial prolyl-endopeptidase) which can degrade gluten into nontoxic components—analogous to the use of lactase in people with lactose intolerance.

A challenge to this enzymatic approach is the right timing of the introduction of the enzyme. The enzyme needs to be in the right place in the intestine at exactly the time that food is being digested (Shan, 2002). A drug like this could also be effective by inhibiting activation of T-cells or the binding of tissue transglutaminase, so that gluten could not be broken down into toxic peptides. However, a problem with inhibiting tissue transglutaminase is that the enzyme plays an important role in the normal repair of the stomach lining. Inhibiting its production reduces the body's maintenance of the stomach lining and this can cause intestinal bleeding.

Another approach in current research is the development of a drug which has a signature similar to the gluten peptides. This stops the

peptides from binding to the HLA-DQ2 or DQ8 genes. This is probably the safer of the proposed therapies (Kim et al., 2004).

After more than 40 years of funded research, all the experiments to create an appropriate drug to stop coeliac disease have failed. This has occurred in all cases of autoimmune diseases. Research is now considering that a single therapy will not be able to break the pathology of the autoimmune responses. Most researchers are now considering the use of a combination of drugs to weaken each of the several steps that occur in the autoimmune response—similar to the triple cocktail approach to treating AIDS.

Why bother with a drug approach?

To assist people who are unsure of the involvement of corn and rice as triggers for their immune related illnesses, I joined with Rob de Castella to produce the world's first totally grain-free bakery. This is an attempt to provide to the public, all types of bakery products, that are guaranteed totally grain/ dairy free.

Deeks foods are made from organic quinoa and amaranth (from medicinal seeds of two South American herbs that the Incas have used as staple foods for more than a 1000 years) and tapioca. They are delicious fun foods, that last an incredibly long time. They are nutritious and are 'healthier foods for you in the long run'.

APPENDIX 1 (skip this if you have some basic understanding)

The Immune System and Coeliac Disease

The immune system is an organisation of cells and molecules with specialised roles in defending the body against infection and damaging chemicals (consider them to be like a combination of policemen and the military in our communities and citizens as normal body cells). The microorganisms (pathogens) that are encountered daily in the life of a normal healthy individual rarely cause perceptible disease. Most are detected and destroyed within hours by innate immunity. It is only if an infectious organism breaches the early lines of defence that an adaptive immune response occurs through the creation of specific antibody (antigen) effector cells that specifically target the pathogen and effect memory cells that prevent subsequent infection with the same pathogen.

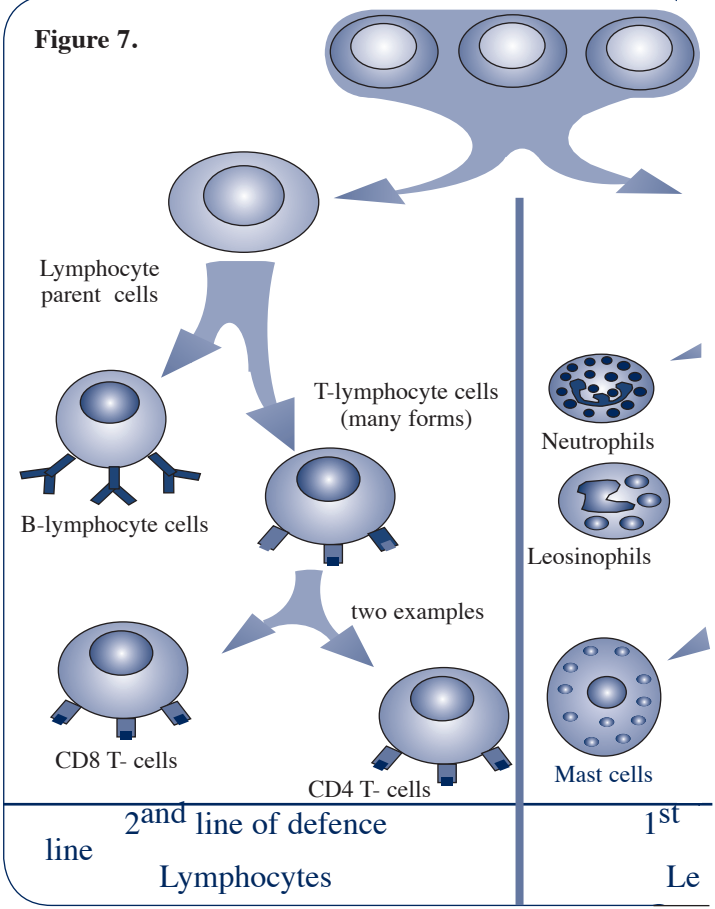
All the different types of immune cells evolve from stem cells which grow in the bone marrow, Figure 7. These mature into leucocyte and lymphocyte parent cells and transform into three types of cells: red blood cells (erthrocyte and blood platlets); cells of the innate immune response; and cells of the adaptive immune response. Immune activity predominantly occurs in the region of the intestinal tract where groups of cells called Payer's patches (mainly M-cells) collect antigen from the epithelial surfaces.

The leucocyte parent cells divide into the red blood cells and a variety of general immune cells. The red blood cells are partly immune cells, carrying oxygen and information to all types of cells throughout the body, including the immune system. The leucocyte cells—neutrophils, eosinophils and basophils are innate immune cells which patrol the blood stream and are involved with general inflammation. Other innate immune cells called monocytes, differentiate into macrophages and mast cells which actively migrate to most tissue of the body when needed. Macrophages play a broad and critical role in host defence whereas mast cells are associated with allergic reactions to foods, chemicals and some pathogens.

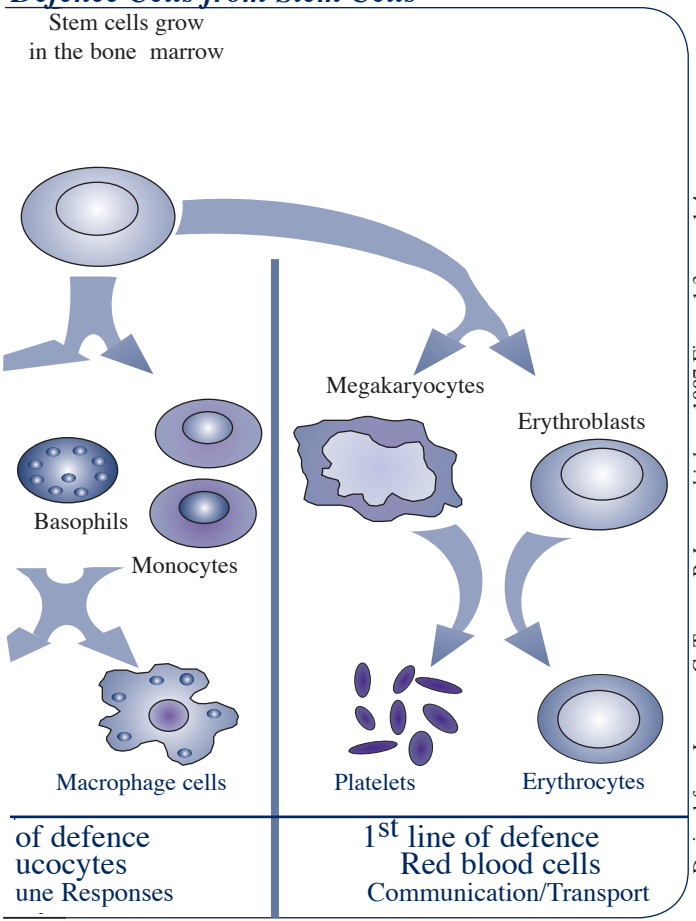
Macrophages are phagocytic cells able to ingest pathogens and certain chemicals and often provide a first line of defence against infection. They can recognise and ingest many types of extracellular pathogens (bacteria mostly) entering the body through the intestinal tract, lungs and skin cuts. After they ingest pathogens they can present peptide 'signatures' of these pathogens to the adaptive immune system (via CD4 T-cells). This can lead to an adaptive immune response against particular pathogens (but it can also induce inappropriate autoimmune responses).

Macrophages can also be activated by types of T-cells of the adaptive immune system to destroy ingested pathogens and convert them into potent antimicrobial effector cells—they must be tightly

Figure 7.


Lymphocyte parent cells
T-lymphocyte cells (many forms)
B-lymphocyte cells
two examples
CD8 T- cells
CD4 T- cells
Neutrophils
Leosinophils
Mast cells
2and line of defence
line
Lymphocytes
1st
Le

Defence Cells from Stem Cells



Derived from Janeway C, Travers P. *Immunobiology* 1997 Figure 1.3 page 1:4

regulated to avoid damage to normal body cells and tissue.

The lymphocyte parent cells either stay in the bone marrow or migrate to the thymus. Those that remain in the marrow develop into B-cells, those that migrate to the thymus develop into T-cells. Active B-cells are known as plasma cells. B-cells recognise antigens outside cells where most bacteria are found and T-cells by contrast, detect antigens infecting cells, eg.viruses. The B-cells secrete antibodies (immunoglobulin molecules) to block pathogen development. Food allergies mostly involve B-cell activation.

Within the thymus the T-cells evolve into a number of forms, the most important for autoimmune diseases being CD8 T-cells and CD4 T-cells. The main role of CD8 T-cells is to inspect all other cells in the body for viruses infecting the cells. T-cells have receptors that recognise peptide fragments of intracellular pathogens transported to the cell surface by glycoprotein molecules (MHC) which act as 'signatures' on cells. If T-cells identify an infection through these signatures, they destroy the cells, along with any viruses in the cells, by using cytotoxic granules.

Two types of MHC molecules transport the peptides from different intracellular compartments to present them to distinct types of effector T-cells: cytotoxic T-cells that kill infected target cells and Th1 and Th2 cells that mainly activate macrophages and B-cells.

The CD4 T-cells are the communicator cells of the immune system. They activate, direct and coordinate other types of immune defence cells to target particular antigens. CD is a term used to describe cells that identify the same cell surface molecules. CD means clusters of differentiation. Innate and adaptive immune responses are both involved in coeliac disease.

Thus T-cells are crucially important for both specific immunity mediated by antibodies as well as cell-mediated responses of adaptive immunity. The adaptive immune response appears to have evolved specific antigen recognition by highly diversified receptors (signatures) onto the innate defence systems. Antigens play a central role in the activation of both B and T-lymphocytes.

For further reading: Janeway C, Travers P. **Immunobiology—the immune system in health and disease** 4th Edition. Garland Publishing NY and London.

Appendix 2

What is an Autoimmune Disease?

The scientists who first studied the functions of the immune system theorised that it was possible for the defence system to turn against the body and create severe tissue damage. Paul Ehrlich, (1854 - 1915), a respected medical researcher into theories of specific immunity caused by antibodies, termed autoimmunity: *horror autotoxicus*. Autoimmune diseases involve a type of misdirected immune response which targets healthy body cells (known as targeting self-antigens). This occurs mostly through inappropriate recoding/subversion of cytotoxic CD8 T-cell responses, as well as the inappropriate activation of leukocyte macrophages (Janeway et al., 2005). Autoimmunity occurs because of the adaptive response of lymphocytes to code to an infinite variety of antigens, both chemical and pathogenic, and this includes the body's own cells. Because of this adaptability, T-cells can potentially code to and destroy the body's own healthy cells. Medical science is still not really sure of the full range of factors that trigger continuous autoimmune responses, but they involve pathogens such as human viruses bacteria, genetic factors and chemicals.

In theory, any person can develop an autoimmune disease at any time of life, however genetic predispositions and abnormal blood/hormone/neuropeptide concentrations are always involved to some

degree. The inherited predispositions really refer to structural and functional deficiencies of organs that are genetically inherited. For example, children of a parent with tuberculosis, inherit a greater chance of having weaker lungs than children from healthy parents. This does not mean that the offspring would contract tuberculosis, rather the person has a greater chance of contracting the disease than those with normal lungs.

Studies have shown that many autoimmune diseases appear to have a sex bias and in experiments with animals, castration usually normalises the bias between the sexes. There is evidence to show that many autoimmune diseases are more common in ovulating females than with other members of the population and while links with estrogen and/or progesterone have failed, there is strong clinical evidence to suggest that hormones are somewhat linked to autoimmune diseases.

When a person has an accident in which physical damage occurs, autoantibodies are often produced following the trauma—however this is not the action of an autoimmune disease since the reaction stops as the healing progresses. However, a continuing disease which has observable pathology and continuing self-targeting immune responses, is classified as autoimmune. Experiments have demonstrated that an autoimmune disease is able to be transferred from one animal to another by simply transferring autoantibodies

and not the pathogen responsible for the original autoimmune response. For example, diseased mothers can transfer IgG antibodies across the placenta to the unborn baby, which then develops the same disease as the mother.

Autoimmune diseases are mostly linked to three responses:
1. Inappropriate production of immunoglobulins by B-cells;
2. Direct targeting by CD 8 T-cells;
3. The orchestration of macrophages by CD 4 T-cells.

There are two types of autoimmune responses involving immunoglobulins:
• Type 1, IgE mediated autoimmune responses do not appear as a major initiator of autoimmune disease however:
• Type 2 mediated autoimmunity involving IgM and IgG responses are quite common (eg autoimmune hemolytic anaemia and autoimmune thrombocytopenic purpura).

The binding of IgG and IgM autoantibodies to cells in tissues causes inflammation due to activated macrophages. Also, natural killer cells along with CD8 T-cells can also complicate autoimmune responses.

All types of body cells can be targeted in autoimmune diseases, however of all the different types of healthy cells attacked, the

pancreas beta cells and intestinal mucosa cells appear to be more commonly targeted. People with coeliac disease quite often develop Type 1 diabetes! The pancreas beta cells produce insulin for the regulation of blood and cellular glucose. A reduction in beta cell numbers reduces the efficiency of insulin production and regulation. Insulin-dependent diabetes mellitus is a disease in which the insulin-producing beta cells of the pancreatic islets are selectively destroyed. While there is evidence of molecular mimicry (mentioned earlier) CD8 T-cells appear to also be involved. CD8 T-cells only live for about two weeks and new cells have to be continually coded incorrectly for an autoimmune disease to continue! Progression of many autoimmune diseases has been reduced through the use of the immunosuppressive drug cyclosporin A, which inhibits T-cell activity but does not cure the disease.

Attention has been focused on MHC molecules as the link between autoimmune diseases and the subverted immune response. MHC molecules are the presented surface 'signatures' indicating the status of cell infection—which CD8 T cells inspect. The association of MHC molecules with autoimmune disease is not surprising since all autoimmune responses are believed to involve some T-cell activity. T-cells respond to a particular antigen depending on peptide information presented by MHC surface molecules!

As laboratory techniques improve, autoimmune diseases will prob-

ably be directly linked to specific pathogens, notably the human viruses such as the herpes group. It is well recorded that epidemics of particular viral illnesses, such as mumps, Coxsackie B, influenza, glandular fever infections and others have often been directly followed by increased incidence of Type 1 diabetes and other types of autoimmune diseases (Janeway et al., 2005). These associated illnesses, along with food defence chemicals, have been labelled environmental co-factors directly involved in the etiology of autoimmune diseases.

In laboratory testing it is much more difficult to demonstrate the link between the autoimmune diseases and CD8 T-cell activity than it is to demonstrate the link between autoimmune diseases and antibody responses such as IgG and IgM in molecular mimicry. In laboratory testing, autoantibodies can be used to stain targeted healthy tissue cells to reveal the occurrence of an autoantigen—whereas the T-cells cannot be used in any way to stain tissue cells. The laboratory methods to allow the use of T-cells to transfer autoimmune diseases to experimental animals has yet to be devised. Similarly there is good evidence, but much difficulty, in linking viruses to all autoimmune diseases through CD8 T-cell subversion. Thus the evidence linking T-cell activity to autoimmune diseases remains mostly clinical and anecdotal whereas the link with molecular mimicry is more obvious.

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