DIGESTIVE DISEASES

The digestive tract is a string of connected organs stretching from the mouth to the bowels. We use it to eat food, digest nutrients and eliminate waste. There are many digestive disorders, caused by such factors as genetics, stress, toxins, infectious diseases and pharmaceutical drugs. This chapter discusses the latest research on glutathione in the digestive tract. GSH plays a role in protecting the mouth and salivary organs from periodontal disease, stomatitis and gingivitis. It must also protect the esophagus from inflammation. In the stomach, it protects against gastritis, peptic ulcer and cancer and in the liver, hepatitis and organ failure. GSH also protects the pancreas from inflammation and the large intestine (bowel) from colitis, inflammatory bowel disease, ulcerative colitis, Crohn's disease and cancer.

GASTRITIS

Gastritis is an inflammation of the stomach lining (gastric mucosa). Acute gastritis produces a short-lived inflammation with symptoms of pain, heartburn, occasional nausea, vomiting and loss of appetite. Chronic gastritis is more prolonged. It has fewer symptoms but more readily progresses to serious illnesses such as anemia, stomach ulcer and stomach cancer. As the population ages gastritis is becoming so common that some scientists consider it a part of the aging process.

One of the many possible causes of gastritis is generalized stress. It may be a psychological reaction to daily life or be physically induced by trauma – the result of major illness, head injury or burns. A long list of toxins has also been implicated with this ailment, the most common ones being coffee, alcohol, tobacco, over-spiced foods and certain infectious diseases. Some common pharmaceutical drugs may also induce gastritis, notably aspirin, corticosteroids, and anti-inflammatory medications. Mixing these drugs may be especially damaging. Consult your physician before you use them in combination.

STOMACH ULCERS

Stomach ulcers – also called peptic ulcers – are spots where the lining of stomach has been eroded leaving an open wound. This can vary in depth and may lead to an actual hole right through the stomach wall (a perforated ulcer). Most ulcers occur in the stomach or duodenum and are rarely found elsewhere along the digestive tract. About one in ten North Americans will suffer at some point in their life from an ulcer, leading to symptoms like those seen in gastritis – abdominal pain, heartburn, and even melena (black or maroon-colored stools caused by oxidized blood leaking into the digestive tract) and anemia (a low hemoglobin or red blood count) if the ulcer is bleeding.

Ulcers develop when the stomach lining loses its ability to protect itself from the acids produced in the digestive juices. It was previously thought that this was caused by high acid levels, but it is now recognized that many ulcer patients have normal acid levels. We know that for various reasons, the lining's defense mechanism against these acids is insufficient, enabling ulcers to develop. Some of the risk factors for developing ulcers are:

Stress & anxiety	Alcohol
Trauma, burns	Vitamin C
Aspirin	Extreme foods
Anti-inflammatories	Tobacco
Corticosteroids	Blood type O
Caffeine	Heliobacter pylori

Several factors contribute to the protective nature of this lining. Mucus production, biochemical cellular barriers and adequate replacement of damaged mucosal cells all play a role in the maintenance of a healthy stomach. Immunological factors are only just now being understood. For example, they seem to explain why blood type 'A' individuals are likely to develop stomach cancer whereas those with blood type 'O' are more prone to duodenal ulcers.

Many factors can disrupt the protective lining. Over-secretion or over-production of stomach acids has already been mentioned. The same drugs that cause gastritis may also lead to ulcers, either by increasing acid production or by modifying the protective factors. These drugs include corticosteroids, aspirin, and dozens of anti-inflammatories known by various brand names.

As with gastritis, other risk factors include cigarette smoking, alcohol abuse, high caffeine intake, overindulgence in fatty foods and consumption of highly spiced foods like whole chili peppers. Even high-dose vitamin C (ascorbic acid) intake has been implicated with ulcers. Stress and anxiety have traditionally been identified as causes, but now seem less significant than previously thought.

Medical science has recently discovered an infectious agent involved with ulcer formation – the bacteria Heliobacter pylori. This is found in 70-90% of ulcer cases. A short course of antibiotics often but now always cures the infection. A significant portion of the population have H. pylori in their digestive tract yet never develop problems. Apparently, other immunological or physiological factors must come into play for this organism to become pathological.

CASE STUDY

Kurt was a 53 year-old vice-president of sales for a large manufacturing company. Among the seventy-hour weeks, two-martini lunches, coffees well into the night, a pack-and-a-half-a-day cigarette habit, and the stress of a poor sales quarter, he developed severe stomach pains. He was lucky. Medical investigation determined that he only had a gastritis (stomach inflammation) but that if his present lifestyle continued he would likely develop an ulcer. Unwilling to quit smoking or working so much, he agreed to a reduction in alcohol and coffee and also to visit a nutritionist. After three weeks on silymarin, melatonin, glutamine, chamomile, selenium, multiple vitamins including B-complex, C and E, he felt "infinitely better", even though sales were still down. He laughs about this now and is thinking of quitting smoking and starting regular exercise. He now believes that if he feels better in his body, his performance at work will improve.

STOMACH CANCER

Stomach cancer – gastric carcinoma – often begins at the site of a stomach ulcer. It is generally believed that ulcers do not necessarily cause stomach cancer, but that this cancer is often preceded by a particular type of ulcer. In America, it is the seventh most common cause of cancer death. However, incidence of stomach cancer varies enormously around the world; in Japan, Chile, and Iceland, it is one of the most common causes of mortality. Scientists have suggested that this may be due to differences in diet or environment. The theory is supported by the fact that certain occupational hazards such as exposure to coal dust or heavy metals like mercury and lead increase one's chances of contracting this disease.

Other risk factors include the consumption of certain types of prepared food and moulds. Foods preserved by smoking, pickling and curing contain added nitrates and other carcinogens. Barbecuing also increase carcinogen levels. Moldy foods may include a type of carcinogen called aflatoxin. This byproduct of fungi can be found growing in nuts, seeds, corn and other dried foods.

The H. pylori bacteria has also been implicated in stomach cancer. Chronic gastritis (stomach inflammation) and polyps (abnormal protruding growth of tissue) may also become cancerous. Medical conditions such as stomach ulcer, chronic gastritis, stomach polyps, toxins like alcohol, tobacco, aflatoxins and foods that are barbecued, smoked, pickled and highly salted may all contribute to the development of cancer.

GSH AND THE STOMACH

Glutathione's ability to protect the stomach is being widely researched. Its therapeutic role is promising and it has been shown to protect the stomach in several different ways. It is a primary shield against oxidative stress, detoxifies potentially harmful or even carcinogenic substances and mediates the immune mechanisms, ensuring a more effective immune response.

ACUTE GASTRITIS

It has recently been shown that when the lining of the stomach faces a toxic challenge GSH levels rise. Several groups of researchers demonstrated this using alcohol to provoke an anti-toxic response by the body. Low to moderate levels of alcohol led to an adaptive elevation in GSH levels, but high levels of alcohol overwhelmed this system, causing subsequent damage. An even more direct clinical application of glutathione's protective role in the stomach was brought to light by G.A. Balint in Hungary. His team studied an all-too-common problem – the gastric side-effects of anti-inflammatory drugs such as indomethacin and piroxicam (Indocid, Feldene, etc.). Subjects given small amounts of glutathione or cysteine at the time of drug ingestion had significantly fewer side-effects. This is a great example of a natural therapy and traditional medicine being used to complement each other.

The increase in free-radical damage and GSH turnover is well known in patients suffering from chronic inflammation of the stomach lining (gastritis) and those carrying

the bacteria Heliobacter Pylori. Both of these conditions may progress to ulcer disease and probably increase the risk of stomach cancer.

Ulcer disease may also be caused in part by high levels of lipid peroxidation and disruption of the antioxidant defense mechanisms in the lining of the stomach. There is certainly a close relationship between GSH-dependent enzymes and the progress of gastric ulcers. Glutathione and its related enzymes are found in very low concentrations within the ulcer, but often rise again when ulcerated tissues heal. When laboratory animals were given drugs to lower their GSH levels, oxidative damage to the stomach lining (gastric mucosa) was significantly higher.

Traditionally, Heliobacter pylori-related ulcers are treated with antibiotics (Amoxicillin, Biaxin, Flagyl, etc.) and proton-pump inhibitors (Losec, Pantoloc, etc.). This treatment is more effective when used in conjunction with antioxidants. A new medication called Rebamipide developed in Japan exerts some of its action by serving as a free radical scavenger. It also slows depletion of GSH. Studies using Rebamipide along with conventional drugs show improved healing.

A Swiss group from the University of Zurich recently studied smokers suffering from ulcers. They combined conventional treatment with the potent GSH precursor NAC (n-acetylcysteine), with good results. This is understandable since smokers in general suffer from much higher levels of oxidative stress than non-smokers and benefit more obviously from high antioxidant levels. Davydenko's team in the Ukraine believe that antioxidant therapy should continue even after conventional treatment has stopped.

When we look at cancer cells in the stomach as well as the immediately surrounding normal cells, we find several recurring characteristics – cells are heavily damaged by oxidative stress, their antioxidant defenses are diminished an the power-plants of each cell (the mitochondria) are defective – possibly due to free radical damage. Notably, GSH-related enzyme systems are impaired. There is little doubt that low glutathione levels go hand-in-hand with increased risk of cancer. The following research results speak for themselves.

T. Katoh at the National Institute of Environmental Health Sciences in North Carolina showed a particular relationship between GSH levels and the development of gastric cancer. For various reasons some people have inactive or inefficient sub-types of GSH enzymes. They are at greater risk for both stomach and bowel cancer.

A group from Italy studied glutathione levels in patients with stomach cancer and came to the unequivocal conclusion that the 'decrease of this tripeptide' was 'dramatical'. Their work suggests that any therapeutic approach should include GSH precursors such as cysteine.

A Japanese team reached similar conclusions while investigating gastric ulcers. They found that levels of gastric mucosal GSH 'are closely related to the etiology and course of gastric ulcer.' Various researchers and theorists have suggested that the antioxidant

capacity of the cancerous tissues has been impaired and, even more significantly, that the body's entire antioxidant defense mechanism may be breaking down.

PANCREATITIS

The pancreas is an organ involved in several important functions, the two most crucial are to secrete digestive enzymes that help prepare food for intestinal absorption and to produce hormones such as insulin and glucagons that are critical to the metabolism of sugars and carbohydrates.

Pancreatitis is an inflammation of the pancreas that leads to pain (often severe), and digestive and metabolic abnormalities. It can be potentially life-threatening and if chronic may lead to other illnesses like diabetes. Acute pancreatitis is an abrupt onset of pancreatitis most commonly caused by blockage of the passage to the intestines. This usually happens when gallstones are lodged there, or sometimes at the site of a tumor. The pancreatic juices contain powerful digestive enzymes which may back up when blocked and start to dige4st the pancreas itself.

Other causes of acute pancreatitis include certain viral and bacterial infections, specific drugs, high fat levels in the blood including cholesterol or triglycerides (hyperlipidemia), abdominal trauma, and critically low blood pressure (severe hypotension). Chronic pancreatitis develops over months or years, usually after repeated bouts of acute pancreatitis. The most common trigger by far for this type is alcoholism. Chronic pancreatitis may impair normal functions such as insulin secretion and lead among other potential problems to secondary diabetes.

Many studies suggest that oxyradicals and free radicals are involved in the development of all types of pancreatitis. The importance of glutathione in the pancreas' antioxidant defense cannot be overstated. J.M. Braganza and his team at the Royal Infirmary in Manchester, UK, have found GSH depletion in all early stages of acute pancreatitis. They surmise that low levels may predict the vulnerability of other organs to pancreatitis. M.H. Schoenberg from the University of Ulm in Germany suggests that GSH supplementation may be a way to avoid extra-pancreatic complications.

Other researchers at the Royal Infirmary developed the 'Manchester oxidant stress hypothesis' to describe the development of pancreatitis. They think that oxidant stress (caused mainly by toxins) opens the door to chronic pancreatitis because diminishing GSH levels allow the eventual breakdown of cells. This team developed a combination of antioxidants: methionine, vitamin C and selenium and tested them in placebo controlled and retrospective cross-sectional trials.

Oxothiazolidine carboxylate (OTC) – a potent GSH-enhancing drug – was successfully used by R. Luthen at the University of Dusseldorf in Germany to decrease the severity of pancreatitis. He found a critical loss of glutathione content in biliary pancreatitis (pancreatitis due to blockage by a gall stone). He and his researchers think that glutathione depletion has something to do with the early activation of auto-digestive enzymes, because the defense against oxidative stress is weakened. M.A. Walling says

that GSH depletion is key to the evolution of chronic pancreatitis caused by external toxins.

The most common cause of chronic pancreatitis is alcoholic pancreatitis. Sufferers of this disease was found to be particularly deficient in levels of vitamins E and A, selenium, and glutathione peroxidase. Researchers have suggested that these patients required higher daily requirements to ward off this oxidative stress.

Another variety of this disease is known as hereditary pancreatitis, an inherited disease which was examined at the Cleveland Clinic Foundation. A correlation was found between the disease and diminished antioxidant defenses, most notably GSH, selenium and vitamin E. The relationships among these three antioxidants are described in chapters 1 and 4. The researchers at Cleveland propose supplementation therapy with natural products to decrease the frequency of attacks.

The major complication leading to death from pancreatitis is multiple organ failure. This is partly because the integrity of cell membranes breaks down, leading to leakages both in and out of these cells. X.D. Wang and his team at Lund University in Sweden successfully used N-acetylcysteine, a potent GSH-raising drug, to prevent damage to most tissues. I. Gukovsky at the University of California also found significant improvement in acute pancreatitis patients using NAC.

INFLAMMATORY BOWEL DISEASES

Inflammatory bowel disease occurs in several forms, including ulcerative colitis and Crohn's Disease, both described here.

ULCERATIVE COLITIS

Colitis is a general term for inflammation of the bowel. Ulcerative colitis (UC) is a chronic inflammatory disease of the large bowel (colon) leading to the development of ulcers in the mucous membranes lining it. This causes pain, bloody diarrhea, gas, bloating and many other symptoms. Fever, weight loss, joint pains and even visual symptoms may accompany the digestive problems.

Most patients develop this disease early on in life, usually between the ages of 15 and 30. This disease ranges in severity from a single brief attack to a progressive course complicated by severe blood loss (hemorrhaging), perforated bowel or the spread of infection into the bloodstream (sepsis). Ulcerative colitis patients bear a higher risk of subsequent colon cancer. However, the ulcerative colitis is rarely fatal and the majority of those affected lead fairly normal lives.

The cause of this disease is still unclear but it has a small tendency to run in families. Various possible causes have been proposed, including infectious agents, immunological abnormalities, dietary factors, toxins, allergies and stress. However, these hypotheses remain unproven.

The large and small intestines are located in the lower abdomen like a loosely-folded fire hose that leads a long and winding patch from the stomach to the anus. Ulcerative colitis is marked by the formation of ulcers that eat away at the intestinal wall. Crohn's Disease is an inflammation that leads to swelling and tenderness in the intestinal wall. Figure 37 shows the location of these diseases and the different ways they affect the intestines.

CASE STUDY

28 year-old Debbie, a massage therapist, had ulcerative colitis but had so far managed to avoid any surgery. She maintained a sensible diet, continued the medications her doctor has prescribed, and avoided foods that disagreed with her. However, the previous few years had been fraught with repeated bouts of cramps, diarrhea and occasional bloody stool. Eventually, she could not make it through her workday without numerous visits to the washroom. A dietary consultant added to her diet a high-dose antioxidant mixture, selenium, L-glutamine, and – when her stool was firmer – psyllium husks. Her blood loss has abated, and she now visits the washroom at lunchtimes only.

CROHN'S DISEASE

Crohn's disease (CD) is similar in many ways to ulcerative colitis (see above). Its differences, however, make this a potentially more severe disease. In ulcerative colitis small ulcers are scattered in the lining of the large bowel. Crohn's disease is less selective and may affect any part of the digestive system, from mouth to anus. It is most common in the ileum (the end of the small intestine where it joins the large intestine). The disease occurs in heavy patches, but areas between these diseased patches are also mildly affected. It is most common in the gut where the intestine wall may grow extremely thick following repeated inflammation. Deep ulcers may pass right through the lining and completely penetrate the gut tissues.

With repeated and prolonged inflammation of the intestine the entire thickness of the intestinal wall becomes affected. The thickening of the wall may narrow the intestinal passage and obstruct it. Symptoms can include spasms of abdominal pain, diarrhea, appetite loss, anemia and weight loss. The elderly are more prone to inflammation of the rectum. Young and old alike may suffer from chronic abscesses, deeps fissures (cracks) and fistulas (abnormal passageways) in the anus. Because the entire digestive system is susceptible, complications are more profound than those following ulcerative colitis. They include bowel obstruction, infection, malabsorption, and elevated cancer risk – as much as 20 times greater than healthy individuals.

Like ulcerative colitis, the exact cause of Crohn's disease is unknown, but there tends to be a stronger familial tendency. Some researchers think this may also be an autoimmune disease. Studies suggest that sufferers may benefit by avoiding certain food additives, allergens and cigarettes.

GSH IN INFLAMMATORY BOWEL DISEASE

It is clear from observing patients with inflammatory bowel disease that inflamed cells in the lining of the intestines are a hotbed of free radicals. However, there is still debate as to whether the free radicals cause or result from the damage characterizing these diseases.

Samples of tissue inflamed by ulcerative colitis and Crohn's disease show consistent evidence of severe oxidative stress. The degree of oxidative damage can even be correlated to the degree of inflammation. Of all the antioxidants that can prevent or retard this damage, GSH is the central one.

Researchers from all over the world – including L. Bhaskar from India and GD. Buffington from Australia have looked at tissues affected by inflammatory bowel disease and Crohn's disease. All have identified a significant depletion of glutathione and alteration of its enzymes. In the past, most researchers believed that GSSH depletion was more likely to be a consequence of ongoing inflammation and oxidative stress than a contributing cause of the problem. But today, opinions may be changing. More recent findings by B. Sido of the University of Heidelberg in Germany have found not only diminished GSH levels but also diminished activity of the enzymes involved with GSH production. This implies that declining GSH production may actually contribute to the development of the disease.

Antioxidant therapy has thus emerged as a treatment for inflammatory bowel disease. One of the more traditional groups of medications applied to these diseases are the aminosalicylates (sulfasalazine, Asacol, Dipentum, etc.). These are potent antioxidants, but are also pharmaceutical drugs, and the hunt for less toxic, more natural products is on.

T. Cruz and J. Galvez and their team from the University of Granada in Spain, were able to protect inflamed bowels with a flavonoid called rutoside – flavonoids are a variety of crystalline compounds found in plants. This worked with both acute and chronic disease. They explained their success by pointing to rutoside's tendency to maintain or increase GSH content in the gut.

Malnutrition results more often from Crohn's disease (CD) than from ulcerative colitis. The reasons are complex but are summarized by the fact that CD is more deeply involved in the bowel. The nutritional status of those suffering from this disease has been investigated at great length, and reveals a generalized GSH depletion throughout the body. These findings have also been reported in children with CD, possibly resulting from ongoing oxidative stress.

Numerous scientists have suggested oral GSH supplementation as a treatment for UC and CD. It is clear from the information we presented in chapters 1 and 4 that oral glutathione is not very effective in raising total body GSH. However, these digestive tissues seem able to make use of locally supplemented GSH. The tissues most positively affected by oral GSH are those in direct contact with it. The intestinal lining (mucosa) provides such an opportunity. In fact Alton Meister – often called the father of GSH research – suggests that both oral GSH and GSH excreted in the bile can protect the intestinal mucosa from injury. Experimental depletion of gut glutathione leads to severe damage of this sensitive lining.

CONCLUSIONS
GSH AND STOMACH DISEASE

Research evidence suggests that glutathione defends the stomach lining against various threats, including toxins, oxidative stress and carcinogenesis. Their results have prompted others to seek ways to raise glutathione levels in humans, for both preventive and curative purposes. Elevated glutathione levels may protect against gastritis, ulcer and cancer and can certainly compliment conventional treatments for these diseases.

PANCREATITIS

The high levels of oxidative stress and the depletion of glutathione in pancreatitis is well documented and scientists are investigating the role of antioxidant therapy in the treatment of pancreatitis and prevention of recurrent bouts. Even though antioxidant therapy is a safe complementary treatment for chronic pancreatitis, its wider adoption as a standard healthcare tool will take time. The lynchpin of this new approach is the search for tools to enhance (modulate) intracellular glutathione levels. As these tools emerge, further research will be needed to use them effectively.

INFLAMMATORY BOWEL DISEASE

An imbalance in the formation of free radicals and a poor supply or availability of antioxidant micronutrients may cause or encourage tissue injury in inflammatory bowel disease. Levels of glutathione and its related compounds are significantly lower in these diseases. Different antioxidants including GSH, GSH monoesters, NAC (N-acetylcysteine), vitamin C (ascorbate), vitamin E (tocopherol), SOD (Superoxide dismutase) and others have been used with varying success. It may not be clear whether GSH loss is a cause or consequence of these inflammatory disorders, but in either case, they are positively affected by therapies that raise or sustain GSH levels. Recent research suggests that raising glutathione levels may be a novel approach to the treatment of ulcerative colitis and Crohn's disease.

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