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STRESS AND ULCERS: FACT OR FANCY?

In recent months, the media have been triumphantly hailing new advances in the cause and treatment of peptic ulcers, based on research demonstrating that a bacterium is the culprit. Although H₂ receptor antagonists like Tagamet and Zantac are among the largest selling prescription drugs, and several can now be obtained over the counter, the implication is that such antiulcer medications may be passé for long term treatment. It has similarly been insinuated that popular putative contributors to peptic pathology, such as stress, smoking, and increased gastric secretion, should also be thrown out the window. The latest findings imply that ulcers and gastritis are due to an infection, and can only be cured by antibiotic therapy. The evidence for this is admittedly overwhelming, and the background for this somewhat revolutionary development reads like a Horatio Alger story.

Although it is generally believed that microbes could not survive in gastric acid, suspicious spiral bacteria were identified in the stomach over 100 years ago. The presence of similar curved microorganisms on the surface of gastric mucosa was also noticed when direct endoscopic examination of the stomach became available, but this was largely ignored. About 15 years ago, J. Robin

Warren, a pathologist at Royal Perth Hospital in Western Australia, became interested in these curious microbes, which he consistently found in biopsies from gastritis patients. Nobody seemed to know anything about them, nor was there much interest in how or why they might be there. Their shape and staining characteristics suggested that they could be *Campylobacter* organisms, but they were difficult to grow with conventional culture methods.

The Hunt For Helicobacter

Warren's research did attract the attention of Dr. Barry Marshall, who had been assigned to the gastrointestinal service as part of his rotating fellowship training in internal medicine at the hospital. Together, they improved the culture procedure, and in 1982, began a prospective study of 100 consecutive patients undergoing upper gastrointestinal endoscopy. Biopsy specimens of the stomach were obtained for culture and microscopic examination, and a strong association was found between gastritis and the presence of these bacteria. However, cultures were positive in every patient with a duodenal ulcer, and in 80% of those with stomach ulcers. When the organisms were not present, the pathologic picture was almost always associated with non-steroidal anti-inflammatory drug treatment.

The microbe was initially considered to be, and was referred to as *Campylobacter pylori*, but careful investigation revealed that it also had features of the *Vibrio* bacterium. They subsequently decided that it most likely represented a new gram negative genus, and named it *Helicobacter pylori*. But how did it get in the stomach?

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The Newsletter of
**THE AMERICAN INSTITUTE OF
 STRESS**

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How could it survive? The most likely explanation was contaminated food, water, and milk, or possibly poor dental hygiene. It appeared able to endure by growing in the grooves between cells that were protected by the alkaline mucosa. Marshall became hooked on the bug.

He recalled that prior to modern drugs, bismuth preparations had been used to treat gastritis and ulcers for almost 200 years. Sure enough, bismuth salts quickly killed *Helicobacter* cultures. However, when he gave bismuth (Pepto-Bismol) to his gastritis patients, although the infection seemed to clear, it recurred unless metronidazole (Flagyl), a drug used to treat certain protozoan infections and bacterial infections was given simultaneously. Commonly prescribed antiulcer medications relieved symptoms, but the bacteria always persisted, which helped to explain why recurrence was often seen after treatment was discontinued. To prove that the organism was a pathogen, he used immunofluorescent microscopy to demonstrate the presence of antibody in the serum of patients that had the bacterium. This ultimately led to accurate blood tests, and a breath test based on the organism's ability to break down urea. These improvements have now made large scale testing for the presence of the organism rapid, simple, and relatively inexpensive.

The Problem Of Proof

In 1983, Marshall conclusively demonstrated for the first time that gastritis could be permanently healed once the bacteria were completely eradicated. However,

this breakthrough received a cool reception when presented at gastroenterological meetings. In addition, his blood testing had revealed that 15% of healthy Australian adults younger than 40, and 40% of those over 50 had evidence of being infected with the organism. Obviously, it could hardly be viewed as a significant pathogen if so many normal people harbored it.

Proving his premise with an animal model failed, since he found it impossible to infect rats, mice or even pigs with the organism. As a consequence, in July 1984, Marshall decided to drink a pure and potent culture of *H. pylori*. He was disappointed that nothing seemed to happen and that he felt fine. However, on the fifth day, he started to experience early morning nausea and vomiting, and cultures and histologic diagnosis on the eighth day confirmed severe acute gastritis, with many *H. pylori* organisms. No treatment was given, and the illness resolved spontaneously after two weeks.

He subsequently received some funding to study the effect of *H. pylori* eradication on peptic ulcer relapse. In 1985, 100 patients with confirmed peptic ulcer and concurrent *H. pylori* infection were treated with either cimetidine (Tagamet), a popular H₂ receptor antagonist drug, or a combination of bismuth with one of three different antibiotics. Ulcers recurred in 90% of the patients that had been healed with cimetidine, but in only 21% of those treated with the single, antibiotic-bismuth combination. The rest is history, and a plethora of reports have now confirmed the cure of peptic ulcer by the eradication of *H. pylori*. In the absence of non-steroidal anti-inflammatory drug treatment or gastroesophageal acid reflux problems, permanent cure can be expected in 90% of ulcer patients with a combination of a broad spectrum antibiotic, Flagyl, and Pepto-Bismol. As yet, there has been no proven effective single antibiotic treatment, although clarithromycin (Biaxin) appears promising.

Helicobacter pylori infection is now generally recognized as the major cause not only of gastritis and peptic ulcers, but also gastric malignancy. The World Health Organization recently classified it as a human carcinogen estimated to account for up to 60% of cases of cancer of the stomach worldwide. The success of Marshall's research has been so stunning, that the medical community has done a complete about-face with respect to supporting his theories. In 1994, the National Institutes of Health convened a "Consensus Panel on *Helicobacter Pylori* in Peptic Ulcer." They fully supported Dr. Marshall's findings, and recommended that patients with *H. pylori* ulcers should be treated with

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antibiotics as well as acid-suppressing drugs. This year, he received the coveted Albert Lasker Clinical Medical Research Award, and established The International Research Foundation for Helicobacter and Intestinal Immunology, to explore the pathogenic role of new Helicobacter species in other gastrointestinal disorders.

Some Unanswered Questions

On the other hand, several observations suggest that the situation is not such a simple cause and effect relationship. *H. pylori* infection reaches epidemic proportions in some underdeveloped countries, where more than 80% of the population are infected. One out of three U.S. adults may also harbor Helicobacter. Infection is probably more common in older individuals because of the greater likelihood of having ingested contaminated food and water prior to 1930. Its prevalence in only 20% of adults under the age of thirty-five attests to the marked improvement in sanitation over the past four decades. In Japan, where proper sanitary standards were not implemented until 1960, most individuals over 40 are infected, while children under 10 have rates similar to controls in the United States. However, the overwhelming majority of infected individuals have no gastrointestinal symptoms, and peptic ulcer develops in only 1% of infected adults per year. The reason for this is not clear, but stress could very well be the determining factor.

Numerous research reports have shown that stress can lower immune system defenses to a variety of infections. In one landmark study, healthy volunteers received nasal drops containing one of five respiratory viruses. Stress levels were evaluated by scores derived from standard measures, including severity of current negative emotions, and the magnitude of life change events over the preceding year. The subsequent infection rates, as assessed by specific antiviral antibody studies ranged up to 90%, but only 25-50% of subjects actually came down with colds. However, the rates for both laboratory evidence of infection and clinical colds correlated precisely with the magnitude of psychological stress scores for each of the viruses! As we shall see, long term studies show a similar relationship between rising stress levels, and the likelihood of developing peptic ulcer.

Stress has also been implicated in the development and aggravation of tuberculosis, herpes simplex, AIDS, and a variety of viral linked malignancies. With respect to its role in peptic ulcer, there is a wealth of clinical and experimental evidence that simply cannot be ignored, and indeed, imply a degree of importance that rivals the role of *H. pylori* infection.

Could Stress Be The Answer?

A possible link between emotional stress and stomach complaints has been suggested by numerous novelists, poets, philosophers, and artists, over the past 2000 years. The first scientific studies were probably those reported in 1833 by William Beaumont, an Army surgeon. Ten years previously, Alexis St. Martin, a nineteen year old boy had been chatting with some friends at a trading post on Mackinac Island in Michigan, when someone tripped over a shotgun. The blast blew a huge hole in St. Martin's stomach, and as he fell down screaming with his shirt on fire, the food he had for breakfast began to pour out of his stomach. Beaumont, who witnessed the scene, saved his life, but the wound never healed, resulting in a fistula that provided an open window on the stomach. Beaumont was able to persuade his grateful patient to let him take advantage of this unusual opportunity to study stomach function, and he made detailed observations over the following years. He discovered that the stomach reacted quite remarkably whenever the young man became upset, noting that "undo excitement... fear, anger, or whatever depresses or disturbs the nervous system..." caused it to lose its smooth and healthy appearance. At times there were "deep red pimples", "irregular circumscribed red patches", or "the rolling up of the mucous coat into small shreds." These physical changes were accompanied by significant disturbances in the stomach's normal secretory and motor activity patterns. Beaumont's report stimulated subsequent researchers to study experimental animals with surgically induced gastric fistulas, that further confirmed the powerful effects of emotions on gastric function.

Ivan Pavlov, Walter Cannon, And Stewart Wolf

The most famous of these was the Russian scientist, Ivan Pavlov, who showed that habitual responses to conditioned stimuli could be developed through repetitive associations, and that these were significantly affected by emotionally disturbing events. Walter Cannon, who was responsible for the "fight or flight" hypothesis, conducted numerous animal experiments which clearly demonstrated that different stressors had varying or even opposite effects on gastric secretion and motility. Using innovative techniques, similar changes were later observed in patients during stressful interviews by Harold Wolff and colleagues. In 1941, one of his

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associates, Stewart Wolf began his famous studies on Tom, a 56 year old man with a gastric fistula. On a sweltering day in 1895, Tom, who was nine years old, sneaked a gulp of what he thought was cool beer that his father had just brought home. Unfortunately, the beer pail contained scorching hot clam chowder, that seared his esophagus. The only way he could survive, was to make a permanent opening through his abdomen, so that food could be poured into his stomach through a funnel. It was difficult for Tom to find work because of this disability, so he eagerly accepted permanent employment doing odd jobs around the laboratory where Dr. Wolf was working. In return, he allowed the young doctor to make careful measurements and descriptions of changes in how his stomach functioned and appeared during different situations.

Wolf found that feelings of being overwhelmed by fright or depression were associated with diminished blood supply that resulted in pallor, reduced acid secretion, and motility. This was precisely what Walter Cannon had described in cats when they had to face a ferocious, barking dog. On the other hand, feelings of anger, resentment, hostility, and aggression resulted in an engorgement of the lining of the stomach with blood, increased secretion of acid and enzymes, and more forceful contractions. On one occasion, when Tom was undergoing an intense emotional crisis, it was possible to see a spontaneous ulceration form in the lining of the stomach, presumably due to persistently elevated levels of hydrochloric acid.

Selye's "Alarm Reaction", was consistently characterized by stomach ulcerations, atrophy of lymphatic tissues, and enlargement of the adrenal cortex in every experimental animal suffering from acute stress. All these findings were due to the markedly increased secretion of cortisone-like hormones. These steroids have now been shown to interfere with the synthesis of prostaglandins, chemicals which normally protect the inner lining of the stomach from the digestive actions of acid and enzymes. Inhibition of prostaglandin production is responsible for the ulcers commonly seen with cortisone, as well as non-steroidal anti-inflammatory drugs like aspirin and ibuprofen.

Stress related ulcers of the upper gastrointestinal tract are also seen in several clinical situations. *Curling's ulcer* commonly occurs in association with the stress of severe burns or bodily injury. It is also seen in patients suffering shock or sepsis, particularly following abdominal surgery. Ulcers are so frequent in other stressed out patients in intensive care units, that prophylactic medications are often routinely prescribed as a preventive measure. *Cushing's ulcer* is associated with brain

trauma or disease, further indicating the importance of central nervous system influences. How this is mediated is not clear. However, around the middle of the nineteenth century, a pathologist who had examined some 30,000 brains from autopsy specimens, had noted that ulcers were apt to be associated with lesions in a certain area of the hypothalamus, which Selye subsequently demonstrated stimulated pituitary and adrenal hormone production during stress.

About 50 years ago, researchers found that stimulation of certain areas of the frontal lobe could markedly increase gastric acid and enzyme secretions. This portion of the brain controls the way we experience and process emotions, like anger, fear and grief. It has strong connections with the hypothalamus, which regulates "fight or flight" responses and autonomic system activities, as well as the limbic system, which is the basic seat of emotions. It is not clear whether direct central nervous system or endocrine mechanisms are primarily involved in stress induced ulcers, whether it is some combination of both.

Stress is difficult to define, since it differs for each of us. However, the sense or feeling of having little control is always distressful. In one study, two groups of rats were periodically subjected to identical electrical shocks. The first group could terminate or abort the shocks for both groups, by learning to turn a small wheel. The second group had absolutely no control over the shocks, but at the end of the study, they had many more ulcers, even though the number and duration of shocks both groups received were identical. However, the second group had no control over when the shocks would come, or how long they would last. To demonstrate that both of these factors were important, a similar study was performed in which the first group heard a warning buzzer before each annoying jolt, so they knew what to anticipate. The second group received the identical shocks, but had no idea when they were coming. These animals similarly developed more ulcers, because even though neither group could control the shocks, the first had more mastery over their situation since they knew what to expect. The second group also became very passive. Such "learned helplessness" lowers immune system defenses, and can contribute to other diseases.

A similar situation may apply in the workplace, where it is often said that top executives and bosses "don't get ulcers, they give them." If true, the explanation might be that their greater degree of control is a powerful stress buffer, compared to subordinates with little decision making latitude.

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The Crucial Importance of Host Defenses

It is difficult to explain how helicobacter infection could explain all these various observations. This would appear to be especially true with respect to the experimental production of ulcers in animals, since they appear rather resistant to this organism. Like stress, and certain medications, *H. pylori* may be more of a risk factor in certain situations. The *causa vera* or true cause of any disease requires that the disorder cannot occur in its absence. In the early nineteenth century, it was generally believed that tuberculosis was due to unsanitary and intimate living conditions. Proof of this seemed to come from the finding that when these were corrected, the incidence of tuberculosis declined dramatically. It was not until Koch subsequently discovered the tubercle bacillus and showed that it was present in every case, and proved that the disease could not occur in its absence, that the true cause of tuberculosis became evident. As in the case of *H. pylori* infection, many individuals who harbor the tubercle bacillus have never had any signs or symptoms of clinical disease. However, during situations of stress, or following the administration of stress related steroids like cortisone, the body's normal defenses are lowered, and clinical signs and symptoms appear.

Further support for the role of stress in ulcers comes from a health and nutrition survey of over 45,000 individuals who were asked a variety of questions, such as "Have you been under or thought you were under any strain, stress, or pressures during the last month?" Responses on a scale of six ranged from "not at all", to "almost more than I could bear or stand". These identical questions were again asked in a follow-up 10 years later. At baseline, 68% reported being significantly stressed, and almost 4 out of 5 of these remained in this category a decade later. For those individuals who had initially reported little stress, about half had now moved up to the increased stress group, confirming numerous reports showing a significant increase in stress over the past two decades. During the period between the two surveys, a peptic ulcer had been diagnosed in 208 subjects. The interesting finding here was that there was a clear correlation between a marked increase in stress, and the likelihood of developing an ulcer. What has this to do with *Helicobacter* infection?

There should be little doubt that activation of autonomic nervous system and endocrine influences can facilitate the development of peptic ulcers through various pathways. It's also apparent that *H. pylori* infection

can play a pivotal role, but it may require a combination of the two to produce clinical disease. Sir William Osler, possibly the greatest of all clinicians, used to tell his students, "Show me what goes on in a man's head, and I will tell you what will become of his tuberculosis." That was long before we knew anything about how stress increases the production of cortisone-like hormones that promote the rapid spread of the disease, or cause it to be reactivated after being dormant for years. It is not unlikely that ulcers are also most likely to occur when stress pulls the trigger of a loaded gun. However, the ammunition, in this instance, is *H. pylori*.

Personality And Ulcers

During the first half of this century, the practice of medicine was quite different than today. Physicians didn't have the wide array of sophisticated laboratory and imaging procedures currently available for diagnostic purposes. Consequently, they had to rely much more on the patient's history and physical findings. They also had much more time to spend with patients, than is possible in the frenetic pace of modern practice. In addition, they were probably more aware and sensitive to psychosocial factors and behavioral traits that might contribute to ulcers, and there are numerous examples of this. Brinton's, *On The Pathology, Symptoms, and Treatment of Ulcer of the Stomach*, published in 1857, maintained that mental anxiety should be regarded as "a more or less immediate cause" of ulcer. The term "psychosomatic" was introduced into American medicine by Flanders Dunbar in 1936, and gave rise to a new specialty that emphasized the role of mental and emotional factors in illness. Certain personality characteristics were proposed as being associated with, or possibly responsible for ulcers, as well as rheumatoid arthritis, asthma, hypertension, ulcerative colitis and headaches. There was even an accident prone personality.

Franz Alexander's detailed psychoanalytic studies of ulcer patients led him to conclude that the disorder often stemmed from an intense but repressed wish to be loved and taken care of. He reasoned that:

"If the intense wish to receive, to be loved, to depend upon others is rejected by the adult ego and consequently cannot find gratification in normal life relations, then only the regressive pathway remains open; the wish to be loved becomes converted in the wish to be fed. The repressed longing to receive love and help mobilizes the innervations of the stomach which are since the beginning of extra-uterine life closely associated with the most primordial form of receiving something, namely, the process of receiving food. These

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innervations serve as the chronic stimulus of the stomach functions and lead to its dysfunction since this stimulus of the stomach is independent of the physiologic state of hunger. Those individuals, who, on account of the described conflict-situation, have to repress and abnegate their own over-strong cravings express them in the tacit physiologic language of the stomach. Such a stomach behaves all the time as if it were taking or were about to take in food... These tendencies we find in most of our cases to be repressed and denied by the patient, and associated with violent conflict."

In other words, the basic infantile need is to be fed, and during our early development, being fed and being loved are equated. These become separated later on in adult life, and the need to be loved may then become regressively translated into the need to be fed, resulting in a chronic increase in gastric secretions.

Zane similarly believed that:

"The peptic ulcer conflict begins in early childhood. The child seeks security by striving to meet the rigid exacting standards set up by the authoritarian figure. At the same time he anticipates failure because of strong fear of his own inadequacy. To allay the fear of failure, he struggles to perform precisely as is expected of him. The same pattern is used throughout life in the search for security, but new circumstances engender fuller development. Resentment inevitably accompanies the need to reject and deny his own inclinations and fancies. At the same time the demand of society becomes more elusive. But he never gives up trying."

Numerous other pioneers in psychosomatic medicine expressed analogous views based on careful personal observation and interviews. In general, ulcer patients tended to be tense, very self-sufficient, independent, distant, critical, stubborn, obstinate, hypersensitive, and always in a hurry. They were over conscientious, painstaking, and punctilious about work and other daily duties, and exhibited an unusual drive. Although they worried a great deal, there were rarely any external manifestations of mental agitation.

However, the notion that personality and coping skills were important contributors to ulcers, was not limited to psychiatrists and psychologists. Draper's *Human Constitution in Clinical Medicine*, published in 1944, noted:

"the interesting observation that a majority of our patients with peptic ulcer are drawn from the ranks of taxicab drivers, policemen, and firemen. These occupations demand constant output of energy in aggressive and often dangerous effort. Consequently, it is understandable that all these occupations expose their representatives to inner doubts concerning the validity of their essential beings... From this conflict arises a fear in

the subconscious of the potential peptic ulcer patient, that when the crucial test comes, he will fail to play the masculine role adequately for the preservation of his body or his soul (ego?) or both."

Peptic ulcer was observed to occur up to 8 times more frequently in men than women in the middle-aged period of their life, when they were most productive. While originally considered to be primarily a male disorder, this has now changed as more and more women have entered the workforce and adopted many male traits. Ulcer patients were also thought to possibly have some genetic predisposition, based on certain common anthropologic and physical characteristics.

Leading gastroenterologists expressed similar views. Henry Bockus' three volume magnum opus, *Gastroenterology*, also published in 1944, was the most authoritative text on the subject for many years. He wrote that at least half of his own ulcer patients had most of the behavioral traits noted above, and cited one authority who believed that 95% of duodenal ulcers were "psychogenic". However, Bockus believed that this was only one component, and that heredity, central nervous and endocrine system influences, nutrition, allergy and infection could be important contributing influences in some cases. Infection was included, since in 1923, Rosenow had demonstrated that he could produce ulcers in the stomach and duodenum of experimental animals by administering strains of streptococci recovered from resected human peptic ulcer tissue. Similar organisms recovered from foci of infection in the nose and throat could also produce the same pathology. A reported increase in ulcers following respiratory infections was thus ascribed to the swallowing of infectious material, but in retrospect, it seems equally plausible that any such association may have been due to increased intake of aspirin and other common cold remedies, and perhaps the ulcer "streptococcus" was *Helicobacter*.

Contemporary specialists are still sensitive to the important role of emotions and personality in peptic ulcer patients, and the conflicts which can result because of a tendency of ulcer patients to repress any outward expression of their true feelings. Howard Spiro cites this illustrative example in *Clinical Gastroenterology*, one of the current, leading, authoritative texts.

"One 40-year-old man, a practicing physician, was most instructive, though hardly unique. For many years he had been a curmudgeon, chasing some of his patients from his office, giving salty advice to others, and generally raising Cain. Six months before, he had decided that it was time for a change; he would become

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sweetness and light and, life being short, he would be kind to everyone, regardless of how he felt. Exactly on the day that he made that decision, he first suffered severe ulcer pain, which within a few weeks began to radiate through to his back. He finally came to the hospital with intractable pain from a posterior penetrating duodenal ulcer for a decision as to whether he needed a gastric resection. Faced with the possibility of losing his stomach, the patient recognized exactly what had happened and what his cure should be. Soon after he resumed his normal and caustic dour exterior, the ulcer for which operation seemed so inevitable stopped paining him and it has not recurred. Unfortunately, not everyone can give vent to his feelings as easily as the successful physician."

Like Draper, Spiro points out that people in certain occupations seem more prone to develop ulcers, such as bus and taxi drivers, and train and street car conductors. Business executives, lawyers, doctors and foremen are also high on the list, but whether this is due to the increased stress of their daily work, or a greater likelihood that they often must suppress their emotions and feelings is not clear. Most modern gastroenterologists would probably support Bockus' overall conclusion, that "Ulcer is a civilization disorder, and as the complexities of life increase, one may expect an even greater incidence of peptic ulcer."

A Disease Of Civilization?

To support this view, Bockus emphasizes that "peptic ulcer is a disorder peculiar to one animal, *Homo sapiens*." Furthermore, it rarely occurred until individuals were subjected to stresses of civilization to which they were unable to adapt. Numerous examples could be cited, such as Sir Robert McCarrison's observations during his assignment as a physician to British forces in India, in the early part of this century. He surveyed some 11,000 Hunza natives in Kashmir, and failed to find a single case of peptic ulcer. There was also no evidence of appendicitis, gall bladder disease, or cancer in these individuals "who were not subjected to the stress and strain of civilized life". Their diet included an ample intake of meat and dairy products, as well as fruits and vegetables, but the distinguishing feature appeared to be that they were **"far removed from the refinements of civilization"**. Certain of these races are of magnificent physique, preserving until late in life the character of youth; they are unusually fertile and long-lived, and **endowed with nervous systems of notable stability.**" (Emphasis added).

It was formerly believed that peptic ulcer did not occur in blacks, since it was extremely rare in native

Africans. However, in the United States, its prevalence is now similar to that seen in whites. Four or five decades ago, the incidence of ulcer and stomach cancer was very low in Malaysians living in Java and Sumatra, but transplanted Chinese had rates similar to those seen in Western societies. This was not the result of any differences in diet or gastric physiology. Although the Malays had somewhat higher concentrations of gastric acid, the Chinese had ten times as much peptic ulcers. This was attributed to the fact that those who migrated to these Dutch Islands had the primary control of business activities in the region, and exhibited the same increased drive and competitive aggressiveness of ulcer prone merchants and entrepreneurs involved in similar ventures in the West. At the time, Bockus pointed out that the highest ethnic incidence of ulcers was in the Jewish race, presumably because of a greater predilection and proclivity to engage in competitive and commercial transactions that caused constant pressures.

The importance of the nature of stress in the development of ulcers was also emphasized by Ross, who noted:

"Sometimes tension gets so bad that it temporarily 'cures' a disease, which was started by another tension. In a Dutch concentration camp, for example, a group of businessmen suffering from ulcers were locked up together. The conditions in the camp were horrible. The men fought over food, toadied up to their German jailers, stole, lived in constant fear of informers. But, these new worries were so different from the business worries that had brought on their ulcers that everyone of them lost the symptoms of his disease while he was in the camp. When they went back to their businesses, however, they went back to their ulcers."

Progressive urbanization and civilization may also explain the observation that duodenal ulcer was practically unknown in the British or American armed forces during the first World War, but became a major cause of disability in World War II. The fact that ulcer rates are now declining, despite evidence of increased levels of job and other sources of psychosocial stress, may seem paradoxical. However, it may represent the development of adaptive mechanisms to sustained stress, much like Selye's "Stage of Resistance", which follows "The Alarm Reaction", in his "General Adaptation Syndrome".

The story of *Helicobacter* and the contributory role of civilization to disease is far from over. A recent report suggests that chronic infection with *H. pylori* may contribute to the development of coronary artery disease. In a study of white London men aged 50 to 69, those with positive blood tests for *H. pylori* were almost four times

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as likely to have electrocardiographic evidence suggestive of a prior myocardial infarction or significant ischemia, than seronegative controls. Researchers theorize that this may be due to the possibilities that chronic inflammation might increase other coronary risk factors. However, both *H. pylori* infection and coronary heart disease are so common in men in this age group, that it is difficult to determine the significance of these findings.

Of much greater concern is evidence that the bug is becoming less susceptible to eradication. Infectious disease experts warned at a recent conference, that strains of *H. pylori* have already become resistant to very high powered antibiotics and that this trend will likely increase. Resistance is growing to Flagyl, which is commonly used to treat trichomonas, amebic, and other protozoan infections, and in some parts of the world, where it is popular as an antidiarrheal agent, large quantities are sold over the counter. Thus, even though combination antibiotic therapy is effective today, it might be useless a few years from now. Some *Helicobacter* strains are already resistant to both Flagyl and clarithromycin, one of the antibiotics most commonly used in combination with this and bismuth. Experience with tuberculosis and flu epidemics has taught us that despite medical advances, many organisms quickly learn to adapt to attempts at their elimination, and may re-emerge as more potent pathogens.

Louis Pasteur, who was preoccupied with microbes as a cause of disease, engaged in numerous debates with his celebrated contemporary Claude Bernard, who was responsible for the concept of the internal environment, and the need to maintain its stability to preserve health. It is reported that on his deathbed, Pasteur said "*Bernard avait raison. Le germe n'est rien, c'est le terrain qui est tout.*" [Bernard was right. The microbe is nothing, the soil is everything.] Similarly, as

most "complete" physicians eventually recognize, it is many times more important to know what kind of patient has the disease, than what kind of disease the patient has.

Paul J. Rosch, M.D., F.A.C.P.

Editor

"The view that a peptic ulcer may be the hole in a man's stomach through which he crawls to escape from his wife has fairly wide acceptance."

J.A.D. Anderson

Books Received For Review

Research Advances in Alzheimer's Disease and Related Disorders, Edited by Iqbal, K., Mortimer, J.A., Winblad, B., Wisniewski, H.M., John Wiley & Sons, Ltd., England, \$130.00

Letting go of ANGER, Potter-Efron, R., Potter-Efron, P., New Harbinger Publications, Inc., California, \$12.95 (paper) \$24.95 (cloth)

Stress and Health Psychology, Edited by Kasl, S.V., Cooper, C.L., John Wiley & Sons, England, \$15.95

Approaching Hysteria: Disease and Its Interpretations, Micale, M.S., Princeton University Press, New Jersey, \$29.95

The Psychobiology of Aggression, Edited by Hillbrand, M., Pallone, N.J., The Haworth Press, Inc., New York, \$49.95

Sex Addiction, Earle, R.H., Earle, M.R., Brunner/Mazel Publishers, New York, \$32.95

Human Growth Hormone, Edited by Shiverick, K.T., Rosenbloom, A.L., CRC Press, Florida, \$85.00

Clinician's Guide to Mind Over Mood, Padesky, C.A., The Guilford Press, Inc., New York, \$19.95

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