

Psychosocial Factors in Peptic Ulcer and Inflammatory Bowel Disease

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Over the past decade, while gastroenterologists' interest in mind–body interactions in organic disorders dwindled, stronger evidence has linked psychosocial factors with the incidence and recurrence of peptic ulcer and with the course of inflammatory bowel disease. Psychological–behavioral approaches to treatment continue to be disappointing. Psychosocial factors may affect ulcer by increasing duodenal acid load, altering local circulation or motility, intensifying *Helicobacter pylori* infection, stimulating corticosteroid secretion, and affecting health risk behaviors; possible mechanisms for inflammatory bowel disease include immune deregulation, gut permeability changes, and poor medication adherence. Both belong to the growing category of diseases thought to have an infectious component: for peptic ulcer the bacterium *Helicobacter pylori*, for inflammatory bowel disease an exaggerated immune response to gut bacteria. Peptic ulcer and inflammatory bowel disease, which present unique interactions among psychological, immunologic, endocrine, infectious, and behavioral factors, are splendid paradigms of the biopsychosocial model.

The occurrence of abdominal pain or diarrhea under stress is so close to a universal human experience that case-control studies documenting an influence of life circumstances on functional gastrointestinal complaints (Bennett, Beaurepaire, Langeluddecke, Kellow, & Tennant, 1991; Creed, 1981; Whitehead, Crowell, Robinson, Heller, & Schuster, 1992) seem nearly superfluous. With organic structurally based diseases the story is less clear. Both peptic ulcer and ulcerative colitis were once featured in the psychosomatic literature (Mittelman & Wolff, 1942; Sullivan, 1936), but recent decades have seen a radical shift in the mind-sets of gastroenterologists. In parallel with a geometric expansion of our understanding of gut pathophysiology, perhaps partly as its consequence, medical thinking about peptic ulcer and inflammatory bowel disease has shifted away from psychosomatic explanations toward a physiological reductionism in which such elements as bacterial flora and immune reactivity are considered the sole etiologic elements of interest. This period has also brought dramatic improvements in medical and surgical treatment, lessening the practical importance of biopsychosocial thinking and further discouraging clinicians and researchers from taking serious interest in the contributions of the mind and allowing them to stay comfortably out of step with the current mania for pop psychosomatics, which writes off to stress everything from athlete's foot to cancer.

At the same time, research into mind–body interactions in functional gastrointestinal disorders has been burgeoning and has garnered notable successes. Interest in psychologically oriented treatments, which has faded for the organic disorders, has been booming for nonulcer dyspepsia and irritable bowel syndrome, and for good scientific reason: These disorders are protracted or even

lifelong, medical treatment is impotent to cure them or often to control their symptoms, and psychosocial factors have a strong influence. It might be added that pharmaceutical companies have a financial stake in using mind–gut research to help develop drugs that a patient might take not merely for years but for decades, an interest which converges with the drive of managed-care organizations to find behavioral approaches with a potential for reducing health care utilization.

The end result of these processes has been a drop-off within the biomedical community in research interest regarding the possible role of psychosocial factors in organic gastrointestinal diseases (Aronowitz & Spiro, 1988; Levenstein, 1998) and some shift of energies among those who do study mind–body interactions toward the realm of functional disorders. In paradoxical synchrony with the growing indifference of the biomedical community at large, the 10 years since the last review of gastrointestinal disease in these pages (Whitehead, 1992) have nevertheless brought forward the most solid evidence to date linking psychosocial factors with the etiology and the course of organic gastrointestinal disorders, whereas recent advances in pathophysiology and in the sophistication of biopsychosocial thinking have made it possible to hypothesize more credible mechanisms than ever before (Maunder, 2000; Mayer, 2000). It is therefore timely to review the recent literature regarding the role of psychosocial factors in peptic ulcer and inflammatory bowel disease, following a brief parenthesis that will sketch some of the relevant medical aspects of these conditions.

Recent research has also been showing the margins between organic and functional disease to be hazier than was once thought. Pieces are being whittled off the block of irritable bowel syndrome as patient subgroups previously considered to carry this diagnosis are found to have clear-cut organic bases for their symptoms (lactose intolerance) or are discovered to harbor inflammatory—perhaps postinfectious—changes in the bowel tissues (Gwee et al., 1999; O'Sullivan et al., 1999). Conversely, the role of “functional” phenomena in “organic” disease is beginning to be explored, from elements of irritable bowel syndrome in inflammatory bowel disease (Bayless & Harris, 1990) to brain–gut sensitization phenom-

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ena as an explanation for persistent symptoms in ulcer patients after eradication of *Helicobacter pylori* (*H. pylori*; Fraser, Schreuder, Chua, & Moore, 1998).

Biological Premises

Peptic Ulcer

When the corrosive effect of gastric acid overcomes the mucosal defenses of the stomach or the duodenum, peptic ulceration occurs. Though ulcers can present as acute emergencies because of pyloric stenosis, upper gastrointestinal bleeding, or perforation, they more often cause a chronic syndrome of gnawing upper abdominal pain, which varies in relation to meals. Most ulcers close within a few months even without specific therapy, but symptomatic relapses are more the rule than the exception, classically occurring once or twice a year. Ulcer incidence surged in the first half of the 20th century but has since been declining (Sonnenberg, 1987), perhaps because improved hygienic conditions have reduced the transmission of *H. pylori* infection. Ulcers run in families (Leoci et al., 1995), partially in relation to an increased susceptibility among individuals with Type O blood (Hook-Nikanne, Sistonen, & Kosunen, 1990) but also because gastric hypersecretion, a risk factor for duodenal ulcer (Peterson et al., 1993), is in part genetically determined. A variety of environmental influences work on this substrate, including the bacterial agent *H. pylori* (National Institutes of Health Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease, 1994), cigarette smoking (Friedman, Siegelau, & Seltzer, 1974), use of nonsteroidal antiinflammatory drugs such as aspirin and ibuprofen (Levy, 1974), skipping breakfast (Levenstein, Kaplan, & Smith, 1997), disturbance of circadian rhythms by shift work (Segawa et al., 1987) or lack of sleep (Levenstein et al., 1997), and probably high alcohol consumption (Levenstein et al., 1997).

Treatment of peptic ulcer has changed radically in its nature and efficacy over the past 30 years. In 1970, antacids, rest, and gastric resection were the mainstay of therapy. More and more powerful antisecretory drugs were then introduced into the therapeutic armamentarium, reducing to a trickle the number of patients sent for surgery but creating a vast army of H₂-receptor blocker dependents. Toward the end of the 1980s, ulcer therapy was again revolutionized by the finding that eradicating *H. pylori* with antibiotics could lead to a lasting cure for many patients (Rauws & Tytgat, 1990).

The *H. pylori* concept is now emerging from its honeymoon phase. Researchers are beginning to notice that many ulcers (25% or more; Ciociola, McSorley, Turner, Sykes, & Palmer, 1999) occur in the absence of the bacterium, and sporadic reports are showing that eradication with antibiotics can sometimes fail to cure symptoms (Fraser et al., 1998) or prevent ulcer recurrence (Miwa et al., 1998) and that it may increase the risk of gastroesophageal reflux (Fraser et al., 1998), which is, in turn, a risk factor for cancer (Lagergren, Bergstrom, Lindgren, & Nyren, 1999). Nonetheless, the discovery of *H. pylori* remains a conceptual and practical milestone.

Inflammatory Bowel Disease

Inflammatory bowel disease is a term used to encompass ulcerative colitis and Crohn's disease. Both ulcerative colitis and

Crohn's disease are severe, relatively uncommon, potentially life-threatening disorders involving inflammation of intestinal tissues—characteristics not shared by *irritable bowel syndrome*, a common functional complaint with which they are often confused. Though in both forms of inflammatory bowel disease periods of diarrhea usually alternate with periods of quiescence, there are salient differences between the two diseases that affect their impact on patients' lives. Ulcerative colitis involves only the large intestine, with bloody diarrhea as its classic symptom; the patient often has prolonged periods of well-being and can look forward, if symptoms become uncontrollable, to being cured by surgery. Crohn's disease, on the contrary, can involve any part of the gastrointestinal tube from the mouth to the anus; often causes unremitting symptoms that include pain, intestinal obstruction, and malnutrition; and invariably recurs after diseased segments are surgically removed.

The currently dominant model hypothesized for inflammatory bowel disease etiology emphasizes inadequate suppression of the immune response to bacterial toxins originating inside the gut (Sartor, 1995). The reasons the resulting inflammation swings between exacerbation and remission remain largely mysterious. In one study (Levenstein et al., 2000), only 10% of the variation in exacerbation occurrence was explained by known or suspected nonpsychosocial risk factors (respiratory infections: Mee & Jewell, 1978; lack of sleep: Levenstein et al., 2000; oral contraceptives: Vessey, Jewell, Smith, Yeates, & McPherson, 1986; nonsteroidal anti-inflammatory drugs: Rampton, McNeil, & Sarner, 1983; and antibiotics: Greenfield et al., 1983). Ulcerative colitis has the dubious distinction of being one of the few diseases that can be prevented and even treated by cigarette smoking (Calkins, 1989).

Maintenance therapy with 5-aminosalicylate derivatives (Salazopyrine, sulphasalazine, Azulfidine, Asacol, etc.) is often prescribed to patients with inflammatory bowel disease and is especially effective in preventing relapses of ulcerative colitis (Misiewicz, Lennard-Jones, Connell, Barton, & Jones, 1965). Treatment of active disease commonly requires corticosteroids, with their well-known central nervous system side effects. An important recent advance in medical therapy is the introduction of agents that counteract tumor necrosis factor (TNF), which are impressively effective in inducing remission in Crohn's disease (D'Haens et al., 1999). The greatest leap forward in surgical therapy has been the ileorectal pouch, which by creating an artificial rectum to substitute for the final portion of the resected large intestine allows many ulcerative colitis patients to regain near-normal bowel functioning free of medications, putting their disease behind them permanently.

Effects of Stress: Recent Evidence

Peptic Ulcer

Since 1980, there have been many case-control studies of the influence of psychosocial factors on peptic ulcer, with mixed results. Though one excellent study found that ulcers often develop in the context of major life difficulties (Ellard, Beaurepaire, Jones, Piper, & Tennant, 1990), another study found an association with goal frustration but not with life difficulties (Craig & Brown, 1984) and both studies were counterbalanced by a series of negative case-control studies finding ulcer patients to report, variously, no excess of stressful life events (Piper et al., 1981), no

particularly demanding work or personal worries (Adami et al., 1987), and no tendency to overrate the severity of negative life events (McIntosh et al., 1985). Studies in former prisoners of war have also reported high rates of peptic ulcer (Goulston, Dent, & Chapuis, 1995; Nice, Garland, Hilton, Baggett, & Mitchell, 1996), although some issues could be raised related to the certainty of diagnoses and the adequacy of control groups.

Methodological limits make even the best cross-sectional studies somewhat suspect, and most researchers in the past decade have preferred a prospective design. One popular prospective approach involves tracking the incidence or relapse of ulcer among defined epidemiologic cohorts. Recent studies of this sort have been remarkably consistent in finding stress to predict ulcer incidence among individuals who had been ulcer-free at baseline or ulcer relapse among patients with a previous episode, whether the stress consists of subjective strain (Anda et al., 1992), social alienation (Levenstein et al., 1997), unemployment (Levenstein, Kaplan, & Smith, 1995), family problems (Levenstein, Kaplan, & Smith, 1995; Medalie, Stange, Zyzanski, & Goldbourt, 1992), wage dissatisfaction (Netterstrøm & Kuel, 1990), conflicts with coworkers (Medalie et al., 1992), or job frustration (Kurata, Nogawa, Abbey, & Petersen, 1992). A weakness shared by most of these studies is dependence on self-report for their ulcer diagnoses, which could lead to bias in favor of an association with psychosocial factors.

Several studies of the effects of shared societal catastrophes have been published during the same period. Following the model of Spicer's classic demonstration that perforated peptic ulcer increased in London during German bombing raids (Spicer, Stewart, & Winsler, 1944), recent researchers have looked at periods of economic collapse in Sofia, Bulgaria (Pomakov, Georgieva, Stantcheva, Tenev, & Rizov, 1993), at the great Kyoto, Japan, earthquake (Aoyama et al., 1998), and at the mass invasion of Hong Kong, China, by "boat people" (Lam, Hui, Shiu, & Ng, 1995); and they have uniformly found ulcers (diagnosed by upper gastrointestinal X-rays, endoscopy, or perforation) to increase in the aftermath of these catastrophes. Yet another line of research has examined the influence of psychosocial factors on the course of endoscopically diagnosed ulcer; such studies have reported stress, anxiety, and depression to impair endoscopic healing (Holtmann et al., 1992; Levenstein, Prantera, Scribano, et al., 1996) and to promote relapse (Armstrong et al., 1994; Jess et al., 1989; Levenstein, Prantera, Varvo, et al., 1996). The effect of stress seems to be reversible, in that patients who are psychologically stable but who develop an ulcer following traumatic life events tend to have a particularly favorable long-term course (Levenstein, Prantera, Varvo, et al., 1996).

In short, there is a strong epidemiologic literature supporting a prospective association between life stress and the development of peptic ulcer and a strong clinical literature supporting a negative influence of stress on the short- and long-term course of existing ulcer.

Inflammatory Bowel Disease

On the basis of case-control studies of patients soon after diagnosis, it is unlikely that psychosocial factors play much of a role in the origins of inflammatory bowel disease (Monk, Mendeloff, Siegel, & Lilienfeld, 1970). Prospective evidence is hard to come by because of the relative rarity of the condition, but what

little there is has similarly been negative (Sieglar, Levenstein, Feaganes, & Brummett, 2000). More plausibly, gastroenterologists (Mitchell & Drossman, 1987) and inflammatory bowel disease patients (Lewis, 1988; Robertson, Ray, Diamond, & Edwards, 1989) are widely convinced that stress can influence the course of established disease. The case-control literature is, however, mixed. Some studies comparing inflammatory bowel disease patients in remission with those in exacerbation have found an association of disease activity with stress or with stressful life events (Fava & Pavan, 1976–1977a; F. Feldman, Cantor, Soll, & Bachrach, 1967; Hislop, 1974; Kiss, Nemeskeri, Maritesch, et al., 1991; Levenstein et al., 1994; von Wietersheim, Kohler, & Feiereis, 1992), while other studies have not (Helzer, Stillings, Chamma, Norland, & Alpers, 1982; Mendeloff, Monk, Siegel, & Lilienfeld, 1970; Paar, Bezzenberger, & Lorenz-Meyer, 1988; Riley, Mani, Goodman, & Lucas, 1990).

As in the case of ulcer, the past decade has brought several attempts to study the issue with a true prospective design, assessing psychosocial factors among inflammatory bowel disease patients during remission and tracking disease activity over the next month or two. One such study found no association between life events or depression and subsequent disease activity (North, Alpers, Helzer, Spitznagel, & Clouse, 1991), and a second study found self-reported stress in 1 month to predict lower disease activity in the following month (Greene, Blanchard, & Wan, 1994). A third group of workers considered their results to be supportive of the stress-exacerbation hypothesis, but the excess burden of stressful life events these workers detected was only in the same month as the increased symptoms (Duffy et al., 1991), leaving doubt as to the direction of causation.

The complex cascade of events involved in exacerbations of inflammatory bowel disease suggest, however, that any influence of stress might best be sought over a longer time scale. Two recent studies along these lines have, in fact, provided the best evidence thus far of an impact of psychosocial factors on inflammatory bowel disease. One study periodically assessed levels of perceived stress levels among ulcerative colitis patients during remission and found that being in the high tertile for stress tripled the rate of subsequent exacerbation both in the medium term (6–8 months) and the long term (up to 5 years; Levenstein et al., 2000). The preliminary results of a second study, which examined mixed inflammatory bowel disease patients who had recently entered remission, suggest that patients with depressive symptoms experience a statistically greater number of relapses over the following year (Mittermaier, Beier, Tillinger, Gangl, & Moser, 1998).

Support for an association between stress and exacerbation in inflammatory bowel disease has come from animal studies as well. In an elegant series of experiments, Collins and colleagues (Collins et al., 1996; Qiu, Vallance, Blennerhassett, & Collins, 1999) induced an experimental colitis in rats or mice using high-dose di- or trinitrobenzenesulfonic acid, allowed the animals to recover, and then attempted to trigger relapses by using lower doses. The intriguing findings are that restraint and noise stress act as potentiators, enabling inflammation to develop after exposure to what would otherwise be subthreshold levels of the chemical.

The conviction held by many patients that oscillations in their disease are tightly linked to stress or distress may be out of proportion to the modest degree of long-term modulation of bowel inflammation by psychosocial factors. This can be due, in part, to the sort of recall bias that has been termed "effort after meaning,"

in which the patient attempts to make sense out of otherwise inexplicable health events (Brown & Harris, 1978) and, in part, to a nonspecific rapid-acting worsening of inflammatory bowel disease symptoms because of the effects of stress on intestinal motility (Bayless & Harris, 1990; Prugh, 1951). Empirical research, thus, supports the impression of gastroenterologists (Mitchell & Drossman, 1987) that psychological factors are unlikely to influence the onset of inflammatory bowel disease but may be able to affect its course.

Personality and Psychiatric Disorders

Peptic Ulcer

The concept of the ulcer personality dates back to a period when psychoanalysis was at the height of its ascendancy and when the dominant mind-body theory held that specific deep-seated character traits determined vulnerability to specific "psychosomatic" diseases (Alexander & French, 1948). In the case of peptic ulcer, the favored traits were dependency and repressed hostility. Cross-sectional studies show ulcer patients to have typical response patterns to challenges, ranging from Likert scales (Van Heck, Vingerhoets, & Van Hout, 1991) to how to shave their facial hair (Rubinstein & Davidovitch, 1992).

In recent years, along with the shift in dominant interest from predispositions to external stressors, skepticism has prevailed, and peptic ulcer patients have more often been used as a low-psychopathology comparison group in studies focusing on patients with functional dyspepsia (Haug, Svebak, Wilhelmsen, Berstad, & Ursin, 1994; Langeluddeck, Goulston, & Tennant, 1990) or irritable bowel syndrome (Dinan, O'Keane, O'Boyle, Chua, & Keeling, 1991). In part, methodological issues are to blame: It has been pointed out that personality scales are often contaminated by gastrointestinal symptoms (Creed & Guthrie, 1991) and that changes in personality characteristics could result from the effects of illness (Jess & Eldrup, 1994).

Evidence from prospective cohort studies has been mixed. Though one study found essentially normal Minnesota Multiphasic Personality Inventories (MMPIs) in individuals destined to develop ulcer in later years (Jess, 1994b), other studies support an increased vulnerability to ulcer in individuals with high levels of hostility, whether overt (Levenstein et al., 1997) or suppressed (Medalie et al., 1992; Mirsky, 1958), and perhaps in those individuals with depression and low ego strength (Levenstein et al., 1997).

Inflammatory Bowel Disease

Early writers considered personality factors, especially immaturity, dependency, and obsessional traits, to be important in the precipitation and recurrence of ulcerative colitis (Daniels, 1944). This has become an unpopular concept, and the current consensus is that any personality traits characteristic of inflammatory bowel disease are likely to be secondary to long-standing illness (Aronowitz & Spiro, 1988), although a patient's preexisting personality structure may influence his or her adjustment to the disease (Gazzard, Price, Libby, & Dawson, 1978).

An impact of inflammatory bowel disease on personality is not implausible, because symptoms often begin during adolescence, forcing patients back into dependent roles during an impression-

able period whose defining characteristic is the search for independence, then further impairing the patients' self-esteem by feelings of being different from other young people and by the specter of fecal incontinence—which, incidentally, can dictate an "obsessional" preoccupation with locating the nearest toilet. Several workers have reported a slight excess of obsessional symptoms (Helzer et al., 1982) or neuroticism in inflammatory bowel disease patients (Robertson et al., 1989; Siegler et al., 2000), especially in Crohn's disease (Gazzard et al., 1978; Schwarz & Blanchard, 1990). The suspicion that any such personality changes are secondary to the disease, rather than causative, are borne out by a preliminary report from a study of MMPI profiles in one cohort of college students: The profiles among subjects destined to develop inflammatory bowel disease are entirely normal, and are indistinguishable from controls' (Siegler et al., 2000). The high levels of alexithymia described among inflammatory bowel disease patients (Fava & Pavan, 1976–1977b; Porcelli, Leoci, Guerra, Taylor, & Bagby, 1996) may similarly result from long-standing illness. The psychological impact of inflammatory bowel disease decreases with time and may be buffered to some extent by social support (Sewitch et al., 2001). It has been shown, on the other hand, that inflammatory bowel disease patients who seek psychological treatment have somewhat more abnormal scores on a variety of personality measures than do nonpatient controls (though somewhat less abnormal than similarly recruited irritable bowel syndrome patients; Schwarz et al., 1993). One intriguing study has looked at patient subgroups among ulcerative colitis patients and has revealed that insecure attachment is found more commonly among patients who lack the perinuclear antineutrophil cytoplasmic antibody (p-ANCA), a disease marker that is, in part, genetically determined (Maunder, Lancee, Greenberg, Hunter, & Fernandes, 2000), suggesting there may be forms of the disease that are more and less sensitive to psychosocial factors.

Psychiatric disorders, per se, are surprisingly rare in inflammatory bowel disease (Fava & Pavan, 1976–1977b; F. Feldman et al., 1967; Hendriksen & Binder, 1980; E. A. Walker et al., 1990). Anxiety and depression are prominent only during phases of acute activity (Porcelli et al., 1996), and ulcerative colitis patients have even been reported to be "supernormal," with lower levels of psychiatric symptoms than controls (Esler & Goulston, 1973).

Psychophysiological Mediators

Ulcer

One of the reasons duodenal ulcer became the classic psychosomatic disease (see Figure 1) was that the pathophysiology seemed so clear (Mirsky, 1958; P. M. Walker & Feldman, 1992; Weiner, 1991): excess acid in the duodenum was the chief cause of ulcer, and psychological distress stimulated the functioning of acid secretory cells. Both these propositions, however, must be considered questionable. The discovery of *H. pylori* has relegated the acid factor to the role of second fiddle, and in any case psychosocial factors are as prominent in gastric ulcer, where gastric secretion is characteristically low to normal, as in duodenal ulcer, where acid secretion is high. Furthermore, strange though it may seem, after nearly a century of research (see Wolf, 1981) we are not even certain of the effect of life stress on human gastric secretion, much less its net impact on duodenal acid load. A few human studies have, in fact, found stress, anxiety, or depression to

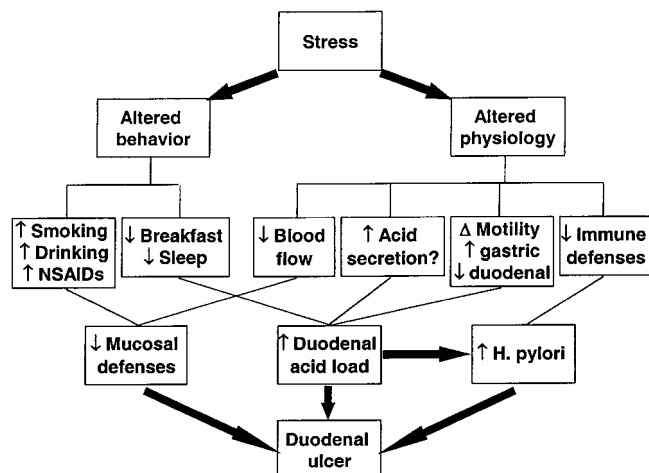


Figure 1. A model postulating behavioral and psychophysiological mechanisms that may link psychological stress with peptic ulcer. NSAIDS = nonsteroidal antiinflammatory drugs; H. pylori = Helicobacter pylori. From "The Very Model of a Modern Etiology: A Biopsychosocial View of Peptic Ulcer," by S. Levenstein, 2000, *Psychosomatic Medicine*, 62, p. 182. Copyright 2000 by the American Psychosomatic Society. Reprinted with permission.

increase acid secretion (M. Feldman, Walker, Goldschmiedt, & Cannon, 1992), especially in subjects prone to peptic ulcer (Bresnick, Rask-Madsen, Hogan, Koss, & Isenberg, 1993; Peters & Richardson, 1983), but some reports have been equivocal (Hojgaard & Bendtsen, 1989; Jess, 1994a), and studies in nonhuman primates have suggested that, on the contrary, stress might actually decrease acid secretion (Natelson, Dubois, & Sodetz, 1977).

Stress and distress have other local physiological effects that could contribute to explaining their association with peptic ulcers. Experimental stress has been shown to decrease upper gastrointestinal blood flow in animals (Kauffman, 1997; Livingston et al., 1993) and might, therefore, render the human stomach and duodenum more susceptible to damage. Motility alterations could also be important, because duodenal ulcer patients characteristically have rapid gastric emptying, which increases the acid arriving on the far side of the pylorus (Fordtran & Walsh, 1973). The usual effect of acute stress on gastric motility is suppression, but a certain number of dyspeptic individuals respond to laboratory stress with an increase in motility (Hausken et al., 1993); it is not known whether duodenal ulcer patients fall disproportionately into this group.

Psychosocial factors seem able to potentiate the pathogenic effects of gastroduodenal H. pylori infection, facilitating or precipitating clinical disease de novo (Matsushima et al., 1999) or after long periods of peaceful coexistence (Levenstein, Pranter, et al., 1995). Though this effect could simply arise from the simple accumulation of different kinds of insults to the mucosa, stress will also directly promote H. pylori invasion of the duodenal bulb if it increases the acid load (Graham & Osato, 2000).

Psychoneuroimmune and psychoneuroendocrine mechanisms may also come into play. Stress interferes with wound healing (Marucha, Kiecolt-Glaser, & Favagehi, 1998), probably by increasing corticosteroid levels (Padgett, Marucha, & Sheridan, 1998), which may contribute to the poor course of ulcers under

stress. Immune defenses against H. pylori could also conceivably be affected by stress.

It thus seems that stimulation of gastric acid secretion may indeed mediate psychosocial influences on ulcers to some extent, but that other psychophysiological mechanisms by which stress and distress can increase duodenal acid load and decrease mucosal defenses may be equally important.

Inflammatory Bowel Disease

A likely candidate mechanism for mind-body interactions in inflammatory bowel disease lies in psychoneuroimmunology. Immune hyperreactivity is a fundamental mechanism in the pathophysiology of ulcerative colitis and Crohn's disease (Sartor, 1995), and by now it is well known that stress can lead to profound deregulation of the immune system (Ader, Felten, & Cohen, 1991). As is perhaps less well-known, such deregulation can result in stimulation as well as suppression (Dhabhar & McEwen, 1996; Monjan, 1981; Rogers et al., 1980) and, thus, could intensify the anomalous immune response involved in inflammatory bowel disease.

Recent research suggests that gut permeability is another key element in the pathophysiology of inflammatory bowel disease (Hollander et al., 1986; Jorgensen et al., 2001; Wyatt, Vogelsang, Hubl, Waldhoer, & Lochs, 1993) and that it can be increased by stress (Saunders, Hanssen, & Perdue, 1997; Saunders, Kosecka, McKay, & Perdue, 1994; Soderholm & Perdue, 2001; Wilson & Baldwin, 1998), possibly with mediation by the hypophyseal-pituitary-adrenal axis (Meddings & Swain, 2000). Corticotropin releasing hormone has also recently been demonstrated to be present in the gut wall of patients with ulcerative colitis (Kawahito et al., 1995), making such mediation more plausible. Animal studies support an interaction between gut permeability changes and immune phenomena in stress exacerbation of colitis (Collins et al., 1996; Qiu et al., 1999): Exposure to stress facilitated penetration of the bowel wall by luminal contents which could then activate previously sensitized CD4 cells, and the permissive effect of stress could not be replicated in animals which had undergone resection of one key immune effector organ, the thymus (Qiu et al.; 1999).

Not atypically for diseases characterized by interactions between mind and body, the complexities of reciprocal effects in inflammatory bowel disease make the larger picture difficult to piece together. Stress could have a nonspecific effect on symptoms, for example, because of autonomic discharge (Prugh, 1951), especially given the frequency of "irritable bowel syndrome" type of phenomena in patients with inflammatory bowel disease (Bayless & Harris, 1990). Classic somatization can further muddy the picture, because anxious or depressed individuals have a notoriously high level of attention and concern for bodily phenomena (Barsky, 1992) and therefore might be more symptomatic at a given level of objective pathology.

Behavioral Mediators of Stress

Ulcer

Behavior largely determines who gets a peptic ulcer: Cigarette smoking, heavy drinking, and nonsteroidal anti-inflammatory drug use impair mucosal defenses, whereas irregular meals and lack of

sleep probably increase duodenal acid load. Common sense, backed by some empirical evidence (Levenstein et al., 1997; Steptoe, Wardle, Pollard, Canaan, & Davies, 1996), tells us that all of these behaviors are more common in people who are experiencing life stress. Even the use of nonsteroidal antiinflammatory drugs increases under stress, both because of worsening of painful conditions such as migraine (Vandenbergh, Amery, & Waelkens, 1987) and because some people use these drugs for a fantasied tranquilizing effect. Because several published studies of the influences of psychosocial factors on ulcer include behavioral factors such as aspirin use and smoking in their multivariate analyses (Armstrong et al., 1994; Holtmann et al., 1992; Levenstein, Kaplan, et al., 1995; Levenstein et al., 1997; Levenstein, Prantera, Scribano, et al., 1996), reexamination of this literature allows us to estimate that a large proportion of the influence of stress on ulcer disease—perhaps as much as half of the effect over and above confounding—is accounted for by behavioral mediators (Levenstein, 2000). Most studies (Armstrong et al., 1994; Reynolds, Schoen, Maislin, & Zangari, 1994; Sonnenberg et al., 1981; Sontag, Graham, Belsito, et al., 1984; Walan, Bianchi-Porro, Hentschel, Bardhan, & Delattre, 1987), though not all (Bank, Wright, Lucke, & Marks, 1986; Chan et al., 1997; Levenstein, Prantera, Varvo, et al., 1996; Nasiry, McIntosh, Byth, & Piper, 1987), have found smoking to worsen the course of peptic ulcer. The effects of stress on ulcer healing and relapse have been shown to be partially mediated by smoking (Armstrong et al., 1994; Holtmann et al., 1992) or by recent increase in cigarette consumption (Levenstein, Prantera, Scribano, et al., 1996), further emphasizing the importance of counseling ulcer patients around health risk behaviors.

Inflammatory Bowel Disease

Few behavioral risk factors have major effects on inflammatory bowel disease, but they may play some role in mediating the influence of psychosocial factors: Smoking can increase activity in Crohn's disease (Tysk, Lindberg, Jarnerot, & Floderus-Myrhed, 1988), whereas nonsteroidal anti-inflammatory drugs (Rampton et al., 1983) and perhaps lack of sleep (Levenstein et al., 2000) can precipitate exacerbations of ulcerative colitis. Another behavioral factor that may substantially affect the course of inflammatory bowel disease is adherence to maintenance medications. Because maintenance therapy requires daily ingestion of multiple pills or frequent self-administration of enemas by a patient who is symptom-free, adherence to prophylactic regimens is potentially vulnerable to mood, personality, and life stress (Nigro, Angelini, Grosso, Caula, & Sategna-Guidetti, 2001).

Socioeconomic Status and Peptic Ulcer

Though the hard-driving business executive groping for the Maalox bottle among the clutter of his desktop remains a popular stereotype, ulcers are in fact more common in lower than in higher socioeconomic strata (LeClere, Moss, Everhart, & Roth, 1992). The corresponding gradient in *H. pylori* infection is chiefly responsible (Graham et al., 1991; The EUROGAST Study Group, 1993); like other bacteria which invade the body during childhood, *H. pylori* is acquired more easily in crowded housing or under less-than-optimal hygienic conditions (Malaty & Graham, 1994). On-the-job physical exertion is another element in the socioeco-

omic gradient in ulcer disease (Sonnenberg, 1988), and stress probably has a role as well (Levenstein & Kaplan, 1998). The strong association of socioeconomic status with *H. pylori* makes the bacterium a potentially treacherous confounder that needs to be kept in mind when evaluating studies of stress and ulcer.

Psychological-Behavioral Approaches to Treatment

If there were good evidence that psychologically oriented approaches are effective in treating organic gastrointestinal diseases, the biomedical community might be more convinced of the role of psychosocial factors. Unfortunately for our patients and for the biopsychosocial model, this is not the case. The situation is not much changed from the last review of the subject in this journal (Whitehead, 1992): The stress management approaches and psychotherapy that are useful in the management of functional gastrointestinal disorders (Guthrie, Creed, Dawson, & Tomenson, 1991; Payne & Blanchard, 1995; Whitehead, 1992) have on the whole proved disappointing when applied to peptic ulcer and inflammatory bowel disease. Though there have been hints that psychotherapy might have some efficacy for peptic ulcers (Svedlund & Sjodin, 1985), two recent prospective randomized trials found cognitive psychotherapy to have no effect on ulcer recurrence (Loof et al., 1987; Wilhelmsen, Tangen, Ursin, & Berstad, 1994), although one did report some symptomatic improvement (Wilhelmsen et al., 1994). Given the efficacy of the current medical treatment of peptic ulcers, it is unlikely that psychologically based interventions will have much to offer, except perhaps in carefully selected cases with refractory disease (Miwa et al., 1998). One study of cognitive therapy in inflammatory bowel disease found an improvement in patients' sense of control but little or no influence on the symptoms of disease (Schwarz & Blanchard, 1991). Another prospective randomized multicentric study found no effect of adjunctive short-term psychodynamic psychotherapy on the course, mood (Jantschek et al., 1998), or quality of life (Wolfram Keller, personal communication, June, 2001) of unselected Crohn's disease patients and did not improve their ability to cope with their disease despite better social functioning and conflict solving (Jörn von Wietersheim, personal communication).

Because psychological factors affect both peptic ulcer and inflammatory bowel disease, it remains, nonetheless, possible that psychologically oriented interventions will have a role in ameliorating the course of some patients. For example, one of the trials in peptic ulcers revealed a hint of benefit from psychotherapy for patients who were more distressed on enrollment (Wilhelmsen et al., 1994). Future research should probably abandon indiscriminate enrollment of subjects with either of these diseases and should rather focus on patient subgroups characterized by high risk (refractory, chronic, or frequently relapsing disease) and/or high vulnerability (high levels of stress or psychiatric symptomatology).

For the time being, at least, clinicians treating peptic ulcer or inflammatory bowel disease, although they should always address behavioral and adherence issues, might find it wise to avoid wasting resources and the time and energy on psychologically oriented therapies for patients who do not have other strictly psychological indications, because the evidence shows that such interventions cannot be expected to improve the medical course of ulcer or inflammatory bowel disease in unselected patients. Among inflammatory bowel disease patients who desire psychological counseling because of distress (Mauder et al., 1997),

professional help can be expected to facilitate adjustment to disease (Maunder & Esplen, 1999) and has been shown to alleviate the impact of disease on the psychosocial functioning of children and adolescents (Gold, Issenman, Roberts, & Watt, 2000).

An irony of the biopsychosocial model is the danger that mind-body thinking can lead to blaming the victim, with the subtext of setting up a dichotomy between "noble" and "base" diseases (Levenstein, 1998). Whereas peptic ulcer has been ennobled by the identification of a causative bacterial agent, many inflammatory bowel disease sufferers feel they must battle stigmatization because of the presumed psychological component of their condition (Spiro, 1990). It is important that any psychotherapist undertaking treatment of patients with inflammatory bowel disease become familiar with the medical aspects of these diseases and the particular tribulations they entail, to avoid the risk of inappropriate psychologizing.

Psychosocial Factors, Bacteria, and Gastrointestinal Disease

An interesting development of recent years has been the accumulating evidence that many idiopathic or degenerative diseases may turn out to have an infectious, often bacterial, component. Diabetes mellitus, Graves's disease, asthma, and rheumatoid arthritis are suspected of having infectious connections, whereas both coronary artery disease (Maass, Bartels, Engel, Mamat, & Sievers, 1998; Sessa et al., 1999) and multiple sclerosis (Sriram et al., 1999) have been tentatively linked with Chlamydia pneumoniae.

Chronic conditions are unlikely to result from hit-and-run organ damage by infectious agents, but more probably involve prolonged cohabitation between a pathogen and its host. In some cases, the destructive effects of overexuberant immune responses may overshadow the direct destructive effects of the infectious agents themselves.

Under these circumstances, the expression of disease will be influenced by various noninfectious factors, some of them specific to the particular organ system. It is interesting to note that the list of chronic diseases with a suspected infectious component closely overlaps with any list of diseases known or believed to be influenced by psychosocial factors. A facilitating effect of stress on at least some viral infections is fairly well established (Cohen, Tyrrell, & Smith, 1991; Glaser et al., 1993; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996), but bacteria have been little studied, and—paradoxically—acute stress may even help protect against acute bacterial infection (Dhabhar & McEwen, 1996; Munck & Guyre, 1991).

The pathophysiological considerations discussed in this article are relevant to the broader question of the relation between stress and chronic bacterial infection, because bacteria are prominent in the pathophysiology of both peptic ulcer and inflammatory bowel disease. Peptic ulcers provide perhaps the most notorious example of an infectious agent appearing unexpectedly on the scene. *H. pylori* is not just an innocent bystander, because the tendency to develop an ulcer can be profoundly altered among most patients who host the organism by eradication therapy (Rauws & Tytgat, 1990). The infection resembles tuberculosis: It is typically acquired in childhood, only to lie dormant in the body for decades before the equilibrium between bacterium and host is thrown off

for some reason and clinical disease ensues; only about 1 in 5 infected individuals ever develops an ulcer (Peek & Blaser, 1997).

In inflammatory bowel disease, bacteria have a variety of roles to play. Atypical mycobacteria may be found in some cases of Crohn's disease (Prantera, Kohn, Mangiarotti, Andreoli, & Luzi, 1994), and superinfection with gut aerobes and anaerobes is important in pathology due to abscesses and fistulas. But in uncomplicated inflammatory bowel disease as well, the normal gut flora seems to be fundamental to pathophysiology: A widely believed though as yet unproven hypothesis is that the pathology results from an exaggerated immune response to antigens found within the intestine, which are thought to be usually of bacterial origin (Blumberg & Strober, 2001; Campieri & Gionchetti, 2001; Sartor, 1995; Sartor, 1997a, 1997b).

Conclusion

Peptic ulcer and inflammatory bowel disease, with the unique interactions they present among psychological, immunologic, endocrine, infectious, and behavioral factors, are splendid paradigms of the biopsychosocial model. During the past decade, major progress has been made toward understanding the importance of psychosocial factors in these disorders and toward delineating possible mechanisms of action. The roles demonstrated or postulated for bacterial agents in organic gastrointestinal disease make them particularly fascinating objects of study, because the interactions between psychosocial factors and bacterial disease are complex and obscure. The chief importance of psychosocial factors in clinical practice at this moment regards behavioral and adherence issues. The excellence of biomedical treatment in the majority of cases, and the discouraging findings of most trials, suggest that formal psychologically based treatments aimed at improving the course of disease will play a relatively minor role and only in highly selected patients.

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