The Very Model of a Modern Etiology: A Biopsychosocial View of Peptic Ulcer

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Objective: Research on ulcer psychosomatics has plummeted since the early 1970s, to the applause of many who argue that ulcer is simply an infectious disease. The purpose of this article is to discuss the relevance of ulcer psychogenesis in the age of *Helicobacter pylori*. **Methods:** A critical literature review was conducted. **Results:** There is a substantial and methodologically sound body of prospective studies linking stress with the onset and course of peptic ulcer. Psychosocial factors can be estimated to contribute to 30% to 65% of ulcers, whether related to nonsteroidal antiinflammatory drugs, *H. pylori*, or neither. The observed association between stress and ulcer is accounted for, in part, by recall bias, misreported diagnoses, and confounding by low socioeconomic status (a source of stress and of ulcer risk factors, such as *H. pylori* and on-the-job exertion) and by distressing medical conditions (which lead to use of nonsteroidal antiinflammatory drugs). Of the residual, true association, a substantial proportion is accounted for by mediation by health risk behaviors, such as smoking, sleeplessness, irregular meals, heavy drinking, and, again, nonsteroidal antiinflammatory drugs. The remainder results from psychophysiologic mechanisms that probably include increased duodenal acid load, the effects of hypothalamic-pituitary-adrenal axis activation on healing, altered blood flow, and impairment of gastroduodenal mucosal defenses. **Conclusions:** Peptic ulcer is a valuable model for understanding the interactions among psychosocial, socioeconomic, behavioral, and infectious factors in causing disease. The discovery of *H. pylori* may serve, paradoxically, as a stimulus to researchers for whom the concepts of psychology and infection are not necessarily a contradiction in terms. **Key words:** peptic ulcer, stress, health risk behaviors, *Helicobacter pylori*, socioeconomic status, nonsteroidal antiinflammatory drugs.

INTRODUCTION

Anyone who shares my suspicion that researchers have been ignoring psychological aspects of peptic ulcer (1) can easily substantiate it by glancing through MEDLINE using the keywords "stress" and "peptic ulcer": The number of publications per year fitting both keywords fell by 39% between the early 1970s and the late 1990s in proportion to all publications about peptic ulcer and plummeted by 73% in proportion to all searched publications (Fig. 1) (2).

Many in the biomedical community might applaud, arguing that psychological factors are irrelevant because the discovery of *Helicobacter pylori* has revealed ulcer to be an infectious disease (3). The US Centers for Disease Control and Prevention, for instance, have mailed educational kits about *H. pylori* to all physicians in the United States, encouraging them to combat ulcer patients' outmoded idea that their problem might have something to do with stress. But, despite manifestations of bacteriologic missionary zeal, the evidence linking psychosocial stress to peptic ulcer is too strong to be ignored.

It must be admitted that some of the ulcer psychosomatics literature is less than iron clad. Much of it must be considered anecdotal, whereas case-control studies finding high stress, anxiety, depressive symptoms, and personality disturbances among ulcer patients (4–11) have the limitation that their results may be inflated by recall bias and by the distressing effects of disease (12). These problems are common to all case-control studies of psychosomatic phenomena but may be exacerbated by the notoriety of the stress-ulcer link: An abnormal finding on gastroscopy plants in even the most placid mind a suspicion that excess stress must be lurking somewhere. Many animal studies (13) attest to the capacity of stressors, such as cold water immersion or bodily restraint, to induce gastric lesions (14) and to the capacity of psychologically based manipulations, such as early separation from the mother (15) or variation in the feedback received in an operant conditioning situation (16), to alter the vulnerability of the animal's stomach to physical stress. The superficial erosions that are generally induced in these studies are, however, imperfect models for the human phenomenon of peptic ulceration.

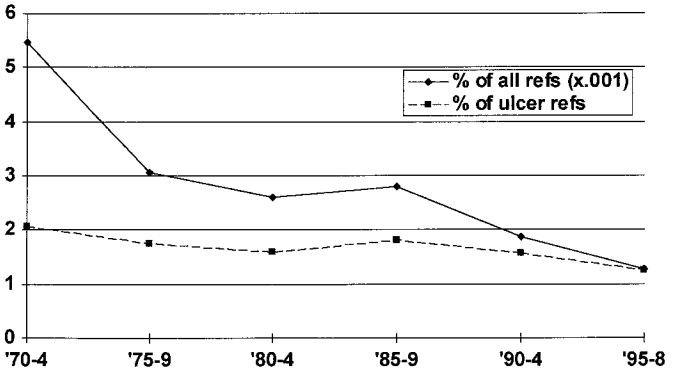

Fig. 1. References found by a MEDLINE search with the keywords "peptic ulcer" and "psychological stress," in proportion to all MEDLINE references for each period and in proportion to all MEDLINE references with the keyword "peptic ulcer."

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There is also a substantial body of prospective studies linking psychosocial factors with clinical ulcer, and it is less assailable on methodological grounds. Longitudinal follow-up of defined epidemiologic cohorts, in my hands and others', has shown that stress or depressive symptoms at baseline increase the risk of ulcer development over the next 9 to 15 years (17–19). One stressful life experience, being a prisoner of war, has been shown to predict subsequent ulcer among survivors of a variety of battlefields (20–22). Similar prospective associations have been found for job frustration (23), family problems (24), and wage dissatisfaction (25), and some data suggest that there may be predisposing personality factors (17, 26). A classic study performed during World War II showed that hospitalizations for perforated ulcers soared in London during the German bombardment (27). Replication of these results after the Kobe earthquake (28), the profound economic crisis in Sofia in 1991 (29), and the thronging of boat people to Hong Kong (30) confirms that collective disasters, both natural and manmade, can trigger peptic ulceration in susceptible individuals. Stress, anxiety, and/or depressive symptoms have also been shown to impede endoscopic healing of duodenal ulcer (31–33) and to worsen ulcer prognosis over several years (33, 34).

This abundant evidence suggests the provocative thesis that research has slumped not because the psychosomatic hypothesis has been disproven but for the opposite reason, that the generic relation between stress and ulcer has been established too well to remain scientifically interesting. What is needed now is a critical update of the relevance of ulcer psychogenesis in the age of *H. pylori*, a much more complex issue requiring openness to multicausal thinking. The aim of this article is to begin moving toward this next step by looking back at the existing literature to ask the following questions: To what extent may the observed association between stress and ulcer be caused by confounding and misreporting? How important, quantitatively, are psychosocial factors? How do psychosocial and nonpsychosocial factors interrelate in ulcer etiology?

CONFOUNDING

Among factors that could be causes of both stress and ulcer and therefore confound the association between them, a prime candidate is socioeconomic status. On one hand, poverty is an obvious source of stress. On the other hand, low socioeconomic status is demonstrably associated with ulcer (35) for reasons largely independent of psychological mechanisms. Chiefly, the rate of *H. pylori* infection decreases steeply with increasing socioeconomic status (36), apparently because low socioeconomic status often entails inferior hygienic conditions during childhood, when the organism is usually acquired (37, 38). Hard on-the-job physical labor, which induces acid hypersecretion (39), is another ulcer risk factor closely linked to socioeconomic status (40, 41). Analyses of psychological factors as predictors of peptic ulcer in the Alameda County Study confirm the importance of such confounding, because adjustment for socioeconomic status decreased the excess risk attributable to psychological distress or concrete life problems by 28% to 36% (17, 19).

Another potential confounder of the stress-ulcer association is medical illness. Chronic liver disease, a life-wrecking disease that apparently promotes peptic ulcer through local circulatory changes, causes confounding but is too uncommon to have much impact. Quantitatively more important are painful medical conditions such as headache or arthritis, common sources of distress that could indirectly cause ulcer by being treated with nonsteroidal antiinflammatory drugs. In the Alameda County Study, adjustment for painful medical conditions reduced the excess risk for ulcer associated with psychological distress by 16% (17).

Contemplation of these sources of confounding offers opportunities to meditate on the complexity of the interactions involved. Adjustment for health risk behaviors, psychological distress, comorbid illness, and heavy on-the-job labor turned out to reduce the excess risk of ulcer associated with low socioeconomic status in the Alameda County Study by 60% to 100% even without taking *H. pylori* into account (42), bringing into question the primacy of this infection in causing the observed disease gradients. In the case of painful medical conditions, the direction of causation is ambiguous, both because depressed or anxious individuals are more prone to a variety of aches and pains (43) and because many people, at least judging by those who have passed through my own office over the last 20 years, use aspirin or ibuprofen as tranquilizers or soporifics, pharmacology textbooks to the contrary notwithstanding.

The observed prospective association between stress and ulcer is thus likely to be confounded by both socioeconomic status and medical illness to an extent that can be estimated as somewhere between 17% (18) and 50% (17).

MISREPORTING

A common methodological pitfall that hampers prospective studies of the incidence of uncomplicated peptic ulcer is reliance on self-report diagnoses. In the

case of such a notoriously "psychosomatic" condition, this might well introduce bias in favor of associations: An anxious or self-absorbed person may interpret the physician's casual "You are on your way toward getting an ulcer" as "You have an ulcer." The psychologically stable individual is less likely to consult a physician for symptoms (44) and is probably more likely to wipe illness episodes from his or her memory once the symptoms have passed. This problem is compounded by the currently fashionable practice of empirical initial treatment of dyspepsia using regimens capable of curing an ulcer (45); such diagnostic nihilism, although defensible on clinical grounds, further conflates peptic disease with nonulcer dyspepsia, a much more stress-sensitive disorder (46).

Two studies allow us to estimate the quantitative importance of differential misreporting. In the National Health and Nutrition Epidemiologic Survey of stress and ulcer incidence, which was able to confirm self-report diagnoses using medical records for a subset of ulcer patients, the chief analyses found only minor differences between self-reported and confirmed diagnoses: The crude risk ratio for any stress was higher for self-reported than for chart-documented ulcers (2.0 vs. 1.6, respectively), but the risk ratios adjusted for major ulcer risk factors were nearly identical (1.8 and 1.9, respectively) (18). The other approach used data from a population-based endoscopy study that found 17% false-positive results among self-reported peptic ulcer cases (false-negative results were negligible) (47). On the basis of these estimates, a worst-case scenario was created for the association of the Alameda County Study psychological risk index with ulcer by shifting 17% of self-reported ulcer cases from the high-index ulcer cell to the high-index nonulcer cell; after this procedure, the crude odds ratio for ulcer development associated with a high vs. a low index was 1.8 and was still statistically significant (17).

Misreporting is a double-edged sword: Not only can diagnoses be misreported, but so can stress. The phenomenon of "effort after meaning," (48) a type of recall bias in which the sick person seeks to find causes for his or her illness, is likely to be especially active in a famously "psychosomatic" disease such as peptic ulcer, leading to inflated cross-sectional associations between ulcer and reported stress. It could even be conjectured that a person who overreports psychological symptoms or life stress may be the same kind of person who will overreport disease, further compounding the problem. Although such distortions can theoretically be minimized by using strictly prospective methodology and by obtaining documentation of diagnoses, in practice misreporting remains a substantial issue.

QUANTITATING THE IMPACT OF PSYCHOSOCIAL FACTORS

The discovery of *Helicobacter* has, of course, given a final debunking to naive monocausal psychosomatic theories of peptic ulcer; even before the *Helicobacter* era, clinicians would have had to have blinders on not to notice at least an occasional happy, well-adjusted ulcer patient.

But if stress is not *the* cause of peptic ulcer, neither is *H. pylori*, an etiologic agent that is neither necessary (many ulcer patients are *H. pylori* negative; 49, 50) nor sufficient (only 20% of infected individuals ever develop an ulcer; 51, 52). Ulcers have long been recognized as nonspecific phenomena that can be the common final end point of a number of different pathways, starting from various mixtures of genetic and environmental factors (53–59). If the etiopathogenetic pathways are multiple, some may be more vulnerable to stress than others, so psychosocial factors are likely to be active only in a subgroup of ulcer patients. We can estimate the size of that subgroup by, again, looking at the published literature.

Among the recent-onset ulcer patients studied by my group in Rome, 62% recalled no recent stressful life event, 40% had normal Minnesota Multiphasic Personality Inventory profiles (scores $\leq$70 on all standard scales), and 32% had anxiety and depression scores below the median for subjects without ulcer (60, 61, unpublished data). A total of 25% had none of these psychosocial vulnerability factors. This gives an outside limit of 75% for the proportion of ulcers in which psychosocial factors could contribute. We can be sure that this limit is high, not only because it includes an unknown background level but also because some of the excess anxiety is certain to be due to the disease and its recent diagnosis; some of the reported life events, to recall bias; and some of the Minnesota Multiphasic Personality Inventory scale elevation, to contamination of items with gastrointestinal symptoms; it therefore seems reasonable to lower the outside limit to a more realistic 65%.

Similar methods can be used to obtain a rough estimate of the lower limit of stress effects. In the methodologically strongest case-control study of stress in peptic ulcer, the Bedford College Life Events and Difficulties Scale (48) was administered to Australian patients with recent-onset duodenal ulcer and to community control subjects drawn from the electoral rolls and matched for age, sex, and socioeconomic status (7). Severe, usually longstanding life difficulties were reported by 44% of patients as having been present during the 6 months before their ulcer developed and by 9% of control subjects as having been present dur-

ing the past 6 months. Thus, the excess rate of severe life stress among ulcer patients was 44% − 9% = 35%. This estimate is likely to be low, because psychosocial factors, including personality patterns, anxiety, and depression, were not examined in this study; only objective life stressors were.

Although the approach used here is crude, it permits the cautious conclusion that more than a few and considerably less than all peptic ulcers (probably within a range of 30–65%) are influenced by psychosocial factors.

MEDIATORS OF STRESS

Health Risk Behaviors

Let us take a reasonably noncontroversial list of nonpsychosocial risk factors for peptic ulcer: *H. pylori* (3), nonsteroidal antiinflammatory drugs (62), cigarette smoking (63), hyperpepsinogenemia (54), type O blood (64), low socioeconomic status (35), hard on-the-job labor (40, 41), skipping breakfast (17), lack of sleep (17, 65), and heavy alcohol consumption (17).

A notable feature of this list is how many "nonpsychosocial" risk factors are behavioral in nature and how many are likely to be related to psychological states. The common-sense notion that people drink more, smoke more, sleep less, eat less regularly, and consume more nonsteroidal antiinflammatory drugs when they are under stress, which boasts some empirical support (17, 66), implies that many behaviors are potential mediators along an etiological chain between stress and ulcer.

Bulgarian researchers who found an increase in radiologically documented ulcers during a period of economic crisis reported their impression that skipped meals and chain smoking were contributory factors (29). This hypothesis can be confirmed and roughly quantified by examining statistical confounding in studies using multivariate analyses. In my analyses of the Alameda County Study, subjects with high levels of psychological distress had an age-adjusted odds ratio of 2.8 for developing ulcer over the following 9 years, signifying an excess risk of 180% over the reference level of 1.0, which fell to 2.2 (120% excess risk) after adjustment for smoking, heavy drinking, skipping breakfast, and lack of sleep, a drop of 33% in excess risk that included modest contributions from each individual behavior (17). Unemployment, marital strain, and children's problems were also associated with ulcer incidence, at least among the women in this population; inclusion of behavioral risk factors in the multiple regression models reduced the risk associated with these concrete life stressors by a mean of 25% (19). In the National Health and Nutrition Epidemiologic Survey, adjustment for aspirin use, smoking, and education reduced the excess ulcer risk associated with high levels of stress by 17% (18).

A study of Swiss and German patients reported that effects of stress on ulcer healing and relapse were partially mediated by smoking (33, 67). In my Italian patients, temporal change in smoking habits was a mediator of the effect of stress on duodenal ulcer healing: Adjustment for a recent increase in cigarette consumption decreased the effect of anxiety on the healing of recent-onset ulcers by 44% (31, unpublished data).

Thus, reexamination of published multivariate analyses allows us to estimate that 17% to 44% of the influence of stress on ulcer disease is accounted for by behavioral mediators.

Psychophysiologic Mechanisms

Do confounding, misreporting, and behavioral changes account entirely for the observed association between stress and ulcer incidence or course? There is reason to think not. In the Alameda County Study data, a high-tertile psychological distress index still increased the risk of developing ulcer (odds ratio = 1.7, 95% confidence interval = 1.0–3.1) after adjustment for health risk behaviors, painful medical conditions, and education (17). In the National Health and Nutrition Epidemiologic Survey, the risk ratio for ulcer incidence was still 2.9 for subjects in the highest stress quintile (18) after adjustment for aspirin use, smoking, and education. In the Swiss study (33), the association of stress with nonhealing and relapse persisted after adjustment for smoking, nonsteroidal antiinflammatory drug use, and heavy physical labor (67). Although none of these studies were able to take *H. pylori* infection into account, this limitation would be relevant only in the unlikely case of a direct association between stress and *H. pylori* above and beyond the link related to socioeconomic status.

It has long been believed that an important mechanism through which psychosocial factors can affect peptic ulcer is through effects on gastric acid secretion (68, 69). Distress has been reported to increase acid secretion (70), and intense psychophysical stress can increase it enormously (39, 71). High acid secretion (70, 72) and increased acid response to stimulation (73) are also associated with mood disorders and maladaptive personality traits.

Doubt has been cast on this mechanism, however, by some studies of acid secretory responses to psychological stressors in humans (74) and in nonhuman primates (75, 76). It may be possible in part to recon-

cile these conflicting reports by differences between responses to acute and chronic stress in humans. Ulcer-prone individuals may also have anomalous reaction patterns; duodenal ulcer patients are particularly likely to respond with acid hypersecretion to laboratory stressors as compared with healthy persons (77), as are subjects with such personality characteristics as impulsivity (78) and hypochondriasis (79). Hyperpepsinogenemia, which is correlated with gastric acid secretion (80), is in part genetically determined but also clusters with psychosocial factors (69), especially among ulcer patients (68).

Duodenal ulcer patients are known to have rapid gastric emptying (81). Laboratory stress suppresses duodenal motility (82, 83), but in a subgroup of dyspepsia patients, stress has been shown to cause a rise in gastric motility rather than the normal fall (84); this combination of motility alterations could increase the time acid remains in the duodenum.

It should be pointed out that what counts in duodenal ulcer formation is not the amount of acid secreted by the stomach but the acid load that is delivered to the duodenal bulb (85). Although the net effect of stress on duodenal acid load has not been directly studied, motility changes, decreased duodenal bicarbonate secretion (14), and decreased food buffering due to irregular eating habits might increase the duodenal acid load in chronic stress states beyond what would result from an influence on acid secretion alone.

A classic effect of stress is activation of the hypothalamic-pituitary-adrenal axis. Interestingly, this occurs in humans partially through behavioral mediators, such as lack of sleep (86). Hypercortisolism may have specific end-organ relevance to peptic ulcer, although the literature is highly contradictory, and even pharmacological doses of corticosteroids are no longer thought to cause ulceration.

Steroids may impair ulcer healing, as they impair wound healing in general. The effect of life stress on wound healing has been studied in several elegant studies in human beings, showing that standardized skin wounds heal more slowly in caregivers of relatives with Alzheimer's disease than in noncaregivers (87) and that palate wounds placed in dental students heal more slowly before academic examinations than during summer vacation (88, 89). These effects seem to be due to steroid-mediated inhibition of interleukin-1β production (87–89). It therefore would be no surprise if high endogenous steroid levels secondary to stress could impair the response of ulcers to therapy. To point out yet again the importance of behavioral mediators, wound healing is adversely affected by smoking (90), heavy drinking (91), and lack of sleep (partly through suppression of growth hormone secretion) (92).

The relation between inflammation, stress, and ulcer is complex: Neutrophil infiltration may have some protective effect against the evolution of *H. pylori* infection into duodenal ulcer (93), but recent clinical evidence suggests that inflammatory responses at the ulcer scar site increase the risk of later recurrence (94). Inflammation is mediated by cytokines, such as interleukin-1β and tumor necrosis factor-α, whose production may be stimulated (95) or suppressed (88, 96) by stress.

Thus, the residual effect of stress on peptic ulcer that is not accounted for by behavioral mediators is likely to be due in large part to effects on duodenal acid load and on the hypothalamic-pituitary-adrenal axis. A variety of miscellaneous psychophysiologic mechanisms could also be involved, from stress stimulation of thyrotropin-releasing hormone, a promoter of gastric ulceration (97), to impairment of the gastroduodenal mucosal barrier by changes in local blood flow (98, 99) or by smoking (100).

PATHWAYS AND SUBGROUPS

It has been aptly remarked that peptic ulceration is "not a disease, only a sign" (56). In the past, various attempts were made to define subgroups of ulcer patients: those with acid hypersecretion and a positive family history vs. those with normal acid secretion and a tendency toward complications (53), early onset and a positive family history vs. late onset and high consumption of alcohol or cigarettes (101), substance use and personality disorder vs. early onset and neurosis vs. life events and depression vs. late onset and psychosocial stability (102). Now, in an era when iatrogenesis and microbiology are both rampant, pathways are defined chiefly in terms of nonsteroidal antiinflammatory drugs and *H. pylori*; each can be examined for evidence of psychosocial influences.

Whereas in the first flush of enthusiasm *H. pylori* seemed to cause all ulcers not specifically excavated by nonsteroidal antiinflammatory drugs (103), it now appears that 10% to 20% of ulcers develop without the benefit of exposure to either (49); a recent pooled analysis calculated that 29% of duodenal ulcer patients have no active *H. pylori* infection (50). Idiopathic ulcer cases are characterized by particularly rapid gastric emptying and hyperpepsinogenemia (55) and are overrepresented among ulcer patients who are older (104) or younger (105) than the usual age group or who have ulcers that are refractory to treatment (106), recurrent after ulcer surgery (107), or complicated by bleeding or stenosis (108).

BIOPSYCHOSOCIAL VIEW OF PEPTIC ULCER

There are a few hints in the literature that psychosocial factors may be disproportionately active in idiopathic ulcers. Our Italian study of recent-onset duodenal ulcer patients found psychosocial risk factors to be present in a statistically inverse proportion to the number of biological risk factors, including *H. pylori* and nonsteroidal antiinflammatory drugs (60). These data among ulcer patients should not be interpreted to indicate an antagonism between biological and other risk factors, as it might if it were in the general population. Rather, it suggests that the two forms of risk factors are additive, persons with a weaker physiological disposition being pushed over the edge into forming an ulcer by the effects of stress or anxiety. Psychological vulnerability seems to be directly correlated with the hyperpepsinogenemia (68) that is prominent in idiopathic ulcer cases (55). The epidemiologic literature on shared catastrophes also supports the concept of a special role of stress in idiopathic ulcers: Any increase in uncomplicated ulcers during times of calamity seems to be outstripped by the increase in complicated and especially perforated ulcers (27, 28, 30), one subtype in which *H. pylori* plays little role (109).

Sometimes *H. pylori* may be an innocent bystander, in that "idiopathic" ulcers would develop in some infected individuals even if their stomachs were sterile. One such case was described recently, in a Japanese man whose ulcer obstinately recurred during a period of life stress after his resident bacterium had been successfully eradicated (110).

The possible role of psychosocial factors in nonsteroidal antiinflammatory drug–related ulcers does not seem to have been directly studied, although there is evidence that some other forms of drug damage to the gastroduodenal mucosa are more likely among people under stress (111). *H. pylori*, in contrast, is so far from being involved in this type of pathology that the presence of *H. pylori* tends to increase the risk of bleeding in nonsteroidal antiinflammatory drug–related ulcers (112), and successful eradication of the organism does not facilitate and may even hinder healing (113–115).

In practice, most peptic ulcers are likely to involve *H. pylori* as an etiological agent (3, 116). The risk factor model so valuable for conceptualizing coronary artery disease may be useful in peptic ulcer as well: Stress and *Helicobacter* may be two independent risk factors with additive effects, just as diabetes and smoking carry additive risks for coronary artery disease. There may also be points at which the two factors potentiate each other's action. Like *Mycobacterium tuberculosis*, *H. pylori* is a pathogen that can reside peaceably in the body for decades until something occurs to disturb the bacteria-host equilibrium. In the presence of intense bacterial loads (60) or particularly virulent strains (51, 52), ulcers may be destined to develop regardless of the individual's psychological characteristics, but there is some evidence that light infections may be helped to evolve into ulcer by psychosocial factors (60). Conversely, the presence of *H. pylori* potentiates the development of stress ulcers in intensive care unit patients (117), and results of a study of patients with bleeding gastric ulcers after the Hanshin-Awaji earthquake suggest that severe stress may be particularly likely to precipitate hemorrhage in carriers of CagA-positive strains (118).

Acid levels seem to be a fundamental determinant of the location and intensity of *H. pylori* infection, both within the stomach (119) and beyond (51). The presence of bile in the duodenal bulb acts as a shield against the passage of the organism through the pylorus (120), a shield that disintegrates at a low pH (120). If chronic stress increases the duodenal acid load in ulcer-prone individuals, it could therefore enable *Helicobacter* to colonize the duodenum, ushering in duodenitis and eventually ulcer.

Other sorts of stress–*H. pylori* interactions could also come into play, including psychoneuroimmunologic mechanisms related to those that promote viral infections (121, 122), but they must remain for now in the realm of pure speculation.

There is thus some evidence of a biologically plausible role of psychosocial factors in each of the major ulcer subtypes: those related to nonsteroidal antiinflammatory drugs, those related to *H. pylori*, and those related to neither.

CONCLUSIONS

This review supports the concept that stress contributes to the etiology of between 30% and 65% of peptic ulcer cases. It also suggests that univariate associations observed in observational studies overestimate the true etiological contribution by a factor of approximately 2 when one takes into consideration recall bias, misreporting of diagnoses, and confounding by socioeconomic status or painful medical conditions. Of the true ulcerogenic effect of stress above and beyond confounding, a substantial portion can be estimated to be due to stress-related increases in health risk behaviors and the rest to direct psychophysiologic mechanisms (Fig. 2).

Peptic ulcer is a valuable model for understanding the complex interactions among psychosocial, socioeconomic, behavioral, and infectious factors in causing organic disease (Fig. 3). There has recently been a modest recrudescence of interest in the biopsychosocial vision of ulcer, although it might be exaggerated to describe ulcer psychosomatics as springing phoenix-

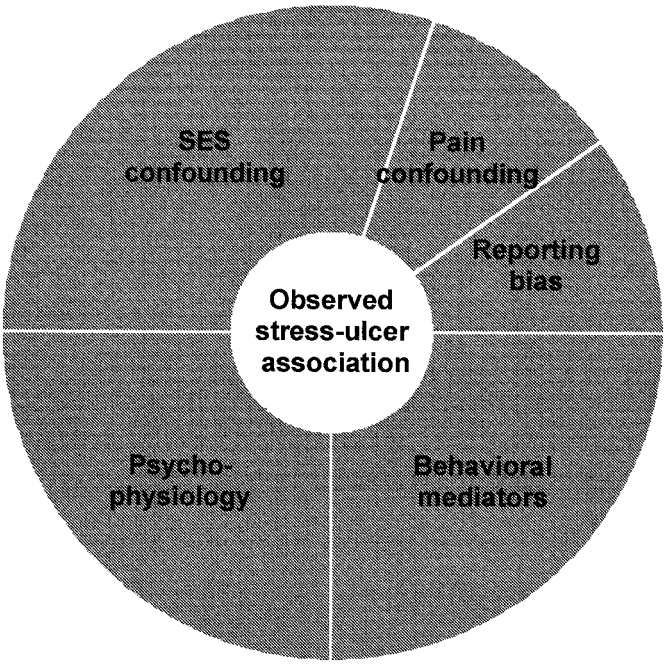

Fig. 2. Components of the observed association between stress and peptic ulcer.

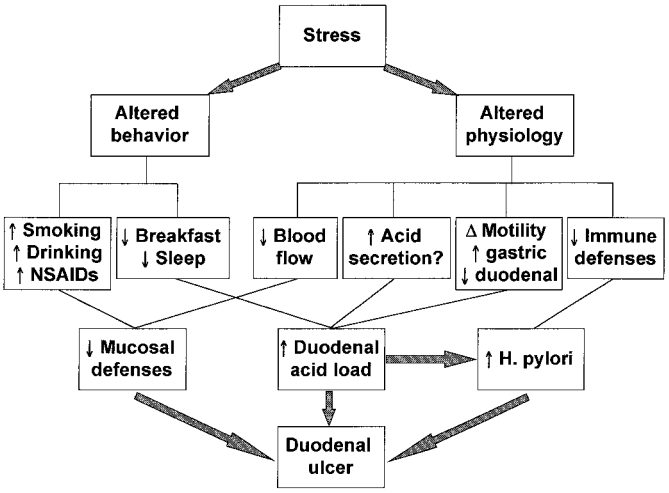

Fig. 3. A model postulating behavioral and psychophysiologic mechanisms that may link psychosocial stress with peptic ulcer. NSAIDs = nonsteroidal antiinflammatory drugs.

like from its own ashes because the articles have remained thus far largely on a theoretical plane (1, 59, 123–127). I would speculate that two developments have brought the concept back on the menu. One is the heightened interest in ulcer pathophysiology spurred by the discovery of *H. pylori*. The other is a revived scientific enthusiasm for the possibility of psychosocial influences on diseases ranging from myocardial infarction (128) to sudden death (129), to diabetes (130), to the common cold (131), which is related in turn to trends in the broader social-cultural scene beyond the borders of the biomedical community (132) and to the discovery of novel and biologically plausible mechanisms from psychoneuroimmunology (133) to arrhythmogenesis (134).

The discovery of *H. pylori*, which at first seemed to deal a death blow to the psychosomatic model of peptic ulcer, may thus in reality have only stunned it. There is hope that this new and important pathogenetic factor will in the end serve as a stimulus to a new set of researchers, weaned on psychoneuroimmunology, to whom the concepts of psychology and infection are not necessarily a contradiction in terms.

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