

Peptic ulcer at the end of the 20th century: biological and psychological risk factors

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S Levenstein. Peptic ulcer at the end of the 20th century: biological and psychological risk factors. *Can J Gastroenterol* 1999;13(9):753-759. The prevailing concept of peptic ulcer etiology has swung over entirely in just a few years from the psychological to the infectious, yet the rich literature documenting an association between psychosocial factors and ulcer is not invalidated by the discovery of *Helicobacter pylori*. Physical and psychological stressors interact to induce ulcers in animal models, concrete life difficulties and subjective distress predict the development of ulcers in prospective cohorts, shared catastrophes such as war and earthquakes lead to surges in hospitalizations for complicated ulcers, and stress or anxiety can worsen ulcer course. Many known ulcer risk factors, including smoking, nonsteroidal anti-inflammatory drug use, heavy drinking, loss of sleep and skipping breakfast, can increase under stress; the association of low socioeconomic status with ulcer is also accounted for in part by psychosocial factors. Among possible physiological mechanisms, stress may induce gastric hypersecretion, reduce acid buffering in the stomach and the duodenum, impair gastroduodenal blood flow, and affect healing or inflammation through psychoneuroimmunological mechanisms. Psychosocial factors seem to be particularly prominent among idiopathic or complicated ulcers, but they are probably operative in run of the mill *H pylori* disease as well, either through additive effects or by facilitating the spread of the organism across the pylorus, while gastrointestinal damage by nonsteroidal anti-inflammatory drugs can also be potentiated by stress. Although the clinical importance of peptic ulcer is fading along with the millenium, due to secular trends and new therapies, it remains worthy of study as a splendid example of the biopsychosocial model.

Key Words: *Helicobacter pylori*; *Nonsteroidal anti-inflammatory drugs*; *Peptic ulcer*

L'ulcère gastroduodéal à la fin du 20^e siècle : facteurs de risque biologiques et psychologiques

RÉSUMÉ : Le concept dominant de l'étiologie de l'ulcère gastroduodéal a viré complètement en quelques années du psychologique à l'infectieux, cependant, la riche littérature documentant une association entre les facteurs psychologiques et l'ulcère n'est pas invalidée par la découverte de *Helicobacter pylori*. Des facteurs psychologiques et physiques stressants interagissent pour induire des ulcères chez des modèles animaux ; les difficultés réelles de la vie ou un chagrin non fondé prédisent le développement d'ulcères dans des cohortes prospectives et des catastrophes partagées, comme la guerre ou les tremblements de terre, entraînent une poussée d'hospitalisations pour des complications dues aux ulcères. Le stress et l'anxiété peuvent aggraver l'ulcère. Ainsi, de nombreux facteurs de risque connus pour induire un ulcère, y compris le tabagisme, l'utilisation de médicaments anti-inflammatoires non stéroïdiens, l'alcoolisme, le manque de sommeil et le fait de sauter le petit déjeuner, peuvent augmenter sous l'effet du stress. De même, l'association entre un statut socioéconomique faible et l'ulcère s'explique en partie par des facteurs psychosociaux. Parmi les mécanismes physiologiques possibles, le stress peut induire une hypersécrétion gastrique, réduire le tamponnage de l'acide dans l'estomac et dans le duodénum, entraver le flux sanguin dans la région gastroduodénale, et nuire à la guérison ou maintenir l'inflammation par le biais de mécanismes psychoneuroimmunologiques. Les facteurs psychosociaux semblent particulièrement dominants parmi les cas d'ulcères compliqués ou idiopathiques, mais ils contribuent probablement aussi à l'ulcère à *H. pylori*, soit par des effets additionnels ou en facilitant la dissémination bactérienne à travers le pylore. Le stress peut aussi aggraver les lésions gastrointestinales induites par les anti-inflammatoires. Bien que l'importance clinique de l'ulcère gastroduodéal s'estompe avec la fin du millénaire à cause des nouveaux traitements et des tendances séculaires, cette affection reste digne d'être étudiée comme un magnifique exemple du modèle biopsychosocial.

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Peptic ulcer as we know it is a disease of the 20th century. After an early career as an occasional affliction of young Victorian women it swept to hyperendemicity among the generation of men born around 1900 (1), only to begin fading away as the century headed into its last stretch (2). Its final decline, following the discovery of *Helicobacter pylori*, promises to be nicely timed to coincide with the rollover from 1999 to 2000. As the century ends, what will be the next phase in our concept of ulcer etiology? Can a synthesis be born out of the thesis of psychosomatics and the antithesis of infection? This review of the literature aims to contribute to that process by summarizing the current knowledge of the interactions between psychosocial and biological risk factors in peptic ulcer.

THESIS: PSYCHOSOCIAL RISK FACTORS

The advent of *H pylori* has thrown doubt into many minds as to whether the older literature relating psychosocial factors to peptic ulcer may have been entirely fallacious – as fatally flawed as those unfortunate psychiatric tracts that, in the 1930s, attributed Down's syndrome to faulty parenting.

Researchers have been claiming to find psychological components in ulcer etiology for as long as the modern psychosomatic concept has existed (3). Careful examination of this literature using strict methodological criteria allows some of it to be discarded as anecdotal or irrelevant. The cross-sectional literature is particularly suspect because of the ever-present possibility that associations can be contaminated by recall bias and by the effects of disease. It should be said, though, that the best of the cross-sectional studies are highly suggestive. One showed, for instance, that among recent-onset ulcer patients given the exhaustive and stringently scored Bedford College Life Events and Difficulties Scale (4), the rate of severe life difficulties during the six months preceding ulcer development was five times higher than that in controls carefully matched from the electoral rolls for age, sex and socioeconomic status (5). Similarly, though doubts remain as to the relevance of animal models to human peptic ulcer, the extensive animal literature (6,7) shows unequivocally that not only physical stressors (8) but also purely psychological manipulations (6) can cause or facilitate erosion of the gastric and sometimes the duodenal mucosa in mammals ranging from rats to monkeys (9).

Several follow-up studies of defined cohorts have shown psychological distress (10,11) and concrete life stressors such as unemployment (12) or being a prisoner of war (13-15) to increase the risk of incident peptic ulcer over the subsequent period. Other more subjective kinds of stress, including difficulties at work or with marriage or children have also proved to predict ulcer development in some prospective studies (12,16,17).

A particularly convincing line of research has compared rates of ulcer in a defined geographical area before and after catastrophic events. The classic study by Spicer et al (18), published while World War II was still raging,

showed a surge in the rate of perforated ulcers in a group of 16 London, United Kingdom hospitals during the months of intense German bombing. Uncomplicated gastric ulcers, and bleeding ulcers at both gastric and duodenal sites, similarly increased following the disastrous earthquake in Kobe, Japan (19). During a profound economic crisis in Bulgaria, upper gastrointestinal x-ray studies were more likely to reveal active ulcers than during the same period of the previous year (20). One clever study in Hong Kong engaged raters to estimate the degree of societal impact of current events on the population by examining newspaper headlines year by year between 1962 and 1985, and found an astonishing correlation of $r=0.57$ with the rate of hospitalization for perforated ulcers (21), with ulcer surgery rates peaking simultaneously with such events as sovereignty negotiations and a massive influx of refugees from Vietnam.

Although the old 'specificity hypothesis', which held that specific intrapsychic conflicts led to specific psychosomatic diseases (22), has fallen into disrepute as a general concept, there is some evidence that personality characteristics may be associated with peptic ulcer. Hostility and low ego strength have been found to be predictive of ulcer in cohort studies (10,23). The many correlational studies with similar findings (24-27) are interesting but must be taken with a grain of salt, especially because chronic peptic ulcer can itself induce considerable distress, reflected in reversible changes in Minnesota Multiphasic Personality Inventory profiles (28).

Once an ulcer has developed, psychosocial factors can have a considerable effect on its course. Having a relatively high level of anxiety (29) or of self-reported stress (30,31) at the time of diagnosis increases the nonhealing rate of duodenal ulcer. Depression and low socioeconomic status increase the frequency of symptoms after initial healing (32), while ongoing stress has been shown to increase the rate of documented relapse over several years (31).

One methodological shadow lies over even prospective reports of an association between stress and peptic ulcer: the possibility of confounding by nonpsychosocial risk factors such as smoking, socioeconomic status and use of nonsteroidal anti-inflammatory drugs (NSAIDs). Fortunately several studies have controlled for all three factors in multivariate analyses, and all found that associations with ulcer incidence (10,11) and course (33) persist even after adjustment.

ANTITHESIS: NONPSYCHOSOCIAL RISK FACTORS

The two main causes of peptic ulceration are *H pylori* and NSAIDs. Some writers have gone so far as to suggest that all ulcers are related to one or the other (34), but this seems not to be true, with 15% of ulcers or more falling into what may be termed an idiopathic category (35-38).

The role of *H pylori* has been amply reviewed (36,39-42). Growth of this organism in the gastric mucosa sets up

local inflammation that can develop into ulcer and can, especially under circumstances such as high duodenal acid load that induce gastric metaplasia in the duodenum and encourage the spread of *H pylori* across the pylorus (36), lead to ulcer formation in the duodenum as well. NSAIDs are important causes of both hemorrhagic gastritis and peptic ulcer (43,44).

Gastric hypersecretion is a classic and well-established risk factor for peptic ulcer development (45,46). There is probably a hereditary component, reflected by levels of serum pepsinogen (47), though many environmental factors can also influence acid levels. The net effect of *H pylori* on acid secretion is still unclear (45,48,49).

Other genetic influences are shown by the clustering of ulcer in families (46,50) and by the special susceptibility to ulcers of individuals with type O blood (51).

Cigarette smoking is another important ulcer risk factor (52), whose destructive effect on mucosal defenses seems to be particularly active in the presence of *H pylori* (34).

Irregular eating and especially skipping breakfast, which prolongs the nocturnal fast period, has recently emerged as a risk factor for ulcer development (10). Shift work (53), and more generally lack of sleep (10), also seem to promote ulcer formation, conceivably through effects on the hypothalamic-pituitary-adrenal axis (54).

Alcohol consumption has been found in some (10,55) but not all studies (56,57) to be a risk factor for peptic ulcer. The reason is probably related to a dose effect: alcohol in low to moderate amounts seems to toughen up the gastroduodenal mucosa, actually inducing a protective effect against ulceration (52) and facilitating healing (58). Only at high levels of alcohol consumption does a damaging effect become evident, whether based on stimulation of acid secretion, on a direct irritant effect on the mucosa or on replacement with calories from alcohol of calories from foods that would otherwise buffer gastric acid.

One ulcer risk factor sits on the fence between psychosocial and nonpsychosocial: low socioeconomic status. The association between low socioeconomic status and peptic ulcer (59) is due in large part to the strong inverse association of *H pylori* infection with socioeconomic status (60,61), which reflects variations in hygienic conditions during childhood according to socioeconomic status (62,63). Also contributing to the association is physical exertion on the job, which seems to be independently associated with ulcer (43,64), perhaps because of stimulation of gastric acid secretion (65).

PSYCHOSOCIAL FACTORS IN RELATION TO OTHER ULCER RISK FACTORS

Interactions with health risk behaviours: A glance at the section entitled 'Antithesis: nonpsychosocial risk factors' reveals something interesting: most of the supposedly nonpsychosocial ulcer risk factors are actually behavioural characteristics that are likely to be adversely influenced by

stress, including smoking, heavy drinking, poor sleep, skipping breakfast and even NSAID use (10,66).

Anecdotal evidence has attributed the increased ulcer risk under stress to behavioural changes (20), and this kind of behavioural mediation can be confirmed by the observation that the stress-ulcer association is reduced by statistical adjustment for health risk behaviours. For example, the association of family problems and unemployment with subsequent ulcer development among women in the Alameda County Study was due in large part to behavioural factors such as smoking, alcohol excess, and irregular sleeping and eating habits (12), as was the association with psychological distress among the population as a whole (10). Lesser but measurable mediating effects of smoking and of acetylsalicylic acid (ASA) use have been shown in other prospective studies as well (11,31,33).

Behavioural mediators, especially smoking (31,33), may also be important in the influence of stress on ulcer course; recent increases in smoking accounted in one study for half of the effect of anxiety in impairing endoscopic healing (29).

Interactions with duodenal acid load – *Gastric acid secretion*: For many years it was assumed that the chief mechanism by which psychological factors promote peptic ulcer was through stimulation of gastric acid secretion (55,67). There is some evidence that stress, distress or anxiety can elevate gastric acid secretion, from the classic studies of patients with gastric fistulas (68) through case studies of changes in secretion over time in relation to life stress (69) to studies of the acute effect of laboratory stressors (70-74). Indirect evidence includes the association of psychosocial factors with serum pepsinogen (55,67) and the prosecretory effect of physical effort (65). The literature is quite inconsistent, however, with some groups instead reporting stress to lower gastric secretion in nonhuman primates (75) and humans (76). The key to resolving this contradictory evidence may lie in a peculiarity of the physiological response to stress among individuals who are prone to duodenal ulcer, because this group seems particularly likely to respond to stress with hypersecretion (69,77).

Motility: Above and beyond acid secretion, another reason for the increased duodenal acid load typical of duodenal ulcer is accelerated gastric emptying (78). While the usual effect of stress on gastric motility is in the direction of paralysis rather than stimulation (79,80), some subgroups of dyspeptic patients have a paradoxical response to laboratory stressors (81) that may be relevant to ulcer formation. *Buffering*: The third component of duodenal acid load is the degree to which acid is buffered in the stomach or the duodenum. Irregular eating habits during periods of life stress, especially skipping breakfast, is likely to reduce food buffering, while there is some evidence that stress may directly inhibit duodenal bicarbonate secretion (8), as does at least one stress-related behaviour, cigarette smoking (82).

Interactions with gastroduodenal blood flow: Circulatory

changes are thought to be a major contributor to the type of gastric stress lesion that develops in the context of the intensive care unit, and some workers have found that gastroduodenal blood flow can be impaired by other kinds of stress (83). The relevance of these findings to clinical ulcer psychogenesis is unclear but may be substantial.

Interactions with socioeconomic status: As mentioned above, there are good reasons unrelated to psychology that may in part explain the increased risk of ulcer among individuals with low socioeconomic status (59). This suggests that much of the association between socioeconomic status and ulcer is due to confounding. But poverty is also a major source of stress, and multivariate analyses indicate that a large proportion of the association between socioeconomic status and ulcer is related to psychological distress and to differences in health risk behaviours between high- and low- socioeconomic status individuals (84).

Interactions with NSAIDs: NSAID use is associated with psychological stress (10), for reasons that can be complex and circular.

Clinical experience shows that many individuals who feel stressed turn to ASA and other NSAIDs as tranquilizers or sleep aids, despite the lack of evidence for such effects in the medical literature. This means that use of NSAIDs joins other health risk behaviours as a potential mediator between stress and ulcer.

It is also true, however, that because of NSAID use, painful medical conditions can confound the association between stress and ulcer, artificially inflating it; the same chronic pain that leads to use of gastrolesive medications can also cause psychological stress. In this case the stress is not a cause of ulcer but an innocent bystander.

To complicate the issue further, psychosocial factors can, in turn, cause, or exacerbate, painful conditions. Such disorders as migraine, for instance, are notoriously influenced for the worse by psychological distress; in addition to direct psychophysiological pathways, symptoms can be worsened by stress-related alterations in patterns of sleep, eating, alcohol consumption and smoking. The phenomenon of somatization has other aspects as well, whereby depressed or anxious individuals are hyperaware of bodily sensations and particularly distressed by phenomena (intestinal contractions, muscle tension) that would normally be ignored (85).

Thus, psychological distress can lead to behavioural changes and other causes of pain, which can lead to the use of NSAIDs and also to further intensification of distress, which can lead to gastroduodenal lesions.

There is a limited amount of evidence that stress and NSAIDs may interact directly, or additively, as well. In one study of patients taking NSAIDs for inflammatory conditions (86), those who were characterized as being under stress were more likely to develop upper gastrointestinal bleeding.

In contrast, the interaction of NSAID lesions with *H pylori* has paradoxical aspects. Though some workers have reported *H pylori* infection to increase the risk of ulceration

among NSAIDs-treated patients (87), others have reported that eradication of *H pylori* does not improve and may even worsen the course of NSAID-related ulcers (88,89), casting doubt on the clinical importance of any damaging interaction between these two prime ulcer risk factors.

Interactions with *H pylori*: It is generally accepted that *H pylori* is the single most important risk factor for peptic ulcer (40). Only 20% of infected individuals ever develop an ulcer (37), however, so cofactors are clearly of vital importance. There is some clinical evidence that anxiety and other aspects of stress may contribute to the formation of ulcer in individuals with low intensity or absent *H pylori* infection (90). Stress may also have a potentiating effect, mediated by duodenal acid load, on the colonization of the duodenum by *H pylori* because an acid environment decreases the protective effect of bile (91). There can also be stress-related decreases in mucosal defenses to *H pylori* damage through behavioural mediators such as cigarette smoking (34).

Interactions with liver disease: Following a pattern that should by now be familiar, cirrhosis of the liver can be both a source and an effect of stress because it is a devastating disease, often caused by heavy alcohol consumption. Cirrhosis, which increases the risk of peptic ulcer through mechanisms largely related to changes in upper gastrointestinal blood flow and not to *H pylori* (92), may, therefore, be a confounder or a mediator of stress in some cases, though it is too rare to have a substantial quantitative impact on the overall association between stress and ulcer.

Interactions with immune and endocrine mediators: The rapidly expanding field of psychoneuroimmunology (93) holds some promise for elucidating the mechanisms that link psychosocial factors with peptic ulcer. It has been suggested, without any supportive evidence, that psychoneuroimmunological mechanisms might be active in *H pylori*-related peptic ulcer (94), as they are in some other infections (95). In particular, it is possible that stress may affect the intensity of local inflammatory responses that help determine the onset and course of ulcer (96,97) by influencing the production of cytokines that mediate the inflammation (98-100).

Stress can also stimulate thyrotropin-releasing hormone, which is a promoter of gastric ulceration (101). This interaction has not, however, been studied as yet in a clinical setting.

It is probably relevant to the impairment of ulcer healing by psychosocial factors that chronic or subacute real life stress has been shown to inhibit the healing of experimental lesions on the skin and in the oral cavity (100,102,103). Corticosteroids, the classic stress hormones, seem to be responsible (100,102).

Refractory and idiopathic ulcers: *H pylori* is turning out to be present in fewer ulcers than was first thought (35). Non-*H pylori* non-NSAID or idiopathic ulcers are particularly likely to be associated with hyperpepsinogenemia (104), which has been reported to be associated in turn

with psychosocial factors (55,67). In one provocative case study, duodenal ulcer persisted in the context of life stress even after *H pylori* had been eradicated with the use of antibiotics (105). There is evidence that psychological vulnerability is more prominent among ulcer patients who have fewer biological risk factors (90), suggesting that psychosocial factors may be particularly active among the idiopathic subgroup, which is often refractory to therapy (106).

Complicated ulcers: Some workers have suggested that acute perforated duodenal ulcer is not associated with *H pylori* infection (107), and others find an even lesser association with bleeding ulcer (108). While these findings have not been consistently replicated, they might contribute to explaining why population studies of complicated ulcer (18,19,21) have shown a particularly marked influence of societal stressors on ulcer incidence.

SYNTHESIS: THE LARGER PICTURE

This review of the literature shows that there is excellent evidence for a role of psychosocial factors in the etiology of peptic ulcer, and suggests several plausible mechanisms. The key point is that, as with other risk factors (including *H pylori*), psychosocial ones are not active in all cases of ulcer. Peptic ulceration can result from a number of differ-

ent etiological pathways (47,104,109-113), some of which are likely to be more responsive to stress than others. We have suggested, for example, that complicated ulcers and those related to neither *H pylori* nor NSAIDs may be particularly susceptible to psychosocial influences.

The clinical importance of the role of psychosocial factors in the *H pylori* era is less clear because of the therapeutic revolution that has taken place. Although the old dictum, 'once an ulcer, always an ulcer', was never more than a half-truth, it has lost its residual validity now that antibiotic treatment for *H pylori* allows many patients the hope of an ulcer-free future unencumbered by medications, lifestyle limitations or the threat of surgery. With this therapeutic breakthrough, which followed close on the heels of the appearance of powerful antisecretory agents and is being abetted by a secular fall in ulcer incidence, peptic ulcer promises to become a disorder as insignificant in the new century as it was prominent in the old one. The practical importance of psychosocial factors will be overshadowed in most cases by powerful pharmacological tools. However, the theoretical importance of peptic ulcer as a splendid example of the biopsychosocial model (114-117) is not diminished by improvements in its therapy and should not be ignored by the research community as we move into the new millennium.

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