Stress and peptic ulcer: life beyond helicobacter

Susan Levenstein

Gastroenterology
Service, Nuovo
Regina Margherita
Hospital, Viale
Trastevere 72,
Rome, Italy
Susan Levenstein,
adjunct research
physician

Correspondence to:
Dr Levenstein,
Via del Tempio 1A,
00186 Rome, Italy
100424.3254@
compuserve.com

BMJ 1998;316:538-41

The discovery that *Helicobacter pylori* is a cause of peptic ulcer has tempted many to conclude that psychological factors are unimportant. But this is dichotomised thinking. There is solid evidence that psychological stress triggers many ulcers and impairs response to treatment, while helicobacter is inadequate as a mono-causal explanation as most infected people do not develop ulcers. Psychological stress probably functions most often as a cofactor with *H pylori*. It may act by stimulating the production of gastric acid or by promoting behaviour that causes a risk to health. Unravelling the aetiology of peptic ulcer will make an important contribution to the biopsychosocial model of disease.

For this review of the role of psychological stress in the aetiology of peptic ulcer disease, I undertook conventional journal tracking and reference tracing, supplemented by Medline searches using Paperchase. The important keywords used in this search included peptic ulcer; duodenal ulcer—psychology; stress; life change events; and personality.

H pylori is not enough

When *H pylori* burst on the scene a few years ago, it revolutionised views on the aetiology and treatment of peptic ulcer. Psychosocial factors were quietly but firmly escorted off the stage, and gastroenterologists in particular banished psychological considerations with something approaching relief.

While this surge of biological reductionism is understandable, it risks throwing the baby out with the bath water. *H pylori* is inadequate as a sole explanation for peptic ulcers. Most people who harbour the organism never have ulcers, while a few who have never been infected with it or taken non-steroidal anti-inflammatory drugs develop ulcer disease.¹ This testifies to the role of factors additional to infection in peptic ulceration (the situation is similar for *Mycobacterium tuberculosis* and, indeed, most infectious organisms). *H pylori* alone does not explain fully the epidemiological patterns of upper gastrointestinal disease.² In addition, Marshall (who first identified *H pylori* on the surface of the gastric antrum) found that Koch's postulates for establishing the aetiological relation between a micro-organism and disease are not met in the case of *H pylori* and ulcers.³ Again, the same might be said for many other established causes of disease.

Explaining the aetiology of a disease is often like assembling a jigsaw puzzle. By the time *H pylori* had been discovered, many pieces of the ulcer puzzle, from

Summary points

Psychosomatic factors in the aetiology of peptic ulcer have become unfashionable since the discovery of *Helicobacter pylori*

Most people harbour *H pylori* so the organism cannot serve as the sole explanation for ulcer disease

Psychological stress has an impact on the onset and course of ulcer disease

Psychological stress probably interacts with *H pylori* and other risk factors in causing ulcer disease

Peptic ulcer is an important example of the biopsychosocial model of disease

cigarette smoking to type O blood, had already been found and fitted together, although we did not know exactly where they belonged in the larger picture. The subsequent discovery of an important and central piece may mean that other completed sections have to be moved around—not that they have to be discarded.

The discovery of *H pylori*, far from eliminating interest in that older assortment of physical risk factors for ulcer disease, has spurred some researchers to re-establish and reinterpret the importance of older factors in the new context. Clinical studies have examined these physical risk factors in relation to their association with or independence from *H pylori* in ulcer patients.^{1 4} Other workers are combing large databases to see how these same factors relate to *H pylori* in the general population.^{5 6}

Why are psychological factors being ignored?

Methodological inadequacies

Why has there been no corresponding flurry of articles on the relation between *H pylori* and psychology?⁷ For one thing, researchers interested in psychosocial factors tend to have little interest or expertise in microbiology, and vice versa. But I suspect the reason is deeper. The current generation of gastroenterologists has lost patience with psychosomatic explanations, at

least where these apply to peptic ulcer. The methodological inadequacies of some of the older published reports on psychosocial factors in ulcer disease are partly to blame. These studies were often flawed by contamination from disease effects, diagnostic uncertainty, and recall bias; did not pay enough attention to adjustment for confounding factors; and sometimes left readers distracted by side issues such as the nature or the measurement of stress.

Resistance to an integrated approach

The main feeling, however, seems to be that psychosomatic reasoning can be discarded as soon as another explanation becomes available. This dichotomised thinking, focused on the possibility of moving peptic ulcer from a stigmatised “psychosomatic” cubbyhole into a more dignified “infectious” one, reflects an ingrained resistance to the difficult but essential task of examining disease aetiology in an integrated manner that incorporates both psychological and biomedical elements⁸—a task begun for peptic ulcer long ago.⁹

Negative case-control studies

In fact, while all references to psychology have been removed from the chapter on ulcers of the 20th (1996) edition of Cecil and Loeb,¹⁰ this is not solely due to *H pylori*. In the 17th edition (1982), published before the discovery of helicobacter, 18 lines were allotted to psychology, but all were dismissive. Around that time a spate of negative case-control studies was sabotaging interest in psychosomatic factors in ulcer disease.¹¹ One reason for the difficulty these studies had in showing a causal role for psychosocial factors is that patients with peptic ulcer are a heterogeneous group. Stress is probably an active factor in only some patients—perhaps those with less exposure to ulcerogenic substances¹² or those with higher pepsinogen concentrations.¹³

Stress is fashionable elsewhere

Ironically, while the gastroenterological community seems to view those who have continued to support a psychosomatic aetiology for ulcer disease as stubbornly clinging to obsolete views, psychosocial factors have the glitter of novelty for researchers in other specialties, who are happily exploring whether you can die of fright or get the sniffles from stress.

Stress and ulcers: the evidence

Since the 1980s there has been a modest resurgence of research interest in the ulcer-stress question, and the resulting body of evidence has generally, though not always, been supportive.¹⁴ A solid series of methodologically sound studies now supports an aetiological effect of aspects of “stress” (a convenient term to cover both life stressors and subjective distress) ranging from depression to war. Considerable prospective evidence has been gathered alongside studies that have found an excess of life stressors in ulcer patients compared with matched controls.¹⁵ In one large longitudinal population study, the occurrence of self reported ulcer over a nine year period was more likely in subjects who reported any of several concrete life stressors or psychological distress at baseline.^{16 17} In another study, self reported stress predicted the occurrence of ulcer disease (diagnosed by a doctor) over the next 13

years.¹⁸ Family and job difficulties increased the risk of ulcer over five years in one sample of Israeli men.¹⁹ Major societal disasters, including German air raids in London and economic collapse in Sofia, have been associated with documented increases in acute ulcers.^{20 21} The ulcerogenic effects of stress have been shown to be robust enough to survive adjustment for behavioural and physical confounding factors.^{16–18}

Stress and prognosis in ulcer disease

Prospective clinical studies have reported that psychological distress impedes ulcer healing (as seen with endoscopy) after H₂ agonist treatment—even when stringent recruitment criteria exclude confounding in relation to disease chronicity.^{22 23} Life stress continued to worsen the prognosis over several years in two prospective case series.^{23 24} This effect seems to be reversible, however: a psychologically stable person who develops an ulcer during a stressful period is likely to remain free of symptoms for years after a short course of treatment, even without medication to eradicate *H pylori*.²⁴

Psychological stress and gastric acid secretion

Psychological stress is not only empirically associated with ulcers, but is a very plausible risk factor for ulcer disease. Gastric acid output is correlated with psychological distress in patients with and without ulcers,²⁵ and increased enormously during intense military training.²⁶ Compared with healthy people, patients with duodenal ulcers are particularly likely to respond to laboratory stressors by secreting more acid.²⁷ In two patients with duodenal ulcers, extraordinary life circumstances resulted in a 10-fold to 20-fold increase in the basal acid output.²⁸

Under stress, the amount of acid reaching the duodenum may increase further because gastric motility has changed or meals have been missed. People affected by stress may also smoke more, sleep less, and take more non-steroidal anti-inflammatory drugs, thereby increasing their susceptibility to ulcer by mechanisms that are not related to acidity. Evidence that prospective epidemiological associations between life stressors or psychological characteristics and ulcer are reduced by adjusting statistically for patterns of eating, sleeping, and substance use support a mediatory role for these health risk behaviours in the psychogenesis of ulcers.^{16 17}

DOLLY THOMPSON

Stress and *H pylori* as cofactors in ulcer disease

- Stress could facilitate the evolution of *H pylori* infection into ulcer by producing gastric hyperchlorhydria³¹
- Stress could disturb the equilibrium between *H pylori* and its host via psychoneuroimmunological mechanisms
- Stress could reduce mucosal defences to *H pylori* invasion through behavioural mediators such as cigarette smoking⁴
- Stress could increase the chances of ulceration in duodenal mucosa that have already been weakened by the effects of *H pylori* infection simply by increasing the acid load which flows past
- Stress induced acid secretion could promote *H pylori* colonisation of the duodenal bulb by neutralising the inhibitory effect of bile³²

An association between stress and *H pylori* infection?

Despite empirical support and biological plausibility, there could in theory still be a reason for abandoning psychogenic causes of ulcer disease. Stress might be associated strongly with *H pylori* infection, inducing the illusion that psychosocial factors can influence ulcer formation. For many of the other classic risk factors, this possibility has been examined directly and discarded. Smoking, alcohol consumption, non-steroidal anti-inflammatory drugs, and type O blood are not correlated with *H pylori* in populations without ulcers.⁵⁻⁶ The story is somewhat different for socioeconomic status. An excess of *H pylori* infection in poor people⁵ suggests that low social class may partly owe its reputation as an ulcer risk factor to confounding by *H pylori*.²⁹

No direct data are available as yet for stress, but there is no reason to expect that infection with *H pylori* is related to any particular psychological state. It is true that life stress, psychological distress, and *H pylori* may all be associated with low socioeconomic status, but epidemiological evidence argues against socioeconomic status being a principal cause of the association between stress and ulcers.¹⁷

How do *H pylori* and psychosocial stress interact in ulcer disease?

If we conclude that the discovery of *H pylori* has not erased the role of psychosocial risk factors in ulcer disease, asking how the two interact becomes logical. In some cases there may be no interaction at all. Given the large increase in acid production under severely stressful conditions²⁶⁻²⁸ and the high secretion of acid³⁰ and pepsinogen¹ in patients whose duodenal ulcers are not related to either *H pylori* or non-steroidal anti-inflammatory drugs, stress may be capable of causing peptic ulceration even in the absence of *H pylori*.¹² In most cases, however, stress probably functions as a cofactor with *H pylori*. Several possible mechanisms can be postulated (box).

Empirical evidence

Again, little empirical evidence exists on the relation between stress and *H pylori*, and that is limited to studies of psychological distress in gastroenterology patients. In

subjects with undiagnosed dyspepsia, those who are depressed or anxious are less commonly infected with *H pylori*.³³ Similarly, in patients with documented peptic ulcer, the higher the absolute titre of *H pylori* IgG antibody (a rough measure of the intensity of bacterial colonisation of the antrum), the less anxious is the patient likely to be.¹² These findings suggest that *H pylori* infection and psychological stress promote ulcer pathogenesis via pathophysiological pathways that are largely additive and therefore independent and complementary rather than synergistic.³⁴ Two different mechanisms of facilitating acid damage to the duodenum would result in a statistically inverse relation in ulcer patients, though not necessarily in the general population

Inverse relation between psychological stress and *H pylori*

In the classic view of the pathogenesis of peptic ulcer disease—that it is the sum of factors that increase acid secretion and those that lower mucosal defences—psychological stress probably acts mostly on the side of increased aggression and *H pylori* on the side of weakened defences.³⁵⁻³⁶ *H pylori* infection does not necessarily raise, and may even lower, acid secretion.³⁰⁻³⁴ Thus, though it has been suggested that the organism contributes to increased acid in the duodenum³⁷ and to raised pepsinogen values,³⁸ the striking increases in gastric acid found in many patients with duodenal ulcer seem to result from mechanisms that are at least partly independent of *H pylori* infection.¹⁻³⁰

Other possible explanations exist for an inverse relation between anxiety and *H pylori* antibody titres in ulcer patients. Stress may, for example, suppress serum antibody titres by stimulating cortisol production. Local processes in the gastric mucosa could also contribute, since a low pH tends to cause antigen and antibody to dissociate. Gastric hyperacidity resulting from stress could therefore suppress mucosal immunity, including *H pylori* antibody formation.

The way ahead

But all this is speculation. Now that the helicobacter earthquake has passed, those of us interested in the effects of psychosocial factors on peptic ulcer must begin investigating again in the new context. This will require scrupulous use of a variety of research tools if we are to have any impact on the many colleagues who think our efforts are a waste of time. We need to be careful to use appropriate measures in examining psychosocial data and to embrace the complexities of the biopsychosocial model. We need to pay great attention to avoiding recall bias, contamination of epidemiologically defined “ulcer” groups by subjects with non-ulcer dyspepsia, and statistical confounding by socioeconomic status.

Far from being obsolete, the concept that psychosocial factors play a role in peptic ulcer presents exciting and varied research opportunities in the age of *H pylori*. We can study the clustering between stress indicators and *H pylori* in the general population, we can look at the relation between *H pylori* and stress in case-control and prospective studies of ulcer patients, we can bring people whose *H pylori* status is known into the physiology laboratory and look at their physical reactions to stress, we can extract data on

H. pylori antibody titres from serum samples frozen for ongoing longitudinal studies, and we can study interactions of *H. pylori* and stress in animal models. These kinds of investigations can serve not only to breathe new life into psychosomatic concepts of peptic ulcer, but also to develop a more general paradigm for applying the integrated biopsychosocial model to medical disorders both infectious and otherwise.

I am indebted to Douglas Drossman, Harold Bourne, and Cosimo Prantera for their encouragement and for many invaluable exchanges of ideas.

Funding: None.

Conflict of interest: None.

- 1p;01 McColl KEL, El-Nujumi AM, Chittajallu RS, Dahill SW, Dorrian CA, El-Omar E, et al. A study of the pathogenesis of *Helicobacter pylori* negative chronic duodenal ulceration. *Gut* 1993;34:762-8.
- 2 Sonnenberg A. The US temporal and geographic variations of diseases related to *Helicobacter pylori*. *Am J Public Health* 1993;83:1006-10.
 - 3 Marshall BJ. *Helicobacter pylori* in peptic ulcer: have Koch's postulates been fulfilled? *Ann Med* 1995;27:565-8.
 - 4 Martin DF, Montgomery E, Dobek AD, Patrissi GA, Peura DA. Campylobacter *pylori*, NSAIDs, and smoking: risk factors for peptic ulcer disease. *Am J Gastroenterol* 1989;84:1268-72.
 - 5 Graham DY, Malaty HM, Evans DG, Evans DJ, Jr., Klein PD, Adam E. Epidemiology of *Helicobacter pylori* in an asymptomatic population in the US: effect of age, race, and socioeconomic status. *Gastroenterology* 1991;100:1495-501.
 - 6 Loffeld RJ, Stobberingh E. *Helicobacter pylori* and ABO blood groups. *J Clin Pathol* 1991;44:516-7.
 - 7 Melmed RN, Gelpin Y. Duodenal ulcer: the helicobacterization of a psychosomatic disease? *Isr J Med Sci* 1996;32:211-16.
 - 8 Drossman DA. Gastrointestinal illness and the biopsychosocial model. *J Clin Gastroenterol* 1996;22:252-4.
 - 9 Mirsky A. Physiologic, psychologic, and social determinants in the etiology of duodenal ulcer. *Am J Dig Dis* 1958;3:285-313.
 - 10 Bennett JC, Plum F, eds. *Cecil textbook of medicine*. 20th ed. Philadelphia: Saunders, 1996.
 - 11 McIntosh JH, Nasiry RW, McNeil D, Coates C, Mitchell H, Piper DW. Perception of life event stress in patients with chronic duodenal ulcer: a comparison of the rating of life events by duodenal ulcer patients and community controls. *Scand J Gastroenterol* 1985;20:563-8.
 - 12 Levenstein S, Prantera C, Varvo V, Scribano ML, Berto E, Spinella S, et al. Patterns of biologic and psychologic risk factors for duodenal ulcer. *J Clin Gastroenterol* 1995;21:110-7.
 - 13 Walker P, Luther J, Samloff IM, Feldman M. Life events stress and psychosocial factors in men with peptic ulcer disease. II Relationships with serum pepsinogen concentrations and behavioral risk factors. *Gastroenterology* 1988;94:323-30.
 - 14 Jess P. Personality pattern in peptic ulcer disease: a cohort study. *J Intern Med* 1994;236:271-4.
 - 15 Gilligan I, Fung L, Piper DW, Tennant C. Life event stress and chronic difficulties in duodenal ulcer: a case control study. *J Psychosom Res* 1987;31:117-23.
 - 16 Levenstein S, Kaplan GA, Smith M. Sociodemographic characteristics, life stressors, and peptic ulcer: a prospective study. *J Clin Gastroenterol* 1995;21:185-92.
 - 17 Levenstein S, Kaplan GA, Smith MW. Psychological predictors of peptic ulcer incidence in the Alameda County study. *J Clin Gastroenterol* 1997;24:140-6.
 - 18 Anda RF, Williamson DF, Escobedo LG, Remington PL, Mast EE, Madans JH. Self-perceived stress and the risk of peptic ulcer disease: a longitudinal study of US adults. *Arch Intern Med* 1992;152:829-33.
 - 19 Medalie JH, Stange KC, Zyzanski SJ, Goldbourt U. The importance of biopsychosocial factors in the development of duodenal ulcer in a cohort of middle-aged men. *Am J Epidemiol* 1992;136:1280-7.
 - 20 Spicer CC, Stewart DN, Winsor DMR. Perforated peptic ulcer during the period of heavy air raids. *Lancet* 1944;i:14.
 - 21 Pomakov P, Gueorgieva S, Stantcheva J, Tenev T, Rizov A. Ulcères gastroduodénaux pendant la période d'une crise économique aigue. *J Radiol* 1993;74:265-7.
 - 22 Levenstein S, Prantera C, Scribano ML, Varvo V, Berto E, Spinella S. Psychologic predictors of duodenal ulcer healing. *J Clin Gastroenterol* 1996;22:84-9.
 - 23 Holtmann G, Armstrong D, Pöppel E, Bauerfeind A, Goebell H, Arnold R, et al. Influence of stress on the healing and relapse of duodenal ulcers. *Scand J Gastroenterol* 1992;27:917-23.
 - 24 Levenstein S, Prantera C, Varvo V, Arcà M, Scribano ML, Spinella S, et al. Long-term symptom patterns in duodenal ulcer: psychosocial factors. *J Psychosom Res* 1996;41:465-72.
 - 25 Feldman M, Walker P, Goldschmiedt M, Cannon D. Role of affect and personality in gastric acid secretion and serum gastrin concentration: Comparative studies in normal men and in male duodenal ulcer patients. *Gastroenterology* 1992;102:175-80.
 - 26 Oektedalen O, Guldvog I, Opstad PK, Berstad A, Gedde-Dahl D, Jorde R. The effect of physical stress on gastric secretion and pancreatic polypeptide levels in man. *Scand J Gastroenterol* 1984;19:770-8.
 - 27 Bresnick WH, Rask-Madsen C, Hogan DL, Koss MA, Isenberg JL. The effect of acute emotional stress on gastric acid secretion in normal subjects and duodenal ulcer patients. *J Clin Gastroenterol* 1993;17:117-22.
 - 28 Peters MN, Richardson CT. Stressful life events, acid hypersecretion, and ulcer disease. *Gastroenterology* 1983;84:114-9.
 - 29 US Department of Health and Human Services. *Current estimates from the national health interview survey: United States, 1983*. Washington, DC: US Department of Health and Human Services, 1986.
 - 30 Chandrakumar K, Vaira D, Hobsley M. Duodenal ulcer, *Helicobacter pylori*, and gastric secretion. *Gut* 1994;35:1022-6.
 - 31 Lee A, Dixon MF, Danon SJ, Kuipers E, Megraud F, Larsson M, et al. Local acid production and *Helicobacter pylori*: a unifying hypothesis of gastroduodenal disease. *Eur J Gastroenterol Hepatol* 1995;7:461-5.
 - 32 Han SW, Evans DG, el-Zaatari FA, Go MF, Graham DY. The interaction of pH, bile, and *Helicobacter pylori* may explain duodenal ulcer. *Am J Gastroenterol* 1996;91:1135-7.
 - 33 Andersson SI, Hovellius B, Mölstad S, Wadström T. Dyspepsia in general practice: psychological findings in relation to *Helicobacter pylori* serum antibodies. *J Psychosom Res* 1994;38:241-7.
 - 34 Peterson WL, Barnett CC, Evans DJ, Jr, Feldman M, Carmody T, Richardson C, et al. Acid secretion and serum gastrin in normal subjects and patients with duodenal ulcer: the role of *Helicobacter pylori*. *Am J Gastroenterol* 1993;88:2038-43.
 - 35 Goggin PM, Marrero JM, Spychal RT, Jackson PA, Corbishley CM, Northfield TC. Surface hydrophobicity of gastric mucosa in *Helicobacter pylori* infection: effect of clearance and eradication. *Gastroenterology* 1992;103:1486-90.
 - 36 Hogan DL, Rapier RC, Dreilinger A, Koss MA, Basuk PM, Weinstein WM, et al. Duodenal bicarbonate secretion: eradication of *Helicobacter pylori* and duodenal structure and function in humans. *Gastroenterology* 1996;110:705-16.
 - 37 El-Omar E, Penman ID, Ardill JES, Chittajallu RS, Howie C, McColl KEL. *Helicobacter pylori* infection and abnormalities of acid secretion in patients with duodenal ulcer disease. *Gastroenterology* 1995;109:681-91.
 - 38 Hunter FM, Correa P, Fontham E, Ruiz B, Sobhan M, Samloff IM. Serum pepsinogens as markers of response to therapy for *Helicobacter pylori* gastritis. *Dig Dis Sci* 1993;38:2081-6.

(Accepted 21 July 1997)

Fifty years ago The new NHS

SIR,—A crucial question at this time which I think is being forgotten is, Do the public gain in health through the introduction of the Service at this stage?

The answer is obviously “No.” The Service will call for more work among doctors owing to more visits by patients and the inevitable form-filling which is the necessary evil of any coordinated service. If we look upon the patients as the material with which we work, and whose medical well-being is our “finished job,” then I'm afraid we're being forced on them at a time when workmen and material are of poor quality. We should have workshops (hospital beds)—the present numbers are inadequate; also assistants (nurses)—whose number is also inadequate.

A little variation in available foods may brighten a few, in mind if not in body. Tuberculous-infected milk can still take its toll of children, and tuberculous patients still linger at home waiting for hospital beds. However bad these are, and however good are the excuses for not remedying them now, the introduction of a health service, which to the patient promises improvement in medical care, can do nothing—in fact, we could be made the scapegoat for its failure.

Let us accept the role of heaven-sent advisers to Aneurin Bevan and tell him gently “No,” or at least “Not yet.”—I am, etc, H. J. Houghton, Newport, Mon.
(Letter, 17 January 1948, p 122. See also editorial by Gordon Macpherson, 3 January 1998, p 6.)