

# Stress and Peptic Ulcer Disease

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**A**LLEXANDER THE GREAT DIED AT THE age of 32 years, with acute abdominal pain that began after several days of binge drinking. Might it have been from a perforated peptic ulcer?

Founding a great empire may be an extraordinary example of life stress, but stress is currently out of fashion as a cause of ulcer.<sup>1</sup> For many years the dominant etiologic model was exquisitely psychosomatic: a vulnerable person—on grounds of personality and pepsinogen—encounters a major life stress, and a duodenal ulcer is born.<sup>2</sup> But after *Helicobacter pylori* proved to be a key and curable element in the ulcer diathesis, many concluded that the “real” cause had been found and had nothing to do with psychology. Research into stress effects on ulcer fell off precipitously, and the earlier literature was dismissed as misguided and naive, given the new, respectable status of peptic ulcer as an infectious disease. In a recent telephone survey of ordinary Americans’ views of what causes an ulcer, the authors seemed to consider the widespread belief in a psychological component tantamount to a superstition deserving eradication.<sup>3</sup>

But attempts to explain ulcer using *H pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs) as sole etiologic factors are destined to fail. More than 80% of *H pylori*-infected people (and the vast majority of NSAID users) never develop an ulcer, while at least 10% of patients with non-NSAID-related peptic ulcers have no *H pylori* infection.<sup>4</sup> The field is therefore open for other factors working in conjunction with *H pylori* or causing ulcers through alternative pathways.

The evidence that psychological stress is 1 of those factors is not invalidated by the discovery of *H pylori*. The German blitz in London,<sup>5</sup> the Kobe earthquake,<sup>6</sup> economic crisis in Sophia,<sup>7</sup> and sovereignty negotiations in Hong Kong<sup>8</sup> have all been followed by an increase in peptic ulcers in both the stomach and the duodenum, as has being a prisoner of war.<sup>9</sup> In defined epidemiologic cohorts, subjects with psychological distress,<sup>10</sup> self-described “stress or strain,”<sup>11</sup> or concrete life stressors<sup>12</sup> at baseline have increased incidence of ulcer over 9 to 15 years, an association that holds up to adjustment for a variety of nonpsychosocial risk factors<sup>10,11</sup> and is similar whether the outcome is assessed by medical records or by self-report.<sup>11</sup>

A large body of research has examined the effect of stress on the upper gastrointestinal tract in animal models. Though most such models produce superficial gastric lesions (better models, using transgenic animals, may emerge in the future), enough is shared with chronic human peptic lesions to make consideration of evidence from these models worthwhile. In rats, susceptibility to gastric lesions is increased by such social stressors as premature separation of the rat pup from its mother.<sup>13</sup> Also, in rats taught to avoid ulcer-producing electric shocks by operant responses, the occurrence of lesions can be drastically reduced if the animal receives more information about the efficacy of its response, demonstrating that perceptions and their integration into retrievable information affect the course of ulcer formation.<sup>14</sup>

Among potential mediators, several known behavioral risk factors for ulcers—smoking, alcohol abuse, and lack of sleep<sup>10</sup>—have clear associations with real-life stress and are known to impair wound healing through their effects on immune function<sup>15</sup>; sleep loss can also elevate cortisol levels. Individuals un-

der stress may also be likely to increase NSAID use.<sup>10</sup> On the physiological side, stress is known to modify gastric blood flow, which plays an important role in the gastric mucosal barrier, and to affect possible mediators such as thyrotropin-releasing hormone, cytokines, and corticotropin-releasing hormone.

Stimulation of gastric acid secretion has historically been considered another mechanism by which stress increases susceptibility to duodenal ulceration, and researchers have reported increases in acid secretion in association with psychosocial stressors,<sup>16,17</sup> especially among patients with duodenal ulcer.<sup>18</sup> Some studies of responses to acute mental stressors in humans<sup>19</sup> and in nonhuman primates<sup>20</sup> have, however, cast doubt on this mechanism. Perhaps these conflicting reports may be reconciled by postulating anomalous reaction patterns among ulcer-prone individuals.<sup>18</sup> Stress seems to have variable effects on gastric motility: delayed gastric emptying could increase the risk of gastric ulcer, while accelerated emptying could increase the net acid load delivered to the duodenum at any given level of gastric secretion, enhancing the risk of duodenal ulcer<sup>21</sup>; skipped meals and poor sleep might increase duodenal acid load still further.

In most ulcer cases where stress is involved, *H pylori* is likely to be present as well. The impact of the 2 factors may be additive. Individuals infected with large

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burdens or particularly virulent strains of *H pylori* may be capable of developing ulcers regardless of their psychological characteristics, whereas persons under severe stress might develop ulcers despite light or nonexistent infection. Psychological stress may also promote the growth of *H pylori* in the duodenum if it increases duodenal acid load, since the *H pylori*-inhibitory effects of bile seem to be reversed by acid.<sup>22</sup> A tantalizing line of research has illustrated the adverse effects of stress on the course of various infections<sup>23</sup>; in the case of *H pylori*, where primary infection occurs chiefly during childhood, stress-triggered exacerbation of the pathology induced by the bacteria, via psychoneuroimmunologic or other mechanisms, could be a cofactor.

Once an ulcer has developed, therapy is less effective in distressed individuals<sup>24</sup>—a vindication of the old-timers who treated ulcers with bedrest?—and their ulcers are more likely to recur over the years.<sup>25</sup> Research into the influence of stress on wound healing elsewhere in the body lends insight into possible mechanisms. Restraint-stressed mice heal more

slowly than control mice, with lower leukocyte infiltration of their wound sites, apparently because of increased glucocorticoid secretion affecting proinflammatory cytokines<sup>26</sup>; even physiologic variations in plasma cortisol can significantly alter cytokines important for wound healing and gastrin release.

In humans, healing of both epidermal and mucosal wounds is impaired by stress. Caregivers for relatives with Alzheimer disease took an average of 24% longer than well-matched controls to completely heal a small, standardized skin wound,<sup>27</sup> and mucosal wounds placed in dental students 3 days before academic examinations healed 40% more slowly than those made during summer vacation.<sup>28</sup> In both cases stress was associated with impaired production of interleukin 1 (IL-1) in response to lipopolysaccharide stimulation; IL-1 also plays an important role in *H pylori*-induced inflammation and in gastrin secretion. Notable among behavioral mediators is fragmented sleep, which can inhibit growth hormone, an enhancer of wound healing.<sup>15</sup>

In short, peptic ulcer is an excellent example of the limitations of monocausal thinking. Like most diseases, it has a multifactorial origin: the grammar of etiology is usually not *either/or* but *and*, although the proportions of various contributing factors will vary from 1 patient to another. Clarification of the role of stress in peptic ulcer must of course take *H pylori* and NSAIDs into account. The research community is rising to the challenge, with a diversity of groups designing studies in animal models, clinical populations, normal subjects, and epidemiologic groupings to see whether, as the present panel concludes, reports of the death of ulcer psychosomatics have been greatly exaggerated.

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