Commentary: Peptic ulcer, Susser and Stein and the cohort phenomenon

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Forty years have elapsed since Susser and Stein used mortality data to examine trends in the impact of peptic ulcer disease. They pointed to evidence that morbidity and mortality attributable to peptic ulcer had increased in frequency from the latter part of the 19th century, with gastric ulcer being the first to rise, and that there was evidence from various sources to suggest an abatement might be occurring in the middle of the 20th century. Using cohort analyses they went on to suggest that mortality data were compatible with a cohort phenomenon thus ‘Cohort analysis—that is, an analysis that follows each age group as it grows older through the years—shows that for each successive generation from 1850 the risks increased with impressive regularity to a peak and then declined.’ Susser speculated about causes, rejecting a simple link with civilization, but not ruling out ‘the hypothesis that it (peptic ulcer) is a disease of an early phase of urbanization’. Later, Sonnenberg and his colleagues confirmed Susser and Stein’s observations of rising and falling mortality, concluding that a birth cohort phenomenon occurred, implying important determinants for developing gastric and duodenal ulcer in early life. Meade and colleagues also observed a fall in ulcer incidence in British doctors of some 40% over a period of just over 15 years from 1947 to 1965.

Advances in medicine may be technology- and/or insight-based. Susser used very simple analyses to demonstrate that populations had become more prone, and then were becoming less prone to ulcer. That insight was not capitalized upon, but why not? The ideas of the time about ulcer causation were well set out by Doll and Card. The former noted both the rise in frequency of ulcer (described mainly through mortality statistics) and the later decline. The rise was accepted as a true rise, but the decline was attributed mainly to improved treatment. Doll also pointed to the marked social class gradient at the time of gastric ulcer incidence and mortality, but without the same for duodenal ulcer indicating intrinsic differences, whilst also casting doubt on the urbanization hypothesis by reference to the lack of significant differences in urban and rural disease rates. Card, by contrast followed a mechanistic path seeing the foci as influences on mucosal resistance and on acid and pepsin secretion. In the wake of two world wars it is understandable that much attention was paid to psychological factors, though with hindsight the supportive evidence seems weak.

Susser himself, in discussing the causes of peptic ulcer 5 years after his civilization paper concluded ‘the specific elements that contribute to the variations (in ulcer frequency) probably include diet, alcohol, cigarette smoking, emotional strain, personality and genotype’. It is noteworthy that the role of anti-inflammatory drugs as causes of ulcer is not considered, nor is the possibility of infection. Magnus in a careful description of the morbid histology of gastritis noted the constant association of chronic atrophic gastritis with duodenal ulcer, but a less consistent association with gastric ulcer, however he did not consider this further. Elsewhere, a particular description of a relationship between the presence of circulating antibodies to gastric urease and the occurrence of gastric ulcer was published in Gut in 1963. This was probably an antibody to the urease produced in large amounts by Helicobacter pylori but its potential importance was missed until John Marshall’s description of the significance of Campylobacter later renamed Helicobacter, pylori was accepted in the causation of ulcer. The role of aspirin in causing gastritis, but not ulcer, was described in 1938, but the significance of anti-inflammatory drugs (NSAIDs) was not underscored until the increasing use of drugs such as indomethacin focused attention on it. Australian work on the ulcer-proneness of younger women, associated with analgesic exposure, had little impact outside that country although the clinical burden imposed by NSAIDs proved to equate to one-third of the total number of ulcer complications.

We now see from a vantage point with understanding of the role of H. pylori and of the effects of NSAIDs, but not necessarily with greater clarity within our context. Thus if H. pylori is the dominant risk factor for gastric and duodenal ulcer which is not drug-induced, then it is unclear why the occurrence of these diseases has not changed in parallel. The disjunction has been apparent since: (1) William Brinton carefully documented the occurrence of gastric ulcer in London in the 1860s, (2) duodenal ulcer’s increasing importance from the 1890s and (3) it was apparent to clinicians and epidemiologists 50 years ago in commenting on the often far higher prevalence of duodenal than gastric ulcer in tropical communities. Secondly, simple colonization by H. pylori is not enough to lead inevitably to peptic ulceration. This suggests that two or more factors have to act. The obvious second candidate is smoking. However, smoking does not seem, as judged as an accessory factor in the genesis of ulcer complications, to have more than a marginal influence on ulcer occurrence, nor does alcohol intake. This position is not very different from that taken by Doll and his colleagues over 40 years ago; ‘smoking can sometimes be a factor in the production or the maintenance of a peptic ulcer’. Eradication of the organism does seem enough to result in prolonged, probably permanent, healing, which argues that H. pylori persistence is the critical factor in maintenance of the disease, and that the likelihood of re-infection is low. Recent evidence indeed indicates that rates of re-infection with H. pylori in children are low. This is consonant with the birth cohort hypothesis of early life determinants of ulcer risk in the sense that it suggests that H. pylori infection might be acquired early in life, or not at all. The existence of other factors influencing
liability to ulcer or its complications may be underemphasized. Simple calculations of the amount of disease which can be accounted for by NSAID exposure and H. pylori infection emphasize that these are insufficient. Increased risk, independent of other factors, seems to occur with vascular disease, but other influences may be important, thus there have been several descriptions of increased ulcer, or ulcer recurrence, risk in patients with herpes simplex.23,24

Cohort and clinical data have suggested that the tide of ulcer is now going out. The reasons are not entirely clear. Practitioners now commonly eradicate H. pylori in those found to be infected, whether or not they have ulcer. Smoking, at best a minor risk factor, may be becoming less prevalent, at least in men, and the use of selective cyclo-oxygenase antagonists plainly reduce the risk of ulcer and its complications,25,26 but the water was receding before these had much or any impact.

References
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