The possible causes of the pandemic of peptic ulcer in the late 19th and early 20th century

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ABSTRACT

- *Helicobacter pylori* is established as a cause of peptic ulcer (PU).
- Less well recognised is that an epidemic of PU began around the middle of the 19th century, reached a peak at the turn of the century, and is now on the wane.
- As the epidemic developed, the risk of PU increased in successive generations throughout life. Then the epidemic diminished in successive generations.
- The risk of gastric ulcer (GU) was highest in people born around 1885, while the risk of duodenal ulcer (DU) was highest in those born about 10–30 years later.
- *H. pylori* infection offers an inadequate explanation of the PU epidemic.
- Although the epidemic coincided with a major rise in cigarette smoking, PU then declined in spite of an increased incidence of smoking.
- None of the other possible causes of ulcer (non-steroidal anti-inflammatory drugs, stress or diet) satisfactorily explains the epidemics of GU and DU and their asynchronicity.
- The best, but inadequate, explanation for the epidemic is the coincidence of the acquisition of a new potent strain of *H. pylori* in childhood and the uptake of smoking in adult life.

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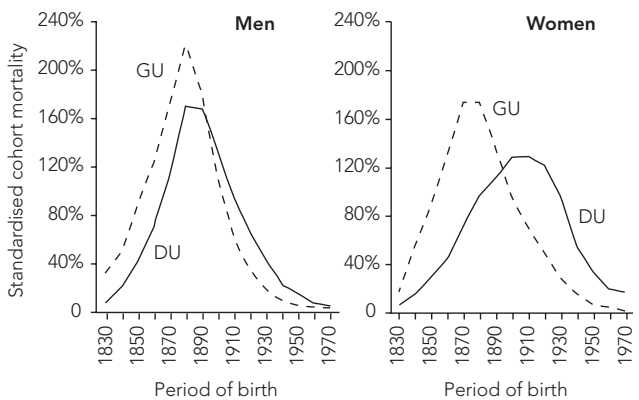
In Western countries, we are seeing the waning of a prolonged epidemic of peptic ulcer (PU) that began in the 19th century. In the 1960s, Susser and Stein first drew attention to the strange temporal behaviour of PU mortality.[1] In the early 19th century, there was a high prevalence, in young women of the servant class, of acute gastric ulcer (GU) that tended to bleed or perforate at the gastric cardia.[2] Remarkably, at the turn of the 19th century, this phenomenon disappeared, but was followed by an increase in the incidence of perforated juxtapyloric ulcers, initially in young and middle-aged men and later in older men. Extensive official data show that in the United Kingdom there was a plateau and then a decline in GU mortality and, after a lag of about 5 years, in duodenal ulcer (DU) mortality. In England and Wales, the risk of ulcer appeared in people born in the middle of the 19th century, with GU and DU reaching their peak in those born around 1885 and 1890, respectively.[3] The risk of death from ulcer rose with age for both sexes, peaking in those born in the late 19th century and then falling steadily to current vanishingly small rates in young people in contemporary Western society (Box).

The geography of these phenomena is intriguing, with a similar cohort effect demonstrated in Japan,[4] Switzerland,[5] New York,[6] Australia[7] and several European countries.[8] There are also data on social class differences. For England and Wales, data available from 1921 show that mortality rates for both GU and DU fell (in younger age groups) with increase in socioeconomic status, but that the trend reversed in old age. Susser and Stein speculated on whether this was related to the early phases of urbanisation or nutritional factors in the UK at the turn of the century,[1] but similar data from Switzerland and Japan, despite their different social conditions, make these explanations unlikely. The possibility that the fall in prevalence of PU was the result of better treatment has been discounted by the long history of use of bismuth preparations for treatment of dyspepsia and their known inhibitory effect on *Helicobacter pylori*.[9]

In seeking a unifying explanation, the major factors to be examined are *H. pylori*, non-steroidal anti-inflammatory drugs (NSAIDs), smoking, stress, alcohol, dietary factors, physical activity and heredity.

Standardised cohort mortality ratio of gastric ulcer (GU) and duodenal ulcer (DU) analysed separately for men and women from England and Wales*



*From Sonnenberg A. A personal history of giving birth to the cohort phenomenon of peptic ulcer disease. In: Marshall B, editor. *Helicobacter* pioneers. Singapore: Blackwell Science Asia, 2002: 56. Reproduced with permission from Blackwell Publishing. ◆

H. pylori

Since the Nobel Prize-winning demonstration of the role of *H. pylori* in PU, there has been a widespread assumption that *H. pylori* is the cause of PU and so implicitly of the epidemic.[10] Baron and Sonnenberg[11] have suggested that an epidemic of a potent strain of *H. pylori* sweeping the world was the cause of the ulcer epidemic, and there are temporal, geographic and theoretical arguments to support this. While there may be reluctance to accept the potent *H. pylori* strain explanation, a birth cohort phenomenon in tuberculosis[12] shows fascinating parallels to the time course of PU: "A plethora of studies ... implicates some sort of generation effect in earlier life experience."[13] This fits neatly into the concept of the childhood acquisition of *H. pylori* leading to an epidemic of PU.[14] Other examples of epidemics of infective disease sweeping the planet include diphtheria (from 1858) and scarlet fever a few decades later.[15]

The data show that people infected with *H. pylori* have a relative risk (RR) of 1.6–5.7 (mean, 3.3) of developing PU compared with non-infected people.[16-18] Calculation of the population attributable risk (PAR) (ie, the proportion of disease cases that can be attributed to a particular factor) shows that, in recent series, *H. pylori* accounts for only about 50% of PU.[19] This is consistent with the evidence reviewed below for other contributing factors. Even if the original pandemic strain were more pathogenic, with, for example, 90% of the population infected and an odds ratio (OR) of 5.0 of developing PU, the PAR (0.78) would still fall short of 1.00, leaving a role for factors such as smoking, which was very prevalent during the same time period.

NSAIDs

Despite a large body of evidence suggesting a role for NSAIDs in causing ulcers, especially in elderly women, aspirin was not available until 1899. Moreover, the first non-aspirin NSAID, indomethacin, was first marketed in 1966, thus excluding NSAIDs as a cause of the PU epidemic.

Smoking

There is evidence that smoking increases the risk of PU. An OR of 2.2 is typical, and a 40-year study of male doctors in the UK has shown a threefold increase in the risk of death from PU in current smokers.[20]

Until the mid 19th century, smoking of coarse pipe tobacco was usual, but about that time, a massive increase in cigarette smoking began.[21] British soldiers returning from the Crimea had seen their Turkish allies using cigarettes; tobacco became more affordable; newer curing methods produced milder tobacco; and, in the United States, Buck Duke used advertising, developed packaging and improved cigarette-making machinery so that cigarettes could be produced cheaply. All wars have led to an increase in cigarette consumption — clearly evident by World War I. In the US, UK, Germany and France, per capita consumption rose between 1920 and 1965, then declined.[22] While these facts support a role for smoking in ulcer epidemics, they ignore one important finding. The rise in tobacco use was largely confined to men. Not until their partial liberation after World War I could women smoke and retain their societal reputation. Yet the PU epidemic affected both men and women. Moreover, in the late 20th century, smoking in women increased while ulcer prevalence fell.

Dietary factors

Alcohol

There is little evidence of an association between alcohol use and PU. A study of UK doctors by Doll et al found no association in 13 years of follow-up.[23]

Fibre

The conflicting data do not support a major role for fibre in causing the PU epidemic.[24]

Caffeine

Given the data and the time course of the PU epidemic, there is little in favour of caffeine as a causative factor in PU.[25]

Sugar

There is some evidence of a link between sugar intake and DU, but not GU,[26] and it does not explain the epidemic.

Dietary salt

There is good evidence of an association between dietary salt and GU, but not DU.[27]

Stress

The sparse evidence for a link between stress and PU is beset with methodological problems. A follow-up of 5388 people in the first US National Health and Nutrition Examination Survey (1986–1992) found a clear positive dose–response curve. Those with the highest level of stress had an adjusted RR of 2.9 (95% CI, 1.2–7.5) of developing PU.[28]

On balance, we can accept a link between stress and PU, but it does not really explain the epidemic.

Physical activity

There is a link between physical activity and PU, and the coincident fall in PU prevalence and in heavy physical work in Western countries typifies this. However, the long-term time trends of occupational workload and its underlying cohort pattern are different from those of PU.[29]

Heredity

A role for hereditary factors in PU is clearly delineated by several Scandinavian studies of large groups of monozygotic and dizygotic twins, reared together and separately. The evidence indicates that 39%–62% of the susceptibility to PU is explained by hereditary factors, the rest by environmental ones.[30,31] There is also a major role for heredity in *H. pylori* acquisition (63% attributable to genetic factors), but genetic influences for developing PU are independent of those for acquiring *H. pylori*, and the transition of *H. pylori* positivity to PU is due to environmental factors.[32] There are two significant implications of these data. Firstly, the sum of the PARs for PU (the joint effects of heredity on PU and *H. pylori* colonisation) exceeds 1.00. Secondly, it is only through these factors that heredity can be considered as having a role in the PU epidemic.

Conclusion

We are left with very inadequate explanations for the waning epidemic of PU in recent years. Why young women of the servant class in the first half of the 19th century should have developed gastric ulcers is a total mystery. The next epidemic, beginning in cohorts born before 1885 and with a 5–10-year gap between GU and DU, is nearly as mysterious. Both *H. pylori* and cigarette smoking can claim a major responsibility in terms of timing. Neither, however, explains the rise in ulcer prevalence followed by a steady decline in prevalence and mortality rates while *H. pylori* colonisation rates remained high in the elderly.

A change in the *H. pylori*–human relationship along the lines of the *Mycobacterium tuberculosis*–human relationship may play a role. Certainly, while we know that *M. tuberculosis* is essential to development of tuberculosis, other factors are involved. There is

overwhelming evidence that its major decline in Western society pre-dates and has been little influenced by medical intervention.[33]

The use of aspirin or other NSAIDs can not account for the PU epidemic, as they were not available in the 19th century, when the epidemic started.

While the beginning of the epidemic of PU in Western societies could have been caused by the coincidence of an epidemic of a highly pathogenic strain of *H. pylori* and the rapid growth of tobacco smoking, the subsequent course of the epidemic does not favour this simple hypothesis. An increase in tobacco smoking in the US between 1920 and 1960 occurred at the same time as a fall in incidence of PU. An alternative explanation is a gradual fall in the pathogenicity of *H. pylori* during the 20th century, similar to the apparent fall in the pathogenicity of organisms such as those causing scarlet fever and tuberculosis, both quite unrelated to the development of antibiotics.

In summary, the best hypothesis at present is that there has been an epidemic of PU at least partly due to the combination of *H. pylori* and cigarette smoking and that it will disappear from the list of important gastrointestinal disorders before we fully determine its cause.

Competing interests

None identified.

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