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REPRINTS AND REFLECTIONS

Civilization and peptic ulcer*

Mervyn Susser[a] and Zena Stein[b]

Remarkable changes have occurred in the sex and age incidence of peptic ulcer in North-West Europe. The fluctuations over the previous hundred and fifty years were studied by Jennings (1940).[1] He examined the incidence of perforations, which provide perhaps the most uniform index of the incidence of ulcers for the total period. His interpretation suggested that during this period there had been three observable syndromes: perforations of acute gastric ulcers in young women; perforations of duodenal ulcers in young and middle-aged men; and perforations of gastric ulcers in older men.[1]

Perforations began to be noted with increasing frequency at the beginning of the 19th century. Half of all perforations were then in young women in their twenties, and these reached a peak in the latter half of the century. They seemed to be *acute gastric ulcers,* which caused death from perforations near the cardia, or from haemorrhage.[1,2] By the end of the century this condition had begun to disappear. But even in 1905 the Registrar General was able to write: 'Gastric ulcer does not appear frequently as a cause of death until the attainment of the reproductive period, when the female rate greatly exceeds the male, while at later ages the male rate is in excess'.[3]

The common perforations of today made an appearance only at the beginning of the 20th century; these are *juxta-pyloric ulcers* occurring mainly in young and middle-aged men.[4] Studies up to 1955 show a continuing trend of increase in perforations of peptic ulcers in men.[5,6] These changes in perforations were reflected in the death-rates. Because of the sharp rise in morbidity and mortality during this century, peptic ulcer, particularly of the duodenum, has earned a place as one of the 'diseases of civilization'.

In the last decade, however, there were signs that the volume of peptic ulcer had at last reached a peak and was beginning to fall. A halt in mortality from *gastric ulcer* was noted in the early 1950s, and it then seemed possible to ascribe this to better treatment.[7] Subsequently the death-rate has continued to fall, and sickness statistics show the same trends. The decline is found in sickness-rates reported from general practice, from the Army, and from insurance certificates.[8–11]

Trends for duodenal ulcer are similar, but follow about five years behind. In the mid 1950s death-rates reached a plateau, and then began to fall. This fall can also be seen from the census of clinically diagnosed peptic ulcers in York, and from the duration and the number of spells of sickness absence.[12] As yet it does not appear in statistics of the last decade from general practice and from the Army, both of which showed stable rates.[8–10]

All these trends together suggest that we are observing a recession of the peptic-ulcer syndrome. This has affected the age-groups unequally. Since the war, mortality from gastric and duodenal ulcers has declined in young men and women, although recently it was still rising at ages over 65 (Figure 1*a, b, c, d*). One possible explanation is that the fluctuations in peptic-ulcer rates represent a *cohort phenomenon,* and that each generation has carried its own particular risk of bearing ulcers throughout adult life. In order to examine this hypothesis the experience of each generation or cohort must be followed separately through its life-cycle.

Analysis by Cohorts

Support for the cohort hypothesis can be found from age changes over time in the manifestations of peptic ulcer. These are apparent in three sets of data—namely, age-specific death-rates, perforations, and social-class death-rates.

Death by age and sex

The data for peptic-ulcer mortality can be cast in the form of a cohort analysis by plotting the deaths in each age-group by year of birth instead of by year of death. In this way the death-rates of separate generations can be followed as they grow older through the years. Technical and theoretical questions raised by this method have been discussed by others.[13–16] In Figure 2 the points along each curve represent the death-rates of successive generations at given ages. The death-rates of a particular generation, as it grows older, are read by passing vertically from curve to curve, along the broken lines which join the points plotted above the year of birth of the generation.

From the middle of the 19th century the risks for successive generations increased to a peak and then declined. A detailed study of death-rates shows that for gastric ulcer in males the generation born around 1885 carried the highest risk, and for duodenal ulcer in males the generation born around 1890.† For females, the graphs are less regular and more difficult to interpret. For all generations in both sexes, however, the risk of death from both gastric and duodenal ulcer can be seen to rise steadily with age.

[a] Department of Social and Preventive Medicine, University of Manchester and Salford Health Department.

[b] Mental Health Research Fund, Department of Social and Preventive Medicine, University of Manchester.

* Read at the annual scientific meeting of the Society for Social Medicine, September, 1961. Reprinted with permission of *The Lancet*. Susser M, Stein Z. Civilisation and peptic ulcer. *Lancet* 1962;**20 January:**115–19.

† *Gastric ulcer* has been recorded by the Registrar General as a cause of death annually since 1901. *Ulceration of the Intestines* was recorded in 1900, not in 1901, 1902, 1903, 1904 but again from 1905 to 1910, and in our graphs this has been classed for convenience as 'duodenal ulcer'. The term '*duodenal ulcer*' has been recorded regularly from 1911.

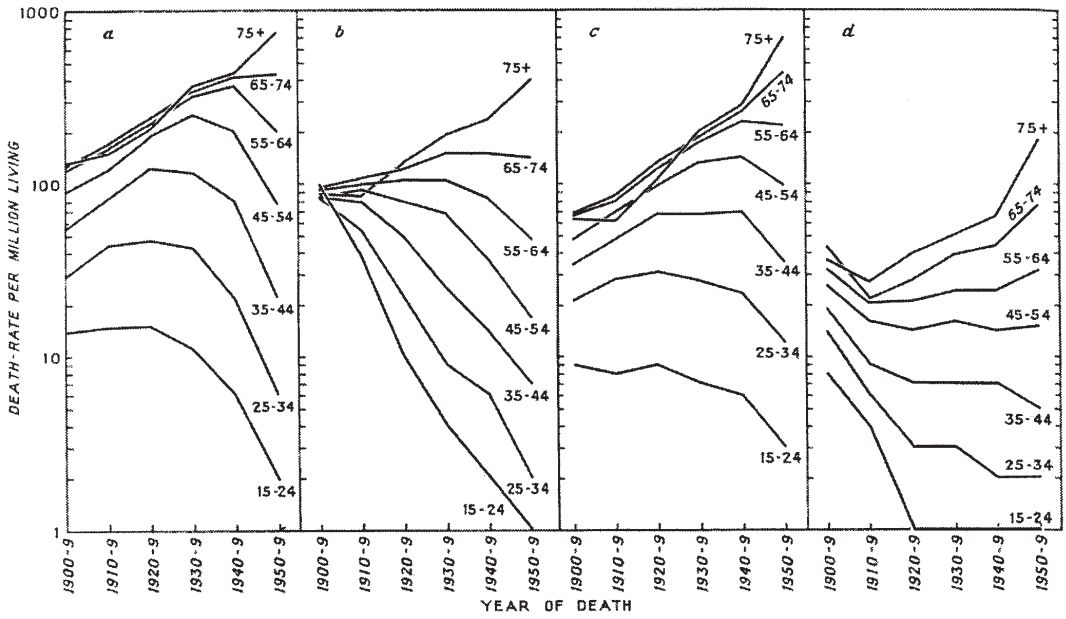

Figure 1 Deaths from peptic ulcer by age and sex and year of death. (a) Gastric ulcer: males. (b) Gastric ulcer: females. (c) Duodenal ulcer: males. (d) Duodenal ulcer: females

Mean rates for 10-year periods were calculated from the Annual Reviews of the Registrar General. Populations include non-civilians. Correction Factors for pre-1940 data to allow for the change in death certification (males 1.034, females 1.042) have not been used. Log. graphs. The Tabulated data on which the figures are based may be obtained from the authors.

Perforations

The average age at which perforations occur has increased year by year. This is shown in the figures for Glasgow from 1924 to 1953, and also by those for Aberdeen and North-East Scotland from 1946 to 1956.[5,6,17] This upward shift of the mean age of perforations concords with the ageing of the generations exposed to the highest risks.

A recent survey of perforations in two hospitals in the South of England suggests that these are becoming fewer each year, and the reduction is particularly marked at young ages.[15] This trend towards a decline in younger generations also concords with the cohort hypothesis.

Social class

Analysis of changes in mortality by social class over the last three censuses again shows upward age-shifts which suggest that each generation is carrying forward its own particular risk. At each successive census, a more or less regular pattern of mortality recurred in age-groups which were older by the interval which had elapsed between the censuses.

Statistics relate only to males, and are first available for the period of the 1921 census.[18] From 1921 to 1923 death-rates from gastric ulcer showed a social-class gradient increasing from the higher to the lower classes up to the age of 55; this gradient flattened between 55 and 70, and was reversed over the age of 70. A decade later, in the period 1930–32, the gradient increasing from higher to lower classes was apparent up to age 65 and then reversed—i.e. ten years older than at the previous census. In the period 1949–52 the gradient increasing from higher to lower classes persisted up to the age of 70 before it flattened (Figure 3*a*). Although death-rates in old age must be interpreted with caution, the trend fits the expectation.

Social-class mortality from duodenal ulcers shows similar age shifts from census to census. In each case the changes affected a generation a few years younger than with gastric ulcer, just as happened with overall mortality rates. For duodenal ulcer in the period 1921–23 there was a slight social-class gradient up to the age of 45, with death-rates increasing towards the lower social classes; after 45 the social-class gradient was reversed with the higher rates in social class I and II. A decade later, at the 1931 census, a similar reversal of the social-class gradient appeared first in the age-group 55–59—i.e. ten years older (although some flattening of the gradient is evident in the age-groups 45–54). Finally, at the time of the 1951 census, twenty years later, the reverse gradient appeared only over the age of 70. At younger ages in the period of the 1951 census, the gradient increasing towards the lower classes had become more conspicuous. This came about because death-rates in young and middle-aged men of the higher social classes had declined, while rates in the lower social classes had changed little in these age-groups.

One may perhaps infer that morbidity shows similar social-class trends, by comparing the survey of men in industry after the war with a recent survey in York.[12,19] No significant social-class gradient was found among the industrial workers (most of whom were under 65), whereas a decade later a gradient rising towards the lower classes was apparent in York.

Thus the recession of the wave of duodenal ulcers seems to have begun in young men of the higher social classes. Perhaps also men

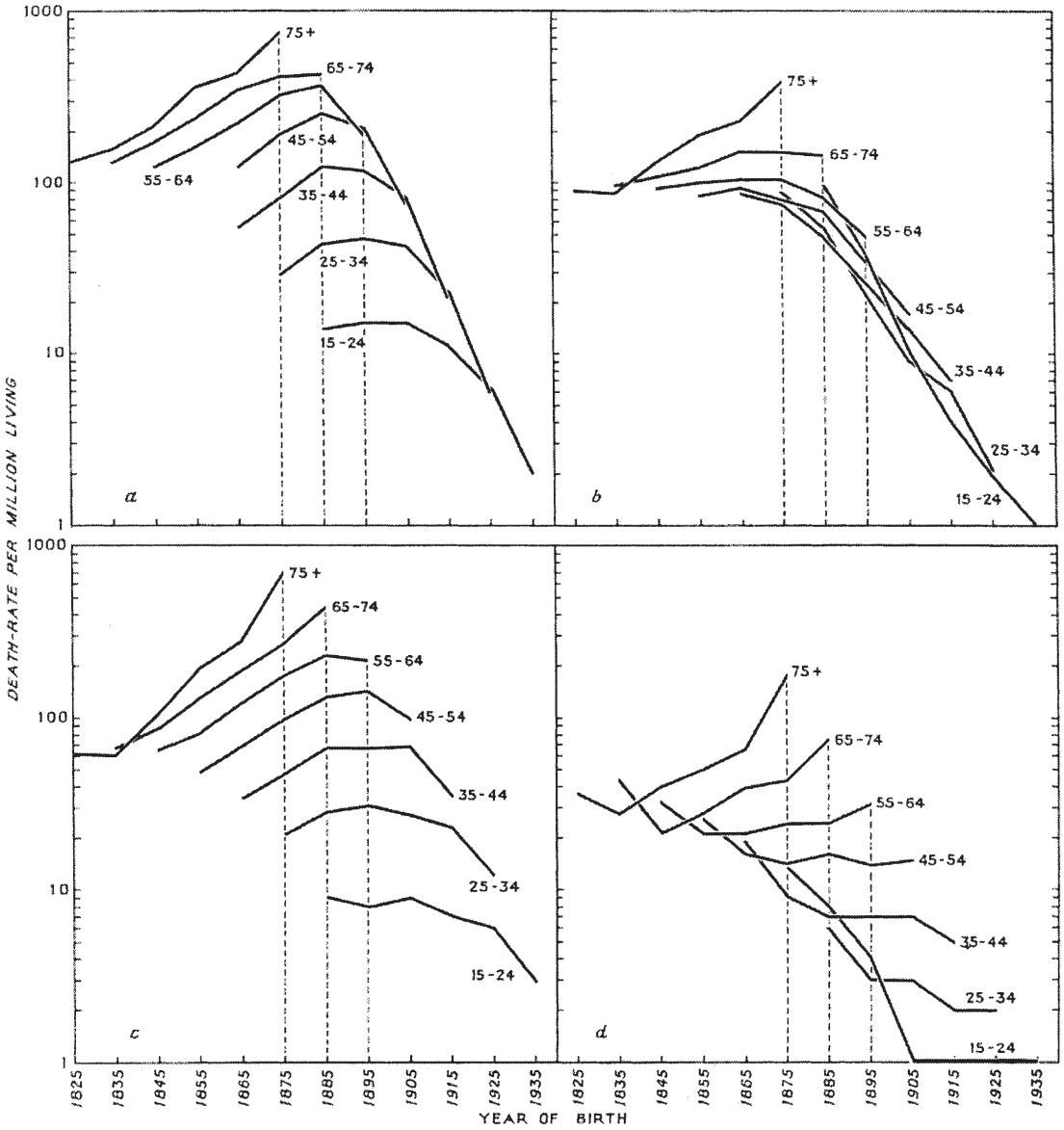

Figure 2 Deaths from peptic ulcer by age and sex and year of birth. Cohorts named by central year of birth. (a) Gastric ulcer: males. (b) Gastric ulcer: females. (c) Duodenal ulcer: males. (d) Duodenal ulcer: females

Mean rates for 10-year periods were calculated as for Figure 1. Log. graphs.

of the higher social classes were first affected when the incidence of peptic ulcer began to rise early this century; but social-class statistics do not go back far enough to support this inference.

We have not here considered the complicating effects of social mobility on social-class patterns, but for the purpose of analysis have tended to treat social classes as static categories.

Discussion

The fluctuations in peptic-ulcer syndromes seem to vary with the experience of cohorts, and this makes interpretations other than real changes in incidence—for example changes in *diagnostic practice*—unlikely. Nevertheless, they must be considered.

The effects of greater accuracy in diagnosis and in certifications would be expected to run counter to the current decline in peptic-ulcer death-rates. The statistical distortions caused by fashions in diagnosis, which like other fashions show both secular trends and social mobility, can also be discounted, for changes in incidence seem to have preceded changes in medical opinion. Thus in the present instance it is the fashionable view that the disease is increasing, although the rates are falling. In a second instance, duodenal ulcer was held to be a disease of young men until recently, when Doll *et al.* (1951) showed it to be common among middle-aged and elderly men. The fashionable clinical view probably arose from the experience of physicians earlier in the century, for the young patients of these physicians

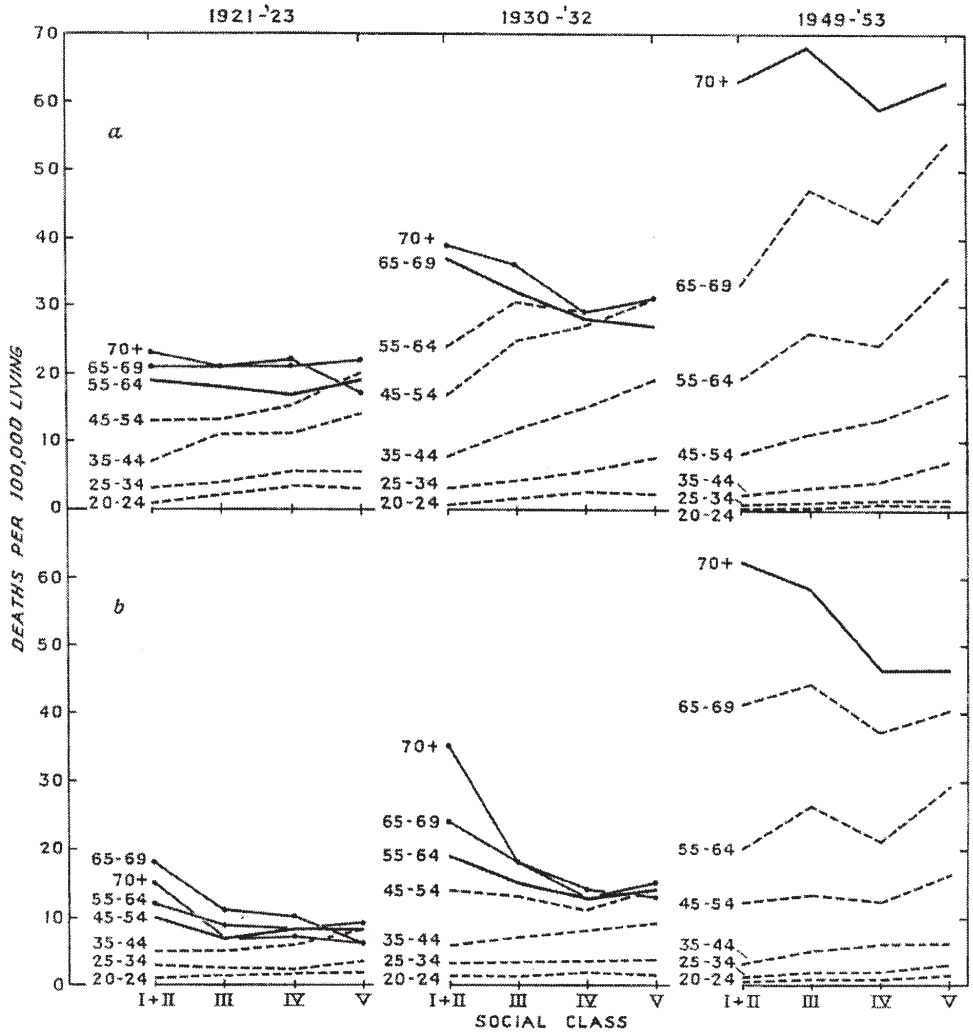

Figure 3 Deaths from peptic ulcer by age and social class at three successive censuses. (a) Gastric ulcer: males. (b) Duodenal ulcer: males

later formed the middle-aged cohorts observed by Doll *et al*. Clinical impression again lagged behind reality.

The social-class gradient now apparent at older ages might be ascribed to unequal and *selective survival* between classes. Sufferers from peptic ulcer in the lower social classes might have died at young ages, leaving survivors of the higher classes to raise the mortality rates in old age. However, the evidence presented here shows that those cohorts who now have high death-rates also had high death-rates in youth.

Uneven distribution of treatment in various age and class groups seems not to account for their unequal death-rates. The high mortality among the older age-groups in the higher social classes is contrary to what would be expected, unless the treatment were harmful, for all studies show that the higher social classes make more use of medical services. The recent popularity of partial gastrectomy is unlikely to be an important cause of the decline in perforations. Cures by gastrectomy could hardly account for the steady rise in the mean age of patients admitted to hospital for perforations, a rise which in Scotland began in 1924. Furthermore, no known treatment seems to be so effective that it could have produced the fall in morbidity suggested by recent statistics.

None of these alternative explanations, therefore, is in accord with all the facts. Indeed, the existence of a cohort pattern is in itself strong evidence that observed changes do not arise from changes in diagnostic practice or treatment. In addition, the prediction that the disease is on the decline, and that the pattern is consistent with a cohort phenomenon, has survived its first test. It was put forward as the tentative explanation for the trend of death-rates up to 1955.[20] Since then statistics for the period 1956–59 have been published by the General Register Office.[3] The trend of these statistics is consistent with what was predicted in practically every age and sex group for both gastric and duodenal ulcer.

Aetiology

On this analysis duodenal ulcer is on the decline and cannot be regarded simply as a disease of civilization, in the sense that it is caused mainly by stresses common to industrial society; for these might be expected to increase or at least to continue as

our society grows more complex, and as a greater proportion of the population is caught up in urban modes of life. However, it could be a disease of an early phase of urbanization. In the most recent times urban stresses may have been outweighed by other consequences of industrialization, such as the abolition of gross poverty and the greater social security in modern Britain. Moreover, changes in the host must also be considered as a cause of fluctuations in disease. Large sections of the population may by now have learned to adapt to the demands of industrial society, so that these are felt as less stressful than before.

On the other hand, the cohort phenomenon might reflect upheavals which have had an uneven impact on past generations. The timing of the first world war, and the unemployment of the 1930s, roughly fit the fluctuations, and the cohorts with the highest peptic-ulcer death-rates were also the chief victims of the first world war. The immediate effects of war are evident in the rise in perforations and deaths from peptic ulcer which followed air-raids and the stress of war.[5,18,21,22] Perhaps in a chronic condition such as this acute events might precipitate prolonged effects.

We have begun to explore possibilities of this kind in populations with different experiences, as for example in Sweden and the United States. Analysis by cohorts may assist us in separating the contribution of past from present experiences in the configuration of this chronic disease.

Summary

Peptic-ulcer death-rates in England and Wales reached a peak in the 1950s and have since begun to decline; signs of a decline can also be found in sickness-rates. These fluctuations are interpreted as a cohort phenomenon. The generations born in the last quarter of the 19th century seem to have been exposed to the maximum risk, and they carried this risk throughout adult life. The wave of gastric ulcers began earlier, and receded earlier, than the wave of duodenal ulcers.

Ideas on aetiology are considered in the light of this interpretation.

We wish to thank Mrs Ann Pendred for her great help with abstracting data and drawing graphs. We are indebted to the department of medical illustration, Manchester Royal Infirmary, and Mrs A Fish for help with illustrations, and to the General Register Office who supplied estimated populations from 1838. We are grateful to Dr AM Adelstein and our other colleagues in the department of social and preventive medicine, Manchester University, for advice and criticism.

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Commentary: Civilization and peptic ulcer 40 years on

Mervyn Susser and Zena Stein

We are happy to see the *International Journal of Epidemiology* reprint one of our papers[1] some 40 years after publication. We are not among the deeply sceptical who would deny that understanding marches on with time. Sometimes, as with peptic ulcer, it is a slow march. Some of the mist and mystery surrounding the condition, as well as a degree of disbelief our conclusions provoked, have cleared. Points of entry to much that seemed impenetrable can be discerned.

Here we take up the editor's invitation to tell how the work came to be written. For us, the story begins in 1959, when MS received a letter from the Editor of the *Practitioner*. That journal planned to publish a symposium on peptic ulcer, and he hoped MS would write a review of its epidemiology.

The invitation was a great surprise. We were not long out of troubles in Apartheid South Africa. With equal surprise and great good fortune MS had been appointed Lecturer in Social and Preventive Medicine at Manchester University under Professor C Fraser Brockington. Soon after moving there, ZS was appointed Research Fellow. In epidemiology, both MS and ZS were untaught novices (in the original sense). We could only assume a wand had been waved by one of the benevolent spirits whose paths we had somewhat fleetingly crossed—perhaps Jeremy Morris, or Theodore Fox at *The Lancet*, or Robert Platt or Douglas Black in the Manchester Department of Medicine, or Cicely Williams (discoverer of Kwashiorkor) at the School of Hygiene. We had at most a half-dozen joint or separate publications of any sort, no track record in the subject of peptic ulcer, and no knowledge of the disease beyond the requirements for the Membership of a Royal College of Physicians. Peptic ulcer was then a rarity in the Black South Africans among whom we had worked.

MS set to work on the literature, beginning with Morris' *Uses of Epidemiology*[2] of 1957. This treasure trove of epidemiological observations and lively ideas had entranced us, not least the idea of diseases of civilization and its identification of coronary heart disease, lung cancer and peptic ulcer as rising epidemics among males of the 20th century. He led us to an intriguing history of peptic ulcer perforations through the 19th century and into the 20th, in which Jennings[3] identified three successive forms of perforated ulcer. The first, gastric ulcer in young women, appeared as a new disease in the early 19th century; by the end of the century it was disappearing only to be replaced in the 20th century first by gastric and then by duodenal ulcers predominantly in males. Next, we followed the references to Morris and Titmuss[4] which had the fullest and best analysis of the vital statistics of the disorder up to that time; to the founding field studies of Richard Doll with Avery Jones *et al.*[5,6] on the occupational epidemiology of this disease; and to much else that seemed relevant to the epidemiology of the disorder.

To examine changes over time, we assembled the mortality data of the Registrar General from Statistical Reviews 1900–1959 and the Decennial Supplements of 1921, 1931 and 1951. The cross-sectional view of mortality across each period by age were utterly confusing. Age curves criss-crossed in every direction, with no discernible consistency given no foreknowledge. Figure 1a is a greatly refined example—developed much later and much clearer for that—of what confronted us. The only conclusion one could draw was disconcerting: contrary to received opinion, there was no consistent rise in the mortality of the major persisting forms of the disease.

The notion of a rising epidemic as a disease of civilization, however, implied that it was a product of our continuously developing industrial society. Fifteen years before, Morris and Titmuss,[4] evidently beset in the same way by their large body of data, spoke of 'existing confusion', and found the results 'surprising' and 'unexpected', and reported changing and irregular patterns in the different forms of the disorder over time and among social classes. Nonetheless, their most valiant effort at analysis and interpretation indicated positive associations with the metropolitan concentration of London, with the heavy air raids over England in World War II, and with employment, and negative associations with the massive unemployment of the preceding Great Depression of the 1930s. For them, as well as for us and for many others, all this seemed to point to ready psychosocial hypotheses about causes connected with the stresses and strains of a rapidly changing society.

One day while MS was staring balefully at the mortality data as he had come habitually to do, ZS looked over his shoulder and said casually, 'How about cohort analysis?'. In this regard, we each of us had an arrow in the quiver. Five years before, ZS had taken advantage of a pregnancy for a study leave from the Alexandra Health Centre and University Clinic in an African township outside Johannesburg.* She elected to study under the mentorship of Sidney Kark at his new national training health centre in Durban. Among much else new to us and relevant to our work—which we were doing without any special training whatever excepting our medical degrees and internship—Sidney led her to Wade Hampton Frost's posthumously published 1939 cohort analysis of tuberculosis.[7]

MS met cohort analysis later, early in 1956 in London. Newly arrived and without employment, Dr Fox kindly suggested he might report for the *Lancet* and begin with the next meeting of the Royal Society of Medicine. It turned out to be a memorable

Joseph L Mailman School of Public Health, Columbia University, 600 West 168 St, New York, NY 10032, USA. E-mail: mws2@columbia.edu

* The arrangement was built in to the collective agreement under which, after our internships, we and another married couple undertook to staff four positions at the Centre with the 2.5 full-time-equivalent positions available.

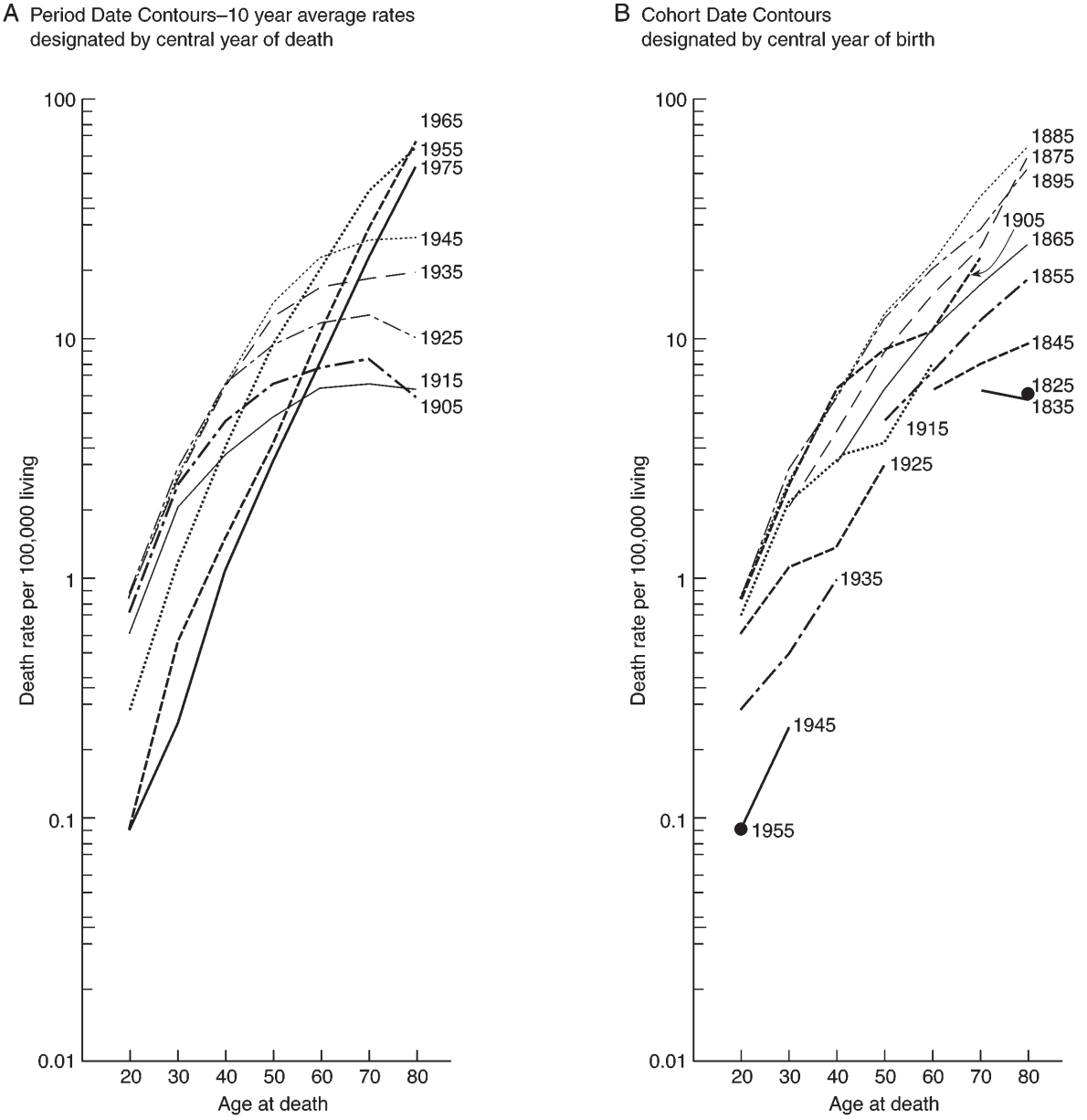

Figure 1 Death rates from duodenal ulcer in males, England and Wales, 1900–77. Reprinted from Susser M *J Chronic Dis* 1982;**35:**29–40 with permission from Elsevier Science

occasion. First one heard Alice Stewart report her unpublished but now famous work on cancer in children following X-rays in pregnancy (Richard Doll and Sir Ernest Kennaway were among the commentators). RAM Case followed with his paper on 'Cohort analysis as an historical or narrative technique', one of the foundation works of the subject to be published later that year.[8]

To return to peptic ulcer, MS followed the lead from ZS, wondering why, as so often, the thought had not also occurred to him. He reassembled the data in conventional form for cohort analysis i.e. 10-year date-of-birth contours (by central year of birth), with year of death along the abscissa and mortality rate along the ordinal. Alas, no evident regularities lit the bleak array of curves. Discouraged, for weeks on end MS resumed staring at the graphs whenever time allowed. Figure 1b is an example of what he had been staring at. Slowly, however, he came to think with relief that he could discern a pattern in the curves for each form of the disorder (gastric and duodenal) and for each sex. Within each cohort, but starting at different points during the 19th century according to the form of the disorder and the sex of the decedent, mortality in successive birth cohorts rose steadily and then declined.

To emphasize the obscurities of the repeated patterns as we then saw them, one need only say that for a longish time Abe Adelstein (then statistician to the department and our close friend and adviser on things numerical and much else) and, ironically, also ZS, wondered if the patterns MS perceived were possibly illusory. After much cogitation, MS settled on a different way of arranging the data, namely in age contours with birth

year on the abscissa so that cohorts are read vertically upward from the abscissa across successive age contours (Figures 2a,b). This device at last made clear the pattern of waxing to a peak for late 19th century births, and then waning through the births of the 20th century.

All will understand by now, in the light of theoretical and technical work on cohort analysis (for instance, by MacMahon and Terry in 1958[9] and many authors since), that inference from it is subject to confounding. In part this arises because generally the cohort approach must be an ecological analysis, but centrally because of the structural and unbreakable linkage between any two of the three variables of birth date, age, and date of observation. Forty years ago, we certainly did not ourselves understand all this. Intuitively, we did understand the need for both external validation of the interpretation and tests of alternative explanations by all means possible.

MS's review for the *Practitioner*, with no more than a mention of the mortality trend, was published with the symposium in 1961.[10] We did report on the new format in London later that year at the annual meeting of the Society for Social Medicine (the annual gathering of the then modest numbers of enthusiasts engaged in the subject). There we were heartened, in the face of doubt and questioning, by the endorsement of our analysis by Richard Doll, the pre-eminent epidemiologist in the field.

While the search for validation proceeded we deferred further publication. The few previous intimations of a decline in mortality or morbidity had been attributed either to the widespread use of gastrectomy or to such other interpretations as selective survival and diagnostic fashion. We had collected morbidity data from several sources, however (the national sickness survey, the British Army, Navy and Air Force morbidity records, hospital admissions, and prevalence rates in cross-sectional field surveys separated by several years). All conformed with the pattern of recent decline cohort by cohort. These findings we reported only briefly in the Discussion section of the now reprinted

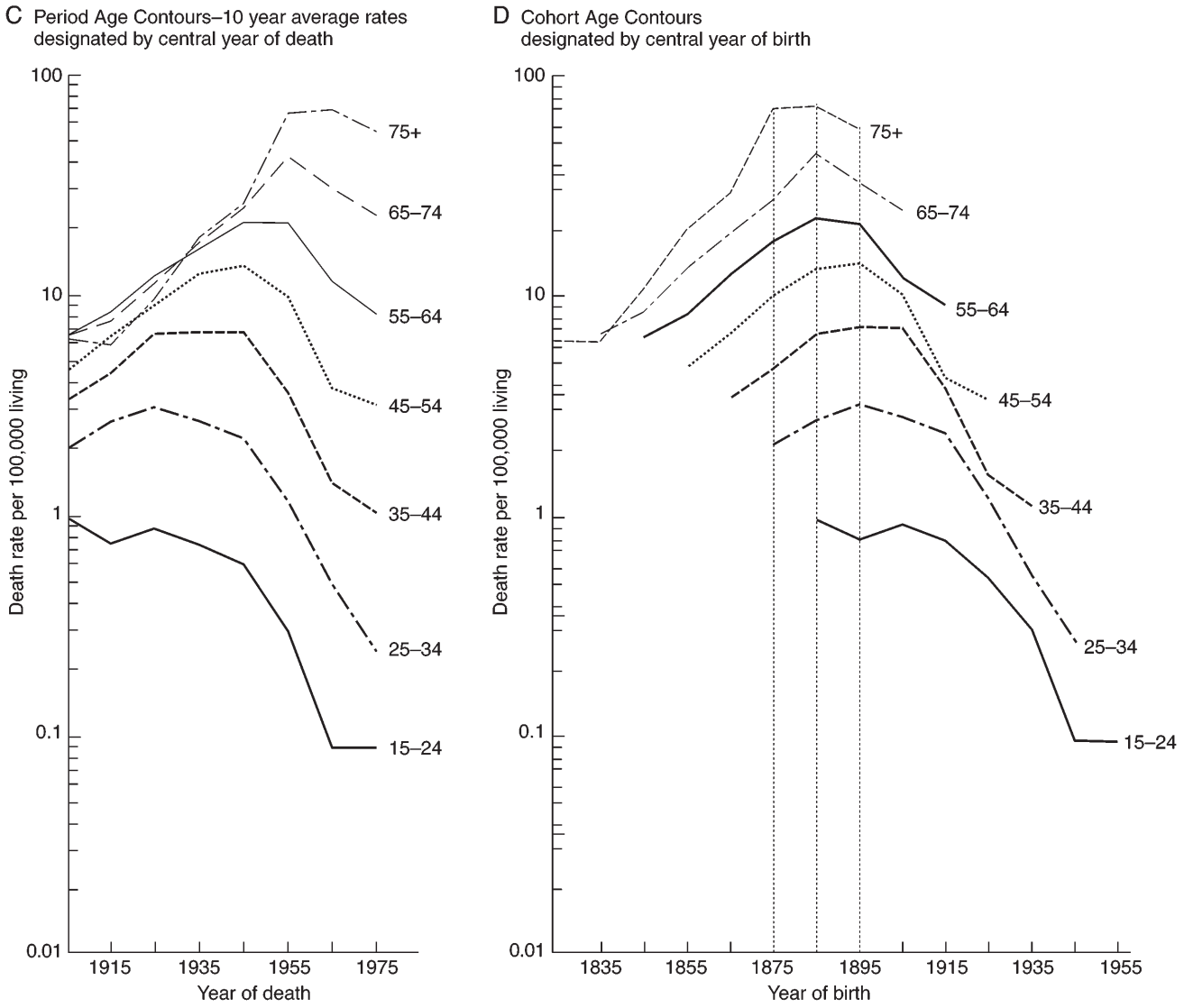

Figure 2 Death rates from duodenal ulcer in males, England and Wales, 1900–77. Reprinted from Susser M *J Chronic Dis* 1982;**35:**29–40 with permission from Elsevier Science

article. For a final test, namely, a prediction of a continuing decline in mortality shifts in social class, we had to await the next census report on occupational mortality of 1971.[11]

In the meanwhile Sonnenberg[12] had applied cohort analysis to national mortality data sets from many European countries to show similar declines, as others did earlier for morbidity data in England and the US. Yet in conversation with MS as late as 1978, two leading internists from a leading American medical school were incredulous, even dismissive, of our account of the history of peptic ulcer and its decline. We cannot deny a degree of satisfaction, not we hope smug, from the present state of the matter.

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Commentary: *Helicobacter* as the 'environmental factor' in Susser and Stein's cohort theory of peptic ulcer disease

Barry Marshall

I am not certain how I became aware of the paper by Susser and Stein in *Lancet* of 1962, I suppose it was from references in another article on peptic ulcer.[1] It did amaze me that 20 years before the discovery of *Helicobacter pylori* the idea of a cohort effect in peptic ulcer had been considered, and various predictions made. Although brilliantly correct about an environmental effect peaking near the turn of the century, Susser and Stein still exhibited some of the tunnel vision regarding 'stress' in all its forms as a peptic ulcer aetiology. One of their hypotheses for changes in ulcer mortality involved urbanization stress, its subsequent 'tolerance' by communities and, more recently, increased affluence lowering the global urbanization stress level.

Susser and Stein's first point was that gastric ulcer perforations in young women were a new disease in the beginning of the 19th century, but a peak of the same disease in older women (the same cohort) occurred in the latter half of the 19th century. According to the original authors, the female epidemic related to 'acute gastric ulcers' of the cardia, a disease characterized by lack of scarring at the ulcer base and location in the top half of the stomach. Similar perforation increases, but for duodenal ulcer in young to middle-aged men, and for gastric ulcer in older men, were later reported.

In the 20th century however, most of the interesting ulcer mortality related to pylor-duodenal ulcers, and occurred in men. Gastric ulcer mortality peaked in the early 1950s and duodenal ulcer mortality peaked in the late 1950s. Of secondary interest is the fact that the supposed 'executive ulcer' never really existed in that no socioeconomic gradient existed for duodenal ulcer in the early 20th century, and its actual predilection for the working classes was well documented after 1940.

To explain some of these observations, we might try to place *H. pylori* into the above scenario. Although it is difficult to determine the prevalence of *H. pylori* in previous generations, some assumptions can be made based on the observed age-related sero-epidemiology in the US and from biopsy surveys of Estonians and Japanese in the past 50 years.[2,3]

First, we may assume that *H. pylori* was ubiquitous at the turn of the 20th century. Faecal-oral contamination of the water supply was present, families were large, children shared beds and in-house piped running water was uncommon so washing

University of Western Australia, Department of Microbiology, Room 1.11, L Block, Queen Elizabeth II. Medical Centre, NEDLANDS WA 6009, Australia. E-mail: admin@hpylori.com.au

was difficult. Thus, most western countries had conditions now only seen in developing countries.

Second, there was a sharp decline in *H. pylori* after about 1960. According to the seroepidemiology reported in the 'epidemiologists survey'[4] and the 'Kaiser cancer study' described by Parsonnet,[5] the majority of 40-year-olds had *H. pylori* in the 1960s but then the prevalence decreased by half every 10 years after that. Similar findings were reported from the Busselton survey in Australia where almost no new cases, and even a slight decrease in infection, was seen between 1970 and 1990.[6] *Helicobacter pylori* declined because of improved hygiene, smaller families and better socioeconomic conditions, but the decline accelerated after 1970. I recall that in 1976 amoxycillin was introduced in Australia and that my children consumed so many antibiotics for ear and throat infections that *Helicobacter* would have had a very difficult time establishing itself.

Although Sonnenberg[7] has considered and discounted a role for aspirin as an explanation of the 19th century ulcer perforation epidemic, my 'amoxycillin theory' has parallels in that era. An example of 'antibiotic effect' on *H. pylori* was seen in the case of Arthur Morris who infected himself with *H. pylori* in 1986.[8] Initially, Morris developed severe pain lasting 48 hours, almost requiring laparotomy. This must have reflected gastric erosion or ulceration in the presence of acid in the very acute stages of the infection, also described by some others.[9] After very severe corpus gastritis developed on day 3, Morris became achlorhydric, without symptoms, for several months. During that time gastric pH remained above 5. Subsequently, Morris treated himself with doxycycline, suppressing but not eradicating the *H. pylori*. After this, acid secretion returned, although gastritis persisted in the antrum. So it is well documented that an asymptomatic low-acid state can convert to an acid secreting *H. pylori* infected state, merely by temporary suppression of *H. pylori.*

Thus, if people in the 19th century were infected with *H. pylori* in childhood, they would have had rather poor acid secretion and 'developing country' gastric histology. However, after exposure to 'antibiotic' they may have switched to the 20th century pattern of acid secretion in the presence of more localized antral gastritis, much as Morris reported. But did antibiotics exist in the 19th century? At least for *H. pylori*, the answer is yes. Use of bismuth was first popularized in Germany about 100 years before, mainly as bismuth subnitrate. In England, in 1864, Ogle advocated the use of bismuth subcitrate 'the fruit acid of bismuth' for 'nervous disorders of the stomach'.[10] So there is no doubt that suppression of *H. pylori* was available and, perhaps as another coincidence, would have been especially advocated for young women with 'nervous stomach'. Use of bismuth as a component of gastric medicines and antacids throughout Europe and the US persisted until the present time.

An alternative theory proposed by Blaser[11] would contend that the changes are connected in some way to a change in the predominant gastric populations of *H. pylori*, with pre-20th century people being continuously infected with multiple strains, whereas in recent years single strain infection, with absent virulence genes in many cases has occurred, resulting in changed expression of the disease.

Regardless, once a cohort effect is taken as the basis for changes in age-related prevalence of *H. pylori* several predictions can be made. First, the incidence is closely reflected by the prevalence in the age group 1–10 years. In some locations, for example parts of Japan[12] and New Zealand,[13] the prevalence of *H. pylori* in children is less than 5% indicating that environmental sources of the infection are now quite rare. We can expect therefore that *H. pylori* related diseases such as new peptic ulcer and gastric cancer will almost disappear in the next generation.

The epidemiology of gastric cancer is another issue with controversy still raging. As expected, recent prospective studies show that individuals without *H. pylori*, even in a high-risk population, rarely develop cancer[14] and, already, the incidence of gastric cancer in young Japanese is declining.

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Commentary: The unresolved mystery of birth-cohort phenomena in gastroenterology

Amnon Sonnenberg, Claudia Cucino and Peter Bauerfeind

In the landmark paper written by Mervyn Susser and his wife Zena Stein, it was shown that the temporal trends of peptic ulcer were more closely related to the time of birth of individual ulcer patients than to the time when they contracted their ulcer and died from it.[1] When the original paper was published in *The Lancet* in 1962, the overall frequency of gastric and duodenal ulcer were still rising in the British population. The British birth-cohorts born between 1870 and 1890 carried the highest risk of developing gastric and duodenal ulcer, respectively. As these cohorts grew older and their general age-related mortality increased, the overall number of deaths associated with bleeding and perforated peptic ulcers was still rising in the population. Susser and Stein speculated that eventually, as these high-risk cohorts grew older and their proportion in the population declined, the occurrence and mortality of peptic ulcer would start to fall again. From their birth-cohort analysis of peptic ulcer mortality in England and Wales between 1900 and 1959, Susser and Stein were able to correctly predict a future decline of peptic ulcer disease 10 to 20 years prior to its actual occurrence.

William O Kermack and his co-workers were among the first investigators to speculate about the influence of early-life exposures on disease appearance in adulthood.[2] The analysis of epidemiological data by year of birth was subsequently applied by Wade Hampton Frost and others to study the time trends of tuberculosis and cancer in the US.[3–5] Although it constitutes an established technique in the armamentarium of epidemiologists, birth-cohort analysis is not well explained by most textbooks, and it takes mental effort to be fully understood. In spite of these obstacles *The Lancet* paper has remained part of the common knowledge among investigators interested in peptic ulcer disease. One obvious reason relates to its publication in a widely distributed and prestigious medical journal. The second reason was that people liked the article for the wrong reasons, as it was assumed to provide evidence for the psychosomatic nature of peptic ulcer. Susser and Stein speculated that the stress associated with urbanization in England around the turn of the century led to strong and lasting mental or physical imprints in subjects born during this transitional time period of English history. These imprints rendered subjects susceptible to peptic ulcer disease for the remainder of their life. When stress and psychological factors were still much in vogue to explain peptic ulcer, the influence of 'urbanization' seemed one of the strongest arguments in favour of such an hypothesis.

The Department of Veterans Affairs Medical Center, and The University of New Mexico, Albuquerque, New Mexico, USA.

Correspondence: Amnon Sonnenberg, Department of Veterans Affairs Medical Center 111F, 1501 San Pedro Drive SE, Albuquerque, New Mexico 87108, USA. E-mail: sonnbrg@unm.edu

The Ubiquity of the Birth-cohort Phenomenon

Subsequent epidemiological analyses tested the presence of birth-cohort patterns in statistical data from other countries in Western Europe, North America, and Asia.[6–8] The data from most countries whose vital statistics covered sufficiently long time periods revealed similar trends. In all statistics alike, the time of birth exerted a stronger and more obvious influence on ulcer mortality than the time of ulcer occurrence. Peptic ulcer mortality was highest among birth-cohorts born before the turn of the 19th century, with similar patterns observed in men and women. It decreased in subsequent generations born during the 20th century. Instead of showing the individual cohort-age contours, as done in the original article by Susser and Stein, one can also calculate an average age-standardized cohort mortality ratio (SCMR), which makes it easier to follow the rise and fall of ulcer mortality associated with consecutive birth cohorts. Figure 1 shows the time course of gastric ulcer, duodenal ulcer and ulcerative colitis from England and Wales. (The relevance of ulcerative colitis in the present context will be discussed later.) The peak of gastric ulcer preceded that of duodenal ulcer by 10–20 years in most countries, and in none of the many countries did duodenal ulcer precede gastric ulcer (Figure 1).

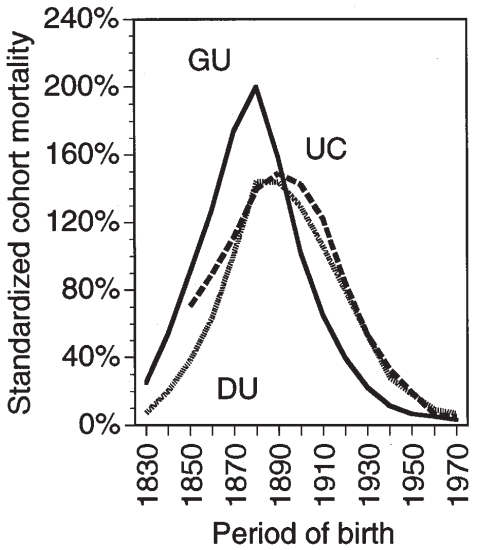

Figure 1 Standardized cohort mortality ratio of ulcerative colitis (UC), gastric ulcer (GU) and duodenal ulcer (DU) in England and Wales, male and female data analysed jointly

This phenomenon was also present in Susser and Stein's original data, but the authors did not take pains to explain it, possibly because the hypothesis of urbanization did not account for such differences in the behaviour of the two ulcer types. Although many of the European countries and the US had experienced an industrial revolution at the beginning of the 19th century and a resultant expansion of their urban population throughout the remainder of 19th century, the socioeconomic changes and their impact on public health and culture, population growth, and the political climate were less dramatic than in England. Urbanization was deemed even less a suitable explanation for the birth-cohort phenomenon.

The Meaning of the Birth-cohort Phenomenon

Since genetically determined mechanisms stay unchanged during historical time periods, the marked temporal trends of gastric and duodenal ulcer disease indicate that their occurrence are largely influenced by exogenous risk factors. The simpler and more consistent pattern obtained by considering the patients' period of birth rather than death implies that influences during or shortly after birth are more important than those during the time of death. A birth-cohort pattern suggests that exposure to the relevant risk factors of the disease occurs during early life between the prenatal period and adolescence. The risk factors must exert their effect within a limited time interval, and the amount or type of exposure must be changing with time. Otherwise successive generations could not exhibit rapidly varying rates of disease occurrence. As the exposure changes over time, consecutive generations, i.e. birth-cohorts, come to reflect its varying influence on the risk of developing the disease.

The relevance of the birth-cohort patterns has been questioned and various critiques have been raised. Some investigators assumed that recent changes in treatment (or diagnosis) had benefited young more than old patients and had, thus, contributed to the differential time trends of old versus young patients. If newer life-saving therapies benefited younger patients more than older patients, for instance, younger age groups would show a more pronounced time-dependent decline of ulcer mortality than older patients. Similarly, the utilization of endoscopic procedures to diagnose peptic ulcers may have been utilized more in young than old patients. A more refined procedure to diagnose abdominal symptoms seemingly reduced the number of true peptic ulcers among young patients, while old patients subjected to less diagnostic scrutiny were still being erroneously diagnosed with peptic ulcers based on symptoms alone that in reality stemmed from other diseases. Other more elaborate schemes were concocted to explain away the birth-cohort patterns. Such arguments failed to account for the fact, however, that in some countries with far reaching vital statistics, the rise and fall of peptic ulcer can be appreciated even in a single age group. Others argued that, considering a case-fatality rate of less than 5%, mortality was an unreliable parameter to assess the time trends of peptic ulcer. The vital statistics are particularly suited to analyse temporal trends of diseases, because they have been recorded for the longest time periods and because they are available from many different countries. Subsequent studies showed that a birth-cohort pattern shaped the time trends of various other parameters of ulcer morbidity besides mortality, such as hospitalization, disability pensions, and perforations.[9–12]

Lastly, people questioned the uniqueness of the birth-cohort phenomenon in peptic ulcer and wondered whether time trends of other diseases would show similar patterns. As a matter of fact, a few other diseases, such as coeliac sprue, tuberculosis, laryngeal cancer, and lung cancer, do reveal birth-cohort patterns, but their individual trends are rather dissimilar. In laryngeal and lung cancer, for instance, it can be related to the acquisition of smoking habits during adolescence. The ascent and decline occur slower and the peak is much broader than in peptic ulcer. Generations born around 1920 are the ones most affected, and the rise and fall of smoking-related cancers show primarily in men. Compared with men, the initial rise appears delayed in women, and the recent decline appears more blunted in women than men.[13–15] Ulcerative colitis is the only other gastrointestinal disease found to present with a clear-cut birth-cohort pattern (Figure 1).

A Strange Link with Inflammatory Bowel Disease

Similar to peptic ulcer disease, the epidemiology of ulcerative colitis and Crohn's disease is also characterized by marked sociodemographic, geographical and temporal variations. Such variations point to the existence of environmental influences that must be shaping the occurrence of both types of inflammatory bowel disease (IBD). In the age-specific mortality data of ulcerative colitis from England and Wales, the cohort-age contours are aligned to form a clear-cut hyperbola with its peak located around 1890.[16,17] Subsequent analyses confirmed similar birth-cohort patterns in the time trends of ulcerative colitis from most western countries.[18] The data further suggest that in many countries alike, ulcerative colitis and duodenal ulcer exhibit similar birth-cohort patterns that affect exactly the same generations with a peak occurring around 1890 (Figure 1). The close similarity between duodenal ulcer and ulcerative colitis is especially striking because it is confined to these very two diseases and does not involve gastric ulcer or gastric cancer, which are both characterized by distinctly different birth-cohort patterns. The similarity indicates that the aetiologies of ulcerative colitis and duodenal ulcer may share a common pathway and that this pathway relates to some environmental exposure before or during childhood.

The trends of Crohn's disease reveal yet another rather peculiar pattern. Ever since its inclusion into vital statistics in 1950 until about 1970, mortality from Crohn's disease was rising and then started to fall upon reaching the level of ulcerative colitis (Figure 2). It appeared as if mortality associated with Crohn's disease failed to continue its rise above the level of mortality associated with ulcerative colitis. This pattern was discernible in each age group, in each gender, and as subsequently shown, in different countries.[16,19] As gastric ulcer is obviously linked to duodenal ulcer, and Crohn's disease is linked to ulcerative colitis, there appears to be some single mechanism that influences a large portion of gastroenterology's most important diseases.

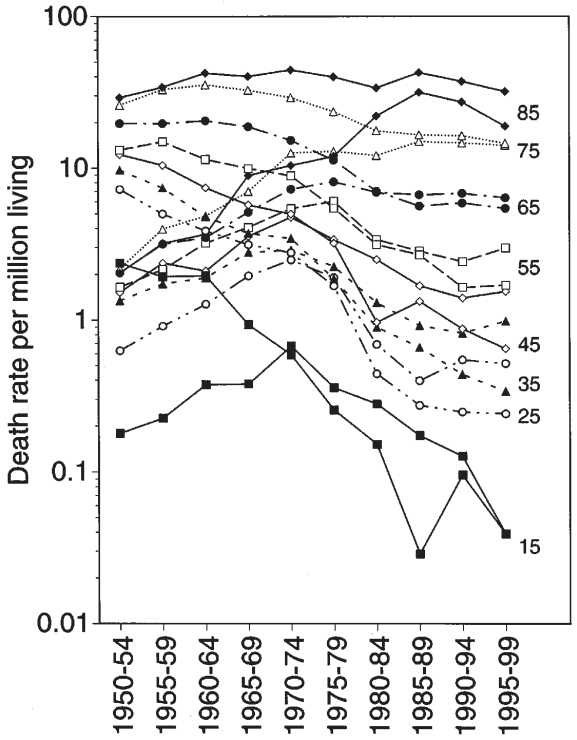

Figure 2 Superimposed curves of age-specific death rates from ulcerative colitis and Crohn's disease from England and Wales between 1950 and 1998. Death rates from ulcerative colitis show a decline that is more pronounced in younger than older age groups. For each separate age group alike, death rates from Crohn's disease show an initial rise, but then fail to continue to rise above the level of mortality associated with ulcerative colitis. Age groups are labelled by their central age, for instance, 25 instead of 20–29, 35 instead of 30–39, etc. Each point represents the average death rate of a 5-year period

The Appearance of *Helicobacter Pylori*

The discovery of *H. pylori* has changed our concepts of peptic ulcer disease and gastric cancer. In developing countries with high prevalence rates of *H. pylori*, the infection is acquired during early childhood, and by the age of 20 years, over 80% of the population have become infected.[20] Since the immune system is unable to rid the body of *H. pylori*, any infection acquired during early childhood remains a lifelong event. The rise and fall of peptic ulcer could, thus, represent the historic scars of rising and falling infection rates experienced during early childhood by large fractions of the population as in a birth-cohort phenomenon.[21] The marked decline in the occurrence of peptic ulcer during the past two decades is matched by a steep decline in the infection rates with *H. pylori* in all western countries.[22] Urbanization and the crowded living conditions of the expanding cities during the beginning of the industrial revolution at the onset of the 19th century probably meant a decline in hygiene for large fractions of the population with a concomitant rise in exposure to *H. pylori*. Subsequently, the increase in knowledge about the importance of hygiene in preventing the spread of diseases led to various governmental and municipal efforts to improve sanitation and supply clean water to urban residents. These efforts probably resulted in a decline of *H. pylori* infection rate.[21]

Unresolved Issues

Even if the decline in peptic ulcer during the second half of the 20th century can be explained by improvements in hygiene and a reduction in *H. pylori* transmission, it remains unresolved why peptic ulcer rose so suddenly 100 years earlier.[23] Most epidemiological evidence suggests that *H. pylori* has been a human pathogen for thousands of years. The world-wide distribution of *H. pylori* even among remote populations on four continents mitigates against the contention that *H. pylori* infection spread only recently among populations of western or industrialized countries.[24] Gastric cancer is actually the only disease whose trends vary in the time-dependent fashion one would expect from a well-behaved *H. pylori*-related disease.[25] It remained stable in among consecutive generations until the turn of the 19th century and has declined ever since. The rise in the occurrence of gastric and duodenal ulcer during the 19th century is difficult to explain utilizing *H. pylori* as the sole explanation.

Some gastroenterologists have tried to explain the initial rise of peptic ulcer based on a set of complex interactions among varying modes of *H. pylori* acquisition, dietary factors, and other childhood infections in the 19th century.[26,27] Malnutrition and weakening of the immune system by infectious diarrhoea or other intercurrent infections may render the host more susceptible to persistent gastric colonization with *H. pylori*. Healthy well-nourished children may be more capable of fending off an early invasion by *H. pylori*. Subjects who become infected with *H. pylori* at a young age are more likely to develop chronic or atrophic gastritis with a subsequent reduction of acid secretion that protects them from developing duodenal ulcer. Such gastritis is associated with development of gastric ulcer, as well as gastric cancer. In contradistinction to gastric ulcer, duodenal ulcer seems to develop primarily in subjects who contract *H. pylori* infection at the end of childhood or later. Some reservation towards these hypotheses stems from their complexity and the ever-increasing number of interrelated factors necessary to explain one characteristic feature of ulcer epidemiology. It is difficult to envisage how a multitude of individual risk factors, each one characterized by its own temporal, geographical and demographic variation, could align in many different countries at the same time to cause a unique, clear-cut and sharp rise and fall of ulcer risk among consecutive human generations. The contribution of several factors should have caused at least some blurs or spread of the cohort pattern, which we do not observe.

Conclusions

It would take probably another landmark paper to resolve the mystery of the interrelated time trends of several gastrointestinal diseases. One potential hypothesis holds that another *Helicobacter* species may be responsible for ulcerative colitis. The birth-cohort phenomenon could stem from an underlying general variation in the yet poorly understood infection mode of *Helicobacter* species. For instance, helminths could affect the acquisition of *H. pylori*, possibly, by functioning as direct carriers (vectors) of the bacterium into the human body or by facilitating its spread among populations through diarrhoea and other influences on the gastrointestinal tract. Infection with helminths rather than *H. pylori* would then be the primary

driving force behind the birth-cohort pattern. Yet another hypothesis assumes that the four birth-cohort phenomena result from the superimposition of one major declining trend and multiple rising trends. This joint influence of declining and rising trends would cause a succession of peaks affecting consecutive generations with gastric ulcer, duodenal ulcer, ulcerative colitis, and lastly Crohn's disease. Rather than being influenced by a single agent, each one of the four diseases would be caused by the interaction of at least two distinct environmental influences. Improvements in hygiene and a general decline in enteric infections, including *H. pylori*, could be responsible for the declining trend, whereas a rise in exposure to different types of viruses or other environmental agents could be responsible for the rising trends. At the present time such concepts are purely speculative, and there is little or no evidence to support or refute them.

It is amazing that even current books and review articles about peptic ulcer fail to mention the birth-cohort phenomenon. It may reflect some general difficulty in understanding complex temporal patterns that defy a simple explanation. Rather than giving a conclusive answer, it keeps pointing at the persistence of a big gap in our understanding of peptic ulcer and inflammatory bowel disease. Once resolved, the mystery of the birth-cohort phenomena carries the potential for finding a profound link among these seemingly heterogeneous diseases.

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

Michael Langman

Forty years have elapsed since Susser and Stein used mortality data to examine trends in the impact of peptic ulcer disease.[1] 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.[2–4] 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'.[5] 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[6] 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.[7]

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.[8,9] 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,[5] 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[10] 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.[11] 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.[12] The role of aspirin in causing gastritis, but not ulcer, was described in 1938,[13] 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,[14,15] although the clinical burden imposed by NSAIDs proved to equate to one-third of the total number of ulcer complications.[16]

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,[17] (2) duodenal ulcer's increasing importance from the 1890s,[18] 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.[19] This position is not very different from that taken by Doll and his colleagues over 40 years ago:[20] '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.[21] 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

Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Birmingham B15 2TH, UK.

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,[19,22] 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.

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Commentary: Peptic ulcer and its discontents

Susan Levenstein

> 'While stress and diet can irritate an ulcer, they do not cause it. Ulcers are caused by the bacterium *H. pylori*.' *Centers for Disease Control and Prevention*[1]

> 'Thus the dialectics of Hegel was placed upon its head; or rather, turned off its head, on which it was standing, and placed upon its feet.' *Friedrich Engels*[2]

Secular Trends in Peptic Ulcer: Whodunit?

Pushing forward to the end of an Agatha Christie novel after you've guessed the murderer is a peculiar reading experience. There is something similar in reading Susser and Stein's 'Civilisation and Peptic Ulcer'[3] with our present awareness that an infectious agent plays a role in this disease. The reader is constantly looking out for whether and how *Helicobacter pylori* (HP) may be the key to the temporal trends in ulcer mortality that seemed mysterious when they were laid out 40 years ago—the appearance of gastric and then duodenal ulcers on the scene beginning in the late 19th century, their swell into an epidemic over 50 years, and their progressive decline thereafter.

Since these classic analyses were published, the dominant model of peptic ulcer aetiology has been flipped topsy-turvy. Like Hegel's dialectics, it has been lifted off its head, upended, and landed solidly with its feet on the ground. The present commentary on Susser and Stein will aim chiefly at a contemporary perspective on the relation between civilization and peptic ulcer, but its subtheme will be to ask whether it was necessary for those who flipped ulcer aetiology from top to toes to finish off the job by abolishing psychosomatic explanations—by, so to speak, lopping off the head altogether.

Helicobacter Pylori Breaks In

In this *Lancet* article Susser and Stein stopped short of using their cohort observations as the basis for a grand conceptual leap when they limited themselves to psychosomatic reasoning, and thus failed to conclude that an important aetiological factor encountered in childhood appeared during a limited historical period in the late 19th century (see ref. 4). But their intuition that ulcer is 'a disease of an early phase of urbanisation' still holds; current knowledge suggests the peptic ulcer syndrome could become widespread only when HP was able to settle into a particular niche due to society's arrival at a certain stage in its economic and social evolution.

Medical history offers examples of the rise and decline of microorganisms, such as the scarlet fever strains of streptococcus, which caused time-limited disease outbreaks as they followed their own evolutionary paths. *Helicobacter pylori* is not one of these. According to prominent theorists HP has always inhabited the human stomach, but the pathology it caused was chiefly, until the late 19th century, not ulcer but gastritis and gastric cancer.[5,6] Public health advances, which improved diet and diminished the overall disease burden in early childhood, then brought relative sparing of the gastric corpus which in turn resulted in some individuals having unimpaired acid secretion. The decreased prevalence of atrophic gastritis and the elevated load of acid being delivered to the duodenum caused a shift to peptic ulcer as the primary HP-related pathology.[5,7,8] Forward displacement of the usual age at acquisition of HP from infancy into childhood[9] may also be relevant, paralleling the emergence of paralytic poliomyelitis as a result of delay in the usual age of exposure to the polio virus. Thus to the extent that the 20th century epidemic of peptic ulcer is due to HP its root cause is the progress in public health that accompanies the process we may call civilization.

The falling tail of the ulcer epidemic, on the other hand, corresponds to HP losing access to its host altogether. By now general hygienic conditions have improved to the point that few young Americans acquire HP, and the current $\geqslant$1%/year age gradient of active infection[10] mainly reflects cohort effects.

Helicobacter pylori thus finds a historical window of opportunity along a society's way toward modernization—public health conditions that are better but not too much better—through which it can induce an epidemic of peptic ulcer.

Such reasoning can contribute to explaining not only the overall shape of the peptic ulcer epidemic but also its relations with socioeconomic status (SES). At the turn of the 21st century, ulcer is inversely associated with SES,[11] largely because children who grow up in crowded households, sleep in shared beds, etc. are more likely to acquire HP;[12] the HP status of adults is affected much more by childhood than by current SES.[13]

The SES trends of ulcer prevalence over time are complex. Susser and Stein's results demonstrate that the wave of ulcers began to recede earlier in the upper classes, but they also suggest that it peaked earlier in the upper classes, so that the socioeconomic gradient around 1900 was the reverse of the present one. This too can be understood in terms of the evolution of HP-host relations if we suppose that the high-SES cohort born in about 1850–1865 experienced the moderate improvement in childhood hygienic conditions required for the ulcer window of opportunity, while the HP which infected their lower class agemates was still causing gastritis and cancer.

It is evident from these observations that much of the responsibility for the sweeping trends in ulcer over the last century has to do with HP. Does 'much' mean 'all'?

Stress and Company: the Usual Suspects

The brief section in which Susser and Stein attempt to make sense of their findings in terms of the demands of industrial society or the upheavals of war is hamstrung by the assumption

Via del Tempio 1A, 00186 Rome, Italy. E-mail: slevenstein@compuserve.com

that psychological factors are the chief determinants of peptic ulcer, which has as its corollary that the task of epidemiologists in explaining observed historical trends is limited to discovering which stressors might be operative, where, and on whom. Since the HP bombshell landed many experts have gone to the opposite extreme, denying that stress or other psychological factors have anything to do with the aetiology of peptic ulcer.[14] One reductionism has been replaced by its mirror image.

Though it was an error to take ulcer psychosomatics as an article of faith, care must be taken not to throw the baby out with the bath water by assuming that with the discovery of HP the case is closed. Only 20% of HP-infected individuals ever develop an ulcer,[15] usually after several decades of infection, and many ulcers develop in the absence of HP.[16] *Helicobacter pylori* must therefore be conceptualized not as the cause of peptic ulcer but as one risk factor among, potentially, many. *Helicobacter pylori* infection has been estimated to carry a risk ratio of approximately 4 for ulcer[17] and to be responsible for 48% of the population attributable risk.[18]

Several previously known risk factors have been shown to act as co-factors in HP-related ulcer. A family history of ulcer, for example, far from being merely a marker of exposure to HP,[19] elevates by 8-fold the risk that an HP-infected person will develop an ulcer.[17] Gastric acid hypersecretion similarly retains its association with ulcer after HP is taken into consideration[20] —patterns of bacterial colonization are affected by parietal cell function,[21] and laboratory studies support the concept that duodenal acid load is likely to be a major determinant of HP-related duodenal ulcer.[22] Smoking is still another ulcer risk factor whose association holds up in the HP era.[23] Hard on-the-job physical exertion also seems to facilitate ulcer formation over and beyond the effect of low SES,[24] perhaps by stimulating gastric acid secretion,[25] though a degree of confounding of these findings by HP cannot be excluded.

What of psychological stress, the dethroned king of ulcer-land? Its position had weakened even before a usurper arrived to claim its seat, since the period just before HP came into the picture saw both the advent of effective medical therapy for ulcer and several case-control studies finding no association of ulcer with stress.[26–28]

Some of the best case-control studies do support an association of ulcer with life stress;[29,30] a cross-sectional association of ulcers with shift work[31] is particularly convincing because of a bias in the opposite direction (sick workers are commonly assigned to the day shift) and is complemented by reports linking ulcer with poor sleep.[32] But it is prospective studies, most of them published since 1990, that have provided the most compelling evidence of a causal role for psychological stress in peptic ulcer. A variety of natural and man-made catastrophes in various populations have been followed by surges in the number of diagnosed ulcers.[33–36] Among defined cohorts initially free of ulcer, psychological stress and distress at baseline have generally been found to predict excess ulcer development over the following years,[32,37–41] though there have also been contrary reports.[42,43] Follow-up studies of patients with endoscopically diagnosed peptic ulcer have uniformly found stress and distress to worsen clinical course over months to years.[44–48] On the basis of the published evidence I have estimated that psychological factors contribute to 30–65% of cases of peptic ulcer.[49]

The interactions among stress, HP, and ulcer have been little studied thus far. From the limited evidence that is available it would seem that emotional stress can precipitate ulcer in HP-positive individuals,[50] and that it may enable ulcer development at low intensities of infection[51] or in HP-negative individuals.[52]

It should be pointed out that bleeding or perforated ulcers, the implied topic of any examinations of trends in ulcer mortality, on the one hand are more often HP-negative than are uncomplicated ulcers[53] and on the other hand have a particularly well documented association with stress.[33–36]

The imperfect coincidence between peptic ulcer and HP leaves room not only for co-factors but also for alternative pathogenetic pathways. Depending on the setting, between 4%[54] and 44%[55] of ulcers have been reported to develop in HP-negative individuals. Non-steroidal anti-inflammatory drugs are the best-recognized factor involved in ulcers which develop in the absence of HP,[56] but it is not true (as once thought) that all HP-negative cases have taken these drugs.[54,55] Bile reflux, intestinal metaplasia,[57] elevated pepsinogen I,[58] and stress[54] have been implicated as other risk factors. On the other hand, smoking[56] and type O blood[59] probably increase the risk of peptic ulcer only in the presence of HP.

Though Susser and Stein may have had the chief culprit wrong, the confirmed importance of a whole cluster of secondary risk factors in the HP era means it was nonetheless correct for them to emphasize the multifactorial nature of peptic ulcer.

Murder on the Orient Express

Though the temporal parabola of peptic ulcer in the 20th century chiefly reflects the ecology of HP, authoritative observers have maintained that others among the factors listed above must also be invoked.[60,61] For example, the two health risk behaviours most relevant to ulcer, cigarette smoking and aspirin taking, both became widespread early in the 20th century and could therefore have contributed to the rise of the peptic ulcer epidemic. Shifts in the workforce toward sedentary jobs in the last 50 years could on the other hand have contributed to its fall.[62] As for whether psychological stress has increased or decreased over the last century, that is still anyone's guess.

At the present moment, when the class differences in rates of HP acquisition are particularly striking, they overshadow all other factors in the SES gradient of peptic ulcer. There are, however, additional, non-infectious, reasons for a high rate of peptic ulcer in lower SES individuals, including their greater likelihood of exposure to hard on-the-job physical labour[24] and to psychological stress.[63] Non-HP factors may also have contributed to the reverse SES gradient of a century ago, if higher socioeconomic strata were the ones to pioneer the use of substances such as cigarettes and aspirin which are important behavioural risk factors for ulcer.

Susser and Stein wrote that no ulcer treatment was effective enough to condition the trends they observed. This is no longer the case: the drop in ulcer mortality has undoubtedly been accelerated by the introduction of effective medical treatments beginning in the late 1970s. Documented morbidity has fallen still more, since a large proportion of ulcers are cured without ever being diagnosed now that ulcer-like dyspepsia is commonly treated empirically with powerful antisecretory drugs and

sometimes even with HP eradication therapy. Current ulcer incidence and prevalence figures are therefore suspect, making it unlikely there will be a Susser and Stein of the year 2012. But the lines of research indicated in 1962—such as explaining the high rate of gastric ulcer perforations in young women around the turn of the 20th century—remain to be fully mined out, though they are by now of more historical than clinical interest.

The detectibility of aetiological factors using epidemiological means can vary according to time and place. In the case of peptic ulcer, a few decades ago virtually all Western adults were infected with HP. Due to this very ubiquity, genetic predispositions and adult modes of life were major visible determinants of who among the infected actually developed an ulcer; this would have been the case even had the existence of HP been known. On a clinical level we may also recall what Osler said of tuberculosis at a time when infection was nearly universal: 'So widely spread everywhere is the seed, that the soil, the conditions suitable for its growth, is practically of equal moment'.[64] Now that HP is harboured by a minority of adults, but a minority substantial enough for it to be involved in most ulcers, the infectious contribution to determining who does and who does not develop gastroduodenal lesions stands out with particular prominence.

Host Factors in the Mix

If ulcer or at least one category of ulcer is in some sense an infectious disease, broader issues of the nature of microbiological aetiology are raised by the peptic ulcer story.

Early in the antibiotic era the medical profession understandably paid little attention to the role of host factors in infectious diseases, as it gloried in drugs that could eradicate ever-wider spectra of micro-organisms. But after several decades of serial triumphs came the first setbacks. The emergence of drug resistance showed that the antibiotic approach had limitations, and revived interest in factors that might impair or bolster host defences. With the advent of iatrogenic immunosuppression and then AIDS, conditions in which fatal infections could result from usually harmless organisms, the potential primacy of host factors became even more evident.

More recently support for the importance of host factors has arrived from a line of research suggesting that many chronic diseases previously considered of unknown origin might be related to infectious processes. Marshall's revelations of the bacterial component in peptic ulcer blazed the trail for similar investigations of diseases ranging from Hashimoto's thyroiditis[65] to coronary artery disease[66] and multiple sclerosis.[67] Though these infectious links are still largely speculative, they have fuelled a new boom of interest in the role of host factors in infectious diseases; even if *Chlamydia pneumoniae* does indeed turn out to prime the formation of arteriosclerotic plaques in the coronary arteries, it will remain difficult to deny the role of smoking or of hypercholesterolaemia. The degree of our knowledge of risk factors for coronary artery disease, and the success of their modification in reducing incidence and case-fatality rates, should make it unlikely that microbiological reductionism will take over aetiological models of, say, coronary artery disease as it did for peptic ulcer.

Mycobacterium tuberculosis provides an instructive parallel to HP as an infection acquired in childhood but causing disease only in a minority of hosts and often after decades of latency. As with peptic ulcer, a vast literature on host factors was discarded once effective antibiotic therapy was developed. And as with peptic ulcer, some of the older observations of non-microbiological risk factors for tuberculosis—poor nutrition, emotional stress, etc—probably have a core of validity[68] and are increasing in relevance as clinicians encounter new difficulties related to drug resistance and to immunosuppressed populations.

Advances in genetic research have added plausibility to the concept of host factors in infection, as hereditary influences are being detected in pathologies as unlikely as otitis media.[69] Psychological stress similarly seems capable of worsening some infections, in part though immune mechanisms.[70] Although this literature has concentrated on viral diseases, immunologically mediated effects of psychosocial factors on bacteria including HP cannot be excluded.[71]

All these developments are forcing a reconceptualization of the interactions between an infectious agent and its host. The emerging model of infectious disease is inherently multifactorial, since the foothold of germ on organism is now known to be influenced by host factors ranging from genetic to iatrogenic to nutritional to behavioural to psychological. A variant of Susser and Stein's multifactorial model of ulcer aetiology, updated to include HP infection as well as heredity, psychology, and lifestyle, is therefore not only plausible but in exciting concordance with the zeitgeist of the new millenium.

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