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EDITORIAL

Precise role of *H pylori* in duodenal ulceration

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Abstract

The facts that *H pylori* infection is commoner in duodenal ulcer (DU) patients than in the normal population, and that eradication results in most cases being cured, have led to the belief that it causes DU. However, early cases of DU are less likely than established ones to be infected. *H pylori*-negative cases are usually ascribed to specific associated factors such as non-steroidal anti-inflammatory drugs (NSAIDs), Crohn's disease, and hypergastrinaemia, but even after excluding these, several *H pylori*-negative cases remain and are particularly common in areas of low prevalence of *H pylori* infection. Moreover, this incidence of *H pylori* negative DU is not associated with a fall in overall DU prevalence when compared with countries with a higher *H pylori* prevalence. In countries with a high *H pylori* prevalence there are regional differences in DU prevalence, but no evidence of an overall higher prevalence of DU than in countries with a low *H pylori* prevalence. There is no evidence that virulence factors are predictive of clinical outcome. After healing following eradication of *H pylori* infection DU can still recur. Medical or surgical measures to reduce acid output can lead to long-term healing despite persistence of *H pylori* infection. Up to half of cases of acute DU perforation are *H pylori* negative. These findings lead to the conclusion that *H pylori* infection does not itself cause DU, but leads to resistance to healing, i.e., chronicity. This conclusion is shown not to be incompatible with the universally high prevalence of DU compared with controls.

Key words: Duodenal ulceration; *H pylori* infection; Not causal; Delays healing

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INTRODUCTION

The award of the Nobel Prize to Warren and Marshall for the discovery of *H pylori*[1] was rightly acclaimed by the medical profession, because the eradication of the organism turns a chronic, relapsing disease into one that in most (but not all) cases can be readily cured. The prevalence of infection with the organism is greater in patients with, than in subjects free of, duodenal ulcer; the organism is present in most (but not all) cases of the disease; and its removal results in most (though not all) cases being cured without relapse. The inference usually drawn from this combination of events is that *H pylori* actually causes duodenal ulcer.

In that case, why do most individuals infected with the organism not develop the disease? There has been considerable work done exploring the concept that the presence or absence of virulence factors explains this anomaly, but in a recent publication[2] we explain why we do not find this hypothesis convincing.

This unsatisfactory situation, the facts that most patients with infection do not have a duodenal ulcer, that, geographically, duodenal ulcer prevalence is not related to the prevalence of *H pylori*, and many other anomalies, has been highlighted in several review articles, such as *H pylori*: the African Enigma[3]. The enigma is two-fold: firstly, that DU prevalence is not higher in countries with a higher prevalence of *H pylori* infection, secondly, that within these countries, despite an uniformly high *H pylori* prevalence, regional differences in DU prevalence are found, that as described later, are related to diet but not to smoking, genetic or other factors.

Our continuing search for an explanation of the anomalies led us to review all the papers that provide evidence about the following: (1) Is *H pylori* infection present at the onset of DU? (2) Is there a dose-response relationship between *H pylori* and DU? (3) Does recurrence or non-recurrence of DU after successful treatment correlate with *H pylori*-status? (4) Can we deduce anything of importance from the prevalence and distribution of *H pylori*-negative DU?

The present paper analyses the evidence of the literature on these subjects and we show how the higher prevalence of *H pylori* in DU than in the normal population and some of the other anomalies can be explained by a self-consistent theory, but only by relinquishing the belief

that *H pylori* causes DU.

To the best of our knowledge, no paper has been published that contradicts statements in this review. We shall be obliged to readers for letting us know about any exceptions that we have missed.

Is H pylori infection present at the onset of DU?

One is entitled to expect that the cause always precedes its effect. The problem with duodenal ulceration is that the patient usually presents to the physician some time after the symptoms start: it is unlikely that evidence of infection has been sought before the symptoms began. It occurred to us to examine the *H pylori*-status of patients with duodenal ulcer in relation to the length of history before the initial biopsy that established the diagnosis of DU. Assuming the organism was the cause of the ulcer, we expected the infection to be manifest at least as often in the first six months as it was more than six months after symptoms started. We studied 37 patients: to our surprise, 5 whose history was of less than six months were *H pylori*-negative, the remaining 32, all with a length of history greater than six months, were *H pylori*-positive. The odds against this happening by chance were (Fisher's exact test) greater than 1000 to 1[4]. It looked as though the DU was causing the infection, rather than the other way about.

Searching the literature at that time (2001), we could find only one paper that gave figures for infection status, distinguished by different lengths of history[5]. Repeating the search in 2005, we were only able to find one further paper with the appropriate data[6]. Both these papers showed a higher infection rate later compared with earlier in the ulcer disease.

There are two reports[7,8] which suggest that pre-existing *H pylori* infection predisposes to DU based on seropositivity. The first paper refers to young inductees into the Israeli army and the second to an older population in Hawaii. In the first paper it is noteworthy that 7 of the 29 reported DU cases were *H pylori*-negative at the time of diagnosis. However, seropositivity does not mean that infection is present. After eradication, it can take 5-10 years for seropositive cases to become seronegative. Many children serorevert after childhood infection and in adults the conversion/reversion rates per annum vary between 0.5% and 1%. An approach along these lines therefore lacks scientific reliability.

Dose-response relationship?

The smallest dose is zero. Many patients develop a DU in the absence of infection with *H pylori*. This fact is usually explained by invoking 'special' causes of DU such as Zollinger-Ellison syndrome and non-steroidal anti-inflammatory agents (NSAIDs) (see later), but such causes are not always apparent.

Before the *H pylori* era, excess gastric hydrochloric acid was the favoured aetiology of DU. 'No acid, no ulcer' has been dogma since Schwartz[9], and there has been no contrary evidence. However, acid is 'statistically' greater than the normal range in only about 15% of (patients with) DU, the rest having acid in the normal range[10], albeit with a tendency to be greater than in the normal population.

In many countries there is no information about the actual prevalence of DU in the overall population, and available information is based on figures obtained from hospital statistics or small population surveys. From information that is available, there is no evidence that there is a higher overall prevalence of DU in those countries where there is a higher prevalence of *H pylori* infection than in other countries. There is evidence from India, China and Africa, however, of differences in DU prevalence between areas known to have a high prevalence of *H pylori* infection[3,11-18] these differences being related to the staple diets of the regions[15-25] rather than to smoking, genetic or other factors such as duodenal gastric metaplasia. There is evidence that different foods contain agents that are either ulcerogenic or ulceroprotective[25-28].

In developed countries, where *H pylori* prevalence is about 35% overall, DUs are about 70% *H pylori*-positive[6,29-39]; in developing countries, *H pylori* prevalence is about 70% overall, and DUs are *H pylori*-positive in about 90% of patients[16,29,30,40-51]. Therefore in all countries *H pylori*-positivity is greater in DU than in non-DU. With reference to further discussion, it is notable that in areas of low *H pylori* prevalence there is a high prevalence of *H pylori*-negative, non-NSAID, ulcers[4,6,16,29,30,35,39,40,52-64].

As mentioned above there is no evidence that the prevalence of DU is any greater in countries with a high prevalence of *H pylori* than in those with a low prevalence (this finding in itself argues against *H pylori* being the prime cause of DU). The prevalence of DU in London is about 11%[10]. Applying this figure to other developed countries, from the figures quoted previously in every 100 of the population, 35 are *H pylori*-positive and 65 *H pylori*-negative. There are 11 patients with DU, of whom perhaps only one is *H pylori*-negative, so only 10 of the 35 *H pylori*-positive subjects get DU. The remaining 25 (25/35, 71%) do not. A similar argument in the developing countries (again assuming an 11% prevalence) yields an estimate that only 10 of the 70 *H pylori*-positive subjects get DU. The remaining 60 of the 70 (86%) do not. The belief that *H pylori* is the prime cause of DU demands an explanation of why in 71%-86% of individuals it does *not* produce a DU.

Weight of infection can be measured by use of the breath test, but no-one has suggested that the greater the weight of infection, the greater is the risk of developing DU. However, there is excellent evidence that the risk of developing DU increases with the rate at which the subject secretes gastric juice when maximally stimulated with intravenous histamine[10]. The *H pylori*-lobby suggests that we cannot demonstrate a dose-relationship of DU with *H pylori* because only some strains of the organism possess virulence factors (of which many have been reported). It is beyond the scope of this paper to go into that topic, but there is considerable evidence that virulence factors have no relationship to clinical outcome[2].

Does recurrence of DU correspond with H pylori-status?

The answer is, apparently not very well. Ulcers heal with effective medical suppression of acid without eradication

of *H pylori*[65,66], and after surgical procedures ulcers remain healed despite persistent *H pylori* infection[67-76].

When *H pylori* was discovered and the first results came in about the effect of its extirpation, it was claimed that removing *H pylori* 'cured' the disease and that relapses never occurred. As time passed that picture had to be modified: there is no doubt that relapses are much less frequent and many patients have no further trouble, but there is increasing evidence of a significant recurrence rate after eradication of *H pylori* despite lack of recurrence of the infection. Excluding subjects taking NSAIDs, 9 papers, involving 2928 DU patients in whom *H pylori* had been eradicated as proven by multiple tests, reported recurrent ulceration in 182 (6.1%) over a period up to 5 years[77-85]. One meta-analysis by Laine of 7 trials subjected to strict criteria reports a recurrence rate of 20% within 6 mo[82]. Interestingly, a recurrence rate of 6.6% (571/8693) up to 2 years is given in 12 papers (including 6 meta-analyses)[77,85-97] involving 8693 cases of DU, not excluding NSAIDs, in whom *H pylori* had been eradicated. These recurrence rates, with and without NSAIDs, are virtually identical ($P = 0.4883$). In other words, recurrence after eradication of *H pylori* cannot be attributed to NSAIDs. The use of multiple tests for *H pylori* reduced the risk that we are dealing here with difficulty in demonstrating the presence of *H pylori* after eradication.

What does H pylori-negative DU tell us?

The phenomenon of *H pylori*-negative DU is an argument against a blanket role for *H pylori* as a "cause preceding effect". As stated above, this prevalence is greater in countries with a low, compared with countries with a high prevalence of the organism, even after excluding DU-associated factors such as Crohn's disease and the taking of NSAIDs. There are 20 such reports[4,6,29,30,35,39,40,52-64] from countries with a low prevalence of *H pylori* infection giving a mean of 14.4% (829/5745) of *H pylori*-negative DU and 5 reports[48,97-100] with a mean of 3.9% (52/1325), $P < 0.0001$) from countries with a high prevalence.

Three papers[101-103] suggest that despite the low *H pylori* prevalence in a population with an increased prevalence of *H pylori*-negative DU, there is no decrease in overall DU prevalence. If *H pylori* were the primary cause of DU then one would expect a lower prevalence of DU.

We can offer one supplementary consideration. Perforation of duodenal ulceration might reasonably be expected to signify an especially large secretion of gastric hydrochloric acid. In this context it is interesting that perforation does not seem to be associated with *H pylori*. In 4 reports about patients operated on for perforated duodenal ulcer *H pylori* prevalence was significantly less than in uncomplicated duodenal ulceration[104-107] (in 2[104,105] they were indistinguishable from normal controls). The only dissenting evidence was from a report by Matsukara[108].

INTERPRETATION

How are we to interpret the undoubted relationships between DU, *H pylori* and gastric acid? The present majority view is that *H pylori* causes DU, not that DU causes *H pylori*. The favourable evidence for the former inference is the greater proportion of *H pylori*-positive cases in DU compared with non-DU subjects, and the fact that clearing the organisms converts the clinical course of DU from chronic relapsing to (mostly) stable healing. However, the second of these points is not proof of initial causation, merely of an interference with healing leading to chronicity of the ulceration.

If H pylori is not the initial cause of DU?

If we reject *H pylori* as the cause of DU, how can we explain the greater proportion of *H pylori* in DU compared with non-DU subjects? *H pylori* can only live within a relatively narrow band of pH. Both highly acid and highly alkaline conditions kill the organism[109,110]. For example, in pernicious anaemia the patient is usually *H pylori*-positive in the early stages (acid production is reduced but still abundant) and then becomes *H pylori*-negative in the later stages (when all acid production has ceased and the stomach is exposed to alkaline reflux from the duodenum)[111,112].

These facts suggest that some patients who develop a DU may well have so much acid that they are *H pylori*-negative. When treated with acid suppression for their early symptoms, the gastric acidity may fall enough to encourage infection with the organism. At this stage they are investigated and found to be *H pylori*-positive. Strange as it may at first seem, we are postulating that one interpretation of the link between *H pylori* and DU in cases that are initially *H pylori*-negative is that DU (*via* its treatment) causes the infection. This would explain the greater prevalence of *H pylori* in the subjects with DU as an outcome of treatment with acid-suppressing drugs. If the likelihood of a first infection increases with the presence of virulence factors in the organism - as seems reasonable - this explains why the virulence factors are more prevalent in the DU than in the non-DU subjects[2].

In developing countries with a high prevalence of *H pylori* infection, and where people do not have access to acid-suppressing drugs and only come to hospital with long-standing chronic conditions, there is another possible explanation. With a high *H pylori* prevalence of 70% it follows that 30% of DU patients initially would be *H pylori* negative and 85% of them will not be hypersecretors of acid (See 'Dose Relationship' above). As a result of continued exposure to the high prevalence of *H pylori* a number of these may become infected, resulting in their ulceration becoming unremitting and chronic, and causing them to seek medical help. The result again would be a higher prevalence of *H pylori* infection in those diagnosed with duodenal ulceration.

In addition, the known lability of *H pylori* infection could result in some *H pylori* positive DUs healing as a result of spontaneous disappearance of the infection, leaving a preponderance of DU cases with persisting infection, thus resulting in a higher prevalence of infection in the DU population.

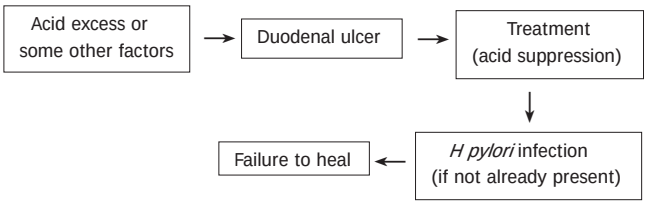
It is possible to calculate the relationship between the fraction of established duodenal ulcer patients who are

H pylori-positive, the fraction of the whole population who are *H pylori*-positive, and the fraction, X, of those initially *H pylori*-negative duodenal ulcer patients who become infected so as to produce the observed increase in established DU patients. We have performed these calculations on data from 18 reports from countries with a high prevalence[16,29,30,36,40-51,113] and 13 reports from countries with a low prevalence of *H pylori* infection[5,29-39,114]. The values of X were 0.6 in the developing countries, 0.58 in the developed. The congruence between these two estimates, while certainly not proof of our hypothesis, at least suggests that our hypothesis should not be rejected out of hand. Details of the derivation of the formula and the statistical interpretations are given in the Appendix.

There remain two important problems. (1) Most patients with DU have gastric secretion within the range of normal (though the chance of getting DU does increase with the rate of secretion). There must be some other factor to explain why some get an ulcer and others do not. Our work[115] demonstrated that this factor was unlikely to be *H pylori*. We favour the idea that the causative agent nevertheless involves interference with wound-healing. NSAIDs can interfere with the healing of *H pylori*-negative ulcer, so they may be responsible for part of the problem, but there is almost certainly more to discover; (2) We still do not know how *H pylori* (which can only live in gastric, not in true duodenal mucosa), makes the ulcer difficult to heal. The presence of colonised gastric mucosa within the duodenum might be a factor. *H pylori* infection inhibits healing of wounded duodenal epithelium in vitro due to vacA[116]. Another factor might be the effect that the organism has of increasing sub-maximally (gastrin-) stimulated gastric juice[117]. While the mechanism is in doubt, the relationship is clear and is the fundamental reason why the discovery of *H pylori* is of such enormous importance for the treatment of duodenal ulcer.

CONCLUSION

Our present view is that the relationship between duodenal ulcer, *H pylori* and gastric acid secretion is most likely to be:



APPENDIX

Fraction (= X) of *H pylori* -ve duodenal ulcers becoming *H pylori* + ve, possibly as a result of antacid treatment

$$X = \frac{\%\ \text{Hp+ve DU minus \% Hp+ve NUD or Controls}}{\%\ \text{Hp -ve NUD or Controls}}$$

Hypothesis

Whether or not a subject is *H pylori*-positive (+ve) or *H pylori*-negative (-ve) makes no difference to the likelihood that s/he will develop a duodenal ulcer (DU).

The diagnosis of most subjects with a DU is only made after the patient has already been treated with agents that reduce gastric acid secretion.

Reduction in gastric secretion is likely to increase the chance that a -ve patient becomes +ve.

When first diagnosed, most DU patients will include some who were +ve before they developed DU and others who had been -ve but became positive during their initial treatment and before diagnosis.

Calculation

Let

P = population

U = fraction having DU

F = fraction of population *H pylori* +ve

(so 1-F = fraction negative)

Then

Confirmed DU (say after 6/12)

$= U \times P$

However, the confirmed DU is made up of two moieties, one originally +ve, the other originally negative.

The originally positive DU number

$= F \times U \times P$.

The originally negative DU number

$= (1\text{-}F) \times U \times P$.

Let a fraction X of the originally negative DU be infected as a result of acid-suppression. Then after 6/12 these will number

$= (1 - F) \times U \times P \times X$.

Therefore the observed positive DUs can be expressed as

$(F \times U \times P) + X[(1\text{-}F) \times U \times P]$.

Therefore, the observed proportion of DUs who are positive is given by

$\{(F \times U \times P) + X(1\text{-}F) \times U \times P\}/(U \times P)$

or, dividing by $U \times P$,

$F + X(1\text{-}F)$.

Therefore, observed +ve DU/(total DU) = $\{F + X(1\text{-}F)\}$

$= F + X - FX$

Therefore, $X(1\text{-}F) = [\text{observed DU+ve/total DU}] - F$

And $X = \{[\text{observed DU+ve/total DU}] - F\}/(1 - F)\}$

Analysis of the figures quoted

High prevalence countries: Mean Hp+ DUs = 89.395; (SD 7.602, SE 1.700). Mean Hp+ NUD = 68.350 (SD 12.759, SE 2.853. Mean X = 60.565 (SD 26.466, SE 5.918).

Low prevalence countries: Mean Hp+DU = 70.221; (SD 14.319, SE 3.183). Mean Hp + NUD = 33.286; (SD 16.014, SE 4.280). Mean X = 58.279; (SD 17.773, SE 4.750)

Difference between high prevalence and low prevalence countries: for Hp + DU, $P = 0.0002$ (highly significant); for X, $P = 0.4109$ definitely non-significant.

This hypothesis suggests that in all countries there is much the same chance of originally *H pylori*-negative becoming infected as the ulcer progresses. This fact provides circumstantial evidence, though certainly not proof, of our hypothesis.

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