and natural history of glucose intolerance, diabetes, and the health risks associated with them are based on the 2 h blood glucose. Although the new FPG has similar cross-sectional associations, when applied to populations it seems to select a rather different set of people. When applied to individual diagnosis, the new fasting diagnostic strategy espoused by the ADA is also likely to reshape some of the average characteristics of patients with newly detected type 2 diabetes—ie, to alter the type 2 phenotype. Only long-term studies will tell whether the hopes for earlier diagnosis of diabetes and better health outcomes vested in the proposed changes in diagnostic strategy will be fulfilled.

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NSAIDs and *Helicobacter pylori*: therapeutic options

See page 1016

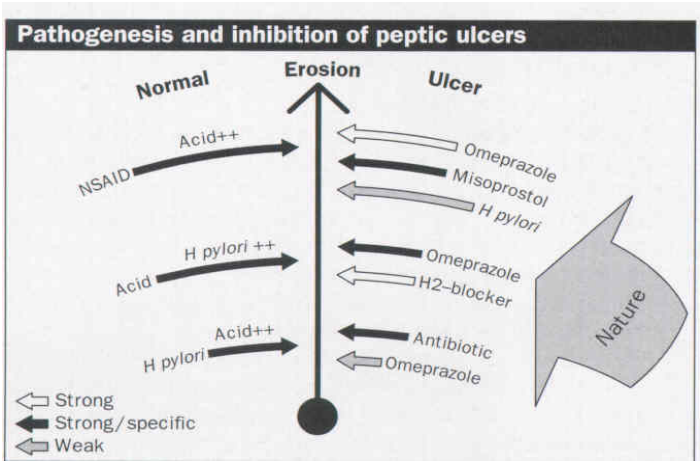
Interest in peptic ulceration induced by non-steroidal anti-inflammatory drugs (NSAIDs) has arisen because such ulcers are so difficult to treat. Recognition that management of these patients is imperfect has led to efforts to find easily remediable ulcer-exacerbating factors. Naturally, *Helicobacter pylori* is the first on the list of such factors since it is an aetiological factor for peptic-ulcer disease and is so easily treated.

Unfortunately, how *H pylori* interacts with NSAID-associated gastroduodenal disease is unclear. Early studies showed that *H pylori* was not commoner among people with than among those without NSAID-associated gastroduodenal lesions,[1,2] so larger, more careful studies were clearly needed to resolve this issue. Soon afterwards, several investigators[3] noted that bleeding duodenal ulcers were less likely to be infected with *H pylori* than were uncomplicated duodenal ulcers, which have an infection rate of 90%. The alternative cause of ulcer—either aspirin or other NSAIDs—was implicated in many patients, which suggested that ulcers caused by NSAIDs were more likely to bleed, and thus NSAID ulcers were over-represented in complicated bleeding ulcers.

In a large double-blind trial of misoprostol use for the prevention of NSAID-induced ulcers, *H pylori* did not seem to be an adverse factor in the development of ulcers.[4] This observation suggested that *H pylori* and NSAIDs induce ulcers in entirely different ways. Animal data and in-vitro data indicated that NSAID-induced ulcers were related to the inhibition of cyclo-oxygenase type 1 (COX-1), with subsequent decrease of prostaglandin concentrations in the mucosa. The useful effects of NSAID drugs were due to their inhibition of cyclo-oxygenase 2 (COX-2), which was induced in inflammatory processes (eg, in inflamed joints) and also in the healing process (eg, at ulcer borders).[5] "Stomach-friendly" NSAIDs would inhibit the inflammatory COX-2 enzymes more than they would the gastric cytoprotective COX-1 enzymes. The simplistic explanation for the relation between *H pylori*, NSAIDs and peptic ulcers, backed by a little experimental evidence,[6] is that the organism partly reverses the defect in the gastric mucosa caused by NSAIDs and may improve healing of NSAID ulcers by stimulating prostaglandin E_2 production, although this effect is easily overcome by NSAIDs.

Proton-pump inhibitors reduce gastric acidity but they have another effect. 20 mg and 40 mg doses of omeprazole result in 30–50% suppression of *H pylori*[7] and therefore can be expected to reduce both harmful and beneficial effects of the organism in some patients.

In their prospective, randomised, and masked study described in today's *Lancet*, C J Hawkey and colleagues asked whether patients with NSAID-induced ulcer or dyspepsia should be investigated and treated for *H pylori*. Patients with NSAID side-effects (ulcers or dyspepsia) were given omeprazole with anti-*Helicobacter* therapy (amoxycillin plus clarithromycin) or with placebo. Patients then took omeprazole until their ulcer healed or the dyspepsia resolved, after which they continued on their NSAIDs, with follow-up assessment of ulcers and symptoms at 1, 3, and 6 months. Eradication of *H pylori* was proven by biopsy urease and breath tests. The only



difference between *H pylori* eradicative therapy and omeprazole alone was that gastric ulcers healed faster if the *H pylori* was not treated. Duodenal ulcers healed in both groups. Thus, *H pylori* eradication did not alter the outcome in terms of recurrence of ulcers or dyspepsia. The message for management of gastric ulcers or NSAID-induced dyspepsia then, is that detection and treatment of *H pylori* are optional during omeprazole therapy.

The new data apparently conflict with an earlier study from Hong Kong by Chan et al,[8] who investigated patients positive for *H pylori* who were about to start on NSAIDs. Chan's patients, unlike those in the Hawkey study, had no history of ulcer disease or NSAID problems and were randomly assigned to either NSAID treatment or a week's pretreatment with bismuth, metronidazole, and tetracycline. In Chan's study, eradication of *H pylori* clearly protected patients from peptic ulceration in that ulcers developed in 14 patients positive for *H pylori* but in only one cured of infection with the organism. A feature of Chan's study is that lesions were deemed to be ulcers when they were 5 mm in diameter and had a definite crater, whereas omeprazole studies have been happy to call 3 mm diameter lesions "ulcers". Another difference between the Hawkey and Chan studies was the cure rate for *H pylori*—89% in Chan's but only 66% in Hawkey's. Moreover, *H pylori* were apparently eradicated in 14% of the control group (no antibiotics) in Hawkey's study. This finding suggest that *H pylori* status was less accurately determined by the urease test and ^{13}C breath-test combination in Hawkey's study.

The figure attempts to explain the observations made in clinical trials on the basis of fundamental processes. Ulcers and erosions are caused by aggressive factors in the gastric mucosa—acid and pepsin, NSAIDs, and *H pylori*. Acid and pepsin work by mere digestion of the mucosa, an effect that can be inhibited by acid reduction and aggravated by *H pylori*, which raises acid production and impairs mucosal defence. NSAIDs act mainly by impairing mucosal defence, but also through a direct erosive action. If *H pylori* stimulates mucosal prostaglandin, then it may inhibit this NSAID effect and therefore, in NSAID-induced ulcers, the presence of *H pylori* may be irrelevant or even be beneficial. In ulcers induced by *H pylori*, a decrease in acid concentration prevents the mucosal lesion and, in the case of the proton-pump inhibitors, the resulting alkaline pH may inhibit *H pylori* almost as antibiotics do.

Overall, most complicated ulcers in patients with NSAIDs are caused primarily by the NSAIDs rather than coexistent *H pylori*. Nevertheless, some ulcers are probably primarily *H pylori* ulcers, especially ulcers in the duodenum.

Hawkey's study shows that, among patients with clinically apparent NSAID complications (dyspepsia and/or ulceration), acid suppression with omeprazole is sufficient therapy and, at least in the case of gastric ulcers, *H pylori* need not be treated immediately. In NSAID takers with duodenal ulcer, however, *H pylori* eradication is more useful. If a more aggressive approach to *H pylori* is preferred, the study of Chan suggests that patients positive for *H pylori* intending to take NSAIDs should first undergo eradication of *H pylori*.

Clearly, patients with major gastroduodenal lesions or ulcer complications should stop taking NSAIDs if possible. If this is not possible, omeprazole treatment will heal about 80% of gastric ulcers and even more duodenal ulcers. Continuation of omeprazole or misoprostol limits subsequent recurrence of ulcer to about 30% per year.[9]

Further work needs to be done on the fundamental process behind such ulcers so that the degree of mucosal defect caused by NSAIDs or *H pylori* or both can be assessed in an individual and hence therapy can be customised. In populations among whom peptic ulcer disease induced by *H pylori* is common, the patients will probably benefit more from *H pylori* eradication than from other anti-ulcer measures, irrespective of NSAIDs. Conversely, among groups with asymptomatic *H pylori* infection, ulcers in patients taking NSAIDs may benefit more from acid reduction or prostaglandin therapy alone, without eradication of *H pylori*. In the future, typing of the *H pylori* infection as cagA positive or negative (which reflects cytotoxin production)[10] will help in therapeutic decision-making in western countries, where these virulence factors are important in the production of duodenal ulcer disease. In developing countries, where cagA-positive isolates predominate,[11] typing of the *H pylori* will be irrelevant.

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Relevance of the first seizure

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Single unprovoked seizures are an important feature of epilepsy meriting a place as a separate entity in the syndromic classification of epilepsies and epileptic syndromes.[1] Nevertheless there has been considerable controversy over their natural history. Hauser and Kurland in 1975 found that the incidence of epilepsy was much higher than that of single seizures, which implied that most such patients will undergo seizure recurrence.[2] The risk of recurrence ranges from 26% to 81%.[3-6] This large variation can be accounted for by study design and such factors as the interval between the occurrence of the first seizure and medical assessment and whether the study is of previously untreated seizures, of tonic-clonic seizures alone, or of acute symptomatic seizures.[7] In the National General Practice Study of Epilepsy (NGPSE), a community-based, prospective, observational study of the prognosis of epilepsy in 564 patients, the overall 3-year actuarial recurrence rate for all seizure types was 78% after a first-ever seizure.[6] 53% of recurrences occurred within the first 24 months of the index seizure. Lower recurrence rates of 48% and 56% for 3 years and 5 years, respectively, were found in the Rochester study,[5] and hospital-based studies tend to show even lower rates.[3,8,9]

Cause, seizure types, past neurological status, certain electroencephalographic (EEG) abnormalities, treatment status, and family history have all been thought to be important in influencing the predictability of recurrence.[7] All patients with congenital neurological deficits and brain tumours in the NGPSE had seizure recurrence within the first 3 years.[6] Recurrence rates are much higher with partial seizures than with tonic-clonic seizures, and with remote symptomatic seizures than with acute symptomatic seizures.[6] Time between initial seizure and assessment for entry into the study has a significant impact on the outcome of single seizures, with more recurrences being reported for patients seen within the first week than for those seen later.[10] The tendency to relapse varies according to whether EEG abnormalities were epileptiform or non-specific.[7] However, the usefulness of EEG for predicting recurrence has been questioned because of its low sensitivity, especially of specific epileptiform abnormalities.[8-10] Neurological imaging also has a low yield,[10] but, unlike EEG, its main value lies in the early detection of treatable brain abnormalities as well as the prediction of outcome.

Treatment of the first seizure and its influence on recurrence is another controversial issue. An inherent bias in most studies examining this issue has been the tendency for the physician to prescribe antiepileptic medicines to patients they deem to be at risk of recurrence.[3,5,10] Two randomised controlled trials have suggested that there is a significant reduction in the risk of recurrence in patients treated after the first seizure,[11,12] although one study included only 31 patients[12] and the other included only tonic-clonic seizures.[11] Undoubtedly, further trials are needed to clarify the influence of treatment in preventing recurrences.

With so many factors influencing the likelihood of recurrence, the prognosis and treatment of a first seizure are difficult to determine. These issues are better characterised in established epilepsy, and Mark King and colleagues have attempted to apply the syndromic classification of epilepsy prospectively to 300 consecutive patients with an apparent first unprovoked seizure; classification was aided by early EEG and the use of magnetic resonance imaging. The report in today's *Lancet* shows that syndromic diagnosis was possible in 81% of all patients, a higher percentage than reported from other community-based cohorts with established epilepsy[13] and higher than that in routine clinical practice. This difference is partly explained by the grouping of a large number of non-specific cases in broad, ill-defined, syndromic categories and by the fact that 74 patients could not be further subclassified. The high rate of diagnosis can also be explained in part by what is implicit in the title of King's article—the first seizure "presentation" rather than the first-ever seizure, since 45% of patients in their cohort had had tonic-clonic seizures or other epileptic features such as myoclonus or absence. The investigators emphasise the value of EEG obtained within the first 24 h for early diagnosis because a significantly higher number were abnormal than those obtained later on. However, logistical difficulties mean that obtaining EEGs may not always be a sensible use of resources. Finally, the diagnosis of epilepsy is not always easy in its early stages, and follow-up is commonly required to clarify the nature of presenting attacks. In the NGPSE, for example, 21% of 1091 patients were characterised as possible epilepsy rather than definite, and a further 7% did not have epilepsy at all. The application of the syndromic classification to the first seizure may therefore be limited by inaccuracy, and, with a substantial number of patients obscurely grouped, the classification may not be adequate enough for use in this situation.

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