Commentaries

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No *H pylori*: less dyspepsia?

Functional dyspepsia is a common disorder of heterogeneous aetiology for which there is no clearly effective treatment. In this issue of *Gut*, Blum and colleagues[1] report their large controlled clinical trial assessing the effectiveness of antisecretory medication in functional dyspepsia (see page 473). Patients with and without evidence of *Helicobacter pylori* infection were recruited into the study.

The study found symptomatic benefit over placebo at the end of two weeks' treatment with omeprazole 20 mg per day in *H pylori* positive patients but no significant benefit in primary outcome with the same treatment in *H pylori* negative patients. The therapeutic gain over placebo for omeprazole 20 mg in the *H pylori* positive patients was 17.6% (95% confidence intervals 4.2–31%; p<0.014). There was no significant benefit over placebo following omeprazole 10 mg or ranitidine 150 mg in *H pylori* positive patients or following any of the three treatments in the *H pylori* negative subjects. The superior benefit from omeprazole 20 mg in the *H pylori* positive versus negative subjects was also apparent with respect to improvement in quality of life.

The reason for symptomatic benefit over placebo with powerful acid suppression being confined to the *H pylori* infected subjects in this study is unclear and needs to be addressed. An earlier large study in which patients with functional dyspepsia were treated with omeprazole 20 mg/day found a 10% benefit over placebo but no relationship to *H pylori* status.[2]

Several aspects of the design of the study by Blum and colleagues may have contributed to the different responses seen in the *H pylori* positive and negative subjects. The investigators were not blinded to the *H pylori* status of the patients. In addition, *H pylori* positive patients not responding to treatment were eligible for recruitment into a second study examining the effect of *H pylori* eradication therapy; an option not open to *H pylori* negative non-responders. The desire to recruit patients into the second study (and any rewards for doing so) may have biased the investigators in favour of categorising the *H pylori* positive subjects as non-responders. The markedly lower response to placebo, as well as to all other forms of treatment in the *H pylori* positive subjects compared with negative subjects, suggests that investigators were indeed much less inclined to recognise a beneficial response in the infected group. The placebo response in *H pylori* positive patients was only 42% compared with 66% in the *H pylori* negative patients. The magnitude of the reduced response to placebo in the *H pylori* positive subjects was actually greater than the therapeutic benefit of omeprazole over placebo in that group. This led to the anomalous situation where the proportion of *H pylori* positive subjects showing a beneficial response following omeprazole treatment (59%) was substantially less than that of *H pylori* negative subjects showing a beneficial response after omeprazole (71%) despite the effectiveness of omeprazole over placebo being confined to the *former* group.

The much lower placebo responses recorded in the *H pylori* positive subjects may have contributed to the benefit of omeprazole over placebo being apparent only in the *H pylori* positive subjects. The ability to detect the benefit of any active treatment is reduced when there is a large placebo response as it can only be observed in the proportion not responding to placebo. Blinding the investigators to *H pylori* status and removing any incentive for categorising *H pylori* positive subjects as non-responders may have produced a different result.

Other reasons for benefit over placebo being apparent only in the *H pylori* positive subjects need to be considered. The authors propose that it was due to the more profound elevation of intragastric pH induced by omeprazole in *H pylori* positive versus negative subjects. However, the effect of this difference in pH control with respect to symptom control and mucosal healing is small. A recent large study by Hatlebakk *et al* in patients with heartburn indicated that omeprazole 20 mg/day produced resolution of symptoms in 86% of *H pylori* positive subjects versus 65% of *H pylori* negative.[3] Similarly, Holtmann *et al* observed that relief of heartburn with pantoprazole in patients with oesophagitis was achieved in 89.2% of *H pylori* positives versus 84.5% of *H pylori* negatives.[4] This small incremental benefit could not explain the efficacy of omeprazole over placebo being confined to *H pylori* positive subjects in the present study.

Blum *et al* propose that the *H pylori* infected mucosa may result in enhanced sensitivity to gastric acid and that this may explain the benefit of omeprazole being confined to *H pylori* infected subjects. Such a condition may be a precursor to peptic ulceration. It is well recognised that a proportion of *H pylori* positive patients with functional dyspepsia develop frank peptic ulcer disease in the near future[5–7] and the proportion doing so is similar to the proportion of *H pylori* positive subjects who responded to omeprazole in this study. The subgroup of *H pylori* positive functional dyspepsia patients with this pre-ulcer condition may account for the beneficial response to *H pylori* eradication in some subjects with functional dyspepsia.[5 6] If the benefit of omeprazole in the *H pylori* positive subjects is due to either an acid sensitive mucosa and/or a pre-ulcer state, then an equivalent and more permanent beneficial response could be achieved in the *H pylori* positive subjects by eradicating the infection and restoring a normal mucosa.

Concentrating on the different effects of omeprazole in *H pylori* positive and negative subjects should not distract from another important finding in this study. The study provides useful information on the relative efficacy of different treatments for patients presenting with functional dyspepsia. It demonstrates that placebo plus simple antacid therapy is a highly effective form of treatment for functional dyspepsia with a response rate of 42% in *H pylori* positives and 66% in *H pylori* negatives. The next most effective factor influencing response may be the doctor's desire for a particular outcome as this may well have accounted for the 20% superior response to all forms of treatment in the *H pylori* negative versus positive subjects. Both of these responses are consistent with functional dyspepsia being a disorder with a substantial supratentorial component.

The main conclusion of this paper, that a relatively small proportion of *H pylori* positive but not negative patients

with functional dyspepsia respond to omeprazole, seems robust. However, it is possible that this same beneficial response could be achieved and in a more permanent form by eradicating the *H pylori* infection.

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Non-Hodgkin's lymphoma after immunosuppressive therapy

The development of renal transplantation in the 1960s, made possible by azathiopine, also allowed the testing of the immunosurveillance proposed by Burnett and Thomas, that cancer has its origins in mutations which would usually be eliminated by a healthy immune system. An increased incidence of non-Hodgkin's lymphoma (NHL) in transplant recipients was soon recognised but not the generalised increases of malignancy that seemed to be predicted by the theory. Instead, increases of skin, liver, and (possibly) cervix cancers, and of Kaposi's sarcoma suggested that immunosurveillance operates primarily against malignancies of infective origin, as animal work had also indicated. It has become clear that this hazard is a feature of other immunosuppressive drugs, including 6-mercaptopurine, cyclophosphamide, cyclosporine, and methotrexate, and is not dependent on the presence of foreign antigens, extending to patients without organ transplants. In fact, an increased incidence of NHL has been found in virtually every type of marked immune impairment (whether or not treatment related) that has been studied in appreciable numbers, included AIDS and rare genetically determined disorders such as the Wiskott Aldrich syndrome.[1]

The paper by Farrell and colleagues[2] in this issue of *Gut* on the risk of cancer in 782 patients with inflammatory bowel disease, 30% of whom received immunosuppressive treatment (other than steroids), provides an opportunity for considering certain aspects of such therapy (see page 514). There can be no doubt that the excess of lymphomas in their study is related to immunosuppressive therapy, not only because the excess was confined to the group treated in this way, but also because of the totality of the evidence referred to above. It is sometimes implied that an excess of lymphomas needs to be established following such treatment for a particular disorder, as if here it might be free of risk. This is not necessary for no example is known of an iatrogenic carcinogenic risk being restricted in this way; it is the *treatment* (the exposure) that is relevant. The size of the risk evident in any given situation is, of course, likely to be influenced by the dosage and the duration of treatment and, as always, the play of chance. The interpretation of an excess of NHL may be complicated by the possibility that it reflects effects of the disorder under treatment, as in rheumatoid arthritis; here, however, the 9.7-fold increase found in seven pooled studies was significantly greater than the 2.2-fold increase in the absence of immunosuppressive treatment (14 studies).[1]

The increased incidence of NHL, reported by Farrell and colleagues in their patients is, at over 55-fold, strikingly large and much greater than that usually reported in non-transplant patients treated with immunosuppressive drugs.[1] Indeed, it also exceeds the ten-fold increase recently recorded in Scandinavian renal transplant recipients.[3] This may partly reflect the doses and duration of treatment but another factor also merits attention. The register of patients with inflammatory bowel disease treated since January 1990, on which the study was based, was only "set up in mid-1996", by which time three of the four cases of NHL had already been diagnosed. Given that all the patients attended one hospital, the authors were likely to have known of some of these lymphomas and, though not mentioned as a reason, this may have influenced the decision to set up the register for the study. But if so, inclusion of all the lymphomas (and the person years of exposure prior to mid-1996) in the analysis would have introduced bias and rendered the statistical tests invalid.

At first sight, the logic may not be obvious of analysing data only *after* the date of diagnosis of the most recent lymphoma to arouse interest. Suppose the "real" increased incidence was only half of that observed, say 25-fold, and that the expected number prior to mid-1996 was 0.04 (not unreasonable given the value of 0.06 for the whole period 1990–99). This would lead on average to one case of NHL (but with a wide range in the confidence interval). Often there would be no lymphoma (as in many transplant centres in the 1970s[4]) but sometimes two or three. The absence of a case could not prompt a study so this might not be undertaken, whereas the atypically increased occurrence of two or three cases, from the upper part of the confidence range, might well do so. As a general principle, inclusion in the analysis of the cases of disease that led to a study in the first place is likely to upwardly bias the magnitude of the risk estimate. It would seem probable that the 58-fold increase recorded by Farrell and colleagues is indeed inflated by chance.

Even marked increases of relatively rare diseases such as NHL can go undetected except in large studies and, even more so, can small increases of other malignancies. Transplant recipients have been the main subject of large comprehensive studies of cancer after immunosuppressive therapy, and recently increases of a wider range of sites have been reported than found previously, including colon and lung cancers.[3]

The statement of the authors that the incidence of lymphomas in their study is low in absolute terms seems inappropriate and invites misinterpretation. Taken at face

value, the four lymphomas caused by treatment (in one in 60 patients) exceeds the total expected number of malignancies of *all* types in this group (2.15). Even if the incidence of NHL has been exaggerated as indicated above, it is clear that any iatrogenic malignancy, especially among patients with a disorder that is not invariably fatal, must represent grounds for great concern. That these risks are not fixed is indicated by the marked decline in the incidence of post-transplant lymphomas that has occurred since 1970 as doses of steroids and immunosuppressive drugs have been reduced.[1] The weighing of benefits and hazards (and explaining these to the patient) is important here as in so much of modern clinical medicine. The study by Farrell and colleagues highlights the risks of immunosuppressive drugs (in any disorder) and the need to keep their use to a reasonable minimum.

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Colorectal cancer survival in Europe: the Will Rogers phenomenon revisited

Colorectal cancer (CRC) is one of the leading causes of cancer death in Europe. In this issue of *Gut*, Gatta and colleagues[1] report survival results from a population based study involving 2270 cases of CRC from 11 cancer registries in six European countries (see page 533). The authors report a surprisingly wide range of overall survival among the registries; three year survival varied from a low of 25% in Cracow, Poland to a high of 59% in Modena, Italy. An understanding of the causes for this wide variation could serve as the database for efforts to improve the overall outcome of CRC.

It is well established that the prognosis of CRC is dependent on factors related to the tumour, the patient, and the treatment of the disease. More advanced stage, location of the cancer in the rectum, poorly differentiated histology, vascular invasion, and older age are all associated with a poorer prognosis of CRC.[2] The surgical approach (extent of resection, elective *v* emergency, skill of the surgeon) and appropriate use of adjuvant therapy also significantly affect overall survival.[2 3] Much of the variation between registries in the report by Gatta and colleagues[1] appears to be due to differences in known prognostic factors. Not surprisingly, the four registries that reported the poorest overall survival also had the four lowest reported percentages of early stage disease and had four of the five highest rates of rectal cancer. After adjustment for these factors, however, the relative risk of death among the registries still ranged from 0.76 to 1.81, with four of the sites being statistically different from the reference site.

Differences in surgical treatment appeared to account for much of the remainder of the differences in CRC survival among the registries. There appears to be a substantial difference in the surgical approach to CRC among the sites. The Cracow registry reported particularly low overall rates of surgical resection (53%), lower rates of resections for potentially curable disease (96% for Dukes stages A+B and 91% for stage C) and much lower rates of elective versus emergency resections (56%) than the other centres. In a model controlling for resection rates, but not elective versus emergency surgery, the variation among registries narrowed, and only the Cracow site, with a relative risk of death of 1.82, remained significantly different from the reference site.

What is the reason for the remaining substantial variance between Cracow and the other registries? A number of established prognostic factors such as the degree of differentiation of the cancers, presence of vascular invasion, or use of surgical adjuvant therapy were not measured in this study. If the registry data were controlled for these parameters, perhaps the differences in survival would narrow further.

It is tempting to speculate that the residual variation in prognosis could be because the aetiology and biology of CRC is different in Cracow than at the other sites. The lower age of patients and higher per cent of rectal cancers in Cracow suggests that there could be differences in aetiological factors or genetic predisposition to CRC in Cracow, and such discrepancies could be reflected in differences in the biological behaviour of CRC. Recently, several specific genetic alterations have been reported to have independent prognostic significance in CRC.[4–7] The presence of microsatellite instability which occurs in almost all CRCs of the hereditary non-polyposis colorectal cancer syndrome and in about 15% of sporadic colorectal cancers has been reported to be associated with an improved prognosis.[4] In contrast, loss of heterozygosity in the region of the DCC gene on chromosome 18q and Ki-ras mutations have been reported to be independently associated with a poorer prognosis in stage II CRC.[5–7] None of these newer genetic prognostic markers was measured in the registry study.[1] Although differences in the biological and genetic basis of CRC could account for the residual variation in reported survival across Europe, a more likely possibility is a variant of the Will Rogers effect.

While commenting on geographic migration during the economic depression of the 1930s, the American humourist Will Rogers is alleged to have said "When the Okies left Oklahoma and moved to California, they raised the average intelligence levels in both states". An analogous phenomenon, stage migration, occurs with more careful staging of cancer.[8] If a population of patients is more accurately staged it will improve the survival of all stages because patients with subtle advanced disease will be upstaged. For example, if liver imaging is routinely included in the staging workup, patients with subclinical liver metastases will be identified, removed from the stage III group and added to the stage IV group thus improving the expected survival of both groups. There is direct evidence in the report by Gatta and colleagues[1] that there was variability in the intensity of the staging protocol among the registries. In 45% of cases, the staging of the CRC was not explicitly stated in the clinical record and had to be reconstructed from the medical records; often the information necessary for accurate staging was not available. In Cracow, for example, a lower percentage of subjects underwent tumour resection so that accurate pathological staging was not

possible in 47% of subjects. Similarly, only 44% of subjects with CRC from Cracow had a liver imaging study performed compared with a mean of 67% for all of the centres. There was also a wide variation in the intensity of the lymph node evaluation among the registries, with as low as 2% and as high as 31% of the resected specimens having 12 or more lymph nodes examined. It seems likely that the reverse of the Will Rogers phenomenon—that is, less careful staging of patients leading to a lowering of the survival of all stages—accounts for much of the residual unexplained variation between CRC survival reported among the registries. Gatta and colleagues[1] recognised this possibility and tried to adjust for it, using the frequency of 12 or more lymph nodes examined and the rate of liver imaging as surrogates for accuracy of staging. This adjustment decreased relative risk from 1.82 to 1.69 for the Cracow registry but the authors could not completely adjust for incomplete staging information.

What can we learn from these types of comparative data between cancer registries? The current study[1] has identified at least two important differences in healthcare patterns that can be used to direct efforts to improve survival of CRC. It appears that late stage of presentation of disease is a major contributor to the poorer survival in some regions, and programmes to increase screening and early detection would probably have a major impact on CRC survival in those areas. Patterns of surgical treatment for CRC appear to account for much of the residual variation in CRC survival across Europe. Efforts to apply elective surgery more consistently and earlier in the course of CRC would pay dividends in improved survival for this disease. Finally, the report by Gatta and colleagues teaches us once again that survival comparisons are limited by the quality of the staging information available and the accuracy with which it is recorded. The Will Rogers phenomenon has been used to illustrate the risks of using historic control groups and to argue for the need for concurrent controls in intervention trials.[8] The same reasoning is applicable to and limits the interpretation of comparisons of registry data. Despite this limitation, Gatta and colleagues[1] have performed a service by identifying important differences in patterns of health care across Europe that are worthy of attention.

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