authorities demanding their collusion in unethical behaviour is illustrated by the recent successful, possibly permanent, suspension of capital punishment in California after a refusal by doctors to administer lethal injections.[14]

Lifton has shown the ease with which doctors can drop their ethical guard, in ways that do not have to be as stark as the horrors of Guantanamo Bay.[1] National and international medical bodies need to understand that not only do they have more power than they generally assume, or choose to use, but that to use that power is a basic ethical duty. This duty is as basic as the application of ethical principles in the daily life of a practising doctor.

Michael Wilks *chairman, Medical Ethics Committee*

(mwilks@bma.org.uk)

British Medical Association, London WC1H 9JP

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Inverse association between appendicectomy and ulcerative colitis

It's too early to recommend prophylactic appendicectomy

An inverse association between appendicectomy and risk of ulcerative colitis was first reported in 1987 as an unexpected finding in a study of childhood determinants of inflammatory bowel diseases.[1] The major impetus, however, for the current interest in the association was a 1994 case-control study which reported that only 0.6% of patients with ulcerative colitis had had their appendix removed before diagnosis, compared with 25.4% of controls from orthopaedic clinics. The corresponding odds ratio of 0.02 launched the idea that appendicectomy protects against ulcerative colitis.[2] But is this so?

Subsequent case-control studies have confirmed the inverse association, although with considerably less extreme odds ratios. In 2001, however, review of the available literature showed that most studies had used inappropriate or questionable methods,[3] and the number of unclear or overtly flawed case-control studies has increased since then. One common problem is the failure to use identical methods and periods for the ascertainment of previous appendicectomies in the patients with ulcerative colitis and in the controls. In several studies, unconditional logistic regression analysis was used in situations where the individual matching should have been retained to avoid over-ascertainment of appendicectomies among controls. Other common problems include the lack of adjustment for confounding factors known to be linked both to appendicectomy and ulcerative colitis risk (such as tobacco smoking) and the use in most studies of hospital controls, who will differ considerably from the background population on many health and lifestyle issues.

Among the more than 25 published studies, only a few research teams who described their methods in sufficient detail to judge the validity of their findings succeeded in applying a sound study design and appropriate analysis strategy to reasonably valid and complete data sources. Two such teams, who focused on appendicectomies in childhood and adolescence, reported significant odds ratios of 0.06 for ulcerative colitis with onset before the age of 17 years[4] and 0.05 for ulcerative colitis with onset between 16 and 45 years of age.[5] Other studies considering appendicectomies in a broader age range reported more moderate but still significant odds ratios of 0.3-0.4.[6–8]

Thus far, there have been only two national cohort studies on the subject. Swedish researchers followed 212 963 people who had had their appendix removed and a control cohort of equal size matched for sex, age, and place of residence. Overall, the incidence of ulcerative colitis was 26% lower in the appendicectomy cohort (relative risk 0.74, 95% confidence interval 0.64 to 0.86), an association that was largely due to 58% lower rates of ulcerative colitis among people who had had an appendicectomy for confirmed appendicitis before the age of 20 (relative risk 0.42, 0.31 to 0.57). In contrast, no subsequent reduction in ulcerative colitis incidence was found for appendicectomies for appendicitis after age 20 (relative risk 0.97, 0.79 to 1.18) or for non-specific abdominal pain (1.06, 0.74 to 1.52).[9] In Denmark, the overall incidence of ulcerative colitis among 154 434 people who had had an appendicectomy was 13% lower than expected based on ulcerative colitis rates in the general population (relative risk 0.87, 0.69 to 1.07). As in the Swedish study, relative risk estimates were lower for people aged <20 years at appendicectomy and for those who had had a perforated appendicitis, although these associations did not reach significance.[3]

If we disregard studies with poor or inadequately described methods, the evidence still supports an

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inverse association between appendicectomy, particularly at a young age, and later risk of ulcerative colitis. Importantly, however, such an association does not automatically imply a protective effect of childhood appendicectomy. One alternative explanation might be that the inverse association occurred, at least in part, because of underlying low rates of appendicitis in children destined to develop ulcerative colitis. In light of the marked and rather selective reduction in ulcerative colitis incidence among people who underwent appendicectomy for confirmed appendicitis before the age of 20 in the Swedish study,[9] such an inverse association between childhood appendicitis, not appendicectomy, and risk of ulcerative colitis seems plausible. Another theoretical alternative is that appendicectomy rates might be low in people from families with a recognised predisposition to ulcerative colitis, if doctors are more hesitant to ascribe non-specific abdominal symptoms in these individuals to appendicitis. If these or similar mechanisms account for the repeatedly observed inverse association, appendicectomies would, at best, be irrelevant in attempts to prevent ulcerative colitis.

To better characterise the inverse association between appendicectomy and risk of ulcerative colitis, carefully designed and properly analysed large studies are required that enable a distinction between effects of appendicectomy and those associated with its most common underlying reason, appendicitis. Without substantive evidence to suggest a genuine protective effect of appendicectomy, any speculation about clinical trials to evaluate its therapeutic or preventive impact in relation to ulcerative colitis[10–13] seems premature. Although appendicectomies are technically simple operations in most situations, complications can be serious and even life threatening. The health and hopes of patients with ulcerative colitis and their relatives are at stake—as is the reputation of the medical profession if premature action is taken on inconclusive evidence.

Morten Frisch *senior researcher*

(mfr@ssi.dk)

Division of Epidemiology, Department of Epidemiology Research, Statens Serum Institut, DK-2300 Copenhagen S, Denmark

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Treating refractory epilepsy in adults

The choice of drug or drug combinations is bewildering

Most adult patients with refractory epilepsy have partial (focal) seizures with or without secondary generalisation. During the 1970s and early 1980s studies showed that in 70-80% of adults with newly diagnosed epilepsy, seizures were controlled successfully by carefully monitored monotherapy with any of the four standard antiepileptic drugs—phenobarbital, phenytoin, carbamazepine, or sodium valproate—all of which seemed to have similar efficacy in partial epilepsy in later comparative trials of monotherapy.[1–4] Furthermore, adding a second drug for patients with continuing seizures on optimum monotherapy led to modest benefit in no more than one third, a deterioration in seizure control or unacceptable toxicity in about a quarter, and no change in the rest.[2 5]

These studies led to important questions. Should patients unresponsive to the optimum use of the first drug be switched to alternative monotherapy or treated with polytherapy? If so, which drug or drug combination is appropriate?

Twenty years later these questions remain unanswered. Meanwhile 10 new drugs have been licensed and marketed in the United Kingdom as adjunctive therapy in adults for resistant mainly partial epilepsies: clobazam, vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, levetiracetam, oxcarbazepine, pregabalin, and zonisamide.

The only pragmatic controlled clinical trial of adjunctive therapy in partial epilepsy that was unresponsive to a single drug showed that the probability of remaining free of seizures over the next year was 16% for patients on adjunctive therapy and 14% for those switched to alternative monotherapy.[6] The authors emphasised that the trial was statistically underpowered and that they had had difficulty in recruitment because of financial competition from commercial sponsors targeting similar patients for new drug trials. In a prospective observational study of 422 newly diagnosed patients, 47% became seizure free on the first drug and only an additional 14% on alternative monotherapy with a second or third drug, whereas only 3% were seizure free on a combination of two drugs—all of which implies a need to consider surgery in appropriately selected patients earlier.[7]

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