Commentaries

See article on page 37

Informed consent

At the beginning of 1999 the British Society of Gastroenterology (BSG) issued guidelines for informed consent for endoscopic procedures.¹ This is the eleventh booklet in the *Guidelines in Gastroenterology* series, all of which contain excellent advice. But is there a down side? Is the practice of medicine becoming too prescriptive?

Firstly, I must come clean. In 1995 I wrote the initial draft of the document on informed consent for endoscopic procedures at the request of Duncan Bell who told me that the BSG Council had commissioned the exercise some years previously, that those nominated had reneged and that the honour of East Anglian gastroenterologists was at stake. Duncan Bell and I aimed to keep the document short and tried to stress two central messages: firstly, the importance of speaking with patients and, secondly, the need for clinicians to devise their own method of ensuring that patients were guided wisely. In the ensuing three or four years the considerably expanded draft document shows all the signs of having been re-written in committee (on several occasions considering the length of gestation). Political correctness has taken over and the general guidelines of both the Department of Health and the General Medical Council are quoted at length and the legal position is clearly enunciated.

In this issue Shepherd *et al* (see page 37) make a case for postal consent for upper gastrointestinal endoscopy. They claim that their study "...confirms that a specifically designed patient information booklet...improves the level of understanding (of the investigation)...(which is) an important component in delivering a quality service to patients." Well, patient information booklets have been around for very many years and the BSG document quoted a previous suggestion that patients may prefer to sign a consent statement at home.² To what extent does this help informed consent? Informed consent concerns empowering people who do not have pre-existing knowledge. In a sense it stems from the American Declaration of Independence (1776) in which it was stated that, "Governments...derive their just powers from the consent of the governed." In the Middle Ages physicians in Europe and the Middle East sometimes made contracts with their patients but designed these to absolve them from responsibility from subsequent adverse events.³ Shades of the present!

Be that as it may it seems that what we might recognise as informed consent first appeared about a century ago in a Prussian directive regarding human experimentation; and re-surfaced in a major way when the Nuremberg Code (1947) addressed the problem of voluntary consent again in respect of human experimentation.⁶ The question of informed consent in clinical practice arose from case law⁵ yet, in the United Kingdom, even today it is virtually impossible for a patient to succeed in suing in respect of being inadequately informed.⁶ Despite this, it is impossible to escape the implications of informed consent in an increasing range of clinical endeavour from using patients in teaching to undertaking human

research. It includes agreeing all invasive procedures and associated problems in anaesthesia, the use of drugs and blood transfusion, the order "not to resuscitate", medical interventions (or cessation of interventions) which may speed death, organ donation, screening for disease, and genetic testing.

What is informed consent? Clearly, as Shepherd *et al* emphasise, it is not just a signature on a consent form. They quote the NHS Litigation Authority in stating that, "appropriate information provided to patients on the benefits and risks of proposed treatment" has its rationale in the observation that, "...complaint or litigation is less likely if patients understand to what they are consenting...". This may be true but it does not necessarily make for good practice. For example, it is easy for a patient to read about the nature of endoscopic retrograde cholangiopancreatography (ERCP) and its attendant risks and then to sign a consent form. In which case if he/she undergoes ERCP and is permanently damaged by an attack of pancreatitis he/she is unlikely to sue.⁷ However, if the procedure has been performed simply as a means of diagnosing diarrhoea or unexplained abdominal pain, has the patient really understood the available options and the risk:benefit ratio of ERCP?

The problem has been well explored by Meisel and Kuczewski⁸ who make a plea for the clinician to discuss therapeutic options rather than reach for the manual on informed consent. Informed consent is not about listing the risks, it does not mean that the patient should be provided with a comprehensive digest of information, nor does it mean that patients should be given information whether they want to hear it or not. Remember the root of the term doctor (*L. docere* - to teach). The gastroenterologist should not allow himself to become a technologist. He should first and foremost be a physician who is there to advise his patients. And he should strive to give the impression that he has time to talk. If this is not done the patient may build up resentment and if this happens no matter how much written information has been provided, he may become angry. And most plaintiffs are angry.

Written information about endoscopic procedures is undoubtedly useful but it does not replace the over-riding need for doctors to speak with their patients about the options for further action. Shepherd *et al* suggest that written information delivers *quality* service (lovely "government speak") but for those interested in the nature of the quality of consent I recommend reading a satirical editorial in the *American Journal of Medicine*.⁹ Advising patients about options is more important than obtaining informed consent.

G NEALE

*Emeritus Lecturer in Medicine University of Cambridge,
30 Bevin Square,
London SW17 7BB*

1 British Society of Gastroenterology. Guidelines for informed consent for endoscopic procedures. *Guidelines in gastroenterology* 11. London: British Society of Gastroenterology, 1999 (<http://www.bsg.org.uk/guidelines/consent.html>).

2 Periera SP, Hussaini SH, Wilkinson ML. Informed consent for upper gastrointestinal endoscopy. *Gut* 1995;37:151-3.

3 Baron JH. History of informed consent. *Lancet* 1996;347:410.

4 Kour NW, Rauff A. Informed consent—a historical perspective and a clinician's view. *Singapore Medical Journal* 1992;33:44-6.

- 5 Kennedy I. Consent to treatment: the capable person. In: Dyer C, ed. *Doctors, patients and the law*. Oxford: Blackwell Scientific Publications, 1992.
- 6 McClean SAM (ed). Litigating disputes in consent to medical treatment: the United Kingdom position. In: *Compensation for damage: an international perspective*. Aldershot: Dartmouth Publishing Company Ltd, 1993.

- 7 Neale G. Reducing risks in gastroenterological practice. *Gut* 1998;**42**:139–44.
- 8 Meisel A, Kuczewski M. Legal and ethical myths about informed consent. *Arch Intern Med* 1996;**156**:2521–6.
- 9 Lacombe MA. The quality of consent. *Am J Med* 1996;**100**:258–60.

See article on page 58

Immunological and genetic links in Crohn's disease

Current consensus holds that the pathogenesis of Crohn's disease involves the interacting elements of multigenic host susceptibility factors and environmental priming from the enteric microflora.^{1,2} Tissue damage is mediated by the immune system, although the contributory mechanisms are still unclear, and may be multiple or varied in different individuals. In addition, many immunological alterations in patients with Crohn's disease seem to have no direct role in mediating tissue injury and are frequently dismissed as epiphenomena. The history of medical discovery is replete with examples of overlooked clues hitherto dismissed as unimportant. Could some of the antibody markers in Crohn's disease yet provide useful clues to disease aetiology and pathogenesis? Could some of these phenomena be manifestations of the linkage across genetic, immunological and environmental contributions to aetio-pathogenesis?

Marker antibodies have attracted considerable attention as putative manifestations of the disease related immune response in inflammatory bowel disease.³ The relative specificity of some of these antibodies for either Crohn's disease or ulcerative colitis indicates that their expression is not a simple epiphenomenon of intestinal injury or mucosal inflammation. At present, the clinical diagnostic utility of antibody detection is of limited value, although combined detection of multiple antibody markers seems promising.^{4,5} In contrast, detection of disease related antibodies may have particular value as markers of heterogeneity within inflammatory bowel disease, as markers of underlying immune dysregulation or cross reactivity with an environmental agent, and as possible immunological traits related to disease susceptibility.³

The value of autoantibodies as markers of disease susceptibility is well established in the case of islet cell antibodies and insulin dependent diabetes mellitus. In inflammatory bowel disease, some but not all antibody markers exhibit familial aggregation, and might, therefore, represent markers of genetic susceptibility. Epithelial and lymphocytotoxic autoantibodies have been reported in familial association with Crohn's disease and ulcerative colitis, whereas antineutrophil cytoplasmic autoantibodies (ANCA) have been controversial in this regard in ulcerative colitis, and pancreatic antibodies which are associated with Crohn's disease do not seem to be familially expressed.³

In this issue, Sutton *et al* (see page 58) report that antibodies to *Saccharomyces cerevisiae* mannan (ASCA) are both disease associated and also a familial immunological trait expressed in both affected and unaffected family members of patients with Crohn's disease. An association between serum antibody reactivity to the cell wall mannan polysaccharide of the yeast *S cerevisiae* and Crohn's disease, but not ulcerative colitis, was noted

over a decade ago and has been confirmed by several investigators.^{4,5} The present study confirms and extends the findings of an earlier report on the familial pattern of expression of ASCA in Crohn's disease.⁶ It is noteworthy that it involved a large study population of family members with appropriate controls and included additional analysis for intraclass correlation of anti-mannan immunoglobulin levels which showed antibody expression to be a trait of family members independent of clinical disease.

Familial aggregation of an immunological observation might reflect environmental or genetic factors, or both. Earlier reports on the increased prevalence of lymphocytotoxic and epithelial antibodies in family members of patients with inflammatory bowel disease varied in their interpretation of potential genetic or environmental contributions.^{7,8} Sutton *et al* provide two circumstantial lines of evidence for a genetic contribution to the familial expression of ASCA; the correlation was stronger for first degree relatives versus all relatives, and concordance was significant in sibling pairs (reflecting genetic and environmental contribution) but not in genetically dissimilar marital pairs (reflecting environmental contribution alone). Thus, the findings cannot be accounted for by close environmental contact alone, although the authors concede that an environmental contribution, perhaps a common childhood exposure, cannot be discounted.

Although the findings of Sutton and colleagues raise the possibility that ASCA might have value as a preclinical marker of Crohn's disease, this will require long term prospective study. A more immediate application for ASCA relates to the assessment of heterogeneity within Crohn's disease. As Sutton *et al* point out, the concordance of seropositivity or seronegativity among probands with Crohn's disease and affected relatives provides evidence for distinct immunological subsets of this disease. What is needed now is careful correlation with other potential markers of heterogeneity in Crohn's disease, incorporating genetic, immunological, clinical, and therapeutic profiles. This will be facilitated by standardisation of serum testing and rigorous clinical categorisation of patients, and can be accelerated by interlaboratory collaboration with exchange and sharing of serum samples and data.

In conclusion, there remains an unacceptable gap in our knowledge of the molecular mechanisms underlying the genetic, environmental, and immunological contributions to the pathogenesis of Crohn's disease. Multidimensional approaches that attempt to link immunogenic and clinical observations with due recognition of the likelihood of distinct disease subsets, are required. Immunological phenomena, including marker antibodies, have provided a bridge between clinical and basic sciences in the investigation of several other diseases,⁹ and promise to fill a similar role in inflammatory bowel disease.

F SHANAHAN

Department of Medicine,
Cork University Hospital,
Co Cork, Ireland
email: FShanahan@iruccvax.ucc.ie

- 1 Stallmach A, Strober W, MacDonald TT, *et al.* Induction and modulation of gastrointestinal inflammation. *Immunol Today* 1998;19:438–41.
- 2 Shanahan F, O'Sullivan GC, Collins JK. Genes, bacteria and T cells: ingredients for inflammatory bowel disease. *Gastroenterology* 1998;115:1595–6.
- 3 Shanahan F. Antibody “markers” in Crohn's disease: opportunity or overstatement? *Gut* 1997;40:557–8.
- 4 Quinton JF, Sendid B, Reumaux D, *et al.* Anti-Saccharomyces cerevisiae mannan antibodies combined with antineutrophil cytoplasmic antibodies in inflammatory bowel disease: prevalence and diagnostic role. *Gut* 1998;42:788–91.
- 5 Ruemmele FM, Targan SR, Levy G, *et al.* Diagnostic accuracy of serological assays in pediatric inflammatory bowel disease. *Gastroenterology* 1998;115:822–9.
- 6 Sendid B, Quinton JF, Charrier G, *et al.* Anti-Saccharomyces cerevisiae mannan antibodies in familial Crohn's disease. *Am J Gastroenterol* 1998;93:1306–10.
- 7 Korsmeyer SJ, Williams RC Jr, Wilson ID, *et al.* Lymphocytotoxic antibody in inflammatory bowel disease. A family study. *N Engl J Med* 1975;293:1117–20.
- 8 Fiocchi C, Roche JK, Michener WM. High prevalence of antibodies to intestinal epithelial antigens in patients with inflammatory bowel disease and their relatives. *Ann Intern Med* 1989;110:786–94.
- 9 Tan EM. Interactions between autoimmunity and molecular medicine and cell biology. Bridges between clinical and basic sciences. *J Clin Invest* 1989;84:1–6.

See article on page 78

IBS: prime problem in primary care

The opening paragraph of the paper by Thompson *et al* (see page 78) goes to the heart of a major problem in clinical research which is that most thinking, research, teaching, and clinical guidance on medical conditions, in this case irritable bowel syndrome (IBS), are based on patients referred by general practitioners to specialists. For a number of reasons our knowledge of the natural history and optimum management of many conditions frequently encountered in general practice and primary care remain relatively scanty. Indeed, the stimulus to undertake this study came from a previous survey¹ in which the same authors found that general practitioners, despite their unfamiliarity with diagnostic criteria for IBS, diagnosed the condition with reasonable confidence, found it less troublesome than many other painful conditions such as pelvic pain, headache and backache and only referred a minority of patients to specialists. In that questionnaire survey general practitioners estimated that they referred about one in seven patients with IBS to specialists and in the present, prospective study, 29% of patients identified were referred to specialists. It is, however, important to remember that in this series, there was a mixture of incident and prevalent cases, and that only 11 (15%) patients had not previously seen a doctor about their symptoms.

If this selection bias causes problems, matters are made more complicated by the fact that general practitioners themselves see only a minority of people with symptoms compatible with a clinical diagnosis of IBS. Community based surveys have indicated that between 10% and 20% of the general population will report a symptom complex compatible with IBS, but only one quarter to one third of these will seek medical attention.^{2–4} In doing so, the decision to consult a general practitioner has as much to do with patients' concerns about the interpretation and possible seriousness of their symptoms as it has with their severity or impact on quality of life.⁵ Psychological factors are also important; although anxiety, neuroticism and depression were originally thought to be part and parcel of IBS, it has become clear that psychological morbidity is associated with health care-seeking rather than with IBS per se.^{6,7} Interestingly, a recent study from Sydney, Australia, has reported conflicting data in patients consulting with dyspepsia.⁸

The long term course of IBS symptoms in the community has been less well described, although Agreus *et al* have studied a stable Swedish population and found that there is a good deal of movement between functional abdominal pain subgroups, with some patients with lower bowel symptoms going on to report predominantly upper abdominal symptoms one year later.⁹ Interestingly, in an

earlier study from Denmark, only 5% of a randomly selected population sample of patients with IBS were completely symptom-free at five year follow up.³ A surprising finding in a recent one year follow up study of patients identified in a large general practice database was that health care resource utilisation was no greater in the year after the diagnosis of IBS was made than in the year before.

The emotional and psychological baggage which accompanies patients seeking medical advice for IBS is described well in this paper. Fear of cancer was present in 46% of the patients with IBS (compared with 30% of those with organic bowel disease), but unfortunately only about a quarter of these patients seem to have been reassured in this respect after seeing the doctor, and a mere 26% felt entirely better about their symptoms after the visit. Although it has to be remembered that these are prevalent as well as incident cases of IBS, many of whom will have established at least the beginnings of an illness career, it does suggest that although general practitioners may be aware of the psychosocial dimensions of their patients' problems, it is often very difficult to deal with deeply rooted concerns about serious disease. Thompson and colleagues point out that this may be in part due to the fact that about 20% of patients with IBS were not correctly diagnosed by general practitioners. These patients, who were left without a clear diagnosis, might well have been more difficult to reassure. Conversely, only one of the patients diagnosed as having IBS by the general practitioners turned out to have organic disease (proctitis), a reassuring finding in view of the fact that most general practitioners are unfamiliar with the Manning criteria and are probably unaware of the Rome criteria.¹

The penultimate paragraph of this paper contains some sound advice to primary and secondary care physicians. Referred patients—those whom general practitioners find difficult to manage—often refuse to recognise that there are psychological facets to their illness; the likelihood of referral also increases with the number of tests performed. The authors point out that repeated testing suggests an unconfident doctor and that investigations can be both beneficial and detrimental, as likely to prolong anxiety as to allay it, deflecting attention from “the crucial business of teaching the patient the nature of their problem and how to handle it”. Wise words indeed.

R JONES

Division of Primary Care and Public Health Sciences,
Guy's, King's and St Thomas's School of Medicine,
5 Lambeth Walk,
London SE11 6SP, UK
Email:gp@umds.ac.uk

- 1 Thompson WG, Heaton KW, Smyth GT, *et al.* Irritable bowel syndrome: the view from general practice. *Eur J Hepatol Gastroenterol* 1997;9:689–92.
- 2 Jones R, Lydeard S. Irritable bowel syndrome in the general population. *BMJ* 1992;304:87–90.
- 3 Kay L, Jorgensen T, Jensen KH. The epidemiology of irritable bowel syndrome in a random population: incidence, natural history and risk factors. *J Intern Med* 1991;236:23–30.

- 4 Talley NJ, Zinsmeister AR, Melton LJ. Irritable bowel syndrome in a community: symptom subgroups, risk factors and health care utilization. *Am J Epidemiol* 1995;142:76–83.
- 5 Kettell J, Jones R, Lydeard S. Reasons for consultation in irritable bowel syndrome: symptoms and patient characteristics. *Br J Gen Pract* 1992;42:459–61.
- 6 Whitehead WE, Bosmajian L, Zonderman AB, *et al.* Symptoms of psychological distress associated with irritable bowel syndrome: comparison of community and medical clinic samples. *Gastroenterology* 1988;95:709–14.
- 7 Van der Horst HE, van Dulman AM, Schellevis FG, *et al.* Do patients with irritable bowel syndrome in primary care really differ from outpatients with irritable bowel syndrome? *Gut* 1997;41:669–74.
- 8 Talley NJ, Boyce P, Jones M. Dyspepsia and health care seeking in a community. How important are psychological factors? *Dig Dis Sci* 1998;43:1016–22.
- 9 Agreus L, Svardsudd K, Nyren O, *et al.* Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability over time. *Gastroenterology* 1995;109:671–80.

See article on page 121

UDCA, PBC and biochemistry: what does normal mean?

In this issue (see page 121), Lueschner and colleagues extend previous reports regarding factors that predict biochemical normalisation in patients with primary biliary cirrhosis (PBC) being treated with ursodeoxycholic acid (UDCA).¹ This study differs from others in having a much longer follow up period, an unusually large percentage of patients with early stage disease, and intensive evaluation during the follow up, including extensive biochemical, immunoserological, tumour marker, HLA typing, and histological evaluations.

They found, perhaps not surprisingly, that the less abnormal the tests initially, the more likely they were to become normal eventually on treatment and, perhaps even more obviously, the patients who had the best response after one year of treatment were most likely to have test values within the normal range when follow up was extended. They also noted histological improvement and the suggestion that symptoms improve in those patients in whom biochemical tests return to normal.

In Lueschner *et al.*'s study, there was a lack of correlation between the percentage of UDCA in serum bile acids and the biochemical response; this is different from previous reports.² Furthermore, there was a lack of correlation between histological stage at entry and the biochemical response. This may be an artefact given that over 80% of the patients were at histological stages 1 and 2 at entry. Also unanticipated is the histological improvement reported in those patients in whom liver function tests returned to normal. This differs from the overall experience in other studies of the treatment of PBC with UDCA in which histological improvement was inconsistently described.^{3–6} The slow rate of histological progression reported in this series, even in the incomplete responders, is also surprising. Based on modelling studies of untreated patients with PBC, substantially more than five of 47 patients would have been expected to develop histological progression over six years.⁷ One of the drawbacks of Lueschner *et al.*'s study, however, is the sparse description of how the histological grading was done. The methods section mentions a scale from 0 to 4 for several parameters, but the authors do not give details of how the score was derived. Furthermore, the histological data are mentioned in a single sentence and are not tabulated or otherwise presented, making it difficult to grasp fully the effects of treatment on the histological features of PBC.

Perhaps the most important unanswered question is the relation between normalisation of liver function tests and clinically relevant findings such as the development of cirrhosis and its complications. The meaning of this work could be as trivial as showing that those patients with the least abnormal liver tests before treatment have the least abnormal tests after treatment. It would be certainly

important to know whether the biochemical normalisation correlated with clinically important outcomes. Given the early stages of disease in these patients, it is unlikely over even a five year period that these patients would die or require liver transplantation or develop the complications of liver disease which the authors have outlined so carefully. Perhaps another measure would be to assess the correlation between biochemical changes and changes in the Mayo Risk Score. This is mentioned only in passing, the authors stating in the discussion that the Mayo Risk Score or European Risk Score (presumably calculated before treatment began) did not predict the biochemical response to UDCA. Although there are hazards in using surrogate markers, two separate series have shown that the Mayo Risk Score predicts prognosis accurately in patients being treated with UDCA.^{8,9} The results of this calculation for the patients in Lueschner *et al.*'s study would be of interest.

Early measures of treatment response will be particularly important when other forms of therapy become available, particularly when they are to be used as adjuncts to treatment with or in place of treatment with UDCA. Lueschner *et al.*'s study suggests that patients with almost normal test results after one year were most likely to go on to complete biochemical normalisation, although as discussed earlier, the clinical implications of this are truly unclear. This study does help to confirm the value of the initial response of alkaline phosphatase activities to UDCA treatment as a potential determinant of candidacy for adjuvant therapy, as has been reported recently.⁹ In the previously reported study, higher alkaline phosphatase activities after at least six months of UDCA therapy correlated with a poorer clinical outcome. Future studies evaluating the issue of predicting response to UDCA will need to focus both on the biochemical response and on carefully described histological findings and other clinically relevant end points.

K D LINDOR

Mayo Clinic,
200 First Street SW,
Rochester, MN 55905, USA
email: lindor.keith@mayo.edu

- 1 Jorgensen RA, Dickson ER, Hofmann AF, *et al.* Characterization of patients with a complete biochemical response to ursodeoxycholic acid. *Gut* 1995;36:935–8.
- 2 Lindor KD, Lacerda MA, Jorgensen RA, *et al.* Relationship between biliary and serum bile acids and response to ursodeoxycholic acid in patients with primary biliary cirrhosis. *Am J Gastroenterol* 1998;93:1498–504.
- 3 Poupon RE, Balkau B, Eschwege E, *et al.* A Multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. *N Engl J Med* 1991;324:1548–54.
- 4 Lindor KD, Dickson ER, Balduz WP, *et al.* Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. *Gastroenterology* 1994;106:1284–90.
- 5 Heathcote EJ, Cauch-Dudek K, Walker V, *et al.* The Canadian multicenter double-blind randomized controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. *Hepatology* 1994;19:49–56.
- 6 Combes B, Carithers RL, Maddrey WC, *et al.* A randomized, double-blind, placebo-controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. *Hepatology* 1995;22:759–66.
- 7 Locke GR, Therneau TM, Ludwig J, *et al.* Time course of histologic progression in primary biliary cirrhosis. *Hepatology* 1996;23:52–6.
- 8 Kilmurry MR, Heathcote EJ, Cauch-Dudek K, *et al.* Is the Mayo model for predicting survival useful after the introduction of ursodeoxycholic acid treatment for primary biliary cirrhosis? *Hepatology* 1996;23:1148–53.
- 9 Angulo P, Lindor KD, Therneau TM, *et al.* Utilization of the Mayo risk score in patients with primary biliary cirrhosis receiving ursodeoxycholic acid. *Liver* 1999;19:115–121.