

Current issues in Crohn's disease

Finding the cause, making the diagnosis and optimising therapy

CROHN'S DISEASE is an important cause of morbidity in Australia, with a prevalence of about 50 per 100 000 population. The disease is most common in adolescents and young adults, but can occur at any age. The cause is still unknown, but research towards finding the cause is proceeding apace, along with improvements in diagnosis and advances in therapy.

The development of Crohn's disease depends upon an interaction between host and environmental factors. The importance of genetic factors is shown by the increased risk among relatives of people with the disease, particularly monozygotic twins, in whom the concordance rate is as high as 35%. Research has shown that the genetics of Crohn's disease is complex, so there was great excitement when the first susceptibility locus, the *NOD2/CARD15* gene, was identified on chromosome 16.¹ This gene is involved in the recognition of luminal bacterial products and is important in mucosal defence. The risk of developing Crohn's disease is 2–4-fold higher than normal in people with one mutated allele and 20–40-fold higher in homozygotes. However, mutation of this gene is found in no more than 30% of people with Crohn's disease, and homozygotes represent only about 5%–10% of patients. Moreover, the mutation is present in 20% of controls.¹ This indicates that other factors are involved in the development of the disorder. Patients with mutations in the *NOD2/CARD15* gene are more likely to have ileal involvement. However, there is as yet no clinical role for testing for these mutations.² At least seven other susceptibility loci in inflammatory bowel disease have been identified or are being investigated.¹ Unravelling the genetics of Crohn's disease will lead to better understanding of the disease variants and of the role of environmental factors, which may facilitate the development of novel therapies.

The diagnosis of Crohn's disease is often delayed, mostly because the disorder is not suspected. Moreover, in some patients the usual investigations, such as small-bowel radiology or ileoscopy, do not show any abnormalities in the small intestine. The advent in the last two years of the revolutionary M2A capsule endoscope (Given Imaging, Yoqneam, Israel) has made the entire small bowel easily accessible. (An article on the initial Australian experience of using this new technology appears in this issue of the Journal [page 537].³) Initial studies have confirmed that the M2A capsule endoscope can demonstrate lesions of Crohn's disease when the diagnosis is suspected but other modalities have not been able to confirm it.⁴ The capsule will also be able to visualise early lesions, particularly in patients who have had surgery, and has the potential to lead to earlier resumption of therapy in disease recurrence.

An infectious cause of Crohn's disease has long been suspected, but a variety of candidate organisms have been

excluded. Considerable attention is focused at present on an atypical mycobacterium, *M. paratuberculosis*, which causes Johne's disease in ruminants. This organism has been isolated from a small number of people with Crohn's disease, and its DNA has been detected in tissue from some patients. However, the role of *M. paratuberculosis* is controversial.^{5,6} In Australia, although Crohn's disease occurs throughout the country, Johne's disease is found in the south-eastern States but not in Queensland, Western Australia or the Northern Territory. The world's first large placebo-controlled trial of antibiotics directed against *M. paratuberculosis* in patients who have Crohn's disease is currently under way in Australia, encompassing all States. This is near completion and the results are eagerly awaited.

Smoking is associated with a 3–4-fold increase in the risk of developing Crohn's disease. It also leads to a more aggressive course with more frequent relapses, more admissions and more time spent in hospital. A recent French intervention study has shown that this pattern can be reversed by cessation of smoking.⁷ Much more attention should be given to this important aspect of therapy when managing smokers with Crohn's disease.

As multiple mechanisms are involved in producing the inflammation seen in Crohn's disease, new targeted biological therapies are being tried. The first of these to gain widespread use is infliximab, a chimeric monoclonal antibody against tumour necrosis factor alpha (TNF- α). A single infusion can induce remission in about two-thirds of patients with active Crohn's disease.⁸ Three infusions over six weeks can also lead to closure of fistulae in 50% of patients.⁹ Repeated infusions at eight-weekly intervals will maintain remission in over 60% of patients who respond initially.¹⁰ In Australia, infliximab is generally used in patients with severe disease not responding to conventional therapy. Because its molecular structure is 25% murine and only 75% human, infusion reactions, such as pruritus, flushing and nausea, are not uncommon and may prevent its repeated use. Antibodies to infliximab produced by the patient also limit its effectiveness, but antibody production can be reduced by concomitant use of corticosteroids.¹¹ The potent immunosuppressive properties of infliximab also increase the risk of infectious complications, particularly tuberculosis. There are also reports of more unusual infections, such as nocardiosis and listeriosis. Infliximab cannot be used in patients who have active infection or symptomatic strictures. Its use in Australia is currently limited by its cost, as it is not yet available on the Pharmaceutical Benefits Scheme.

Following the success of infliximab, other methods of inhibiting TNF- α are being evaluated. These include "humanised" antibodies (which should be less immunogenic) and oral TNF inhibitors. A variety of other molecules

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involved in the inflammatory process, both stimulatory and inhibitory, are being targeted for research into new treatments. With multiple trials under way in many countries, including Australia, we can look forward to having new therapies available in the future.

Warwick S Selby

Clinical Associate Professor of Medicine
University of Sydney and AW Morrow Gastroenterology and Liver Centre
Royal Prince Alfred Hospital Medical Centre, Newtown, NSW
warwicks@mail.med.usyd.edu.au

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Debriefing: care and sympathy are not enough

Psychological first aid after traumatic events does not prevent later psychological disorders

IN THIS ISSUE OF THE Journal, Priest and colleagues report a further study showing the lack of effectiveness of “debriefing” after a traumatic event in preventing psychological disorders — in this case, in women after childbirth.¹ Their use of debriefing for this purpose indicates how widely the enthusiasm for this intervention has spread in the past decade. On superficial examination, early interventions are an appealing and inexpensive approach to dealing with events that can be followed by predictable psychiatric morbidity.² This negative study adds to the now substantial evidence that psychological debriefing has no value in prevention.^{3,4}

The failure to establish the effectiveness of debriefing means that more expensive, longer term programs need to be evaluated. The challenge is only too apparent, with the recent publication of the Australian Gulf War Veterans' Health Study, which found that 31% of service personnel returning from the 1990–1991 Gulf War developed a psychiatric disorder in the subsequent decade, and that the veterans of the current conflict in Iraq are likely to be at similar risk.⁵

The community-driven imperative for early care and support was highlighted by the Bali bombing in October 2002 and the Canberra bushfires in January 2003. Similarly, the September 11 terrorist attack in New York provoked a demand for action and posed an enormous challenge because of the large number of people exposed to the collapse of the World Trade Center. The call for action after such events is spurred by the articulated policy that prevention should be a primary aim of mental health services.⁶ The public health principle is that people who have had a toxic exposure are at risk, and that the predicted morbidity should be prevented if possible. However, a brief examination of the history of debriefing reveals some of the reasons for its ineffectiveness.

Debriefing began to be advocated when the impact of traumatic events became more generally recognised in the 1980s.⁷ Debriefing is an adaptation of the PIES approach (“proximity, immediacy, expectancy and simplicity”⁸), which was developed to treat acute combat stress reactions in World War II. As a consequence of the effectiveness of this approach in combat, crisis intervention was embraced in the postwar period for patients presenting after a range of adversities. There was a belief that groups with repeated traumatic exposures, such as emergency service personnel, would benefit from psycho-education and articulation of the details and emotions associated with an event.⁷ Subsequent research has concluded that this approach has no benefit.^{3,4} The logical error is the assumption that a treatment that works for acute stress disorder will necessarily keep people healthy in the longer term.

The rationale for debriefing presumes that an individual reaction in the first days after an event is the critical determinant of the longer term outcome. However, while a substantial proportion of people with an acute stress disorder do develop post-traumatic stress disorder (PTSD), most people who develop PTSD have not had a severe acute reaction.⁹ The latter group function effectively and are not highly distressed during the acute stress, and it is easy to assume they are not at risk. This group represent the major conceptual challenge in understanding the adverse effects of traumatic stress and how to prevent the longer term effects. The imperative for effective interventions is considerable, as the burden of disease attributable to PTSD is akin to that of depression,¹⁰ which is ranked second to ischaemic heart disease in projections of disease burden for the year 2020 by the World Health Organization.¹¹

The challenge from a public health perspective is how to minimise and manage predictable post-traumatic psychiatric morbidity. The evidence is that a long period of observa-