

be understood that when an excessive number of variables are evaluated in a relatively small sample size, positive results might occur by chance. This, however, does not undermine the importance of this analysis; there are very few sites in North America that would have the patient population to even attempt this study. The number of variables, however, might explain why at least one variable seems unusual as a predictor.

In larger studies of sclerosing cholangitis and other cholestatic liver diseases (*i.e.*, primary biliary cirrhosis) in which predictive models were constructed, ALP has not been an important factor predictive of mortality. Other factors, such as bilirubin and albumen, tend to be more critical in these patients. In this study by Ko *et al.*, within the limitations of the study, increasing ALP was shown to be a negative predictor of survival. The other findings of a low CD4 lymphocyte count and the presence of opportunistic infections, from a logical point of view, would seem to correlate with survival. Viral loads and resistance pattern have only recently come into routine measurement but clearly might play a significant role in the survival of these patients.

What should the clinician learn from this? ERCP in these patients is helpful with the diagnosis of cholangiopathy; however, therapeutic ERCP is helpful only in reducing pain, not in extending survival. Additionally, this disorder is becoming a rarity, and ERCP should only be considered in those patients with very low CD4 lymphocytes counts after other noninvasive diagnostic modalities have been exhausted. The presence of opportunistic infections and a very low CD4 count is a marker of advanced disease, and the emphasis should be on the HIV disorder, not on the AIDS cholangiopathy. Therapy of both is directed (and outcomes improved) by elevation of CD4 count and depression of viral loads, which can only be obtained by HAART. A multidisciplinary approach to this disorder is critical, particularly because the disease rapidly changes, depending on therapy. With the changing modalities of treatment, it is hopeful that the disorder of AIDS cholangiopathy might become of historical interest.

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Stress and Ulcerative Colitis: Convincing the Doubting Thomases

Since ulcerative colitis was first described, stress has been said to trigger exacerbations (1). Yet this idea could arise from a series of fallacies: confusion of inflammatory bowel disease with irritable bowel syndrome, nonspecific effects on motility, patients' hunger for explanations, confusion of effects with cause, and a fondness among the general public for attributing any and all disease processes to "stress." This emphasizes the need for caution and attention to methodologic rigor in interpreting studies that purport to show an association between psychological factors and inflammatory bowel disease, especially because erroneous or exaggerated attribution of psychological causes can harm patients by leading to stigmatization or trivialization of their complaints. In the 1970s, the recognition of these fallacies and methodologic pitfalls led to widespread skepticism among experts (2), though many inflammatory bowel disease patients (3), and physicians (4) continue to be convinced that there is a causal nexus.

Recently the pendulum might be beginning to swing again, with authoritative reviews including psychological stress among ulcerative colitis risk factors (5), and the report by Bitton *et al.* in this issue (6) lends new empiric support. Among 60 patients enrolled during clinical/endoscopic remission and followed prospectively for 1 year, the number of important life events reported by patients who experienced exacerbations was significantly higher during the month or two before symptoms began than during the corresponding period for patients who remained in remission. The number of subjects was small, and the effects detected were subtle: relapsing patients reported no more life events overall during the study period and no more stress related to them than the no-relapse group, and neither perceived stress or distressed mood were associated with relapse. But the study's solidly prospective design, its insistence that patients be enrolled only in complete remission, and its adjustment for previous disease course probably enabled it to escape confounding by either recall bias or the distressing effects of disease—the Scylla and Charybdis of clinical psychosomatic research.

The detection of even a relatively weak prospective association of psychological factors with inflammatory bowel disease activity is notable, because the reasons for swings between exacerbation and remission still remain largely mysterious. In one study of ulcerative colitis, only 10% of the variation in exacerbation occurrence was explained by a set of commonly suspected risk factors (respiratory infections, oral contraceptives, nonsteroidal anti-inflammatory drugs, and antibiotics) (7).

Bitton *et al.*'s findings are strengthened by their concordance with those of a very similar report previously published in these pages by my own group, which found high levels of perceived stress to predict earlier exacerbation among ulcerative colitis patients (7). There are discrepancies between the two studies, especially in the time scale over which stress influenced disease activity, but these differences do not substantially weaken the take-home message.

Studies of rodent models of inflammatory bowel disease have consistently found effects of stress. Restraint and noise exposure facilitate the development of intestinal inflammation after exposure to di- or trinitrobenzenesulfonic acid (8, 9) or dextran sulfate sodium (10), and mild inflammatory processes in the intestinal wall can be set off by water deprivation (11) or simply by housing in hectic surroundings (12). Support for an integrated biopsychosocial model of inflammatory bowel disease can also be found in findings that have begun to blur the borders between organic intestinal inflammation and the so-called functional disorders. On the one hand, irritable bowel syndrome after acute gastroenteritis, an evolution that is facilitated by psychological factors, involves persistent inflammatory changes in the bowel tissues (13). On the other hand, inflammatory bowel disease patients often have symptoms consistent with irritable bowel syndrome (14).

Stress is likely to be an active factor in only a subset of inflammatory bowel disease patients, partially in relation to psychological or genetic predispositions. Among rats, early weaning predisposes to the development of intestinal inflammation when the animals are exposed to stressors during adulthood (15). The attachment disorders that can result from similar human events have been reported to be particularly frequent in ulcerative colitis patients who lack perinuclear antineutrophil cytoplasmic antibody (16), possibly paralleling the relation of genetic subtype to anomalous stress reactivity in arthritis-prone rats (17).

A link between psychological stress and inflammatory bowel disease is highly plausible. If, according to current pathophysiologic concepts, immune hyperreactivity and increased gut permeability combine to intensify the activation of immune effector cells in the intestinal wall by bacterial and alimentary antigens originating in the lumen (18), stress has the potential to affect this chain of events at several points. Intestinal permeability has been found to increase under stress in a variety of animal models (9, 12, 19, 20), chiefly because of decreased mucus production; the hypothyseal-pituitary-adrenal axis (15, 20, 21), cholinergic nerves (22), and mucosal mast cells (23) seem to play mediating roles. A leaky gut would in turn allow luminal antigens greater exposure to immune effector cells, a mechanism clearly active in at least one animal study (9) in which previously sensitized CD4 cells in the gut wall were crucial in mediating a proinflammatory effect of stress that was absent in thymectomized animals. In addition to these local phenomena, intestinal immune reactivity could be heightened through systemic effects of stress on the immune system, which can include immune stimulation as well as suppression (24–26).

The knottier question of how stress can affect clinical inflammatory bowel disease has been less studied than the mechanisms in animal models. Mediation by the immune system is suggested by the tantalizing finding that high perceived stress is associated with increased numbers of proinflammatory chemokine receptor-5-positive lymphocytes in the circulating blood and in colonic tissues of patients with semiquiescent Crohn's disease (adjusting for the Crohn's Disease Activity Index; Arck P. *et al.*, unpublished data). Behavioral mediators could contribute to an effect of psychosocial factors on inflammatory bowel disease, because patients experiencing severe life stress might be particularly likely to neglect their prophylactic medication regimens (27). Exacerbations might also be furthered by other stress-related behaviors, including poor sleep (7) and consumption of nonsteroidal anti-inflammatory drugs.

The issue of psychological influences on organic medical pathology arouses polarized passions, and psychosomatic researchers often risk preaching to the choir. Methodologic difficulties, especially confounding by disease effects, make it particularly difficult to convince doubting Thomases. Confusion between cause and effect makes all cross-sec-

tional studies suspect and can cast doubt even if the design is prospective. In the Bitton *et al.* study, patients who reported large numbers of life events might have been experiencing the after effects of previously intense disease activity, a risk factor in turn for future exacerbation. The authors attempted to factor out such confounding by adjusting for the total number of previous exacerbations; similarly, in the Italian study, we adjusted for remission duration and for an index of recent severity. But for some critics, no degree of statistical adjustment will ever be enough to exclude the suspicion of unmeasured confounding by the distressing effects of disease.

Considering all these limitations, the link between stress and ulcerative colitis is now probably as well established as it can be on the basis of observational research. Equally convincing studies of Crohn's disease might not be forthcoming, because the rarity of complete remission and the dependence on self-report to gauge activity (compounded by the relative inaccessibility of tissues to biopsy) erect formidable methodologic barriers.

If psychological factors can in fact exacerbate the course of inflammatory bowel disease, an exciting prospective opens up for psychologically oriented approaches to helping patients whose symptoms are refractory or who require toxic therapies. A demonstration of efficacy for such interventions would also be unimpeachable evidence that the psyche does in fact affect human inflammatory bowel disease. It should be recognized that demanding this level of evidence sets the bar high. Even with medical conditions that are clearly stress-reactive, psychological intervention studies can fail for such reasons as inadequate therapist training, flawed patient selection, and the inevitably limited ability of any such interventions to substantially alter stressful external life circumstances. And in the case of inflammatory bowel disease, the occurrence and severity of inflammatory episodes is biologically driven to such an extent that it might be difficult if not impossible to demonstrate effects on disease course from psychological interventions, even if some of the variance in that course is indeed due to stress and distress. Improvement in subjective symptoms and in disease-related quality of life are more achievable, and intrinsically valuable, goals.

Two controlled intervention trials, one of cognitive therapy (28) and one of short-term psychodynamic psychotherapy (29), have failed to demonstrate improvement in inflammatory bowel disease symptoms or prevention of exacerbations. One of these studies was very small, however, and the other might have loaded the dice against success by enrolling unselected Crohn's disease patients. Now is the time for investigators to attempt carefully designed trials of psychological interventions in inflammatory bowel disease, offering enrollment (for ethical as well as scientific reasons) only to patients who are likely to benefit. Well-motivated patients with high risk and/or high vulnerability—persistently active disease or frequent exacerbations

despite adequate medical therapy, high levels of stress, or psychiatric symptomatology—are the ones who might hope to gain from therapies aimed at coping, stress management, and improved psychological health, at least in terms of lower distress levels and also possibly in terms of harder endpoints, such as inflammatory markers or time to relapse. Appropriately-targeted trials of psychologically oriented therapies might thus join studies of pathophysiologic mechanisms as the logical next phase of research.

Even pending such trials, on the basis of current evidence clinicians can feel justified in approaching the issue of life stress with their inflammatory bowel disease patients though taking care to avoid giving the wrong message; some inflammatory bowel disease sufferers confess they consciously avoid mentioning their life difficulties to their physicians for fear they will be blamed for their own disease (30). It could be appropriate to suggest, cautiously and to selected patients, that lifestyle changes or psychologically oriented therapies aimed at lightening their burden of perceived stress might help them bring their disease under control.

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Chronic HBV Without e Antigen: Using HBV DNA to Guide Management

Although the mainstay for hepatitis B (HBV) diagnosis has been serologic testing with HBV antigens and their corresponding antibodies, HBV DNA detection and quantitation are now playing an increasing role in the assessment of viral activity and response to therapy. In the chronically infected individual, the conventional marker of HBV replication is the hepatitis B e antigen (HBeAg); however, an amino acid substitution, most typically in the precore region of the viral genome ("precore mutant"), prevents secretion of the HBeAg from the hepatocyte, resulting in negative serology for HBeAg in many chronically infected patients. In these patients with the precore mutation, HBV DNA is the sole marker of viral activity (1).

The loss of HBeAg and the development of its corresponding antibody, anti-HBe, generally indicates a reduction in viral activity and improvement in biochemical and histologic parameters. This less-active chronic carrier state of hepatitis B surface antigen (HBsAg)⁺, HBeAg⁻, anti-HBe⁺ needs to be differentiated from the precore mutant-infected individual who might have higher risk of continued viral activity and progressive liver disease. It has also become clear that the seroconversion from HBeAg⁺ to anti-HBe⁺ might not mean complete cessation of viral replication. Hsu *et al.* (2) described the long term follow-up of 283 patients who had converted from HBeAg⁻ positivity to anti-HBe positivity and found that over an 8-yr median follow-up, 33% had elevation of ALT and HBV DNA consistent with development of necroinflammation, with 8% eventually developing cirrhosis.

The prevalence of HBeAg-negative chronic hepatitis B-infected individuals might be increasing worldwide. Chan *et al.* reported 17% of HBeAg-negative patients were viremic and had evidence of chronic hepatitis (3). Minute amounts of precore mutant HBV, present even in those who are HBeAg⁺ in serum, are selected after long-term infection and a host immune response that has been directed against the HBeAg. Precore mutant-infected individuals might have severe reactivation of viral activity and a reduced likelihood of response to viral activity (4). Definitive diagnosis of a precore mutation requires direct sequencing of the viral genome; however, in the clinical setting, diagnosis of the precore mutant-infected individual might be suggested by routine testing.

Papatheodoridis and Hadziyannis described the key diagnostic criteria to suggest HBeAg-negative chronic HBV: infected individuals are persistently HBeAg negative for