Critical care dysmotility: abnormal foregut motor function in the ICU/ITU patient

E M M Quigley

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As medicine changes so should all aspects of medical care and knowledge; as more and more patients are subjected to surgical procedures of increasing complexity and risk and as survival rates from catastrophic illness rise, due to advances in surgery, anaesthesia, and intensive care, one would expect an associated growth in awareness of, and research into, the effects of critical illness on gut motor function. However, motor function and dysfunction, in this context, have received scant attention and have remained, for the most part, poorly understood. While a high prevalence of such phenomena as gastro-oesophageal reflux and gastroparesis are assumed, their true rates of occurrence have been scarcely documented. Similarly, while potential consequences of these entities, such as aspiration, oesophagitis, nosocomial pneumonia, feeding difficulties, and even gastric perforation are well known and, justifiably, feared, the effects of critical illness on oesophageal and gastric motor function have been little investigated. There are, it must be conceded, many reasons for this. Several factors, intrinsic to any intensive care (or therapy) unit (IC/TU) patient population, deter the clinician-scientist from difficulties in relation to consent and rarely fully conscious. Symptoms cannot be expressed, thereby ensuring that the consequences of motor dysfunction will be, for the most part, silent. These same factors may give rise to difficulties in relation to consent and ability to cooperate with research protocols.

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oesophageal body function may ultimately prove to be more appropriate than, or should be administered in addition to, acid suppression in the ICU. In the second study, in this issue of Gut,² efforts were exerted further "south", in the stomach and duodenum, but the findings were equally alarming (see page 1384). Fifteen mechanically ventilated ICU patients were subjected to antro-pyloro-duodenal manometry and gastric emptying in the fasted state and following intragastric and intraduodenal nutrient infusion at the very modest rate of 1 kcal/min. The most striking finding was the profound inhibition of antral motility which resulted from either intragastric or intraduodenal nutrient installation; a similar rate of nutrient infusion to healthy volunteers had no effect on this parameter of gastric motor function. Intraduodenal nutrient also provoked profound inhibition of antral motility, phenomena which would serve to further impair gastric emptying. Gastric emptying, was, not surprisingly, delayed. Taken together, these findings indicate a profound "upregulation" of the feedback loop which normally regulates the gastric emptying of nutrients and guarantees the steady delivery of 2–3 kcal/min to the small intestine, thus ensuring optimal digestive function. In the ICU patient, this very same mechanism appears to be preventing the egress of gastric contents in response to a duodenal nutrient delivery rate of just 1 kcal/min, an observation that may go some way towards explaining the frequency of intolerance to enteral nutrition in this population. To add insult to injury, duodenal motility was disrupted with a failure to convert to a fed pattern and a persistence of burst activity, hardly the ideal accompaniment for the digestive process.

In both of these studies, the investigators were careful to control for some of the factors that have bedevilled prior investigations; nevertheless, the pathophysiology of these oesophageal and gastric motor changes remains unclear and the relative contributions of such factors as underlying illness, mechanical ventilation, or hypotension remain unresolved. The Chapman study, by invoking an abnormality in the intestinal sensing of nutrient, does indicate that, in terms of gastric function, the primary abnormality may not be simply "pump" failure, as has been described by others in the critically ill,⁶,¹⁰ but rather a hypersensitive intestino-gastric feedback loop.³

Regardless of the pathogenesis of these findings, everyone who cares for these patients must be aware of the triple jeopardy to which these patients are prone: LOS hypotension, oesophageal body dysmotility, and gastroparesis (fig 1). When combined, these factors expose the ICU patient to an extreme risk of aspiration of acid or, alternately, pathogen enriched, acid depleted gastric juice. These findings demand that we pay much more attention to motor dysfunction¹ and the delivery of enteral nutrition to a highly vulnerable patient population. Here we are presented with a dramatic example of the need for ever greater emphasis on the "organic" manifestations of gastrointestinal myoneural pathology.¹²


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REFERENCES

Melatonin: a novel treatment for IBS?

S Elsenbruch

Can poor sleep affect gastrointestinal symptoms in IBS? More on the ‘bad dreams cause bad bowels’ hypothesis with reference to new treatment options

The issue of sleep in irritable bowel syndrome (IBS) is intriguing and relevant for several reasons. Firstly, complaints of poor sleep are extremely common in patients with IBS. In fact, self-reported sleep disturbance can be regarded as one of the most important extraintestinal symptoms of IBS, which markedly affects quality of life and psychosocial well being.1 In spite of this, little is known about treatment options for this important extraintestinal symptom of IBS. Secondly, there is an overlap between IBS and fibromyalgia syndrome (FS), another pain syndrome which has also been linked to disturbed sleep physiology,3 as well as stress.5 If indeed a proportion of IBS patients share a common pathophysiological mechanism with FS, addressing the treatment of sleep related functions in patients with IBS would be a promising venue. Thirdly, hypervigilance has been discussed as one possible pathophysiological mechanism in IBS.3 In this context, sleep studies using electroencephalogram techniques may be useful to reveal disturbed brain activity consistent with the hypothesis of hypervigilance/altered arousal mechanisms in IBS. Finally, it has been suggested that reports of night time awakenings due to gastrointestinal symptoms, mainly abdominal or epigastric pain, may be used as a discriminatory factor between organic and functional disorder.4

A review of the existing literature confirms that a large percentage of IBS patients report sleep disturbances.7–14 Despite this overwhelming evidence of subjective sleep problems, it remains difficult to answer the question of whether these reports are based on objectively measurable abnormalities in sleep physiology. A total of eight studies have used objective methods to study sleep in IBS.7 8 10 13–15 Of those, three studies found no differences between IBS patients and controls on any polysomnographic measure and concluded that sleep architecture is normal in patients with IBS.7 10 17 Only one study found what one might expect based on patients’ subjective reports of insomnia-type symptoms as well as disrupted, non-restful sleep—namely, markedly decreased slow wave sleep, higher arousal and awakening index, longer wake period after sleep onset, and more downward shifts to lighter sleep stages.7 A number of explanations exist for these heterogeneous results, including differences in patient populations in sex (that is, some have only included women), psychiatric comorbidities (some studies have excluded subjects with concurrent psychopathology, including depression and/or use of antidepressants), relatively small sample sizes,16–18 and inclusion of patients with sleep apnoea.19 Given this conflicting evidence, one could conclude that subjective sleep disturbances are not necessarily substantiated by objective sleep abnormalities in all IBS patients, although it is likely that subgroups of patients with objective sleep abnormalities exist. Determinants of subjective sleep problems in patients with IBS have been shown to include gastrointestinal symptom severity or profile10 11 12 and psychological disturbances/distress.10 13 15 In this context, it is of further interest to note that a large proportion of IBS patients do indeed report night time gastrointestinal symptoms, even if they do not show polysomnographic evidence of sleep disruption. Therefore, the presence or absence of night time gastrointestinal symptoms is neither a valid discriminator between organic and functional disease20 nor a good indication of whether objective sleep abnormalities are in fact present.

Can bad sleep cause bad bowels or vice versa? This question, which ties into the relationship between sleep disturbance and severity of daytime gastrointestinal symptoms, remains difficult to answer.20 Sleep complaints have been found to be associated with perceived intensity of gastrointestinal symptoms.21 Using prospective diary assessments, two studies found that poor subjective sleep was associated with higher gastrointestinal symptoms the following day.8 22 Lending support to the hypothesis that ‘bad sleep causes bad bowels’ rather than vice versa. A more sophisticated way to address a possible cause-effect relationship between sleep disturbance and IBS is the experimental manipulation of sleep functions and subsequent study of effects on gastrointestinal symptomatology. This is what Song and colleagues22 have attempted, and the first randomised, double blind, placebo controlled trial on the effects of melatonin in IBS patients who reported sleep disturbances is described in this issue of Gut (see page 1402).22 Following two weeks of treatment, melatonin treated IBS patients demonstrated a significant reduction in reported abdominal pain, measured with an adapted version of the IBS symptoms evaluation score questionnaire, whereas no significant change was observed in the placebo group. In addition, rectal pressure and volume thresholds for both urgency and pain sensations were significantly increased following melatonin treatment. On the other hand, melatonin treatment had no effect on polysomnographic parameters, or measures of anxiety and depression.

In their study, the authors screened IBS patients for the presence of self reported sleep disturbance.22 Given the apparent inaccuracy of IBS patient reports concerning sleep disturbance and lack of consistent polysomnographic evidence of sleep abnormalities in IBS in the literature, it remains unclear what proportion of patients included in the trial did actually have manifest sleep problems. The lack of treatment effects on polysomnographic parameters in this study would lend support to the speculation that at least a proportion of the patient sample may not have had objective sleep abnormalities. Unfortunately, patients’ basal polysomnographic data are difficult to evaluate in this respect as no healthy control group was included to show the extent to which a ‘first night effect’ affected sleep at baseline.22 23 A recent meta-analysis on the soporific effects of exogenous melatonin found that melatonin treatment significantly reduced sleep onset latency by 4.0 minutes, increased sleep efficiency by 2.2%, and increased total sleep duration by 12.8 minutes.22 Given these modest effects, one may speculate that adaptation effects from the first to the second night (that is, improved sleep due to habituation) may have masked the effects of melatonin treatment. Future studies may consider screening of patients using polysomnography rather than questionnaires, which would have the further advantage of providing an adaptation night to minimise ‘first night effects’, and make treatment induced changes in objective sleep parameters more easily detectable.

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Another issue that demands careful consideration when designing sleep (treatment) studies in IBS in the future is selection of patients with regard to psychiatric comorbidity. Song and colleagues did not report screening for mood disorders in their patient population. However, mood disorders, especially anxiety and depression, are associated with alterations in sleep physiology, irrespective of the presence of other disorders such as IBS. Therefore, inclusion of IBS patients with mood disturbance can introduce difficulties regarding interpretation of sleep data, unless appropriate psychiatric control groups (for example, patients with depression but without IBS) are included. Psychological distress can affect the perception of sleep quality and daytime fatigue, and may modulate perception of other bodily symptoms (visceral and non-visceral) also. Anxiety and depression scores were not affected by melatonin treatment in the study by Song et al., and hence the mechanism by which melatonin treatment improved reported abdominal pain, and rectal pressure and volume thresholds for urgency and pain sensations remains unclear. Autonomic dysfunction has been implicated in the pathophysiology of IBS, including findings of autonomic disturbances during sleep in IBS patients. Based on evidence showing inhibitory effects of melatonin on the sympathetic nervous system in healthy humans, it is intriguing to speculate that modulation of autonomic functions may have played a role in the results reported by Song et al. Overall, these findings are intriguing and call for replication and further study.

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genome sequence, recent development of high throughput genotyping technologies and knowledge of the patterns of genetic variation, it is now possible to perform genome wide association studies for common human diseases. Such genome wide approaches, although comprehensive, still face the analytical challenges of identifying true causal disease alleles. The prospects of identifying potentially significant associations must therefore be tempered by the perils of inaccurately drawn conclusions. Specifically, population progressions made in this new frontier will rely critically on proper execution and interpretation of genetic studies that are able to: (1) detect true positive from false positives; (2) distinguish causal variation from that which is in linkage disequilibrium (LD) (that is, cosegregation or non-random association of nearby alleles within a population); and (3) explain gene-function, gene-gene, and genotype-phenotype relationships.

The challenges presented by these three goals are nicely illustrated in the study of the genetic susceptibility of inflammatory bowel diseases (IBD). Despite the limitations of past genetic tools for complex diseases, the genetics of IBD has enjoyed a near unique situation of having successfully identified multiple associated alleles using these techniques. Several genome wide searches for IBD susceptibility loci had previously identified numerous genominc regions potentially containing IBD risk factors. Subsequently, association studies using positional mapping and candidate gene approaches further identified a few genetic regions that were independently replicated in various populations, including CARD15

The initial excitement regarding DLG5 is now being tempered with prudent realism. Difficulties such as replication of associations and the translation of genetic association to causal functional consequences provide reason for cautious interpretation of results from genetic analyses of IBD and other complex diseases. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges. The articles in this issue of Gut, by Török and colleagues in Germany and by Noble and colleagues in Scotland, highlight several of the challenges.

The current dilemma with DLG5 is not unique in the genetic elucidation of complex human diseases. An analogous situation was observed with type II diabetes, where PPARG was conclusively confirmed as a susceptibility locus only after examination of pooled data among studies, despite inconsistent findings among many small studies. Therefore, large collaborative efforts will be necessary to improve study power and enable adequately sized subpopulations to be studied for potential phenotypic associations with DLG5. Such large collaborative efforts will need to pay particular attention to phenotype, as this will not only be crucial for establishing the association of a genetic risk factor to disease but also for
determining the relationship to clinical phenotype. Without a doubt, additional functional studies that provide convincing evidence of causality will be powerful adjuncts to any positive statistical findings. Finally, given the current status of the replication findings for DLG5, more work is required to define the exact nature of potential association to IBD.

In contrast with DLG5, the IBD5 risk haplotype has been firmly established as an IBD susceptibility region. Rioux et al first reported linkage for CD on chromosome 5q21 in a Canadian population with subsequent fine mapping of this locus to a 250 kb risk haplotype. Several groups have independently confirmed this as a CD associated risk haplotype in different European and Caucasian populations. Unfortunately, identification of the underlying causal genetic variants within this region has been a more daunting task due to the strong LD across this region. In addition, specific phenotypic associations have not been clearly defined. Recently, a provocative study by Peltkova and colleagues proposed two causal SNPs in the carnitine/OCTN cluster located within the IBD5 risk haplotype that was associated with CD. The two mutations were in strong LD and created a two allele risk haplotype (TC haplotype) that was associated with CD independent of the extended IBD5 risk haplotype in their patient population. They provided preliminary functional studies demonstrating that these two SNPs resulted in impaired OCTN transporter function of various organic cations as well as carnitine, an essential cofactor in lipid metabolism. Based on the observed association of this TC haplotype with CD independent of the IBD5 extended haplotype, and a speculative link between OCTN function and intracellular homeostasis, they suggested that these two specific variants rather than other closely linked alleles were causal variants in CD susceptibility.

The recent study by Török and colleagues is the first published study that attempts to replicate the findings reported by Peltkova et al. Although they also found an association of the OCTN-TC haplotype with CD and an interaction with CD associated CARD15 mutations in their German case control cohort, they did not find conclusive genetic evidence that the OCTN polymorphisms were the likely causal variants. This was based on their observation that the association of the OCTN-TC haplotype with CD was not independent from another SNP (IGR2078a_1) also located within this tightly linked region that was chosen as a proxy for the extended IBD5 risk haplotype. The study highlights the difficulty in distinguishing a genetic variation that is causal from that which it is in LD (that is, are the OCTN genes or other unassayed SNPs in the IBD5 region the causal variants?). To firmly establish that the OCTN genes are the susceptibility genes within the IBD5 risk haplotype would require genetic evidence that OCTN-TC is not only independently associated with but also more strongly associated with IBD than the other genetic variants within the extended haplotype on which it exists. This has not yet been convincingly demonstrated. In both of the above studies, the SNP IGR2078a_1 was chosen as a proxy for the IBD5 haplotype. Previous analysis of the IBD5 haplotype structure indicates that this marker is located in a haplotype block at a significant distance from the block containing the OCTN1 and OCTN2 genes. A more relevant comparison to examine whether the OCTN variants are acting independently of the IBD5 haplotype would be to test other hSNPs within the same block. In addition, the relatively small numbers of samples in the two studies preclude a definitive answer to this question of independence of the OCTN variants and the other IBD5 haplotype variants. What are the factors that will influence studies seeking to address this question? In addition to the factors that affect our ability to replicate a true finding of association, the degree of recombination between the putative causal allele(s) and surrounding variants will determine our ability to distinguish the independence of the association signals.

Given the difficulties in resolving these dilemmas, future progress made with respect to OCTN and IBD5 will likely require supportive evidence from functional studies. Information providing a compelling biological explanation for how impairment of these OCTN genes leads to the clinical phenotypes in CD would further strengthen any positive associations. Although Peltkova et al provide preliminary data linking the OCTN mutations with impaired cation transport, it is unclear how these defects would translate to an increased risk for intestinal inflammation. In fact, the OCTNs are widely expressed in various human tissues (that is, brain, intestine, skeletal muscle, heart, kidney, intestines). In addition, previously reported mutations in the human and mouse OCTN2 genes are associated with systemic carnitine deficiency, a condition characterised by diseases of skeletal muscles, cardiac muscles, and liver, rather than the intestinal system. However, these two common variants in the OCTN genes may in the end turn out to be caustive for IBD; much additional work will be necessary to prove causality and determine the precise mechanism of action.

Another apparent inconsistency in the literature regarding the IBD5 risk haplotype is its association with specific clinical phenotypes. Several groups have reported a lack of association between the IBD5 region and specific disease sites. A UK group reported an association of the IBD5 haplotype with both perianal CD and ileal CD; however, on further analysis, they found that in fact the strongest association was for perianal CD with associated ileal disease. Recently, Newman et al reported an association of the OCTN-TC haplotype with ileal CD, independent of perianal disease involvement, which was further strengthened by the presence of CARD15 alleles. In this issue, Török and colleagues report novel phenotypic associations with the IBD5/OCTN-TC haplotype and colonic CD, and with non-fistulising and non-stricturing behaviour. This disparity among the literature reflects the inherent difficulties in genotype-phenotype correlation studies: small sample size of individual stratified subgroups and differences in phenotypic classification systems among studies. Future collaborative efforts to incorporate large data sets using standardised and rigorously defined phenotypic classification schemes will indeed be critical in clarifying these conflicting observations.

Genetic epistasis between both DLG5 and IBD5 with CARD15 was also extensively studied by these various groups, albeit with contrasting findings. This is not surprising, as interpretation of epistasis can be quite challenging. As discussed by Cordell, the same terminology has been used to apply to quite different definitions, as well as statistical and biological concepts. To add to this confusion is the dilemma in interpreting epistasis once it has been statistically identified. Statistical interaction does not necessarily imply interaction on a biological level. Until we can better define the correlation between statistical models and biological models, any interpretation of genetic epistasis should be made with caution.

In conclusion, the genetic revolution continues to progress with great momentum. This has been particularly evident in the field of IBD where the previously impossible task of identifying multiple causal genes has now become a reality. As we continue to generate interesting findings that have promising prospects in advancing our understanding of disease pathogenesis and ultimately, in the care of our patients,
we must be aware of the perils and challenges that come with interpretation of the data. Keeping in mind these intermediate goals of finding true positive associations, identifying actual causal variants, and identifying true gene and genotype-phenotype associations, we can guide our study design and data interpretation to ensure that our ultimate goal, furthering our knowledge of the genetics of complex diseases, is achieved.

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The importance of keeping in touch: regulation of cell-cell contact in the exocrine pancreas

M V Apte, J S Wilson

New insights into the mechanisms regulating acinar cell-cell contact in the exocrine pancreas, with evidence to support a role for PTPs as a key molecule in stabilisation of the adhesion complex in acinar cells via continuous dephosphorylation of the cadherin-catenin complex

The formation of tissues and organs of multicellular organisms during embryonic development involves a highly regulated process of integration and segregation of heterogeneous cell populations into organised cell patterns.1 One of the major regulators of the processes of cell migration, proliferation, and differentiation during organogenesis is cell-cell adhesion, which is predominantly mediated by cell surface glycoproteins. These cell adhesion proteins can respond to cell signalling events and can also transduce signals into the cell.2 Four major groups of cell adhesion proteins have been described, including integrins, immunoglobulins, selectins, and cadherins.

Cadherins are a superfamily of integral membrane proteins that are subdivided into six gene families.1 E-cadherin, a member of the classical cadherin type I family, has been widely studied in a variety of epithelial cell systems.2–5 Like most cadherins, E-cadherin is a transmembrane glycoprotein with an extracellular domain that interacts with the extracellular domains of cadherin molecules of adjacent cells in a calcium dependent homophilic manner. The highly conserved intracellular (cytoplasmic) domain of E-cadherin functions as a binding site for catenins (cytoplasmic proteins that anchor E-cadherin to the cell cytoskeleton). Typically, E-cadherin binds to β-catenin or p120 catenin in the cells; these catenins in turn are associated with α-catenin which links the cadherin-catenin complex to the cytoskeletal protein F-actin within the cell. The formation of cadherin-catenin complexes is critical to cell-cell adhesion. Both cadherins and catenins contain phosphorylation sites which regulate their function at intercellular junctions.6 It has now been established that cell adhesion complexes do not function as static structures but are subjected to highly regulated changes during tissue development and/or repair.7 Loss or alteration of cell-cell contact is a feature of many pathological states, including the relatively slow process of tumour invasion and metastasis and the relatively rapid events of inflammation and oedema formation. Regulation of adhesion complexes in tumorigenesis and inflammatory conditions of the skin has been widely studied8–10 but little is known about the factors regulating cell-cell contact in a complex epithelial organ such as the pancreas. The functional unit of the exocrine pancreas is the acinus, comprising individual acinar cells arranged around a central lumen.11 Each acinar cell is in close contact with adjacent acinar cells through cell-cell adhesions, including tight junctions (which seal the paracellular routes between adjacent cells), GAP junctions (intercellular channels connecting the cytoplasm of adjacent cells), and adherens junctions (specialised regions of adhesion at the basolateral plasma membrane). Acute inflammation of the pancreas (acute pancreatitis) is characterised by the development of interstitial oedema (associated with loss of contact between acinar cells within the tissue12) and infiltration of inflammatory cells into the parenchyma.

The study by Schnekenburger and colleagues13 in this issue of Gut deals with the regulation of adherens junction integrity in pancreatitis and represents a logical progression of previous work by this group14 15 describing the dissociation, internalisation, and reassembly of the adherens junction during acute experimental pancreatitis (see page 1445). In the current study,13 the authors have endeavoured to identify the mechanisms responsible for adherens junction dissociation in pancreatitis using both in vitro (isolated acini exposed to supramaximal caerulein stimulation) and in vivo (mouse model of mild caerulein induced pancreatitis) approaches. The self limiting nature of pancreatic injury in the caerulein pancreatitis model enabled the authors to study cell adhesion regulation not only during injury but also during the restitution (repair) phase.

Cell-cell contact can potentially be disturbed by alterations in the expression or function of adherens junction proteins and/or by disruptions in the actin cytoskeleton. A number of reports in the literature (using cancer cell lines, metastatic fibroblasts, epithelial cells) have described a role for tyrosine phosphorylation of adherens junction proteins in the perturbation of cell-cell contacts.4 14 15 18 Corollary evidence has been provided by studies demonstrating that a dephosphorylated state of cell adhesion proteins (via the action of protein tyrosine phosphatases (PTPs)) is essential for the maintenance of an intact cell adhesion complex.14 19 20

Using a number of elegant experimental protocols, Schnekenburger and colleagues13 have been able to describe a time course of the changes occurring in the adhesion complexes of acinar cells during the development (at one hour after caerulein injection) and resorption (at 48 hours after caerulein injection) of oedema in acute pancreatitis. A significant increase in tyrosine phosphorylation of catenins (β-catenin and p120 catenin) and E-cadherin was observed early in the course of injury (at one and two hours after caerulein injection), although expression of the proteins themselves remained unchanged. The increase in tyrosine phosphorylation of β-catenin and E-cadherin coincided with dissociation of the complex from the transmembrane phosphatase PTPs (known to be constitutively associated with the cadherin-catenin complex in normal cells), redistribution of adhesion proteins from the lateral and apical cell membrane to the cytosol (internalisation), and subsequently, an association of the complex with the cytosolic protein tyrosine phosphatase PTP SHP-1 over 2–4 hours. At 48 hours, resorption of oedema was associated with the reassembly of the adhesion complex and its relocation to the lateral and apical cell membranes. In vitro studies with isolated acini demonstrated that inhibition of PTPs by orthovanadate induced acinar cell dissociation in a manner similar to that observed with supramaximal caerulein, supporting the concept that tyrosine phosphorylation was a key regulator of the cadherin-catenin complex.

Two observations of interest in this study were: (i) the lack of any changes...
in protein expression of the adhesion complex during caerulein pancreatitis in vivo and (ii) the in vitro finding that disruption of the actin cytoskeleton did not influence cell dissociation. Both of these observations strengthen the concept that pancreatic acinar cell dissociation during caerulein pancreatitis is predominantly regulated by tyrosine phosphorylation and dephosphorylation of the proteins of the adhesion complex, and is independent of any alterations in protein levels or the integrity of the actin cytoskeleton.

This study makes a significant contribution to our understanding of the mechanisms regulating acinar cell-cell contact in the exocrine pancreas, with evidence to support a role for PTPs as a key molecule in stabilisation of the adhesion complex in acinar cells via continuous dephosphorylation of the cadherin-catenin complex. However, important questions remain with respect to disruption of acinar contact in the pathophysiological setting. Schnekenburger et al.13 assert that acinar dissociation in caerulein pancreatitis is observed ultrastructurally before the development of oedema, thereby excluding a “physical” cause (such as increased pressure due to accumulation of fluid in the interstitium) for acinar cell dissociation. If acinar dissociation precedes (and is not the effect of) oedema, it would be logical to ask what factors disrupt the mechanisms regulating cell-cell adhesion in the earliest stages of pancreatitis and what factors stimulate reassembly of disrupted adhesion complexes during the repair phase of the disease. Future studies in this area will no doubt be designed to address these issues by examining: (i) the cellular events during acute pancreatitis which disrupt the constitutive association of PTPs with the adhesion complex and/or trigger tyrosine phosphorylation of the complex; (ii) whether proteolytic cleavage of E-cadherin during acute necroinflammation plays a role in triggering tyrosine phosphorylation of the adhesion complex leading to cell dissociation and; (iii) the potential roles of intracellular catenins in restitution of the adhesion complex after internalisation. Elucidation of the above processes has the potential to identify specific molecules/pathways that could be therapeutically targeted to: (i) prevent/inhibit disruption of cell adhesion in the initial phase of acute pancreatitis (thereby maintaining a physical barrier to inhibit inflammatory cell infiltration into the gland) and (ii) stimulate the reassembly of the cell adhesion complex during recovery from the disease.


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Preventing TB in patients with Crohn’s disease needing infliximab or other anti-TNF therapy

D S Rampton

In patients with Crohn’s disease, the increased risk of active tuberculosis (TB) associated with infliximab makes it necessary to screen for active and latent TB before this or other anti-tumour necrosis factor treatment is begun. This paper outlines how such screening should be undertaken, and how to decide which patients need antituberculous treatment or chemoprophylaxis before infliximab.

SUMMARY
The increased risk of active tuberculosis (TB) associated with infliximab makes necessary a screen for active and latent TB before this or other anti-tumour necrosis factor (TNF) treatment is begun in patients with Crohn’s disease. This paper outlines how such screening should be undertaken, and how to decide which patients need antituberculous treatment or chemoprophylaxis before infliximab. All patients need a careful history for TB and a chest x ray. The minority of patients with a history of TB or an abnormal chest x ray should be referred for assessment by a TB specialist. Of the remainder, those with Crohn’s disease who are on immunosuppressive therapy do not require tuberculin testing. Comparison of their risk of TB while on anti-TNF therapy with the risks of chemoprophylaxis induced hepatitis indicates that black Africans aged over 15 years, South Asians born outside the UK, and other ethnic groups resident in the UK for less than five years should be considered for chemoprophylaxis with isoniazid for six months. For how to minimise the risk of TB in the small minority of patients with inflammatory bowel disease not on immunosuppressive treatment, readers are referred to the more detailed guidelines published in Thorax.

INTRODUCTION
Infliximab is of proven benefit in the treatment of chronic active Crohn’s disease as well as in rheumatoid arthritis, most, although not all, cases being extrapulmonary and occurring within the first three months of treatment. Although the incidence of infliximab related TB may now be falling due to improved risk assessment, chemoprophylaxis (see below), and/or reporting fatigue, complacency is clearly inappropriate: mortality of TB in the early days of its recognition in association with the use of infliximab approached 10%.

HOW CAN THE RISK OF TB BE MINIMISED IN PATIENTS TO BE GIVEN INFlixIMAB (FIG 1)?
Recommendations from several sources, including the European Agency for Evaluation of Medicinal Products (EMEA) and the National Institute for Clinical Excellence (NICE) (see below), agree that patients in whom the use of anti-TNF therapy is being considered should be meticulously questioned about prior TB and its treatment, and have a chest x ray taken. Patients with a history of TB or an abnormal chest x ray should be referred directly to a specialist with expertise in TB. Those with active TB should receive standard antituberculous chemotherapy for at least two months before starting on infliximab. Patients with a chest x ray showing previous TB, or with a history of previous extrapulmonary TB which has been fully treated, should be carefully monitored during infliximab therapy; those in whom treatment may have been inadequate should have active TB excluded by appropriate investigation and should be started on chemoprophylaxis two months before starting infliximab.

Patients with no history of TB and normal chest x ray
Some guidelines have suggested that a tuberculin test should be used to direct the optimal approach in this group of patients. Recent data however have confirmed a very high incidence of anergy in patients with Crohn’s, and the EMEA recommendations specifically warn prescribers of the risk of false negative skin test results in severely ill or immunocompromised patients with Crohn’s disease. Indeed, since under existing (2002) NICE guidelines all patients with Crohn’s disease in the UK needing infliximab will be chronically ill and currently or recently taking corticosteroids and/or immunomodulatory drugs, tuberculin testing will not assist in decision making and is considered unnecessary. (There are no data on the incidence of anergy to tuberculin...
in patients with ulcerative colitis; in these, currently exceptional patients, the guidelines described in full by the British Thoracic Society should be followed.)

What does need to be considered is the annual risk of TB in individual patients to be given infliximab: as indicated above, this is increased about fivefold by infliximab and still further in some ethnic groups. This risk needs to be balanced against the risk of side effects caused by TB chemoprophylaxis, which is dependent on the regimen to be used. The commonest regimen, isoniazid for six months, has a hepatitis risk rate of about 280/100 000 treated patients. Two shorter regimens, rifampicin with isoniazid for three months and rifampicin with pyrazinamide for two months, cause serious hepatitis much more often (1800 and 6600/100 000 treated patients, respectively).

These considerations mean that, in general, Caucasians in the UK with no history of TB and a normal chest x ray need no TB chemoprophylaxis. In contrast, even if they have no TB history, and their chest x ray is normal, Black Africans aged over 15, South Asians born outside the UK, and other ethnic groups resident in the UK for less than five years have such a high risk of TB while on infliximab that they should usually be offered isoniazid for six months when starting it. In other non-Caucasian ethnic groups, data on the risk of TB are too limited for it to be possible to make definitive recommendations.

Monitoring for TB in patients on infliximab

All patients on infliximab should be monitored carefully for symptoms such as fever, weight loss, or cough: gastroenterologists should be alert to the possibility of extrapulmonary as well as the more familiar lung disease. The slightest suspicion of TB should prompt immediate referral to a specialist TB physician.

CONCLUSIONS

Tuberculosis is one of the most serious complications of the use of infliximab. In each patient in whom therapy with infliximab is being considered, a plan should be drawn up based on their history, chest x ray, ethnicity, place of birth, and duration of residence in the UK (see fig 1). Implementation of these recommendations is likely to reduce dramatically the risk of TB in patients given infliximab and other anti-TNF agents.

REFERENCES

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The promise and perils of interpreting genetic associations in Crohn's disease

T T Trinh and J D Rioux

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