Intestinal intraepithelial lymphocytes and anti-transglutaminase in a screening algorithm for coeliac disease

We have noticed the frequent publication of important advances in the serological screening of coeliac disease (CD), such as the interesting and useful technique described by Baladas et al (Gut 2000;47:628–31). Humoral screening of CD is coming closer to a test by adding anti-tTG. But CD is the only entity in which a decrease in the natural killer (NK)-like subset is observed, although to a lower extent, in food withdrawal (and challenge) if it fitted into the coeliac pattern and histology showed a typical coeliac enteropathy. If the lymphogram shows negative values for γδ and NK-like IEL, it has a high negative predictive value of 95% against the existence of CD. If the interpretation of the immunohistological study is not straightforward, the classical ESPGAN criteria can be followed.7 We believe that this algorithm, which can be conveniently adapted to the needs of each centre, can correctly classify the vast majority of patients, saving time and money, and avoiding morbidity.

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Figure 1 Proposal of an initial diagnostic algorithm for coeliac disease (CD). After screening with anti-transglutaminase (tTG), and taking into account the high negative predictive value of tTG, study of mandatory intestinal biopsy would include phenotyping of intraepithelial lymphocytes (IEL). The proportion of ‘total IEL’ is calculated with respect to the cellularity of the epithelium while the proportions of ‘γδ IEL’ and ‘natural killer [NK]-like IEL’ are relative to the total IEL. The combined analysis of the pathology and the ‘IEL lymphogram’ allows for a correct classification of >95% of patients after the first biopsy, reducing the need for subsequent invasive procedures. N, normal values.
These values show that the age-standardised incidence of colorectal carcinoma has increased in both sexes over the period studied (proximal more than distal) while the incidence of rectal cancer has remained relatively constant. These data suggest that the changing pattern of distribution of colorectal cancer which we have observed is unlikely to be due to a decreased incidence of distal and rectal cancers. These results may well represent a true increase in proximal colorectal cancers, although as Boland and Savides suggest, they could also be explained by a rising incidence in all subsites, with rela- tive sparing of the distal colon and rectum due to either the protective effect of non-steroidal anti-inflammatory drugs or endoscopic polypectomy.

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A Paneth cell surrogate?

We read with interest the article by Cunliffe et al (Gut 2001;48:176–85) on defensin 5 stored in normal Paneth cells and in metastatic Paneth cells in inflammatory bowel disease (IBD). In recent years a great deal of interest has centred around Paneth cells as carriers of innate host defence, effective through their content of antimicrobial peptides and proteins.1 In humans, that mechanism seems to be conveyed by a complex system of proteins present in the granules of the Paneth cells: lysozyme, secretory phospholipase A, and probably α defensins (that is, cryptidins, so far recorded in mice).

The lysozyme rich granules in Paneth cells appears to be one of the main sources of anti-microbial peptide in the normal small bowel (where Paneth cells are normally present). Although such cells are not found in the normal colorectal mucosa, Paneth cell metaplasia may be present in the colorectal mucosa of some (but not all) patients with longstanding IBD. Demonstration of human neutrophil defensins (HNP 1–3) and lysozyme in epithelial cells of active IBD has fuelled interest in the molecular events behind defensin mediated intestinal host defence.

Against that background, it may be of interest to point out that another source of cytoplasmic lysozyme has recently been unveiled.1 Thirty five years ago, Azzopardi and Evans2 found mucin containing macrophages (denominated muciphages) in the colonic mucosa. Those cells were described as normal phagocytes in an otherwise normal mucosa. The mucoprotein present in their cytoplasm stained with a variety of mucous colors (alcian blue, aldehyde fuchsin, and mucicarmin). Macrophages which were subsequently found to be associated with mucosal abnormalities induced by an inflammatory disruption of the crypts would officiate as scavengers to keep the lamina propria free from the liberated mucin. Until now, muciphages have been considered as a non-specific manifestation of mucosal damage.

We investigated the occurrence of those cells in rectal biopsies from patients with a variety of diseases, we found muciphages either scattered in the lamina propria mucosa or distributed in a more “organised” fashion underneath the superficial epithelium and along the base of the crypts, near the muscularis mucosae.

Immunostain (CD68) confirmed the macrophagic nature of those cells and histochemistry showed the presence of cytoplasmic lysozyme (Lysozyme-Muramidase stain; Dako) in those macrophages (fig 1). In some patients with IBD in remission, the macrophagocytes were strongly positive for lysozyme (Lysozyme-Muramidase stain; Dako A/S, Denmark) (fig 1).

The presence of lysozyme in muciphages suggests that those particular macrophages are not an accidental happening but expression of a more targeted active biological mechanism of lysozyme dependent mucosal defence.

In some patients with IBD in remission, the macrophagocytes may enter the host through the rectal mucosa. The fact that muciphages also contain lysozyme may open new vistas for those previously unattended cells. It is conceivable...
that muciphages may be an important source of antimicrobial peptides in mucosa in protracted remission from earlier inflammatory episodes.

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References

Frontiers in Inflammatory Bowel Disease Grants
Funds for inflammatory bowel disease (IBD) research are available immediately from the Broad Medical Research Program—Inflammatory Bowel Disease Grants. For more information, please visit www.broadmedical.org. Applications should include:

• Curriculum vitae of the applicant
• Research project (max three typewritten pages) including a financial plan to use the stipend
• Covering letter inclusive of formal application
• Address where an acknowledgement of the receipt of the application and any further correspondence should be mailed, including telephone, fax, and email address.

• Letter of nomination of a sponsor of known reputation in the field of hepato pancreatic and biliary surgery.

Broad Medical Research Program—Inflammatory Bowel Disease Grants
This conference will take place on 30 June to 1 June 2002 in Amsterdam, The Netherlands. Further information: Secretariat, Nicolaes Tulp Institute, Academic Medical Center, PO Box 21323, 1100 DS Amsterdam, The Netherlands. Tel: +31 20 566 8395; fax: +31 20 696 3228; email: asge@shore.net

11th International Symposium on Hepatic Encephalopathy and Nitrogen Metabolism
This conference will be held on 30 May to 1 June 2002 in Brussels, Belgium. Further information: Nancy Beaufrez, Gastroenterology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 (0)20 555 49 00; fax: +32 (0)20 555 49 01; email: beaufrez@ulb.ac.be

EASL Monothematic Conference on Vascular Function in Liver Disease
This conference will take place on 30 June to 2 July 2002 in London, UK. Further information: Professor Jordi Bruix, EASL Liaison Bureau, c/o Keneis International, 17 rue du Cendrier, PO Box 1726, CH-1211 Geneva, Switzerland. Tel: +41 22 908 0486; fax: +41 22 732 2850; email: info@easl.com; www.easl.com. Deadline for abstract submission 15 May 2002. Further information: kmoores@rIFIC.ucal.ac.uk; tel: +44 (0)207 433 2876.

5th International Workshop on Pathogenesis and Host Response in Helicobacter Infections
This conference will be held on 4–7 July 2002 in Helsingor, Denmark. Further information: Dr Tina Ken Hansen, Department of Cardiology-Endocrinology E, Frederiksborg Hospital, Ndr. Fasanvej, DK-2000 Frederiksborg, Denmark. Fax: +45 3545 7708; email: helpatim@biobase.dk

NOTICES
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CORRECTION