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LETTERS

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High magnification chromoscopic colonoscopy as a screening tool in acromegaly

We read with great interest the paper by Jenkins *et al* (*Gut* 2002;**51**:V13–14) regarding screening guidelines for colorectal cancer (CRC) and polyps in patients with acromegaly and the subsequent discussion by Renehan addressing screening inconsistencies compared with other high risk groups.[1 2]

The optimal colorectal screening modality and frequency in this group however requires clarification. Colonoscopy in this patient group is technically demanding and often complicated by inadequate bowel preparation.[3] However, despite current controversies regarding true CRC risk categorisation in acromegaly, previous data from the largest published series showed a trend for adenoma and carcinoma formation in the right hemi colon.[4] This is an important observation for many reasons.

Flat adenomas and carcinomas can be difficult to detect by conventional colonoscopy alone, often presenting as subtle mucosal erythema, mucosal pallor, fold convergence, interruption of innominate grooves, air induced deformation, or loss of vascular net pattern.[5] The neoplastic risk for this morphologically distinct group has additionally been shown by many authors to be higher when compared with exophytic polypoid lesions and exhibit a propensity for the right colon.[6–9] De novo neoplastic lesions and ''minute'' colorectal cancers are also associated with an increased risk of lymph node metastasis due to early invasion of the submucosal layer.[10] Tada *et al* found extensive submucosal invasion in a cohort of flat colorectal neoplasms,[11] with Shimoda's series corroborating these data with submucosal invasion demonstrable in 69% of flat carcinomas compared with only 35% of sessile and broad based polypoid carcinomas.[12]

Morphologically flat and depressed lesions are also known to occur in chronic ulcerative colitis[13] where the need for CRC screening with total colonoscopy and now adjunctive chromoscopy is adopted by many centres. Failure to detect such lesions may in part account for those cases of CRC which occurred in Winawer's study, despite clearance of all exophytic polyps, and thus stresses the requirement for accurate diagnosis and definitive treatment of these high risk lesions.[14]

Given the lack of standardised and uniform reporting regarding the morphology of colorectal lesions in many of the existing prevalence studies of adenomas and CRC in acromegaly however, at present we can only hypothesis that the high incidence of right hemi colonic neoplasia may be an indicator of an alternative morphologically distinct lesion such as the flat adenoma and carcinoma with a trend towards a de novo pathogenic sequence.

In our prospective study, 38 patients with acromegaly underwent total colonoscopy by a single endoscopist using the Olympus C240Z magnifying colonoscope. Preparation was with 4 litres of Kleanprep 24 hours prior to the procedure. Pancolonic chromoscopy using 0.5% indigo carmine sprayed onto the colonic mucosa using an Olympus diffusion catheter (CS12890) was applied. Identified lesions were morphologically grouped according to the Japanese Research Society Classification (JRSC).[15 16] A flat lesion was defined as mucosal change with a flat or rounded surface combined with a height of less than half the diameter of the lesion.[17] High magnification views of all suspected lesions were then obtained and reported according to the modified Kudo criteria.[18] Tissue sampling was performed with cold biopsy or endoscopic mucosal resection following exclusion of a Kudo type V(n)/IIIs invasive crypt pattern which suggests deep submucosal invasion. Mean intubation and extubation times were recorded. Neoplastic change was classified according to the Vienna criteria.[19]

Caecal intubation was achieved in 37/38 (97%) patients with 36/38 (94%) receiving confirmatory terminal ileal biopsies. Males represented 14/37 (37% of the cohort, mean age 64 years (range 40–75)). The mean duration of intubation to the caecum was 16.5 minutes (range 3–31) and extubation (excluding interventional procedures) was 35 minutes (range 20–55). There were no complications.

A total of 28 lesions were identified in 15 patients. Twenty two hyperplastic lesions were identified (79%) of which 17 (77%) were flat (JRSC II). Twenty (91%) were located in the left colon and rectum. Of the five adenomas identified, four (80%) were present in the right colon with 4/5 (80%) being of JRSC II morphology. A single adenoma with high grade dysplasia was present in the right colon and was flat with a small area of central depression. No invasive carcinomas were diagnosed. Results are summarised in table 1.

Although the numbers entering this study are small, our results show a clear prevalence for JRSC class II lesions in this select patient group. Although only one adenoma with high grade dysplasia was detected, it was small (5 mm) and was not identified prior to chromoscopic and magnification enhancement, and therefore carries major clinical connotations.

We suggest that further large prospective studies are required to establish the true prevalence of flat and depressed colorectal lesions in acromegaly so that the optimal screening modality and frequency can finally be established. Furthermore, colonoscopists require training in chromoscopic techniques if a higher endoscopically ''treatable'' lesional frequency is to be detected at a screening level, so as to avoid the high apparent incidence of interval neoplasms.

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Table 1 Lesion demographics

		Morphology (JRSC)				Anatomical location	
Histology	n	I	II	Dominant crypt pattern	Mean size (mm)	Rt colon	Lt colon/rectum
Hyperplastic	22	5	17	I/II	6	2	20
Adenoma LGD	5	1	4	IIIL	6.5	4	1
Adenoma HGD	1	0	1	V(a)	5	1	0
Invasive neoplasia (T2 or beyond)	0	0	0	NiII		0	0

LGD, low grade dysplasia; HGD, high grade dysplasia.

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Fetal ''cardiac mucosa'' is not adult cardiac mucosa

De Hertogh *et al*'s autopsy study of the fetal gastro-oesophageal region provides valuable insight into the development of foregut epithelium in the 13–24 week gestational period (*Gut* 2003;**52**:791–6). Coincidentally, two other studies appeared on the same subject in April 2003.[1 2] These studies were stimulated by our hypothesis that cardiac mucosa does not exist as a normal structure in humans.[3 4]

Three columnar epithelial types are reported between squamous epithelium and parietal cell containing gastric mucosa in De Hertogh's study (*Gut* 2003;**52**:791–6). These are called ''primitive oesophageal mucosa'', ''primitive stomach mucosa'', and ''cardiac mucosa''. Careful anatomical correlation place all of these mucosae in the oesophagus, proximal to the gastro-oesophageal junction. ''Primitive oesophageal mucosa'' is a ciliated epithelium that disappears at 24 weeks. ''Proximal stomach mucosa'' is a layer of flat columnar cells containing depressions that correspond to early gland pits distally. ''Cardiac mucosa'' is composed of foveolar and surface epithelium overlying glandular structures containing no parietal cells. The description of ''cardiac mucosa'' and figs 2 and 4 show a very thin columnar epithelium composed of uniform mucous cells with foveolar pits and rudimentary sac-like structures devoid of any inflammation. Derdoy *et al*'s ''cardiac mucosa''[2] and Park *et al*'s ''transitional zone''[1] are identical in appearance. I have never seen this fetal epithelium in any adult patient. The fact that these authors call it ''cardiac mucosa'' does not make it identical to the more conventional cardiac mucosa seen in adults. The only similarity is that it is a glandular mucosa composed of mucous cells only. It is much thinner than adult cardiac mucosa, it has no inflammation, and its glands are much less developed if present at all.

I would like to propose an alternate explanation for the changes seen in all three papers that I believe provides a better explanation of the data in the papers. The early fetal oesophagus is lined by primitive undifferentiated ciliated columnar epithelium. It begins differentiating into squamous epithelium proximally and gastric mucosa distally. Gastric differentiation is marked by the appearance of true glands containing parietal cells. In the second trimester, the oesophageal squamous epithelium is separated from parietal cell containing gastric mucosa by a columnar epithelium composed of foregut columnar stem cells forming a flat surface and a foveolar pit. This is uncommitted fetal columnar epithelium. This continues to develop into either squamous epithelium proximally or parietal cell containing gastric mucosa distally, so that its overall length decreases as fetal age increases (as shown in De Hortogh *et al* and Derdoy *et al*'s studies[2]). With completion of the development of the lower oesophageal sphincter in early infant life, the physiological gastro-oesophageal junction is defined and the uncommitted columnar foregut epithelium completes its development into squamous in the oesophagus and gastric mucosa with parietal cells distal to the lower oesophageal sphincter. The uncommitted foregut columnar epithelium disappears. The only normal mucosae seen after development is complete are squamous and gastric with parietal cells. This is proven by illustrations that show children with a direct transition of squamous epithelium to gastric mucosa with parietal cells (Chandrasoma and colleagues[4] and fig 2A of Park and colleagues[1]). The absence of cardiac mucosa in these illustrations is proof that cardiac mucosa is not universally present in children. Adult-type cardiac mucosa is also absent universally in fetuses. The only reason why De Hertogh *et al* reach the conclusion that it is universally present in fetal life is that they erroneously apply the term ''cardiac mucosa'' to the uncommitted fetal columnar epithelium that is universally present in fetal life.

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Author's reply

We would like to thank Dr Chandrasoma for his attentive reading and kind comments on our work published in *Gut*. He has also provided the readers with an admirable synthesis of the most recent research on the development of the different mucosal types in the gastro-oesophageal junction region. By means of this letter, we want to reflect on some of his comments.

The quintessence of Dr Chandrasoma's vision on cardiac mucosa (CM) is that it is not a normal structure but develops through metaplasia in the context of gastro-oesophageal reflux disease. The presence of a small length of CM in many ''normal'' adults could be the result of asymptomatic low level reflux. According to his view, the ''non-ciliated non-glandular late fetal foregut epithelium'' (which we call CM in our study) will develop into either oesophageal squamous epithelium or gastric mucosa with parietal cell containing glands. The necessary corollary of his theory is that there can be no such thing as a normal CM. He also puts forward the notion that the presence of CM in some infants might be due to deviant differentiation of the uncommitted epithelium in the context of reflux or other trauma such as nasogastric intubation. Even if this hypothesis is correct, we think that other possibilities should be considered. One possible situation could be the persistence of the uncommitted epithelium with development of a sort of heterotopic CM (analogous to the heterotopic fundic-type mucosa described in the upper third of the oesophagus). Clearly, much more research is needed.

Obviously, our work is not completely representative of the development of the gastro-oesophageal junction region throughout gestation. Notably, we need extra specimens from third trimester fetuses. At this moment we are gathering this material for future research. As Dr Chandrasoma himself says, the most important reason for the divergent conclusions of his work and ours are the terminology and interpretation of the data. What we call CM is, in Dr Chandrasoma's opinion, an uncommitted epithelium devoid of glands. He specifically warns against applying the designation ''gland'' to the tangentially cut tortuous ends of the foveolar pits (our fig 2 and fig 4). We believe glands are present in these illustrations. We formed this conclusion both on a purely morphological basis (the gland cells are cuboidal to triangular and contain a centrally located round nucleus, as opposed to the tall columnar foveolar and pit cells with basically located nuclei) and after histochemical evaluation (the foveolar and pit cells contain a large amount of mostly neutral mucins, whereas the gland cells for a long time contain only a small amount of mostly acidic mucins). We used the term CM

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for this zone interposed between squamous and fundic mucosa because of its morphological analogy with adult CM (whether normal or abnormal). Its principal characteristic is the presence of mucus producing glands devoid of parietal cells. We stated that CM develops during gestation and is present at birth. We do not know what happens with this CM in infants and children. We cannot comment on the identity of adult CM: has it always been there or did it develop through metaplasia? To prove or disprove Dr Chandrasoma's theory, evidently much further research has to be done.

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Helicobacter pylori infection in Africa and Europe: enigma of host genetics

Helicobacter pylori infection is one of the most common bacterial infections. The prevalence varies from 25–50% in developed countries to 70–90% in the third world.[1] Despite improved treatment modalities, *H pylori* related gastrointestinal pathology, in common with gastritis, peptic ulcers and consecutive bleeding events, gastric MALT lymphoma, or carcinoma, remains a major burden on Western health systems. In the USA, approximately four million people have active peptic ulcers and about 350 000 new cases are diagnosed each year. Four times as many duodenal ulcers as gastric ulcers are diagnosed.[2] Epidemiological evidence suggests that both infection with *H pylori* and the consecutive development of clinically relevant pathology are influenced by genetic predisposition as only a fraction of exposed individuals develop infection and likewise a fraction of infected individuals develop ulcers or even gastric cancer.[3]

Thye *et al* used *H pylori* reactive serum immunoglobulin G as a marker of *H pylori* infection in Senegalese siblings and provided for the first time concrete statistical evidence for a genetic predisposition to *H pylori* infection. The authors reported an association between *IFNGR1* polymorphisms and high antibody concentrations.[4] Inclusion of the three variants (H318P, L450P, −56 T/C) in the linkage analysis increased the LOD score to 4.2. The two African amino acid exchange variants, H318P and L450P, were not found in 100 unselected Germans.[4]

Immediately, the question arises of whether variation in the interferon γ receptor 1 (IFNGR1) locus is related to *H pylori* infection or pathology in Caucasian populations We genotyped two polymorphisms at the IFNGR1 locus (rs608914, rs11914) in 344 *H pylori* infected individuals undergoing upper gastrointestinal endoscopy from northern Germany and 311 healthy blood donors. *H pylori* infection was tested by rapid urease test from a gastric biopsy or histology. Patients were grouped according to the severity of the mucosal inflammation, ranging from mild inflammation such as gastritis or duodenitis, to erosions and ulcer disease. Polymorphisms were selected from the Applied Biosystems ''Assay on Demand'' service (https://store.appliedbiosystems.com) and genotyped by Taqman using standard protocols. Because both polymorphisms were non-functional single nucleotide polymorphisms (rs11914: synonymous T/G exchange in exon 1, frequency in blood donors 13.5%; rs608914: C/T exchange about 6.5 kb downstream of the transcriptional start site, frequency in blood donors 31.3%) a haplotype case control analysis was performed using Hapmax[5] to assess the association of the locus with the respective phenotypes. The markers exhibited a low degree of linkage disequilibrium (LD) ($D' = 0.174$) yielding a highly informative haplotype analysis of the locus (frequencies in normal controls: TC 0.586; TT 0.100; GC 0.279; GT 0.035). No significant association with infection status or severity of *H pylori* associated inflammation was found (table 1).

We conclude that INFGR1 is unlikely to be involved in the aetiology of *H pylori* infection or the development of clinical sequelae in German Caucasians. This may be due to aetiological differences between African and Caucasian individuals, as suggested pathophysiologically by Mitchell *et al*, who demonstrated major differences in the IgG subclass response to *H pylori* infection in the first and third world.[6] In relation to clinical disease manifestations, the IFNGR1 locus may affect antibody concentrations but not the clinical course of *H pylori* infection in Caucasians. Alternatively, other immunoregulatory genes in the vicinity of the IFNGR1 locus such as the interleukin 20 receptor α (200 kb distance) or MAP kinases 5 (600 kb distance) could harbour the causative variants. High densitiy LD mapping of the locus is required to unravel the causative genetic variants in both African and Caucasian populations. Our data support the hypothesis that the genetic diversity of the host immune system may contribute to the differences in *H pylori* prevalence and clinical outcome in African and Caucasian populations.

Table 1 Haplotype analysis of infection status and clinical manifestation of *Helicobacter pylori* infection

Comparison groups	n (groups)	p Value
Infection status (normal controls versus all *H pylori* positive patients)	311 *v* 344	0.39
Moderate versus mild pathology in *H pylori* infected patients (gastric/duodenal erosions versus no pathology or gastritis/duodenitis)	66 *v* 166	0.33
Severe versus mild pathology in *H pylori* infected patients (gastric/duodenal ulcers versus no pathology or gastritis/duodenitis)	112 *v* 166	0.61

The table shows the comparative frequencies of the IFNGR1 haplotype described above. Susceptibility to *H pylori* infection was tested by comparison of all *H pylori* positive patients (n: all subgroups: 66+112+166 = 344) against normal controls (top row). Genetic predisposition for complications of *H pylori* infection was tested by comparison of patients with moderate pathology (gastric or duodenal erosions, n = 66) and severe pathology (gastric or duodenal ulcers n = 112) against patients with mild or no pathology grouped together (no pathology, gastritis, or duodenitis, n = 166). Significance was assessed by a χ^2 test of the global likelihood ratio of the case control haplotype estimations.

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Platelet activation in patients with irritable bowel syndrome may reflect a subclinical inflammatory response

We read the recent article by Houghton *et al* and found the results very interesting (*Gut* 2003;**52**:663–70). Their observations included higher platelet concentrations of 5-hydroxytryptamine among patients with diarrhoea predominant irritable bowel syndrome (d-IBS) compared with controls. It is interesting that a small but significant subgroup of IBS patients report onset of their symptoms after an episode of acute gastroenteritis and a role of subclinical inflammatory aetiology has been suggested for the condition.[1] The role of platelets in various inflammatory conditions has previously been demonstrated but their importance in IBS remains largely unknown.[2–7] We recently looked at the possibility of platelet activation in IBS patients by determining surface expression of the activation markers at baseline and after stimulation. Stimulation involved the use of thrombin receptor activating peptide (TRAP), activation markers P-selectin (CD62) and glycoprotein 53 (CD63), and glycoprotein (GP) receptors GPIb-IX and GPIIb/GPIIIa, using whole blood flow cytometric analysis (Becton Dickenson Flow Cytometer).[8 9]

Twenty consecutive IBS patients (18 females), mean age 29 years (20–62), fulfilling the Rome II criteria (90% d-IBS) and 15 healthy controls (11 females), mean age 28 years (22–49), were included. Raised inflammatory markers, previous bowel dis-

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ease or surgery, diverticulosis, and current or recent (past four weeks) use of non-steroidal anti-inflammatory drugs were exclusion criteria.

Standard venepuncture precautions were observed for sample collection and final analysis.[8] A fluorescein isothiocynate (FITC) conjugated GP1b specific antibody was used to gate around the platelet population and list mode data on 10 000 platelets acquired. Mean fluorescence intensity (MFI) was used to quantify FITC labelled GPIIb/GPIIIa and GPIb-IX specific antibody binding. Binding of P-selectin and GP53 to a phycoerythrin labelled monoclonal antibody was expressed as the percentage of platelets positive for that antibody (% fluorescence). We tested varying strengths of TRAP, ranging from 110 to 670 mm, in five controls and found maximal reactivity of circulating platelets at a concentration of 223 mM (concentration used for activation studies). Differences between groups (p) were assessed using the Mann-Whitney U test for unpaired data. All analyses were performed using the Minitab statistical software and SPSS for windows (10.0.5).

Baseline expression of P-selectin was significantly increased in the IBS group (median 5.9 (interquartile range (IQR) 4.4 –8.9)) compared with healthy controls (median 4.1 (IQR 3.2–5.9)) ($p = 0.03$), all values representing per cent expression. Baseline expression of GP53 was higher in the IBS group (median 3.0 (IQR 1.9–4.0)) compared with normal controls (median 2.3 (IQR 1.9–2.8)) but failed to reach clinical significance. TRAP stimulation resulted in increased expression of P-selectin and GP53 in both groups. Glycoprotein reactivity post stimulation was significantly lower in the IBS group compared with normal controls ($p<0.05$).

The numbers of GPIIb/IIIa and GPIb-IX receptor sites on the platelet surface for each group were calculated using a calibration curve where MFI and the corresponding number of antibody sites of multiple bead populations were plotted using a log log scale. The results in the two groups were comparable.

In IBS patients with normal routine inflammatory markers, we demonstrated a significant increase in surface expression of baseline P-selectin. The observed changes in baseline and reactive expression of platelet activation markers may support the theory of an ongoing subclinical inflammatory process in IBS. Reduced glycoprotein reactivity following TRAP stimulation in IBS may possibly signify a continuous low level platelet activation and degranulation with consequent platelet ''exhaustion'' and reduced expression of antigens. Precise interpretation of our results remains unclear due to the small number of included patients. Future studies involving a wider IBS population with possible subdivision based on the various disease characteristics, including determination of the possible disease triggering event, particularly a past history of gastroenteritis, may help to further clarify these observations.

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CORRECTIONS

Two errors have been noted in the paper by CJ Hawkey *et al* in the June issue (Incidence of gastroduodenal ulcers in patients with rheumatoid arthritis after 12 weeks of rofecoxib, naproxen, or placebo: a multicentre, randomised, double blind study. *Gut* 2003;**52**:820–6). On page 822, the lower 95% CI for the difference between rofecoxib and placebo (4.05), is given as 93.37 rather than 3.37. Also, in the key to fig 2, the dose of rofecoxib is given as 500 mg instead of 50 mg.

In the letter by Siveke *et al* (*Gut* 2003; **52**: 1531) the author list was ordered incorrectly as JT Siveke, C Folwaczny and C Herberhold. The correct order for the listing of authors should have been JT Siveke, C Herberhold and C Folwaczny. This was due to a technical error for which the journal apologises.

NOTICES

British Society of Gastroenterology Paul Brown Travel Fellowships

The Paul Brown Travel Fellowships are awarded by the Endoscopy Committee of the BSG. They are intended to assist trainee gastroenterologists and established consultants in visits to units outside the United Kingdom for specialist experience and training in endoscopy.

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This conference will be held on 14–17 February 2004 in Hong Kong. The topic of the conference is ''Liver Diseases in the Post-Genomic Era''. Further details: Ms Kristie Leung, Room 102–105 School of General Nursing, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Tel: +852 2818 4300/8101 2442; fax: +852 2818 4030; email: kristieleung@hepa2004.org; website: www.hepa2004.org

PET/CT and SPECT/CT Imaging in Medical, Radiation, Surgical and Nuclear Oncology

This continuing medical education programme will take place on 19–20 March 2004 at Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. Further details: Office of Continuing Medical Education, Johns Hopkins University School of Medicine, Turner 20, 720 Rutland Avenue, Baltimore, Maryland 21205-2195. Tel: +1 410 955 2959; fax: +1 410 955 0807; email: cmenet@jhmi.edu; website: www.hopkinscme.org

39th Annual Meeting of the European Association for the Study of the Liver

This meeting will be held on 15–19 April 2004 in Berlin, Germany. Further details: Secretariat, c/o Kenes International, 17 rue du Cendrier, PO Box 1726, CH-1211 Geneva, Switzerland. Tel: +41 22 908 0488; fax: +41 22 732 2850; email: info@easl.ch; website: www.easl.ch/easl2004

- Deadline for receipt of abstracts: 16 November 2003
- Deadline for early registration 10 February 2004

Second Sheffield Multi-Disciplinary Colorectal Meeting

There will be a multi-disciplinary symposium for surgeons, physicians, radiologists and specialist nurses on 9 January 2004. The faculty includes: Wendy Atkin —St Mark's (London), Professor Jonathan Rhodes —University of Liverpool, Professor John Scholefield —Nottingham, Dr S Taylor—St Mark's Hospital, Mr Andrew Shorthouse—Sheffield, Dr Stewart Riley—Sheffield, and Karen Smith—Nurse Endoscopist at Sheffield. The Second Sheffield Multi-Disciplinary Colorectal Meeting takes place between 10am and 5pm at the Postgraduate Centre, Northern General Hospital, Sheffield. The registration fee is £25. For further details, please contact: Anne Smedley, Secretary to Mr AJ Shorthouse, Royal Hallamshire Hospital, Glossop Road, Sheffield, S19 2JF.

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