Correspondence

DNA aneuploidy in ulcerative colitis

SIR.—We wish to take issue with several of the statements made by the St Mark’s group but it is first necessary to summarise our data with regard to patients and samples in a manner analogous to that given above.

| Number with DNA aneuploidy in non-cancerous mucosa |
|-----------------|-----------------|
|                  | Patient | Sample |
| Cancer in UC     | 8/12     | 20/90 (22%) |
| Longstanding UC  | 8/12     | 19/85 (22%) |
| Short duration UC| 3/14     | 3/95 (3%) |

The aims of our study were to determine the prevalence of DNA aneuploidy in UC and to assess its predictive usefulness as an independent indicator of concurrent carcinoma, thus we did not use dysplasia, a potentially dependent characteristic to define our patient groups. In so far as the St Mark’s group found DNA aneuploidy in four patients who did not have concurrent carcinoma, and failed to detect it in 10 of 21 patients who did, we find it surprising that they take exception to our conclusion regarding its lack of predictive value.

If we discount the short duration cases (the St Mark’s series is too small to be contributory), the overall prevalence of DNA aneuploidy in non-cancerous samples is very similar in the two studies – 55/258 (21%) at St Mark’s and 39/175 (22%) in our study. Translated into patients this represents 48% (15/31) and 67% (16/24) respectively. Where our results diverge most is in the prevalence of DNA aneuploidy in samples from non-cancer patients in that we found DNA aneuploidy in 22% whereas the St Mark’s group found it in only 9% (14/153). It is suggested that such discrepancies arise from shortcomings in our flow-cytometric technique.

We believe that the methods we have used for retrospective DNA analysis to be reliable, reproducible, and accurate. Studies have been carried out which validate the method when comparing fresh and fixed samples, by cytogenetic measurements, and using lesions with known abnormalities of DNA content. We are surprised that the St Mark’s group have experienced difficulties in manipulating paraffin embedded tissue; the procedures are straightforward and have recently been substantiated by other workers. The difference in coefficients of variation is irrelevant to the central problem as the slightly higher CV in our study would lead if anything to a reduced rate of detection of DNA aneuploidy, not an increase.

In parallel studies we have investigated DNA aneuploidy in 196 samples of colon derived from resections either for non-neoplastic disease or for adenocarcinoma. No sample of normal mucosa was found to be DNA aneuploid and only 3% of resection margins from the cancer cases were DNA aneuploid. Our published work on DNA aneuploidy in colorectal neoplasia is in close agreement with other published studies on both fresh and paraffin-embedded tissues, which together with the above data support the validity of our measurements. We therefore reject the criticisms of our flow cytometric methodology. The low prevalence of DNA aneuploidy in the cancers complicating UC in our report was caused by the small number of samples measured. In a current study in collaboration with Dr H Thompson the prevalence is presently 46% suggesting that there is no difference between carcinoma arising in UC and those that do not.

Where we take most issue with the St Mark’s group is over their reliance on the histological diagnosis of dysplasia and their use of this criterion in concluding that aneuploidy is a specific marker of neoplastic change. We find it remarkable that the finding of DNA aneuploidy (the detection of which involves little subjectivity) was strictly limited to mucosa from dysplastic colon when the recognition of dysplasia is such a subjective business. We have recently concluded a multicentre interobserver study in which 100 coded sections from cases of UC were categorised independently by six histopathologists experienced in this field (in preparation). The pairwise agreement based simply on the presence or absence of dysplasia varied from 68–84% (x=0.371–0.667) and the conditional probability of agreement for low- and high-grade dysplasia was 0.52 and 0.72 respectively. In other words in this study the chance of a pathologist randomly selected from the panel agreeing with the first observer’s diagnosis of dysplasia is around 60%. We would therefore predict that in a ‘blind’ assessment the chances of another pathologist agreeing with all the allocations to the dysplasia group in the St Mark’s study or conversely, agreeing that all 72 samples in the long and short duration groups are non-dysplastic, are slim indeed.

Finally, the presence of DNA aneuploidy in samples from long standing colitis with no evidence of dysplasia has previously been reported by Hammarberg et al. This in no way repudiates the status of DNA aneuploidy as an early neoplastic change, but underlines the necessity to distinguish between sub-
Correspondence

jective assessments of precancer by histopathologists and the more objectively determined, and not necessarily parallel, changes in DNA content revealed by flow cytometry.

J B J Fozard, R Quirke, and M F Dixon
Departments of Surgery and Pathology, University of Leeds, Leeds

References

DNA aneuploidy in ulcerative colitis

SIR.—We read with great interest the article by Mr JBJ Fozard and colleagues on the value of DNA aneuploidy in assessing malignant changes in ulcerative colitis. We have carried out a similar study but unlike Mr Fozard we found that aneuploidy was strongly associated with malignancy and with dysplasia, and was not found in any patient in the absence of these changes. We have studied 262 non-cancerous mucosal samples from 50 patients undergoing colectomy for ulcerative colitis. The clinical groups and findings are summarised in the Table overleaf.

Our results indicate aneuploidy to be a specific marker of neoplastic change in extensive ulcerative colitis and suggest that flow cytometry may be of value in detecting such changes. In contrast the Leeds group concludes that 'the finding of DNA aneuploidy in a colorectal biopsy would have no predictive value in deciding whether or not a patient has concurrent carcinoma elsewhere in the bowel'.

This discrepancy is surprising as both Mr Fozard and ourselves used the method of Hedley et al1 in preparing samples for flow cytometry. Possible explanations may lie in differences of tissue preparation (we did not remove excess tissue with a scalpel), in the interpretation of DNA histograms (our average coefficient of variation was lower than theirs), and in the interpretation of the histopathology. We do not believe that differences in histopathological interpretation are important in our study because high levels of inter observer agreement have been found for pathologists studying our specimens (data in preparation). On the other hand we have noted that manipulating tissues with a scalpel blade leads to unsatisfactory DNA histograms and an unacceptably high coefficient of variation, and we think this may explain the difference in our results.

Whilst the discrepancy between the Leeds results and our own suggests that flow cytometric findings may be less objective and reproducible than is generally realised, we have found our own technique to produce reliable and repeatable results. We therefore wonder whether the Leeds group findings (of a high incidence of aneuploidy in tissues not showing neoplastic changes, and of a relatively low incidence of aneuploidy in established cancers) may be misleading.

D M Melville, J M A Northover, J R Jass, N A Shepherd, and J E Lennand-Jones
ICRF Colorectal Cancer Unit, St Mark's Hospital, London EC1V 2PS

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J B Fozard, P Quirke and M F Dixon

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doi: 10.1136/gut.28.5.642

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