

LETTERS TO THE EDITOR

Caffeine phenotyping in patients with familial adenomatous polyposis may shed light on sporadic colon cancer and acetylator status

EDITOR,—The age at which patients with familial adenomatous polyposis (FAP) develop colorectal cancer (CRC) is variable, as is the development of extracolonic tumours in the syndrome. This could be due to the effect of different mutations in the responsible gene,¹ environmental factors or the influence of risk modifier genes. Enzymes that metabolise dietary carcinogens such as *N*-acetyltransferase2 (NAT2) and cytochrome P450 CYP1A2 are potential modifier genes and fast metabolisers for NAT2 and CYP1A2 have been reported to be at greater risk of sporadic CRC.² In addition bile from FAP patients has been found to contain higher concentrations of carcinogens³ than that from controls. Therefore, Spigelman *et al* (*Gut* 1995; **36**: 251–4) have examined the frequency of phenotypes for NAT2 and CYP1A2 in FAP against controls and also examined the influence of colectomy on the caffeine metabolite ratios used for phenotyping. We believe that a re-examination of their data questions the use of the phenotyping method for NAT2 in these patients and may help to explain the excess risk for fast acetylators seen in phenotyping studies of colorectal cancer.

NAT2 has a well characterised polymorphism⁴ and patients can be classified as fast or slow acetylators either by means of phenotyping, using a probe drug such as caffeine, or by genotyping using a simple PCR based assay for the four common alleles. In healthy young subjects the two methods are well correlated.⁴ In their paper Spigelman *et al* state that there is no significant difference in the value of the metabolic ratio for NAT2 phenotype in a group of six patients before and after surgery. However, if we re-examine the data from Fig 2 and look at the apparent phenotype in each subject rather than the metabolic ratio it would seem that one subject had changed from a slow to a fast acetylator after colectomy, one has done the reverse, and another who seems very close to the cut off point of 0.48 before surgery is now clearly a fast acetylator. Thus possibly as many as 50% of subjects seem to have changed their phenotype in this small group of subjects. If this finding were repeated in a larger sample it would invalidate the conclusion that there are more slow acetylators in the FAP group.

While fast acetylator status has been associated with greater risk for sporadic CRC in a number of phenotyping studies in white subjects,² two genotyping studies in Japanese subjects found no increased risk.^{5,6} It may be that this is due to different dietary risk factors or the high (90%) prevalence of fast acetylators in Japan but clearly it could also result from a disease effect on the phenotyping procedure causing misclassification of patients in the phenotyping studies in white subjects. We believe that phenotyping may be inaccurate in people with concurrent diseases and that the study by Spigelman *et al* gives some support to this theory. In contrast, genotyping offers a quick and simple

means of assessing acetylator status, which is unaffected by concurrent illness or drugs. Until further studies have validated phenotyping in patients with FAP or CRC we believe that genotyping is the method of choice for NAT2 analysis and a genotyping study is required to establish whether fast acetylator status is truly a risk factor for this disease in white subjects.

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Reply

EDITOR,—We thank Dr Welfare and colleagues for their valued remarks. We entirely agree that genotyping studies are required to evaluate further the role of pharmacogenetic polymorphisms in carcinogenesis, and said as much in our paper. Moreover, the context in which we made this point shows just why we did not use genotyping in our study – the techniques, which are now ‘quick and simple’, were not available at the time our work was conceived and executed. We have since, however, been able to use genotyping¹ to investigate this question, and have found, for example, that the GST Mu polymorphism (GST Mu being a carcinogen detoxifying enzyme system) is unequally distributed between patients with familial adenomatous polyposis (FAP) and others. FAP patients express the null phenotype significantly more frequently than do controls (70% versus 40%, $p < 0.0003$). This supports the supposition that carcinogen metabolising genes act as modifiers of phenotypic expression in FAP patients, as is the case in the animal model for FAP.² If this is indeed so in humans, then the concept of FAP as a single gene disorder must be questioned.

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Urinary excretion of TNF receptors

EDITOR,—We would like to comment on the paper by Dr Hadziselimovic and colleagues (*Gut* 1995; **37**: 260–3) investigating urinary excretion of TNF receptors in children with inflammatory bowel disease (IBD). Their findings of increased urinary concentrations of p55 and p75 soluble TNF receptors in patients with active disease is in agreement with studies showing increased systemic concentrations of these receptors in adult patients with Crohn's disease and ulcerative colitis.^{1–3}

Soluble TNF receptors are released in Gram negative sepsis and experimentally in response to endotoxin, formylated oligopeptides, and TNF.⁴ It is unclear whether these soluble TNF receptors act as inhibitors of TNF activity or as carrier molecules for TNF.⁴ The biological implication of increased circulating and urinary TNF receptors in patients with IBD is equally uncertain. In a recent study, administration of the anti-TNF antibody cA2 to 10 patients with Crohn's disease was associated with a normalisation of Crohn's disease activity index scores in eight patients, but no change in the serum concentration of the soluble TNF receptors p55 and p75.⁵

Irrespective of the exact role that soluble TNF receptors have in IBD, measurement of urinary or circulating concentrations of these receptors may prove useful in predicting those patients likely to relapse.

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Reply

EDITOR,—The authors are quite right in their assertion that the biological function of the soluble TNF receptors is still unknown. But for whatever reason, when patients with IBD are in stable remission for at least three months, the concentration of the soluble TNF receptors p55 and p75 in the urine normalises. Although Van Dullemen *et al*¹ reported that there was no change in the serum concentrations of the soluble TNF receptors in their patients, their results cannot be compared with those of our study. Despite