Matters arising

captopurine, and local steroid cream. Bleeding problems worsened and she became dependent on transfusions. Platelets remain around $6 \times 10^9/l$ and white cell count is normal but with highly dysplastic neutrophils at the time of writing.

These two patients showed red cell hypoplasia with refractory anaemia and later developed myelodysplastic and myeloproliferative features. Both had a normal karyotype, ran a chronic course, and developed a second malignancy. Neither fits easily into the current classification of myelodysplastic syndromes.

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Reference

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Differential diagnosis of metastatic undifferentiated carcinoma

Ellis and Hitchcock recently described the possible use of a panel of antibodies in the differential diagnosis of metastatic undifferentiated carcinoma with an unknown primary site.¹ It was suggested that there are characteristic patterns of immunoreactivity which may help indicate the primary site. This is clearly an important study as it paves the way for histopathologists to provide the clinician with valuable information in the hunt for the unknown primary. This is a not uncommon clinical problem and, with improvements in therapeutic options for some tumours, one of real practical importance.^{2,3} But we would welcome the authors' comments regarding the following points.

Given that little information about the "differentiation" of these cases is provided, they may just be relatively typical examples rather than difficult, poorly differentiated tumours which are so characteristic of the difficult cases where histopathologists depend on help from immunohistological techniques. There is also some evidence to suggest that metastatic deposits are less well differentiated than primaries and exhibit variable, but often pronounced, phenotypic diversity. Therefore the hypothesis that

immunophenotypic patterns may indicate site of origin must be tested on secondary deposits, preferably those that presented as adenocarcinoma of unknown origin. Such a study could be based on cases in which post mortem examination or other investigation defined the primary site of disease.

A further point of relevance to the problem of the unknown primary relates to the identification of endocrine neoplasms. Hainsworth *et al* identified 29 patients who presented with metastatic carcinoma of unknown primary in which electron microscopic examination or immunohistochemical techniques (primarily using anti-NSE) indicated a neuroendocrine tumour.⁴ In four patients a well recognised tumour was eventually found (gut carcinoid $n=2$, oat cell in lung $n=1$, mediastinal germ cell tumour with pronounced neuroendocrine differentiation $n=1$). Although the total population from which these cases were drawn is not stated, they do remark that they were found in a single institution and that 24 were found between 1981 and 1987, suggesting that they may be relatively common. Given these data, it may be that antibodies which recognise endocrine cell differentiation should be included in panels for the characterisation of the "unknown primary".

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- 3 Hainsworth JD, Dial TW, Greco FA. Curative combination chemotherapy for patients with advanced poorly differentiated carcinoma of unknown primary site. *Am J Clin Oncol* 1988;**11**:138-45.
- 4 Hainsworth JD, Johnson DH, Greco FA. Poorly differentiated neuroendocrine carcinoma of unknown primary site. A newly recognised clinicopathological entity. *Ann Intern Med* 1988;**109**:364-71.

Drs Ellis and Hitchcock comment:

To illustrate the potential of tumour marker immunohistology we felt it essential to determine tumour marker profiles of adenocar-

cinomas at their known site of origin prior to a study of metastatic tumour from an unknown primary site. The baseline information we presented justifies detailed study of metastatic tumours. We would clearly support the view that study of the primary and secondary tumour from patients presenting with metastatic disease, in whom the primary is subsequently identified, is vital before this approach could be advocated as a useful routine procedure.

Our work was based purely on adenocarcinomas. The tumours from each primary site were consecutive cases presenting to our department and included a range of tumours with varying differentiation. Again for the above reason, we feel it was important to study a representative range of tumours from a given site rather than to select unusual or poorly differentiated examples.

This type of approach could be applicable to all forms of metastatic tumour. In our study we chose to examine only adenocarcinoma because of the wide range of tumour markers available for these tumours. As Hall and Levison point out, other groups have shown the value of new endocrine markers to identify tumours of neuroendocrine origin.

We suggest that use of immunocytochemistry on metastatic tumours to determine a likely site of origin has considerable potential. We have illustrated that in adenocarcinoma a panel could help to identify the site of origin. In undifferentiated tumours other such panels may prove helpful in identifying the cell type or site of origin.

Role of Verotoxin producing *Escherichia coli* in the aetiology of haemorrhagic colitis

We read with some surprise the recent report by Larson and Welch.¹ Our own study of the incidence of Verotoxin producing *Escherichia coli* (VTEC) in haemorrhagic colitis was conducted from 1 January 1986 to 31 December 1987.² During this time we searched for VTEC in faecal samples from 40 patients with haemorrhagic colitis (sudden onset of grossly bloody diarrhoea, usually with an absence of fever but sometimes preceded by abdominal pain and cramps and watery non-bloody diarrhoea), and 229 age and sex matched control patients with acute non-bloody diarrhoea. Faecal samples were examined for the presence of *E coli* 0157 by culture on sorbitol MacConkey agar (Oxoid CM813), followed by biochemical identification of all apparently sorbitol negative colonies. Those confirmed as sorbitol negative *E coli* were checked for agglutination with *E coli* 0157 antiserum (Difco) using

a tube agglutination method, and those found to be *E coli* 0157 were grown in a modified brain heart infusion broth and tested for verotoxin production. Samples were also examined for free faecal verotoxin; if this was found in the absence of *E coli* 0157 then other toxigenic serogroups were sought by culture of the faecal sample on ordinary MacConkey agar (Oxoid CM7b) and by checking all *E coli* isolates for verotoxin production as above. All samples were also examined for the presence of other recognised enteric pathogens. All methods have been detailed in previous reports.²³

We found VTEC in 31 (78%) of 40 patients with haemorrhagic colitis, but in only two (0.9%) of 229 control patients ($p < 0.001$). With the exception of one verotoxin producing *E coli* 0128, all VTEC isolated were sorbitol negative *E coli* 0157. Other recognised enteric pathogens were not isolated from any patients with haemorrhagic colitis; they were recovered from 52 (23%) of 229 control patients.

Thus our findings differ sharply from those of Larson and Welch.¹ Our findings are, however, similar to those of workers who studied sporadic cases of haemorrhagic colitis in England and Wales² and Canada.³ We therefore disagree with the view expressed by Larson and Welch, and indeed regard VTEC, particularly serogroup 0157, as the major aetiological agent in sporadic cases of haemorrhagic colitis.

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- 2 Chapman PA, Wright DJ, Norman P. Verotoxin-producing *Escherichia coli* infections in Sheffield: cattle as a possible source. *Epidemiol Infect* (in press).
- 3 Chapman PA, Mitchelmore DL. A two-year survey of the incidence of heat-labile enterotoxin-producing *Escherichia coli* and other enteric pathogens in travellers returning to the Sheffield area. *Epidemiol Infect* 1988;101:239-47.
- 4 Smith HR, Rowe B, Gross RJ, Fry NK, Scotland SM. Haemorrhagic colitis and verotoxin-producing *Escherichia coli* in England and Wales. *Lancet* 1987;i:1062-5.
- 5 Pai CH, Gordon R, Sims HV, et al. Sporadic cases of haemorrhagic colitis associated with *Escherichia coli* 0157:H7. *Ann Intern Med* 1984;101:738-42.

Dr Larson comments:

If acute diarrhoea in adult patients caused by *Salmonella*, *Shigella*, *Campylobacter* and *Clostridium* species are regarded as separate clinical entities, haemorrhagic colitis not due to these organisms is the single most common clinical presentation of acute diarrhoea to our infectious disease unit.¹ It was patients with this clinical presentation whom we subsequently studied for evidence of infection with verotoxin producing *Escherichia coli* and failed to find it. If these cases are, in fact, caused by infection with *E coli* 0157, this organism would be the single most prevalent gastrointestinal pathogen in the community. But I continue to be sceptical about this conclusion.

Drs Chapman, Wright, and Norman do not describe the patient population which was the source of the faecal samples they tested. Thus it is not possible to estimate a prevalence for *E coli* 0157 infection from their data (nor from data in their references 6 and 7) to compare it with our own. The percentage of cases of haemorrhagic colitis they found to be due to *E coli* 0157 is very high, however, significantly higher even than that found by Smith *et al*, or Pai *et al*. This suggests that they describe not sporadic but epidemic haemorrhagic colitis.

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Staphylococcus lugdunensis endocarditis

We were interested to read the description of a new type of staphylococcal endocarditis by Smyth *et al*.¹ No species identification was done for the staphylococcal strain which has most of the characteristics of *Staphylococcus lugdunensis*, a new coagulase negative staphylococcal species.² This species produces smooth, glossy colonies, initially cream-coloured, but becoming pale yellow to golden after five days. Using the API Staph gallery (AIP-System, Montalieu-Vercieu, France), *S lugdunensis* is incorrectly recognised as *S hominis* biotype 3. Such strains are identified as *S lugdunensis* if they have an ornithine decarboxylase and a fibrinogen affinity factor. They also have a thermostable DNAase activity, like *S aureus* but not like *S epidermidis*.

S lugdunensis, however, is probably more responsible for infections such as infective endocarditis. Three cases of infective endocarditis due to *S lugdunensis* occurred in France in 1977, 1982, and 1983.³ The three strains, primarily recognised as coagulase negative staphylococci close to *S hominis* but with atypical characters, were correctly identified in 1988.² Unlike the usual hospital *S epidermidis* isolates, the strains were susceptible to all the antibiotics tested (benzylpenicillin, meticillin, aminoglycosides, chloramphenicol, tetracycline, macrolides, fusidic acid, vancomycin . . .).

If *S lugdunensis* seems, like *S epidermidis* and *S saprophyticus*, to be a coagulase negative staphylococcus isolated from human infections, its correct identification is a necessity and can be done easily. Coagulase and fibrinogen affinity factor (clumping factor) must both be detected, and the positivity of the second test suggests only that the isolate is *S lugdunensis*; its definite identification is achieved by the other biochemical tests, including ornithine decarboxylase detection.¹²

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- 2 Freney J, Brun Y, Bes M, et al. *Staphylococcus lugdunensis* sp. nov. and *Staphylococcus schleiferi* sp. nov., two species from human clinical specimens. *Int J Syst Bacteriol* 1988;38:168-72.
- 3 Etienne J, Pignon B, Leport C, et al. *Staphylococcus lugdunensis* endocarditis. *Lancet* 1989;i:390.

Dr Smyth *et al* comment:

We agree that the organism we described as causing endocarditis can probably be identified as *S lugdunensis*, a new species first described by Etienne *et al* in 1988. This description was not available to us at the time we studied the strain from this patient but we were cognisant that ornithine decarboxylase positive staphylococci resembling