

Gieson's stain for elastic fibres, Gordon and Sweet's technique for reticulin fibres and mucin stains. An angiocentric tumour (fig 1) in nests and cords of round to polygonal tumour cells and occasional spindle cells had transmurally infiltrated the bowel wall, occluding some vessels; others had centrifugally expanded.

Tumour cells had replaced the lamina propria in some villi causing a broadleaf configuration. Variable sized intracytoplasmic vacuoles were observed within tumour cells (attempts at vessel formation) and also a mitotic activity of two per 10 high power fields. In and around tumour submucosal and serosal fibrosis were noted in conjunction with vascular sclerosis, subintimal foam cells, and atypical or radiation fibroblasts. Immunoreactivity with factor VIII related antigen (Dako, Denmark) using the conventional PAP method with trypsinisation was positive. Ultrastructure examination of the tumour cells showed round and tubular structures consistent with Weibal Palade bodies (fig 2).

Epithelioid haemangioendothelioma has been described in the colon³ and the stomach.⁴ Induction of malignant tumours as a result of radiation is well documented. An acceptable case should show a time lapse of probably 10 years or more between a detectable lesion and the completion of radiotherapy. The radiation exposure should be relatively great and radiation damage to the tissue should be demonstrable in and around the tumour.⁵ This case satisfies the above criteria.

It is difficult to predict the biological behaviour of epithelioid haemangioendothelioma on the basis of histological features alone: the presence of cellular pleomorphism, mitotic activity in excess of one per 10 high power fields, necrosis and a tendency to spindling of the cells, have been associated with a more aggressive behaviour.¹ This tumour exhibited some of these features and its aggressive nature was confirmed by the extent of tumour spread on the second laparotomy. Angiosarcoma induced by radiotherapy is well documented but not that

of epithelioid haemangioendothelioma.

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Matters arising

Red cell hypoplasia associated with myeloproliferative and myelodysplastic syndrome

A report of three cases¹ showing red cell hypoplasia with myeloproliferative and myelodysplastic features in this journal prompts me to report two more.

Case 1

A 69 year old man presented in 1986 with clinical features of anaemia. Haemoglobin was 5.1 g/dl, mean corpuscular volume 117.9 fl, reticulocytes $13 \times 10^9/l$; white cell count, differential, and platelets were normal. Marrow aspirate was hypercellular with hyperactive myelopoiesis showing left shift and toxic granulation but no excess blasts. Erythropoiesis was hypocellular with a myeloid:erythroid ratio of 26:1. Only 3.5% of marrow cells were erythroid. Megakaryocytes were normal.

No vitamin deficiency or metabolic abnormality was present. Pure red cell aplasia was diagnosed but the patient failed to respond to prednisolone 40 mg daily and required regular transfusion. Subsequently, increasing hepatosplenomegaly, a rise in white cell count and raised lactate dehydrogenase

activity occurred. In December 1986 a rise in white cell count to over $60 \times 10^9/l$ (with monocytes $7 \times 10^9/l$, neutrophils $53 \times 10^9/l$) took place. Raised lysosyme activity was probably the cause of accompanying severe renal dysfunction. A repeat marrow aspirate showed absent erythroid precursors, grossly hypercellular myelopoiesis, with absent secondary granulation and highly abnormal miniature megakaryocytes.

Cytogenetic analysis yielded only two mitoses both of normal karyotype. 6-Mercaptopurine was introduced to control the white cell proliferation which brought the white cell count and monocyte count to normal, and also improved renal function. Transfusion requirements were increased. Severe thrombocytopenia limited the use of 6-Mercaptopurine which was given intermittently over the next 18 months.

In 1988 he developed carcinoma of bronchus from which he died.

Case 2

An 83 year old housewife presented in 1983 with clinical features of muscular aches, anaemia, and cardiac failure. Her haemoglobin concentration was 8.5 g/dl, mean corpuscular volume 86 fl, erythrocyte sedimentation rate 138 mm/first hour, and reticulocytes were $46 \times 10^9/l$; white cell count, differential, and platelets were normal.

A marrow aspirate showed hyperplastic myelopoiesis and a probable absolute reduction in erythroid precursors with a myeloid:erythroid ratio of 11:1. Polymyalgia rheumatica was provisionally diagnosed and she responded slowly to prednisolone, with complete return to normal of her blood count after some weeks.

In 1985 she became pancytopenic. Haemoglobin was 9.9 g/dl, mean corpuscular volume 79 fl, platelets $68 \times 10^9/l$, white cell count $3.3 \times 10^9/l$, with granulocytes $1.2 \times 10^9/l$. A marrow aspirate showed increased megakaryocytes, hyperplastic myelopoiesis with defective primary and secondary granulation and 6% blasts. The myeloid:erythroid ratio was 5.5:1, erythroid precursors being reduced. Prednisolone restored her blood count to normal but pancytopenia recurred when the steroid was withdrawn. At this time it was thought she had a myelodysplastic syndrome which had probably been developing since 1983.

In 1986 bruising and bleeding began. Haemoglobin was 8.8 g/dl, platelets fell to $12 \times 10^9/l$, neutrophils rose to $18 \times 10^9/l$ with a few blasts in the blood film. Neutrophils were remarkably hypogranular and bizarre. Cytogenetic analysis of marrow cells showed normal female karyotype.

In 1988 she developed mycosis fungoides which was treated with prednisolone, 6-Mer-

captuprine, 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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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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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