the latter case, by day 4, a yellow, non-water soluble substance was precipitated. The fluorescence spectrum of the incubating solution of the slides and also that of the supernatant of the precipitated albumin-glucose are identical: the excitation maximum was 370 nm, that of emission, 435 nm.³ The fluorescence parameters of the brown incubating solution diluted with G-6-P were: excitation 410, 470 nm; emission, 525, 540 nm. These values agree with the maxima of fluorescence measured for lipofuscin *in situ*.⁴

Lipofuscin (and wear pigment) are known to be PAS, protein, performic acid-Schiff and lipid positive, fluorescent pigments chiefly found in tissue rich in glycogen or glucose (muscle, liver, nerve cells).⁵ The causes of PAS positivity and the fluorescence of lipofuscin have so far not been conclusively clarified.

The paraffin wax slides of the resin-like fluorescent substance forming from albumin-glucose *in vitro* are PAS positive, and give the Schmorl and NBT protein reaction. On the basis of our data we believe that besides lipoproteins and glycoproteins the glycosylated proteins are also considerable constituents of the lipofuscin-like pigments.

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Sensitivity of anti-HBc IgM kits and the diagnosis of acute hepatitis B

It was suggested by Morris that the presence of HBeAg and subsequent seroconversion to anti-HBe is a better indication of acute hepatitis B infection than the presence of anti-HBc IgM in cases where the patient is hepatitis B surface antigen (HBsAg) positive.¹ This conclusion is based on data showing that anti-HBc IgM concentrations remain high, even on dilution, for some months after HBeAg/anti-HBe conversion.

That anti-HBc IgM can be a useful diagnostic aid in active disease has been shown by other authors,^{2,3} and the detection of increased concentrations of anti-HBc IgM is normally associated with the acute phase of hepatitis B virus infection. One reason for the various opinions on the value of core IgM tests is the different cut-offs recommended by kit manufacturers of the assay methods used. We compared the performance of five commercial kits using a panel of sera with medium and low anti-HBc IgM concentrations and expressed the results in units of the Paul Ehrlich Institute reference preparation (U/ml). The effects of the different cut-offs of

Comparison of sensitivity, range, and detection of chronic cases in five commercial anti-HBc IgM kits

Kit name (manufacturer)	Cut-off antibody titre U/ml	Approximate antibody titre at assay response plateau U/ml*	No of positive or (retest) results on 20 sera from chronic HBV cases
Amerlite anti-HBc IgM Assay (Amerlite Diagnostics, Amersham)	250	800	0 (2)
Corzyme-M (Abbott Diagnostics)	290	800	0 (0)
Wellcozyme anti-HBc IgM (Wellcome Diagnostics)	60	350	4 (3)
Core IgM K EIA (Sorin Biomedica)	30	500	7*
Hepanostika anti-HBc IgM Micro ELISA (Organon Teknica)	15	510	12†

*Estimated using a panel of 22 samples. The anti-HBc IgM titres of these samples was determined from a calibration of Amerlite results and the Paul Ehrlich Institute reference preparation.

these tests can be seen in the results for a panel of 20 samples from chronic carriers (table).

It is evident that the antibody titre at the recommended cut-off for these assays varies by a factor of up to 20, and the assays where the cut-off is positioned at a low level give a higher detection rate with sera from chronic carriers. Using a panel of serial samples, we also showed that the mean period of positivity after the acute phase of infection varies from about two months for the less sensitive (high cut-off) assays to more than seven months with the most sensitive assay. The assay used by Morris was of high sensitivity and it would account for the finding of positive anti-HBc IgM results after the HBe/anti HBe seroconversion.

Detailed clinical studies have shown that an anti-HBc IgM concentration of > 600 U/ml is the best indication of the acute phase of HBV infection.² It is therefore important to consider not only the cut-off sensitivity but also the response range of the assay to be used. The assays have a variable upper level range (table) and some have limited or no ability to discriminate medium antibody titres from the more clinically important high (> 600 U/ml)

titres of antibody. It is these variations in sensitivity and response range that contribute to the divergence of opinions on the value of anti-HBc IgM in the diagnosis of acute hepatitis B. With an appropriate choice of cut-off, anti-HBc IgM concentrations remain positive only in the period of active disease (typically two months), and such a test is a useful vehicle for this application.

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ICAM-1 expression in normal liver

The paper by Smith and Thomas describes the distribution of the intercellular adhesion molecule-1 (ICAM-1) in a range of normal tissues,¹ including the liver on which we have also reported.² The results of their study are of great interest and provide a useful baseline for future studies on inflammatory conditions affecting the sites examined. The authors have interpreted our findings in a slightly misleading manner, however, and we would like to comment on two of the points they have raised.

Firstly, Smith and Thomas claim that their finding of positive staining for ICAM-1 in centrilobular hepatocytes is "in disagreement with" our study in which "predominantly sinusoidal staining for ICAM-1 was observed". While we would agree with the latter, we did in fact show that hepatocyte staining was commonly present in normal liver (donor specimens obtained at transplantation). Staining had a membranous pattern,

was generally faint, and tended to be dispersed fairly evenly throughout hepatic lobules, in contrast to the centrilobular distribution reported by Smith and Thomas. The clinical importance of ICAM-1 expression in normal liver cells is uncertain, and another recent study has shown no staining for ICAM-1 in normal hepatocytes.³

The second point concerns the expression of ICAM-1 in rejecting liver allografts. Although the distribution may be similar, the intense membranous staining pattern we observed in perivenular hepatocytes from rejecting livers was quite different from the faint staining reaction illustrated in fig 9 of Smith and Thomas's paper. The latter may, in part, be related to changes occurring after death, a point acknowledged by the authors in their discussion.

The expression of adhesion molecules is a dynamic process which can be modulated by many extracellular and intracellular events. Factors known to upregulate adhesion molecule expression include exposure to pro-

inflammatory cytokines such as interleukin 1, tumour necrosis factor, and gamma interferon,⁴ T cell activation,⁵ conversion T of lymphocytes from naive to memory cells⁶ and viral infection.⁷ One or more of these factors may be responsible for causing the increased expression of ICAM-1 that occurs during liver allograft rejection. The factors regulating ICAM-1 expression in normal hepatocytes remain uncertain.

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Drs Smith and Thomas comment:

We thank Hubscher and Adams for clarifying the ICAM-1 expression they found in normal liver and agree that the factors they mention may be responsible for the upregulation of ICAM-1 they detected in the rejecting liver allografts.

Thrombocytosis and follicular thyroid carcinoma

We report a rare case of thrombocytosis associated with thyroid follicular carcinoma.

Thrombocytosis associated with malignant disease has been described in lung carcinoma, pleural mesothelioma, gastrointestinal tract carcinoma, lymphoma and acute leukaemia, hepatocarcinoma, neuroblastomas, histiocytosis and other epithelial cell origin tumours; it has not been described in association with thyroid carcinoma.¹⁻⁴

A 72 year old woman was diagnosed as having a follicular thyroid carcinoma because of progressive enlarging goitre. A fine needle aspiration biopsy specimen was consistent with follicular lymphoma, the diagnosis of which was confirmed when the excised thyroid was examined microscopically. Pre-

operative tests had shown increased numbers of platelets ($746 \times 10^9/l$ and $731 \times 10^9/l$, respectively). The haemoglobin concentration was 14.4 g/l, the haematocrit 41.8%, while red blood cell count, white cell count, mean corpuscular volume, mean corpuscular haemoglobin concentration, and serum ferritin and serum iron concentrations were normal. Haemostatic evaluation showed normal prothrombin and partial thromboplastin times. FDP concentrations were within the normal range. Two months after surgical resection the platelet count returned to normal.

Most cases of thrombocytosis secondary to malignant disease have a platelet count from 4 to $6 \times 10^9/l$. Iron deficiency may also contribute to an increased platelet count.^{2,3} In other cases slow activation of clotting and disseminated intravascular coagulation have occurred and FDP was detectable.^{3,5} It was not specified, however, whether these cases also had thrombocytosis. Although haemorrhagic and thrombotic episodes are characteristic of primary thrombocytosis,^{2,4} in these patients platelet production probably occurs in the tumour itself or in bone marrow by a protein produced by the neoplasm (thrombocyte stimulating factor) (TSF).^{2,3} The occurrence of unexplained thrombocytosis precludes malignancy.⁴

We suggest that clinicians should be aware of this rare sign in malignant diseases.

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Malignant melanoma and stage of disease

The paper by Calder, Campbell, and Plastow addresses an important practical problem that is faced by surgical pathologists when examining cases of malignant melanoma.¹ Although it does not detract from the main theme of the publication, however, the first sentence is incorrect. The single most important prognostic factor in determining the outcome of any malignant melanoma is the stage of the disease at the time of diagnosis. The tumour thickness is probably the second most important prognostic indicator and is

the best indicator of metastatic potential in stage I melanomas.² Unfortunately, this simple but very important fact about the role of the stage of the disease is often forgotten amid the plethora of articles, meetings, and examination questions which emphasise Breslow's thickness measurements or Clark's level of invasion.

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Drs Calder, Campbell and Plastow comment:

We read with interest the comments on our recent paper and agree that the stage of the disease is of prime importance. Our paper was addressing the microscopic measurement of the Breslow thickness of excised melanomas where the stage of the disease might not necessarily be known—a situation commonly encountered by surgical pathologists.

BOOK REVIEWS

Breast Pathology: benign proliferations atypias and in situ carcinomas. RE Fechner, SE Mills. (Pp 190; book \$170.00; slides \$170.) Raven Press. 1990. ISBN (Book) 0-89189-298-2. ISBN [Slides] 0-89189-307-5.

This book comes at a time when British pathologists are beginning to come across the types of lesions, such as in situ carcinoma and atypical hyperplasia, that are more common in screening for breast cancer than in the general symptomatic workload. The illustrations are, for the most part, good, and many of the rarer lesions which can cause diagnostic difficulties, if unrecognised, are included. In contrast to a number of other texts, the lesions are in general recognisable as the entity they are stated to portray, no mean feat in an area as controversial as atypical hyperplasia.

A refreshing finding is the adoption of nomenclature similar to that of the National Screening Programme and hence the avoidance of confusing terminology such as the British "epitheliosis" and the American "papillomatosis". These lesions are now correctly termed "hyperplasia" and qualified by the terms "typical" or "atypical".

If criticism has to be found in this work one can only say that some of the more modern oncogene work has not been mentioned, the typing of in situ ductal carcinoma of comedo-type is slightly suspect, being primarily dependent on necrosis; some of the references at the chapter end are not referenced in the text; and the book is a little expensive, but these are minor criticisms in a useful diagnostic text.

The accompanying optional set of slides