classify them according to the patterns of infiltration proposed by Schmid and Isaacs. This proved surprisingly difficult because many of the infiltrates showed a combination of the two or more patterns. In particular, “dense” is not a pattern and a paratrabeclular distribution may still be dis-
cerned even at an advanced stage of marrow replacement. If one considers specifically whether the infiltrate showed application to the bone trabeculae in a laminar manner, 15 of 34 trephines from cases of ML cb/cc showed a degree of paratrabeclarity, compared with two of 12 ML cc. None of the infiltrates was convincingly nodular. Our experience is therefore consistent with the published findings from the University of Minnesota14 and contrary to those of both Bartl et al12 and Schmid and Isaacs12.

Paratrabecular distribution

Samples of liver were obtained from 10 patients who had undergone liver transplantation at the Liver and Hepatobiliary Unit, Queen Elizabeth Hospital, Birmingham, England. A diagnosis of end stage cirrhosis as result of primary biliary cirrhosis was con-

firmation was of non-Hodgkin’s lymphomas in the bone mar-


5 Conlan MG, Bart M, Armitage JO, Weisenburger DD. Bone marrow involve-


Glutathione S-transferase expression in primary biliary cirrhosis supports the concept of “ductular metaplasia” of hepatocytes

Bile duct proliferation is a feature of many cholestatic diseases. The mechanism of this phenomenon is unknown but there is some support for the concept of “ductular metaplasia”. For example, Van Eyken et al20 used an immunocytochemical approach to show, in a variety of cholestatic diseases, that hepato-
cytes can express epithelial antigens which are normally restricted to the bile duct cells. The glutathione-S-transferases (GST; EC 2.5.1.18) are a family of enzymes that play a key role in the conjugation of glutathione with a variety of electrophiles. By immunological and catalytic criteria, the major cytosolic isoenzymes can be cate-
gorised into four classes, α, μ, θ and π.21 Time and tissue specific changes in the expression of these GST classes has been described in developing human tissues and these data suggest that changes in GST expression are related to changes in cell phe-
notype. 22 23 We now describe observations of glutathione-S-transferase expression in primary biliary cirrhosis which provide further evidence for the concept of “ductular metaplasia”.

Expression of GST classes in cells with intermediate phenotype

Hepatocytes

<table>
<thead>
<tr>
<th>α</th>
<th>μ</th>
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<td>+</td>
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Bile duct epithelium

“Ductular metaplastic” cells

In all cases the cirrhotic nodules of hepato-
cytes were positive for α and μ GST as were bile duct epithelial cells.

The polymorphic GSTM1 gene encodes the predominant μ class isoenzyme in human liver. In those who expressed this gene, GSTM1 isoforms demonstrated strong positivity in hepatocytes but were not expressed in bile duct epithelium or those cells putatively undergoing metaplasia.

In general, μ class expression was restricted to the bile ducts and “ductular metaphasia” cells, those both strongly positive. In some cases a weak diffuse positivity was also observed in occasional regenerating nodules of hepatocytes.

As shown in the table cells with an inter-
mEDIATE phenotype undergoing “ductular metaplasia” from hepatocyte to bile duct-
type cells expressed π class GST but not the α or μ class isoforms. Although such cells were seen only on the periphery of the cir-

rotic nodules, in many instances they were clearly continuous with surrounding hepatocytes. These “metaplastic” cells, therefore, did not show the typical hepatocyte pattern of strong positivity for α and μ class isoforms but, rather, similar GST expression to bile duct epithelial cells. This observation is con-
sistent with the concept of “ductular meta-
plasia” and confirms data in patients with extrahepatic biliary atresia showing altered expression of π GST in hepatocytes.

It was interesting to note diffuse positivity for π class GST in some regenerating nod-
ules, though it is not usually expressed by adult hepatocytes. Expression of π class GST by hepatocytes is normally seen only in fetal liver and may therefore be an indication of increased cell proliferation. 24

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References

1. Van Eyken P, Sciot R, Desmet VJ. A cytoker-
tatin immunohistochemical study of chole-


5. Hiley CG, Fryer AA, Bell J, Hume R, Strange RC. The human glutathione S-transferases: immunohistochemical studies of the develop-

6. Hiley CG, Bell J, Hume R, Strange RC. Differential expression of alpha and pi iso-

enzymes of glutathione S-transferase in develop-


On Drs Matthew and Burt Comments:

We have read the letter of Dr Hiley et al with interest. Their observations of π class GST in cells with “an intermediate phenotype” between that of hepatocytes and bile duct epithelium in primary biliary cirrhosis are in keeping with the results of our study.21 As the authors point out it is likely that this represents a similar phenomenon to that found in our cases of neonatal cholestatic liver disease. However,24 we agree that these findings provide fur-

ther evidence that under certain circumstances hepatocytes may undergo a form of transdifferentiation. It is pertinent to note, however, that this so-called ductular meta-
plasia may not be the only mechanism by which increased numbers of ductular struc-
tures develop in the cholestatic liver. There is strong experimental evidence that in acute biliary obstruction, proliferation of true bile duct epithelial cells has a crucial (if not exclusive) role. 25 Although this may be less important in the “atypical ductular prolifera-
tion” seen in chronic biliary disease, 26 a significant contribution cannot be discounted. Furthermore, it is conceivable that the duct-
tural structures may be derived from prolif-
eration and differentiation of a putative stem cell population within portal tracts. Although controversial,27 there is growing acceptance of the concept that the mam-
alian liver contains a stem cell compartment at this site. 28


