Hepatocyte growth factor

Stir.—We read with interest the recent leading article entitled Growth factors and the liver (Gut 1991; 32: 601–3). However, although the recently characterised hepatocyte growth factor (HGF) undoubtedly plays an important part in the control of liver regeneration, in the last year there have been several major developments which add further insight into the biological role of this increasingly important polypeptide.

HGF, far from being specific for liver cells as suggested, seems to belong to a family of factors that act on epithelial cells from a number of different tissues and are probably synthesised and released by cells of mesenchymal origin. Scatter factor, which induces epithelial cell migration and is synthesised by mouse and human fibroblasts, has close amino acid sequence homology with HGF. Another member of the family, keratinocyte growth factor (KGF), although having no homology with HGF, is also epithelial cell specific and is released by fibroblastic cells. More recently, a third factor, lung fibroblast derived growth factor, which is a potent mitogen for epithelial cells from skin, breast, and lung but not for fibroblasts from different origins, has been shown to be expressed at least at closely homologous sites to HGF. HGF itself stimulates growth of melanocytes, keratinocytes, and renal tubular epithelium.

Increasing excitement arose with the report that the normal cellular homologue of the oncogene met, first identified some seven years previously as a transforming gene in a chemically transformed human osteosarcoma cell line, was the plasma membrane receptor for HGF. Met is a membrane spanning receptor with tyrosine kinase activity. HGF, therefore, belongs to the major family of growth factors which includes epidermal growth factor/transforming growth factor α (TGFαs), platelet derived growth factor, and the insulin like growth factors with associated receptor tyrosine kinase activity. These developments clearly have important implications with regard to the possible role of HGF in the pathogenesis of diseases, including neoplasia, in various tissues in addition to the liver.

Although tissue non-specificity is established, this in no way devalues the potential importance of HGF in regulation of liver regeneration. The time course of increased HGF expression after partial hepatectomy or CCl4 administration in the rat is sufficiently early for it to act as the growth initiating mitogenic signal and it remains the prime candidate as the elusive hepatotrophic agent.

Furthermore, as pointed out by Drs Hodgson and Selden, HGF is a potent mitogen for hepatocytes. What is particularly striking, however, is that on a molar basis HGF is 100 fold more potent than the hitherto most active hepatotrophic factor known, namely TGFα. HGF stimulates growth of human hepatocytes at a half maximal concentration (EC50) in contrast to TGFα at approx 500 pM.

The role of HGF in developmental liver growth, however, remains an open question. Although HGF seems to be expressed at least at the mRNA level in fetal liver, the sites of expression and target cell types are not known and this may simply reflect an involvement in haemopoietic lineage. Therefore, it may be an important source of HGF, and one of the major functions of human fetal liver of the gestational age studied is the generation of cells of haemopoietic lineage. To conclude that similar contractions might occur during developmental liver growth and regeneration after tissue damage is, therefore, premature.

If, as seems to be the case, HGF is a true epithelial cell growth factor with a broad tissue specificity, then the consequence of the raised circulating concentrations found in experimental models of liver growth or clinically in acute hepatic failure, may be to induce hyperplasia in various peripheral tissues. This does not occur experimentally, or clinically (at least as far as is known), testifies to the fact that liver specificity under these circumstances must result from critically regulated and at present poorly understood control mechanisms. These might include modulation of HGF (c-met) receptor expression on cells or a prerequisite for the correct cocktail of the other growth factors and inhibitors implicated in the process, or both. It would be naive to predict that one single factor could by itself regulate such a complex repair process.

With the recent availability of bioactive recombinant HGF and the reagents to monitor expression of HGF and its receptor, further rapid progress in understanding the biology and pathology of liver regeneration is anticipated.

A J STRAIN
J M NEUBERGER
Liver Research Laboratories, Queen Elizabeth Hospital
Edgbaston, Birmingham B15 2TH

8 Mead JR, Fielder TB, Hepatocyte growth factor α may be a physiological regulator of liver regeneration by means of an autocrine mechanism. Proc Natl Acad Sci USA 1989; 86: 1558-62.
adult human liver, and have since investigated expression in a number of other fetal tissues. We found evidence of expression in tongue, brain, intestine, mandible, eye, sternum, pancreas, spleen, and in placenta and umbilical cord, but not in adrenals, thymus, skin, or lung; high expression, however, was only observed in liver, intestine, and placenta. This pattern makes its unlikely that expression of the 6 K b HGF mRNA merely reflects haemopoietic tissue.

Finally, for completeness there are now two mRNA species for HGF, the most recently described being an alternatively spliced 1.5 K b transcript with an identical 5 prime cDNA sequence for the first 856 nucleotides downstream of the termination codon, but completely divergent at the 3 prime end. In summary, although the concept that only one growth factor is entirely responsible for liver regeneration is outdated, the insights and implications of the HGF story seem likely to have an impact on our understanding of benign and perhaps malignant liver cell growth for many years to come.1,2

Is gastric emptying faster or slower in patients with early stage of non-insulin dependent diabetes mellitus?

Skr.,—I have read with keen interest two recent reports on the effect of hyperglycaemia and gastric emptying.3,4 Though these two studies differed in the subjects recruited and the techniques and design, they were centred on the same theme and, interestingly enough, the authors reached contrary conclusions.

Phillips et al showed much more rapid gastric emptying in patients with early non-insulin dependent diabetes mellitus (less than two years disease duration). Their study is based on scintigraphic measurement of the emptying rate of a liquid glucose meal from the stomach. The approach is straightforward and impeccable. The physiological response during the study period was not very different from the real-life situation in diabetes. However, their speculation on the role of rapid gastric emptying in the aetiology of non-insulin dependent diabetes mellitus is unfounded and too fanciful. It has been shown that insulin secretion is not altered in response to gastric emptying of a glucose load in healthy subjects.5 Rapid gastric emptying, as in patients with dumping syndrome, definitely reduces the glycaemic responses but these patients are not normal human subjects unless risk factors such as obesity coexist.

Fraser et al,6 based on localised gastric-duodenoanal manometric measurement of healthy subjects in whom hyperglycaemia was induced with dextrose, concluded that hyperglycaemia stimulates pyloric contraction and suppressed antral motility. They concluded that hyperglycaemia delayed gastric emptying, but acknowledged that the motility of the proximal stomach, which was not assessed in the study, might play an important role in determining the rate of gastric emptying. Therefore, too many loopholes were left unfilled when the authors tried to generalise from data on localised motility and contraction to give an overall picture of gastric emptying. By the same token, caution must be exercised when results from acutely hyperglycaemic normal subjects are extended to diabetic patients. Hyperinsulinaemia by itself will affect the motility of the gastrointestinal tract.7

Although the conclusions reached by these studies are exactly contrary, they do not necessarily contradict each other. The differences cannot be attributed to the consistency of the food or intraluminal acidic pH as these have either no effect on or may even delay gastric emptying time.8 Fraser’s work actually showed the predominantly suppressive effect of a raised blood glucose concentration on the vagal tone of the gastrointestinal tract, whereas Phillips’s study included the effect on paracrine control by the gut on gastric emptying in response to an oral glucose load. These two mechanisms act in opposition, and presumably in non-insulin dependent diabetes mellitus patients the paracrine control is more dominant. Continuous hyperglycaemia may partially blunt the acutely suppressive effect of a surge in blood sugar on the gut vagal tone. Hence the loss of the negative feedback to the stomach fails to ‘brake’ the meal and the outpouring of glucose into the intestine and further reduces the glycaemic response in diabetic patients.

Lastly, I would like to share my anecdotal observation of hyperglycaemia and diarrhoea in the early stages of type 1 diabetes. I keep some alloxaon induced diabetic rats in metabolic cages for microalbuminuria study. The rats with poor metabolic control were incidentally found to suffer from diarrhoea (large daily output of loose stools with an offensive smell). Perhaps this dumping like syndrome may play some role in the diarrhoea of early diabetes.

Reply

Skr.,—We believe that there is no discrepancy between the results reported in our study and those reported by Phillips et al as they address different issues. The first concerns the motor effects of hyperglycaemia in healthy humans, while the second relates to the control of gastric emptying rates in patients with diabetes mellitus.

In the study by Phillips et al,9 gastric emptying of a liquid meal was found to be accelerated in nine patients with type 2 diabetes mellitus and in eight non-diabetic controls. This is consistent with our studies in islet cell transplantation patients where we found that gastric emptying of liquid meals is delayed in about 40% of patients with diabetes mellitus,10 the initial empying rate of liquid meals is accelerated in some patients.11 It has been suggested that rapid liquid emptying in diabetes mellitus may reflect impaired proximal stomach adaptation to distension.9 We have reported that in diabetes mellitus, gastric emptying is slower at increased blood glucose concentrations,12 indicating that diabetic patients are more prone to delayed gastric emptying and do not always reflect irreversible nerve damage. While this observation is not surprising (increased hyperglycaemia is known to slow gastric emptying in normal subjects),13 it indicates that studies of gastric emptying in diabetic patients should take into account blood glucose concentrations. Thus, while the report by Phillips et al is interesting, the data as presented in the letter form no palpable evaluation criteria to the patients (there is a clear racial difference between the patients and controls), nor on the blood glucose concentrations during the study. Although gastric emptying of digestible food in healthy subjects is not constant, as each meal is different in composition and content, we decided to present a mean value of the fasting meal because it probably reflects the overall effect of insulin and vagal tone on gastric emptying. Although this value is obviously not the same as the control group, we believe that these results are reliable and reproducible. It is therefore difficult to interpret.

In our recent study,12 induced hyperglycaemia resulted in a pattern of antecedent emptying and postprandial delay of gastric emptying associated with slow gastric emptying in normal subjects.13 It seems reasonable to suggest that hyperglycaemia may account for...