one of 74 untreated children (or 12% of spontaneous responders) lost HBsAg.[2] In an untreated group of children with chronic hepatitis B followed over approximately 13 years, eight of 117 (7%) lost HBsAg spontaneously.[15] Indeed, enhanced rates of clearance of HBsAg in children responding to interferon α were also found in the paediatric cohorts reported here. HBV clearance may be a treatment outcome surpassing the natural history of chronic hepatitis B.

In summary, interferon α can be used successfully to treat selected children over two years old who have chronic hepatitis B. Children with moderately elevated serum ALT and comparatively low viral load are most likely to respond with HBeAg seroconversion. These are the same children most likely to experience spontaneous HBeAg seroconversion. Further observations are still needed to determine whether artificially speeding up the natural history of chronic hepatitis B is worthwhile. It is possible that the development of cirrhosis—and consequently HCC—will be avoided. Moreover, successful treatment may lead to complete loss of HBV infection, a highly desirable outcome.

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Hepatic regeneration and TGF-β: growing to a prosperous perfection†

It is widely accepted that TGF-β1 is a potent growth inhibitory and profibrotic cytokine which plays a pivotal role in the physiological process of wound healing as well as in the pathogenesis of organ fibrosis.[1] TGF-β expression has been shown to be increased in a wide range of fibrotic diseases. In the liver, TGF-β1 mRNA expression has been demonstrated to correlate with ongoing fibrotic injury in both experimental animal models and in human liver diseases. TGF-β1 mediates its profibrotic actions by stimulating fibroblasts and related cell types, including in the liver the hepatic stellate cell (HSC), to secrete a wide range of extracellular matrix proteins. In pathological conditions this leads to accumulation of fibrotic matrix or in a more physiological context to the efficient healing of wounds.[2–4] Furthermore, blocking TGF-β activity by a variety of strategies has been shown to inhibit fibrosis in a series of experimental models. However, TGF-β has other important actions, namely its immunomodulatory properties and its antiproliferative effects on epithelial cells, including hepatocytes. The regenerative capacity of the liver is well documented and is characterised not only by hepatocyte proliferation but also by increased TGF-β1 expression. Thus hepatocytes proliferate despite the presence of a powerful antiproliferative stimulus. Date *et al* have begun to examine this apparent paradox in a paper in this issue of *Gut* (see page 719).

Regulation of TGF-β activity is primarily achieved by the process of its activation. TGF-β1 mRNA is expressed by a wide range of cell types, including in the liver: Kupffer cells; endothelial cells; HSC; and possibly hepatocytes.[5] Similarly, the three high affinity plasma membrane receptors through which TGF-β exerts its downstream effects have been shown to have a ubiquitous distribution.[6] However, a cytokine with such powerful biological effects needs to be tightly regulated. TGF-β is secreted from cells in a latent form and can be activated in vitro by a variety of means including heat, extremes of pH, and various proteases. The mechanism of activation in vivo has yet to be fully determined although it is known to rely on proteolytic cleavage, probably mediated by plasmin.[7] TGF-β activity can also be controlled at other levels including inhibition by soluble receptor and binding of the mature peptide by other proteins, such as α2 macroglobulin. Date *et al* report a series of data that suggest a novel additional level of TGF-β regulation, namely that TGF-β signalling in liver injury may be regulated by differential receptor expression.

In their study, Date *et al* use the well defined and reproducible rat CCl_4 model of hepatic injury. They have previously shown increased TGF-β mRNA expression following CCl_4 administration and now demonstrate a similar increase in TGF-β1 protein, maximal at 48 hours, following a single dose of CCl_4. They then go on to demonstrate that hepatocytes isolated from CCl_4 treated animals have reduced sensitivity to the antiproliferative effect of TGF-β1 in comparison with hepatocytes from normal rats. Concurrently, they have shown a dose dependent induction of fibronectin expression by TGF-β1 in HSC, which is not differentially regulated by CCl_4 treatment.

To attempt to account for the observed differential sensitivity of HSC and hepatocytes to TGF-β following CCl_4 injury, Date and co-workers then examined binding of

radiolabelled TGF-β1 to TGF-β receptors in HSC and hepatocytes from normal and CCl_4 treated livers. They identified proteins corresponding to the expected molecular weights of the three TGF-β receptor subtypes in hepatocytes and HSC from normal rats, and in HSC from injured rats. However, in hepatocytes extracted from rats 48 hours after CCl_4 injury, TGF-β receptors I and II (the subtypes responsible for mediating intracellular signalling) were downregulated and only returned to baseline levels of expression after 72 hours.

Date *et al* postulate that decreasing hepatocyte TGF-β receptor I and II expression following CCl_4 injury may provide an explanation for the observed reduction in TGF-β mediated growth inhibition of hepatocytes. This may explain the apparent paradox of hepatocellular regeneration corresponding temporally with increased TGF-β expression and increased extracellular matrix deposition. This paper provides consistent evidence to support this elegant hypothesis but raises with it further unresolved questions and many avenues worthy of investigation. For example, the present study does not quantify active TGF-β, which is perhaps the most relevant form to measure, as only the active peptide can bind to the cell surface receptors. Local activation of TGF-β may provide a further method of eliciting differential cellular responses. Moreover, it would be fascinating to ascertain the relationship between decreased TGF-β receptor expression and hepatocyte apoptosis.[8] But the mechanism by which hepatocytes regulate TGF-β receptor expression is perhaps the key question raised by this study. By attempting to answer these questions we may obtain significant insight into the complex and sometimes apparently contradictory biological effects of TGF-β in liver injury and fibrosis, and further unravel the exquisite control of hepatic regeneration.

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†".. it will grow to a prosperous perfection", William Shakespeare. *Measure for Measure*, Act 3, Scene 1.