


Thyroid function and interferon treatment in chronic hepatitis C

EDITORS.—We read with much interest the article by Marcellin et al (Gut 1992; 33: 855–6) about two cases of sustained hypothyroidism induced by recombinant interferon α in patients with chronic hepatitis C. The presence of antithyroid antibodies in both patients suggested an autoimmune cause of the hypothyroidism.1

We have recently seen a 51 year old woman with chronic active hepatitis C proved on biopsy examination randomised to receive 3 MU of recombinant interferon alfa 2-b (INTRON-A, Schering-Plough Corporation) subcutaneously three times a week for six months. The patient had no history of thyroid disease and had not received any drug known to be toxic to the thyroid. Serum triiodothyronine, thyroxine, free thyroxine, and thyroid binding globulin were determined by RIA kits (Farms Diagnostic Ltd, Turku, Finland); serum thyroid stimulating hormone, thyroid microsomal antigen autoantibodies, and thyroglobulin autoantibodies were measured by IRMA kits (Biocode, Switzerland). Serum samples were collected before treatment and every month for 12 months thereafter.

A transient reduction in triiodothyronine, thyroxine free thyroxine values started at month 4 and an increase in thyroid stimulating hormone values was recorded (Figure). The patient had no clinical signs of hypothyroidism; thyroid autoantibodies remained negative. On this basis, we suggest a multifactorial cause of thyroid function change induced by recombinant α interferon. In our case, a direct inhibition of thyroid hormone synthesis and secretion, or both by recombinant α interferon could have played a determinant role. This mechanism has been shown in vitro experiments with γ interferon.2

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We agree that, in the absence of antithyroid antibodies, the role of a direct inhibition of thyroid hormone synthesis and secretion by α interferon, or both, might be considered. Indeed, among 22 patients developing thyroid abnormalities while receiving interferon, we found antithyroid antibodies (anti-thyroglobulin and anti-peroxydase) in only half of them (unpublished data). Ex vivo studies of patients’ thyroid cells, if considered ethical, might provide pertinent information about the mechanisms of the cell damage induced by interferon in these patients.

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Biliary endoprostheses and common bile duct stones

EDITORS.—The report from Peters et al (Gut 1992; 33: 1412–5) of a group of patients with bile duct stones treated with a biliary endoprosthesis is of considerable interest. This technique has been used by many centres, provides excellent immediate drainage, and reasonable medium term results — but I wish to sound a note of caution. The justification for using stents as permanent treatment must depend on the results in the long term, indeed can only be assessed by lifetime follow up which no one has yet reported. Our own series with a follow up of 2–5 years was encouraging,1 but more than half of the patients were still alive (despite being apparently at very high risk initially),1 and many problems may have occurred subsequently.

The number of patients having stenting for bile duct stones in the King’s series seems very high — no fewer than 40 of 146 of a consecutive series, including 27 (18%) as projected permanent treatment. The authors suggest that their low rate of duct clearance reflected their referral practice but referral centres should have special expertise. Of 343 patients with duct stones referred to this unit during the last two years, the clearance rate using standard techniques and mechanical lithotripsy was 94%. Stents were used as ‘permanent’ treat-

Reply

EDITORS.—We read with interest the comment by Picciotto et al on our paper reporting another case of hypothyroidism, probably induced by recombinant interferon alfa 2-b in patient treated with this drug. No antithyroid antibodies were found and the authors suggest a multifactorial mechanism by which thyroid abnormalities are induced. We agree that, in the absence of antithyroid antibodies, the role of a direct inhibition of thyroid hormone synthesis and secretion by interferon, or both, might be considered. Indeed, among 22 patients developing thyroid abnormalities while receiving interferon, we found antithyroid antibodies (anti-thyroglobulin and anti-peroxydase) in only half of them (unpublished data). Ex vivo studies of patients’ thyroid cells, if considered ethical, might provide pertinent information about the mechanisms of the cell damage induced by interferon in these patients.

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The authors found a great emphasis upon duct cells. They stated that in some patients diagnosed as having Barrett's oesophagus, it is reasonable to conclude that the small intestinal bacterial overgrowth is a cause of reflux, and it is for this reason that we selected the size of the gate for the epithelial cell populations. It is clearly stated at the end of the second subsection in the methods section of our paper. We have not had the opportunity to study the recent paper by Mr Gray and his colleagues as it has not yet appeared in print. It would seem, however, that they have been examining different types of Barrett's oesophagus rather than comparing Barrett's mucosa with gastric or oesophageal squamous mucosa. The relevance of their results with respect to our findings is therefore difficult to understand.

**Assessment of proliferation of squamous, Barrett's, and gastric mucosa in patients with columnar lined Barrett's oesophagus**

**Editor,**—I comment on the interesting paper by Itzikkar et al on assessment of proliferation in oesophageal squamous, Barrett's, and gastric epithelium by flow cytometric evaluation of Ki67 immunolabelling (Gut 1992; 33: 733-77). The authors found that biopsy specimens from squamous lined oesophagus contained cell populations with a higher percentage of Ki67 positive cells than Barrett's, and gastric mucosal biopsy specimens. Barrett's and gastric mucosal biopsy specimens have similar percentages of Ki67 positive cells. Their results may be misleading as the proportion of stromal cells in Barrett's mucosa greatly exceeds that in gastric and squamous mucosal biopsy specimens, which have over 90% pure epithelial populations; stromal cells are not excluded from the total cell count by their technique and dilute the epithelial cell population. Thus the finding that Barrett's mucosal biopsy specimens contain a similar percentage of Ki67 cells to gastric biopsy specimens (by this technique) is more likely to imply a considerably higher epithelial Ki67 labelling index in Barrett's than in gastric epithelial cell (as opposed to the total mucosal cell population).

This agrees with the studies performed on stained sections of mucosal biopsy specimens, including our own. In our study of epithelial proliferation in Barrett's oesophagus we used PCNA immunostaining of specialised Barrett's junctional metaplasia to evaluate proliferation in the epithelial cells only (excluding stromal cells). In our study specialised type Barrett's had a higher proportion of cells in cycle and an expansion of the proliferative compartment out of the crypt and into the luminal and gland cell compartments; implying a higher level of proliferative activity in the specialised Barrett's than in the other types of metaplasia. Our findings are consistent with the proved association of specialised type Barrett's epithelium with malignant change (in smokers).**

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**Reply**

**Editor,**—Thank you for giving us the opportunity to reply to Mr Gray's comments. We share his concern about the increased population of stromal cells in Barrett's oesophagus and it is for this reason that we selected the size of the gate for the epithelial cell populations identified by staining with anticytokeratin. This is clearly stated at the end of the second subsection in the methods section of our paper.

We have not had the opportunity to study the recent paper by Mr Gray and his colleagues as it has not yet appeared in print. It would seem, however, that they have been examining different types of Barrett's metaplasia rather than comparing Barrett's mucosa with gastric or oesophageal squamous mucosa. The relevance of their results with respect to our findings is therefore difficult to understand.

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**Strategies for hepatitis B infection**

**Editor,**—In their comprehensive leading article Catterall and Murray-Lyon (Gut 1992; 33: 576-9) discuss strategies for hepatitis B immunisation. With regard to the need for booster vaccinations it seems to us that option I (no booster and reliance on immunological memory) has gained additional strength in new in vivo and in vitro data. Some of these have already been mentioned in the addendum. Our own data have been supported by the findings of Jilg's group.**

To our knowledge, not a single case of clinically evident hepatitis B or carcinoma following hepatitis B virus infection has been reported in a confirmed serologically to hepatitis B vaccine.

A spot ELISA assay, which visualises the surface immunoglobulin production of either IgG or IgM class by individuals in whom stimulated B cells in vitro, is able to show latent immunological memory and adds further support to this strategy. Long term follow up data confirm the presence of persisting circulating B cell memory despite undetectable anti-HBs in the serum seven to nine years after the first vaccination. Further studies with an even longer interval are in progress. Moreover, follow up data carefully monitored the course of events after accidental infection (such as needlestick injuries) will give additional information.

Omitting booster vaccinations completely despite theoretical objections, in all those who have been known to react to the initial vaccination series with an anti-HBs titre in excess of 100 IU/l, seems to be a perfectly reasonable alternative approach, in expensive and complicated, and probably unnecessary booster immunisation programmes. This policy is actually being evaluated on a world wide scale at present (be it uncontrolled) because many vaccines with known responder status will not have received a booster vaccination.

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**Overview of screening and management of familial adenomatous polyposis**

**Editor,**—In their review article Rhodes and Innes (Gut 1992; 33: 181-5) have discussed the relevance, and potential benefits, of long term screening of family members and siblings of probands diagnosed as having familial adenomatous polyposis. These screening programmes have identified B variants in asymptomatic subjects, usually by identification of rectal polyps at sigmoidoscopy, and reduced the occurrence of invasive colorectal carcinoma to less