Letters to the Editors

Altered lipid pattern explains increased cardiovascular mortality in hypopituitary patients with growth hormone deficiency

Sirs, We read the paper by Bülow et al. (1997) where an increased cerebrovascular mortality was found in patients with hypopituitarism, with much interest. This is in agreement with our previous finding (Rosén & Bengtsson, 1990), although premature death from cardiovascular disease was more pronounced in our study.

We have hypothesized that untreated growth hormone deficiency (GPD) is the principal factor behind this increased cardiovascular mortality. Further studies have linked several cardiovascular risk factors such as hyperlipidaemia, hypertension, overweight, truncal obesity (Rosén et al., 1993), insulin resistance (Johansson et al., 1995), elevated fibrinogen levels and decreased fibrinolysis (Johansson et al., 1994), but not smoking (Rosén et al., 1993), to the adult GHD syndrome. However, it is unclear to what extent the individual risk factors explain the premature cardiovascular mortality. The major risk factors for coronary heart disease (CHD) are hyperlipidaemia, smoking and hypertension. The increased prevalence of treated hypertension noted among our hypopituitary patients with GHD (Rosén et al., 1993) was counterbalanced by decreased smoking.

Serum total cholesterol concentrations were not elevated among the GHD patients (6·16 mmol/l; males and 6·48 mmol/l; females compared with the general population (6·17 mmol/l;

Table 1 Mean serum triglycerides and HDL cholesterol concentrations in 47 male and 30 female GHD patients and in controls (N=1019), aged 35–64 years (MONICA, Göteborg).

|        | Males |     | Females |     |
|--------|-------|-----|---------|-----|
|        | Patients | Controls | Patients | Controls |
| Triglycerides (mmol/l) | 1·80 | 1·51 | 1·06 | 1·16 |
| HDL-cholesterol (mmol/l) | 0·99 | 1·33 | 1·32 | 1·66 |

Fig. 1 Estimated incidence of coronary heart disease (CHD) by level of triglycerides (mmol/l) and HDL cholesterol (mmol/l) according to the Framingham study model in patients with GHD, (●) as well as in controls (■) (MONICA, Göteborg). ● indicates cells with too few subjects for meaningful calculation. a, males; b, females.
males and 6.22 mmol/l; females). To study the role of increased triglycerides and decreased HDL cholesterol concentrations noted among the GHD patients, we have used data obtained from the Framingham Study, which predicts the risk of CHD from triglyceride and HDL cholesterol levels (Castelli, 1986). The mean serum concentrations of triglycerides and HDL cholesterol in both GHD patients and controls (MONICA-Study, Göteborg, Sweden, N = 1019; age groups 35–64 years) in a previous study (Rosén et al., 1993) are shown in Table 1.

According to the Framingham model (Fig. 1a, b) the male GHD patients had ‘low’ HDL cholesterol and ‘high’ triglycerides levels, in contrast to the ‘high’ HDL cholesterol and ‘medium’ triglycerides levels noted in the male controls. The female GHD patients had ‘medium’ levels of both HDL cholesterol and triglycerides, while the female controls had ‘high’ HDL cholesterol and ‘medium’ triglycerides levels. The triglycerides-HDL cholesterol results for both male and female GHD patients and controls were then placed into the appropriate Framingham ‘boxes’, which thus predict the incidence of CHD by the level of HDL cholesterol and triglycerides.

The male GHD patients had an estimated CHD incidence of about 130 events/1000 individuals, compared with the incidence of 40 events/1000 individuals among the male controls. The CHD incidences for the female GHD patients and controls were 47 events/1000 individuals and about 10 events/1000 individuals, respectively. According to these calculations both male and female GHD patients had at least a twofold increase in the CHD risk compared with healthy controls. As the calculations are based upon an American risk function and used in Swedish GHD patients, the absolute risks may be somewhat biased, but the estimations of relative risk are less open to criticism. Thus, our data indicate that the disturbed lipid pattern plays a major role in the premature cardiovascular mortality among adult hypopituitary patients with GHD.

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**Transient hypothyroidism after iodine-131 therapy for Graves’ disease**

*Sirs,* We read with interest the article by Aizawa et al. (1997) dealing with the finding of transient hypothyroidism after iodine-131 therapy for Graves’ disease. The authors report transient hypothyroidism in 15% of patients treated, which is similar to values reported previously (Dorfman et al., 1977; Sawers et al., 1980; Connell et al., 1983; Gómez et al., 1995).

In the study of Aizawa et al. (1997) the prevalence of permanent hypothyroidism 1 year after iodine-131 therapy was 11% compared with 33% in our experience with individualized dose of iodine-131 and their prevalence of hyperthyroidism at 1 year was 42.3% vs. 26.1% in our study (Gómez et al., 1995). This important difference in the outcome between the two studies may be due to deficient iodine intake in our country (Serra-Majem et al., 1993).

Their results suggest that measurement of TSAb activity at the onset of hypothyroidism may differentiate transient for permanent hypothyroidism. In our experience basal TSH levels were high at the onset of transient hypothyroidism in 51% of cases, normal TSH in 35% and low TSH in 14% and no patient with basal TSH higher than 45 mU/l had transient hypothyroidism. Thus TSH plays some role in the recovery of hypothyroidism.

Our results and the results of Aizawa et al. (1997) do not support the hypothesis that transient hypothyroidism is a central hypothyroid phase during recovery of the hypothalamic axis after iodine-131 treatment, as suggested by Uy et al. (1995). A slow decrease in thyroid function in the first months due to imbalance between radiation damage and higher TSAb and TSH activity is presumably relevant in these patients and in some of them a sluggish response of the pituitary thyrotrophs to the presence of low serum thyroid hormone levels might therefore be expected.

The final outcome in our patients showed that thyroid function did not differ from that of patients without previous transient hypothyroidism and was independent of TSH levels during the transient hypothyroid phase.

Although the mechanisms underlying transient hypothyroidism are not homogeneous and its occurrence was not a
prognostic indicator of future thyroid function, its clinical significance lies in accurate diagnosis.

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Retinoid X receptor γ mRNA expression is reduced in recurrent non-functioning pituitary adenomas

Sirs, Non-functioning tumours (NFTs) of the anterior pituitary are usually benign and slow growing, although not all tumours behave in a universal and predictable manner. There are no reliable clinical, histological, biochemical or molecular markers that predict the likelihood of tumour recurrence following pituitary surgery; thus, specific targeted treatment of ‘at risk’ tumours with post-operative radiotherapy is not feasible. Retinoid X receptors (RXRs) are members of the nuclear steroid receptor superfamily that bear ligand specificity for 9-cis retinoic acid (RA). We have previously documented reduced expression of RXRs in NFTs compared with the findings in normal pituitaries (Gittoes et al., 1998). In a number of human cell lines, 9-cis RA has been shown to cause reduced cell proliferation, increased cell differentiation and increased apoptosis; hence abnormal expression of RXRs in NFTs may be expected to influence the growth pattern, and thus the overall biological behaviour of these tumours. We have determined the relative levels of expression of RXR isoform (α, β, γ) mRNAs by semiquantitative RT-PCR in recurrent NFTs (n = 10) and compared the findings with those obtained from newly diagnosed NFTs (n = 10) and normal pituitaries (n = 6).

Pituitary RNA was extracted using RNAzol B and was reverse transcribed using oligo(dT)15 primers and AMV reverse transcriptase. RXR isoform-specific primers were generated and comparative kinetic analysis was used to determine the phase during which there was exponential generation of PCR product. β-actin mRNA expression was used as an internal control to account for variability in RNA degradation and RT efficiency between pituitary samples. RXRα and RXRβ mRNAs were expressed at similar levels in normal pituitaries, recurrent and non-recurrent NFTs (Table 1). The level of RXRγ mRNA was significantly reduced in recurrent NFTs (0.75 (0.69–0.82); median (25th–75th centiles)) compared with the levels in normal pituitaries (1.04 (0.91–1.51); median (25th–75th centiles)); P < 0.005 by Mann–Whitney U-test) and newly diagnosed NFTs (0.91 (0.80–0.98); median (25th–75th centiles); P < 0.05 by Mann–Whitney U-test). We propose that reduced RXRγ mRNA expression observed in recurrent NFTs may prevent the anti-proliferative action of its ligand, 9-cis RA, allowing tumour growth and aggressive clinical behaviour, RXRγ mRNA expression may be of value as a prognostic indicator in NFTs.

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Table 1 Retinoid X receptor mRNA expression (median (25th–75th centiles)) in normal pituitaries and in NFTs as a function of recurrence following initial pituitary surgery

| mRNA      | Normal pituitaries | No recurrence | At least one recurrence | Two recurrences |
|-----------|--------------------|---------------|-------------------------|-----------------|
| RXRα mRNA | 0.58 (0.45–0.60)   | 0.40 (0.33–0.65) | 0.49 (0.39–0.51)        | 0.39 (0.33–0.48) |
| RXRβ mRNA | 0.85 (0.66–1.38)   | 0.84 (0.66–0.91) | 0.76 (0.68–0.92)        | 0.79 (0.78–0.92) |
| RXRγ mRNA | 1.04 (0.91–1.51)   | 0.91 (0.80–0.98) | 0.75 (0.69–0.82)        | 0.76 (0.69–0.80) |

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