

## PAPERS AND SHORT REPORTS

## Low serum testosterone concentrations in patients with carcinoma of the pancreas

BRIAN GREENWAY, M J IQBAL, P J JOHNSON, ROGER WILLIAMS

### Abstract

The detection of high activities of two sex-steroid biosynthetic enzymes—aromatase and 5- $\alpha$ -reductase—in pancreatic carcinoma tissue suggested the possibility that these enzymes may influence the circulating concentrations of sex-steroid hormones. Mean serum testosterone concentrations in 22 men and women with exocrine carcinoma of the pancreas were significantly lower than those in 20 healthy controls and 27 patients with other known malignancies, who were of similar age and sex composition. Low serum testosterone concentrations may be due to uptake by and metabolism within the tumour; alternatively, patients with low androgen concentrations may be at greater risk of developing pancreatic carcinoma.

### Introduction

We reported the presence of high concentrations of oestrogen receptors in pancreatic carcinoma tissue,<sup>1</sup> and subsequently, as in other sex-steroid responsive tissues, we showed the presence of two sex-steroid biosynthetic enzymes: aromatase, which converts the androgens testosterone or  $\Delta_4$ -androstenedione to the oestrogen oestradiol, and 5 $\alpha$ -reductase, which converts testosterone to its more active androgen metabolite 5 $\alpha$ -dihydrotestosterone (Iqbal and Greenway, submitted for publication). Similar findings have been reported in carcinoma of the breast, where abnormalities of both urinary and serum androgens have also been described.<sup>2,3</sup>

The possibility that high activities of these two enzymes may

influence the circulating concentrations of sex steroids has now been examined, and we report measurements of the serum concentrations of testosterone, 5 $\alpha$ -dihydrotestosterone, and oestradiol in male and female patients with pancreatic carcinoma and in two control groups of similar age and sex composition, one of which comprised patients with malignancies of other sites.

### Patients and methods

Blood was taken between 9 and 10 am before treatment began from 22 patients with pancreatic carcinoma (13 men, nine women; age range 45-82, mean 68); 27 patients with malignancies of other primary sites (13 men, 14 women; age range 51-88, mean 67) (gastrointestinal tract 16, prostate 3, breast 2, lung 2, ovary 2, myeloma 1, lymphoma 1); and 20 healthy subjects (10 men, 10 women; age range 48-87, mean 69) who had been admitted to hospital for minor surgical procedures such as inguinal herniorrhaphy, varicose veins, excision of sebaceous cysts, etc. Serum was stored at  $-20^{\circ}\text{C}$  for up to three months.

The steroids were extracted with diethyl ether (Hopkin and Williams) and measured by radioimmunoassay, a version of the method of Emmert *et al*<sup>4</sup> being used for oestradiol and of Collins *et al*<sup>5</sup> for testosterone. Since the antibody to dihydrotestosterone is not highly specific because of substantial competition from testosterone, the method of Buratti-de Hoghton and Iqbal<sup>6</sup> was used to eliminate interfering 17 $\beta$ -hydroxyandrogens. The technique entails prior oxidation of the ether extract with potassium permanganate after which the oxidised solution is again extracted with ether. The rest of the procedure for the radioimmunoassay of dihydrotestosterone was similar to that described for testosterone. Results were analysed by Student's *t* test for parametric data.

The published normal range for serum testosterone concentrations in all age groups measured by radioimmunoassay is 7.0-30.0 nmol/l (2.0-8.7 ng/ml) for males and 0.5-4.0 nmol/l (0.1-1.2 ng/ml) for females.<sup>7</sup> Our normal range for men aged 50-90 is  $10.6 \pm 4.5$  nmol/l ( $3.1 \pm 1.3$  ng/ml).

### Results

Men with pancreatic carcinoma had significantly lower values of serum testosterone when compared with the healthy control group ( $t=5.34$ ;  $p<0.001$ ;  $df=21$ ) and patients with other known malignancies ( $t=4.7$ ;  $p<0.001$ ;  $df=24$ ). Women with pancreatic carcinoma

Liver Unit, King's College Hospital and Medical School, London SE5 8RX

BRIAN GREENWAY, MRCP, FRCS, Cancer Research Campaign clinical research fellow (present address: Bristol Royal Infirmary, Bristol 2)

M J IQBAL, PHD, research fellow

P J JOHNSON, MB, MRCP, senior lecturer

ROGER WILLIAMS, MD, FRCP, director of liver unit

similarly had significantly lower values of serum testosterone when compared with the healthy female control group ( $t=7.48$ ;  $p<0.001$ ;  $df=17$ ) and women with other known malignancies ( $t=4$ ;  $p<0.001$ ;  $df=21$ ) (figs 1 and 2).

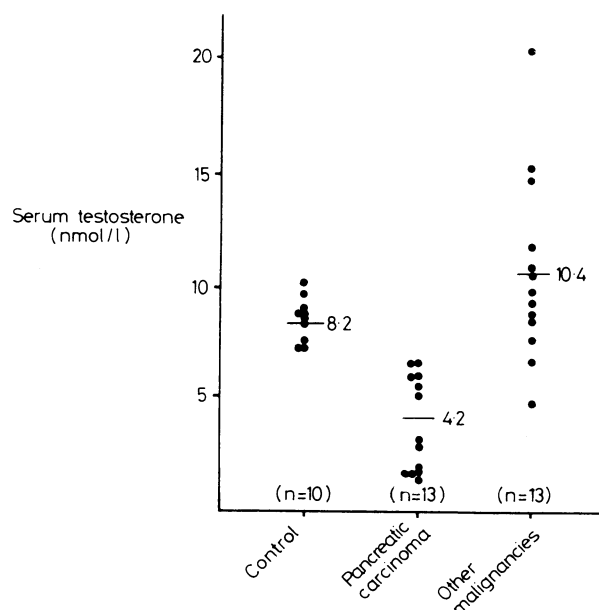


FIG 1—Serum testosterone concentrations in men. Bars are means.  
Conversion: SI to traditional units—Testosterone: 1 nmol/l  $\approx$  0.3 ng/ml.

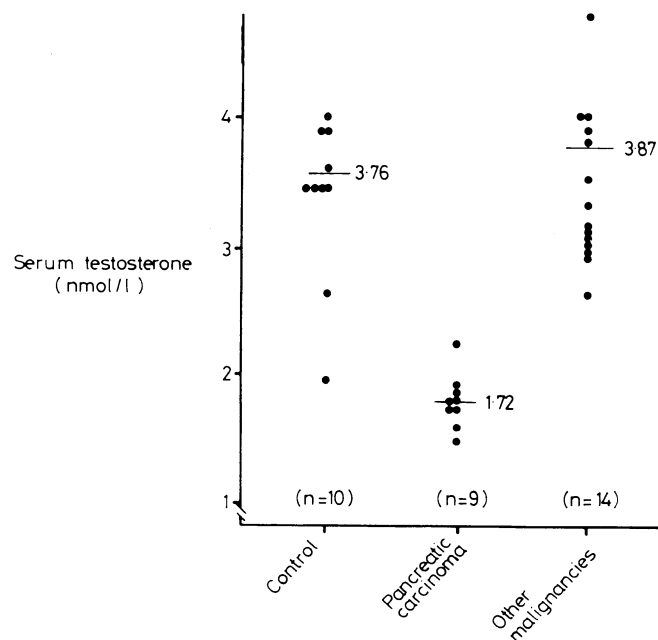


FIG 2—Serum testosterone concentrations in women. Bars are means.  
Conversion: SI to traditional units—Testosterone: 1 nmol/l  $\approx$  0.3 ng/ml.

Of the 13 men with pancreatic carcinoma, four had a value of serum dihydrotestosterone below the normal range, and, overall, the mean concentration was significantly lower than that of male healthy controls ( $p<0.05$ ) and men with malignancies of other sites ( $p<0.01$ ). Values in women with pancreatic carcinoma and in both control groups were not significantly different and fell within the normal published range.

Serum oestradiol concentrations were within the normal range in both men and women with carcinoma of the pancreas as well as in patients with malignancies of other sites.

## Discussion

Serum testosterone concentrations were significantly reduced in both men and women with pancreatic carcinoma, even after allowing for the reduction in circulating concentrations with increasing age seen in men.<sup>8</sup> The possible effect of severe illness or the general effects of a malignant disease in reducing testosterone values was eliminated by comparing these patients with pancreatic carcinoma with a group of patients with malignancies of other sites, some of whom were terminally ill.

It is possible that the low testosterone concentrations may be related in some way to the presence of the tumour. Our previous finding of high activities of aromatase and 5 $\alpha$ -reductase in pancreatic carcinoma tissue, which both require testosterone as a substrate, may provide a possible mechanism, in that the tumour could take up testosterone for its metabolism and growth. Recent studies in an animal model of human pancreatic carcinoma xenografts which showed that testosterone enhanced tumour growth support this suggestion.<sup>9</sup>

The low mean serum dihydrotestosterone values found in men with pancreatic carcinoma suggest either that the major metabolic pathway of testosterone is by aromatisation to oestradiol rather than 5 $\alpha$ -reduction to dihydrotestosterone, or that dihydrotestosterone is further catabolised within the tumour to the two androstenediols. We have not measured this second pathway.

The finding of low serum androgen concentrations in patients with pancreatic carcinoma is a further example of the striking hormonal similarities between pancreatic carcinoma and breast carcinoma, in which oestrogen receptors, aromatase and 5 $\alpha$ -reductase,<sup>10</sup> and abnormalities in serum and urinary androgens have been shown. Bulbrook *et al* suggested that abnormalities in androgen concentrations may be a primary risk factor in the development of carcinoma of the breast, following the demonstration that abnormal urinary androgen excretion had antedated the diagnosis by up to nine years.<sup>11</sup> An analogy could be made with carcinoma of the pancreas, with low serum androgen values being a risk factor for its development. The rise in incidence of pancreatic carcinoma and the fall in serum testosterone concentration with age would be consistent with this. The tumour, however, is significantly less common in women, in whom serum testosterone concentrations are much lower, suggesting either that a low serum testosterone value is not by itself a risk factor or that different aetiological factors are concerned in men and women.

The change in oestradiol values in postmenopausal women with carcinoma of the breast<sup>12</sup> contrasts with the finding in pancreatic carcinoma, where no difference from normal was detected in any of our patients.

Our findings provide additional support for the possibility that the metabolism and growth of pancreatic carcinoma may depend on the sex-steroid hormones, in particular testosterone, which in turn suggests that antiandrogens may offer a new approach to treatment.

We acknowledge the support of the Cancer Research Campaign as well as the Ned Foundation and the Frances and Augustus Newman Foundation.

## References

- Greenway B, Iqbal MJ, Johnson PJ, Williams R. Oestrogen receptor proteins in malignant and fetal pancreas. *Br Med J* 1981;283:751-3.
- Wang DY, Moore JW, Thomas BS, *et al*. Plasma and urinary androgens in women with varying degrees of risk of breast cancer. *Eur J Cancer* 1979;15:1269-74.
- Bulbrook RD, Hayward JL. Abnormal urinary steroid excretion and subsequent breast cancer. *Lancet* 1967;i:519-22.
- Emment Y, Collins WP, Sommerville IF. Radioimmunoassay of oestrone and oestradiol in human plasma. *Acta Endocrinol (Copenh)* 1972;69:576-82.
- Collins WP, Mansfield MD, Alladina NS, Sommerville IF. Radioimmunoassay of plasma testosterone. *J Steroid Biochem* 1972;3:343-8.

- <sup>6</sup> Buratti-de Hoghton R, Iqbal MJ. Total 17 hydroxyandrogens, 5 $\alpha$  reduced hydroxyandrogens, and sex hormone binding globulin in assessing androgen dependent syndromes. In: Genazzani AR, Thijssen JHH, Siiteri PK, eds. *Adrenal androgens*. New York: Raven Press, 1980:301-7.
- <sup>7</sup> Ismail AAA. Testosterone. In: Loraine JA, Bell ET, eds. *Hormone assays and their clinical application*. 4th ed. London: Churchill Livingstone, 1976:580-629.
- <sup>8</sup> Vermeulen A, Rubens R, Verdonck L. Testosterone secretion and metabolism in male senescence. *J Clin Endocrinol Metab* 1972;**34**:730-5.
- <sup>9</sup> Greenway B, Duke D, Pym B, Iqbal MJ, Johnson PJ, Williams R. The control of human pancreatic adenocarcinoma xenografts in nude mice by hormone therapy. *Br J Surg* 1982;**69**:595-7.
- <sup>10</sup> Miller WR, Hawkins RA, Forrest APM. Steroid metabolism and oestrogen receptors in human breast carcinomas. *Eur J Cancer Clin Oncol* 1981;**17**:913-7.
- <sup>11</sup> Bulbrook RD, Hayward JL, Spicer CC. Relation between urinary androgen and corticoid excretion and subsequent breast cancer. *Lancet* 1971;iii:395-8.
- <sup>12</sup> England PC, Skinner LG, Cottrell KM, Sellwood RA. Serum oestradiol—17  $\beta$  in women with benign and malignant breast disease. *Br J Cancer* 1974;**30**:571-6.

(Accepted 13 October 1982)

## Changes in clinical features of coeliac disease in adults in Edinburgh and the Lothians 1960-79

RICHARD F A LOGAN, GEORGE TUCKER, EDITH A RIFKIND, ROBERT C HEADING, ANNE FERGUSON

### Abstract

From 1960 to 1979 there was a threefold increase in the number of cases of coeliac disease diagnosed annually in adults in Edinburgh and the Lothians. Women accounted for 80% of the increase and their mean age at diagnosis was significantly reduced. The ratio of female to male new cases changed from 1.25 in the '60s to 2.5 in the '70s. In the period 1975-9 56 of 102 adults with coeliac disease presented with no gastrointestinal symptoms, including 30 cases diagnosed as a result of minor biochemical or haematological abnormalities, such as red-cell macrocytosis without anaemia. Over the same period, only 13 presented with a typical malabsorption syndrome compared to 24 of 38 (63%) in the years 1960-4. During 1975-9 58 new cases had no anaemia, compared with eight (21%) in the earlier period. Hypoproteinaemia (concentration <60 g/l) and hypocalcaemia of <2.00 mmol/l (8 mg/100 ml) were also less common.

Though a real increase in the incidence of coeliac disease cannot be discounted, these changes are more likely to be the result of greater awareness of the disease and a lowered threshold for investigation.

### Introduction

With the introduction of peroral jejunal biopsy for the diagnosis of coeliac disease estimates of the prevalence of the disease in the United Kingdom have steadily risen from 1 in 8000, suggested in 1950, to recent estimates in children of around 1 in 1000.<sup>1,2</sup> In 1979 the crude prevalence in Edinburgh and the

Lothians was 61/100 000 (1 in 1637) with a peak of 90/100 000 in the age group 5-14 years.<sup>3</sup> While textbook descriptions of coeliac disease emphasise features such as diarrhoea, weight loss, anaemia, and malabsorption, recent series have drawn attention to the numbers presenting with trivial, often unrelated, illness.<sup>4,5</sup> Although it is generally assumed that the rising prevalence reflects increased awareness and improved diagnosis, the apparent decline in coeliac disease in childhood reported recently from Glasgow and Leeds suggests that pronounced changes in incidence may be occurring.<sup>6,7</sup> Increased awareness of any chronic disease may increase numbers and also lead to a decline in severity at diagnosis and to earlier diagnosis.

We describe the current presentation of coeliac disease in adults in Edinburgh and Lothian and, by comparison with an earlier period, attempt to determine whether there has been any change in severity that might account, at least in part, for a rise in prevalence.

### Methods

In 1979 a register of patients with coeliac disease was established in Edinburgh and the Lothians. The population of Lothian Region at the time of the 1971 census was 746 000. Cases of coeliac disease were identified from the records of the gastrointestinal units at the Royal Infirmary of Edinburgh and the Western General Hospital; hospital discharge records (Scottish Hospital In-patient Statistics); the histopathology records of the four pathology laboratories in the region from 1955 to 1980; and a postal survey of all general practitioners in Edinburgh and the Lothians. For all patients included in the register a clinical diagnosis of coeliac disease has been substantiated by abnormal findings at jejunal biopsy. All biopsy specimens were reviewed by one of two pathologists (Dr A Busuttil, Dr H Gilmour) without knowledge of the clinical details.

Patients who had dermatitis herpetiformis were recorded separately and have been excluded from this report. The study is confined to those patients in whom coeliac disease was diagnosed after their 15th birthday, and who are therefore classified as adults with coeliac disease; patients re-presenting because of a lapse in treatment of childhood coeliac disease have been excluded.

An analysis of sex, age, and year of diagnosis was performed on all of the adults registered. In addition, a more detailed analysis of clinical features was performed on those presenting to the two major teaching hospitals in the region, the Royal Infirmary and the Western General Hospital. These patients fulfilled two criteria: an appropriate abnormal finding on jejunal biopsy and a clinical or histopathological response to a gluten-free diet.

The date of diagnosis has been taken as the time of clinical diagnosis, which also was the date of the first abnormal finding at biopsy in all but three cases in the 1960-4 period and in all cases in the 1975-9

University of Edinburgh Gastrointestinal Unit, Western General Hospital, Edinburgh EH4 2XU

RICHARD F A LOGAN, MSc, MRCP, senior registrar (now: Wellcome research fellow, department of therapeutics, University of Nottingham, City Hospital, Nottingham)

EDITH A RIFKIND, BSc, research associate

ANNE FERGUSON, PhD, MRCPATH, reader in medicine and honorary consultant physician

Department of Therapeutics, Royal Infirmary, Edinburgh EH3 9YW

GEORGE TUCKER, MB, FRACP, registrar

ROBERT C HEADING, MD, FRCP, senior lecturer and honorary consultant physician