Letters to the Editors

Cortisol response in short synacthen tests

Sirs, The recent paper by Clark *et al*. (1998) highlighted many issues regarding the interpretation of short synacthen tests (SST). In 1995 as part of an extensive pre-launch evaluation of the cortisol method on the Bayer/Chiron ACS180 (ACS) we compared responses to SST with two established methods (Abbot TDx, n = 45 and Farmos, n = 46). Like Clark *et al*. (1998) we noted the non-gaussian nature of the data and used non-parametric regression analysis (Thiels) and found the slope and intercept were significantly different in samples 30 minutes post synacthen (SST30) [ACS = 0·79*TDX + 110; ACS = 0·79 *Farmos + 176] compared to basal (SST0) [ACS = 0·86*TDX +51; ACS = 1·08*Farmos + 14] (Price & Ross, 1996). 105 samples taken from patients on hydrocortisone treatment for adrenal insufficiency showed no dose dependant bias (ACS180 = 0·96*TDX + 18). Our theory has been that in response to synacthen the adrenal produces a short lived metabolite which cross reacts in the TDX and Farmos assays but not the ACS180 assay. Such an explanation could be applied to the data found by Clark *et al*. (1998).

We thought the lower values post synacthen would affect the interpretation of the SST so, using a peak cortisol response of 550 nmol/l or greater as adequate (Lindholm *et al*., 1978; May *et al*., 1985; Stewart *et al*., 1988; Axelrod *et al*., 1993; Howlett *et al*., 1994; Jackson *et al*., 1994; Tietz *et al*., 1995), we compared the results from the ACS with the other methods and found only 1 out of 95 patients to give a discrepant response. This was in a male aged 54 with chronic renal failure. The other 3 patients with chronic renal failure for whom we had data did not give discrepant responses. Therefore, the lower results produced by the ACS has a minimal effect on the interpretation of the SST.

Previous investigators may have found a change in incremental response in SST with basal cortisol because they did not account for a difference in response between males and females noted by Clark *et al*. (1998). We re-analysed our data (Price & Ross, 1996) for both the Farmos and TDX methods and found no significant change in the incremental response of cortisol against the basal concentration for males but found a significant ($P < 0·01$) decrease in incremental response against basal concentration for females.

Wood (1998) highlighted the need for rationalization of SST. However, why stop at SST? The problem for laboratories and manufacturers of cortisol methods, is the multitude of methods that are used by clinicians to assess adrenal reserve. The problem is further exacerbated if the definition of an adequate response for one method is linked to the demonstration of an adequate response for another, for example SST and the insulin stress test (IST) (Lindholm *et al*., 1978; Stewart *et al*., 1988). This raises the question of whether it is valid to establish the cut off for the SST without reference to results from IST in the same patient using the same cortisol method.

A multi-centre evaluation of tests used for adrenal reserve is required. For example, a clinician performing an IST would also do a SST and a glucagon test. Sufficient serum would be taken at agreed time points and stored in multiple aliquots at −80°C allowing responses to be established for a variety of cortisol methods for a variety of adrenal insufficiency tests all linked to the gold standard of IST. Sufficient serum should be taken that many surplus aliquots are available and at the end of the trial these should all be transferred and stored at one site. Manufacturers who then produce a new cortisol method would have a reference laboratory where they can evaluate and produce their own response cut off for the variety of methods. Such a multi-centre evaluation is needed for the benefit of patients who have to undergo these tests, for clinicians and for laboratories who have to try and interpret them.

Alun Price*, T. A. Gray* and A. P. Weetman†
*Departments of *Clinical Chemistry and †Medicine, Northern General Hospital, Sheffield, U.K.*

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Obesity in the Prader–Labhart–Willi syndrome is not due to leptin deficiency but is accentuated by hypogonadism in male patients

Sirs, Prader–Labhart–Willi (PLW) syndrome classically comprises obesity, hyperphagia, learning difficulties and infertility. Hypothalamic dysfunction is central to PLW. This accounts for the hyperphagia, aberrant control of body temperature and daytime hypersomnolescence, as well as disturbances to the hypothalamic–pituitary axes particularly the gonadal axes (Donaldson *et al*., 1994). Information on the role of the hypothalamus in controlling appetite has increased dramatically since the discovery, in 1994, of leptin (Zhang *et al*., 1994). This research has led to the proposal that circulating leptin concentrations accurately reflect adipose mass and regulate adiposity in healthy human subjects via a feedback inhibition loop involving neuropeptide Y and the appetite centre within the brain (Mantzoros & Moschos, 1998). Since the association of a hypothalamic defect, obesity and infertility are common to both PLW and human leptin deficiency (Montague *et al*., 1997) we undertook to establish the status of this hormone in patients with PLW syndrome.

The study population consisted of 23 patients (13 males; 10 females) with PLW syndrome and 21 (11 males: 10 females) obese weight and sex matched controls. Of the seven adult male patients four had pre-pubertal testosterone concentrations and three were receiving replacement doses of testosterone.

Our results showed that circulating leptin concentrations in patients compared to controls were $53{\cdot}3 \pm 10{\cdot}2$ (mean ± SEM) *vs*. $38{\cdot}3 \pm 6{\cdot}7$ μg/l in females and $32{\cdot}6 \pm 8{\cdot}2$ *vs*. $17{\cdot}7 \pm 3{\cdot}4$ μg/l in males. There was a significant positive association between leptin and BMI in sex matched control subjects ($P < 0{\cdot}01$) (Fig. 1). As anticipated from many other studies in which circulating leptin concentrations are related to BMI the gradient of the regression plot is significantly steeper for female compared to male controls ($m = 2{\cdot}13$ cf, 0·59; $P < 0{\cdot}001$ using *t* test to compare gradients). Male patients, who were not receiving testosterone, had a significantly higher gradient than male controls ($m = 25$ cf 0·59, $P < 0{\cdot}001$, $n = 10$ cf $n = 11$) resulting in lack of a gender difference in circulating leptin concentrations in PLW patients. To account for age related differences in leptin concentrations patients were matched for both age and BMI. Patients were, however, not matched for gonadal status and many of the PLW patients were hypogonadal as a consequence of the hypothalamic dysfunction that is central to PLW syndrome. Interestingly, the three PLW males receiving testosterone replacement had the lowest circulating leptin concentration relative to BMI (Fig. 1).

In a number of recent studies circulating leptin concentrations have been measured in PLW patients. The most comprehensive of these studies (Butler *et al*., 1998) involved comparing serum leptin concentrations in 33 PLW patients (19 males and 14 females) with 44 controls (17 males and 27 females). Although patients and controls were matched for gender they were not matched as precisely for age and BMI as are the patients in the current study. Despite this difference our results confirm a lack of gender difference in circulating leptin concentrations in PLW patients. We were, however unable to confirm that plasma leptin concentrations in non-obese males were increased by a factor of five. Our results suggest a more modest increase in non-obese male PLW patients. Furthermore, obese PLW males in our study showed a 50% rather than 25% increase in circulating leptin concentrations. We suggest that these discrepancies are related to the fact that our patients are better matched for age and are therefore more sensitive to differences in gonadal status between patient and controls.

Testosterone is believed to be responsible for the gender difference in circulating leptin concentrations in adults (Saad *et al*., 1997). This difference becomes apparent during puberty (Foster & Nagatani, 1999). It is therefore likely that the lack of a gender difference in leptin concentrations in our PLW patients is related to the associated hypogonadism in male patients. This is supported by the finding that in the three adult male patients who were receiving testosterone replacement circulating leptin concentrations were lower, on a BMI basis, than for other male PLW patients and more in keeping with age matched control males. Lowering of circulating leptin concentrations has been shown in non PLW hypogonadal men receiving testosterone (Jockenhövel *et al*., 1997). Our study indicates that it is extremely important to take gonadal and hormonal replacement status into account when interpreting leptin results in PLW patients. If these factors are considered our results suggest a normal function relationship between leptin and body composition in Prader–Labhart–Willi syndrome.

A. Michael Wallace*, Ian Hunter†, Peter Galloway*, Steve A. Greene† and Malcolm D. Donaldson‡
**Department of Clinical Biochemistry, Royal Infirmary, Glasgow, †Department of Paediatrics, Ninewells Hospital Dundee and ‡Department of Child Health, Royal Hospital for Sick Children, Glasgow*

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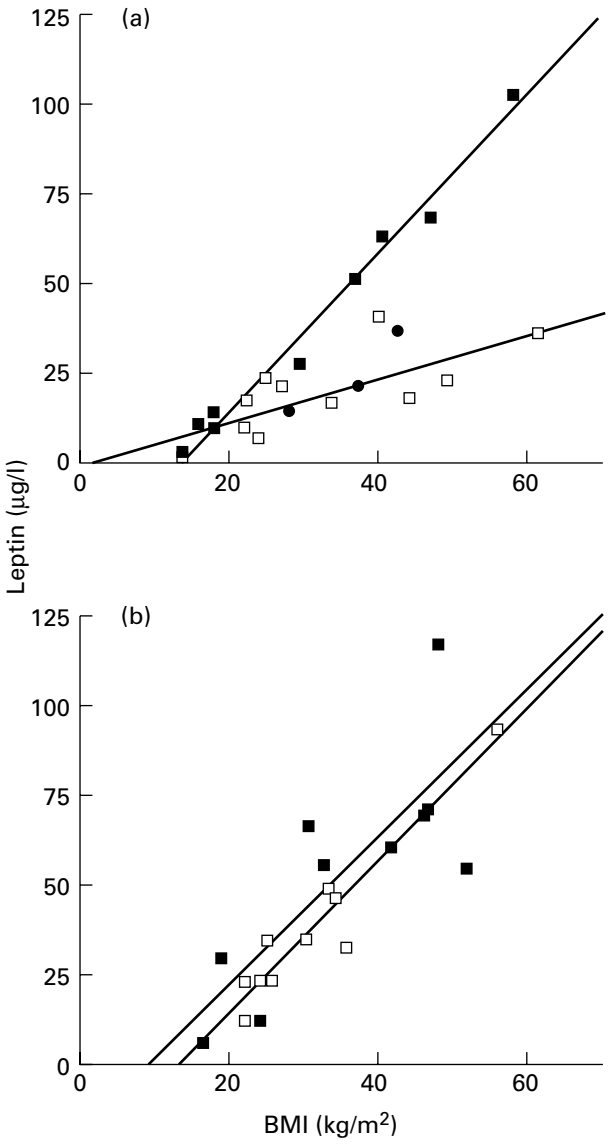

Fig. 1 Relationship between serum leptin concentrations and Body Mass Index (BMI) in a) Male and b) Female Prader–Labhart–Willi (PLW) patients and controls. □ Controls; ■ PLW patients; ● Male PLW patients on Sustanon.

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Kallman's syndrome: is it always for life?

Sirs, Quinton et al. (1999) have recently described five men with Kallmann's syndrome who underwent spontaneous puberty between 19 and 36 years of age. The authors attributed the first report of a similar case to Rizvani et al. (1975). It is likely, however, that similar cases have been observed more than 800 years ago by Rabbi Moshe ben Maimon (Rambam) who is better known in the West as Moses Maimonides.

Rambam (1135–1204) was one of the greatest Jewish theologians and philosophers of all times. Born in Spain, he spent most of his life in North Africa and was buried in Tiberias, Israel. Importantly, Rambam was also a preeminent physician of his day, and served as court physician to Saladdin in Cairo. He had a very busy practice, tending to the royal family and court and maintaining daily private clinics, where he treated, in his words 'Jews and Gentiles, nobles and common people.' It is, perhaps, his rich clinical experience that served as a source of Rambam's observations on normal and delayed puberty in males.

In the tracate 'Nashim' (Women) of his magnum opus 'Mishne Torah' (Reviews of the Scripture) Rambam addressed the topic of male sexual maturation. This issue is of major importance in Judaism, as only a combination of both chronological age and sexual maturity grants a multitude of religious, social and legal rights and obligations to a 13-year-old boy (bar mitzvah). Rambam described clinical signs of male hypogonadism: 'absence of beard, fine hair, soft skin, thin sperm, high-pitched voice.' He clearly distinguished a man with hypogonadism from a 'permanent eunuch' in whom the testicles are destroyed. The former may be regarded as a legal minor until sexual maturity occurs, but the latter is viewed as a legal adult even at age 13, since his condition is irreversible and sexual maturity is not expected. Below is a slightly edited translation of Rambam's guidelines to define maturity in a male.

'Before age 13 he is called a minor or a boy. When he reaches age 13 and exhibits two (pubic) hairs he becomes an adult or a man. If at that age he doesn't yet have two (pubic) hairs, even

though there are other signs of (hypogonadism), we still regard him as a minor until he reaches age 20. After that, if he still has no facial or pubic hair and if there is even one other sign of (hypogonadism) he is regarded as a eunuch, but from a legal perspective he is viewed as an adult. However, if he does not exhibit signs of (hypogonadism), he is still regarded as a minor until he either shows two (pubic) hair or reaches age 35. After that he is regarded as a permanent eunuch. If, however, at age 20 he still has no (pubic) hair but has two facial hairs, even though he may have some signs of (hypogonadism) he is not a eunuch. He shall be viewed as a minor either until he develops every sign of (hypogonadism) or until he reaches age 35.'

Here Rambam describes delayed sexual maturation in a boy with intact testicles, e.g. with central hypogonadism. While current guidelines set age 18 as the dividing line between delayed adolescence and true hypogonadotropic hypogonadism, Rambam was obviously more cautious and deferred judgement until age 20. Perhaps, delayed sexual maturation was relatively common in the 12th century as a result of poorer nutrition, in which case there would be no major contradiction between Rambam and modern endocrinologists. Remarkably, however, Rambam recommended further delay in the final verdict until age 35. Obviously, he saw examples of sexual maturation occurring unusually late in life, despite some clinical suggestions of hypogonadism. The time span between 20 and 35 years of age when, according to Rambam, sexual maturation may still occur is remarably similar to that observed by Quinton et al. (1999) in their group of patients (19–36 years of age).

Di Kadva *et al*. (1995) suggested a term 'Bauman variant of Kallmann's syndrome' after Bauman's description of such a patient (Bauman, 1986). In fact, it was Maestre de San Juan (who, like Rambam, hailed from Spain), rather than Kallmann, who first described a syndrome of hypogonadotropic hypogonadism with anosmia (Maestre de San Juan, 1856). Perhaps we should start calling this disease 'Maestre de San Juan syndrome' and refer to its 'Rambam variant.' Indeed, as it said in the Talmudic tractate 'Ethics of the Fathers', 'Whoever attributes a saying to its proper author, brings redemption to the world.'

Ariel L. Barkan

Division of Endocrinology and Metabolism, University of Michigan Medical Center, Ann Arbor, Michigan, USA

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Editor's Note: *This letter was previously published in* Clinical Endocrinology, **51***(1), July 1999. Due to postal delays in Yugoslavia the reply was received only recently so the letter is reprinted here with the reply.*

Neoplasia in patients with pituitary adenomas

Sirs, The report of increased incidence of neoplasia in patients with pituitary adenomas (Popovic *et al*., 1998) contains a number of errors and substantial limitations. In the summary, patient and methods and elsewhere in the paper, standardized incidence ratios (SIRs) are referred to as standardized incidence rates. The SIR is a ratio of observed to expected incidence, it is therefore clearly a ratio and not a rate.

The cancer incidence in the patients under study was obtained from the hospital case records, whilst the population data were obtained from the Serbian Tumour Registry. This is not the correct way of comparing such data, as there is a strong possibility of bias. Data on the patient group of interest should be obtained from the same source as the general population. A substantial proportion of the patients with acromegaly developed cancer some years prior to the diagnosis of acromegaly. In Table 3, if we assume a mean duration of symptoms in acromegaly of $8{\cdot}0 \pm 0{\cdot}5$ years prior to diagnosis (quoted in Table 2), 12 out of 27 acromegalic patients appear to have developed cancer prior to acromegaly being diagnosed. Such patients should be excluded from the analysis as they do not contribute anything to either the numerator (case numbers) or the denominator (person years at risk since diagnosis of acromegaly). Similarly, up to 7 malignancies out of 11 observed in nonfunctioning pituitary adenomas probably occurred prior to a diagnosis of a pituitary tumour. Again these cases these should have been excluded from the analysis.

The person years programme that is widely used in other epidemiological studies (Coleman *et al*., 1986) could have been used to greatly improve the statistical analysis. The authors do not state the method used to calculate the confidence intervals for the SIRs. The accuracy of the confidence intervals depends on the method used for calculation (exact or approximate). Caution must be exercised, because approximate methods tend to be inaccurate when the numbers are small. It is stated that the significance of the observed SIR was assessed by a

conventional approach based on a simple continuity corrected chi-square statistic. However, when the observed number of cases is small as is clearly often the case here, the Poisson distribution is somewhat skewed. This means that the normal approximation implicitly used in the continuity corrected chi-square statistic will be inadequate. Either an exact method should be used or another approximation (see, for example, Breslow & Day, 1987).

In summary, because of the design shortcomings and the relatively small numbers in this study, coupled with difficulties in the data analysis, we feel that the results and conclusions in this report have to be viewed with caution. It is interesting to note that a much larger and better designed study, recently published, produced somewhat conflicting results (Orme *et al*., 1998). This study had much greater statistical power, because of the much larger number of cases in the cohort and the much larger number of person years of follow up.

There is a need for properly controlled epidemiological research in this area, to prevent the publication of spurious and chance findings, which could influence clinical practice and distort priorities for health care provision.

Stephen M. Orme* and Richard J. Q. McNally†
Department of Endocrinology, The General Infirmary at Leeds, Leeds and †CRC Paediatric and Familial Cancer Research Group, Royal Manchester Children's Hospital, Stancliffe, Manchester, UK

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Sirs, Drs Orme and McNally have been highly critical of our paper (Popovic *et al*., 1998). We will try to answer their comments:

- In our Summary and elsewhere in our report, we stated that SIR is the ratio of observed to expected, and we agree with the comment that we should have used the word ratio and not rate.
- The cancer incidence of patients under study was obtained from Pituitary Tumour Register (PTR) which mostly comes from two biggest centres in our country i.e. Neurosurgical Clinic to where every single patient with pituitary tumour in the country is referred for surgery, and our Institute of Endocrinology, Belgrade, so that patients not included represent a minority of cases. PTR is included in the National Tumour Registry.
- None of the patients with pituitary adenomas developed cancer prior to the diagnosis of the pituitary adenoma. Drs Orme and McNally must have misread our Tables 1 and 2 where in parenthesis the estimated duration of pituitary tumour (years) prior to the diagnosis of malignancy is shown.
- Confidence intervals for the SIRs were calculated with an exact method based on the equation involving Poisson probabilities generating exact Poisson limits. The significance of SIR was assessed both by simple continuity corrected χ^2 statistics for which is though that 1/2 correction in the numerator is intended to improve the correspondence between the percentiles of discrete Poisson distributions and the continuous normal one (treating X as an equivalent normal deviate) and Poisson probabilities which are not cited in the paper except through the fact (see methods) that if exact lower limit in CI just excludes 1·0, we know that the exact two-sided significance level must be just under 0·05 (Breslow & Day, 1987) since we were aware that the number of deaths is small and consequently the Poisson distribution is rather skewed. The results of the two approaches were not conflicting one another.

We thank Drs Orme and McNally for their thoughtful comments in order 'to prevent the publication of spurious and chance findings, which could influence clinical practice … '. After concluding our report we have continued to see in our clinical practice more patients with pituitary adenoma and neoplasia possibly due to our awareness of the possibility (not only in acromegalies). Thus we have stumbled across a patient with cerebrovascular insult aged 57 years of age whose MRI incidentally showed a pituitary tumour. This was clinically a non-functioning pituitary tumour. The patient was scheduled for trans-sphenoidal surgery but routine chest X-ray raised a possibility of lung cancer. Bronchoscopy confirmed adenocarcinoma of lung. The Neurosurgeons thought that the mass in the pituitary was a metastasis. Fortunately, immunohistochemistry confirmed an FSH producing pituitary adenoma and thus this patient was properly staged for his lung cancer and proceeded to further surgical treatment. Another patient aged 60 years with a prolactinoma, a abromocriptine, responder with three years follow up, developed bowel problems and upon evaluation was confirmed to have a carcinoma of the colon. Thus we believe that practising physicians might use our

information, at least when making decisions about the care of individual patients and this most certainly will not 'distort priorities for health care provision' as concluded in the letter of Drs Orme and McNally. We enthusiastically support further 'properly controlled epidemiological investigations with respect to this problem', as suggested.

Vera P. Popovic and
The Pituitary Study Group, Belgrade Yu
Institute of Endocrinology, University Clinical Centre,
Dr. Subotic 13, 11000 Belgrade Yu

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