Sensitive thyrotrophin assays: excellent when properly used

The honeymoon period of initial enthusiasm for a medical development is often followed by scepticism as its limitations become apparent. This has certainly been the experience with thyroid function tests, which to non-endocrinologists must seem to have proliferated almost exponentially. It is now three years since the introduction of sensitive immunometric assays for thyrotrophin capable of discriminating between serum specimens from hyperthyroid and euthyroid patients made the thyrotrophin releasing hormone test redundant.¹ In some centres measuring thyrotrophin is now used as the first test of thyroid function; it has the advantage over thyroid hormone measurements of being unaffected by changes in the concentration or affinity of binding proteins and of identifying subclinical disease. No test is perfect, however, and caution is necessary in its interpretation.

Normal thyrotrophin values may be recorded in patients with thyroid failure secondary to pituitary or hypothalamic disease² and in some hyperthyroid patients with pituitary tumours that secrete thyrotrophin.³ Using a measurement of thyrotrophin as a screening test may cause these diagnoses to be missed, but they are rare and secondary hypothyroidism is usually associated with clinical features of other deficiencies of trophic hormones. Another occasional problem is that in some assays spuriously detectable concentrations of thyrotrophin are recorded in hyperthyroidism because antibodies in the patient's serum bind to the reagent antibodies.⁴ On the other hand, thyrotrophin concentrations may be undetectable in euthyroid women in early pregnancy⁵ and in patients with severe endogenous depression.⁶

The greatest source of concern, however, is in patients with non-thyroidal illness: in them biochemical assessment of thyroid function is notoriously difficult, particularly when kit methods for free thyroxine and triiodothyronine, using tracer analogues, are used.⁷ The newer thyrotrophin assays have greatly improved measurements in this group,⁸ but diagnostic specificity is still impaired because of the pathophysiological suppression of thyrotrophin in severe illness (particularly in those patients receiving treatment with corticosteroids and dopamine^{9 10}) and the rise in thyrotrophin occasionally seen during recovery.¹¹

Fortunately thyroid disease is not usually a clinical consideration in such patients, but in one large series of unselected admissions to an acute medical unit an undetectable thyrotrophin value was three times as likely to be caused by non-thyroidal illness as by hyperthyroidism and raised thyrotrophin was attributed as commonly to illness as to primary hypothyroidism.¹² These studies in which thyroid investigations are performed on patients irrespective of the clinical suspicion of thyroid disease may test the specificity of an assay to unrealistic lengths. There is, however, a regrettable tendency to request thyroid function tests in all patients admitted to hospital, a practice that increases laboratory workload disproportionately in relation to the yield of thyroid disease.^{13 14} It would be unfortunate if because of this policy measuring serum thyrotrophin were to be devalued; users must appreciate that abnormal results in patients with no clinical evidence of thyroid disease are not a fault of the assay but an accurate reflection of the physiological response of the thyrotroph to illness.

We strongly advise that thyroid function tests are not

performed in ill patients unless there is a clear clinical suspicion of thyroid disease. Those who advocate screening all patients on admission should normally delay further investigation of an abnormal thyrotrophin measurement until the patient has recovered from the non-thyroidal illness.

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AIDS: the need for data

The urgent need for more and better data on infection with human immunodeficiency virus (HIV) was the strongest message to come out of the recent meeting of the Royal Statistical Society on the statistical aspects of HIV infection. It is because of this need that the society has supported both making the acquired immune deficiency syndrome (AIDS) a notifiable disease and the anonymous testing of blood samples for antibodies to HIV.

Statisticians have developed mathematical models of the transmission of HIV infection, but, Dr Valerie Isham of Imperial College explained, the models cannot reliably predict the spread of HIV infection without better data to feed into them. The models can be used, however, to identify which risk factors for spread are most important, and Professor Roy Anderson from Imperial College hoped that the existence of the models would stimulate doctors to collect good prospective data. We particularly need data on patterns of sexual activity. Available data relate to rates of changing sexual partners, but other data — on, for instance, the numbers using safe sex — may be more important. Some of those at the meeting thought that the models were unrealistically simple.

Dr Anne Johnson from the Middlesex Hospital emphasised the need for social and behavioural studies on representative groups — not only high risk groups but also heterosexuals.

Many were worried that reliable data could not be collected, but Sir Richard Doll decried the fact that six years into the epidemic we know so little about crucial aspects of the spread of AIDS. In particular there is a desperate need for knowledge about the transmission rate of HIV infection by vaginal intercourse, and several speakers pleaded for anonymous testing for HIV antibodies of routine blood samples from pregnant women. Sir Richard and others have recently written to the *Lancet* calling for reconsideration of parliament's rejection of anonymous testing: they point out that "population based screening is . . . an essential accompaniment of mathematical modelling."¹

We do at least have monthly figures of newly diagnosed cases of AIDS, and Professor Michael Healy of the London School of Hygiene and Tropical Medicine has used them to predict the number of new cases in the short term. A model that gave more weight to recent years showed that the present doubling rate of cases of AIDS is about 14 months, but data for 1987 have shown the prediction to be slightly too low. None of the models suggest that the epidemic is abating. The doubling time of the epidemic may be increasing in Europe and the United States, but this is to be expected as those at highest risk tend to become infected early in the epidemic.

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Seasonal affective disorder: the miseries of long dark nights?

In 1921 Kraepelin described patients who regularly became depressed in the winter months: "Repeatedly I saw in these cases moodiness set in in autumn and pass over in spring 'when the sap shoots in the trees' to excitement, corresponding in a certain sense to the emotional changes which come over even healthy individuals at the changes of the seasons."¹ His words were largely forgotten until this decade, when a group of American psychiatrists became interested in the condition, calling it seasonal affective disorder.²

Seasonal affective disorder has now been studied in several centres in the United States and Europe, and the findings are strikingly similar. It is characterised by recurrent depressions that occur regularly in the winter months, remitting in spring and followed in some cases by hypomania. Its incidence is unknown, but it occurs most often in women, with the onset usually in early adulthood. The anxious, irritable mood is accompanied by fatigue, loss of libido, and a profound reduction in socialisation, commonly reflected in work and interpersonal difficulties.³ In contrast to non-seasonal depression, the appetite is generally increased, with carbohydrate craving and weight gain, and total time spent in sleep is increased.

After the observation that some patients improved symptomatically on travelling south in the winter, artificial light was tried therapeutically. It is now agreed that up to 85% of patients will respond to bright light given for between two

and six hours a day.^{4,6} The intensity used is less than that of a normal sunny day and may be easily given using a fluorescent lamp box. Patients show improvement on standard mood scales within two to four days of starting treatment and relapse within three days of withdrawal.⁶ Adverse effects of phototherapy have not been described, and there is no evidence that light induces mania in patients with seasonal affective disorder.

Similarities have been drawn between seasonal affective disorder and hibernation. Thus studies have been done in animals to try to explain both the aetiology of seasonal affective disorder and the mechanism of action of light treatment. In many animals seasonal rhythms are synchronised by environmental time cues. Of these, the photoperiod—that is, the length of daylight hours—is the most important.⁷ Experimental alteration of the photoperiod affects seasonal behaviour.⁸ For example, in hamsters the infertility and weight gain of hibernation can be prevented in winter by laboratory exposure to long summer type photoperiods. Information about the environmental photoperiod is relayed from the retina through the hypothalamic suprachiasmatic nucleus to the pineal gland, where it influences secretion of melatonin.⁹ Melatonin is released nocturnally and suppressed by light¹⁰ and is thought in animals to be crucially important in mediating the effect of light on seasonal behaviour.¹¹

If the photoperiodic model is applicable to seasonal affective disorder and symptoms are caused by a short day length light therapy should act by prolonging the daylight hours. If this were the case only light given at either end of the day would be effective. The timing of light therapy is not critical, however, and it is equally useful when given in the middle of the day.¹² As light is known to suppress melatonin it was suggested that it might be working in seasonal affective disorder by correcting an abnormal activity or secretory rhythm of the hormone. It was reported that the onset of nocturnal release of melatonin in seasonal affective disorder may be delayed by two hours and that light resynchronises the rhythm.⁴ Current work disputes this, however, and shows that the secretion of melatonin is normal in seasonal affective disorder¹³ and that the antidepressant efficacy of light is independent of its effect on melatonin.^{13,14}

Thus the initial expectation that winter depression might be a photoperiodic phenomenon has not been confirmed, and the method by which light treatment works is still not clear. The extent to which light exerts a placebo effect has still to be resolved. In other groups of patients depression recurs exclusively in spring, summer, or autumn. Such annual rhythms in mood may have either a biological or a psychosocial basis.

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