therapy or neoadjuvant chemotherapy followed by surgery with or without thoracic irradiation. Certainly the results of cancer treatment policies are depressingly poor.

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Intact parathyroid hormone assays

Interpretation must take account of biological variation

Since their first development in 1963 parathyroid hormone immunoassays have been invaluable in assessing patients with disorders of calcium metabolism.1 The interpretation of the results of these immunoassays has, however, been complicated by the molecular heterogeneity of circulating parathyroid hormone. As a result of the proteolytic metabolism of parathyroid hormone, both within the parathyroid gland and elsewhere in the body, the circulation contains amine and carboxy terminal fragments of parathyroid hormone in addition to the intact parathyroid hormone (1-84) peptide.2 In an attempt to improve clinical discrimination immunoassays were developed with specificities for amino terminal and mid-terminal or carboxy terminal parathyroid hormone. In general these assays either lacked the required sensitivity or showed overlap between values in normal people and in groups of patients.

The recently developed two site immunometric assays for parathyroid hormone allow the intact parathyroid hormone (1-84) peptide to be measured without interference from fragments.3,4 The sensitivities of these assays are in the low picomolar range—sufficient to measure the hormone in normal people.

The main application of parathyroid hormone assays is in the differential diagnosis of hypercalcaemia. Initial evaluations of the new assays for intact parathyroid hormone showed improved clinical discrimination between patients with hyperparathyroidism and hypercalcaemia of malignancy.5,6 The distinction was not, however, complete; though the concentrations of intact parathyroid hormone in these groups are well separated, 3-5% of patients with hyperparathyroidism have values at the upper end of the reference range for normal people and 20-30% of patients with hypercalcaemia of malignancy have low but detectable concentrations of intact parathyroid hormone.

Secondary hyperparathyroidism is a consistent feature of advanced renal failure. In the past the measurement of parathyroid hormone in patients with renal failure has been compromised by the presence of an excess of biologically inactive carboxy terminal fragments. Because the new assays are not affected by parathyroid hormone fragments they should overcome this problem. In patients with renal failure they should be sufficiently specific to follow either the clearance of intact parathyroid hormone after parathyroidectomy5 or the suppression of intact parathyroid hormone after treatment with calcium. This may not be the case for all assays.4

Since the new assays are sensitive enough to measure intact parathyroid hormone concentrations in normal people and follow changes within the reference range they have been used to study the physiology and control of its secretion.7 This work has defined the circadian rhythm of intact parathyroid hormone secretion in normal men. It was shown to rise in a broad peak outside the reference range from 0200 to 0600. This was accompanied by a parallel rise in concentrations of nephrogenous cyclic AMP, indicating that the intact parathyroid hormone released was biologically active. There was considerable variation in the return to baseline concentrations among normal people, with the period between 0600 and 1000 characterised by great variability among individuals. The assessment of the intact parathyroid hormone concentrations in an individual must take this variability into account. Early morning samples, such as those typically collected from patients in hospital, may have spuriously raised concentrations. Further studies have shown the absence of a synchronised circadian rhythm in patients with primary hyperparathyroidism.8 Comparison of 24 hour profiles indicates that the best discrimination between normal people and patients with hyperparathyroidism is achieved when samples are taken between 1100 and 1400.

Most patients screened for hypercalcaemia of malignancy have undetectable concentrations of intact parathyroid hormone. Finding detectable intact parathyroid hormone in such patients has been ascribed to a change in the calcium set point of the parathyroid glands.9 In patients with hypercalcaemia of malignancy with undetectable intact parathyroid hormone concentrations studies of the effects of treatment to lower calcium have confirmed that an increase in intact parathyroid hormone concentration occurs as the calcium decreases but while the patient remains hypercalcaemic.10 When assessing these patients, therefore, intact parathyroid hormone concentrations should be measured before giving any treatment to lower calcium.

Although intact parathyroid hormone seems more stable than previously suspected,11 there is some variability. Short delays in separation and freezing of samples would not normally be expected to have substantial adverse effects on the clinical value of the assays, but such delays might lead to the misclassification of patients with only borderline increases in circulating intact parathyroid hormone concentration.12 The development of assays of intact parathyroid hormone is an important advance in the laboratory assessment of calcium disorders. The improved sensitivity and specificity of the new assays make it possible to achieve better discrimination between clinical groups. But the use of these assays has also highlighted the extent of biological variation in intact parathyroid hormone and its rapid response to treatment. The
taking of blood samples must be carefully timed if the results of the assays are to be of maximum clinical value. Clinicians should contact their local laboratory to confirm the method in use and for recommendations on the handling and timing of specimens.

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Pneumocystis carinii pneumonia

Aerosolised pentamidine gives effective prophylaxis

As many as 85% of patients with AIDS will develop pneumonia due to Pneumocystis carinii at some stage in their illness, and the mortality of acute infections ranges from 9% to 35%. 1 Of those patients who survive, between 40% and 60% develop recurrent disease within one year in spite of the use of zidovudine, 2 and the mortality of these recurrent episodes is high. 3 The incidence of early relapse seemed higher, but adverse effects were less frequent than with cotrimoxazole. Aerosolised pentamidine seemed less effective in patients with abnormal chest radiographs at presentation. 4 (P-M Girard et al.)

The use of aerosolised pentamidine as a secondary prophylaxis (after an acute episode of P carinii pneumonia) has been studied in greater detail. Early uncontrolled clinical studies showed a low incidence of breakthrough of pneumonia in patients given 300-500 mg pentamidine every one to four weeks with a variety of apparatus. 5, 6 There was recurrence in only 8% of 382 patients over follow up periods of five to seven months—a substantial improvement over historical controls. Three recent studies are of particular importance: reductions in recurrence of Pneumocystis carinii pneumonia from 34%-6% (placebo) to 6% (aerosolised pentamidine) were reported when 60 mg pentamidine was given every two weeks through a Fisonsen ultrasonic nebuliser in 84 patients over 24 months (J S G Montaner et al.), and from 61% to 9% with 4 mg/kg pentamidine monthly (every two weeks for the first month) given through an Ultraneb 99 nebuliser in 51 patients over 8-7 to 10 months. 7 In a controlled study on 408 patients a substantial reduction in the incidence of recurrent pneumonias was shown with 150 mg every two weeks or 300 mg monthly in comparison with 30 mg every two weeks through a Respirgard II nebuliser (G S Leoung et al.). These authors considered that even the 30 mg dose of pentamidine was of some benefit. The results of this study were instrumental in the decision of the United States Food and Drug Administration to license the use of nebulised pentamidine as secondary prophylaxis in a monthly dose of 300 mg monthly given through Respirgard II.

Patients with evidence of profound immune deficiency (those with a count of CD4 lymphocytes < 200 x 10^4/l) have a probability of a first episode of P carinii pneumonia of 34% after six months and 61% after 18 months (R Weber et al.), so many centres are now offering these patients primary prophylaxis. Few studies have been reported with enough patients and length of follow up to show conclusive benefit, but in one


10.1136/bmj.300.6719.210