Pathogenesis of Hyperparathyroidism

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With the advent of routine screening procedures for serum calcium, primary hyperparathyroidism has been recognized as an extraordinarily common disorder, increasing in frequency in the elderly. Secondary hyperparathyroidism, which is associated with chronic renal failure, may also occur in patients with malabsorption, vitamin D deficiency, and other causes of low serum calcium. The papers in this session dealt with various aspects of normal parathyroid cell biology and biochemistry as well as abnormalities identified in hyperplastic or adenomatous glands. Although recognition of the clinical disorders is relatively straightforward and diagnosis by radioimmunoassay relatively simple (despite the caveats of PTH radioimmunoassay), much needs to be learned about normal and abnormal control mechanisms, as well as pathogenetic factors, particularly in primary hyperparathyroidism.

During the past two decades, PTH from humans, the cow, and a number of other species has been purified and sequenced, and the critical features of peptide structure necessary for biologic activity determined (Fig. 1). The biosynthesis of hormone and its precursor forms has been elaborated, the precursor has been synthesized in cell-free systems, and the complete sequence of DNA coding for hormonal mRNA has been identified. These issues were reviewed in the discussion by Sherwood and colleagues (pp. 131 ff.). Extraordinarily little information is available at present about control mechanisms operating at the biosynthetic level, but our laboratory has provided the first evidence for a direct effect of calcium on levels of pre-pro PTH mRNA in the parathyroid cell (J Clin Invest, in press). A great deal of new information needs to be obtained, but the sophisticated tools of molecular biology are readily available, and these issues should be understood more clearly in the near future.

*Departments of Medicine and Biochemistry, Albert Einstein College of Medicine, Bronx, NY
Address reprint requests to Dr. Sherwood, Albert Einstein College of Medicine, Department of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461.
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paucity of data exists on the regulation of biosynthetic mechanisms in normal glands, but no data exist at all on these issues in adenomatous or hyperplastic glands. That should also be forthcoming.

The regulation of hormone secretion has been explored extensively in vitro and in vivo by many workers, including Sherwood, Brown, Cohn, Fischer, Mayer, Aurbach, Potts, Williams, and others. Brown, et al (pp. 139 ff.) reviewed the use of isolated parathyroid cells to study aspects of normal and abnormal secretion; they discussed the definition of parameters of secretion such as maximal secretory rate, set point, slope of the curve at its midpoint, and minimal secretory rate. It has been well documented that minimal secretion occurs both in vivo and in vitro despite calcium concentrations higher than normal. This factor contributes to the overall secretory rate in hyperparathyroidism. Increases in set point (the calcium level at which 50% suppression of PTH secretion occurs) in some patients with primary hyperparathyroidism is considered a significant factor in the oversecretion of hormone. Both set point and minimal secretory rate are related to cell number. Agents other than low calcium have been identified as secretagogues for PTH, including beta agonists, dopamine, histamine, secretin, and prostaglandins. These appear to act through adenylate cyclase and cyclic AMP, but their physiologic importance has not been defined. Likewise, failure to demonstrate convincingly that beta blockers or histamine receptor antagonists are useful in controlling secretion of hormone on a chronic basis lessens the potential therapeutic significance of these agents. Mechanisms are being defined by which low calcium, other divalent cations such as magnesium, and other agonists which activate cyclic AMP stimulate PTH secretion. Data on the interaction of calcium and other regulators in abnormal parathyroid glands are incomplete.

Finally, little information is available about the regulation of cell growth and number, either benign (hyperplasia, adenoma) or malignant (carcinoma). Jackson (pp. 135 ff.) described an interesting means of assessing pathogenesis through the measurement of glucose 6-phosphate hydrogenase in parathyroid adenomas. Although these fascinating studies suggest that adenomas are polyclonal and imply that stimulatory factors may lead to primary hyperplasia, the nature of such factors is very obscure. The only known stimulus to parathyroid hyperplasia is a low serum calcium. Hyperplasia, readily produced in animals maintained on a low calcium diet, occurs in patients with renal failure and other disorders such as malabsorption or vitamin D deficiency in which the serum calcium is low. These patients have low or normal serum calcium unless marked hyperplasia of the glands causes a hypercalcemic state. This unusual occurrence has been described in both chronic renal failure and in malabsorption, but the hypercalcemia that occurs in the postrenal transplant state is much more common. In these individuals, who have developed marked hypertrophy and hyperplasia of their glands secondary to hypocalcemia and vitamin D deficiency and have resistance to PTH action, renal function is corrected by transplantation. With the loss of resistance to PTH action and the restoration of normal vitamin D metabolism, hypercalcemia commonly results. Usually, the parathyroid tissue is not functionally autonomous but behaves like hyperplastic glands. In many of these patients the parathyroid hyperplasia persists for years after renal transplantation. Once developed, the hyperplastic glands may never regress completely. We know very little about the factors that generate parathyroid hyperplasia, particularly at the subcellular or membrane level, or about the factors that might lead to regression.