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Primary hyperparathyroidism (PHPT) in the United States is predominantly an asymptomatic disease characterized by mild hypercalcemia and elevated levels of parathyroid hormone (PTH). Over the past 28 years, this research project has defined clinical, biochemical, densitometric, and histomorphometric features of PHPT. The project has also led to new insights into mechanisms of bone loss, with particular reference to PTH's actions at cortical and cancellous sites. We have also characterized new phenotypes of PHPT in patients whose serum calcium concentration is normal but in whom PTH levels are chronically elevated in the absence of any underlying secondary cause. Some of these patients already have indications of skeletal or renal involvement. Others, particularly those who are identified from community-dwelling subjects, are asymptomatic. In the renewal period, we propose to study further specific microstructural aspects of PHPT as they relate to cortical and trabecular compartments of the skeleton as well as to characterize further normocalcemic variants of PHPT. In hypercalcemic subjects, we will determine whether interventions such as surgery, denosumab (a RANK L inhibitor) or mechanical stress can reverse or ameliorate specific features that are present at baseline. The project is also designed to test the hypothesis that PTH is a regulator of both cortical and trabecular compartments of bone. State of the art techniques include: new approaches to non-invasive microstructural skeletal analysis with High Resolution peripheral Quantitative Tomography, Individual Trabecula Segmentation Analysis, and microfinite element modeling. With well defined cohorts of PHPT and these new technologies and approaches, we are in position to define microstructural, elements of PHPT to an extent never before accomplished and with an array of methodologies that will be unique to this disease. The following specific aims will be pursued: 1. to determine the extent to which trabecular and cortical indices are abnormal in PHPT; 2. to determine whether and to what extent abnormalities in skeletal microstructure are improved after parathyroid surgery, with denosumab; or after mechanical loading; 3. to determine the extent to which PTH regulates both cortical and skeletal compartments of bone. By the end of the renewal period, we will have fully characterized in PHPT: microstructural features of cortical and trabecular compartments of bone; their reversibility; and the role of PTH as a regulator of microstructural features of skeletal compartments. We will also have identified completely 2 variants of normocalcemic PHPT. The results of these studies will enhance our understanding of PHPT and also be highly relevant to clinical management of this common metabolic bone disease.