INTRODUCTION:

Our understanding of the evolving clinical profile of primary hyperparathyroidism has changed significantly. Recently substantial insights have been gained into its metabolic bone profile in particular. The epidemiology of primary hyperparathyroidism has fluctuated widely, in large part due to the availability of multi-channel chemistry screening. Many patients nowadays are thus discovered through work-up of hypercalcemia detected by routine biochemical screening or as part of an osteoporosis evaluation, which may also uncover the normocalcemic variant of hyperparathyroidism.

Primary hyperparathyroidism is characterized by hypercalcemia and elevated parathormone (PTH) levels. The classical presentation of hyperparathyroidism has shifted from a symptomatic disorder of complaints from “bones, stones, abdominal moans, and groans” to an asymptomatic one in Western countries. Indeed, nephrolithiasis, bone disease, and musculoskeletal complaints are present in only one-fifth of patients in developed countries, but symptomatic disease is still the commonest presentation in developing countries such as India and China, in part due to ascertainment bias and possibly hypovitaminosis D which is widely prevalent in these countries.

PATHOLOGY:

Solitary, benign parathyroid adenoma, occurs in 80% of patients. While in most cases, a single adenoma is found, multiple parathyroid adenomas have been reported in 2-4% of cases. These may be familial or sporadic. Parathyroid adenomas can be ectopic sometimes. The most common sites for ectopic adenomas are within the thyroid gland, the superior mediastinum, and within the thymus. All four parathyroid glands are involved up to 15% of cases. There are no clinical features that differentiate single versus multiglandular disease. The etiology of 4-gland parathyroid

![Fig. 1: Radiologic appearance of Primary HPT from one of our patients: Subperiosteal resorption of digits (1), Picture Frame-vertebra (2), Osteitis fibrosa cystica (3), Cortical erosions (4).]
hyperplasia is multi-factorial. It may be associated with a familial hereditary syndrome, such as multiple endocrine neoplasia, Types I and 2a. Very rarely, in less than 0.5% of patients with primary hyperparathyroidism, the parathyroid disease will be malignant.

MOLECULAR PATHOGENESIS:
The clonal origin of most parathyroid adenomas implies that defects in specific genes, such as those capable of controlling parathyroid cell growth. The first gene to be associated with primary hyperparathyroidism is the cyclin D1 oncogene (formerly PRAD 1). Over expression of cyclin D1, on human chromosome 11q13, is thought to have an important role in the pathogenesis of some sporadic parathyroid adenomas. The second genetic abnormality that has been described as etiologically important in primary hyperparathyroidism is the gene associated with multiple endocrine neoplasia, type 1 (MEN1). Although, much more information is needed about the molecular pathogenesis of primary hyperparathyroidism, the implication of several genes so far suggests that perhaps most patients with this order will ultimately be shown to have some underlying molecular defect that leads to the abnormal set point for calcium in this disorder.

CLINICAL FEATURES:
Primary hyperparathyroidism occurs predominantly in middle years with peaking between 50 to 60 years of age. However it can present at any age. Women are affected more frequently than men (3:1)

THE SKELETON (FIG 1):
Overt skeletal disease in primary hyperparathyroidism has become infrequent. Osteitis fibrosa cystica is a hallmark of PHPT. Salt and pepper skull, subperiosteal resorption, cortical thinning with generalized decrease in bone mineral content are other manifestations of PHPT. PTH is known to be catabolic at sites of cortical bone such as the distal 1/3 site of the radius and it is an anabolic one, at cancellous sites, such as the lumbar spine. Histomorphometric analysis of the bone biopsy specimen in primary hyperparathyroidism demonstrates cortical thinning, maintenance of cancellous bone volume and a very dynamic process associated with high turnover and accelerated bone remodeling.

Table 1: Differential Diagnosis of Hypercalcemia

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<tr>
<th>Diagnosis</th>
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<tr>
<td>Primary Hyperparathyroidism</td>
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<tr>
<td>Hypercalcemia of malignancy</td>
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<tr>
<td>Nonparathyroid endocrine causes: Thyrotoxicosis, Pheochromocytoma, Addison's disease and islet cell tumors</td>
</tr>
<tr>
<td>Drug Related Hypercalcemia: Vitamin D and Vitamin A toxicity, Thiazides Lithium, Estrogens and anti-estrogens</td>
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<tr>
<td>Familial Hypocalciuric Hypercalcemia (FHH)</td>
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<tr>
<td>Miscellaneous: Immobilization, Milk-alkali syndrome, Parenteral nutrition</td>
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</table>

RENAL INVolvement:
With regard to the changing clinical profile of the disease is the reduction in the incidence of stone disease. Still, stone disease is the most common complication of primary hyperparathyroidism. Specific polymorphisms of the calcium receptor gene might be an important pathogenetic factor in the development of renal stones in certain individuals. Other renal manifestations of primary hyperparathyroidism include hypercalciuria, and nephrocalcinosis, the frequency of which is unknown. An unexplained reduction in the creatinine clearance has also been regarded to be a potential renal manifestation of primary hyperparathyroidism.

GASTROINTESTINAL MANIFESTATIONS:
About 10% of PHPT patients are having Peptic ulcer disease. On the other hand, in genetic syndromes such as MEN1, in which 40% of patients have clinically apparent gastrinomas, one does see more peptic ulcer disease. Pancreatitis is less common manifestation of PHPT.

NEUROLOGICAL MANIFESTATIONS
Neuropsychiatric and cognitive complaints are common and remain an area of active interest. One of the issues related to this set of complaints is that they are non-specific and are found in many chronic disorders.

CARDIOVASCULAR MANIFESTATIONS
Hypertension has long been regarded to be associated with PHPT. Myocardial and valvular calcifications are clearly demonstrated in PHPT patients with marked hypercalcemia. Left ventricular hypertrophy (LVH), has been associated with PHPT. And recently there are reports of association between serum calcium concentration and carotid plaque thickness.

OTHER ORGAN INVOLVEMENT:
Many organ systems were affected by the PHPT in the past. Anemia, band Keratopathy, and loose teeth are no longer part of the clinical syndrome of PHPT. Gout and Peudogout are seen infrequently, and their etiological relation to PHPT is not clear.

VITAMIN D DEFICIENCY:
An interesting association has been made between the presence of overt vitamin D deficiency and clinical manifestations of primary hyperparathyroidism. Primary hyperparathyroidism is worse in the presence of vitamin D deficiency.

EVALUATION:
The diagnosis PHPT is confirmed by an elevated PTH level with hypercalcemia. Serum Phosphorus, Alkaline Phosphatase, Vitamin D, Albumin and Creatinine needs to be measured. 24 hours urinary calcium along with creatinine should be obtained. Routine skeletal radiography may be relevant in Indian subcontinent
Serum Calcium >1.0 mg/dl (0.25 mmol/L) above normal individuals who are symptomatic. Surgery is clearly the right choice, unless extenuating medical conditions preclude the surgery. Most patients with PHPT are asymptomatic. They have neither symptoms nor complications that are clearly and commonly associated with hypercalcemia or excessive parathyroid hormone. The preponderance of asymptomatic individuals is due, in large part, to multichannel screening tests but raise important questions as to how to manage such individuals once the diagnosis is made. To this end, there have been three International Workshops since 1990. Last International Workshop was held in 2008. Among those with asymptomatic primary hyperparathyroidism, the following guidelines for surgery are shown in Table 2.

**DIFFERENTIAL DIAGNOSIS:**

Ninety percent of cases hypercalcemia will be shown to have either PHPT or Malignancy. Although other causes exist (Table 1), they constitute only 10% of the cases.

**MORTALITY:**

Mild, asymptomatic primary hyperparathyroidism is not associated with increased mortality rates. On the other hand, when the disease presents in more symptomatic forms, mortality may be increased.

**PARATHYROID GLAND IMAGING**

Pre-operative imaging is of value prior to surgery in the localization of abnormal parathyroid tissue. The diagnosis of PHPT is based on the biochemical findings and is not affected by the results of the imaging studies. Sestamibi scans are helpful in identifying ectopic tissue, particularly in the mediastinum and can be a useful tool in guiding the surgical approach to parathyroidectomy. It has a sensitivity of 90% for single adenomas. Ultrasound is a non-invasive modality which is easily available at low cost and sensitivity can range from 42-82%. CT scanning of the neck and mediastinum is a valuable tool in assessing the parathyroid anatomy. MRI with contrast can be of value for lesions in the mediastinum and for those individuals who have persistent disease following parathyroidectomy. Arteriography and selective venous sampling can be of value in those individuals with persistent or recurrent disease and in whom other imaging modalities have not been fruitful in identifying the abnormal parathyroid tissue.

**THERAPY:**

There is no controversy about the appropriate decision in individuals who are symptomatic. Surgery is clearly the right choice, unless extenuating medical conditions preclude the surgery. Most patients with PHPT are asymptomatic. They have neither symptoms nor complications that are clearly and commonly associated with hypercalcemia or excessive parathyroid hormone. The preponderance of asymptomatic individuals is due, in large part, to multichannel screening tests but raise important questions as to how to manage such individuals once the diagnosis is made. To this end, there have been three International Workshops since 1990. Last International Workshop was held in 2008. Among those with asymptomatic primary hyperparathyroidism, the following guidelines for surgery are shown in Table 2.

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<th>Measurement</th>
<th>Surgery Recommended</th>
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<tr>
<td>Serum Calcium</td>
<td>&gt;1.0 mg/dl (0.25 mmol/L) above normal</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>&lt; 60m1/min /1.73 m2</td>
</tr>
<tr>
<td>Bone Mineral Density</td>
<td>T score &lt; -2.5 SD at spine, hip (total or femoral neck) or radius (distal 1/3 site) or presence of fragility fracture</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 50 years</td>
</tr>
</tbody>
</table>

- Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible.
- If any one of these criteria are met, the patient is considered to be a candidate for parathyroid surgery.

Bone densitometry is not routionly required. Bone densitometry conversely is performed in all patients. A urinary bone resorption markers such as DPD (deoxypyridinoline) or N-telopeptide can be helpful. It is not unreasonable to obtain a radiographic view or ultrasound of the abdomen to determine the presence of occult nephrolithiasis. Bone biopsy is not part of the routine evaluation.

<table>
<thead>
<tr>
<th>Table 2 : Guidelines for parathyroid surgery in asymptomatic PHPT from the NIH Workshop of 2008</th>
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<tbody>
<tr>
<td><strong>Measurement</strong></td>
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<tr>
<td>Serum Calcium</td>
</tr>
<tr>
<td>Creatinine Clearance (calculated)</td>
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<th>Table 3 : Management guidelines for patients with asymptomatic PHPT who do not undergo parathyroid surgery</th>
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Currently guidelines for monitoring are shown in Table 3. The serum calcium should be measured, annually. Also an annual creatinine clearance should be assessed. Bone mineral densitometry should be performed every 1 or 2 years.

**NON-SURGICAL APPROACHES TO PHPT:**

Many patients who do not meet guidelines for surgery are followed conservatively. Medical options for treating the skeletal complications of PHPT include antiresorptive treatments, such as bisphosphonates, HRT, and raloxifene. Bisphosphonates and HRT are treatment options for those individuals with PHPT for whom skeletal protection is the primary reason for intervention. Of the two agents, bisphosphonates are clearly preferred. The calcimimetic cinacalcet effectively lowers serum calcium and PTH levels, however long term data is awaited.

**BISPHOSPHONATES:**

Although they do not affect parathyroid hormone secretion directly, bisphosphonates could reduce serum and urinary calcium levels. An additional benefit would be to increase bone mineral density. The cumulative investigative experience with alendronate in primary hyperparathyroidism suggests a use for this drug in subjects whose bone density is low, but not in the osteoporotic range. No bisphosphonate has received yet an indication for use in PHPT by the FDA.

**CALCIMIMETRICS:**

These calcimimetics would be expected to increase the signal generated by the calcium-calcium receptor complex and lead to an increase in intracellular calcium. An increase in the intracellular calcium, should inhibit the synthesis and secretion of parathyroid hormone.
hormone from the parathyroid cell. A more potent calcimimetic, cinacalcet hydrochloride has shown promising results. In one of the initial pilot study involving Cinacalcet hydrochloride, most patients treated with cinacalcet hydrochloride achieved the primary endpoint, namely normocalcemia. The serum calcium remained normal for the entire duration of the study. Further studies are certainly in order to document unequivocally the potential utility of this drug in primary hyperparathyroidism.

**SUMMARY**

Primary hyperparathyroidism (PHPT) is a common endocrine disease, especially in countries where multichannel biochemical screening, is routinely used. As this disorder appears to be evolving in several ways, the decision to recommend parathyroid surgery in patients with symptomatic PHPT is clear. The decision to recommend parathyroid surgery in patients with asymptomatic PHPT is clearer than it was 10 years ago. It is apparent that more research will be needed in this field to keep abreast of the changing profiles of this disease and to remain current with regard to management guidelines.

**REFERENCES**