

Henry Ford Hospital Medical Journal

Volume 31 | Number 4

Article 19

12-1983

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Recommended Citation

Talpos, G. B.; Kleerekoper, M.; Kambouris, A.; and Moore, D. R. (1983) "Management of Primary Hyperparathyroidism: Report on a Workshop," *Henry Ford Hospital Medical Journal* : Vol. 31 : No. 4 , 236-238.

Available at: <https://scholarlycommons.henryford.com/hfhmedjournal/vol31/iss4/19>

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Management of Primary Hyperparathyroidism: Report on a Workshop

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Ed. Note - This overview was originally presented at the International Symposium on Clinical Disorders of Bone and Mineral Metabolism, May 9-13, 1983.

Earlier presentations and discussions at this Symposium left many questions unanswered about the optimal management of patients with primary hyperparathyroidism (PHPT) in whom the hypercalcemia is minimal and in whom signs and symptoms directly referable to hypercalcemia and/or HPT are lacking. Although this condition has often been referred to as "asymptomatic PHPT", this term has been deliberately excluded from this paper because many patients with mild HPT are not truly asymptomatic. Clinically, their symptoms cannot be readily recognized, unlike the symptoms of PHPT, and the clinician cannot predict which of the many complaints might be alleviated by "corrective" surgery (1).

With this in mind, a workshop was held to discuss a prospective study of the management of PHPT. Generally, everyone agreed that the current literature on PHPT does not provide adequate answers about optimal management of patients with mild PHPT. Few studies have addressed this issue, and only one is randomized and prospective (2). Although documentation exists that a skilled surgeon can correct hypercalcemia due to PHPT in more than 95% of patients (Wells, et al, pp. 152 ff.), little evidence exists that this is of short- or long-term benefit in mild diseases. In fact, there is a paucity of information about the benefits of surgery in patients with any degree of hypercalcemia (Posen, et al, pp. 154 ff.).

Answers to many of these questions could be provided by a well-designed, prospective, randomized clinical trial to evaluate the benefits and risks of surgical and nonsurgical management of patients with PHPT. Some of the questions that could be addressed, as generated by the participants of the workshop, are given below.

Patient's Questions

- If I feel well now, how will I feel better after surgery?
- How long before complications develop if I don't have surgery?
- What will happen if I don't have surgery at all?

Physician's Questions

- What is the natural history of skeletal complications, and how is this history affected by surgery?
- How does the cost of surgery compare to the cost of medical follow-up?
- Are there factors present at the time of diagnosis that can predict the clinical course of the disease in an individual patient?
- Do different forms of PHPT exist, and do these relate to the different secretory abnormalities (set-point change versus non-set-point change) or to different histologic abnormalities?
- What is the success rate of surgery?
- Are these complications reversible?
- What constitutes cure?
- Which surgeons should perform the initial parathyroidectomy?

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Primary Hyperparathyroidism

- Which surgeons should perform follow-up explorations?

Serious concerns were raised about the feasibility of conducting such a trial. The best recognized, published prospective clinical trial of the management of PHPT was conducted at the Mayo Clinic (3). A principal investigator of that trial, Donald Scholz, reported at the workshop that the single limiting factor to the conduct of their trial was inadequate funding. Another major difficulty encountered was the waning enthusiasm of the patient's primary care physician through the necessarily long follow-up period. These concerns were echoed by many of the participants. Without attempting to minimize these difficulties, it was agreed to proceed with the design of a clinical trial in order to better seek funding for such an undertaking.

Discussion then concentrated on establishing a diagnosis of PHPT in a cost-effective manner. Table I contains the minimal criteria required to confirm PHPT. It also contains the parameters used to exclude nonparathyroid causes of hypercalcemia, such as sarcoidosis, milk-alkali syndrome, and various types of malignancy. Although some investigators had different operational definitions, those present agreed to incorporate these criteria as the minimum guidelines for the proposed trial. Data which had been collected could always be excluded if not relevant, but data which had not been collected could never be assessed.

The next issue addressed by the workshop participants was to determine which patients with PHPT could be ethically randomized into different treatment categories.

TABLE I

Minimal Criteria to Diagnose PHPT and Exclude Nonparathyroid Causes of Hypercalcemia

History and Physical Examination

- Serum calcium greater than or equal to two standard deviations above the mean on more than one occasion (calcium measurements can be either ionized or protein-corrected total serum calcium)
- Multi-channel biochemical profile
- Complete blood count
- Urinalysis
- Chest radiograph
- Serum and urine protein electrophoresis
- Immunoreactive PTH
- 24-hour urine for calcium and creatinine
- Intravenous pyelogram
- T₄, T₃ if age greater than 70

TABLE II

Conditions Mandating Parathyroidectomy if Present at Any Time

Signs and Symptoms

- Renal lithiasis
- Clinically evident bone disease
- Pancreatitis
- Recurrent peptic ulcer disease
- Disabling "soft" PHPT-associated symptoms
- Distance from medical care, making follow-up unlikely
- Intercurrent thyroid surgery

Laboratory Investigations

- Serum calcium greater than 13 mg/DL on one occasion, greater than 12 mg/DL on two occasions, or greater than 11.5 mg/DL on three occasions.
- Urinary calcium greater than 400 mg/24 hours on 750 mg calcium diet for 48 hours
- Metabolic bone disease (bone mineral content greater than two standard deviations below the mean)
- Renal insufficiency
- Anemia less than 10 gm hemoglobin/DL

Patients with any of several serious conditions associated with hypercalcemia would be immediately moved into the surgical treatment group. Providing these patients with the usual treatment for hypercalcemia from PHPT (i.e., surgery) should protect them from possible detrimental effects of the study. A list of the conditions that would mandate surgery is found in Table II.

Although the major categories for randomization of appropriate patients were surgical and nonsurgical, interest was expressed in further subdividing the nonsurgical category. This would allow inclusion of other treatments also discussed at the Symposium, such as cimetidine, propanolol, estrogen, and diphosphanates, in addition to a simple observation group (Bilezikian, pp. 159 ff.; Marcus, et al, pp. 162 ff.). The services of a biostatistician would be used to construct the overall experimental design, and a determination would be made about the practicality of assessing the number of patients necessary to provide statistical significance with this increased number of treatment categories.

The desirability of surgical input and especially standardization of the surgical approach was briefly discussed when it was announced that the American Association of Endocrine Surgeons (AAES) was interested in supporting this study. The consensus of the workshop participants was to leave further deliberations in this area to the AAES. Continued communication with this surgical organization was encouraged.

After four hours of discussion the workshop closed. A strong initiative was begun to evaluate current treatment of PHPT, and a commitment was made to continue developing a protocol with which to seek proper funding. Individuals interested in participating in the design of this study were invited to contact the authors.

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