CURRENT PROBLEMS IN THE CLINICAL PHYSIOLOGY OF THE PARATHYROID AND THYROID GLANDS

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TO the investigator concerned with the fundamental aspects of endocrine control mechanisms and the practical application of such knowledge, regulation of the secretion of the parathyroid and thyroid glands offers much that is both challenging and new, and also lends itself easily to further development. One need look no further than the recent discovery of thyrocalcitonin for an example of contemporary endocrinological research which has provided not only obvious therapeutic advantages (such as the management of hyperparathyroid or hypercalcemic "crisis"), but also appears likely to be a key to the understanding of parathyroid control mechanisms which heretofore have uniformly thwarted investigators working in this area.

In a more methodical but no less compelling way, evidence of the participation of the central nervous system in the stimulation and inhibition of thyroid hormone secretion makes it clear that there is a more mature and inclusive control of thyroid secretion than the conventional pituitary feedback mechanism. This is important not only for its own sake, but also as a model of organization that can be applied to other endocrine systems previously considered to be under exclusive feedback control of the pituitary gland. That therapeutic advances may develop from such basic information seems highly likely. This brief review seeks to direct interest to some of the significant observations contributing to these and related advances.

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PARATHYROID GLANDS

Thyrocalcitonin

Working independently, Copp *et al.* [8] and Hirsch *et al.* [22] have identified a hypocalcemic principle which was eventually shown to be of thyroid origin and present in a variety of mammalian species. Originally designated as calcitonin but now more correctly known as thyrocalcitonin, this material will promptly and efficiently lower the serum calcium of many vertebrates, including man.

Recently Aliapoulous and Watts [1] have surveyed a series of human thyroid glands for thyrocalcitonin activity. The standard technique of utilizing the ability of thyroid gland extracts to decrease the serum calcium of rats was used as an assay system for the measurement of thyrocalcitonin activity. In normal thyroids removed in conjunction with radical surgery for carcinoma of the larynx, thyrocalcitonin was consistently found although in variable amounts. Autonomous thyroid neoplasms, such as follicular adenoma and papillary adenocarcinoma, yielded no thyrocalcitonin activity, and a series of patients with hyperparathyroidism revealed an apparent suppression of thyrocalcitonin since almost no

activity was found in the extracts of their thyroid glands. Of added interest was an extremely high titer of thyrocalcitonin activity found in one patient with pseudo-hypoparathyroidism.

A great deal of work is currently in progress which will further define the physiological role of thyrocalcitonin more precisely. An accurate analytical technique, possibly immunoassay, would be most helpful and apparently is not beyond solution [1].

Critical questions to be answered regarding thyrocalcitonin's activity are: (1) what effects may this hormone exert on the renal tubular excretion of calcium and, (2) to what degree is parathyroid hormone secretion physiologically influenced by variations in thyrocalcitonin release. It is probable that thyrocalcitonin can block the resorption of calcium from bone [23, 27] and, it may conceivably influence renal tubular transport of calcium as well. It is known that serum calcium variations by themselves do not change the setting of renal mechanisms influencing calcium excretion [20]. In addition, Barnes and his co-workers [3] have shown a prompt and striking urinary conservation of magnesium in subjects on a low-magnesium diet who exhibited no changes in serum magnesium. Unpublished work from the same laboratory has demonstrated a similar prompt and strict urinary conservation of calcium in subjects placed on a calcium-poor diet. Whether or not thyrocalcitonin is implicated in this sensitive and efficient homeostatic response appears to be a question of fundamental importance. It is known that thyrocalcitonin will lower the serum calcium and phosphate of nephrectomized rats [16, 23], a finding conceivably related to its action of blocking calcium resorption from bone; however, there may remain a specific action of thyrocalcitonin directly on renal tubular epithelium. This possibility should be investigated.

Thyrocalcitonin has been used successfully to reverse so-called parathyroid crisis. It appears to be the most rational emergency measure available to such patients before definitive surgical control of their hyperparathyroidism. Intravenous sodium sulfate has been used to good advantage in this same situation of hyperparathyroid and hypercalcemic crisis [6].

Primary Chief Cell Hyperplasia

Another contemporary insight into parathyroid disease of particular pertinence to surgeons treating hyperparathyroidism is the recognition by Cope *et al.* [7] of the macroscopic appearance of primary chief cell hyperplasia of the parathyroid glands. The diagnosis can be made by a perceptive surgeon at the operating table. These hyperplastic lesions resemble multiple small adenomata grossly. The practical significance of this lesion to the surgeon is that it is apt to involve all parathyroid tissue. Thus, when it is found to be the cause of primary hyperparathyroidism it makes mandatory the exposure and subtotal resection of all the parathyroid glands rather than of just one or two of the more prominent parathyroid nodules.

Diagnosis of Hyperparathyroidism

A variety of sophisticated diagnostic measures have been proposed in hyperparathyroidism. None have proved infallible; the diagnosis in difficult and borderline cases frequently requires clinical expertness and a willingness to observe the disease under well controlled conditions of dietary calcium intake and over a prolonged time with repeated determinations of serum calcium and phosphorus and urinary calcium and phosphorus excretion. The hope that latent, mild hyperparathyroidism might be detectable by loss of calcium-conserving ability in response to a low-calcium diet has proved fruitless. Hyperparathyroid subjects placed on such diets were able to conserve calcium as efficiently as normal subjects [2].

The association of pancreatitis and peptic ulcer disease with hyperparathyroidism is now well established, as is the frequent occurrence of hyperparathyroidism in patients with endocrine adenomatosis, including those with the Zollinger–Ellison syndrome. Obviously, patients with these conditions should be just as carefully screened for hyperparathyroidism as are patients who have urinary tract calculi.

THE THYROID GLAND

The suspicion that the central nervous system might be involved in the stimulation and inhibition of thyroid hormone secretion is not a contemporary one even though compelling experimental support of it has been developed only in the past twenty years.

Graves in his original description of thyrotoxicosis in 1835 [14] referred to a 20-year-old female patient who "became affected with symptoms supposed to be hysterical; . . . her health had previously been good. After she had been in this nervous state for three months it was observed that her pulse had become singularly rapid." The conviction, on clinical grounds, that hyperthyroidism might in some instances arise from a background of psychic upheaval has been expressed repeatedly. Gibson's critical review has covered much of this material and the interested reader is referred to it for amplification of this point [13].

The earliest experimental suggestions that the central nervous system is intimately involved in the control of the pituitary gland, and of thyroid secretion in particular, have been amply confirmed but seldom acknowledged [5, 24]. The more recent and well known observations of Greer [15] showed that in rats certain hypothalamic lesions prevented thyroid hyperplasia in response to thiouracil, a reaction known to depend on the pituitary secretion of thyrotropic hormone. This work quickly stimulated a number of related observations such as noting the ability of hypothalamic lesions to decrease circulating and hypophyseal thyrotropin levels [9] and also to decrease thyroidal I_{131} uptake and produce thyroid atrophy in dogs [12].

In a more direct way Harris and Woods stimulated chronically implanted hypothalamic electrodes and demonstrated acute increases in I_{131} release curves from the neck region of conscious rabbits [17]. The validity of this technique of measuring thyroid secretion had previously been established in Professor Harris' laboratory [4]. The time resolution of such release curves is several hours, however, and it would be useful to apply even more acute techniques, such as those used by Söderberg [29], to define more precisely the time course of the thyroid response to hypothalamic stimulation.

Microinjections of L-thyroxine into the same hypothalamic loci have been used to determine whether or not a thyroxine-sensitive receptor is located in the central nervous system [19, 31]. In the region of the mammillary body and ventromedian hypothalamic nucleus such injections are without effect; however, in the anterior lobe of the pituitary gland itself, identical microinjections will inhibit release curves of I_{131} from the neck. Knigge claims to have recently developed evidence supporting the existence of a thyroxine receptor more anteriorly located in the hypothalamic nuclei—in the region of the tuber cinereum [25]. A variety of other naturally occurring substances of probable significance in central nervous transmission of reflex activity (notably epinephrine and purified substance P) will inhibit release curves following microinjection into the mammillary body and ventromedian hypothalamic nucleus [19]. These substances were ineffective elsewhere in the central nervous system and when directly injected into the pituitary. Other catecholamines, specifically dopamine and norepinephrine which are present in the central nervous system, were without any clear effect in any location tested [19].

This battery of information appears to unequivocally implicate the central nervous system in the control of thyroid secretion. It is therefore not at all unreasonable to suppose that stimuli of psychic origin arising in the central nervous system may stimulate thyroid secretion through identical or comparable mechanisms, and that on occasion such stimulation may result in overt thyrotoxicosis. Reference has been made to the recurrent clinical convictions that hyperthyroidism may occur in response to psychic disorder. The excellent descriptive studies of Lidz can be referred to for further development of this concept [26]. Experimental approaches to this question have been devised and have documented thyroid hypersecretion in sheep in response to chronic exposure to barking dogs [11] and to both

acute and chronic avoidance conditioning in "Executive" monkeys [21, 28]. None of these techniques is sufficiently established to provide the ideal model for experimental production of thyroid hypersecretion to the degree seen in human thyrotoxicosis. Nevertheless, the approach of chronic avoidance conditioning appears promising and should be developed further. The obvious laboratory expedient of producing hypermetabolism by administering large doses of exogenous thyroid hormone as a model for thyrotoxicosis has some serious limitations which are only beginning to be realized. This material has been reviewed in detail elsewhere [18].

What therapeutic advantages, if any, will develop from these insights into the control of thyroid secretion is not immediately apparent. Conceivably, drug treatment directed at blocking central nervous system stimulation of the thyroid is possible. Therapy of this type would be highly desirable because it could spare the thyroid from the destructive measures now routinely used in the control of hyperthyroidism.

Knowledge of thyroid hormone synthesis continues to accumulate, greatly aided by double radioactive isotope techniques. A recent review of this area by DeGroot summarizes this information [10]. With the development of sensitive radio-immunoassay techniques for measurements of plasma thyrotropin [30], considerable progress can be expected in understanding the kinetics of thyrotropic hormone release from the pituitary gland and variations in the thresholds of thyroid gland response to thyrotropic hormone. Information of this type should be valuable in helping to understand the mechanisms by which the persistent and dramatic hypersecretion of thyrotoxicosis is stimulated.

SUMMARY

Contemporary advances continue to develop in our understanding of the fundamental physiology of the control of secretion by the parathyroid and thyroid glands. The discovery of thyrocalcitonin and the early research on its mechanisms of action gives promise of defining many aspects of parathyroid control which have been obscure until now.

Appreciation of central nervous system mechanisms influencing thyroid secretion and sensitive techniques for thyrotropin measurement give promise of continued development in understanding thyroid secretion control and the secretion disorders that commonly occur clinically. Direct, obvious and valuable therapeutic advances have resulted from the fundamental approaches used in the study of these endocrine glands. Such practical applications can be expected to continue to occur in the future.

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