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YEAR BOOK OF ENDOCRINOLOGY®
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The Year Book of ENDOCRINOLOGY®

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Journals Represented

Year Book Medical Publishers subscribes to and surveys more than 700 U.S. and foreign medical and allied health journals. From these journals, the Editors select the articles to be abstracted. Journals represented in this YEAR BOOK are listed below.

Acta Endocrinologica
Acta Medica Scandinavica
Age and Ageing
American Journal of Clinical Nutrition
American Journal of Epidemiology
American Journal of the Medical Sciences
American Journal of Medicine
American Journal of Obstetrics and Gynecology
American Journal of Pathology
American Journal of Physiology
American Journal of Preventive Medicine
Annals of Internal Medicine
Archives of Internal Medicine
Arteriosclerosis
Atherosclerosis
Australian and New Zealand Journal of Medicine
Bone
British Medical Journal
Cancer Research
Chinese Medical Journal
Circulation
Circulation Research
Clinical Endocrinology
Clinical Science
Contraception
Diabete et Metabolisme (Paris)
Diabetes Care
Endocrinology
European Journal of Clinical Pharmacology
Fertility and Sterility
Hypertension
International Journal of Eating Disorders
International Journal of Gynaecology and Obstetrics
Israel Journal of Medical Sciences
Journal of the American Geriatrics Society
Journal of the American Medical Association
Journal of the Applied Physiology
Journal of Bone and Mineral Research
Journal of Endocrinological Investigation
Journal of Clinical Endocrinology and Metabolism
Journal of Clinical Investigation
Journal of Gerontology
Journal of the National Cancer Institute
Journal of Nuclear Medicine
Journal of Pediatrics
Journal of Pharmacology and Experimental Therapeutics
Journal of Sports and Physical Fitness
Lancet

Life Sciences
Metabolism
Nature
Nephron
New England Journal of Medicine
Obstetrics and Gynecology
Physiology and Behavior
Postgraduate Medical Journal
Presse Medicale
Proceedings of the National Academy of Sciences
Radiology
Scandinavian Journal of Clinical Laboratory Investigation
Science
Surgery
Western Journal of Medicine
World Journal of Surgery

Standardized Abbreviations

Many articles in this edition concern gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), releasing hormone (RH), follicle-stimulating hormone (FSH), adrenocorticotropin hormone (ACTH), growth hormone (GH), thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone or thyrotropin (TSH), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very-low-density lipoprotein (VLDL). Rather than spell out these terms in full each time that they appear, we have chosen to use their abbreviations.

Publisher's Preface

We welcome Robert S. Sherwin, M.D., as an Editor of the YEAR BOOK OF ENDOCRINOLOGY. Dr. Sherwin is a Professor in the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut. He selected and commented on material related to diabetes mellitus and carbohydrate metabolism.

Introduction

Those among us who earn their livings seeing patients often find themselves practicing "defensive" medicine—a posture made necessary by the litigious society in which we live, fired by the surfeit of hungry lawyers we've turned loose on the public in recent years. Was there ever really a perceived shortage of lawyers as there was once thought to be for physicians? Rather than adversarial positions, a kind of symbiosis has developed between the practicing medical and legal professions. Physicians must practice "risk averse" medicine, which by its very nature is expensive, keeping the coffers of the clinical laboratory and x-ray department full. And, the advice lawyers give us on a wide range of subjects often deals with limiting liability (protecting ourselves from the suits brought by other lawyers!) The fact is that the "risk averse" life is costly.

In a recent article in the *New Republic* (Jan 13, 1989) entitled "Fear of Living," Henry Fairlie describes "America's morbid aversion to risk." So what if the idea "that our individual lives and the nation's life can and should be risk-free has grown to be an obsession..."? This uniquely American desire for a risk-free society is a powerful influence that has contributed significantly to the weakening of our economic base and crippled invention. And, regrettably, this has involved the medical sciences. When writing grants for research support, it's now essential to include not just preliminary data to demonstrate that you have the capacity to carry out a particular project. Rather, the more data you have, the more of the project you've completed, the more likely the proposal will be funded. Simplify decision-making for that NIH study section by removing the risk associated with the proposal. The "risk-averse" grant is more than likely to come from an institution with a large research establishment—the Program Project, the SCOR (the Specialized Center of Research) in a given area that can rapidly generate preliminary and supporting data. This need to minimize risk and fund the safe is reinforced when resources are short, as they are today. In this climate, the rich tend to get richer and the chap in left field at the smaller places is likely to fare less well.

We need to be bold, to take risks involved in testing new ideas. This is as traditionally American as Mother and apple pie. Yet, when there's far too little money to go around, the unusual idea, the off-the-wall hypotheses remain just that. That breakthrough we've all been waiting for in cancer research, or more recently in the AIDS area, seems more remote than ever if "risk-averse" continues to enter into the funding equation. My former mentor in Seattle, Ed Bierman, told me long ago (even before the NIH's golden teat ran dry) that one should make application for "safer" projects but, while carrying them out, be free to pursue those far-out ideas, those long shots. I fear that we're preoccupied with "short shots." Unfortunately, the scientific environment reflects the prevailing "risk averse" attitude of our society. Is it the runners who say "No pain, no gain"? With regard to scientific ideas and innovation it might be that "no gain...if not occasionally a bit off the wall." Our conservatism in this regard borders on the reactionary.

John D. Bagdade, M.D.

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The material covered in this volume represents literature reviewed up to October 1988.

1 Neuroendocrinology

Introduction

Information in this field continues to expand at a tremendous rate. The molecular biologists have moved beyond identifying and cloning and are now performing basic physiology at a molecular level. Through such techniques we now learn that TRH biosynthesis in the hypothalamus is affected by thyroid status. This fits better with the dual regulatory feedback mechanisms common to the other pituitary hormones than the hypothesis of the pituitary as a sole site of feedback of thyroid hormones.

In the area of GH research, we now learn that a bit of the GH receptor breaks off and floats around in the circulation bound to GH itself. For the first time, an alteration in the G_S regulatory protein has been found in the tumors of some patients with acromegaly. Additional experiments will be necessary to tell us how widespread this phenomenon is. The molecular defect for familial isolated GH deficiency type 1A has now been identified. It is only a matter of time before the defects for all such isolated hormone deficiencies are identified and then it's time for gene therapy.

An interesting new concept has also arisen with regard to prolactin (PRL) regulation. A number of workers have found vasoactive intestinal peptide (VIP) in lactotroph cells, and now it appears that such VIP works in an *autocrine* fashion to regulate the secretion of PRL from its own cell. The issue of whether prolactinomas cause osteoporosis has been settled in favor of hypoestrogenism mediation of this effect.

I have been worried about what intervention with hormones might do to the natural history of child development, e.g., giving GH to normal, short kids or GnRH agonists to those with premature development. In an excellent example of the need to do long-term studies, it has now been shown that normal puberty resumes in children with precocious puberty treated for a few years with a GnRH agonist. I hope similarly well-designed studies are being done for GH.

This year we again find lots of substances produced by the pituitary—human chorionic gonadotropin, neuromedins B and U, 7B2, synaptophysin, gastrin, bullets. Why? Drs. Kovacs and Horvath and their colleagues in Toronto continue to elucidate different aspects of pituitary tumors.

I guess nephrogenic diabetes insipidus is a neuroendocrine disease. Anyway, we find in a collection of papers here that it is a heterogeneous disorder with respect to the defect in the V_2 receptor. As I had hoped, atrial natriuretic factor has become a true neuroendocrine peptide, playing a role in the syndrome of inappropriate secretion of antidiuretic hormone and being present in the hypothalamus and neurohypophysis. Of course, I had also always viewed the kidney as an endocrine organ, but I had my doubts about the heart.

Mark E. Molitch, M.D.

The Hypothalamus

Thyroid Hormone Regulates TRH Biosynthesis in the Paraventricular Nucleus of the Rat Hypothalamus

Segerson TP, Kauer J, Wolfe HC, Mobtaker H, Wu P, Jackson IMD, Lechan RM (New England Med Ctr Hosp, Boston; Brown Univ)

Science 238:78–80, Oct 2, 1987 1–1

The important role of thyroid hormone in the regulation of TSH syn-

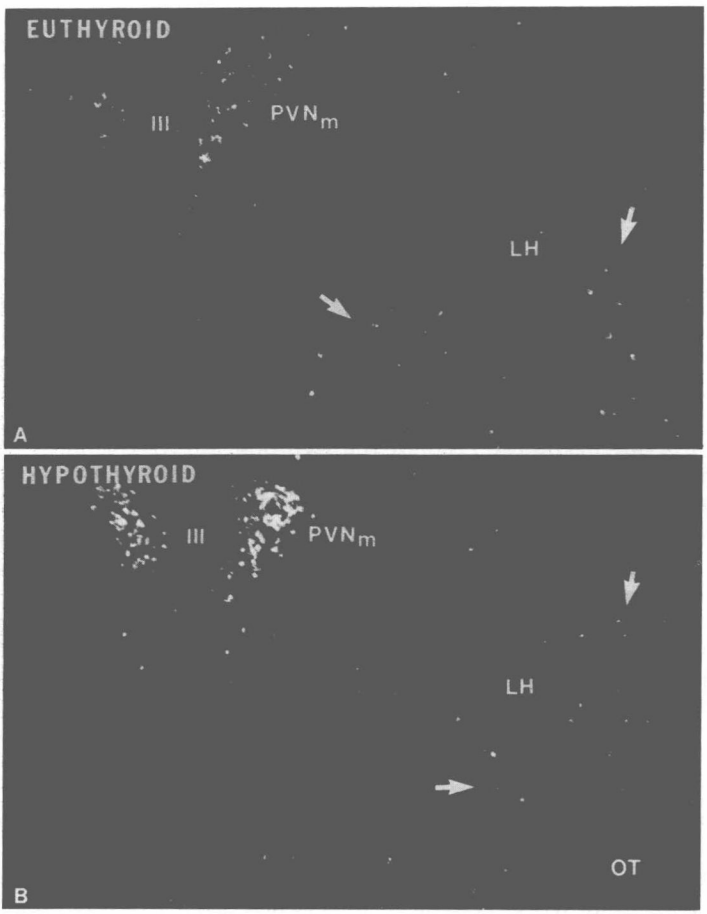

Fig 1–1.—In situ hybridization histochemistry (dark-field illumination) of hypothalamus (10-μm coronal section) at level of medial parvocellular division of paraventricular nucleus using probe for pro-TRH mRNA in (**A**) euthyroid (normal saline controls) and (**B**) hypothyroid animals. Marked increase in hybridization is seen in medial parvocellular neurons of paraventricular nucleus neurons (PVN_m) but not lateral hypothalamic neurons *(arrows)* in hypothyroid animals (*LH*, lateral hypothalamus; *OT*, optic tract; *III*, third ventricle). Original magnification, ×79. (Courtesy of Segerson TP, Kauer J, Wolfe HC, et al.: *Science* 238:78–80, Oct 2, 1987.)

thesis and secretion in the anterior pituitary is well known, but its role in the regulation of hypothalamic TRH is controversial. The recent isolation of a complementary DNA that encodes the TRH prohormone and the development of antisera that interact specifically with the TRH prohormone have provided a means to determine whether thyroid hormone regulates the function of TRH in the hypothalamic tuberoinfundibular system.

Male Sprague-Dawley rats were made hypothyroid by injection of propylthiouracil and by mixing methimazole into their drinking water. After decapitation, the effect of hypothyroidism on TRH messenger RNA (proTRH mRNA) and TRH prohormone in the paraventricular nucleus was measured as follows: Extracts of rat hypothalamic paraventricular nucleus were examined by quantitative Northern blot analysis, and coronal sections of rat brain were examined by in situ hybridization histochemistry and immunocytochemistry (Fig 1–1).

Hypothyroid rats had a nearly twofold increase in paraventricular nucleus proTRH mRNA when compared with control animals. This increase could be obliterated by levothyroxine treatment, suggesting an inverse relationship between circulating thyroid hormone and proTRH mRNA. In situ hybridization demonstrated that this response occurred exclusively in medial parvocellular neurons of the paraventricular nucleus. A marked increase in the intensity of staining of immunoreactive proTRH also occurred in this area.

The simultaneous increase in proTRH mRNA and immunoreactive TRH prohormone in this region suggests that hypothyroidism induces both transcription and translation of the TRH prohormone in the paraventricular nucleus.

▶ It was formerly thought that the increases in TSH and PRL in hypothyroidism resulted from increased sensitivity to TRH because of decreased inhibitory feedback by thyroid hormones at the pituitary level. Of course, this is still true (see below). However, these investigators, using cDNA probes to the TRH precursor (1987 YEAR BOOK OF ENDOCRINOLOGY, p 30) now nicely document that TRH synthesis is increased in hypothyroid rats. In studies in the same animal model by Rondeel et al. (*Endocrinology* 123:523, 1988), on the other hand, found that the increases in portal vein and total (excluding the preoptic region) hypothalamic TRH concentrations were not statistically significant; however, they did find a significant decrease in TRH in the portal vein in hyperthyroid rats. The localization of TRH to the parvocellular region of the paraventricular nucleus may mean that a twofold increase in TRH there may not be detectable when the whole hypothalamus is extracted. Mori et al. (*Neuroendocrinology* 48:153, 1988) have also shown that hypothyroidism results in an increase in pituitary TRH binding that is caused by an increase in the number of TRH receptors and a change in binding affinity. This change appears to result from alterations in thyroid hormone feedback and not from changes in TRH concentrations, as shown by hypothalamic deafferentation studies.

Previous studies have suggested a possible beneficial effect of TRH in motor neuron disease (1987 YEAR BOOK OF ENDOCRINOLOGY, p 31). Now, a British group has shown in a placebo-controlled study that RX77368, a long-acting TRH analogue that is 14 to 200 times more potent than TRH and has 4 times greater systemic availability, causes an acute improvement in bulbar symptoms and muscle force in such patients (Guiloff RJ, et al.: *J Neurol Neurosurg Psychiatry* 50:1359, 1987). Furthermore, repeated treatments for 2 weeks appeared to cause slight to moderate improvement in bulbar function but no major improvement in other areas (Modarressadeghi H, et al.: *J Neurol Neurosurg Psychiatry* 51:1146, 1988). Although there were transient rises in TSH, thyroxine, PRL, and GH, these were not sustained.—M.E. Molitch, M.D.

The Anterior Pituitary

GROWTH HORMONE

Growth Hormone Receptor and Serum Binding Protein: Purification, Cloning and Expression

Leung DW, Spencer SA, Cachianes G, Hammonds RG, Collins C, Henzel WJ, Barnard R, Waters MJ, Wood WI (Genentech Inc, South San Francisco; Univ of Queensland, Australia)

Nature 330:537–543, Dec 10, 1987 1–2

The importance of GH is well known, although the way in which it acts has not been fully elucidated. It stimulates the liver to release insulin-like growth factor-I (IGF-I) that induces cartilage and bone growth, but tissues other than the liver may also be stimulated by GH. If the GH receptor were isolated and analyzed, the signaling mechanism involved in GH could be understood.

Several advances have been made in this area, including purification of the GH receptor from rabbit liver, identification of a 130K protein as the probable GH receptor, and purification of rabbit GH serum-binding protein, M_r 51K. Rabbit and human GH-receptor protein sequences are similar and can be aligned without additions or deletions. The amino terminal amino acid sequence for both the GH receptor and the binding protein are the same, demonstrating that the serum-binding protein is the extracellular hormone-binding domain of the membrane-bound receptor. The complete amino acid sequences derived from complementary DNA clones give evidence of a new class of transmembrane receptors, because these sequences are not like those of other known proteins. When expressed in mammalian cells, both the cloned rabbit and human receptors bound hGH with high affinity.

The purification and protein sequence data described here establish the structural identity of the GH serum-binding protein as the extracellular, hormone-binding domain of the membrane-bound GH receptor. Actual proof will depend on future analysis of animal or human populations. Both Laron dwarfs and African pygmies have reduced IGF-I levels, although their GH levels are normal. The fact that hGH-binding activity is

not found in the liver or serum of Laron dwarfs offers evidence that the receptor cloned here is indeed crucial in the growth process.

▶ It has been known for years that high-molecular-weight forms of GH exist in plasma. Ymer and Herington (*Mol Cell Endocrinol* 41:153, 1985) in the rabbit, and Baumann et al. (*J Clin Endocrinol Metab* 62:134, 1986) and Herington et al. (*J Clin Invest* 77:1817, 1986) in humans, demonstrated that much of this results from GH binding to a larger protein. Immunochemical similarities between the GH-binding protein to the GH receptor (Barnard R, Waters MJ: *Biochem J* 237:885, 1986; Baumann G, Shaw MA: *Biochem Biophys Res Comm* 152:573, 1988) and the absence of the binding protein in patients with Laron dwarfism (Daughaday WH, Trivedi B: *Proc Natl Acad Sci USA* 84:4636, 1987; Baumann G, et al.: *J Clin Endocrinol Metab* 65:814, 1987) in whom the receptor is known to be defective or absent (1985 YEAR BOOK OF ENDOCRINOLOGY, p 37) led to the conclusion that the binding protein was probably a fragment of the receptor. The study abstracted here provides an elegant conclusion to this part of the story, showing that the binding protein is indeed the extracellular, hormone-binding domain of the membrane-bound GH receptor. The function of such binding remains unknown. Baumann et al. (*Endocrinology* 122:976, 1988) have shown that about 50% of 22K hGH and about 30% of 20K hGH are bound in plasma, and that bound hGH is relatively confined to the vascular compartment with a lower metabolic clearance rate compared to "free" hGH (*J Clin Endocrinol Metab* 64:657, 1987). Thus one function of the binding protein might be to confine the hGH to the vascular compartment, thereby protecting it from degradation and prolonging its biological half-life. In this respect it may function like the binding protein for its target organ hormone, IGF-I.—M.E. Molitch, M.D.

Altered G_S and Adenylate Cyclase Activity in Human GH-Secreting Pituitary Adenomas

Vallar L, Spada A, Giannattasio G (Univ of Milan, Italy)

Nature 330:566–568, Dec 10, 1987 1–3

Two guanine nucleotide-binding heterotrimer proteins, G_s and G_i, regulate the activity of adenylate cyclase. In addition, they transfer hormone signals from cell surface receptors to the enzyme catalytic unit. An altered G_s protein has not previously been reported in a human disease state. The secretory activities, intracellular cyclic adenosine monophosphate (cAMP) levels and adenylate cyclase responses to regulatory agents of hGH-secreting adenomas were studied.

The responses of some tumors (group 1) were similar to those in normal rat pituitary glands, but in other tumors (group 2) both GH secretion and cAMP levels were much higher even under nonstimulated conditions. Furthermore, these levels were not appreciably increased by GHRH, forskolin, or guanine nucleotides. In group 2 tumors a greatly modified regulation pattern of adenylate cyclase activity also was observed, magnesium having a markedly augmented stimulatory effect.

Analysis of group 2 tumors suggests disturbance of stimulating transmembrane signaling associated with adenylate cyclase resulting from alteration of the stimulatory G protein. It is possible that a direct causal relationship exists between alteration of G_s and the high secretory rate and growth of these pituitary cells.

▶ This exciting paper demonstrates, for the first time, an alteration in the regulatory aspects of the growth and secretion pattern of an endocrine cell that may be important in its transformation into a neoplastic cell. Although these tumors had altered responses to stimulatory agents, they had normal responses to somatostatin. What is not stated in the article is whether there were any differences in how the group 1 and group 2 tumors acted clinically. Were the latter tumors more invasive or larger, or did they secrete more GH? As only some of the tumors (20 of 68) displayed this regulatory defect, it is clearly not a basic feature of neoplastic transformation of all endocrine or even pituitary tumors. One also would like to see data from 68 normal human pituitaries. Because many GH-secreting tumors are really somatomammotrope tumors containing both GH and prolactin (PRL) in the same secretory granules, as Beckers et al. (*Acta Endocrinol* 118:503, 1988) remind us, it would be interesting to know if there is any correlation between cell types and, if so, whether they were in group 1 or group 2. Furthermore, some of these somatomammotrope tumors contain PRL by immunohistochemistry but do not hypersecrete it, although they hypersecrete GH. Does this regulatory defect pertain to that phenomenon? Although Vallar et al. in this abstract report 2 groups of tumors that respond differently to GHRH in terms of the cellular responses, Ikuyama et al. (*J Clin Endocrinol Metab* 66:1265, 1988) found normal binding of GHRH to specific GHRH receptors in tumors from patients with acromegaly. However, there was considerable variation in the plasma GH responses to GHRH in these patients before surgery that could not be explained by the binding characteristics of these cells when studied subsequently in vitro; perhaps this variation is related to alterations in their G_s protein.—M.E. Molitch, M.D.

Articular Manifestations of Acromegaly

Podgorski M, Stiel J, Robinson B, Wang S, Weissberger A, Brooks PM (Royal North Shore Hosp of Sydney, Australia)

Aust NZ J Med 18:28–35, February 1988 1–4

Acromegaly and gigantism are often complicated by axial and peripheral joint abnormalities. Although these abnormalities are usually mild, severely disabling problems are not infrequent. Also, soft tissue, cartilage, and bony proliferation make acromegaly a peculiar model of noninflammatory joint disease. The association between joint disease and acromegaly was studied in 45 patients with acromegaly or gigantism.

Abnormalities of the peripheral joints and spine, noted in 74% and 47% of the patients, respectively, led to significant morbidity. Joint abnormalities most often affected the large joints, such as the hips, knees, and shoulders, but the wrist and hand also were affected.

Patients who did not respond to treatment of acromegaly had little relief of joint symptoms. Three of the 4 nonresponders had long-standing acromegaly refractory to treatment. Patients who had complete responses to treatment had less severe arthropathy: 14 patients had no joint disease or only mild problems, whereas only 3 of those who responded completely had moderate or severe joint problems. Those with incomplete responses behaved similarly: 14 had no or mild joint disease, and only 4 had moderate or severe arthropathy.

Musculoskeletal abnormalities are common among those with acromegaly and can cause considerable morbidity. If response to treatment of the acromegaly occurs, then arthropathy may be less disabling and associated with a better overall functional outcome.

▶ According to the authors, acromegalic arthropathy results from hypertrophy and hyperplasia of the cartilage, which leads to disruption of joint geometry. Within the cartilage there is continued proliferation and regeneration. Over time, osteophytes develop, the surface cartilage fissures with loss of cartilage over weight-bearing surfaces, and excessive regeneration of fibrocartilage then develops, worsening the process. In this paper, the authors note that 22% of the males and 36% of the females had moderate to severe disability from arthropathy. In a similar review of the arthropathy present in 90 NIH patients with acromegaly, Dons et al. (*Clin Endocrinol* 28:515, 1988) found 25.5% of them to be disabled; there was a trend to lesser joint involvement with earlier therapy, but it was not significant. The inability to show a more significant effect may result in part from the very slow rate of fall of GH levels after radiotherapy, the mode of treatment for most of these patients. It is likely that the cartilage overgrowth is related to increased GH and insulin-like growth factor I (IGF-I) made in the liver or locally in the cartilage. Therefore, if treatment successfully lowers GH levels, it could partially arrest this process. However, it appears that once destructive changes in the joint are initiated, they can progress even if the GH levels are lowered. I think these papers provide additional evidence that virtually all acromegalic patients should be treated aggressively to lower their GH and IGF-I levels to as close to normal as possible, unless there is some contraindication to treatment.

Bengtsson et al. (*Acta Med Scand* 223:327, 1988) have provided epidemiologic statistics for acromegaly occurring in the population of Göteborg, Sweden, from 1955 to 1984. At the time of follow-up, 11 of 15 patients had had transcranial surgery, 15 of 40 had transsphenoidal surgery, 24 of 91 had been irradiated, and 12 of 20 never treated had died. No data were available concerning the efficacy of treatment, however. As in previous series, deaths were increased in the vascular and malignancy categories. Interestingly, of the 15 patients who died of malignancies, none had colon cancer, in contrast to what has been reported previously by Klein et al. (*Ann Intern Med* 97:27, 1982) and Ituarte et al. (*Ann Intern Med* 101:627, 1984).

Sleep disturbances in patients with acromegaly have been reported previously (1983 YEAR BOOK OF ENDOCRINOLOGY, p 54). Pekkarinen et al. (*Clin Endocrinol* 27:649, 1987), in a careful study of this phenomenon, noted that excessive daytime sleepiness or habitual snoring occurred in all 11 of their