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13. ABSTRACT

This issue of Present Concepts is an attempt to solve some of the diagnostic dilemmas which the physician encounters when he considers clinically a patient who appears to have an endocrinopathy. The authors have approahced their subjects in a practical and up-to-date fashion (perhaps at times dispelling some of the old "standards" and introducing some of the newer concepts which have evolved from recent research). The articles are titled as follows: "Diagnosis of hypothalamic-pituitary dysfunction", "Evaluation of secondary amenorrhea", "Acromegaly. Diagnosis and treatment", "Diabetes insipidus", "Pathophysiology of the thyroid gland", "Hyperparathyroidism", "Evaluation of adrenal dysfunction", and "Mineralocorticoid hormones (MCH) in hypertension".

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PRESENT CONCEPTS IN INTERNAL MEDICINE

GUEST EDITOR FOR FEBRUARY 1971

COL John J. Deller, Jr., MC
Endocrinologist, and
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PRESENT CONCEPTS IN INTERNAL MEDICINE
VOLUME IV *February 1971* Number 2

ENDOCRINOLOGY SYMPOSIUM

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HYPOPLASTIC ANEMIA

HEMOPHILIA A

HEMOSTATIS AND INTRAVASCULAR COAGULATION

FOREWORD

Often when an Endocrinopathy is considered clinically, one finds himself in a quandry as to how to expeditiously, economically, and yet accurately pursue the diagnosis – and perhaps also when to stop the pursuit!

This issue of *Present Concepts* is an attempt to solve some of these diagnostic dilemmas. The authors have approached their subjects in a practical and up-to-date fashion, perhaps at times dispelling some of the old "standards" and introducing some of the newer concepts which have evolved from recent research.

Our own staff, Doctor Eichner, Doctor Panagiotis and I would like to express our appreciation to our three guest authors for their unique contributions which stem from a vast experience with their topics.

Doctor Levin, one of Doctor Peter Forsham's shining stars, has given us the benefit of his studies on acromegaly and the most gratifying results being obtained at the University of California's San Francisco Medical Center with cryohypophysectomy.

Doctor Goldsmith's reputation as an endocrinologist is enviable and his studies and publications on the parathyroid gland are well-known to all students of metabolism. I'm always eager to read his latest thoughts.

A long-time friend and much-admired colleague (but late getting his manuscript in – and that's why it appears last!) is Doctor Biglieri. Ed's work in the area of mineralocorticoid metabolism has been fascinating and illuminating His paper for *Present Concepts* is another gem.

As we go to press with this issue, I wonder what's left for me to tell my house staff —— guess I can always talk about Diabetes

COL JOHN J DELLER, JR., MC
Guest Editor

To learn how to treat disease, one must learn how to diagnose it. The diagnosis is the best trump in the scheme of treatment.

Jean Martin Charcot
(1825-1893)

DIAGNOSIS OF HYPOTHALAMIC-PITUITARY DYSFUNCTION

COL John J. Deller, Jr., MC

In recent years, research into the functional status of the anterior pituitary gland has centered around studies directed at defining the chemotransmitter mechanisms of the hypothalamus. It has been found that neurohormones liberated from the region of the median eminence of the hypothalamus into the hypophyseal portal circulation regulate secretion of the pituitary tropic hormones. /1-3/ Hypophysiotropic factors affecting all the pituitary hormones have been described . /4/ Most of the known neurohormones elaborated by the hypothalamus act as "releasing factors". There is evidence that there are both releasing and inhibiting factors for growth hormone and melanocyte stimulating hormone, and an inhibiting factor for the release of prolactin. /2/ It may well be that all releasing factors have dual controls, which have not been defined. The focus on the hypothalamus and the discovery of these neurohormones has relegated the anterior pituitary gland to a position of secondary importance, removing it from its previously esteemed position as the "master gland". It now appears that the anterior pituitary simply serves as a factory for production and storage of hormones which can only be released upon signalling from higher brain centers. When considering failure of the anterior pituitary gland, therefore, one must also consider the potential of the basic disease process lying in the hypothalamus and, indeed, in a number of syndromes this has proven to be the case.

Etiology

Classically, the etiology of anterior pituitary failure has been considered in two general categories — non-neoplastic conditions and tumors. The classic prototype of the non-neoplastic lesions is Sheehan's syndrome — infarction of the anterior pituitary gland subsequent to postpartum hemorrhage.

A variety of other forms of vascular disease, however, have also produced infarction of the anterior pituitary, namely, carotid artery occlusion, temporal arteritis and vascular complications associated with diabetes. Many cases are on record also of granulomatous disease of the anterior pituitary and hypothalamus which have led to pituitary insufficiency; in children, Hand-Schuller-Christian disease, hemochromatosis, sarcoidosis, tuberculosis and non-tuberculous giant cell granulomas (a syndrome often associated with multiglandular granulomas). /5/

A number of tumors arising within the pituitary gland have caused both syndromes of hypopituitarism and a variety of syndromes of hyperpituitarism. Over 80 percent of such tumors arise from chromophobe cells, somewhat less than 10 percent from acidophils and rarely from basophils. Tumors arising outside the pituitary have occasionally destroyed the gland by encroachment. The most common of these have been craniopharyngiomas. Other tumors arising in the area of the hypothalamus have led to syndromes reflected by partial pituitary insufficiency, probably by interfering with neuroendocrine secretions from the hypothalamic nuclei.

Clinical Features

The purest form of anterior pituitary insufficiency is that which occurs following hypophysectomy. Total hypophysectomy results in signs of adrenal insufficiency within the first two weeks following surgery. Hypothyroidism occurs within eight weeks and subsequently there is gradual atrophy of the gonads and hypogonadism. A total hypophysectomy also produces "posterior pituitary" failure with diabetes insipidus. However, the diabetes insipidus which develops in the face of anterior pituitary failure is generally milder than when the anterior pituitary remains intact. (This is probably attributable to decreased glomerular filtration rate and increased tubular reabsorption of water which occurs in patients who are growth-hormone and cortisone depleted.) Although it is true that total hypophysectomy without replacement therapy is incompatable with life, most pathologic conditions which cause anterior pituitary insufficiency occur gradually, with symptoms appearing subtly after the destruction of approximately 75 percent of the gland. It is these cases which

frequently present as diagnostic problems.

In the classic situation of anterior pituitary failure of gradual onset a characteristic "dropout" of pituitary function occurs; first with gonadotropins followed by growth hormone, thyrotropic, and adrenocorticotropic hormones. It is evident, however, that the clinical features of anterior pituitary failure will vary with the age at onset, sex, suddenness of onset, basic etiology (whether there is a space-occupying lesion or only tropic hormone loss) and the site of the lesion, i.e., pituitary or hypothalamus. If anterior pituitary failure occurs during childhood the major manifestation will be failure to grow. (This subject has been covered in a previous issue of this journal.) /6/ When the disease occurs in a woman during the childbearing years the most common presenting complaint is amenorrhea. This is the topic of another paper in this symposium. (pp *119-129*) Although Sheehan's syndrome is not nearly as common a cause of anterior pituitary failure today as it once was, it is a dramatic enough occurrence that the symptoms of this particular form of anterior pituitary failure should be briefly reviewed.

Sheehan's Syndrome /7/

The pathophysiology of Sheehan's syndrome is based on the fact that there is hypertrophy of the anterior pituitary gland during pregnancy with an involution occurring postpartum. If postpartum hemorrhage results in ischemic shock, the pituitary gland is subject to infarction. An early clue to the diagnosis of Sheehan's syndrome is rapid mammary involution and failure of lactation in the early postpartum period. This is usually followed by asthenia, weight loss, failure of return of menses, and progressive signs of end-organ failure. If these patients go unrecognized, they will develop palor, and take on a waxy myxedematous appearance. They gradually lose axillary and pubic hair and usually develop a mild anemia. Frequently such patients are mistaken as having anorexia nervosa. However, a careful history and physical examination will differentiate this condition from that form of hypopituitarism in which patients do not develop the profound wasting of anorexia nervosa, while patients with anorexia nervosa do not develop the alopecia pattern as described above. The laboratory evaluation will

separate any clinically confusing problems.

Although Sheehan's syndrome serves as a prototype of an accelerated form of total anterior pituitary failure it should be emphasized that whenever a patient presents with any manifestations of end-organ endocrine failure, either unihormonal or multihormonal, one must consider that the basic pathology may lie in the hypothalamus as well as in the pituitary. /8/ When the patient's disease is due to a tumor, in addition to endocrine deficiencies, the patient may present with headache and a variety of visual disturbances due to encroachment on the optic chiasm and the cranial nerves controlling extraocular motion which cross above the diaphragma sellae. If the tumor is arising in the hypothalamus a number of functions may be disturbed which frequently require careful clinical analysis: sleep-wakefulness, appetite-satiety, thirst, temperature regulation, libido and various behavorial and motivation alterations. A carefully performed neuro-ophthalmologic examination is critical in such cases. As a number of intrasellar tumors produce excessive tropic hormones, patients may present with a combination of a syndrome of pituitary excess such as acromegaly or Cushing's syndrome while at the same time they have evidence of insufficiency of other pituitary functions. Thus, a wide spectrum of pituitary dysfunction may be seen with hypersecretion of one hormone and insufficiency of others. A number of syndromes due to the loss of individual pituitary or hypothalamic functions have been described. /9/

Laboratory Evaluation

A complete evaluation of the hypothalamic-pituitary system should include direct assay of hypothalamic releasing and inhibiting factors, pituitary tropic hormones, target gland functions, and in addition, studies to detect space-occupying lesions. There are currently available both indirect methods of evaluating hypothalamic function as well as direct assays of some neurohormones. At present, however, despite the concentrated research in this area, the direct approach to hypothalamic function in the clinical evaluation of hypothalamic-pituitary syndromes is not yet practical.

It is worthwhile, however, even at this point in time to consider those tests which might point to the hypothalamus as the primary site of a lesion. Krieger et al /10/ have recently published a comparative study of endocrine tests of use in hypothalamic disease. These authors studied 14 subjects who presented with neurologic symptoms (visual disturbances or headaches for the most part) and no clinical endocrine dysfunction. Discrete lesions were defined in 12 of these subjects. Of the three studies compared — circadian periodicity of plasma 11-OHCS levels, insulin-hypoglycemic stimulus for growth hormone and 11-OHCS, and metapyrone responsiveness — abnormalities in the circadian rhythm of plasma 11-OHCS were found to be the earliest and most consistent endocrine alteration in these patients. Thus, in the evaluation of a patient with a suspected hypothalamic syndrome such testing may be of value in placing the lesion.

Another approach to "differential testing" of hypothalamic-pituitary function which may have practical clinical application is comparing plasma 11-OHCS responses to vasopressin and ACTH infusions.

It should be recalled that the "posterior hypophysis" is not in itself an endocrine gland, but rather it is merely the distal end of the supraoptico-hypothalamic tract which synthesizes vasopressin at its hypothalamic end and discharges it from the posterior lobe of the pituitary. Thus, vasopressin originating in the hypothalamus may be considered a "releasing factor" for certain anterior pituitary hormones.

Both synthetic lysine vasopressin and natural aqueous vasopressin have been administered to determine ACTH (via cortisol assay) and human growth hormone (HGH) (via radioimmunoassay) responses. /11,12/ A normal response is a rise of approximately 10 micrograms per 100 ml of plasma cortisol and generally at least a doubling and usually a three or four-fold rise in human growth hormone following ten pressor units of aqueous vasopressin given intramuscularly. The peak rise of plasma cortisol usually occurs within 30 minutes and the peak rise of human growth hormone within 60 minutes. Failure to respond to this "releasing factor" would suggest pituitary gland failure (and not hypothalamic dysfunction).

An ACTH infusion following this test and producing a normal cortisol response would confirm that the lesion was

pituitary rather than adrenal. This test can be accomplished by obtaining plasma samples for 11-OHCS in the basal state and 30 minutes after intramuscular injection of 25 units of ACTH or 0.25 mgm of cosyntropin, a synthetic corticotropin. The normal response is at least a 10 microgram per 100 ml increase in 11-OHCS over the basal sample. /13/ A similar differential test for the hypothalamic-pituitary gonadal system using clomiphene citrate (Clomid®) and gonadotropins is presently under study by Paulsen at the University of Washington. These methods approach the ultimate use of specific hypothalamic-produced neurohormones in stimulation testing for dysfunction of the hypothalamic-pituitary system. With the rapid progress in defining and synthetizing the specific neurohormones, /14/ these indirect methods of assaying endocrine function and attempting to isolate the site of pathology will be replaced by more specific tests in the near future.

Pituitary Function

The greatest advance to date in evaluating pituitary function is the current availability of methodology for hormonal analyses on serum rather than urine. The use of blood specimens rather than 24-hour urine collections has at the same time shortened the "work-up", and improved the accuracy of diagnostic testing. Our current approach to the evaluation of suspected hypopituitarism, whether it be initiated because of a suspected single hormonal deficiency (i.e., growth retardation, infertility, amenorrhea), panhypopituitarism or a tumor, includes a survey of all endocrine functions of the pituitary gland. The usual procedure for evaluating pituitary function consists of three phases: (1) pituitary hormone assay, (2) target gland function, and (3) search for an anatomically definable lesion.

TABLE I lists the pituitary hormones and the basic approach to their study. Presently, there are no clinically available assay procedures for melanocyte stimulating hormone (MSH) or prolactin. Rarely decreased pigmentation may be noted in MSH deficiency and galactorrhea may be present with prolactin inhibiting factor deficiency (the latter finding would suggest a hypothalamic lesion).

TABLE I

TESTS OF PITUITARY FUNCTION

PITUITARY HORMONE	DIRECT ASSAY	TARGET GLAND FUNCTION TEST	COMMON STIMULATION TEST
Melanocyte stimulating hormone (MSH)	Not available	Physical: Hypopigmentation	None
Prolactin	Not available	Physical: Galactorrhea	None
Growth hormone (GH)	Radioimmunoassay	Physical: Children, growth delay	Insulin, hypoglycemia, vasopressin
Adrenocorticotropic hormone (ACTH)	Radioimmunoassay	Plasma, 11-OHCS, urine 17-OHCS, 17-KS	ACTH or cosyntropin
Thyroid stimulating hormone (TSH)	Radioimmunoassay	T_4, RAI	TSH
Follicle stimulating-luteinizing hormone (FSH-LH)	Radioimmunoassay	Female: Medical D&C, vaginal corn index, urinary estrogens. Male: Semen analysis, urinary testosterone	None

Growth hormone measurement by radioimmunoassay is currently the most widely available direct assay of a pituitary hormone. The standard test employs the use of insulin-hypoglycemia (0.15 units regular crystaline insulin/kilogram body weight given intravenously). A fall in blood glucose of greater than 50 percent of the baseline value should be followed by a rise in growth hormone by 60 minutes to at least twice the fasting value in normal individuals.

The vasopressin test for growth hormone stimulation has already been mentioned. Recently, measuring the growth hormone level after the potent natural stimulus of normal sleep

has been reported to be perhaps the most sensitive "stimulation test". /16/ This, however, is generally an impractical procedure. Failure to appreciate a peak growth hormone rise following natural sleep might, however, be indicative of a hypothalamic lesion (author's speculation)!

Immunoassay of ACTH is a difficult procedure and does not have widespread availability. The most practical test, therefore, is the measurement of plasma 11-OHCS (so-called "Plasma F"). The evaluation of the circadian periodicity of the plasma 11-OHCS has already been mentioned as has its usefulness as a parameter of measurement after ACTH or cosyntropin stimulation. Although this rapid plasma test may be discriminating between primary and secondary adrenal failure, if there is no response after a single test one must revert to a three-day urinary ACTH stimulation procedure. In this instance, a baseline 24-hour urine is collected for 17-OHCS and 17-KS, then 25 units of ACTH or 0.25 mgm cosyntropin is administered intravenously in 1,000 cc saline over eight hours on three successive days. Urine is collected on the second and third day of the infusion. In pituitary insufficiency there is a gradual steady rise in the daily excretion of these steroids while in Addison's disease there is no rise and often there is a fall.

Direct assay of TSH is also not generally available and one usually relies on serum thyroxin (T_4) testing, radioiodine (RAI) uptake by the thyroid gland, or both studies. Abnormally low values on these tests call for the use of a TSH stimulation procedure. This test is best conducted by administering 10 units of TSH intramuscularly daily for three days and repeating the T_4 and RAI uptake on the third day. A normal end-organ response would be indicated by the T_4 value falling within the normal range and the RAI uptake doubling itself. Failure of such a response would indicate primary hypothyroidism. The use of synthetic thyrotropin-releasing factor in man has just recently been reported. /17/

The use of tests for the hypothalamic-pituitary-gonadal axis (FSH-LH) are outlined in a subsequent paper in this issue. (pp 122-123) The standard measurement of urinary gonadotropins by bioassay is an insensitive index of pituitary function. However, repeated determinations which fail to show a significant excretion of gonadotropins is indicative

of hypothalamic or pituitary insufficiency. Recently radioimmunoassay procedures have been developed for both FSH and LH, but these methods are not yet generally available. /18/ Thus, indirect methods are still commonly employed, such as, when evaluating the female patient one usually uses the "medical D and C", vaginal cornification count or urinary estrogen excretion; and when dealing with the male patient a semen analysis and urinary testosterone levels are used.

COMMENT

The search for an anatomically definable lesion in the pituitary-hypothalamic region falls in two disciplines: (1) neurophthalmology, and (2) neuroradiology. Although precise visual field examinations are painstaking and time consuming and are best done by an ophthalmologist, the great bulk of significant field defects, particularly those arising around the optic chiasm can be demonstrated by simple confrontation techniques and should be part of the basic "work-up". A careful neurophthalmological evaluation may also detect other more subtle defects than the classic bitemporal hemianopsia and can indicate extension of tumors beyond the chiasm.

Neuroradiology of the sella and suprasellar region plays the final role in localizing tumors of the pituitary and hypothalmus. The first step in this area is to obtain plain films and laminograms of the sella turcica. Arteriography and pneumoencephalography provide additional and complementary data and are important procedures in final localization of tumors, especially whenever a surgical approach is contemplated. More detailed and specific aspects of these studies are covered in a recent excellent review in the Annals of Internal Medicine. /4/

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After I thought I was beginning to understand the functioning of the pituitary gland I came across a summary of the work of Doctor Alvarez-Bvilla who found that the effects of hypophysectomy are almost entirely reversed by placing SALIVARY GLAND grafts into the emptied sella of dogs! The dogs so grafted are reported to have normal thyroid, adrenal and gonadal function - they can even reproduce and apparently lack only the ability to grow in a normal fashion and to lactate![1]

But don't be a skeptic - this makes sense (ha) when one considers the report by Narasimban and Ganla from Poona, India. These authors removed the submandibular (salivary) glands from littermates of several different animal species up to monkeys and guess what they discovered? The animals without submandibular glands showed severe *retardation* in their growth![2]

Who would have ever thought that the SALIVARY GLANDS were so omnipotent?

[1]Hospital Practice, Sept., 1968.
[2]Ann. Endo., Sept-Oct., 1968.

EVALUATION OF SECONDARY AMENORRHEA

COL John J. Deller, Jr., MC

Few events in the reproductive life of a woman give rise to more emotional reaction than a missed period. This event is even more upsetting when she also discovers hair on her chin. When these events occur in any given woman a red flag goes up - and it is up to her doctor to reel it in. This discussion will be concerned with the practical approach to secondary amenorrhea with or without associated hirsuitism or virilism. Figure 1 depicts the "anatomy of amenorrhea".

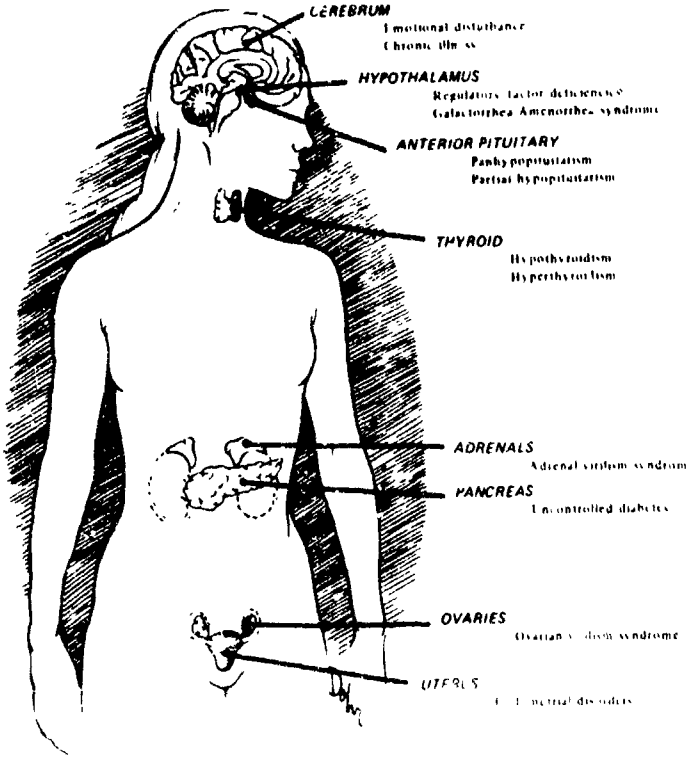


Fig 1 The "anatomy of amenorrhea"

Before embarking on an evaluation of the various pathologic causes of secondary amenorrhea, one must always consider first the two most common physiologic causes — pregnancy and the menopause. The first of these is easily screened by the Gravidex® pregnancy test; the latter, however, may be somewhat more difficult to define outside the immediate perimenopausal period.

The "psyche and the soma" in some rather obscure ways also frequently affect menstruation. A variety of psychogenic mechanisms have been proposed for the amenorrhea which is not infrequently seen in girls leaving home to attend school or in girls whose husbands leave them for military duty, or at anytime when a strong emotional attachment has been broken. A more profound psychogenic amenorrhea may take the form of pseudocyesis, a rare condition seen in young women disturbed over their inability to get pregnant. In these cases, there is probably a persistent hypothalamic stimulus which causes continuous release of luteinizing hormone (LH) which in turn maintains the corpus luteum and permits the development of the symptom complex of early pregnancy. Those chronic medical conditions which can lead to amenorrhea are usually obvious after a careful history and physical examination. There is generally evidence of malnutrition (either emaciation or gross obesity) or a chronic wasting illness such as tuberculosis, end-stage renal or cardiac failure or cancer. The amenorrhea in these instances is merely one feature of a number of bodily dysfunctions. After these considerations have been excluded, the bulk of the remaining amenorrheas must be explained on some specific endocrinopathy. The approach to the patient with a suspected endocrine amenorrhea, (with or without hirsuitism or virilism) should be preceded by three things: (1) a damn thorough history; (2) a pregnancy test; and (3) accurate determination of the size and shape of the ovaries — if you can't feel them (and you often can't because of commonly associated obesity in many of these patients), do pelvic pneumography BEFORE surveying the entire endocrine system. You will be 'way ahead in the end — and your patient will have a good bit more money left in her pocket.

TABLE I lists the galactorrhea-amenorrhea syndromes which have been defined. The occurrence of amenorrhea and persistent lactation following pregnancy was first described by Chiari in 1885 and later fully characterized by Frommel in 1882. /1/ More recently Ross and Nusynowitz /2/ in 1968 reviewed cases of postpartum amenorrhea and galactorrhea associated with primary hypothyroidism and cured by thyroid administration. Argonez and Del Castillo /3/ characterized a nonpuerpual syndrome of galactorrhea and amenorrhea in 1953. Forbes et al /4/ described a similar set of patients in 1954, but half of theirs had pituitary tumors and they proposed that the others probably also had tumors. Within the past few years this combination has also been described in women having taken birth control pills. /5/ There are logically two mechanisms to explain such syndromes: (1) a pituitary tumor may be producing excessive prolactin (or growth hormone, i.e., galactorrhea may occur in acromegaly) while at the same time impairing gonadotropin production, or (2) since the hypothalamic releasing factor for LH (LRF) and the inhibiting factor for prolactin (PIF) are frequently located in the same area of the hypothalamus, a lesion in that area could at the same time block LRF and PIF. If a pituitary tumor cannot be defined, it is likely that when galactorrhea is present the defect lies in the hypothalamus and the lesion may be definable anatomically or it may be a "functional" alteration.

TABLE I

AMENORRHEA/GALACTORRHEA SYNDROMES

SYNDROME	RELATIONSHIPS	DURATION
Chiari (1885) - Frommel (1882)	Postpartum	Usually temporary
Ross-Nusynowitz (1968)	Postpartum first degree hypothyroidism	Responds to thyroid
Argonz-Del Castillo (1953)	Idiopathic	Usually permanent
Forbes-Albright (1954)	Pituitary tumor	Usually permanent
"Post-Pill" (1966)	Oral contraceptive use	Usually permanent

PITUITARY AMENORRHEA

Amenorrhea of pituitary origin may be associated with panhypopituitarism, isolated deficits of FSH-LH, or syndromes of pituitary excess, i.e,. Cushing's syndrome and acromegaly. /6/ Thus, a general assessment of pituitary function (pp *112-115* in this symposium) is indicated. When menses cease due to pituitary gland failure, one can assume there is a deficiency in pituitary-gonodotropin secretion and this is termed "hypogonadotropic amenorrhea". To confirm this diagnosis one of the simplest tests to apply is the "medical D & C". This test simply defines the adequacy of endogenous estrogen production — in an estrogen deficient environment there can be no withdrawal bleeding after progesterone administration. This test can be done by administering one injection of medroxyprogesterone acetate intramuscularly (375 mg Delalutin®) or giving it orally for five days (20 mg Provera® daily). A positive response — vaginal bleeding within a week following progesterone administration — effectively rules out a hypothalamic-pituitary deficiency as the cause of amenorrhea. This test, however, does not definitely pinpoint the lesion regardless of the response. Another simple test for "hypoestrogenism" is the use of vaginal cytology or the cornification index. /7/ Again, this alone is not a discriminating test — that is, a deficiency index may be seen with primary ovarian failure as well as pituitary failure, but when associated with absent gonadotropins and taken in the total context of the case it is further evidence of pituitary insufficiency.

The measurement of urinary gonadotropins is a highly variable and frequently unreliable index of hypothalamic-pituitary activity. However, when several determinations are made and the gonadotropin levels are consistently less than five mouse-uterine units one can accept the results as being indicative of a deficiency of gonadotropin secretion. More recently radioimmunoassay procedures for both FSH and LH have become available and with more widespread usage will provide the most sensitive index of hypothalamic-pituitary-gonadotropin production. The absence of FSH by immunoassay would place the lesion in the pituitary or hypothalamus. The ability of clomiphene citrate to produce a measurable rise in FSH may further localize the lesion to the hypothalamus (author's speculation).

Of course, the radiographic features of a lesion in the pituitary region provides the best localizing evidence, but normal radiographs early in the course of an amenorrhea

syndrome do not rule out hypothalamic or pituitary disease.

THE THYROID – Malfunction, a cause of amenorrhea

Secondary amenorrhea may be seen in association with either thyrotoxicosis or hypothyroidism. In the case of thyrotoxicosis the diagnosis is usually evident. Hypothyroidism as the cause of amenorrhea, however, is often subtle. Even when considered there may be only borderline low thyroid function tests. These should not be overlooked, because these may provide the answer, and a trial of thyroid therapy is occasionally rewarding in such cases.

ADRENAL VIRILISM

Up to this point the causes of secondary amenorrhea have been unassociated with hirsutism or virilism. When these features are part of the amenorrhea syndrome, one is most likely dealing with either adrenal or an ovarian dysfunction and the adrenal cortex is by far the more frequent source of true virilism than the ovary. /9/ The adrenal virilizing syndromes causing secondary amenorrhea may be conveniently divided into three types: (1) primary adrenal hyperplasia (frequently called acquired adrenogenital syndrome); (2) secondary adrenal hyperplasia; and (3) functional adrenal tumors (benign adenomas and carcinomas).

The work of Eberlein and Bongiovanni /10/ has clarified the basic pathogenetic mechanisms of primary adrenal hyperplasia. The lack of one or more of the enzymes in the adrenal cortex (most commonly the C-21 hydroxylase) necessary for the synthesis of hydrocortisone from pregnenolone results in a deficient production of hydrocortisone and a subsequent increased production of ACTH by the pituitary which forces the adrenal to produce increasing amounts of other pregnenolone metabolites — etiocholanolone, androstenedione and testosterone. When such a defect is only partial or minimal, it may not become evident until adult life and thus be the cause of variable degrees of oligomonorrhea, hirsutism and virilism.

Secondary adrenal hyperplasia is the result of a primary overproduction of ACTH which generally results in Cushing's syndrome. However, such patients are also subject to excessive producetion of "weak androgens", and menstrual alterations with minor virilism may be predominant clinical features.

Adenomas of the adrenal are also more commonly considered to be the cause of Cushing's syndrome rather than adrenal virilism, yet if the adenoma is comprised primarily of cells destined to produce androgens (a "less sophisticated process") an adrenal virilizing syndrome may result.

The most severe forms of virilism occur with functioning adrenal malignancies. Adrenal carcinomas tend to occur in women over 40 and they usually develop rapidly with full virilization appearing over a few months. Fortunately, however, such tumors are relatively uncommon because the mortality rate of those individuals who develop them approaches 75 percent. /9/

A complete schema for evaluating patients with suspected adrenal virilism is depicted in TABLE II. In primary adrenal hyperplasia, a typical "steroid profile" usually is found. If these tests do not confirm primary hyperplasia, a suppression test is necessary to distinguish between secondary hyperplasia and tumor. If the basal urinary 17-ketosteroid and/or 17-hydroxysteroid excretion is moderately elevated and cannot be depressed significantly with 2 mg Decadron® given four times daily for three days, one is dealing with a "tumor". There is little point in attempting to further resolve whether the pathology in such a case is an adenoma or a carcinoma. It should be promptly located by radiographic techniques — pyelography with tomography, retroperitoneal CO_2 insufflation, renal arteriography or adrenal venography — whichever your hospital is most capable of doing and the patient should be treated surgically.

TABLE II

SCHEMA FOR EVALUATING PATIENTS WITH SUSPECTED ADRENAL VIRILISM

TEST	PRIMARY ADRENAL HYPERPLASIA	SECONDARY ADRENAL HYPERPLASIA	BENIGN ADENOMA	CARCINOMA
Plasma "cortisol"	↓	↑	↑	↑
Urine 17-OHCS	↓	↑	↑	↑
Urine 17-KS	↑(modest)	↑(modest)	↑(moderate)	↑(marked)
Pregnanetriol	↑	Normal	Normal	Variable
Testosterone	↑	Normal	Normal	Variable
Suppression of 17-KS/17-OHCS with cortisol	+	+	-	-
	. . .	(8 mg Deca/day)	(8 mg Deca/day)	(8 mg Deca/day)
X-ray diagnosis	No tumor ±bilateral enlargement	No tumor ±bilateral enlargement ±pituitary enlargement	Unilateral tumor may require vascular contrast study	Unilateral tumor usually can be demonstrated by tomography

OVARIAN VIRILISM

Although the ovaries may be a cause of virilism in association with amenorrhea, it is usually mild and limited to obesity and hirsuitism in the polycystic syndrome. Tumors of the ovary, although potential causes of virilism are rare in their occurrence and are frequently unassociated with excessive androgen production when they do occur. As mentioned in the introduction, an accurate description of the ovaries -- size, shape and symmetry — should be established at the outset of any approach to the amenorrhea syndromes. Our approach to this is that if two competent observers cannot satisfy themselves that the ovaries and uterus are normal in size, shape and relationship to each other, then pelvic pneumography is performed (or peritonescopy if your favorite gynecologist prefers).

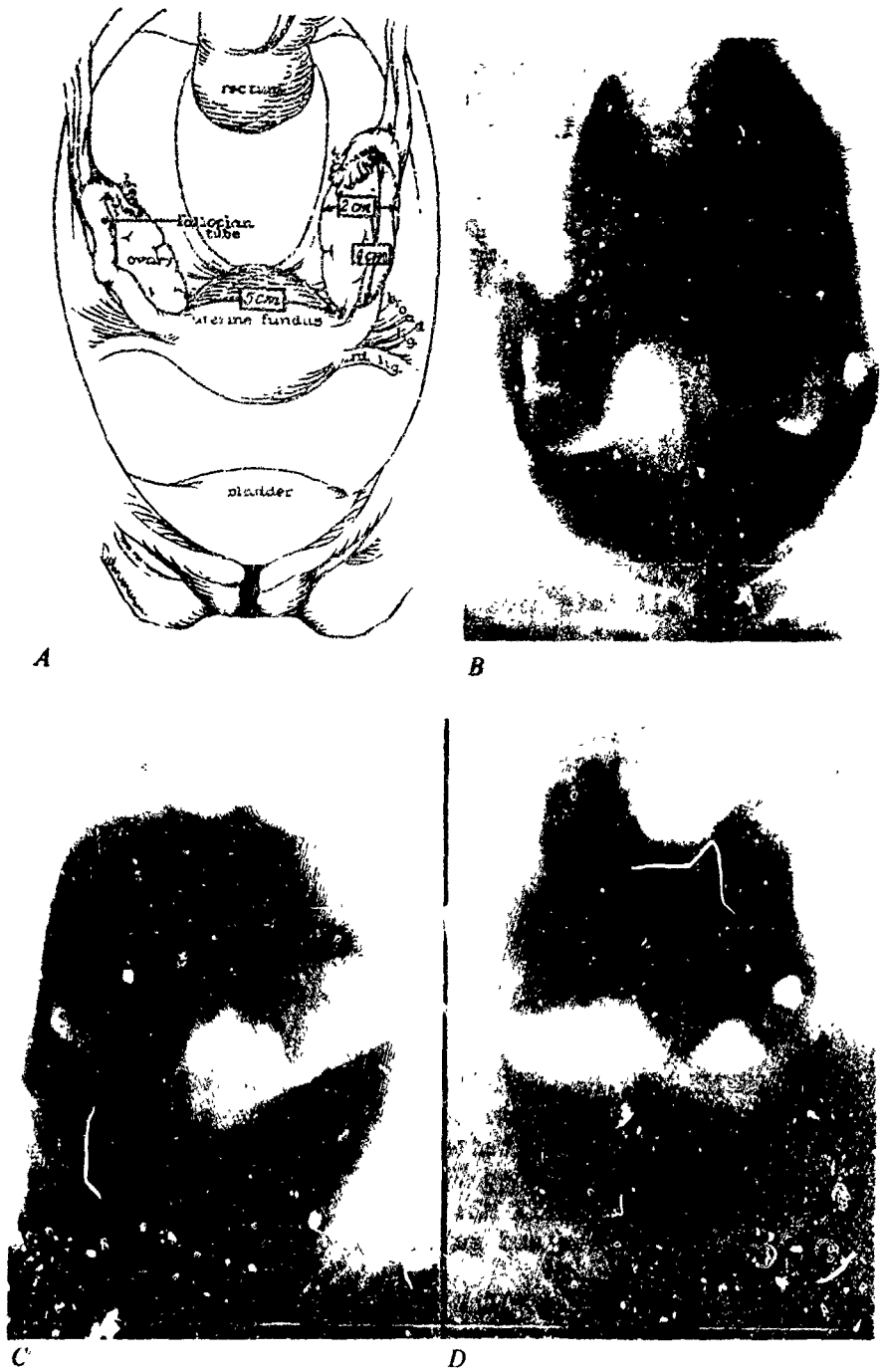
The technique of pelvi pneumography is relatively simple and uncomplicated. /11/ It can be performed in the radiology department and either CO_2 or nitrous oxide should be used. A gas is instilled into the peritoneal cavity under a gravity flow (water bottle displacement is the safest technique) via a 20 gauge spinal needle inserted into the left periumbilical region. After approximately two liters have been so placed the patient is tipped into a prone, 45 degree, head down position (use shoulder bars) and a PA projection is taken through the pelvis. Additional views (lateral and obliques can be obtained but rarely add significant information). The results to be expected from such a study are shown in Figure 2.

Why all this fuss about the pelvic pneumogram? — simply because it alone provides the most important diagnostic information about the role of the ovaries in these patients. Bilateral enlargement means polycystic disease and unilateral enlargement signals a tumor!

In our experience by far the most common pathologic ovarian cause of amenorrhea is the polycystic ovary syndrome. This often becomes manifest in the teens or occasionally after a single pregnancy with the development of menstrual irregularity progressing to amenorrhea and usually associated with obesity and mild to modest hirsuitism (but not always). Characteristically, 17-ketosteroid production is normal or at most "borderline high". Of course, the "adrenal steroids", 17-OHCS and pregnantriol, are always normal. Testosterone is frequently elevated and an exaggerated response to stimulation with gonadotropin is the rule in cases of the chorionic polycystic ovary syndrome. /12/

The rarer syndrome of hyperthecosis can not be clinically differentiated from polycystic disease although it apparently has a more common association with hypertension and glucose intolerance. The indications for treatment of these two syndromes are the same.

There are four types of ovarian tumors which have the potential of inducing virilization: (1) arrhenoblastomas (sertoli and Leydig cells), (2) hilus cell tumors (Leydig cells), (3) lipoid cell tumors (adrenal rests) and (4) gonadoblastomas.



A *B*

C *D*

Fig 2. Pelvic pneumograms *A* pelvic anatomy, *B.* normal pneumogram, *C & D* polycystic ovaries

Even the most common of these, the arrhenoblastoma, is rare — only about 200 cases having been reported. These tumors may occur bilaterally and may be malignant (20 percent). This tumor is prone to occur during the early reproductive years and therefore, is the one of most concern in the differential diagnosis of amenorrhea during this period. /9/ The majority of ovarian tumors can be palpated and most of those that cannot can be discovered on pelvic pneumography.

COMMENT

After all this discussion, I have left little to say in conclusion except that an accurate diagnosis of amenorrhea can be a most gratifying experience. The therapy for the different etiologies of amenorrhea is often quite different and specific. Although the evaluation can sometimes be quite simple on other occasions it may require long and complicated study. However, one happy mother makes it all worthwhile!

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We now have quite effective means of treating patients with ovulatory failure. Usually the main call for therapy is infertility. When such is the case, differentiating whether the functional lesion is in the hypothalamus, the pituitary or the ovary can direct the course of therapy. When there is evidence of significant estrogenic deficiency and hypogonadotropism, Clomiphene citrate is unlikely to be effective. On the other hand, in such instances "FSH" may be quite effective, either alone or in combination with "LH". Patients with positive estrogenic activity often respond well to Clomiphene citrate.[1] In the treatment of the infertility of the Stein-Leventhal syndrome, these agents should be given an adequate trial before surgery is contemplated – but if they fail, rest assured, Wedge Resection is still quite effective even though we still don't understand why.[2]

[1] *Lancet*, 21 Dec 1968
[2] *J Obstet Gynaec Brit Comm*, Nov 1968

ACROMEGALY
Diagnosis and Treatment

Seymour R. Levin, M.D.*

Acromegaly is a clinical condition resulting from autonomous secretion of growth hormone (GH) during adult life.

Normally, GH has a relatively predictable diurnal pattern. Upon arising, the healthy subject has a fasting immunoreactive GH level of less than 5 mug/ml Meals are followed by low values for the first two hours and then GH rises, somewhat, three to four hours after eating. During the first hour or two of sleep, the growth hormone rises appreciably, reaching a peak during the first period of deep sleep. This is "slow wave sleep," after the rapid eye movement (REM) phase.

Acromegalic patients, however, have high fasting GH which responds incompletely or atypically to meals and have a high, inconsistent nocturnal pattern. This secretion may come from an adenoma (basophil or eosinophil) or a hyperplastic pituitary gland.

Many stimuli of GH release have been studied; including emotional and physical stress, hypoglycemia, amino acid infusion, and acute lowering of free fatty acids. Estrogen enhances these GH rises. On the other hand, some substances lower GH. Prominent suppressants are rises in serum glucose and free fatty acids. Medroxyprogesterone, cortisol, and thorazine appear to blunt induced rises in serum GH.

Diurnal variation and responses to stimuli and suppressants appear to be mediated through a hypothalamic growth hormone releasing factor.

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Diagnosis

The diagnosis of acromegaly requires both clinical and laboratory clues. High, relatively autonomous hypersecretion of GH, as seen in acromegaly, forms the basis for what we believe is the best single test for the diagnosis, i.e. the nonsuppressibility of elevated fasting GH by 100 grams of oral glucose, one hour after ingestion. The inability of glucose to suppress GH, coupled with the essential clinical features, makes the diagnosis.

CLINICAL ASPECTS

Symptoms

In our experience with over 70 acromegalic patients, we have seen that they come to us with the disease detected at various stages. Early symptoms are non-specific and include sweating, easy fatigability, and hand paresthesias. Later, headaches appear, and increasing foot, hand, and head size are noted. Loss of libido and menstrual disorders emerge. Late symptoms are cosmetic deformities and problems secondary to diabetes, cardiovascular disease, pain in the joints, or impingement on the optic chiasm with resultant bitemporal hemianopsia.

Signs

The best physical sign is the doughy feeling of the hand during the hand clasp. There is usually a warm sweat reflecting hypermetabolism. Acral enlargement is usually seen. Coarse facial features vary in degree. A characteristic voice due to vocal cord thickening is present. We have seen skin papillomas and acanthosis nigricans in some of our patients. Those with a carpal tunnel syndrome have a Tinel's sign (tap over extended volar wrist and paresthesias spread over the palm).

Laboratory Findings

Fasting GH in our laboratory is 5 mug/ml in normal subjects. However, factors mentioned above can elevate this fasting level. We thus give 100 grams oral glucose and, in normal subjects, GH falls usually to 1 mug/ml. Mean fasting GH in 50 of our acromegalic patients was 52 mug/ml and showed non-suppression or incomplete suppression after glucose.

In addition to glucose non-suppressible elevations in GH, 50 percent of patients have glucose intolerance. An additional 10 percent have clinical diabetes mellitus. In most cases, without clinical diabetes, serum insulin is elevated, reflecting the effect of GH in impairing the action of insulin. The serum phosphorus, fasting, is elevated or normal, but this chemical fails to show normal diurnal variation (normally lower at 7 A.M. than at 4 P.M.). Seventy percent of patients have hypercalcuria (history of stones in 10 percent). Adrenal and thyroid function are usually normal preoperatively.

Tests have confirmed tumors of other endocrine glands (predominantly thyroid and parathyroid) in some patients.

Radiographic Signs

The best single radiologic sign is the presence of thickened heel pads. Measuring the shortest distance between the calcaneus and plantar skin surface, normal subjects average 17.8 mm (range 13-21). Acromegalic individuals average 25 mm (range 17-34). Negroes have a higher mean value, and edema, habitual barefootedness, and myxedema may also thicken the heel pads. An enlarged sella was seen in most of our patients (98 percent) and usually is accompanied by an elongated mandible and large frontal sinuses ("diagnostic triad"). Radiologically detectible osteoporosis was often seen in middle aged and older patients. The sesamoid index is the product of the largest and smallest perpendicular diameters of the thumb sesamoid. Normal range is from 12-29 mm. Acromegalic subjects often have an index of over 30 mm. Preparatory to most forms of treatment patients have pneumoencephalography and angiography to evaluate the direction of tumor growth.

Differential Diagnosis

Active acromegaly must be distinguished from "inactive" acromegaly, myxedema (sometimes called "myxomegaly" because thick lips, coarse skin, and deep voice in both conditions can cause some confusion), pachydermoperiostitis (a condition with thick skin folds and lips, prominent brows), other pituitary tumors, and constitutional cosmetic changes. These can all be distinguished by their normal growth hormone and careful clinical differentiation.

The joint deformities of acromegaly may simulate rheumatoid arthritis, since both may have enlarged proximal interphalangeal joint enlargement and pain. But acromegalic patients do not have morning stiffness characteristic of rheumatoid arthritis. Pain in large joints with or without effusion may simulate osteoarthritis, but in acromegaly. the joint space appears large, due to cartilagenous overgrowth. In osteoarthritis the joint space is often small. It is of interest that several other conditions may sometimes have glucose non-suppressible GH levels. These include severe starvation, some neoplasms, uremia, chronic liver disease. Clinical evidence, in these cases, however, helps to rule out acromegaly.

TREATMENT

The rationale for treatment involves an attempt to reduce the progression of metabolic abnormalities and cardiovascular disease which shorten and disrupt the patient's life. The idea method of treatment would reduce growth hormone and relieve pressure on adjacent structures while preserving remaining pituitary function.

The various means of treatment in use today are transphenoidal cryohypophysectomy, radiofrequency, yttrium implantation, surgical hypophysectomy, alpha particle radiation, and conventional x-irradiation. Except for the last modality, all have shown appreciable reduction in GH within a few days to one year. Measured GH of patients after conventional radiation has indicated that this treatment is relatively ineffective. Recently, medroxyprogesterone has been shown to reduce GH in acromegaly. Its permanence and

its place in therapy remain to be fully evaluated. At the University of California Medical Center we have treated 65 cases of active acromegaly with cryohypophysectomy in the past four years. We have observed the complications and response to treatment. Transient postoperative complications included diabetes insipidus (16/65); extraocular muscle weakness or visual field impairment, or both (10/65); hyponatremia (8/65). These problems remitted in several days. Two patients have had diabetes insipidus for several months postoperatively, which has responded to chlorpropamide. Three patients developed cerebrospinal fluid rhinorrhea, two of whom contracted pneumococcal meningitis, which responded to penicillin. Rhinorrhea remitted spontaneously. There have been no deaths.

In the six-day postoperative period there is a decrease in hand volume and ring size. In the six-week to four-year followup, growth hormone was reduced to less than 10 mug/ml in 51 of 65 patients. Six patients have required adrenal steroid replacement based on inadequate steroid response to tests with metyrapone and/or insulin hypoglycemia. Reduction in GH has been accompanied by subjective improvement, reduction in serum insulin, and the presence of improved glucose tolerance.

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DIABETES INSIPIDUS

MAJ Harvey L. Eichner, MC

Despite the presence of two hormones, antidiuretic hormone (ADH) and oxytocin, in the posterior pituitary secretion, disorders of the neurohypophysis alone have no clinical significance. Lack of oxytocin causes no impairment of parturition or breastfeeding, while ADH secretion is not determined by the competence of the neurophyophysis. ADH, or arginine vasopressin in man, is formed in the supraoptic and paraventricular nuclei of the hypothalamus. Axons of the ganglion cells in these nuclei extend down the neurohypophysial tract into the posterior pituitary; and secretory granules containing vasopressin are transported within the axons from the site of formation in the hypothalamus to the site of release in the posterior pituitary. Permanent diabetes insipidus (DI) results from destruction of the hypothalamic nuclei or the axons above the median eminence but damage to the neurohypophysial tract below the median eminence or ablation of the posterior pituitary itself causes only transient polyuria. Vasopressin may also be produced by non-endocrine tumors such as oat-cell carcinomas of the lung, which is among the causes of the syndrome of inappropriate secretion of antidiuretic hormone. This discussion concerns itself with defects in the secretion or action of vasopressin rather than the posterior pituitary gland.

Regulation of Vasopressin Secretion

The two factors exerting primary effects on vasopressin secretion are extracellular fluid volume and osmolality. Reduction in the blood volume by as little as ten percent results in an increase in vasopressin secretion. It is thought that the volume receptors are located in the left atrium and aortic arch or carotid arteries. Somewhere in the distribution of the internal carotid arteries, probably in the anterior hypothalamus, are the osmoreceptors that sense slight changes in extracellular fluid osmolality. Vasopressin is secreted in man when the plasma osmolality

exceeds 290 mOsM per liter. Of the two, volume change appears to be the more powerful stimulus. Increase in fluid volume or decrease in osmolality inhibits vasopressin release. Other stimuli of vasopressin secretion include pharmacologic agents such as nicotine, morphine, barbiturates, ether and acetylcholine, emotional factors such as pain, anger and fear and exercise or physical stress.

Thirst is also regulated by osmotic changes and by volume changes, with the volume changes taking precedence. The thirst center is located in close proximity to that for antidiuresis in the hypothalamus and in the absence of normal vasopressin release, an intact thirst center will maintain osmolality by increasing the desire for fluids. Even with a total absence of ADH, plasma osmolality will remain in the normal range unless there is a lesion in the thirst center also or drinking is prevented by unconsciousness.

Action of Vasopressin

Vasopressin acts on vascular smooth muscle to produce vasoconstriction; decreases secretion of sweat; decreases salivary, gastric, pancreatic, and biliary secretion; decreases water and sodium reabsorption by intestinal mucosa; increases gastrointestinal motility and peristaltic activity, primarily of the large bowel; decreases coronary blood flow and cardiac output, probably as a result of its pressor effects; and has some oxytocic activity. These extrarenal effects, however, occur only when much larger doses than those required to produce antidiuresis are administered.

The major physiologic action of vasopressin is on the distal portion of the nephron, primarily the collecting duct, to allow passage of water from the hypotonic urine into the renal medullary interstitial space which is hypertonic. Tubular permeability is altered to allow movement of water by the formation of cyclic 3', 5' - adenosine monophosphate (cyclic-AMP) as a result of stimulation of adenyl cyclase by vasopressin. The renal effects of vasopressin can be mimicked by cyclic-AMP but the exact means by which cyclic-AMP increase in tubular cells affects cellular water permeability is not known.

When ADH is deficient, diuresis of dilute urine results but a significant increase in serum osmolality occurs only in the absence of an increased water-intake. A triphasic response has been noted to destruction of the hypothalamic center for antidiuresis or pituitary stalk section. This consists of four to five days of polyuria and polydipsia followed by about six days of intense antidiuresis due to degeneration of nerve tissues in the neurohypophysis carrying vasopressin. This is then followed by permanent polyuria and polydipsia. Diabetes insipidus is characterized by the failure of the kidney to concentrate the urine despite a decrease in extracellular fluid volume or increase in osmolality and the correction of this defect by exogenous vasopressin.

DIFFERENTIAL DIAGNOSIS

Polyuria may be the result of a pathologic defect in vasopressin release, of the physiologic suppression of ADH or of renal factors including unresponsiveness to vasopressin and increased solute load per nephron. TABLE I lists the significant causes of polyuria and major etiologic categories. Some types of polyuria are produced by more than one mechanism but only the most important is listed. In psychogenic polydipsia for example there is not only suppression of ADH by the excessive water intake but also renal unresponsiveness due to reduced renal medullary tonicity.

All of these disorders can be readily distinguished in a single outpatient visit with the exception of nephrogenic diabetes insipidus, true diabetes insipidus and compulsive water drinking. An adequate history, urinalysis, blood urea nitrogen, glucose, potassium and calcium will for all practical purposes allow the physician to narrow the diagnostic possibilities to the three disorders.

TABLE 1

CLASSIFICATION OF POLYURIA

Polyuria with diminished vasopressin secretion
- Inability to secrete ADH - true diabetes insipidus
  - Tumors
  - Granulomatous disease
  - Surgery and trauma
  - Hereditary
  - Idiopathic
- Physiologic suppression of ADH
  - Psychogenic polydipsia
  - Lesion of the thirst center
  - Pharmacologic suppression with alcohol

Polyuria of renal origin
- Renal unresponsiveness to vasopressin
  - Nephrogenic diabetes insipidus
  - Hereditary anatomic defects - cystic disease of the kidney, medullary cystic disease
  - Inflammatory disease - glomerulonephritis, pyelonephritis
  - Toxic - hypercalcemia, copper and mercury poisoning
  - Fanconi syndrome
  - Hypokalemia
  - Miscellaneous - sickelcell disease, cystinosis, renal arterial disease
- Increased solute output per nephron (Osmotic diuresis)
  - Chronic nephritis
  - Glycosuria
  - Mannitol
  - Salt diuresis following relief of urinary obstruction

Nephrogenic Diabetes Insipidus

Nephrogenic diabetes insipidus is a hereditary disorder manifested by unresponsiveness of the distal tubular cells to normal endogenous vasopressin secretion. Half of the male offspring of heterozygous female carriers are affected but the sons of affected males are not, while the female heterozygotes may have a partial defect; all of this is in keeping with an X-linked mode of inheritance. It has been postulated that all cases in North America are descendants of female Ulster Scottish settlers who arrived in Halifax, Nova Scotia on the Hopewell in 1761. The patients have polyuria and polydipsia from infancy and, if unrecognized, develop chronic dehydration and resultant mental deficiency. Although they are unresponsive to vasopressin, they will frequently have a reduction in polyuria on treatment with thiazide diuretics and a low-salt diet. The history is usually suggestive although hereditary pituitary diabetes insipidus may be confused with the nephrogenic type. Patients with psychogenic polydipsia and even with true diabetes insipidus may be relatively unresponsive to vasopressin after prolonged high intake of water and medullary solute washout but will respond after a period of reduced water intake. Patients with nephrogenic diabetes insipidus have no increase in cyclic-3',5'-AMP in the urine after vasopressin. Those who normally respond to ADH do have this increase, and this difference may become a technique for distinguishing between nephrogenic type true diabetes insipidus.

Differentiation between Diabetes Insipidus and Compulsive Water Drinking

Since there are methods of determining vasopressin in plasma by rat bioassay of antidiuretic activity and by radioimmunoassay, it should be relatively simple to diagnose diabetes insipidus by confirmation of a lack of vasopressin after a period of dehydration or saline infusion. Unfortunately, the current assay methods are not sensitive enough to give diagnostic assistance; therefore a number of indirect tests must be used. The occurrence of polyuria and polydipsia following head trauma or pituitary surgery, or in the presence of a brain tumor or eosinophilic granuloma does not lead to

much difficulty in diagnosis but a large percentage (30-45 percent) of cases are idiopathic.

Distinguishing the initial event — polyuria or polydipsia — has been considered an important diagnostic clue, but this can be a challenge in a patient with no other evidence of organic illness. A preference for ice-water and abrupt onset of polyuria followed by polydipsia in the patient with diabetes insipidus is a helpful clue (polydipsia which precedes polyuria is more gradual in onset and these patients usually have other evidence of emotional disturbance, i.e., psychogenic polydipsia). These findings are not constant, however, and can only suggest the diagnosis; neither is there anything characteristic on physical examination. A comparison of serum and urine osmolality will rule out diabetes insipidus when the urine osmolality is higher than that of the serum in the hydrated patient, but this will not differentiate most patients with psychogenic polydipsia as they also have low urine osmolality in the hydrated state. The serum osmolality tends to be lower than normal in the compulsive water drinker and higher than normal in the diabetes insipidus patient but there is considerable overlap.

Several tests have been devised to confirm the diagnosis of diabetes insipidus and each has its difficulties — both in performing the test and in interpreting it. The saline infusion test first described by Hickey and Hare, with subsequent modifications, most notably those of Carter and Robbins, is essentially a stimulus to vasopressin release by increasing plasma osmolality with hypertonic saline. In the hydrated normal subject or compulsive water drinker a 75 percent decrease in urine flow rate and a rise in urine osmolality is expected. Variations in results may be due to previous degree of hydration, individual sensitivity and the rate of infusion. The infusion may cause an osmotic diuresis with false positive results in psychogenic polydipsia or it may be inadequate to stimulate antidiuresis. There is also the danger of producing congestive heart failure due to salt and fluid overload. For these reasons, saline infusion tests are not the best means of discriminating between psychogenic polydipsia and true diabetes insipidus and should be reserved for those few in whom the diagnosis is not clear after a water deprivation test.

The use of nicotine to stimulate vasopressin release has had its advocates, but it is unreliable, is accompanied by

unpleasant side-effects, and will not be considered further.

The water deprivation test is preferred as the most useful diagnostic test for the diagnosis of diabetes insipidus. Its stimulus is the most physiologic and, if properly done, is safe and sensitive. The patient should be restricted to a daily fluid intake below three liters for a week before the test, since prolonged polydipsia reduces renal responsiveness to ADH. A method for performing the water deprivation test is given in TABLE II. The patient with true diabetes insipidus will remain in a negative water balance with low urine osmolality and serum osmolality rising above 300 mOsM/kg. He may give evidence of clinical dehydration with tachycardia and hypotension and, if severe enough, the glomerular filtration rate will fall. This may cause a rise in the urine osmolality above that of the plasma with a false negative test result, but this may be prevented by discontinuing the test if blood pressure falls significantly or dehydration reaches five percent of body weight. The patient with psychogenic polydipsia may experience severe anxiety with water deprivation and may surreptitiously drink water despite instructions to the contrary. It is, therefore, imperative that patients be constantly observed during dehydration. If prepared with partial water restriction, the compulsive water drinker will raise his urine osmolality to above 600 mOsM/kg. This increase in urine osmolality may begin early in the test period and steadily progress. His urine volume will be reduced and the body weight and serum osmolality will usually stabilize. The patient with severe diabetes insipidus will not tolerate dehydration for long and an adequate weight loss occurs usually within four to eight hours, at which point vasopressin injection will cause a 50 percent or greater increase in urine osmolality. Failure of urine osmolality to rise above plasma osmolality on dehydration and failure of a further rise with vasopressin is diagnostic of nephrogenic diabetes insipidus. The psychogenic polydipsia patient may take considerably longer for adequate dehydration and that is why a standard length of time for the water deprivation test will not pick up some of these patients.

The greatest problem has arisen in making the diagnosis of partial vasopressin deficiency. In this group is probably the majority of diabetes insipidus patients. The response to dehydration in these patients ranges from levels indicative of severe diabetes insipidus to elevations in

TABLE II

EVALUATION OF PATIENT SUSPECTED OF DIABETES INSIPIDUS
Method for Performing Water Deprivation Test

Initial workup — History, neurological examination, skull roentgenogram, visual field studies, laboratory tests including plasma and urine osmolality, complete blood cell count, urinalysis, fasting blood sugar, blood urea nitrogen, creatinine, and others

By these studies the diagnostic possibilities are narrowed down to true diabetes insipidus, nephrogenic diabetes insipidus, and compulsive water drinking (including psychogenic polydipsia and the rare patient with a thirst center lesion)

Water Deprivation Test

→ Restrict fluid intake to 3000 cc daily for one week, or 1500-2000 cc for three days preceding the test (a small amount of vasopressin may be used).

→ Begin test in early morning. Have patient void and record weight; determine urine and serum osmolality. (Other measurements of hydration and solute concentration, such as hematocrit, serum sodium, and urinary gravity are superfluous.)

→ After starting test, allow patient to have no fluid intake (he may wet mouth with no more than 30 cc of water per hour or ice chips). Supervise him constantly.

→ Determine urine output, urine osmolality, and post-voiding weight every hour. Determine serum osmolality every two hours.

ENDPOINT OF TEST. When. . . (a) serum osmolality exceeds urine osmolality; (b) weight loss is greater than five percent of body weight, or (c) hypotension develops. . whichever comes first.

Urine osmolality failing to surpass plasma osmolality is indicative of true diabetes insipidus or nephrogenic diabetes insipidus

If serum osmolality does not exceed the urine osmolality. . .
Inject 5 u aqueous vasopressin subcutaneously and measure urine output and osmolality for several hours.

Response to vasopressin is diagnostic of true diabetes insipidus and lack of response is diagnostic of the nephrogenic type. If serum osmolality is exceeded by urine osmolality, it usually indicates compulsive water drinking but a further elevation in urine osmolality after exogenous vasopressin suggests partial diabetes insipidus

urine osmolality undistinguishable from normal. A further rise in urine osmolality with exogenous vasopressin on completion of water deprivation has been proposed as a means of diagnosing partial diabetes insipidus with high urine osmolality as opposed to psychogenic polydipsia. It has been the practice in the past to push for a diagnosis in order to prevent the compulsive water drinker from undergoing a lifetime of painful injections. With the recent advent of chlorpropamide (Diabinese®) therapy for partial vasopressin deficiency and lypressin (synthetic lysine-vasopressin) nasal spray, the treatment is not as difficult for the patient and is certainly cheaper than psychotherapy.

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PATHOPHYSIOLOGY OF THE THYROID GLAND

MAJ N.M. Panagiotis, MC

Over a century has passed since Graves' recorded the history of a young girl with exophthalmos and hyperthyroidism. Since that time this small gland has been the focus of investigation by a parade of distinguished physicians and scientists. Consequently more is known about the physiology of thyroid gland than any other endocrine gland. It is the purpose of this review to try to provide some of this information in a manner which helps the clinician evaluate patients with thyroid disorders. We will deal primarily with extremes of function —- hyperthyroidism and hypothyroidism. An attempt has been made to review briefly the pathophysiology of these disorders, provide meaningful information to help in the diagnosis, and review some principles of therapy.

Embryology and Phylogeny

In its embryogenesis, in certain aspects of its function, and in its phylogenetic development, the thyroid gland reveals its primitive relation to the gastrointestinal tract. The human thyroid anlage is first recognized at about one month after conception when the embryo is approximately 3.5 to 4.0 mm in length. Normally the thyroglossal duct dissolves and fragments about the second month after conception. Evidence suggests that fetal thyrotropin (i.e., thyroid stimulating hormone, TSH) influences the rate of anatomical maturation of the thyroid. Later in fetal life the thyroid is definitely responsive to TSH because fetal goiter occurs when the mother is given a goitrogen, although maternal TSH does not cross the placental barrier. Functional differentiation of the gland occurs concomitantly with anatomical development and its chronology follows the sequence through which the thyroid hormones are normally synthesized in the mature gland.

Anatomy

The thyroid is normally one of the largest endocrine organs. It weighs approximately 20 grams in North American adults. The normal thyroid gland is comprised of two lobes joined by an isthmus. The right lobe of the thyroid is normally more vascular than the left, is often the larger of the two, and tends to enlarge more in disorders associated with diffuse increase in size.

Major Aspects of Normal Thyroid Hormone Economy

Formation of normal quantities of thyroid hormone ultimately depends upon the availability of adequate quantities of exogenous iodine. The sources of iodine are dietary and peripheral deiodination of thyroid hormones; and the avenues of iodide removal are via the thyroid and kidney. The apportionment of iodide between the thyroid and kidney is a function of their individual accumulative capacities for this anion. Such activity can eminently be expressed by the conventional clearance concept which relates the amount accumulated per unit time to the plasma concentration. Since, under most circumstances, renal clearance of iodide is constant, homeostatic adjustment to maintain normal iodide accumulation are mediated by changes in thyroid clearance sites.

Intrathyroidal iodine metabolism is a complex of steps leading to the end product which is production of thyroid hormones, thyronine (T_4) and triodothyronine (T_3). These six steps include: active iodide transport; organic-binding which yields monoiodothyrosine (MIT) and diiodotyrosine (DIT) in thyroglobulin; coupling which yields thyronines, mainly thyroxine (T_4) and 3,5,3 triiodothyronine (T_3) in thyroglobulin; storage which is a unique feature of thyroid gland; proteolysis which allows the release of MIT, DIT, T_4 and T_3 from peptide bonds; and deiodination of MIT and DIT which is the process of partial re-utilization and partial loss of resulting iodide.

The nature, physical state and turnover of thyroid hormones in the blood, includes the components of venous effluent

from thyroid T_4, T_3, iodine and binding of hormonal product, i.e., thyroxine binding globuline (TBG); and thyroxine binding pre-albumin (TBPA) and albumin. The nature of the interaction is a reversible binding of equilibrium of the type T_4 plus TBG $\rightleftharpoons$ T_4-TBG complex. The intensity of the interaction reveals that T_4 binds firmly with 99.95 percent bound and 0.05 percent free. Triiodothyronine (T_3) is not bound by TBPA, and binds weakly to TBG.

A mass of evidence, which will not be reviewed in this paper indicates that only the free hormone is available to tissues and is metabolically active and susceptible to degradation, while the bound hormone acts as a metabolically inert reservoir. Additional evidence indicates that homeostatic mechanisms, when normally operative, are sensitive to a normal concentration of free hormone in the blood and seek to defend it, even though the total and protein-bound hormone may be required to change when achieving this end.

In the case of T_4, an amount equal to that contained in about one liter of plasma is cleared by peripheral tissues each day. In the case of T_3, the clearance rate is about seven liters per day. Therefore, even if the hormones were secreted in equal amounts, the concentration of T_4 in the plasma would be seven times greater than the concentration of T_3. Actually, less T_3 than T_4 is secreted and so the ratio of T_4:T_3 in the plasma exceeds 7:1. Because of its rapid turnover, physiologic replacement doses of T_3, or even doses sufficient to produce thyrotoxicosis, do not materially contribute to the measureable concentration of thyroid hormone in the blood.

The peripheral degradation and metabolism of thyroid hormone is primarily deiodination by all tissues. In the liver, biliary excretion occurs in a conjugated form such as glucuronide as well as sulfate esters.

The homeostatic regulation of thyroid function normally adjusts to meet the needs of peripheral tissues. The feedback regulation of TSH secretion is affected by free T_4 and free T_3. These hormones probably effect the hypothalamic TSH releasing factor (TRF); there is also a direct inhibition of TSH production. An autoregulation exists within the thyroid itself. There is an inverse relation which exists between (a) the glandular content of organic iodine and (b) the activity or hormone-forming processes and their responsiveness to TSH.

Assessment of Thyroid Hormone Economy

Virtually every aspect of thyroid hormone economy is susceptible to investigation, although some do not lend themselves well to study in a clinical setting. For clinical use, procedures fall into four major categories. A. Tests of thyroid function per se; B. Tests related to the concentration and transport of hormones in the blood; C. Tests which assess the metabolic impact of thyroid hormones in tissues; and D. Tests which assess the integrity of homeostatic mechanisms.

TESTS OF THYROID FUNCTION, *per se*

^{131}I labels endogenous non-radioactive iodide ^{127}I in the extracellular fluid (ECF). The fraction of a dose of ^{131}I which is accumulated in the thyroid therefore indicates the proportion of endogenous iodide within the ECF which enters the thyroid. It does not measure the absolute amount of iodine which enters the gland. In a steady state, percentage uptake approximates the percent of the iodine intake which is accumulated within the thyroid. The percentage uptake in any condition is a function of the relative magnitudes of the thyroid and renal clearance rates. Factors which influence the ^{131}I uptake are, in general, (1) exogenous thyroid hormone which usually suppresses the uptake; (2) factors which affect glandular hormone content, including the antithyroid drugs; (3) and normality of intrathyroidal iodine metabolism.

MEASUREMENT OF HORMONE CONCENTRATION

Tests which measure directly the low concentrations of intact thyroid hormones in the blood are generally available. Sensitive methods are also available to measure the iodine which the thyroid hormones contain. These include protein bound iodine, butanol-extractable iodine, total iodine, and total T_4.

Protein-bound iodine (PBI) usually is a measure of iodine in T_4 bound rather firmly to surface of a protein molecule, but is not an integral part of the molecule itself. Normally, PBI is 4-8 ug/100 ml.

Butanol-extractable iodine (BEI) is in the blood when acid butanol splits T_4 and T_3 from binding proteins; then these, with iodide, are extracted from serum into butanol. Iodide is removed from butanol by an alkaline wash, leaving T_4 and T_3 in butanol. Normally, BEI is no more than 0.6 percent lower than PBI.

Total iodine is the measurement of all forms of iodine ---- T_4, T_3 iodide, exogenous iodinated compounds, abnormal endogenous products. Normally, it is no more than 1.0 ug/100 ml greater than PBI.

Total T_4 is now measured by a binding displacement method first described by Murphy-Pattee. It has the advantage of eliminating exogenous ^{131}I contamination. Its disadvantage is that it is a difficult test to perform and expensive. However, this is the thyroid test of choice. Range is 1-2 ug/100 ml lower than the PBI. A column method is also available, but does not exclude contaminants as well as Murphy-Pattee.

ASSESSMENT OF HORMONE-BINDING INTERACTIONS

Electrophoretic analysis of individual binding proteins assesses the endogenous distribution and the binding capaci- (TBG, 18-25 ug T_4/100 ml serum; TBPA, approximately 200 ug T_4/100 ml serum).

The measurement of free T_4 is indirect and performed on an experimental basis. It is normally 0.05 percent of the total T_4. There is a formula to assess the absolute concentration of free T_4 (assume PBI is composed only of T_4 iodine).

PBI/0.66 = concentration of T_4
concentration of T_4 x % free = concentration of free T_4.
(Normally 2.5 mug/100 ml serum)

Another indirect assessment of thyroid function is the T_4 index. This is based on total T_4, and the in vitro uptakes of ^{131}I labeled T_3. (T_4 x T_3 uptake = T_4 index). The index is increased in hyperthyroidism and decreased in hypothyroidism.

The percent of a hormone in the blood which is unbound varies directly with the concentration of the hormone and inversely with both the concentration of the individual binding proteins and their specific affinities for the hormone in

question. The concentration of free T_4, rather than the proportion of free T_4, is closely related to the metabolic state. However, the proportion of free T_4 may be a helpful diagnostic index. TABLE I.

FACTORS WHICH ALTER THE CONCENTRATION OF HORMONE IN THE BLOOD

Since the removal of thyroid hormones from the blood conforms to a first order reaction (constant percent per unit time), changes in hormone secretion will result in comparable changes in circulating hormone concentration. Consequences of increased secretion will result in (1) increased hormone in blood with no appreciable change in TBG; (2) increase in PBI; (3) increased percentage of free T_4 (increased fractional T_4 turnover); (4) increased absolute T_4 (increased total T_4 turnover and thyrotoxicosis); and (5) increased *in vitro* uptake of T_4 and T_3. Consequences of decreased secretion are the converse of (1) through (5).

In these situations, homeostatic mechanisms are inoperative, usually because of underlying thyroid disease. The concentration of free hormone is not defended and hyperthyroidism or hypothyroidism ensues.

When there is primary alteration in binding proteins, there is no malfunction of homeostatic mechanisms, merely a change in the activity (presumably in the concentration) of one of the binding proteins. Therefore, a normal concentration of free T_4 and a normal metabolic state can be defended.

Primary changes in hormone binding appear to influence to concentration of hormone in the blood and the kinetics of its turnover, but do not basically alter the metabolic status of the patient. Clinically they have significance because they affect laboratory tests commonly used in the diagnosis of thyroid disease.

The factors which produce alterations in binding proteins are (1) increased TBG -- pregnancy, estrogen administration, contraceptive steroids ("the pill"), estrogen-producing tumors, hydatid moles, acute hepatitis, acute porphyria, familial idiopathic syndrome; (2) decreased TBG --- androgen administration, anabolic steroids, Dilantin® and derivatives, familial idiopathic syndrome, nephrosis; (3) increased TBPA --- none are known; and (4) decreased TBPA --- salicylates and congeners, severe non specific illness (malignancy, infection, surgery, etc).

TABLE I

USUAL RESULTS OF COMMONLY EMPLOYED LABORATORY TESTS IN VARIOUS THYROID CONDITIONS

	^{131}I UPTAKE	T_4	PBI	BEI	% FREE T_4 or IN VITRO T_3	BMR	T_3 SUPPRESSION	TSH STIMULATION
Iodine Deficiency	↑	N,↓	N,↓	N,↓	N,↓	N,↓	N	. . .
Iodine Excess (eumetabolic)								
Iodide	↓	N	↑	N	N	N	. . .	↑BEI
Organic dyes	↓	N	↑	↑	N	N	. . .	↑ ^{131}I, occ.
Iodide Myxedema	↓	↓	↑	↓	↓	↓	. . .	No response
Biosynthetic Defects	Variable	N,↓	N, ↑, ↓	N, ↓	N,↓	N,↓	N	. . .
Thyrotoxicosis Factitia								
T_4 or Desiccated thyroid	↓	↑	↑	↑	↑	↑	. . .	↑ ^{131}I, PBI variable
T_3	↓	↓	↓	↓	↓	↑	. . .	↑ ^{131}I, PBI variable
Functioning Adenoma								
Non-toxic	N,↑	N	N,↑	N	N	N	Abnormal	. . .
Toxic	↑	↑	↑	↑	↑	↑	Abnormal	. . .
Toxic Multinodular Goiter	↑,N	↑	↑	↑	↑	↑	Abnormal	. . .
Diffuse Toxic Goiter								
Active	↑	↑	↑	↑	↑	↑	Abnormal	. . .
Latent	N, ↑	N	N	N	N	N	Abnormal	. . .
Inactive	N	N	N	N	N	N	N	. . .
Active Ophthalmopathy (non-toxic)	N, ↑	N	N	N	N	N	Abnormal	. . .
Myxedema								
Primary	↓	↓	↓	↓	↓	↓	. . .	No response
Pituitary	↓	↓	↓	↓	↓	↓	. . .	↑ ^{131}I, PBI variable
Hashimoto's Disease								
Eumetabolic	N,↑	N	N,↑	N	N	N	N	. .
Hypometabolic	↓,N	↓	↓,N	↓	↓	↓	N	No response
Decreased Thyroid Reserve	N,↓	N,↓	N,↓	N,↓	N	↓	. .	No response
Subacute Thyroiditis	↓	N,↑	↑ ,N	N,↑	N,↑	N,↑	. . .	Variable

NOTE: Where more than one result is indicated, the first is the more common. Ellipsis (. . .) denotes test is not indicated for diagnostic purposes.

There are also non-hormonal factors which influence the measurements of hormone concentration and it is important to differentiate between (a) protein-bound iodine in which the iodine is part of a molecule (such as T_4 or iodinated dyes) which is bound to the surface of a protein molecule and (b) the variety of iodine-containing proteins (iodoproteins) in which the iodine is part of an iodinated amino acid which, in turn, is an integral part of the amide skeletion of the protein itself. The factors which increase apparent hormone content are (1) endogenous iodoproteins -- thyroglobulin and albumin-like iodoproteins, which are secreted by thyroid, but are hormonally inactive. These are found in Hashimoto's disease and in some cases of non-toxic goiter; measured in PBI, but not in BEI; (2) pharmacological doses of iodine result in increased total iodine, increased PBI (iodoprotein formed), and have no effect on serum thyroxine or on T_4 by binding displacement method when carefully administered; (3) organic iodinated dyes, such as those used for contrast media, which bind to plasma proteins (are extracted into butanol and not re-extracted into alkaline wash) and therefore increase total iodine, PBI and BEI but not total thyroxine; and (4) iodine containing medications which generally act like inorganic iodide.

Mercurial diuretic complex with iodine and interferes with the measurement and decreases the apparent hormone content. The factors indicated in this section do not interfere with the interaction between the thyroid hormones and their binding proteins, because even those which are bound to protein, such as x-ray contrast media, are bound to albumin, rather than TBG and TBPA. Therefore, they do not interfere with tests which assess these interactions, i.e., percent free T_4, in vitro uptake tests, or total T_4 measured by Murphy-Pattee method or theoretically by column.

TESTS WHICH ASSESS THE METABOLIC IMPACT OF THYROID HORMONES IN TISSUES

The basal metabolic rate (BMR), which measures the resting energy requirement, varies directly with the quantity of thyroid hormone available to tissues, and is also influenced by other hormones (epinephrine, glucocorticoids, growth hormone). Normally the BMR ranges from -10 to +10 percent.

There are sources of possible error. An increase in the

BMR is caused by the patient's smoking, eating, anxiety, fever, dyspnea, or shivering. There is also an increase in the BMR if he has heart failure, pheochromocytoma, a perforated ear drum or an acromegalic tendency; or there may be an outward leak in the apparatus. There is a decrease in the BMR if the patient is starved, has a thiamine deficiency, Addison's disease, or nephrosis; or there may be an inward leak in apparatus, i.e. poor soda lime. Serum cholesterol is increased in hypothyroidism and tends to be decreased in hyperthyroidism, but this is not pathognomonic. Normally, it ranges between 120-250 mg/100 ml.

TESTS WHICH ASSESS THE INTEGRITY OF HOMEOSTATIC MECHANISMS

Suppression Tests

The suppression test is a method of evaluating the integrity of the hypothalamic pituitary thyroid axis. Exogenous thyroid hormone normally suppresses secretion of TSH and leads to a decrease in thyroid ^{131}I uptake. Usually T_3 is used (75 ug for 2-3 weeks), however, T_4 can also be used. The latter the advantage that the drug is given in one dose and evaluation of radioactive iodine uptake is performed in seven days. When TSH secretion is inhibited, secretion of T_4 by the thyroid is slowed and T_4 concentration in the blood declines. This parameter is lost with the use of the T_4 suppression test. Since T_3 does not contribute materially to the PBI, the PBI decreases. Either the PBI or ^{131}I uptake response can be used as an index of thyroid suppression with the use of T_3. A normal suppressive response is reflected in a decrease of ^{131}I uptake to less than 10 percent or less than half of control value, and a decrease of PBI or T_4 into subnormal range. An abnormal response signifies breakdown of homeostasis possibly caused by autonomy of thyroid function, absolute or relative autonomy of suprathyroidal regulation, or presence of an ectopic thyroid stimulator. It is almost universally accepted that a patient with a normal suppression response cannot be thyrotoxic. However, in some circumstances (i.e., Graves' disease and hyperfunctioning adenoma) an abnormal suppression response may be present without thyrotoxicosis. The test is most useful in diagnosing borderline hyperthyroidism and in evaluating therapy.

TSH Tests

The TSH test methods and normal responses are highly varied, but their potential of assessing the ability of thyroid to increase its level of function makes their use significant. When the ^{131}I uptake reflects an expected increase, it indicates ability of the thyroid to increase new hormone synthesis. Uptake may be absent when the gland is rich in organic iodine, for example, when plasma iodide concentration is high. When the PBI reflects an expected increase, it indicates ability of the thyroid to enhance release of pre-formed hormone. PBI may be low when glandular hormone stores are low, for example after absence of TSH stimulation.

These tests are clinically useful to differentiate the primary form pituitary myxedema, to evaluate function capacity of thyroid during thyroid hormone therapy, and to diagnose decreased thyroid reserve.

PATHOPHYSIOLOGY OF MAJOR THYROID DISEASES

Non-toxic Goiter; Simple Goiter; Colloid Goiter

Goiter is not a single disease, but a group of diseases of diverse etiologies manifesting themselves via a final common pathophysiologic and pathological pathway. There are two basic pathogenetic prerequisites: (1) a thyroid gland which is, anatomically, intrinsically normal at the onset, (2) superimposition of any of a variety of factors which impair the capacity of the gland to synthesize adequate quantities of active hormone. Compensatory TSH response leads to goiter formation and stimulation of those processes in hormone biosynthesis which are uninvolved in the basic disturbance. Usually, this compensatory response makes possible secretion of adequate amounts of hormone, so that the patient is euthyroid, but goitrous (non-toxic goiter). In some instances, when the impairment of synthesis is severe, the compensatory response is inadequate and the patient is hypothyroid (goitrous hypothyroidism). Thus the metabolic state of the patient with these disorders may range from severe hypothyroidism to normal. The causes are both extrinsic and intrinsic.

The extrinsic factors are dietary habits permitting iodine deficiency (and resulting in classical endemic goiter, but rarely causing hypothyroidism, except for endemic cretinism, the precise pathogenesis of which is not understood), and dietary goitrogens (coming from plants of the Brassica series, cabbage, turnips, mustard and others, or being transmitted through animal vectors, such as milk from animals given goitrogenic feed); and pharmacological agents, including common antithyroids, para-amino-salicylate, resorcinol, phenylbutazone, cobalt (possibly most goitrogenic in children), and iodide. In a small proportion of peculiarly susceptible individuals, iodide in large doses acts as a goitrogen, producing a sustained blockade of organic binding (iodide goiter or iodide myxedema). The precise pathogenesis is not understood, but this response to iodide is especially prone to occur in the fetuses of mothers given iodide during pregnancy. The major action of the other goitrogens cited above is also to block organic-binding and coupling.

The intrinsic factors include a number of biochemical disorders involving discrete steps in hormone synthesis, storage, or release. The biochemical lesion is usually inborn and familial. When severe, it is usually manifest in childhood as goitrous hypothyroidism. When less severe, it is manifest as non-toxic goiter, often not discovered or prominent until times of "thyroid stress" during adolescence, pregnancy, or menopause.

In these disorders, laboratory findings are exceedingly variable in view of the diverse etiologic factors and varying severity of the physiological lesions. Some of the most characteristic results are listed in TABLE I. Treatment is thyroid hormone to block the stimulus (TSH). If this is not successful or if there is mechanical obstruction of the underlying anatomical structures then ablative therapy is recommended.

Disorders Associated with Thyrotoxicosis

Thyrotoxicosis is a syndrome, not a disease, and is produced by an oversupply of thyroid hormone to the tissues. These include thyrotoxicosis facticia - i.e., an over-ingestion of thyroid hormone, and struma ovarii. The latter is rare. In addition, one may have a patient with hyperfunctioning adenoma ("hot nodule"). This is a benign adenoma which does not

require TSH stimulation. Hormone secreted by adenoma suppresses TSH, so the remainder of gland is hypoactive and atrophic. The ^{131}I uptake is increased in the adenoma and the uptake in surrounding tissue stimulated by TSH. Not all adenomas of this type produce thyrotoxicosis. Some secrete quantities of hormone approximately equivalent to normal output ("warm nodule"). The laboratory data are reviewed in TABLE I. The most important group of disorders in thyrotoxicosis are those of Graves' disease or diffuse toxic goiter ---- a disease clinically characterized by goiter, thyrotoxicosis, and exophthalmos. However, the thyroid and ophthalmic manifestations may antecede one another by years or may never co-exist in the same patient. Another feature of the disease is a tendency toward cyclicity, either the thyroid or ophthalmic manifestations, or both, undergoing periods of activity or inactivity for reasons which are not known. An intrinsic feature of the disease is a breakdown of homeostatic regulation of thyroid function, as evidenced by an abnormal suppressive response to exogenous hormone. The disease may be staged in three phases ---- (a) active, characterized by thyrotoxicosis, active ophthalmopathy, or both, and an abnormal suppression test; (b) latent, characterized by no thyrotoxicosis or active ophthalmopathy and an abnormal suppression test; or (c) inactive, characterized by no thyrotoxicosis or active ophthalmopathy and a normal suppression test.

The pathogenesis of Graves' disease remains unsolved. In the last decade a great deal of attention has been directed to thyroid abnormalities in particular the long-acting thyroid stimulating hormone (LATS). Accumulating evidence indicates that LATS is a gamma blobulin, that it is synthesized in lymphoid tissue and that it interacts with thyroid microsomes. Lately its role as the cause of Graves' disease has come under attack and at present time the subject is controversial.

Clinical Picture

The clinical findings of Graves' disease are listed in TABLE II. It is important to note that the diagnosis is doubtful without finding increased thyroid tissue.

Of interest, but rare is thyrotoxicosis resulting from increased production of T_3 by the thyroid instead of T_4. New methods are presently being described including a T_3 radioimmunoassay which will allow the clinician to make this diagnosis.

Therefore, if one presents with clinical picture of thyrotoxicosis and total T_4 is normal or low, T_3 toxicosis should be suspected.

Treatment

The types of therapy fall into two major categories: (1) blockade of hormone formation which includes (a) inhibition of iodide transport --- thiocyanate and perchlorate; (b) inhibition of coupling and organic binding --- thionamedes; (c) inhibition of hormone release --- iodide; (d) inhibition of peripheral effect --- reserpine, guanethedine; and (2) ablation of thyroid tissue with radioactive iodine, subtotal thyroidectomy, or both.

Chemotherapy

Of the drugs used in the blockade of hormone production, propylthiouracil and tapazole are used most often. Although the dose of propylthiouracil varies with the patient, in general, dosage will start at no less than 300 mg per day. Doses as high as 1200 mg have been used. Since tapazole is 20 to 30 times more potent than propylthiouracil, the dose is accordingly smaller. The drugs are effective within two weeks and within six weeks patients are usually eumetabolic. Reactions to the drugs are numerous, of which agranulocytosis is the most serious. The long term therapeutic results have been unimpressive, with less than 50 percent of patients remaining euthyroid after 12 to 18 months of treatment. There is no intrinsic damage to the thyroid gland, and lasting myxedema does not occur, which are advantages, but there are also disadvantages ---- long period of treatment and high recurrence rate when treatment is discontinued.

Surgery

Subtotal thyroidectomy is a definitive ablative procedure which effectively removes hyperthyroidism. The surgical complications are well known. Unfortunately, the reduction in hypothyroidism is not significantly less with surgery than with radioiodine therapy.

Radiotherapy

Radiotherapy offers the advantages of being economical and definitive. The dose range is variable; but, in general,

is in the range of 140-160 uc/gm of tissue. The incidence of leukemia and carcinoma of the thyroid is no greater when these patients are compared to the population as a whole. The complication of hypothyroidism is common in patients with thyrotoxicosis and in some series of treated patients has been reported to be as high as 70 percent of the group.

COMMENT
on the Choice of Therapy

In patients not likely to be parents, the treatment of choice is radioiodine. The question of treatment remains open in the case of young adults. Since our experience in treating these patients with radioiodine is limited and our knowledge of genetic damage sparse, it is generally accepted practice to treat them with surgery or antithyroid drugs. However, some communities are now using radioidine in this group routinely, and are willing to handle the hypothyroidism with replacement medications. Surgery is of course the treatment of choice in obstructive complications, but this should be recommended only after thorough evaluation.

Disorders Associated with Insufficient Hormone Production

The syndrome which results from an inadequate supply of thyroid hormone to the tissue is designated as hypothyroidism or myxedema, although the latter term usually connotes a severer disorder. The clinical symptoms associated with myxedema are noted in TABLE III. Hypothyroidism can be broken down into two major classes: goitrous hypothyroidism and non goitrous hypothyroidism. The former includes the severe variant of non-toxic goiter and Hashimoto's disease. The latter includes the athyrotic patient (i.e., one who has an inadequate functioning thyroid mass). This group is comprised of patients suffering from primary myxedema, postoperative myxedema, and post ^{131}I myxedema. In athyroitic varieties, the secretion of TSH is increased. The laboratory findings are summarized in TABLE I. In pituitary myxedema, the thyroid is basically normal but TSH is decreased. In differentiating between the two, TSH stimulation test is useful. Hashimoto's thyroiditis disease is the culprit which led to the current vogue of interest in immunological disorders. A variety of antithyroid antibodies is found in the sera of patients with Hashimoto's disease but the role of these antibodies in the pathogenesis

TABLE II

INCIDENCE OF SYMPTOMS AND SIGNS
OBSERVED IN 247 PATIENTS WITH THYROTOXICOSIS*

SYMPTOM	PERCENT	SYMPTOM	PERCENT
Nervousness	99	Increased appetite	65
Increased sweating	91	Eye complaints	54
Hypersensitivity to heat	89	Swelling of legs	35
Palpitation	89	Hyperdefecation	
Fatigue	88	(without diarrhea)	33
Weight loss	85	Diarrhea	23
Tachycardia	82	Anorexia	9
Dyspnea	75	Constipation	4
Weakness	70	Weight gain	2

SIGN	PERCENT	SIGN	PERCENT
Tachycardia†	100	Eye signs	71
Goiter‡	100	Atrial fibrillation	10
Skin changes	97	Splenomegaly	10
Tremor	97	Gynecomastia	10
Bruit over thyroid	77	Liver palms	8

* Ingbar SH. *Used with permission.*
† In other studies thyrotoxic patients with normal pulse rate have been observed.
‡ According to Williams, R.H. *J Clin Endocrinol* 6:1, 1946

TABLE III

SYMPTOMATOLOGY OF MYEDEMA *
(77 Cases – 64 Women, 13 Men)

SYMPTOMS	PERCENT OF CASES	SYMPTOM	PERCENT OF CASES
Weakness	99	Constipation	61
Dry skin	97	Gain in weight	59
Coarse skin	97	Loss of hair	57
Lethargy	91	Pallor of lips	57
Slow speech	91	Dyspnea	55
Edema of eyelids	90	Peripheral edema	55
Sensation of cold	89	Hoarseness or aphonia	52
Decreased sweating	89	Anorexia	45
Cold skin	83	Nervousness	35
Thick tongue	82	Menorrhagia	32
Edema of face	79	Palpitation	31
Coarseness of hair	76	Deafness	30
Pallor of skin	67	Precordial pain	25
Memory impairment	66		

*Ingbar SH *Used with permission.*

of the disease is unclear. The functional abnormalities consist of mild defect of organic binding, and release of abnormal iodoprotein. The course may be broken into two phases. In the early phase, function of thyroid is increased --- it has an increased ^{131}I uptake and a higher PBI rate; however, the BEI or T_4 and metabolic state is normal. Occasionally, the clinical and laboratory picture of thyrotoxicosis is seen in patients whose thyroid glands appear to demonstrate Hashimoto's disease, both clinically and histologically. Here, the thyrotoxicosis may disappear or be followed by hypothyroidism even in absence of treatment.

Subacute Thyroiditis

This disease, also termed giant-cell-thyroiditis, pseudotuberculous thyroiditis, or deQuervain's thyroiditis, is a self-limited and often a massively inflammatory disorder of the thyroid. The onset may be gradual or abrupt, but the spontaneous course is usually prolonged.

The functional abnormalities reveal a loss of biosynthetic function with ^{131}I uptake almost invariably subnormal. There is a disruption of storage function with a release of preformed iodoproteins and peptides which yields a high PBI. Occasionally active hormones are release, the BEI is high and the patient transiently thyrotoxic. A markedly elevated erythrocytic sedimentation rate is characteristic.

Treatment of Hypothyroidism

The result of treatment of hypothyroidism in the adult is generally one of the most gratifying to the physician because of the ease and completeness with which the disease responds to the administration of thyroid hormone. Treatment is carried out with one of two general types of preparation: either synthetic hormone or thyroprotein dervied from animal thyroid glands. In the former category, both sodium thyroxine (levothyroxine) and sodium triiodothyronine (liothyronine) have been employed. In the second category, desiccated thyroid extract, USP, is most commonly used. The approximate equivalence of biological potency is as follows: thyroid

extract one grain (60 mg), levothyroxine (T_4) 100 ug and liothyronine (T_3) 25 ug. Recently a number of preparations have been prepared compounding T_4 plus T_3 (T_7, if you please). These offer no particular advantages except the restoration of a normal PBI.

When first diagnosed, hypothyroidism usually has been long-standing and seldom requires prompt reversal. Consequently, according to a consensus of authorities in the field, restoration of a normal metabolic state should be undertaken slowly. It should be kept in mind that the untreated hypothyroid patient is inordinately sensitive to small doses of thyroid hormone. The initial daily dose therefore should not exceed 30 mg of thyroid abstract or 50 ug of levothyroxine. Care should be taken in the hypothyroid patient with heart disease and in the patient with long standing hypothyroidism, because over enthusiastic treatment may precipitate heart failure or myocardial infarction or may provide relative adrenocortical insufficiency in the latter. In these cases an initial daily dose of 8 or 15 mg of thyroid extract is recommended. Thereafter the dose is increased 15 to 30 mg daily until a maintenance dose and eumetabolic effect is achieved within three weeks. This usually requires 120 to 180 mg of thyroid daily.

The interval between initiation of treatment and appearance of first evidence of improvement depends upon the size of dose employed. An early clinical response is a diuresis, followed by increase in pulse and blood pressure, increased appetitie and decrease in constipation. Psychomotor activity increases and delay of deep tendon reflex abates. Hoarseness abates slowly and changes in the integument may require months to disappear.

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HYPERPARATHYROIDISM

Ralph S. Goldsmith, M.D.*

Hyperparathyroidism is, perhaps, a unique disease — it has long been considered interesting, and even exciting, despite its being thought to be relatively uncommon. This seems all the more unusual in view of our lack of knowledge of the natural history of the disease, a fact directly attributable to the simultaneous publication of the description of the disease and the method of curing it (surgical extirpation). /1/ Increasingly, evidence is accumulating that either the disease is not nearly so rare as we once thought or we are smack in the middle of an epidemic. Although we do not perform analyses for serum calcium routinely in our own institution, in 1969 we recognized 165 patients with primary hyperparathyroidism. Indeed, our incidence (based on the total number of serum calcium determinations not number of patients) was one diagnosis of hyperparathyroidism for every 250 serum calciums! It has been reported previously /2/ that one in 800 patients coming through the door of a clinic in Bluffton, Indiana, had this disease, diagnosed solely on a basis of routine measurement of serum calcium. Our own data are incomplete in this regard, but it is clear from a small survey which we performed on a series of patients undergoing routine health examinations that the incidence of this disease may be even higher than one in 800.

The foregoing is intended to make the additional point that a good serum calcium determination is an important mainstay in recognition of at least the majority of these patients, irrespective of whether or not one requires the presence of hypercalcemia to make the diagnosis. As reported previously from this institution, even before the advent of superior analytical techniques such as atomic absorption spectrometry, a careful laboratory can have a narrow normal range of serum

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calcium. /3/ Without going into great detail about these data, it suffices to emphasize that we consider a serum calcium of 10.2 mg/100 cc as representing hypercalcemia (this varies a little with age and sex). Furthermore, this degree of hypercalcemia may be enough to warrant parathyroidectomy.

A few words are warranted about our indications for surgery, because we are following a protocol which is designed to teach us something of the natural history of the disease, untreated and treated. Therefore, with the exception of several specific indications for surgery, we are operating on only half of the patients, but following all of them closely. Our specific indications for surgery are:

(1) serum calcium in excess of 11 mg/100 cc

(2) roentgenographic osteitis fibrosa

(3) active nephrolithiasis (passage of gravel, growth or increase in number of stones during previous six months

(4) impaired renal function

(5) associated, otherwise unexplained problems (recurrent pancreatitis, intractable peptic ulcer symptoms, excessive gastric acid, psychogenic difficulties

(6) inability to "live with the diagnosis".

Without these indications, patients are randomly assigned to surgery or follow-up appointments.

To date, the untreated group has yielded some surprising data; namely, that more than ten percent of them have progressed into the "surgery now" category by virtue of having developed one or more of the indications for surgery. It appears, therefore, that hyperparathyroidism may not be the benign disease we once thought it might be. The big questions, of course, are (1) how many patients will ultimately develop problems calling for surgery and (2) do parathyroidectomized patients fare better in the long run than do untreated patients? We have no answer to the first question, but we are reasonably certain that the answer to the second is "yes", with the exception of patients with familial hyperparathyroidism or multiple adenomas. These

latter groups are unique and present formidable, unresolved problems into which I cannot delve further at this point.

To return to diagnosis, let me begin by saying that, in the majority of patients, the diagnosis is clearly evident. In some, however, other causes for hypercalcemia must be sought actively before resorting to the knife. Since we always perform a number of tests in addition to serum calcium in suspects, we have a moderate amount of information at hand to assist in the diagnosis. Features which suggest further studies to look for other causes of hypercalcemia are listed in TABLE I.

TABLE I

FEATURES OF HYPERCALCEMIA

Features which suggest further studies are necessary to find the causes of hypercalcemia
Features which exclude the diagnosis of hyperparathyroidism*

High normal serum phosphorus
Urinary excretion of calcium in excess of 400 mg/day
Absence of roentgenographic osteitis fibrosa in the presence of severe hypercalcemia
Elevated alkaline phosphtase in the absence of osteitis fibrosa
Abnormal plasma protein electrophoresis
Elevated erythrocyte sedimentation rate
Unusual roentgenographic appearance of bones
Weight loss
Clinical deterioration
Serum parathyroid not in keeping with serum calcium

**The last feature (Serum parathroid not in keeping with serum calcium) is a possible exception*

I must emphasize, however, that none of these features (with the exception of the last one — (serum PTH not in keeping with serum calcium) excludes the diagnosis of hyperparathyroidism. We do not ordinarily perform calcium infusions or phosphorus deprivation tests because of the amount of time required, the large number of patients, and the availability of PTH

measurement. Prior to having the latter available, I have used both of the other tests extensively and have found them to be helpful.

The recent development of a sensitive and specific radioimmunoassay for serum parathyroid hormone (iPTH) has made life much simpler in many ways for those who see large numbers of patients. The particular assay which we use has just been reported by Arnaud and associates /4/ in the January 1971 issue of the Journal of Clinical Investigation. Without going into detail about the method, there are several points to mention specifically. First, normal subjects show a negative correlation between serum calcium and iPTH concentrations, so that serum calcium must be taken into consideration when evaluating iPTH. In other words, a value for iPTH which is normal for a calcium of 9.1 mg/100 cc may be distinctly elevated for a calcium of 10 mg/100 cc. In contrast, patients with hyperparathyroidism show a positive correlation between these variables. As a result, a two-point discriminant function has been derived to distinguish normal from hyperfunction. Secondaly, impaired renal function causes iPTH to begin increasing early. Interpretation of iPTH in the presence of azotemia is therefore fraught with hazard. Response to calcium infusion may not resolve the difference between primary and secondary disease, as we shall report shortly. Thirdly, in contrast to Reiss' assay, our assay usually distinguishes between the PTH from parathyroid glands and that from malignant tumors (of other than parathyroid origin). The practical consequence of the latter observation is that iPTH in patients with cancer is abnormally low (or undetectable) for the height of the serum calcium and generally permits identification of these patients.

It is not possible to describe all of the facets of hyperparathyroidism which were brought out at the First Keating Memorial Sumposium, but I recommend it to you for a comprehensive view of the current state of knowledge. It will appear in the May 1971 issue of the American Journal of Medicine.

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Diseases of the parathyroid gland, a new classification based on etiologic and physiologic considerations*

Hormonal deficiency or hypoparathyroidism

Hypoparathyroidism from absence or damage of parathyroid glands (primary hypoparathyroidism)

- Following therapy of thyroid disease
  - Post-thyroidectomy, permanent or transient
  - Post-radioiodine, permanent or transient
- Cause unknown or idiopathic hypoparathyroidism
  - Early onset
    - Sex linked
    - Non-sex linked with congenital aplasia of 3rd and 4th pharyngeal pouches [DiGeorge syndrome]
  - Late onset
    - Familial
      - With Addison's disease and/or moniliasis [HAM syndrome]
      - Without Addison's disease and/or moniliasis
      - With pernicious anemia

Hypoparathyroidism from suppression of parathyroid activity by hypercalcemia (secondary hypoparathyroidism)

- Post-resection of parathyroid adenoma
- Neonatal from maternal hyperparathyroidism
- Physiologic from hypercalcemia of non-parathyroid origin

Hormonal unresponsiveness due to partial or total lack of parathyroid hormone-sensitive adenyl cyclase in renal tissue (pseudohypoparathyroidism)

- Familial
  - With brachydactyly and/or subcutaneous bone formation
  - Without brachydactyly or subcutaneous bone formation
- Sporadic
  - With brachydactyly and/or subcutaneous bone formation
  - Without brachydactyly or subcutaneous bone formation
  - With osteitis fibrosa cystica [pseudohypohyperparathyroidism]
- Related conditions
  - Idiopathic brachydactyly, sporadic or familial (pseudopseudohypoparathyroidism)
  - Osteoma cutis
  - Basal cell nevus syndrome
  - Steatorrhea?

Continued on page 187

EVALUATION OF ADRENAL DYSFUNCTION

MAJ Harvey L. Eichner, MC

Hypofunction of the Adrenal Cortex

Decreased production of hormones from the adrenal cortex may be the result of trophic hormone deficiency, congenital defects in corticosteroid synthesis or acquired damage to the adrenal gland. The latter, Addison's disease, is most commonly an auto-immune disorder associated with lymphocytic infiltration of the adrenal cortex and circulating antiadrenal antibodies. Granulomatous diseases are next in frequency, particularly tuberculosis which was once the leading cause of adrenal insufficiency. Adrenal destruction may also occur in malignancy and amyloidosis; may be caused by infection, trauma, or abdominal surgery; or may be the result of hemorrhage with necrosis.

Defects in cortisol formation may occur as the result of a decrease in the activity of enzymes necessary for steroid biosynthesis. Deficiencies of 21-hydroxylase, 11B-hydroxylase, 17-hydroxylase and 3B-hydroxysteroid dehydrogenase have been shown to occur as well as other rare forms not as well characterized. As a result of the lack of cortisol, adrenocorticotrophic hormone production is increased, the adrenals become hyperplastic and there are excessive amounts of precursors that accumulate immediately behind the block in synthesis. Depending on the site of the defect, lack of secondary sexual characteristics, virilization, hypertension or hypotension with salt loss or combinations may occur. This group of diseases is referred to as congenital adrenal hyperplasia and they are diagnosed by the pattern of those steroids deficient and those elevated and by the response to glucocorticoid replacement which will suppress ACTH and thus suppress the elevated steroids.

Hypopituitarism as a cause of adrenal insufficiency is easy to distinguish from Addison's disease. Frequently the cause of the pituitary lesion is obvious (as in head trauma) hypophysectomy or after prolonged steroid therapy. In diseases affecting the pituitary, ACTH is usually one of the last hormones to be lost and therefore other features of hypopituitarism such as hypothyroidism and gonadotrophin deficiency will be present. Patients with secondary adrenal insufficiency are generally pale rather than pigmented (due to lack of ACTH, rather than excess) and are not usually severely lacking in mineralocorticoid hormone secretion since aldosterone is influenced by the renin-angiotensin system and serum potassium and to a lesser degree influenced by ACTH. Except in the case of surgical ablation of the pituitary there is not a total lack of ACTH and most patients with hypopituitarism will not manifest frank adrenal insufficiency except during stress. Defects in secretion of the hypothalamic hormone, corticotrophin releasing factor (CRF), may be responsible for some cases of secondary adrenal insufficiency but without a means to measure CRF this can only be suspected.

The clinical picture of adrenocortical insufficiency itself consists of nonspecific symptoms but if there is an intact pituitary and hyperpigmentation occurs, the diagnosis is more readily made. Fatiguing easily and weakness ranging from mild to complete prostration; anorexia, nausea, vomiting and diarrhea; dehydration, hypovolemia, small heart size and hypotension; nervousness, emotional instability, dizziness and syncope; and hypoglycemia are common findings. Hyperpyrexia may be seen in acute cases and lymphoid hyperplasia and muscle cramps in some chronic cases. Evaluation of the increased melanin pigmentation may be difficult as it is identical to natural pigmentation but the change in pigmentation is more important than the amount or location. Because of the insidious onset in most cases, these symptoms are frequently not noticed until an intercurrent infection or surgical procedure results in acute collapse which may be fatal if not rapidly treated. Peripheral blood eosinophilia, lymphocytosis and decreased serum sodium to potassium ratio may also be found.

The diagnosis of adrenal insufficiency can only be confirmed by laboratory tests which measure adrenal steroid output, adrenal reserve and, directly or indirectly, ACTH production. Numerous procedures have been devised for assaying adrenal steroids but the most widely used test is one for steroids with

hydroxyl groups at carbon 17 and 21 and a ketone at carbon 20 which give a specific color reaction with phenylhydrazine, the Porter-Silber reaction. Porter-Silber chromogens or 17-hydroxycorticosteroids (17-OHCS) are mainly cortisol and when performed on plasma this procedure is a highly specific screening test for adrenal insufficiency. If tests for urinary or plasma cortisol are abnormally low under basal conditions, functional adrenal reserve must be tested with corticotrophin stimulation, because cortisol measurements may be diminished in patients with severe wasting diseases, liver disease, myxedema, and in patients taking certain medications, such as diphenylhydantoin. The most expeditious stimulation test is the assay of plasma 17-hydroxycorticosteroids (sometimes incorrectly referred to as plasma "cortisol") in the basal state and 30 minutes after 25 units of ACTH (or equivalent in synthetic corticotrophin) intramuscularly. The second sample should be at least 10 mg/100 ml greater than the first. For a more reliable test the assay of 24-hour urine specimens (collected daily) for 17-OHCS should be performed. At the start of the second day, an intravenous corticotropin infusion should be begun in one liter of saline with 25 units of ACTH and given over eight hours. If hypopituitarism is suspected this may be continued for two or three consecutive days. In Addison's disease, there will be a failure of the urinary 17-OHCS to approach normal levels, even after the third day, while in ACTH deficiency there is a stepwise increase in 17-OHCS output. The normal range is about 3-12 mg/24 hours rising to 15-45 mg/24 hours after a single eight-hour infusion.

If there is no response to corticotropin, even after three days, the diagnosis of Addison's disease is confirmed and there is no reason to measure pituitary reserve. If hypopituitarism is suspected and ACTH stimulation gives either a normal or a sluggish response, pituitary reserve may be tested. The slowest and safest method is the 11B-hydroxylase inhibition method using metyrapone and measuring the ACTH-induced rise in urinary 17-OHCS caused by blocking cortisol production. The standard procedure, although modifications are rampant, is to collect urines for four days, two as controls, one during and one after the oral administration of 750 mg metyrapone every four hours for 24 hours and assay them for 17-OHCS. Normal individuals increase their urinary 17-OHCS two to four times and this is greatest in the 24-hour period following treatment. Vasopressin or insulin-induced hypoglycemia are more rapid methods fo.

determining pituitary reserve causing secretion of corticotropin releasing factor from the hypothalamus. Both plasma 17-OHCS and growth hormone may be measured and this is a procedure which can be completed in about 90 minutes and does not require hospitalization. Direct measurement of plasma ACTH by radioimmunoassay is available at some centers but is not yet in wide enough use to make it a standard test.

Other diagnostic procedures are used to determine the etiology of Addison's disease and the extent of adrenal failure. Assays for aldosterone may be performed and 2-deoxyglucose infusion (as a test of adrenal medullary function) may also help to distinguish between tubercular and "auto-immune" Addison's disease (adrenal medulla is more likely to be normal in the "auto-immune" type). Of course the usual diagnostic aids in the granulomatous diseases such as delayed cutaneous hypersensitivity may be helpful and tests for antiadrenal antibodies are also available.

Hyperfunction of the Adrenal Gland

While the suspicion of adrenal insufficiency is usually late in coming forth, confirming the diagnosis is a simple matter. In Cushing's syndrome, however, the disease is suspected far more often than it occurs and confirming the diagnosis is sometimes difficult. The clinical findings of Cushing's syndrome depend on the relative amounts of glucocorticoids, mineralocorticoids*, and androgens secreted, and include mental changes, muscle wasting, thinning of the skin, red cheeks, purple striae over the abdomen, thighs and upper arms, truncal obesity with buffalo hump and supraclavicular fat pads, moon facies, easy bruisability, poor wound healing, osteoporosis, diabetes, hypertension, polyuria, deepening of the voice, hirsutism and baldness, acne, clitoral enlargement and amenorrhea in the female, and impotence in the male. Since obesity, hirsutism, osteoporosis, hypertension, diabetes and striae are extremely common in the population and combinations of these findings are not infrequently seen, there are many more negative workups for Cushing's syndrome than positive.

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* Excess mineralocorticoid secretion is discussed by Doctor Bigler in this issue (pp *179-186*)

Cushing's syndrome may be caused by exogenous steroid administration, primary adrenal disease or increased adrenal stimulation. Adenomas are the most common adrenal lesions producing excessive steroids but adrenal carcinomas may also be secretory, although they tend to be associated more often with androgen excess. Adrenal tumors are more common in women and may be associated with other endocrine tumors. Nodular adrenal hyperplasia, to be distinguished from diffuse hyperplasia, may be responsible for Cushing's syndrome, and, like the other adrenal lesions it is accompanied by low plasma ACTH and non-suppressibility by dexamethasone. Corticotropin over-production may be from the pituitary or various carcinomas most commonly of the lung. While pituitary tumors may produce ACTH, most of the patients with diffuse adrenal hyperplasia who have increased corticotropin production have no demonstrable pituitary lesion. It is postulated that in some of these people the regulatory mechanism for ACTH release is set too high, so that plasma cortisol does not exert a negative feedback effect at the usual levels.

In a patient who is suspected of having Cushing's syndrome, laboratory studies must first establish the diagnosis of adrenocortical hypersecretion, and then the cause of the problem. The most widely used screening test is also subject to the greatest error, namely urinary Porter-Silber chromogens. A single plasma "cortisol" (plasma 17-OHCS) will sometimes be high enough to confirm the diagnosis but more helpful is a loss of diurnal variation in plasma 17-OHCS when the late evening level is found to be as high or higher than the morning value. Other findings in laboratory studies include erythrocytosis, neutrophilia, lymphopenia and eosinopenia of the peripheral blood, hyperglycemia or glucose intolerance, and hypercalciuria. Measurement of urinary free cortisol has been recommended as a reliable means of distinguishing Cushing's syndrome from other causes of elevated cortisol excretion such as obesity, thyrotoxicosis, emotional disorders, surgery and acromegaly. This value will be greater than 200 ug/24 hours in Cushing's syndrome and usually below 125 ug/24 hours in other states. The free cortisol test is not available in all centers, however, so the overnight dexamethasone suppression test is usually used to confirm the presence of Cushing's syndrome. One milligram of dexamethasone is given at 11:00 PM along with a sedative to insure rest; a plasma 17-OHCS determination is obtained the next morning. Normal persons will usually suppress their plasma 17-OHCS below 5 ug/100 ml while levels above 12 ug/100 ml are evidence for the diagnosis of Cushing's syndrome. The dexamethasone suppression test using urinary 17-OHCS measurements (the small dose dexamethasone

suppression test of Liddle) requires two days to complete and is subject to greater error than the overnight suppression test, and also offers no advantage in sensitivity.

Once a diagnosis of Cushing's syndrome has been made, the specific site of the lesion responsible must be identified. Primary adrenocortical lesions are associated with low plasma ACTH; ectopic corticotropin producing tumors are associated with elevated ACTH levels; while plasma ACTH may be normal or elevated in Cushing's syndrome of pituitary origin. The ACTH assay is therefore valuable although not all assays are reliable. The large dose dexamethasone suppression test of Liddle, using 2.0 mg every six hours for two days can be used to rule out inappropriate pituitary ACTH secretion (the other causes of Cushing's syndrome are not suppressed by this dose. Also in diffuse adrenal hyperplasia the glands are usually still responsive to exogenous ACTH or to metyrapone-induced endogenous ACTH increases and these tests may be used. Appropriate radiological studies to rule out a pituitary tumor, locate a potential extra-pituitary source of ACTH production and identify a primary adrenal lesion are important adjuncts to the function tests. The more sophisticated vascular contrast studies of the adrenal gland (renal arteriograms or adrenal renograms) have been extremely useful in localizing an adrenal tumor.

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MINERALOCORTICOID HORMONES (MCH) IN HYPERTENSION

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The adrenal gland secretes three steroid hormones whose major action is the regulation of electrolyte composition in the body. Aldosterone, the most potent, deoxycorticosterone (DOC) and corticosterone (B) are secreted in small quantities (a mean secretory rate of 114 ug 150 ug and 2.5 mg, respectively). Chronic overproduction of these steroids will lead eventually to hypertension and potassium depletion. This result is clearly expressed by an aldosterone-producing adenoma (APA). These MCHs demonstrate a unique duality of regulation — aldosterone by the state of activation of the renin-angiotensin system (RAS) and DOC and B by adrenocorticotropin. The measurements of the individual hormones and the plasma renin activity (PRA) or plasma renin concentration (PRC) will provide meaningful information for the diagnosis of a hypermineralocorticoid state.

ALDOSTERONE EXCESS STATES

Clinical History

There are no clinical stigmata of aldosterone excess as one might expect with cortisol; headaches, however, are very common in primary aldosteronism and are almost immediately relieved postoperatively. Most of the symptoms, tiredness, weakness, polyuria, nocturia, are related to potassium depletion. Demonstration of transient hypertension during a pregnancy is an important point in the history, and is invariably present in APA patients. This also seems common in patients with insipient renovascular hypertensive disorders. Numbness and tingling are frequently associated with the alkalosis. It is important to note whether patients have been taking any kinds of steroids, diuretics, licorice and most important, oral contraceptives. It is

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normokalemic patient when 2.0 grams of sodium chloride are administered with each meal for four days; sodium, potassium, chlorine, carbon dioxide, and hematocrit are then measured. Usually an electrocardiogram is taken at this time since potassium depletion is intensified by this maneuver and hypokalemia is observed in the patient with primary aldosteronism. If either unprovoked hypokalemia or provoked hypokalemia has been demonstrated on more than one occasion, the measurement of aldosterone is indicated. Patients on diuretic therapy do cause problems, and a useful rapid screen to determine whether this is a cause of the hypokalemia is to measure the excretion of potassium immediately after discontinuing diuretic therapy. Frequently in this instance the urinary potassium ranges between 20-30 mEq/24 hours, which indicates intense potassium conservation. The finding of greater than 50 mEq of potassium/24 hours with hypokalemia is again presumptive evidence of aldosterone excess.

Aldosterone Measurement

Outpatient aldosterone measurements are fraught with difficulty. Aldosterone determinations were performed on specimens from 192 outpatients who did not have an APA. This represents a highly selected group in that (1) the specimens accepted were patients who demonstrated recent onset of hypertension; (2) at one time or another had had a borderline or low serum potassium, or (3) were young individuals or patients with apparent abrupt onset of hypertension. Elevated values were found in 70 (36 percent).

The abnormal elevations not due to an APA were usually due to four major factors. (1) failure to observe the requirement of an increased salt intake; (2) the variations in day-to-day aldosterone production (aldosterone is quite sensitive to stress, trauma and ACTH discharge and the outpatient hypertensive patient is subject to these pressures); (3) influence of drug therapy -- usually the volume depletion associated with recent use of diuretics. (We routinely measure urinary sodium, and if it is less than 50 mEq/24 hours, the assessment of aldosterone is not performed); and (4) estrogen therapy which usually elevates aldosterone production.

Attempts to try to control this great variability of the outpatient measurement of aldosterone is accomplished in several ways. Ingestion of a large quantity of salt has proven to be useful at times, but is poorly tolerated by the patients. Our approach is to use 9-α-fluoro-hydrocortisone (Florinef®), 100 ug four times in one 24-hour period. This is continued for three days. The aldosterone is collected on the third day. The patient is also instructed to have a liberal salt intake. This is a form of an outpatient DOCA suppression test. Secondary hyperaldosteronism will supress into the normal range. If, however, the level of aldosterone in such a specimen is elevated, we feel that the patient should be hospitalized for more definitive testing such as the administration of large amounts of DOCA and the measurement of plasma renin activity.

HIGH LEVELS OF ALDOSTERONE IN HYPERTENSIVE PATIENTS

Elevated aldosterone production in the hypokalemic hypertensive patient is further presumptive evidence for an APA but other possibilities must be considered. Secondary hyperaldosteronism in hypertensive patients is usually easily identified by either history or physical examination. This group includes malignant hypertension, renovascular hypertension, essential hypertension on estrogen therapy (birth control agents), and essential hypertensive patients recently started on diuretic agents.

Two additional measurements are most helpful in the distinction between primary and secondary hyperaldosteronism: (1) the measurement of PRA or PRC and (2) the aldosterone level after the administration of 10 mg of DOCA intramuscularly every 12 hours for three days. Primary adrenal oversecretion of aldosterone results in hypertension and hypervolemia which suppresses renin production as measured by PRC and PRA. In secondary hyperaldosteronism, PRA or PRC are elevated due to probable intrarenal nephrosclerosis and vasospasm in malignant hypertension; decreased renal arterial pressure in renovascular hypertension, increase in renin substrate and activity, but not concentration in estrogen-treated patients, and reduced circulating blood volume after diuretic treatment.

The administration of DOCA, as described, helps establish autonomy and a functioning RAS. The already high levels

of aldosterone in patients with an APA are never reduced into the normal range by DOCA. However, suppression of the elevated levels into the normal range occurs after DOCA in secondary hyperaldosteronism.

There are at least three primary adrenal causes of the syndrome of primary aldosteronism: aldosterone-producing adenomas (APA); idiopathic hyperaldosteronism (IHA) (pseudo-primary aldosteronism or nodular hyperplasia); and glucocorticoid remediable hyperaldosteronism. Treatment with 1.0 mg of dexamethasone for one week will correct the hypertension and hormonal abnormalities in the latter group. This observation makes a strong point for the existance of still another aldosterone-stimulating agent. Glucocorticoid remediable hypertension is a rare occurrence.

The distinction between an APA and IHA is difficult. Patients with IHA are more than likely male, whose mean serum potassium concentration is subnormal, but not as low as patients with APA; and have aldosterone production rates that are not as elevated as seen in APA. PRA levels are more reduced in APA than in IHA. The distinction between the two is significant because the removal of nodular hyperplastic glands usually does not effect cure or amelioration of the hypertension although the potassium depletion and its effects are corrected. The overnight recumbent PRC on a normal salt intake, at this time, seems to be the most useful discriminant between APA and IHA. The levels are usually less than 1.0 ng/ml in APA and between 1-3 ng/ml in IHA (normal 3-9). Care must be exercised in the interpretation of the measurement of PRA after salt depletion, often aided by a diuretic and after 4 hours in the upright posture. APA are still responsive to this stimulus if it has sufficient magnitude. In both APA and IHA, PRA levels usually are still subnormal after these maneuvers. Adrenal venography and bilateral adrenal vein catheterization for aldosterone concentrations may be helpful, but are still only consistently and successfully performed in specialized units.

NORMAL ALDOSTERONE LEVELS IN HYPERTENSION

The hypertensive patient whose activity and salt intake are well-controlled rarely has increased aldosterone production. At the present time the most important observation is the renin values — up to one-third of patients with

essential hypertension have subnormal values. The cause is not known, but some may harbor a subclinical APA.

In the APA patients whose potassium depletion is profound the adrenal production of aldosterone may reach the normal range. Potassium repletion effects great increases in aldosterone levels.

REDUCED ALDOSTERONE LEVELS IN HYPERTENSION

The observation of a subnormal aldosterone level in a hypokalemic, hypertensive patient should immediately suggest the possibility of the over-production of another mineralocorticoid hormone, especially if PRA is also reduced. Further evidence can be obtained by the administration of spironolactone. Correction of the hypokalemia and blood pressure could be further evidence that DOC secretion is increased--and if not DOC, possibly an unrecognized MCH. In adults, these findings would be seen in patients with the 17-hydroxylation syndrome. These patients are usually hypogonadal females with primary amenorrhea. Aldosterone and 17-hydroxy steroids are low, but excessive amounts of corticosterone and deoxycorticosterone are secreted.

COMMENT

This is the approach to the investigation of a hypertensive patient for a hyperminera ocorticoid state in the Clinical Study Center. All hypertensive patients should have several serum potassium concentrations measured after salt loading. Only after the repeated demonstration of hypokalemia should the scheme outlined in this discussion be followed. PRA as a screening test is not to be condoned because of the great variability of levels in hypertensive subjects.

A "decision diagram" is presented in TABLE I.

TABLE I

DECISION DIAGRAM

Approach to the Investigation of a Hypertensive Patient for a Hypermineralocorticoid State

		ADRENAL CAUSES	PRA	DOCA
Hypertension ↓ ↓ Hypokalemia ↓ ↓ ↓ Aldosterone Level ⟹	ELEVATED	*Primary*		
		(1) APA	↓	→
		(2) IHA	↓	→
		(3) Glucocorticoid responsive	↓	→
		Secondary		
		(1) Malignant hypertension	↑	↓
		(2) Renovascular hypertension	↑	↓
		(3) Estrogens and essential hypertension	↑	↓
		(4) Diuretics and hypertension	↑	↓
	NORMAL	(1) Essential hypertension	N or ↓	↓
		(2) APA with serum K depletion	↓	→
	REDUCED	Other mineralocorticoid hormones (Correction of hypokalemia would suggest another MCH)		
		(1) 17-hydroxylation deficiency (DOC excess)	↓	–
		(2) 11-hydroxylation deficiency (aldosterone N or ↓)	–	–
		(3) Primary DOC lesion	↓	–

Legend

→ unchanged
↓ reduced
↑ increased
N normal
PRA plasma renin activity
DOCA change in aldosterone production after DOCA administration

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Hormonal excess or hyperparathyroidism

- Hyperparathyroidism from tumor of parathyroid glands (primary hyperparathyroidism)
  - Benign chief cell adenoma, single or multiple
    - Sporadic
    - Familial
    - With tumors of the pituitary and pancreas [multiple endocrine neoplasia Type 1]
    - With medullary carcinoma of the thyroid and pheochromocytoma [multiple endocrine neoplasia Type 2]
    - Due to chronic hypocalcemia [tertiary hyperparathyroidism]
  - Functioning parathyroid carcinoma
  - Functioning benign cysts
  - Functioning lipoadenoma
- Hyperparathyroidism from hyperplasia of parathyroid glands
  - Chief cell hyperplasia
    - Neonatal, sporadic or familial
    - Adult [Cope syndrome]
  - Wasserhelle cell hyperplasia
- Hyperparathyroidism from chronic stimulation of parathyroids by hypocalcemia (secondary hyperparathyroidism)
  - Intrauterine from maternal hypoparathyroidism
  - Chronic azotemia with or without renal osteodystrophy
  - Steatorrhea with or without osteomalacia
  - Hormonal unresponsiveness
- Hyperparathyroidism from anomalous secretion of parathyroid hormone by a non-endocrine tumor [pseudohyperparathyroidism]
  - Renal cell carcinoma
  - Oat cell carcinoma of lung
  - Other malignancies (specify)

Nonfunctioning tumors of the parathyroid glands

- Carcinoma
- Benign cyst
- Lipoadenoma

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*This new classification of parathyroid disease has been proposed by Doctor David Bronsky of the University of Illinois. For further explanation and references, read his article in *The Journal of Clinical Endocrinology and Metabolism*, September 1970, pp 271 276

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