ENDOCRINOLOGY
for the House Officer
SECOND EDITION

Warner M. Burch

Williams & Wilkins

S

Endocrinology for the House Officer

Second Edition

Warner M. Burch, M.D.

Departments of Medicine and Pharmacology
Duke University Medical Center
Durham, North Carolina

WILLIAMS & WILKINS
BALTIMORE • HONG KONG • LONDON • MUNICH
PHILADELPHIA • SYDNEY • TOKYO

Editor: Nancy Collins
Associate Editor: Carol Eckhart
Copy Editor: Gail Naron Chalew
Design: JoAnne Janowiak
Illustration Planning: Wayne Hubbel
Production: Raymond E. Reter

Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible that they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

Printed in the United States of America

First Edition 1984

Library of Congress Cataloging in Publication Data

Burch, Warner M.
Endocrinology for the house officer.

(The House officer series)
Includes bibliographies and index.
1. Endocrine glands—Diseases. I. Title. II. Series. [DNLM: 1. Endocrinology —handbooks.
WK 39 B947e]
RC648.B87 1988 616.4 87-34532
ISBN 0-683-01133-2

93 94
5 6 7 8 9 10

Endocrinology for the House Officer

Second Edition

About the Author

Warner M. Burch, M.D., a Phi Beta Kappa graduate of Wake Forest College, attended Bowman Gray School of Medicine as a William Neal Reynolds Scholar. After a rotating internship at Charlotte Memorial Hospital, Dr. Burch completed his medicine residency and fellowship in endocrinology at Duke University Medical Center. While in the military, he taught students in U.S. Navy and Air Force Physicians' Assistants Programs. Dr. Burch holds the rank of Associate Professor of Medicine and Assistant Professor of Pharmacology. He is also Director of the Medical Endocrine Laboratory at Duke. He wrote the companion book, *Case Studies in Endocrinology for the House Officer*, in this series.

Preface

Endocrinology for the House Officer addresses endocrine problems commonly encountered in medical practice. This second edition is larger than the first. A chapter on hyperlipidemia has been added and several chapters expanded. Its approach is largely problem-oriented with emphasis on workup, diagnosis, and treatment. It is not intended to be a textbook of endocrinology but a convenient and practical "how to" and "why" source that can be used on the wards and in the clinic. The author would appreciate any feedback and tips that might be included in future revisions. We all remain students of medicine and servants to others.

Warner M. Burch, M.D.

Acknowledgments

Writing a book requires time and support from many people. I thank the many physicians who helped make this a useful book. My family continues to support my effort and deserves recognition. I love you: Vivian, Pweebe, Greta, Marcus, Joshua, and Seth.

Contents

Chapter 1

Endocrine Tests

WHEN, HOW, and, WHAT THEY MEAN

Probably nothing is more confusing than the myriad of endocrine studies available to the house officer. There are numerous studies but only those which are widely available will be discussed in this chapter. As with any laboratory study, one must have a clinical diagnosis or suspicion from the history or physical exam that leads one to order a particular study. What to do with the laboratory results can be a problem. When there is discordance between the clinical diagnosis and the lab results which "don't fit," then most often it is the laboratory that is in error. Somehow clinicians have been "sold a bill of goods" regarding the infallibility of a laboratory result. If your clinical diagnosis seems firm and yet the lab says something else, then call the laboratory; ask for a repeat run; check to see if the proper patient sample was assayed; how good was that assay?; etc. With endocrine studies in general, it is very important that you know the quality and reliability of the laboratory to which the specimen was sent. This point cannot be overemphasized.

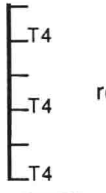
THYROID TESTS

Serum thyroxine (T4): The most widely used method for measuring total serum T4 is the radioimmunoassay (RIA). It is reliable, inexpensive, and specific. Normal serum T4(RIA) levels range between 5 and 12 µg/dl. Serum T4 is affected by two major factors: thyroidal secretion of T4 and the serum binding capacity for T4. Since > 99.9% of the T4 circulating is bound to protein, any alteration in the binding capacity as well as in T4 secretion leads to abnormal serum T4 levels. To accurately interpret the level of T4 one also needs to know about the serum T4 binding capacity The following case illustrates a common situation: A 24 yr-old woman was referred because of symptoms of anxiety and rapid heart rate; her serum T4(RIA) 14.5 µg/dl (normal 5-12). She was taking an ora

contraceptive. On physical exam the pulse was 95 and no goiter was palpated. Is this hyperthyroidism? Unlikely, but what one really needs is a measure of the serum T4 binding capacity since estrogens increase thyroid binding globulin (TBG), the major T4 binding serum protein. The T4 binding capacity of serum is assessed by measuring the T3U.

T3U or T3 resin uptake: The T3U measures indirectly the number of unoccupied protein binding sites for T4 and T3 in serum. The test gets its name from the radiolabeled T3 which is used in the in vitro assay. Radiolabeled T3 is added to the patient's serum and competes for binding sites on the TBG molecule. Radiolabeled T3 is used instead of T4 because the assay time is shorter. A resin or some other inert material is then added to adsorb any unbound radiolabeled T3. The radioactivity of the resin is then counted and expressed as per cent of total counts added to the assay tube.

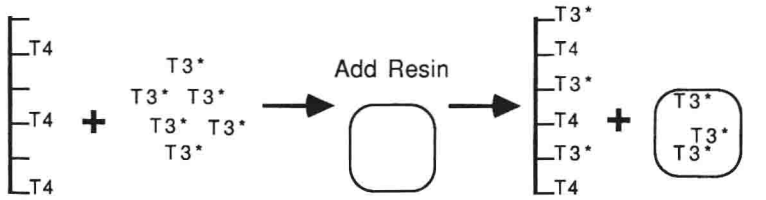
Schematically the T3U assay is performed as follows:



represents the TBG with T4 bound to several binding sites;

T3* represents radiolabeled T3;

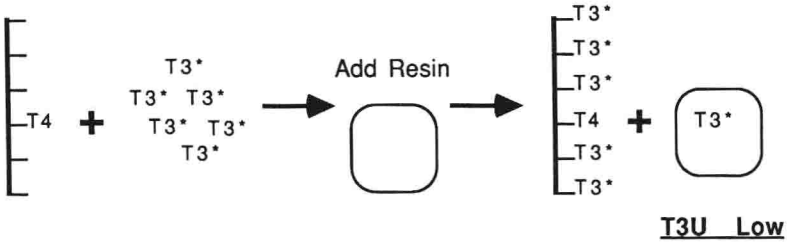
depicts the resin which is later counted for radioactivity yielding the T3U value:



T3U Normal

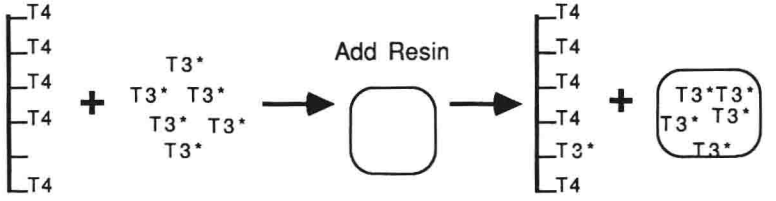
If the sites on TBG are under-occupied by T4 (as in hypothyroidism with decreased T4 secretion), then more radiolabeled T3 binds to the

protein and less radiolabeled T3 is adsorbed to the resin. Thus, the T3U is low. Schematically the T3U assay of hypothyroid serum would be as follows:



T3U Low

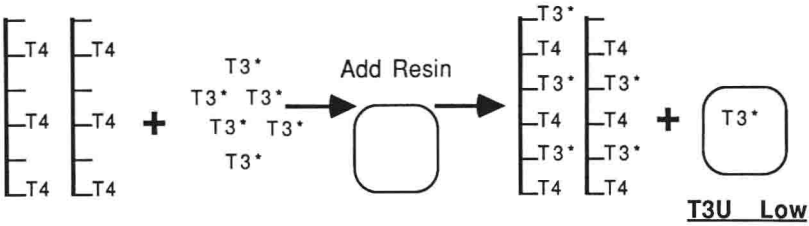
In patients with hyperthyroidism (increased T4 secretion), the T3U is elevated since most of the sites on TBG are occupied by T4 so that less radiolabeled T3 can be bound by the protein and more to the resin. Schematically the T3U assay would look like this:



T3U High

The normal range of values for the T3U depends on the particular type of resin used, which means various laboratories have different normal ranges for T3U. In all cases, however, the T3U is inversely proportional to the number of unoccupied binding sites on TBG (low T3U--high TBG; high T3U--low TBG).

When TBG levels are raised (i.e., more binding sites for radiolabeled T3, less radioactivity for resin to adsorb), the T3U will be low. The most frequent medication that raises TBG is estrogen. The T3U assay in this situation is diagrammed as follows:



The patient mentioned above who was taking an oral contraceptive did have raised TBG levels which accounted for the elevated serum T4 and this was confirmed with a low T3U. There are numerous factors that may affect TBG and thus the T3U value. These factors are listed in the following table.

Increased TBG	Decreased TBG
Estrogen therapy	Androgen therapy
Pregnancy	Severe hypoproteinemia
Acute hepatitis	Chronic liver disease
Acute intermittent porphyria	Glucocorticoid excess
Hereditary TBG increase	Hereditary TBG deficiency
	Acromegaly
T3U LOW	***T3U HIGH***

Some medications, such as salicylates (high doses), phenytoin, and clofibrate, compete with T4 to bind on TBG. This leads to high T3U values but also to lower T4(RIA) levels. It should be remembered that the T3U has nothing to do with the serum levels of T3.

To correct for variation in TBG (and therefore the T4 and T3U values), a calculated value called the Free Thyroid Index (FTI) may be used. The FTI is an attempt to normalize discordant serum T4 and T3U values and is the product of the T4(RIA) times the T3U. This calculated number correlates well with the levels of free T4 and thus is named Free Thyroid Index.

Free thyroxine (FT4): The unbound or free thyroxine (FT4) is the metabolically active hormone fraction. It accounts for less than 0.05% of the total T4 circulating in the blood. Ideally, the measurement of the free T4 would eliminate most of the confusion regarding binding protein abnormalities because it circulates within well-defined limits in the euthyroid patient. Free T4 levels have not been routinely available because the measurement of this small quantity of unbound T4 is technically difficult, time-consuming, and often requires dialysis techniques for quantitation. However, the commercial kits for measurement of free T4 have improved considerably. If one uses radiolabeled T4 derivatives that do not bind significantly to TBG and high affinity antibodies that bind both T4 and T4 derivative, then a classical equilibrium radioimmunoassay can be applied. This technology gives reliable Free T4 values and promises to replace T4(RIA).

T3(RIA): The primary hormone secreted and the major circulating thyroid hormone is thyroxine (T4). However, T4 is rapidly deiodinated into triiodothyronine (T3) by 5'-deiodinase found in many tissues but especially in the liver. T3 is the metabolically active thyroid hormone which binds to nuclear receptors of target tissues. T3 circulates in the blood but at concentrations 50 times lower than T4. Radioimmunoassays of T3 are specific and are generally available. Serum T3(RIA) levels range between 90 and 190 ng/dl. T3 is also bound to TBG but the affinity is less avid. Nevertheless, serum T3(RIA) measurements are subject to the same limitations regarding protein binding as with T4 determinations (e.g., estrogens increase TBG and therefore raise T3(RIA) levels). Serum T3(RIA) levels are elevated in hyperthyroidism, often to a greater degree than the T4(RIA). Serum T3(RIA) is useful in iodine deficient states where the T4 may be low yet T3 is normal. T3(RIA) is particularly useful in hyperthyroid states such as toxic nodular goiter where the serum T4(RIA) may be normal. Free T3 determinations are commercially available using techniques comparable to Free T4 measurements described above.

Thyroid stimulating hormone (TSH): TSH is a glycoprotein secreted by the pituitary. The rate of TSH production is dependent on the levels of free thyroxine and is regulated by a classical negative feedback system: Low levels of T4 lead to TSH secretion which stimulates thyroid hormone production and release which in turn decrease pituitary TSH output. Conversely, high T4 or T3 levels suppress TSH secretion. Serum TSH is measured by radioimmunoassay with normal ranges from 0-6 μU/ml. Current TSH assays using immunoradiometric assays (IRMA) are

sensitive enough to tell the difference between 0 and 2 μU/ml, something older assays could not do. The improved sensitivity allows differentiation between euthyroid and hyperthyroid subjects whose TSH levels are low (0-0.2 μU/ml). Make sure your laboratory uses an ultrasensitive TSH assay before assessing the value of a low TSH. The serum TSH is elevated in primary hypothyroidism, reaching levels > 100 μU/ml. If there is a question of primary hypothyroidism clinically, serum TSH determination is extremely helpful.

Thyrotropin releasing hormone (TRH): TRH is a tripeptide secreted by the hypothalamus and circulated to the pituitary via the portal-hypophyseal capillary system. TRH stimulates the certain pituitary cells called thyrotropes to secrete TSH. If ambient levels of T4 or T3 are high, then the thyrotrope does not respond to TRH with a rise in TSH. In primary hypothyroidism in which the TSH is already elevated, TRH greatly augments the release of TSH. TRH administration is extremely useful clinically in states in which hyperthyroidism is suspected and the diagnosis is not clear using static determinations such as T4(RIA), T3U, and T3(RIA). Ultrasensitive TSH assays which measure very low TSH levels might be used in such patients when TRH is not available. Giving TRH provides a dynamic test which assesses the functional integrity of the thyrotrope. The TRH study is performed as follows:

> **Blood is drawn for baseline TSH (0 time). TRH (protirelin) 500 μg is given iv over 15-20 sec and blood drawn again at 30 minutes for TSH determination. TSH levels peak normally around 20-30 minutes post TRH. The normal response depends upon age and sex. Females generally have at least 6 μU/ml rise above the basal level. Males < 40 yrs of age should have a similar rise (> 6 μU/ml) whereas males > 40 should have at least a 2 μU/ml rise.**

In primary hypothyroidism the response to TRH is increased. Hyperthyroid patients, patients with euthyroid Graves' disease, or subjects taking excessive doses of replacement thyroid (T4 or T3) or pharmacological amounts of glucocorticoid will not have a rise in serum TSH. In patients suspected of having hyperthyroidism the TRH study has nearly replaced the use of exogenous thyroid hormone to see whether radioiodine uptake is suppressed or not.

Thyroidal 24-hour radioactive iodine uptake: The thyroid gland concentrates iodine which it uses for thyroxine production. Because the

thyroid acts as a sump for iodine and relatively little iodine is trapped anywhere else in the body, the uptake of radioactive iodine (RAI) is a useful marker of thyroid function. The source of radioactivity has traditionally been 131-Iodine. The RAI uptake is calculated as the percentage of total administered radioactivity taken up by the thyroid. This determination is usually made 24 hours after an oral ingestion of tracer doses of I-131 (6-8 μCi). The normal 24-hr RAI uptake is 10-30%.

If the thyroid is not functioning (e.g., hypothyroidism or in subacute thyroiditis where the follicular cells cannot concentrate iodine), then the 24-hr RAI uptake is low.

If the iodine content of the plasma pool is elevated secondary to ingestion of iodine-rich foods (kelp) or medications (saturated solution of potassium iodide, amiodarone, etc.) or secondary to the administration of radiographic agents, the 24-hour value for tracer uptake is low even though the thyroid may function normally.

In diffuse toxic goiter the thyroidal trapping of iodine is increased, and the 24-hr I-131 uptake will be elevated. 123-Iodine is now a frequent source of radioactive iodine since there is less radiation exposure to the thyroid. The amount of radiation delivered to the thyroid by I-131 is approximately 1.5 rad/μCi (assuming normal size gland and 20% 24-hr uptake) which is 100 times the radiation exposure of I-123 (0.015 rad/μCi). All radionuclide tests are contra-indicated during pregnancy.

Thyroid imaging or scan: Imaging of the thyroid is possible by utilizing radionuclides. These are useful in ascertaining whether a particular area of the thyroid such as a nodule is functioning, that is, is it able to trap and concentrate the radionuclide? The most often used radiotracers are technetium-99m pertechnetate, I-131, and I-123. TcO4-99m (5 mCi) is administrated iv and thyroid imaging is performed within 30 min. TcO4-99m assesses only the transport ability of the follicular cells whereas iodine radionuclides assess both transport and organification of iodine to thyroglobulin. The amount of radiation delivered to the thyroid is 0.2 rad/mCi TcO4-99m. I-131 (50 μCi) is administrated po and the scan performed 24 hours later. The thyroid scan with pertechnetate is more convenient for the patient and also has considerable less thyroidal radiation (i.e., 1 rad vs 75 rads for I-131). I-123 may also be used for imaging but this is not always available because of its short half-life (13 hrs).

PITUITARY TESTS

Growth hormone: Growth hormone (GH) is measured in three circumstances: 1) when there is clinical evidence of acromegaly or gigantism; 2) when there is evidence of growth failure (e.g., short stature); 3) when it is necessary to ascertain whether there is adequate pituitary reserve. Mass lesions (e.g., tumors, cysts) often impair GH secretion by the pituitary somatotrope, making GH levels a sensitive marker of deranged pituitary function. Growth hormone is assayed in serum or plasma using radioimmunoassay. A single determination of GH can be useful in few cases, but often dynamic studies (stimulation or suppression tests) are necessary.

If the question is acromegaly, obtain a blood sample after the patient has fasted overnight and is at bedrest. A GH level > 10 ng/ml is highly suggestive of acromegaly. Any form of stress (exercise, surgery, smoking, etc.) raises GH and thus caution must be taken on borderline elevated values. Acromegaly is usually confirmed using an oral glucose tolerance test (GTT) [see Diabetes Mellitus, page 41]. Blood is obtained at 0, 60, 120, and 180 minutes for GH determination. Since rises in blood glucose suppress GH levels in healthy patients, normal subjects will exhibit a decrease in GH to < 2 ng/ml within two hours. Up to a third of acromegalic patients have a paradoxical rise in the GH levels during the GTT. GH stimulates somatomedin production, so serum somatomedin C (Sm-C) levels are elevated in acromegaly as well.

If the question is growth hormone deficiency, then a single determination using any form of stress to raise GH may be all that is necessary. In children blood drawn for GH 90 minutes after sleep is helpful since GH is secreted during REM sleep. However a more practical study is to have the child exercise (run up and down steps for 15 minutes) and then draw blood for GH level. Any values > 5 ng/ml excludes GH deficiency. A variety of stimulatory tests are available to raise GH levels. Determining when to order these studies and how to interpret them requires discernment. In children with short stature and low GH value after exercise or in the patient with possible hypopituitarism, a stimulatory test is indicated.

The "gold standard" dynamic study is insulin-induced hypoglycemia. Hypoglycemia produces a profound stress reaction that is followed by GH and ACTH release, with a subsequent rise in the serum cortisol.

The insulin-induced hypoglycemia test (IIHT) is performed in the AM after an overnight fast with the patient at bedrest. An indwelling needle in the forearm is recommended so that multiple samples can be obtained. Blood for basal levels of GH and cortisol is taken at -15 and 0 minutes. Regular insulin (0.1 U/kg for normal-sized patients and 0.15-0.2 U/kg for patients with insulin resistance, e.g., obesity) is injected as an intravenous bolus over 10-15 seconds. If there is clinical evidence of hypopituitarism, then a lower dose of insulin is used (0.05 U/kg), since profound hypoglycemia is more likely. Plasma glucose is measured at 0, 15, 30, 45, and 60 minutes. A decrease of the plasma glucose to 50% of the baseline value or < 40 mg/dl is considered an adequate hypoglycemic response, which is necessary to interpret the GH and cortisol levels. Blood for GH and cortisol is measured at 0, 30, 60, and 90 minutes. Dextrose (50%) should be available to treat severe hypoglycemia (e.g. obtundation, seizure).

After hypoglycemia is assured (hunger, palpitations, perspiration), the patient may drink fruit juice to decrease symptoms if necessary. The nadir for the blood sugar is usually 20-30 minutes, with rises of GH and cortisol later (fig. 1.1).

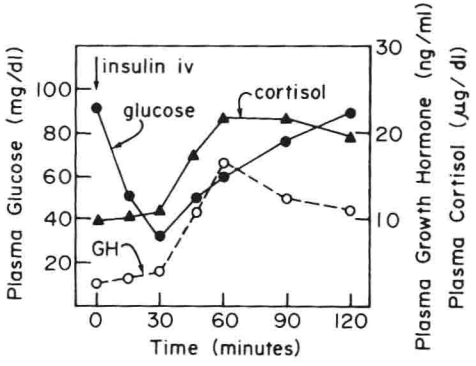


Figure 1.1 The response of plasma growth hormone and cortisol to insulin-induced hypoglycemia.