CLINICAL EXERCISES IN INTERNAL MEDICINE

VOLUME 1

THYROID DISEASE

HAMBURGER

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THYROID DISEASE

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To Hilda

PREFACE

Clinical Exercises in Internal Medicine: Thyroid Disease is not a textbook or a substitute for a textbook. Rather, it is a teaching device which has the objective of bridging the gap between didactic instruction and clinical practice. Self-assessment sections constitute the core of the book. I would like to emphasize that the case records are those of real patients, and the dilemmas the reader is asked to consider are the very ones faced by the author. However, the reader has the important advantage of having followup information available. Thus he or she is able to compare his or her solutions with mine. Since thyroid problems often take many years to evolve, the result that may be apparent soon after a given treatment may differ considerably from the result that is ultimately achieved. Hence, to become an experienced clinical thyroidologist requires many years. This book attempts to compress those years into a volume which can be digested in a few days, more or less.

Since these patients are real and their problems are real, it should not be surprising that the actions I chose at the time were not necessarily those that I might now prefer. After all, one is not born with clinical experience and will rarely have the opportunity to acquire very much while in training. The mastery of clinical skills is a slow process that should not cease until the physician stops caring for patients.

Furthermore, the reader should not approach the self-assessment challenges with the idea that the purpose is to select the "right" answer. Should he do so, he will be disappointed to find that more than one answer may have merit in some cases, and that what is called for is not so much selection as analysis. The goal of this volume is to encourage an analytical approach to the consideration of alternative methods for dealing with thyroid problems. Experts may differ on therapeutic decisions, but all should agree that the best decision is most likely to result from a careful consideration of the advantages and disadvantages of possible alternatives.

The didactic portions which precede each of the self-assessment sections should be viewed as introductory material containing the more valuable clinical lessons I have learned over the years. It is not intended that these portions of the text cover all aspects of thyroidology comprehensively; there are a number of reference volumes available for this purpose. This book is structured to advance the reader (who presumably has a basic knowledge of the subject and some clinical experience) rela-

tively quickly through basic principles of pathophysiology, clinical diagnosis, laboratory diagnosis, and therapy to the application of these principles in selected clinical problems. The reader will soon appreciate that certain concepts are presented repetitively. These are points which I consider both important and inadequately emphasized in the literature. It is my intention that no one who reads this volume will continue to be unfamiliar with these concepts.

References are listed, and the principal messages (as I see them) of the references are noted. In some instances, serial references are employed to show how certain important concepts have evolved in the literature.

In sum, I expect that this book will serve as a modern clinical learning source for students and practitioners who are interested in improving clinical skills that are important for the accurate and efficient diagnosis and treatment of thyroid patients. I trust that it will prove both instructive and fun to read.

NOTE: For all case studies the normal ranges for laboratory values are those cited in Table 1–1 unless otherwise noted.

ACKNOWLEDGMENTS

My appreciation is extended to Mrs. Hanica Ullmann, Ph.D. candidate, Instructor of English Literature, Wayne State University, Detroit, Michigan, for her review of the manuscript which greatly improved its readability.

I am particularly indebted to Dr. J. Martin Miller, my teacher and friend of many years, for taking the time to review this book just prior to publication. Among his perceptive observations are two that deserve comment.

Dr. Miller correctly noted that the high frequency with which lymphoepithelial goiter (better known to most as Hashimoto's disease) is seen in clinical practice is in stark contrast with the limited reference to the condition in this book. This reflects my experience that the clinically relevant aspects of the disease are expressed in terms of goiter (usually diffuse but occasionally nodular) and hypothyroidism. The problem is therefore dealt with primarily in the chapters on simple goiter and hypothyroidism. The immunologic features of the disease which have received so much attention in the literature have little importance from the standpoint of management.* Furthermore, there are few therapeutic problems in Hashimoto's disease, and the treatment is generally rather straightforward. Hence, I simply do not have very much to say about it. Nevertheless, the reader should have no doubt that Hashimoto's disease is indeed one of the more common afflictions of the thyroid gland seen in clinical practice.

Dr. Miller also correctly observed that although a self-assessment section might be expected to assess the reader's comprehension of the preceding didactic material, in this book such is not necessarily the case. Here the self-assessment sections are not supplemental to the text; on the contrary, they are the text. They assess the reader's total fund of knowledge and experience with thyroid patients by means of problems which are generally of more than elementary difficulty. The didactic

*For the latest on autoimmunity in the thyroid read:

1. Allison AC: Self-tolerance and autoimmunity in the thyroid. *New Eng J Med* 295:821–827, 1976.
2. Volpé R: The role of autoimmunity in hypoendocrine and hyperendocrine function with special emphasis on autoimmune thyroid disease. *Ann Intern Med* 87:86–99, 1977.

portions serve to highlight certain principles which will be exemplified by the cases; but mastery of these lessons will not be enough to permit the reader to appreciate all the points illustrated by the cases. However, this is not important. The reader who diligently spends the time to think through each of these problems and then compares his judgments with mine, should find that he or she has not only expanded his clinical horizons but also has had some fun in doing it.

My associates Drs. Donald A. Meier, Sheldon S. Stoffer, Charles I. Taylor, and Michael Garcia contributed greatly to this effort by providing cases for the self-assessment sections, suggesting many improvements in the text, and proofreading extensively.

Dolores Stachura and Tina Eller, our secretaries, deserve special commendations for bearing with good grace the tedium of endless retyping and proofreading of the material.

DEFINITIONS AND ABBREVIATIONS

Certain terms commonly encountered in the literature on thyroid disease are used rather loosely by some physicians (e.g., adenoma, nodule), but in this volume these terms will be used precisely as defined. Other terms will be defined because they might not be familiar to many physicians.

Abbreviations are a standard practice in scientific literature and serve the dual purpose of reducing the size of a book and permitting more rapid reading of the material. However, unfamiliar abbreviations may constitute a hindrance to the reader's comprehension. Therefore, I have included a list of abbreviations in this section.

The following guidelines have been employed with respect to abbreviations:

1. Abbreviations familiar to all scientists (e.g., cm, mm, etc.) are used throughout the text without definition.
2. Abbreviations peculiar to thyroidology, although familiar to all physicians, will be defined in this glossary but not necessarily in the text.
3. Abbreviations used by me alone are defined here and in each section of the text where they are employed.

DEFINITIONS

ADENOMA, THYROID: A discrete thyroid mass which fulfills the histologic or pathophysiologic criteria for a benign neoplasm.

COLLOID GOITER: I dislike this term because it is often employed to imply some profound understanding of pathophysiologic mechanisms, whereas actually the term is meaningless. All goiters have colloid—so what? This term carries with it no specific diagnostic or therapeutic implications. For these reasons I use the term "simple goiter" as de-

fined below. I consider the latter preferable because it implies no in-depth analysis or understanding of pathophysiology and because for most patients the further study necessary to define the underlying abnormal mechanism will not be useful in determining the treatment.

DYSHORMONOGENESIS: Defective synthesis or secretion of thyroid hormone resulting from insufficient activity of one or more essential enzymes. Dyshormonogenesis may be compensated or decompensated.

COMPENSATED: Because of compensatory hyperplasia of the thyroid, a normal output of thyroid hormone may be maintained, and the patient is euthyroid.

DECOMPENSATED: In spite of thyroidal compensatory hyperplasia, output of thyroid hormone is subnormal, and the patient is hypothyroid.

GRAVES' DISEASE: A syndrome of which the principal features are hyperthyroidism, diffuse goiter, and ophthalmopathy. However, not all of these features need be present in any given patient at any given time. For example, it is proper to speak of euthyroid Graves' disease as a stage in the evolution of the illness during which the patient may not have hyperthyroidism but only goiter or ophthalmopathy.

HYPERTHYROIDISM (THYROTOXICOSIS): The clinical syndrome resulting from the delivery of an excessive quantity of thyroid hormone to the patient, regardless of the source of the hormone.

HYPOTHYROIDISM: The clinical syndrome resulting from the lack of an adequate supply of thyroid hormone.

IMAGE: A pictorial representation of the thyroid gland produced after the administration of a radioactive tracer which is selectively concentrated by the thyroid. This term is preferable to "scan," because images are now more often obtained by means of gamma cameras (stationary devices) than by rectilinear scanners.

MYXEDEMA: This term is often used synonymously with hypothyroidism, but in general it should be restricted to indicate a severe deficiency state.

NEOPLASM: A new growth, benign *or* malignant.

NODULE, THYROID: Any discrete thyroid mass whether neoplastic or non-neoplastic, detectable by *physical examination.*

SIMPLE GOITER: A generalized enlargement of the thyroid gland, whether smooth, irregular, or nodular, in an euthyroid patient who presents no evidence of abnormal hormonal secretory activity.

ABBREVIATIONS

AFTA:	Autonomously functioning thyroid adenoma
AST:	Acute suppurative thyroiditis
ATD:	Antithyroid drugs
BEI:	Butanol-extractable iodine
BMR:	Basal metabolic rate
DIT:	Diiodotyrosine
DT_4:	Dextrothyroxine
EKG:	Electrocardiogram
ENT:	Extranodular thyroid tissue

ESR:	Erythrocyte sedimentation rate
FTI:	Free thyroxine index
I:	Iodide
^{131}I:	The isotope of iodine most widely employed for thyroid function testing and therapy
^{125}I:	An isotope of iodine used chiefly in testing
^{123}I:	A newly available isotope of iodine with a very short half-life which is advantageous for thyroid imaging
LATS:	Long-acting thyroid stimulator
LT_4:	Levothyroxine
μCi:	Microcurie
μg:	Micrograms
μU:	Microunit
mCi:	Millicurie
MIT:	Monoiodotyrosine
MNG:	Multinodular goiter
ng:	Nanograms
NG–NH:	No goiter–no hypothyroidism
PBI:	Protein-bound iodine
PII:	Plasma inorganic iodide
PTU:	Propylthiouracil
RAI:	Radioactive iodine uptake, the 24-hour value unless otherwise specified
RIA:	Radioimmunoassay
SAT:	Subacute thyroiditis
SD:	Standard deviation
SSKI:	Saturated solution of potassium iodide
ST_4:	Supplemental thyroid hormone
T_3:	Triiodothyronine
T_3(RIA):	A test which measures the serum concentration of T_3 by RIA
T_4:	Thyroxine
T_4(D):	A test which measures the serum concentration of T_4 by displacement, or competitive protein binding
T_4(RIA):	A test which measures the serum concentration of T_4 by RIA
TBG:	Thyroxine-binding globulin
TBG(S):	A test that estimates the saturation of TBG. Formerly (and still widely) referred to as the T_3 resin uptake test or T_3 test. The older term is less accurate because the test does not measure the serum T_3 concentration, and there is another test – the T_3(RIA) test – that does.
TBPA:	Thyroxine-binding prealbumin
Tc:	Technetium-99m
TDG:	Toxic diffuse goiter, hyperthyroidism of the Graves' type
TMNG:	Toxic multinodular goiter
TRG:	Toxic recurrent goiter (after previous thyroidectomy)
TRH:	Thyrotropin-releasing hormone
TSH:	Thyroid-stimulating hormone
TSH(RIA):	A test that measures the serum concentration of TSH by RIA

CONTENTS

CHAPTER 1

LABORATORY EVALUATION OF THE THYROID

PART I. THYROID PHYSIOLOGY

A basic knowledge of thyroid physiology is essential to the understanding of laboratory methods. Figure 1–1 illustrates the important aspects of normal thyroid physiology.

IODINE METABOLISM

In the United States the dietary content of iodine varies from 70 to 300 μg daily. In the past, as a result of removal of iodine from the soil by glaciers, iodine deficiency goiters were common in the area of the Great Lakes. The advent of iodized salt and improved methods of food distribution and mineral fortification have almost eliminated iodine deficiency as a dietary problem in this country. Recently, an increased iodine content in commercially baked bread has been recognized in the United States.

Ingested iodine is reduced to iodide in the gastrointestinal tract. Absorption is virtually complete. It may take place throughout the gastrointestinal tract, but it is maximal in the small intestine. Ingested iodotyrosines, triiodothyronine (T_3), thyroxine (T_4), and iodinated radiographic contrast media are absorbed intact. Absorbed iodide has a volume of distribution numerically equal to about 35 per cent of the body weight and is confined largely to the extracellular space. The plasma inorganic iodide level is usually less than 1.0 μg per 100 ml except in the post-absorptive state. Iodide is cleared from the plasma chiefly by the kidneys and the thyroid, with renal clearance normally three to four times that of the thyroid. Renal clearance of iodide is closely related to glomerular filtration rate. There is no evidence of tubular secretion.

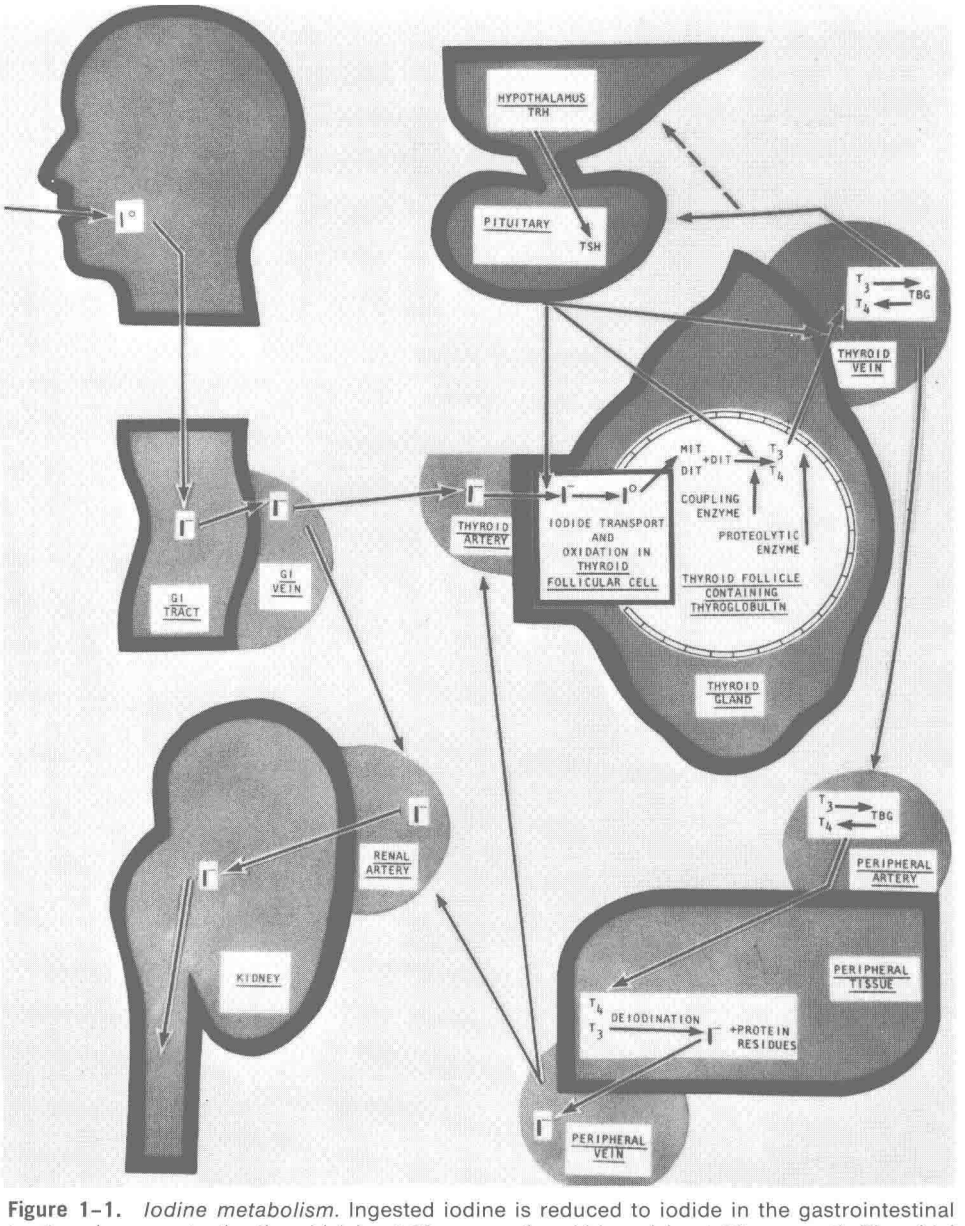

Figure 1–1. *Iodine metabolism.* Ingested iodine is reduced to iodide in the gastrointestinal tract and passes to the thyroid (about 20 per cent) or kidney (about 80 per cent). Thyroidal iodide is oxidized to iodine and utilized in the synthesis of T_3 and T_4 and the regulation of TSH. T_3 and T_4, bound principally to TBG, circulate to the tissues where they are metabolized, releasing iodide.

IODIDE TRANSPORT

Iodide enters the thyroid by active transport, an energy-dependent process which is augmented by thyroid-stimulating hormone (TSH). It then either is rapidly organified or remains free to diffuse passively from the thyroid back into the circulation. Transport of iodide from the plasma to the thyroid is subject to an autoregulatory mechanism which functions by inhibiting further transport of iodide as glandular iodide stores are increased. However, when iodide stores are depleted,

iodide transport is enhanced. Thyroidal clearance of iodide is also related to the plasma inorganic iodide (PII) concentration. Within a range of 1 to 6 μg per 100 ml, acute changes in PII do not alter thyroidal iodide clearance significantly. Sharp reductions in PII below 1 μg per 100 ml will lead to an abrupt increase in thyroidal iodide clearance, whereas increases in PII over 6 μg per 100 ml will depress this clearance.

SYNTHESIS, STORAGE, AND SECRETION OF THE THYROID HORMONES

Figure 1–1 indicates the steps in the production of the thyroid hormones, beginning with the transport of iodide from the plasma into the thyroid follicular cell. Oxidation of iodide to iodine occurs under the influence of a peroxidase enzyme. At the colloid-cell interface iodide becomes incorporated in tyrosine components of thyroglobulin as either monoiodotyrosine (MIT) or diiodotyrosine (DIT). The ratio of MIT to DIT depends principally upon the availability of iodide and the rate at which hormonal synthesis is proceeding. The ratio may be altered by injury—inflammation or radiation—to the thyroid and also by some thyroid neoplasms. Coupling of MIT and DIT produces T_3, whereas two molecules of DIT combine to produce T_4. This coupling is enzymatically mediated. Under circumstances favoring MIT production, there may be a shift toward the production of T_3 rather than T_4. This may be a compensatory process in which the thyroid gland, which may be either deficient in iodide or functionally injured, shifts to the preferential production of a hormone which has relatively greater metabolic activity per molecule (i.e., T_3), thus possibly forestalling the development of hypothyroidism.

T_3 and T_4 are produced within the stored thyroglobulin of the follicular colloid. The thyroglobulin repository normally contains enough hormone to maintain the euthyroid state for 2 months without new synthesis. In response to TSH, the thyroglobulin molecule is split by proteases and peptidases into the component iodotyrosines and iodothyronines (T_3 and T_4). The iodotyrosines are enzymatically deiodinated, conserving iodide for reutilization in the synthesis of thyroid hormone. Normally, only negligible quantities of iodotyrosine are present in the circulation.

Although the thyroid hormonal secretion contains T_4 predominantly, since there is peripheral conversion of T_4 to T_3 and T_3 is more active, it seems likely that T_3 may actually be of greater importance than T_4 to the body economy. In fact, it has been suggested that T_4 actually serves only as a prohormone or precursor for T_3. However, the enthusiasm for this rather extreme view seems to be subsiding.

REGULATION OF THYROID FUNCTION

TSH (thyroid-stimulating hormone) is the principal regulator of thyroid function. Figure 1–1 presents diagrammatically the functional interrelationships between the hypothalamus, pituitary, and thyroid. It can be seen that TSH stimulates not only transport of iodide into the cell but also both synthesis and secretion of thyroid hormones. The action of TSH at the thyroid cell is mediated via activation of adenyl cyclase, with the subsequent generation of cyclic AMP. TSH secretion is provoked by low serum concentrations of thyroid hormone and is inhibited by high concentrations.

TRH (thyrotropin-releasing hormone) is a tripeptide secreted by the hypothala-